PART II
ANAESTHESIA REFRESHER COURSE

2015

Department of Anaesthesia
University of Cape Town

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Index of lectures

1.	Paper 3	*Prof. M James*
2.	Myocardial protection	*Dr A Myburgh*
3.	Peri-operative myocardial infarction- Current management strategies	*Dr T Kisten*
4.	Interpretation of the literature – How to read a scientific paper	*Prof. M Jamest*
5.	Liver disease- An anaesthetist's perspective	*Dr T Kisten*
6.	*Data interpretation 1* – Liver function tests	*Dr S Dwyer*
7.	*Data interpretation 2* – Thrombo-elastogram	*Dr M Miller*
8.	*Data interpretation 3* – Pulmonary function tests	*Dr A de Vaal*
9.	*Data interpretation 4* – The intra-aortic balloon pump	*Prof. I Joubert*
10.	Enhanced recovery after surgery (ERAS)	*Dr M Nejthardt*
11.	Aspects of spinal surgery	*Dr R Llewellyn*
12.	Anaesthesia for shoulder surgery	*Dr L Montoya-Pelaez*
13.	Anaesthetic considerations in chronic kidney disease	*Dr T Kisten*
14.	Evidence-based anaesthesia for renal transplantation	*Dr G Picken*
15.	ARDS – Evidence-based strategies to improve outcome	*Dr T Kisten*
16.	Post-operative pulmonary complications	*Dr J Piercy*
17.	*How to do it 1* – Anaesthesia for laryngoscopy and microlaryngeal surgery	*Prof. P Gordon*
18.	*How to do it 2* – Awake fibre-optic intubation	*Dr B Brennan*
19.	*How to do it 3* – Anaesthesia for flap surgery	*Dr M Hendricks*
20.	Assessment, management and complications of post-operative pain	*Dr J van Nugteren*
21.	Managing complications of regional anaesthesia	*Dr A Ernst*
22.	Troubleshooting in the recovery room	*Dr G Davies*
23.	New oral anticoagulants (NOACs) and anaesthesia	*Dr G Wilson*
24.	The assessment of effort tolerance	*Dr A Marais*
25.	Epidural labour analgesia	*Dr D van Dyk*
26.	Vasopressors and caesarean section	*Prof. R Dyer*
27.	*How to do it 4* – Anaesthesia for the bleeding tonsil	*Dr R Gray*
28.	*How to do it 5* – Anaesthesia for Whipple procedure	*Dr S Heijke*
29.	*How to do it 6* – Awake craniotomy	*Dr N Meyersfeld*
30.	Neuroprotection in anaesthesia	*Dr K Bergh*
31.	Anaesthesia for interventional neuroradiology	*Dr A Reed*
32.	Pituitary surgery	*Dr R Haylett*
33.	Autonomic neuropathy	*Dr E Cloete*
34.	Organ transplantation, death and brain death in South Africa	*Dr D Thomson*
35.	Management of massive blood transfusion	*Dr V Koller*
36.	Management of the severely injured patient: current concepts	*Dr F Roodt*
37.	*How to do it 7* – Management of the patient with a coronary stent	*Dr K Timmerman*
38.	*How to do it 8* – Anaesthesia for infantile pyloric stenosis	*Dr K Kemp*
39.	*How to do it 9* – The fractured neck of femur	*Dr N Khan*
40.	Emergence delirium	*Dr K Bester*
41.	Update on management of postoperative nausea and vomiting (PONV)	*Dr M Rademeyer*
42.	Perioperative concerns & considerations for bariatric surgery	*Dr D Nolte*
43.	Nitrous oxide	*Dr C Simons*
44.	Anaesthesia for thoracic surgical emergencies	*Dr D Visu*
45.	New tools & trends – Airway rescue	*Dr R Hofmeyr*
46.	Endovascular aortic surgery	*Dr O Porrill*
47.	Anaesthesia for minimally invasive cardiac surgery	*Prof.* J Swanevelder

Paper 3

Prof. M James

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Notes:

Myocardial Protection

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1. Introduction:

Myocardial protection means a great many things to a great many people, depending on who you talk to: To a dietician it might mean limiting fat intake (or not!), a cardiologist might suggest daily use of aspirin and a glass or two of red wine; a sport scientist might advise daily aerobic exercise; the pharmaceutical industry might try and peddle expensive statins; a country singer might advise against booking in at the Heart Break Hotel, and so on.
What does myocardial protection mean to the Anaesthetist in the cardiac theatre?

2. Pre- and post- conditioning, stunning and hibernation:

Prolonged ischaemia causes irreversible necrotic tissue damage during the ischaemic period and after reperfusion, further injury is sustained by the latter.

What is Pre-conditioning?
Exposure to a short period of ischaemia protects the heart from a longer period of ischaemia (and lessens the size of the infarct)

What is Post-conditioning?
Short periods of ischaemia during the reperfusion stage following ischaemia lessens heart damage.

What is the mechanism of ischaemia / reperfusion injury?
Ischaemia causes necrosis with the release of free radicals and lipid hydroperoxides. In the early phase, small amounts of adenosine, bradykinin and opioids are released that protect the cells through G-protein coupled receptors, with resultant cascades culminating in cytoprotection.
Late protection is associated with the expression of pro-survival genes, e.g. Heat shock protein.
There is also a reduction in opening of mitochondrial permeability transition pores (mPTPs). If these pores stay open for a long time, mitochondrial contents is released into the cytosol leading to cell death.[(1)] (So it goes)
Isoflurane, Sevoflurane and Desflurane offer preconditioning benefit.
Ischaemic pre- and post- conditioning have been shown experimentally to reduce ischaemic / reperfusion injury by 75%.

What is myocardial stunning?
The transient systolic and diastolic dysfunction persisting after reperfusion. The dysfunction is usually longer than the period of ischaemia. The function gets better over time, and improves with inotropes.

What is myocardial hibernation?
Regional wall motion abnormalities in patients with prolonged ischaemia without infarction. There is a loss of sarcomeres and mitochondria. Long-standing changes include fibrosis. Revascularisation improves the condition over time.

3. How does the neonatal heart differ from an adult heart?

Parasympathetic innervation (which slows the heart) is functional, while the Sympathetic system (which increases heart rate and contractility) is not.
The neonatal heart has fewer contractile elements, with limited ability to increase stroke volume (SV) and difficulty in maintaining cardiac output (CO) with an increase in afterload.
They also have reduced compliance due to deficiency of elastic elements.
The LV **:** RV mass of 2 **:** 1 (in response to change in resistance, once the foetal circulation has ceased to exist) occurs only several months after birth.
The neonatal heart has fewer mitochondria and less cytoplasmic reticula and depends on extracellular calcium for contraction, however, it is more tolerant to ischaemia and recovers rapidly after an ischaemic event.

4. Why do we use cardioplegia solution?

To produce a bloodless field and a flaccid heart, the aorta needs to be cross clamped with resultant interruption of coronary blood flow and myocardial ischaemia. This can be limited by the use of cardioplegia solution (myocardial protection). Potassium is used as the arresting agent, along with various other electrolytes and substrates to a volume of 1 liter or more. Hypertrophic hearts will require more volume.
Both crystalloid and blood containing cardioplegia are in use.
Cardioplegia is usually topped up every 20 - 30 minutes, but some solutions (e.g. Bretschneider) will keep the heart arrested for 2 - 3 hours.
Blood cardioplegia is mixed with crystalloid solution in different ratios (this ratio varies and in children the ratio can be 60 **:** 1).
This has the advantage of delivering oxygen to ischaemic myocardium with the theoretical advantage of improved buffering and free radical scavenging.
The inactivation of the heart renders it susceptible to overstretching. Decompression must therefore be performed (venting).
By emptying the heart, the contractility decreases and so the Oxygen consumption drops. By reducing the temperature the oxygen consumption drops even more. With cardiac arrest following cardioplegia the metabolic requirements are reduced by 90%.

The solution is cooled to 5 - 8° C and perfused into coronary arteries and / or the coronary sinus (antegrade and retrograde perfusion). High risk patients have better outcomes if the perfusion is both antegrade and retrograde.[2]

What's better: Hot or cold?
Cold cardioplegia solution decreases the metabolic requirements but also increases the risk of cell oedema (through ion pump activity inhibition).
Surgeons often pack the heart with ice to induce asystole. This can cause phrenic nerve injury.
As clotting proteins are temperature dependant, hypothermia will cause coagulation disorders.
Cold solution also decreases the viscosity of the fluid and decreases erythrocyte deformity.
Therefore, there is a trend towards using warmer cardioplegia solution.
Warm blood cardioplegia appear to restore energy stores more quickly, however at 37° C almost continuous infusion is needed as the added asystolic effect of hypothermia is lost.
Tepid cardioplegia solution is kept between 27 - 30° C and seems to be a good compromise.[3]

When to use antegrade or retrograde cardioplegia?
Retrograde cardioplegia is used in the presence of aortic incompetence (AI); for aortic- and mitral-valve surgery; to perfuse severely diseased coronary arteries, and when using tepid or warm solution (the perfusion is then maintained continuously).
The retrograde cannula is placed by the surgeon through the right atrium (RA) into the coronary sinus.
Trans-oesophageal echocardiography (TOE) is helpful in directing the surgeon and confirming the correct placement of the cannula.
It is important to rule out a persistent left sided superior vena cava (SVC) on TOE (the coronary sinus has a large diameter, with bubbles clearly noted if injecting fluid into a cannula in the left arm), as the heart will not be adequately protected.
Using retrograde cardioplegia alone will render the right ventricle (RV) and interventricular septum (IVS) vulnerable as the RV and IVS will receive inadequate cardioplegia.

What is in cardioplegia solution?

St. Thomas Cardioplegia solution: (Used in most adult cardiac cases)

Ingredient	Concentration mmol / L
Na	110
K	16
Ca	1.2
Mg	16
Cl	160
NaHCO3	10

Different centres add additional drugs, e.g. Lignocaine and KCl.
(Additional KCl is not added for paediatric surgery)

Bretschneider HTK solution (Histidine-tryptophan-ketogluterate) - (Custodiol®):
Used in minimally invasive mitral valve surgery, donor hearts, and some paediatric surgical cases.

Active ingredient	Concentration mmol / L
NaCl	15
KCl	9
$MgCl_2$	4
$CaCl_2$	0.015
Histidine	180
Tryptophan	2
Manitol (5.46 g)	30
Potassium hydrogen 2-oxypentandioate	1
pH = 7.02 - 7.2	

Infusion time is usually 6 - 8 minutes. 1 ml solution per minute / gram estimated heart weight.
In adults the normal heart weight is 0.5 % of body weight and for infants about 0.6% of body weight.
Given simultaneous systemic hypothermia of 27 - 29° C, the ischaemic tolerance of the heart on pump should cause no problems up to an aortic clamping time of 3 hours.

The prolonged ischaemic tolerance time is due to the electrolyte composition that prevents energy consuming activation processes and the inhibition of glycolysis.
Furthermore potassium hydrogen 2-oxopentandioate acts as a substrate for aerobic energy production.
Tryptophan has membrane protective actions.
Mannitol prevents cell oedema.
Histidine / histidine HCL acts as a buffer to prevent a fall in pH.

After cardioplegia the myocardium is extremely flaccid and it is advised to perfuse initially at a low pressure (mean 40 mm 'Hg') for 2 min)

Post operatively, if cardiac rhythm does not revert to sinus rhythm, then pacing or defibrillation will be required.
Due to composition of the solution, electrolyte abnormalities may occur (hypo-Ca, hypo-Na, hyper-Mg, hyper-K).
The hypo-Na will usually correct itself over a few hours and in adults it is usually not necessary to treat this.

5. What are the causes of poor myocardial protection?

It goes without saying that if there are regions of pre-existing myocardial infarction, these regions will not benefit from revascularisation. Technical factors, e.g. premature warming, myocardial distension, prolonged periods of fibrillation (a fibrillating heart at 22° C will uses twice as much oxygen as an arrested heart at 37° C) or inadequate de-airing with resulting coronary air emboli, will also have poor outcomes.

6. How can we best protect the kidneys against acute kidney injury (AKI) during cardiopulmonary bypass(CPB) - (renal protection)?[4]

1. Start with a low priming volume. Do not haemodilute.
2. 2.Try to keep oxygen delivery (DO_2) >270 ml / min / m^2.
3. Increase DO_2 by increasing pump flow and P_aO_2.
4. Avoid haemolysis (low suction pressure as possible). Perfusionist needs to liaise with surgeon.
5. Rewarm slowly as rewarming is critical to DO_2
6. No drugs help.
7. Do not do angiography with contrast media n day of surgery.

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3. Ho KM, Tan A. Benefits and Risks of Maintaining Normothermia during Cardiopulmonary Bypass in Adult Cardiac Surgery: A Systematic Review. *CardiovascularTherapeutics* **29**(2011)260–279
4. de Somer F, Mulholland J, Bryan R, et al. O_2 delivery and CO_2 production during cardiopulmonary bypass as determinants of acute kidney injury: time for a goal-directed perfusion management? *Critical Care* 2011, 15:R192 doi:10.1186/cc10349

Recommended reading

Core Topics in Cardiac Anaesthesia Edited: Mackay, Arrowsmith Cambridge University press

Kaplan's Cardiac Anesthesia, the echo era. 6th edition Edited Kaplan J. Elsevier

Kurt Vonnegut: Slaughter House Five

Perioperative Myocardial Infarction:
Current management Strategies

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Myocardial infarction is the most common major perioperative vascular complication in patients undergoing non-cardiac surgery. As anaesthetists we are expected to identify the patients that are at high risk of a perioperative myocardial infarction (PMI), optimize their therapy to avoid this complication and appropriately treat a PMI. This refresher course article will focus on the diagnosis of a PMI and other prognostically significant entities e.g.troponin leak & myocardial injury after non-cardiac surgery. The management of a PMI with reference to the pathophysiology of PMI will be explored.

Definition of Acute Myocardial Infarction (AMI)

- Evidence of myocardial necrosis
- Clinical setting of acute myocardial ischaemia

Any one of the following will meet the criteria of AMI

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischaemia.
  - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
  - Development of pathological Q waves in the ECG.
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  - Identification of an intracoronary thrombus by angiography or autopsy.

Cardiac death:

- with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

Percutaneous coronary intervention (PCI) related MI:

- is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

Stent thrombosis associated with MI:

- when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.

Coronary artery bypass grafting (CABG) related MI:

- is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

(Third Universal definition of Myocardial infarction, European Heart Journal 2012 doi:10.1093)

Clinical classification		
Type 1	Spontaneous MI	Coronary atherosclerotic event
Type 2	Ischaemic imbalance	Not related to coronary atherosclerosis
Type 3	Sudden Death	Signs or symptoms of ischaemia
Type 4a	Related to PCI	cTn > 5x 99th centile or > 20$^{\%}$ rise above baseline
Type 4b	Related to Stent Thrombosis	Ischaemia & rise & fall in cTn
Type 5	Related to CABG	> 10x rise in cTn

Since an elevation in biomarkers is central to the diagnosis, it is important to exclude causes not related to myocardial ischaemia e.g. cardiac contusion following surgery or defibrillation, myocarditis, rhabdomyolysis. Other clinical scenarios can lead to multifactorial/indeterminate causes of troponin elevation e.g. heart failure, pulmonary embolism, sepsis, renal failure, severe acute neurological diseases e.g. subarachnoid haemorrhage, infiltrative diseases e.g. amyloidosis, sarcoidosis.

Troponin "leak": Elevated but below 99th centile with no ischaemic symptoms, no diagnostic ECG changes, no RWMA on echo.

Meta-analysis of outcomes in vascular surgery patients with an isolated troponin leak showed a significantly increased risk of 30-day mortality[1]. Isolated troponin elevation and troponin leak in the perioperative period has prognostic significance as demonstrated by the VISION study[2]. 11.6$^{\%}$ of that study population of patients undergoing non-cardiac surgery had prognostically relevant increase in 4th generation Trop T of >0.02ng/ml & 1.9$^{\%}$ of those patients died within 30 days of surgery. The third universal definition of myocardial infarction does not address the limitations of applying the criteria in a perioperative setting where symptoms are often masked by analgesia and ECG abnormalities are often not detected in clinically significant myocardial infarction. Post-operative troponin elevation above the upper reference limit was the strongest independent predictor of mortality with population-attributable risk of >40$^{\%}$[2]. A peak troponin ≥ 0.03ng/ml due to myocardial ischaemia (Myocardial Injury after non-cardiac Surgery -MINS) had the same predicted 30-day mortality as a MI diagnosis which fulfilled the criteria of the universal definition. 8$^{\%}$ of the patient experienced MINS but only 58.2$^{\%}$ would have fulfilled the full criteria for MI.[3]

Pathophysiology of Perioperative MI

The pathophysiology is not fully understood as the perioperative period has many triggers that are not present in a "medical myocardial infarction". Perioperative MI (PMI) is usually Type 1 or Type 2 if using the above the above classification. Type I is usually due to plaque rupture with occlusive thrombus formation. Vasospasm or endothelial dysfunction, fixed atherosclerosis with supply-demand imbalance or supply-demand balance alone can contribute to a Type 2 MI.
In the perioperative period hypotension, hypercoagulability, inflammation & increased oxygen demand worsened by stress of surgery, pain & sympathetic stimulation lead to:

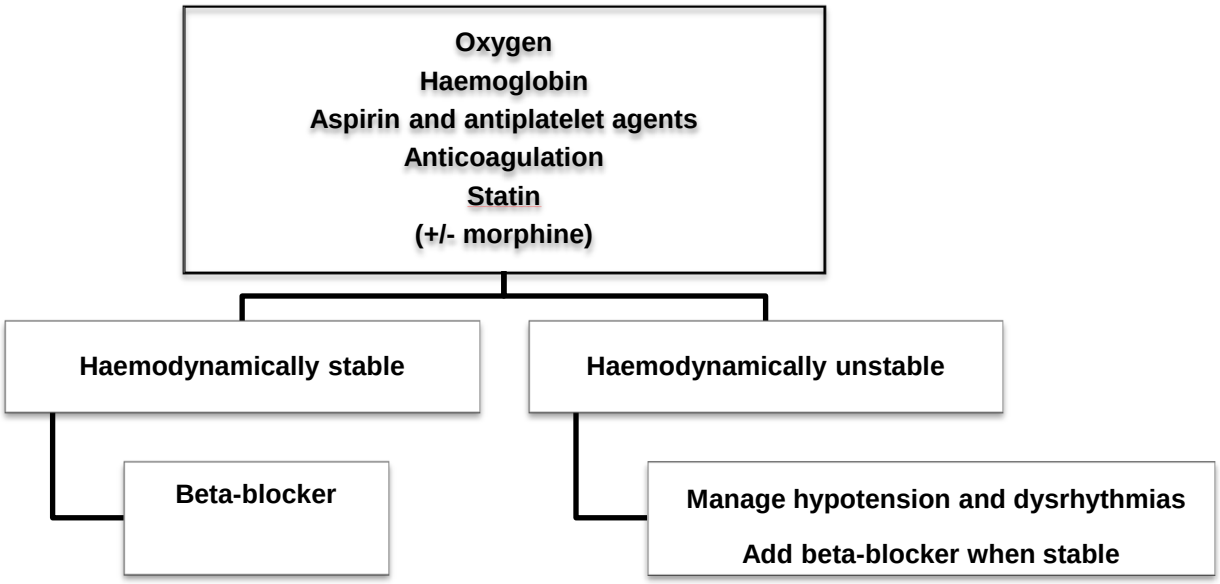
- Relative flow-mediated hypo-perfusion
- Supply- demand imbalance
- Infarction at the site of significant stenosis

Early studies[4] proposed that plaque rupture is consistent with early perioperative myocardial infarction (within 24hrs) due to the rapidity of change in troponins while a sustained myocardial oxygen supply-demand imbalance in the postoperative period is consistent with a delayed myocardial infarction (> 24 hrs - 72 hrs). Later studies looked at the post-mortem results of fatal PMI & there incidence of plaque rupture (44-55$^{\%}$) and supply-demand imbalance (45-56$^{\%}$) were almost equivalent. But in the first 3-4 days oxygen supply-demand imbalance predominates with plaque rupture peaking after 7-8 days.

Management

The understanding of pathophysiology of perioperative myocardial infarction is essential in guiding the therapy to prevent and treat PMI. Targets for intervention include optimising the oxygen supply-demand balance, reducing inflammatory hyper-coagulation and endothelial dysfunction. The key supportive measures like haemoglobin targets & the pharmacological therapies that can be used for the treatment of PMI will be highlighted. Much research has been directed to AMI in the non-operative setting. For PMI we need to adapt the recommendations for AMI to the perioperative setting especially for the antiplatelet agents and anti-thrombotics.

Aim to restore the supply-demand balance by optimising DO2 and targeting perioperative factors that increase the VO2 e.g. tachycardia, anaemia, hypoxaemia & inflammation.



Oxygen (*2010 AHA guideline)*

- Dyspnoeic, heart failure, shock, SaO_2<94%
- No evidence to recommend use in uncomplicated AMI or ACS without signs of heart failure or hypoxemia
- Avoid routine oxygen in uncomplicated patients for > 6 hrs

Morphine

AHA/ACC 2010: Class IIa for use in AMI. Use to decrease post-operative pain that may cause a tachycardia but note that relief of angina does not imply improvement in the underlying pathology. CRUSADE study in large cohort of NSTEMI patients that received morphine within 24hrs had worse in-hospital mortality .The hypotension, bradycardia and respiratory depression caused by inappropriate morphine use can result in decreased myocardial oxygen delivery, decreased arterial oxygenation, increase in arterial carbon dioxide, and perhaps even cerebral hypoperfusion.

Anaemia and blood transfusion

The TRICC study by Herbert et al.compared restrictive vs. liberal strategy of blood transfusion in euvolaemic critically ill patients.

Subgroup of ACS (MI/UA)

- Liberal (20.5%) vs. Restrictive(22.9%) strategy– restrictive group showed a trend towards lower 30 day mortality rate (p=0.69) & better in-hospital mortality
- Incidence of MI, Angina & pulmonary oedema higher in the liberal group

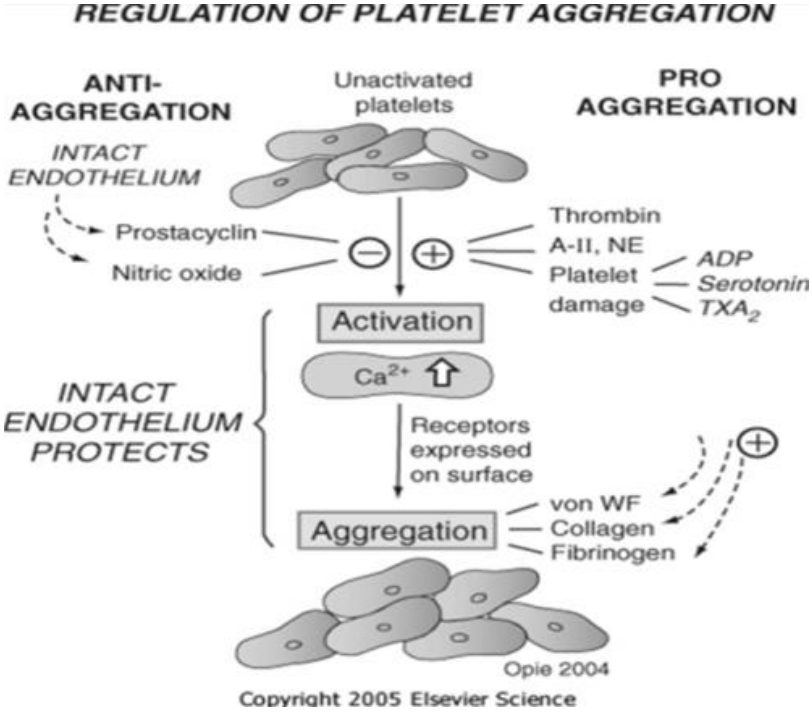
In 2011, the CRIT pilot RCT of 45 pts with AMI who presented with Hct ≤ 30%.

- Conservative (Hct 24-27%) vs. Liberal (Hct 30-33%)
- In-hospital& 30-day mortality, recurrent MI, new or worse CCF- significantly better in restrictive group
-

Systematic reviews of red cell concentrate transfusion in hospital patients with acute coronary syndromes. Outcomes assessed were the effect of PRBC on all-cause mortality, re-infarction rates & congestive heart failure. Patients receiving transfusion vs. no transfusion had:

- Greater risk for congestive heart failure & re-infarction in transfused group
- Identify the optimum transfusion threshold
- Transfusion target of Hb 8g/dL – All-cause mortality reduction (or neutral)
- Target of >11g/dL – no survival benefit (likely harm)
- Inconclusive for the 8 -11g/dL range

Antiplatelet agents



Aspirin

- Inhibits Thromboxane A2 production
- 2010 AHA :Class IA -all patients with suspected ACS
- Dose : 50-150 mg/day .Greater than 150mg/day , increased bleeding risk without increased cardiovascular protection
- 2011 AHA : Class 1A- aspirin should be started as soon as possible for UA/NSTEMI
- NOT if at risk of closed space haemorrhage
- Middle ear, posterior chamber of the eye, intracranial, intramedullary, spine &? TURP

The POISE 2 [(5)] study investigated the use of perioperative aspirin to **prevent a PMI**. Once a PMI is diagnosed, aspirin should be initiated. In the cases above where it is contraindicated in the perioperative period, we could use the data from POISE 2 (bleeding risk <0.3% after day 8-30) to estimate when the risk of post-operative bleeding would decrease and weigh the risk of haemorrhage with the cardio protective effect of aspirin.

Clopidrogrel

- ADP-receptor antagonist (prodrug)
- $t_{1/2}$ = 4hrs but irreversible platelet inhibition clinical effect for up to 7days
- AHA 2011 : 600-300mg load (<75yrs)then 75mg /day p.o
- Proton pump inhibitor –may affect metabolism but COGENT found no difference in cardiovascular end point ***(****Bhatt DL,Cryer BL,Constant CF,et al.NEJM 2010;363:1909-17)*
- TIMI- 38 study showed that patients with genetic polymorphisms (CYP2C19 reduced function allele) reduced clinical effect
- AHA 2011-Platelet function or genotype testing if considering changing management

Prasugrel vs Clopidrogrel : Not affected by iso-enzyme alleles

In patients undergoing PCI it does have better reduction of cardiovascular events and stent thrombosis. This benefit was not seen in patients with previous CVA, TIA, >75yrs or wt <60kg. But this was at the cost of increased risk of haemorrhage

- In patients age >75 ,with ACS without PCI & given together with aspirin
- No difference in composite (death, nonfatal MI, stroke). ↓recurrent ischaemic events
- No difference in significant intracranial bleeding

GP IIb/IIIa antagonists

- Tirofiban & Eptifibatide if used for NSTEMI/UA has the theoretical advantage of having shorter $t_{1/2}$.2-2,5 hours and available as IV preparation.
- Studies have shown that Eptifibatide before PCI does not improve outcomes & lead to increased haemorrhagic risk
- AHA 2011: GPIIb/IIIa antagonist should not be used if PCI not planned (Class III A) & not in low-risk patients (Class III B)

Anti-Thrombotics

To decrease thrombus propagation & embolization

Low molecular weight heparin (LMWH) vs. unfractionated (UFH) in NSTEMI

- In the TIMI –II at a dose of 30mg IV bolus followed by 1mg/kg s.c q12hrly for at least 7 days
- Enoxaparin significantly reduced risk of death, MI or urgent revascularization (compared to UFH)

LMWH vs. UH in STEMI

- Extract-TIMI 25 included 20 506 STEMI planned for fibrinolysis & compared Enoxaparin vs. weight-based heparin
- Enoxaparin lead to significantly less nonfatal MI at 30 days, less urgent revascularization & a reduced composite of death, MI, revascularization within 48hrs
- BUT: Major bleeding (including intracranial haemorrhage) at 48hrs, 8 days & 30 days
- The superiority of LMWH in cardiovascular protection must be weighed against the increased bleeding risk especially in a post-operative patient. Disadvantages of UFH e.g. IV administration, unpredictable individual response & need for frequent monitoring with aPTT could be an advantage in a post-operative setting. IV administration will lead to more reliable absorption in a patient in shock or with tissue oedema. The monitoring will allow for titration of the dose and protamine to reverse the effect of UFH will be helpful should a patient require urgent surgery.

Statins

HMG Coenzyme A Reductase inhibitors

Lipid-lowering effect (4-6 weeks): Decreased hepatic synthesis, up-regulation of LDL receptor, increased clearance of plasma-LDL, reduce triglycerides & ↑ HDL's

Pleiotropic effects (within 24hrs): Anti-inflammatory & anti-oxidant, plaque stabilization, macrophage modulation, anti-thrombogenic & platelet inhibition

Disadvantages:

- Myopathy- increased risk if impaired renal function or drug interaction e.g. steroids
- Rebound effect with discontinuation
- Only oral formulation- use long $t_{1/2}$ (atorvastatin) or extended release formulas (lovastatin)

2014 ESC/ESA:

- Class 1C recommendation to continue statins in perioperative period, favouring statins with long half-life or extended release formulation.
- Consider preoperative initiation at least 2 weeks before vascular surgery (Class IIa).

Evidence:

- 2012 systematic review & meta-analysis ,15 RCT's (4 non-cardiac), statin-naïve ,acute perioperative statins
- Reduced MI, AF in cardiac surgery patients and hospital LOS .Non–significant decrease in mortality. *Chopra V et al. Arch Surg 2012;147(2):181-189*
- 2014 Cochrane review of 3 studies in 145 vascular patients(statin-naïve)
- Insufficient evidence for mortality outcome and adverse events(non-fatal MI within 30d)
- 2014 review [7]16 RCT's(3 non-CABG) in statin naïve patients

- Outcome :overall significantly reduced mortality, reduced MI, reduced atrial fibrillation & hospital LOS
- Non-cardiac surgery: only mortality (RR0.5) and MI (RR0.53) reduced
- Duration of treatment- If >1 week : reduction in mortality & MI. If ≤ 1 week: reduction in AF, stroke, hospital LOS
- Potency :High -potency (atorva- & rosuvastatin) lead to reduced mortality & MI. Low-potency (fluva-, simva- & pravastatin) lead to reduced AF, stroke, hospital LOS

High-risk patient should be on statin preoperatively & continued in perioperative period. If statin-naïve and PMI diagnosed, start high dose (80mg/day), long acting/extended release statin.

Beta-Blockers

No benefit in acute intravenous *B*-Blockade 24-72hrs. A meta-analysis found that only a subgroup which excluded high-risk patients with Killip class III, resulted in a significant reduction in 6-week mortality. Another retrospective observational study of NSTEMI patients showed that if they had > 2 risk factors for shock & received IV beta-blockade in the emergency department, their risk of death or shock was significantly increased.

2011 AHA:

- **Oral** *B*-Blockers within 24hrs of hospitalisation with **stable ACS**
- Continue chronic *B*-Blockade ,if not in cardiogenic shock .Target HR 60-70/min
- Exclude contra-indications: Mod-Severe LV failure (EF ≤ $35^{\%}$), symptomatic hypotension, bradycardia (<60/min), $2^0/3^0$ heart block, reactive airways disease

Nitroglycerine

Coronary dilator. Aim to redistribute flow to ischaemic areas & dilatation of arterial & venous capacitance beds

AHA recommendation:

- Stable angina :up to 3 doses oral or topical 3-5 min apart (Class 1B)
- Consider IV in persistent /recurrent stable angina for up to 48hrs
- Contra-indications: Hypotension, SBP<90mmHg, HR <50>100/min, RV infarction- preload dependent & nitrate will reduce return from venous beds.

2010 ESC & 2014 ESC/ESA: poor evidence to support use of nitrates in PMI (Class IIb , LOE B)

Percutaneous Intervention

<u>2007 AHA/ACC/SCAI focused guideline update on PCI</u>

- **Class 1A**: NSTEMI with coronary lesions amenable & elevated risk for clinical events (TIMI/GRACE)
- **Class IB:** Refractory angina, haemodynamic unstable, electric instability

<u>2011AHA focused update UA/NSTEMI</u>

- Sub -group analysis of TACTICS-TIMI 18 found that patients with mild-moderate chronic kidney disease (Stage II-III) had significantly lower incidence of death, MI or Angina at 6 months when an early invasive strategy was used.

The consideration for a perioperative patient is that stents cannot be used as the dual antiplatelet & therapy that is required following a stent may lead to post-operative haemorrhage.

Multivariable regression analysis of 8351patients from POISE 1 cardiovascular medication showed that in patients with PMI

- Aspirin use: risk reduction of 30d mortality (OR 0.54)
- Statin use: risk reduction of 30d mortality (OR 0.26) *Annals of Int. Med 2011;154:523-528*

A retrospective case controlled analysis of patients post-major vascular surgery and diagnosed with a PMI. Compared those PMI patients whose cardiovascular treatment was intensified to those that were not. Primary outcome of 12 month survival without major cardiac event (death, MI, coronary revascularization, pulmonary oedema) was significantly better with treatment intensification.[6]

Early diagnosis with institution of appropriate therapy will reduce the mortality and mortality associate with peri-operative myocardial infarction.

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Interpretation of the Literature
How to read a scientific paper

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Medicine is an ever-changing discipline and an understanding and ability to interpret the literature is an essential component of maintaining an acceptably current level of practice. The major journals all have a characteristic structure composed of editorial comments, investigative articles, reviews and correspondence. Many of them have now dropped case reports from their main publications although some journals maintain a case report format on the websites.

Editorials

These are important contributions to the academic content of the journal. Most editorials in the quality journals are "peer-reviewed" although, since are generally invited commentaries, the level of peer review is often lower than that for the investigative articles. They highlight important issues and give valuable guides to current thinking, particularly in controversial areas where they can provide useful summaries.

Investigative articles

These are the lifeblood of the journals and form the bulk of the published material. There are a number of types of studies including retrospective data analysis, focussed studies dedicated to a narrow topic, large multicentre studies and systematic reviews with or without meta-analysis. Almost invariably, they are structured into well-recognised sections including the summary, introduction, methods and materials, results, discussion and references sections. Virtually all of the journals specify precisely what format submitted articles must take.

Title

The title of the article is assuming increasing importance and journal editors are tending to prefer titles that indicate the results of the study in preference to more non-descript, bland headings. This is because many readers tend to scan only the titles and, unless the title is interesting, will gloss over the paper.

Summary or abstract

The summary or abstract is very important as this is often the only part that is read by the average subscriber. In the past, the restrictions imposed by the National Library of Medicine of truncating abstracts at 250 words resulted in many journals insisting on this as the maximum length for a summary. This is unfortunate as it is often difficult to convey the full importance of the study in such a short abstract and many editors are now favouring more generous space allocations. Most journals are now moving towards a structured abstract with specific categories of items within the article. However the summary must always be approached with caution, as it cannot possibly give the full picture and often gives an overstated view of the importance of the findings.

Introduction

This section should summarise the basis for the conducting of the research project and should contain a sufficient summary of the literature to justify the performance of the study, and no more. Most importantly, it should contain a clearly stated hypothesis that is the ultimate justification for the piece of scientific work. If an hypothesis is not clearly stated then the validity of what follows is questionable.

Methods and Materials

This is the most important part of the article as it provides the scientific basis on which the research was conducted. It should clearly describe the ethical considerations in conducting such a study in either animal models or in human subjects and even simple patient data review studies should have both ethical approval and patient consent. Preferably, a reference number from the ethical committee should be stated.

The formal conduct of the research should be described in sufficient detail to allow another researcher to replicate the study without difficulty. The methods should be based on the requirements to establish and test the underlying hypothesis and must form a consistent and coherent approach to the research question.

A clear description of randomisation and blinding should also be given. Randomisation is a critical component of most investigative studies, some sources of bias are subtle and can easily influence the collected data unless every subject entering the study has an equal chance of becoming a participant in either control or study populations. The method of randomisation should be clearly stated together with an indication of how the patient allocation was concealed from the clinicians. Blinding is also an important part of the study, since subtle biases will inevitably affect the results if the investigator can influence the study through knowledge of the group into which the subject has been placed. Difficulties with blinding may arise where a study cannot reasonably blinded as a result of the subject under consideration. For example, it is almost impossible to conceal which patients received a regional anaesthetic procedure and in others, it is essential for the clinician to know what study medication was given. In such cases, the analysis should be performed by an individual blind to the allocation group. Some studies, particularly where the investigator cannot influence the result, are single-blinded, that is, only the patient is unaware of the group allocation. This is to minimise the risk of a placebo effect influencing the outcome. More commonly, studies are double-blinded and the investigator should not be aware of any group allocations until all study data has been collected and the study records sealed.

Most high-quality journals now insist that, for any large clinical study, the methods are published in advance of the study performance on an internationally available database such as *clinicaltrials.gov*. This ensures that the primary outcome and any secondary outcomes are specified in advance and cannot be subsequently manipulated to advance some chance outcome that emerges during the study. In any case, when reading a study, make sure that the primary outcome that derives from the original hypothesis is clearly stated and reported in the results. Secondary outcomes may be interesting but are not robust as they are not included in the power calculation and thus more likely to be random observations.

The Jadad score may be used to evaluate the integrity of a study. A Jadad score of ≥ 3 is regarded as the minimum acceptable for a quality study. The scoring is based on the randomisation (0 - 2 point for non-randomised to full, concealed randomisation), blinding (0 - 2 points ranging from open label to full double blinding with proper allocation concealment) and the treatment of dropouts and withdrawals (1 point). This latter consideration has been the matter of some contention. It is critical that the investigator does not 'pick and choose' which subjects are to be included after randomisation has occurred as this may result in serious data manipulation. This has led to the concept of 'intention to treat' analysis. This means that every subject enrolled in the study to the point of receiving a randomisation number is included in the analysis. This is generally good practice, but may result in difficulties if the subject does not subsequently receive the planned treatment or if, after enrolment, some major exclusion criterion is discovered that was not apparent at enrolment. Also, subjects may voluntarily withdraw from the study at some point during the treatment. At very least, the methods section should include provision for the management of withdrawals and dropouts with clearly specified a priori criteria for exclusion of a subject from the analysis. Simple outlier exclusion is not acceptable.

Probability

The logic underlying the scientific process argues that if a theorem cannot be proven directly, the safer strategy is to assume that the theory is not true and then test that assumption. This is referred to as the "Null Hypothesis" (H_0 in statistical parlance) and the stated theorem is referred to as the "alternative hypothesis" (H_1). The purpose of statistical analysis of the data used to test any given assumption is to assist the scientist in deciding whether or not to accept the assumption that the theorem is false - i.e. whether or not to accept the null hypothesis. Since it is uncommon in medical science that any given theory can be proven beyond any doubt, it is usual to set a level of probability at which the theory will have been tested to a level of "reasonable" doubt. This level of acceptable doubt is usually set at 5%, hence the ubiquitous use of $p < 0.05$. This level of reasonable doubt is referred to as the alpha value and must always be established prior to commencing an investigation. While it implies a reasonable degree of certainty it carries with it the risk of making an error. When the alpha level is set at 0.05, there is a 95% chance that the data obtained were not the result of random events, but there is also a 1:20 risk that these results were pure chance. This is the compromise that is usually accepted in medical science, but it must be understood that it is only a compromise.

A more subtle error occurs when the null hypothesis is taken to represent the true state of affairs whereas, in reality, a genuine difference does exist. This is referred to as a Type 2 or β-error and is usually the result of an inadequate sample size in the setting up of the experiment. This problem can be minimised by power analysis in which the sample size can be calculated from pre-existing assumptions of the magnitude of the effect being examined and of the size of the effect that is felt to

be of clinical relevance. A sample size calculation is now a requirement for publication for most studies in the serious scientific literature and an absolute requirement where negative results are reported.

Data and Descriptive Statistics

Information collected during a scientific study includes the defining characteristics underlying the assumptions in the study and the value of events from observations that vary over time or with certain conditions. The former are called explanatory or independent variables and the latter are called response or dependent variables. Data can be classified into various groups as indicated in table 1.

DATA TYPE	DEFINITION	EXAMPLES
Interval		
Discrete	Data measured on an integer scale only (whole numbers	Parity, number of teeth
Continuous	Data measured with a constant scale interval	Body temperature, airway pressure
Ratio	Continuous data related to an absolute zero	Kelvin, barometric pressure
Categorical		
Ordinal	Ordered data but without a constant scalar interval	Scoring systems
Nominal	Qualitative data that can be ordered or ranked	Any kind of category or grouping
Dichotomous	Binary data	Mortality, gender

Table 1. Types of data.

Hypothesis testing

The purpose of hypothesis testing is to allow an experimenter to make a choice regarding the validity of the data that has been collected in relation to the original hypothesis. The nature of the data collected is critical in determining the nature of the statistical technique that is to be applied. The basic ethical principle of medical research is that the smallest number of subjects possible should be studied in order to minimise any possible harm as a consequence of conducting the research. This means that the most powerful and robust test available for the dataset under examination should always be used.

Types of test

Parametric statistics are the usual choice for the analysis of all types of interval data, as these tests require the smallest numbers of samples in order to demonstrate statistical significance. The parametric tests most widely used are the Student's t-test when 2 sample means are being compared and various forms of analysis of variance (ANOVA) when multiple samples are considered. The rule for the application of parametric tests is that the data must be normally distributed. A useful 'eyeball' test to look at when reading an article is that if the standard deviation is greater than the mean value the data are unlikely to be normally distributed.

Student's t-test is a statistical technique with various forms. When the dataset to be compared is obtained from a single subject who is tested twice under different conditions, a *paired* test is used as the repeated use of a single subject produces a lower variability in the sampling process. More commonly, data are obtained from different individuals subjected to different conditions and in this case the non-paired or two-sample test is appropriate. The underlying theory of the t-test is that the calculated statistic gives a probability value for a given number of degrees of freedom for a single comparison only. This means that if more than a single pair of data are compared, the likelihood of an error arising increases directly with the number comparisons made. For this reason, use of the t-test for multiple comparisons requires recalculation of the level of probability to be accepted (the Bonferroni correction) or, preferably, the use of a more robust technique designed specifically for multiple comparisons.

ANOVA is a technique in which the variability within the samples is examined and a likelihood expressed as to whether or not the samples all arise from a single dataset. There are numerous forms of ANOVA, the choice of which is made depending on the nature of the comparisons to be made and

the format of the data. On its own, ANOVA is limited to a report that states that the samples probably do or do not arise from a single dataset. Identifying precisely where the differences arise requires some form of post-hoc testing but it is important to understand that such post-hoc testing may not be conducted until the ANOVA has clearly demonstrated that a real difference exists within the dataset.

Non-parametric tests are used to analyse non-normally distributed data and data that arise from analysis of categorical information. It is very common in medical research to employ scoring systems to identify graded responses in response to various imposed conditions. Such scoring systems include pain scores, APGAR scores, ASA scores and so on. Nonparametric tests that are analogous to Student's t-test include the signed rank test for paired comparisons and the Mann-Whitney U-test, which is equivalent to the non-paired t-test. The Kruskal-Wallis ANOVA is an analysis of variance for multiple comparisons of non-parametric data. For categorical or grouping data where the presence or absence of a specific characteristic is being studied (for example presence or absence of vomiting) the Fisher's Exact test is very useful for small numbers where 2 x 2 comparisons are being made. Where larger numbers of comparisons are made, the Chi-square test is used, provided that the sample size is largely enough. In this test, the data are grouped into cells that describe the characteristic being studied for which the expected results (if the null hypothesis is valid) can be calculated. A minimum number of expected results of 5 in each cell is required for a standard Chi-square test, or else the Yates correction factor must be applied.

An important statistical method that does not rely on probability is one that was introduced by Altman and Bland to test the comparability of two pieces of equipment that purport to measure a similar clinical value, such as cardiac output or blood pressure. In this test, simultaneous measurements are made using both devices and the results plotted across the range used in clinical practice by calculating the average measurement obtained by each device at each measurement interval and plotting this against the difference between the to measurements. This produces a scatter plot from which a number of values can be deduced. The first is the bias or offset of one device against the other which is obtained by averaging the differences. Ideally, this should be close to 0. The standard deviation of the differences can be calculated and a value called the "limits of agreement" established as 2 SD from the mean. This can then be interpreted by a potential buyer as indicating the range within which the two pieces of equipment will be in agreement, rather than any kind of probability that the two devices of the same. This is a substantially more robust technique than the previously used correlation and regression.

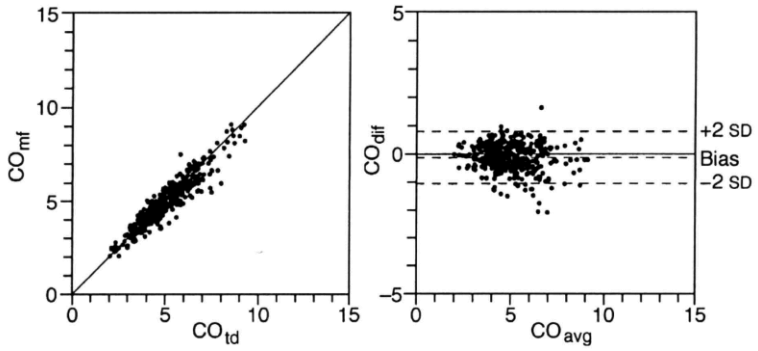


Figure 1. A correlation scatter plot and an Altman and Bland plot of the same data investigating the performance of two different types of cardiac output monitors.

Results

The results of any particular study will generally be presented in the appropriate statistical format. It is important for the reader to understand the results and thus they must be reported in a clear and intelligible manner. It is all too common for an author who understands the study extremely well to present the results in a confused and unclear fashion. A good reviewer should always prevent such results being published, but the review system is not infallible. Another important consideration is whether or not the results realistically reflect the methods. The Boldt fraud was picked up because the presented results were unrealistic and could not have been achieved with the methodology used. It is important to assess whether or not the authors have excluded any patients or data records and, if so, how those exclusions were handled. As discussed above, intention-to-treat analysis means that any patient who is randomised should be included in the analysis, but obviously circumstances arise that make such all-inclusive data analysis impossible. Where the protocol has specifically made provision for exclusions occurring during the course of the study, analysis is generally referred to as being "per

protocol". Finally it is important to decide how the results relate to the original hypothesis. Surprisingly often, results are reported that do not reflect on the validity of the original ideas of the study.

In interpreting the results, a final scan of the statistical method should be performed, particularly looking at the initially stated statistical methods and what was actually performed. All too often, an interesting observation is made that turns out, by chance, to be statistically significant. It is acceptable to report such a finding as an observation requiring future investigation, but it may not be reported as a primary conclusion. Again this has frequently occurred and resulted in misleading changes in practice. Where no differences are found and the null hypothesis is accepted, it is very important to consider that the sample size was simply too small. For small studies 95% confidence intervals are often useful and it is occasionally acceptable for the authors to present a post-hoc power analysis allowing them to estimate how big a study would have to be performed to demonstrate any possible differences.

Discussion

The discussion must be focused entirely on the original hypothesis and the results. All too often, papers are published in which extraneous concepts are discussed and new hypotheses advanced to explain and unexpected result. The discussion should simply summarise the results and place them in context with clinical practice and the original hypothesis. Finally the conclusions drawn must be justified by both the methods and the results.

Systematic Reviews and Meta-Analysis

One of the major problems with many clinical studies is that the power of the collected data is insufficient to allow firm conclusions to be drawn. Review articles frequently contain compilations of such studies, but are not generally presented in a structured fashion that allows the reader to draw conclusions about the bias of the author. In a systematic review, data are obtained from all of the randomised controlled trials that have dealt with in a single research question. The researchers then proceed through a very structured protocol that includes definitions of study inclusion/exclusion criteria, explicitly defined literature search strategies, techniques for extracting the data, appraisal of data quality and systematic pooling of the data. Provided the collected data are sufficiently consistent, the results can then be combined using meta-analysis techniques. Binary outcomes (yes or no, alive or dead) are then analysed using either an odds ratio of the occurrence of these events or a relative risk analysis. The results are then presented as a Forest plot (see figure 2).

The far left column identifies the studies included in the analysis followed by incidence of the effect under consideration in the treatment and control groups. The horizontal lines under the column headed OR indicate the range of treatment effect for each study and the boxes indicate the median value expressed as an odds ratio and a 95% confidence interval. The diamond at the bottom of this column indicates the overall analysis of the effect and the confidence interval. The next two columns give the weighting attached to each study (based on the quality of the data, the number of patients included in the number of events identified) followed by the odds ratio and 95% CI for each study. An odds ratio of 1 indicates no difference between the treatment and control groups. Thus, if the 95% CI includes 1 no difference can be assumed. It is also useful to look at the test for heterogeneity. This analyses the consistency of the studies included in the review. Where the value for heterogeneity is significant it means that there is considerable variability between different studies and the results of the analysis should be viewed with caution.

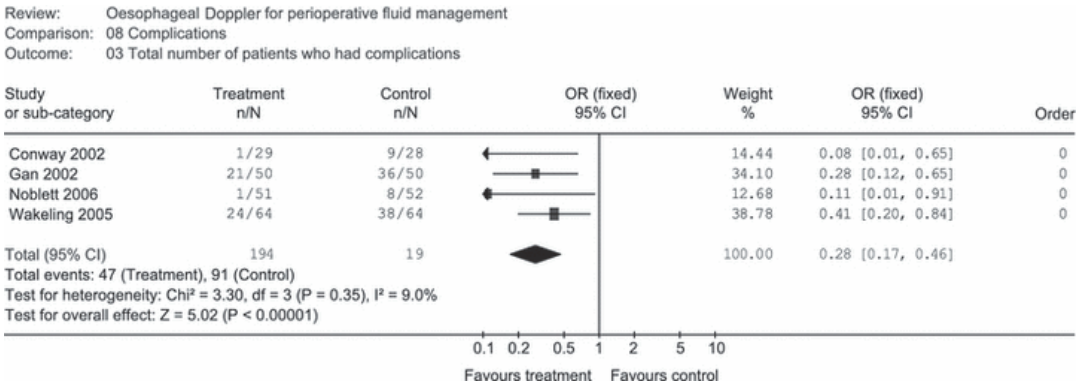


Figure 2. A forest plot of data collected in a systematic review of the effect of fluid management using the oesophageal Doppler-guidance on the incidence of post-operative complications.
(Abbas SM, Hill AG. Anaesthesia, 2008, 63:44-51)

Occasionally, a Forest plot may be presented containing quantitative data such as the volume of fluid needed in each study to achieve given results. In such a case, the researchers would present the weighted mean difference (WMD) between the two groups and the line of equivalence would have a value of zero, as opposed to the value of unity where an odds ratio is used.

This particular analysis (Figure 2) looked at the use of oesophageal Doppler techniques for fluid management and the influence that this had on the overall incidence of postoperative complications. The conclusions that can be drawn from this forest plot are that a significant treatment effect can be seen with a mean reduction in the likelihood of a complication occurring in the treatment group of 72% (OR 0.28) and a confidence interval of 0.17 to 0.46. As this confidence interval does not include unity, this is likely to be a statistically significant effect and the significance is expressed in the last line of the Forest plot. It is important to understand that the data resulting from such meta-analysis is limited by the quality of the data in the original studies. Data from meta-analysis should not be used as conclusive evidence or proof of an effect, but rather for the purpose of hypothesis generation.

An offshoot of this technique is the calculation of the number needed to treat (harm). This number can also be obtained from large single studies. This statistic calculates how many patients need to be treated to achieve the desired benefit or alternatively the number of patients who are at risk of injury where the number needed to harm is calculated. The size of this number depends on both frequency of occurrence of the event and the effectiveness of the treatment.

Interpretation

Finally, interpretation of the literature involves an assessment of internal and external validity. Internal validity implies that the results follow in a straightforward and unproblematic way from the methods and that the presented results are logically coherent. A study in which there is a single statistically significant result that is not supported by other data in the rest of the paper is likely to be problematic. External validity is the degree to which the results can be transferred to other situations or whether or not the results could only be obtained in the specific set of circumstances under which the study was performed.

Conclusion

Finally, you should assess for yourself whether or not the intellectual sequence was sound in terms of the observation on which the hypothesis was based; the appropriateness of the data collection for the hypothesis to be tested; the statistical methods used and the conclusions drawn. Only then should you consider whether or not a paper will impact upon your practice.

Summary

This set of notes represents a brief summary of some of the major statistical points that are likely to be relevant to students of anaesthesia particularly those preparing for the FCA examination or those involved in performing an MMed dissertation. Students need to understand the basics of data collection and analysis including the principles of the types of data and the statistical techniques that can be applied to each form of collected information. The principles of probability theory and the logic of proof need to be understood, together with the limitations of statistical analysis.
Parametric data should generally be analysed using parametric statistical tools such as various forms of the students t-test for the comparison of 2 means or ANOVA were multiple comparisons are to be made. Equivalent tests for non-parametric, ordinal data include the Wilcoxon signed ranks test, Mann-Whitney U-test and the Kruskal-Wallis non-parametric ANOVA. The limitations of correlation and regression analysis must be borne in mind.
Equipment comparisons should generally be conducted using the Bland and Altman technique rather than correlation and regression.
Systematic reviews and meta-analysis provide tools for pooling large quantities of data from various studies into a single point estimate that can be used to guide choices, dependent on the quality of the original data.
This set of notes is intended entirely as a supplement to more definitive statistical texts. It should not be regarded as a definitive source for statistical information.

Further Reading

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Liver disease: An Anaesthetist's Perspective

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The patient with either acute liver failure or chronic liver disease presents many challenges in the perioperative and critical care setting. Identifying the patient with liver disease, evaluating the systemic organ involvement and risk stratification for surgical intervention are the key elements in management. The anaesthetic plan should account for the altered pharmacokinetics and avoid further hepatic injury.

Acute liver failure (ALF)

The key presenting features in acute liver failure are jaundice, encephalopathy(with cerebral oedema),coagulopathy, vasodilatory state, renal dysfunction, hypoglycaemia, immune dysfunction. It is usually defined by the time between jaundice and onset of encephalopathy .

	Hyperacute	Acute	Subacute
Time from jaundice to encephalopathy	0–1 week	1–4 weeks	4–12 weeks
Severity of coagulopathy	+++	++	+
Severity of jaundice	+	++	+++
Degree of intracranial hypertension	++	++	+/–
Survival rate without emergency liver transplantation	Good	Moderate	Poor
Typical cause	Paracetamol, hepatitis A and E	Hepatitis B	Non-paracetamol drug-induced liver injury

Data from O'Grady and colleagues[12] and Ichai and Samuel.[13] +++=high severity. ++=medium severity. +=low severity. +/–=present or absent.

Bernal W et , Lancet 2010;376:190-201

Aetiology of acute and chronic liver failure

	Acute liver failure	Chronic liver failure
Drug induced	Paracetamol Ecstasy Cocaine Halothane Non-steroidal anti-inflammatory drugs Antibiotics: (augmentin, ciprofloxacin, doxycycline, isoniazid, erythromycin)	Alcohol
Viral	Hepatitis A, B, E Cytomegalovirus Epstein—Barr virus	Hepatitis B, C, D
Metabolic	Wilson's disease	Haemochromatosis Wilsons disease α-1-antitrypsin deficiency Non-alcoholic fatty liver disease
Autoimmune	Autoimmune hepatitis[a]	Autoimmune hepatitis Primary biliary cirrhosis Primary sclerosing cholangitis
Vascular	Budd—Chiari syndrome Portal vein occlusion Hepatic artery thrombosis Ischaemic hepatitis	Budd—Chiari syndrome
Pregnancy	HELLP syndrome Acute fatty liver	

[a] Acute presentation although patients usually cirrhotic.

For ALF there are a few aetiology–specific interventions that, if implemented early, may improve survival eg. N-acetylcysteine for paracetamol toxicity, nucleoside analogue therapy for Hepatitis B infection and acyclovir for HSV infection.

N-actylcysteine(NAC) for paracetamol-induced ALF: improves survival in paracetamol induced ALF. Time elapsed between ingestion and administration correlates with outcome. Immediate initiation of

NAC is ideal but at least within the first 24 hours to avoid further liver damage. Studies have suggested that NAC may improve transplant-free survival(by improving hepatic oxygen consumption & hepato-sphlanchnic flow)even in non-paracetamol toxicity, especially if they have early grade of encephalopathy.Special consideration should be made for the slow release preparations where standard treatment algorithms may not apply.

Hepatic Encephalopathy

Cerebral oedema leading to intracranial hypertension complicates approximately 50% to 80% of patients with grade III or IV hepatic encephalopathy, in whom it is the leading cause of death.

Pathogenesis: Development of encephalopathy and cerebral oedema is multifactorial and ammonia plays a central role with inflammatory cytokines accentuating the process. Other factors, such as hyponatraemia, gastrointestinal bleeding and infection may contribute to the development of hepatic encephalopathy

The Ammonia-Glutamine Hypothesis(Cytotoxic oedema)

Increased serum ammonia (>117umol/L) is associated with development of cerebral ammonia but is not directly correlated to the severity of symptoms of encephalopathy or intracranial hypertension. Impaired metabolism of circulating ammonia by the liver (and the kidneys & muscle) leads to the ammonia crossing the blood-brain barrier and accumulating in astrocytes. Glutamine synthetase from the endoplasmic reticulum of the astrocytes converts this to glutamine. The glutamine causes astrocyte swelling leading to cerebral oedema. The cerebral glutamine concentration correlates directly with the neuropsychiatric symptoms and degree of intracranial hypertension.

Toxic-liver hypothesis(Vasogenic oedema)

Severe ALF also results in the accumulation of various other toxins,CNS depressants and inflammatory mediators eg TNF α, IL-1β, IL-10 which further induce CNS injury. Autoregulation is lost in patients with severe ALF due to abnormal regulation of vasoactive mediators within the brain and cerebral hyperaemia will occur. This in turn then leads to vasogenic oedema in severely encephalopathic patients.

Diagnosis:

- Clinical- The West Haven grading should be used for hepatic encephalopathy after other causes of altered consciousness, confusion or delirium have been excluded.

Table 1 West Haven hepatic encephalopathy grades with Amodio modifications

Grade	Level of consciousness/ cognitive function	Psychiatric symptoms	Neuromuscular function
1	Sleep disturbance	Euphoria/ depression	Tremor
	Mild confusion		Incoordination, ± asterixis
	Impaired computations		
2	Inattentive	Irritability	Asterixis, slurred speech
	Moderate confusion	Decreased inhibitions	Impaired handwriting
	Disorientation to time	Personality changes	
3	Marked confusion	Anxiety or apathy	Slurred speech, ataxia
	Completely disoriented	Inappropriate	Asterixis, nystagmus
	Lethargic, but arousable	Bizarre behavior	Hypoactive or hyperactive reflexes
	Command following	Paranoia, anger or rage	
4	Non-command following		Coma, dilated pupils
			Loss of cranial nerve reflexes
			Signs of herniation
			Flexor or extensor posturing
			Loss of reflexes

- Diagnostic studies: only if clinical assessment is inconclusive and recommended for grade III/IV encephalopathy only. Transcranial Doppler, jugular venous oximetry or ICP monitoring can be used. ICP monitor insertion is controversial due to the associated risk of haemorrhage and infection & therefore should be individualised.

Management of Hepatic Encephalopathy

Identify and treat reversible triggers (i.e. gastrointestinal bleeding, hypokalaemia, alkalaemia, hypoglycaemia, hypovolaemia and infection)

General measures : The following measures should be employed to control intracranial pressure (ICP) to less than 20 mmHg:

- Early intubation in grade III or IV encephalopathy
- Modest hyperventilation ($PaCO_2$ 4.5-5 kPa) & adequate oxygenation (PaO_2 >10 kPa)
- 30° head up position, optimize cerebral venous drainage , avoid excessive PEEP
- Avoid hyperthermia and hyperglycaemia
- Adequate sedation (propofol preferred because of cerebral metabolic suppression, minimal pharmacokinetic changes)
- Early recognition and treatment of seizure activity (EEG required to diagnose).No evidence for use of phenytoin for seizure prophylaxis

If intracranial hypertension is refractory,then consider :

- Osmotherapy : Mannitol: (1 g/kg iv q6h) Target:300-320 mOs/L, or Hypertonic saline (10%).Target Na:145-155 mEq/L .
- Hypothermia- core temp 32-34°C

Other rescue therapies for patients that are transplant candidates include haemodialfiltration to decrease serum ammonia and indomethacin –but these have no proven benefit.

Lactulose: decreases colonic pH & reduces mucosal absorption of glutamine from the gut. Aim to decrease serum ammonia but overtreatment can cause severe dehydration, hyponatremia, worsening of encephalopathy. Not recommended in ALF, consider in decompensated cirrhosis. Non-absorbable antibiotic rifaximin with few adverse effects and drug interactions is often used with lactulose

Referral for Transplant in ALF: early identification and transfer after resuscitation

Modified King's College criteria for liver transplantation in ALF

Paracetamol induced ALF	Non-paracetamol induced ALF
Either one of:	INR >6.5
• pH < 7.30	Or, three or more of:
• lactate >3.0 mmol/L after 12 h of appropriate resuscitation or >3.5 mmol/L after 4 h of appropriate resuscitation	• >40 years old or <10 years old
Or, all of:	• Bilirubin >300 μmol/L
• INR >6.5 or PT >100 s	• >7 days between jaundice & encephalopathy
• Creatinine >300 μmol/L	• INR >3.5
• Grade 3 or 4 encephalopathy	• Aetiology of ALF (non-A non-B or halothane hepatitis, idiosyncratic drug reaction)

The Clichy – Villejuif criteria can also be used to select recipients of emergency liver transplant. It uses the grade of encephalopathy, factor V concentration & age as factors for grading.

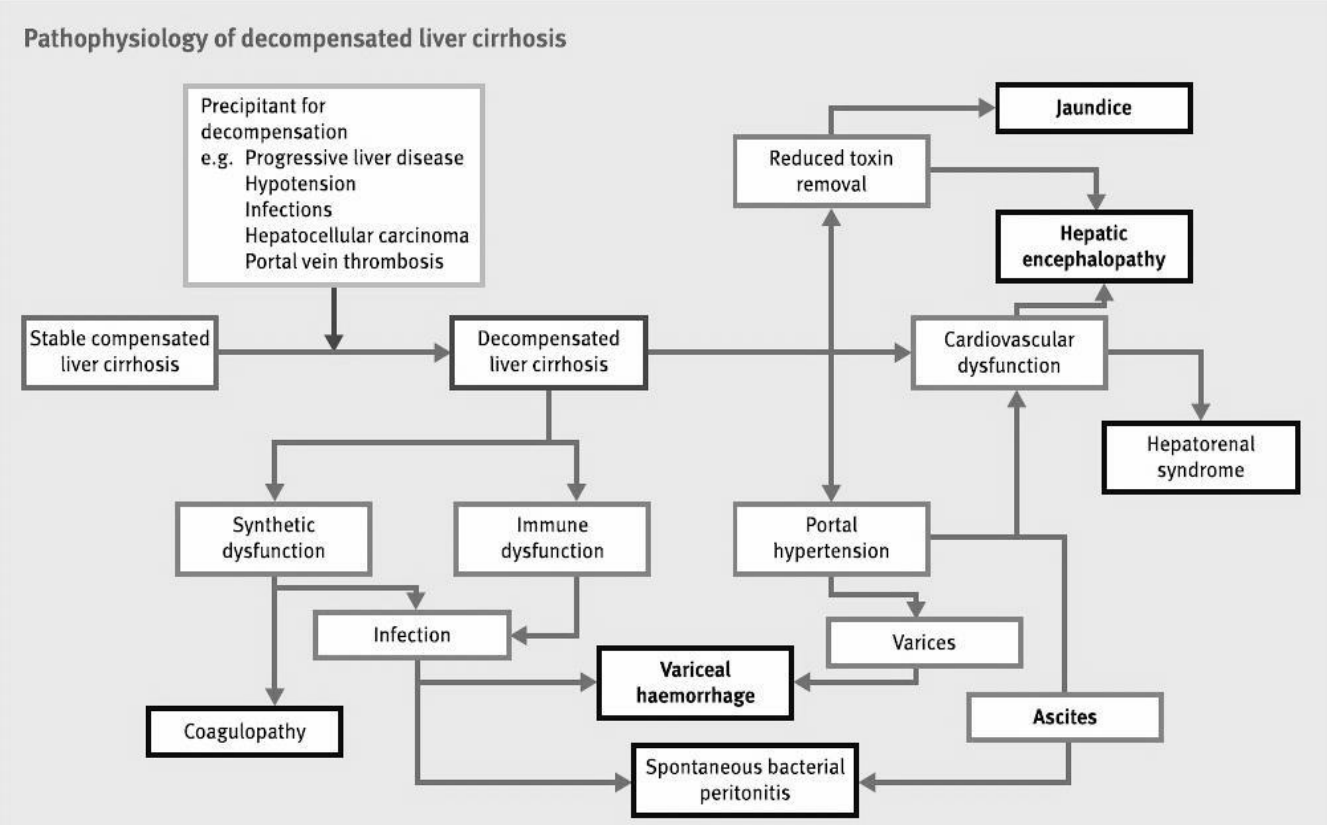
Novel Liver assist Devices: if do not have access to a transplant centre temporary assist device can be considered. However MARS (Molecular Adsorbent Recirculating System) , Prometheus (fractionated plasma separation & adsorption),ELAD(extracorporeal liver assist device) & NELP (normothermic extracorporeal liver perfusion) remain experimental.

Chronic liver Disease

Cirrhosis occurs as the end stage of a chronic fibrotic process following protracted exposure to a variety of insults. Cirrhosis results in the gradual decline of the normal metabolic and synthetic function of the liver. Fibrosis progressively destroys normal hepatic histological and vascular architecture resulting in a progressive increase in hepatic blood flow resistance and portal hypertension.

Decompensated liver cirrhosis :" development of clinically evident complications of portal hypertension (ascites, variceal haemorrhage) or liver insufficiency ((jaundice,encephalopathy)"

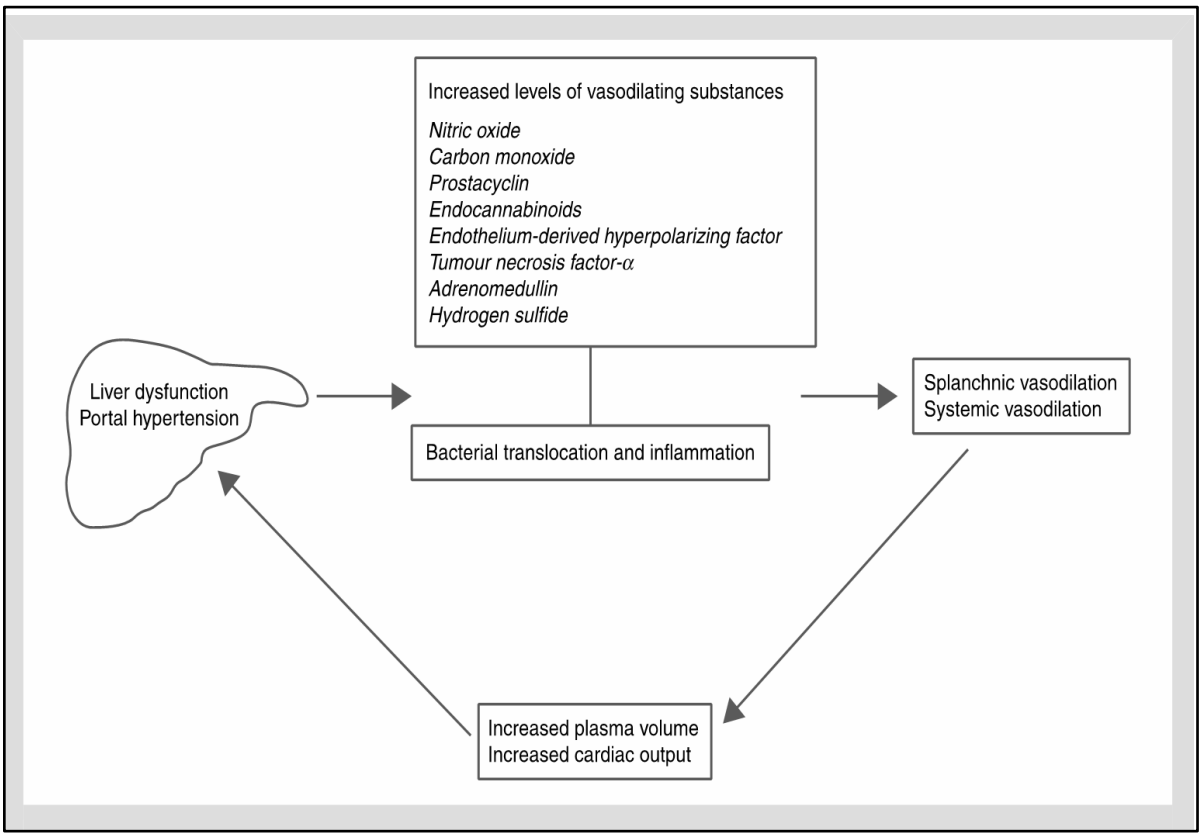
Precipitants of decompensation are shown in the figure below :



Schematic representation of the progression from cirrhosis to decompensated liver disease and its associated problems.
Definitions of liver decompensation are shown in bold.

Organ system effects in chronic liver disease

Cardiovascular



Increased production or decreased hepatic clearance of vasodilating substances listed in diagram above lead to systemic and splanchnic vasodilation. In response to the splanchnic vasodilation and low SVR, the body retains sodium and water leading to an increased plasma volume and cardiac output. Venous capacitance is increased by development of porto-systemic shunts with portal hypertension. These changes lead to a hyperdynamic circulation with tachycardia & low systemic blood pressure Cirrhosis is associated with a cardiomyopathy(cirrhotic cardiomyopathy), independent of alcoholic cardiomyopathy, due to decreased β-receptor response & down regulation and impaired systolic and diastolic contractility. An echocardiogram is suggested to detect this cardiomyopathy, with a dobutamine-stress echo being the recommended investigation.

The QT interval is prolonged in 50% of patients with cirrhosis. ECG should be done to detect a prolonged QT interval, which significantly correlates with the severity of liver disease, elevated (BNP) level and decreased survival. Caution with perioperative drugs which prolong the QT interval.Coronary artery disease is prevalent in cirrhosis due to the common co-morbidities of diabetes, alcohol abuse & smoking.

Porto-pulmonary hypertension: 6-9% of patients with advanced liver disease.

Pathogenesis: not completely understood but the histological changes are similar to idiopathic pulmonary artery hypertension with medial hypertrophy, intimal proliferation, thrombosis & fibrotic changes. Presents clinically with exertional dyspnoea, chest pain and syncope.

Diagnosis: The European Respiratory Society recommends screening for porto-pulmonary hypertension with transthoracic Doppler echocardiography and right heart catheterisation.

- Mean Pulmonary pressure at rest are > 25 mmHg or Pulmonary vascular resistance is >240 dynes/sec/cm5.
- Moderate (pulmonary artery pressure of 35–45 mmHg ,pulmonary vascular resistance of >250 dynes/s/cm5) .Increases the risk of mortality associated with liver transplant to >50%
- Severe porto-pulmonary hypertension (PAP>50mmHg), liver transplant mortality increased to nearly 100%.

Intraoperative considerations:

Avoid triggers that could increase the pulmonary artery pressures eg. Hypoxia, hypercarbia, hypothermia, acidosis, pain. Calcium channel blockers should not be used as they can worsen portal hypertension via mesenteric vasodilatation. Consider using other pulmonary vasodilators eg. Sildenafil

Monitoring: Invasive monitors for moderate to high–risk patients. Cardiac output monitor may be used and though there is concern that trans-oesophageal echocardiography may cause variceal bleeding, there has not been substantial evidence for this.

Vasoactive agents: While many of the available vasopressors and inotropes will increase the systemic pressure and cardiac output in chronic liver disease, they have varying effects on hepato-splanchnic circulation. There have not been conclusive human studies on which agent is best to maintain regional mesenteric perfusion and microcirculation. In fact when adrenaline and noradrenaline were compared, both decreased mesenteric flow and impaired microcirculation in jejunum. Adrenaline effect was dose dependent more pronounced than noradrenaline. Studies in septic shock patients comparing noradrenaline with dobutamine vs. adrenaline only, showed that splanchnic circulation was better preserved with the dobutamine.

Vasopressor: Phenylephrine can be used for the arterial vasodilatation. Caution with use of vasopressin in patients with intracranial hypertension as it causes cerebral vasodilatation.

Pulmonary Effects

Pulmonary complications that may be present include :

- Pleural effusion & hepatic hydrothorax
- Atelectasis and diaphragm displacement& wasting from massive ascites
- Aspiration pneumonitis –in hepatic encephalopathy
- Portopulmonary hypertension as discussed above
- Hepato-pulmonary syndrome

Pathogenesis of Hepato-pulmonary syndrome: Enhanced production or impaired hepatic clearance of endogenous vasodilators (i.e. nitric oxide, vasodilator prostaglandins, substance P) or inhibition of vasoconstrictive substances (i.e. tyrosine, serotonin, and endothelin) lead to diffuse or localized dilatation of pre & post-capillary pulmonary vessels. The increased pulmonary blood flow without an increase in ventilation leads to a V/Q mismatch. The dilatation of the vessels causes an increased diffusion distance and abnormality. There are intrapulmonary arterio-venous shunts that are forms & sometimes porto-venous anastomoses. The hypoxic vasoconstriction response is blunted.

Diagnostic criteria: The triad of liver disease and/or portal hypertension, widened age-corrected alveolar–arterial oxygen gradient while breathing room air and documented intrapulmonary vascular dilation define hepato-pulmonary syndrome

Table 1. Diagnostic Criteria for the Hepatopulmonary Syndrome.*

Variable	Criterion
Oxygenation defect	Partial pressure of oxygen <80 mm Hg or alveolar–arterial oxygen gradient ≥15 mm Hg while breathing ambient air
Pulmonary vascular dilatation	Positive findings on contrast-enhanced echocardiography or abnormal uptake in the brain (>6%) with radioactive lung-perfusion scanning
Liver disease	Portal hypertension (most common) with or without cirrhosis
Degree of severity†	
Mild	Alveolar–arterial oxygen gradient ≥15 mm Hg, partial pressure of oxygen ≥80 mm Hg
Moderate	Alveolar–arterial oxygen gradient ≥15 mm Hg, partial pressure of oxygen ≥60 to <80 mm Hg
Severe	Alveolar–arterial oxygen gradient ≥15 mm Hg, partial pressure of oxygen ≥50 to <60 mm Hg
Very severe	Alveolar–arterial oxygen gradient ≥15 mm Hg, partial pressure of oxygen <50 mm Hg (<300 mm Hg while the patient is breathing 100% oxygen)

Rodriguez-Roisin R & Krowka MJ .NEJM 2008:358;2378-87

Clinical features:

- Exertional dypnoea, fatigue, clubbing & may have spider angiomata
- Platypnoea (dyspnoea in the upright position relieved by recumbency)
- Orthodeoxia (arterial oxyhaemoglobin desaturation in the upright position).

Platypnoea & orthodeoxia may be due more rigid and fixed pulmonary vascular tone, which is less able to proportionately accommodate gravitational blood-flow changes in dependent alveolar units. Preferential perfusion of intrapulmonary shunts with the patient upright might cause these clinical manifestations.

Medical therapy has been ineffective, with liver transplantation being the only treatment option.

Gastrointestinal Effects

Portal hypertension: Intrahepatic vascular resistance and portal venous blood flow increase the gradient between the portal & hepatic vein to > 5mmHg.Increased vascular resistance may be due to liver fibrosis, regenerative nodules, endothelial dysfunction,imbalance between endogenous vasodilators and vasoconstrictors. As the pressure gradient increase gastro-oesophageal and haemorrhoidal varices develop to decompress the portal system. Portal hypertension induces splanchnic vasodilatation but this itself increases portal blood flow and increases the portal hypertension further.

Complications of portal hypertension include: bleeding from varices, formation of ascites and pleural effusion.

Ascites

Pathogenesis:Portal hypertension induces splanchnic vasodilation which stimulates ADH and renal sodium reabsorption .In addition, abdominal lymph production exceeds the resorption.

Management: Dietary salt restriction, diuretics (spironolactone or furosemide).

- V2 receptor antagonists(Vaptans) have been tried but there isn't sufficient evidence to recommend use.
- Paracentesis for tense/refractory ascites. Paracentesis induced cardiovascular dysfunction can be avoided if done while vasopressors administered & 8g Albumin IV given/litre of ascitic fluid removed.
- Ascites is associated with a poor prognosis and high perioperative risk. If ascites is diuretic resistant, can consider trans-jugular intrahepatic porto-systemic shunt (TIPSS)

Anaesthetic considerations: Massive ascites can decrease venous return, hepatic hydrothorax and pleural effusions decrease pulmonary reserve, tense ascites may decrease gastric emptying and increase aspiration risk–consider rapid sequence induction.

Variceal Haemorrhage

Oesophageal varices are present in up to 60% of patients at time of cirrhosis diagnosis. 30% of these will bleed with the mortality associated with the first bleed up to 50%.

Management of Acute Variceal bleed: Control airway and ensure adequate breathing (intubation if needed). Protect against aspiration of blood.

Fluid resuscitation, packed cell transfusion as needed, Treatment of underlying coagulopathy (if present) with appropriate factor concentrates & platelets, preferably guided by thromboelastogram. Vitamin K 10mg IV.

Endoscopic ligation (banding or sclerotherapy) is the first line of therapy. If can't control haemorrhage with ligation, balloon tamponade (Sengstaken Blakemore) and refer for TIPSS.

Secondary prevention : Non-selective β-blocker(eg. Propranolol), somatostatin analogue (eg. Octreotide)

Spontaneous bacterial peritonitis

Patients are often asymptomatic, ascitic tap is needed to diagnose - ascitic fluid neutrophil count >250/ml.

Treat with appropriate antibiotics, Intravenous albumin (1.5 g/kg at diagnosis and 1 g/kg on day 3) has been shown to reduce the incidence of hepato-renal syndrome & improve survival. High recurrence rate & secondary prophylaxis with co-trimoxazole or quinolone is indicated. The long-term prognosis for patients with SBP is poor, with mortality rates in excess of 70% reported at 2 years.

Renal

The causes of renal dysfunction in cirrhosis include:

- Hypovolemia induced : following haemorrhage from variceal bleed , excessive diuresis, lactulose-induced diarrhoea
- Acute tubular Necrosis(ATN)
- Drug-induced:nephrotoxins eg. NSAID's , aminoglycosides
- **Hepato-renal syndrome (HRS):** portal hypertension induces splanchnic vasodilation leading to a reduction in effective arterial blood volume, subsequent activation of the sympathetic nervous system and renin-angiotensin-aldosterone system and consequently profound renal vasoconstriction. Functional renal vasoconstriction that leads to a severe reduction in GFR with minimal histological abnormalities. Often precipitated by bacterial infections eg.SBP and some may resolve when the infection is treated while other cases persist and progress.

Diagnosis: Cirrhosis with ascites, doubling of serum creatinine serum creatinine >1.5 mg/dl (133 mol/liter), which is not reduced (to <1.5 mg/dl) with the administration of albumin(1 g/kg of body weight) and after a minimum of 2 days without diuretics.

Difficult to differentiate between HRS and ATN as both may have granular urinary casts. Renal tubular epithelial cells in sediment indicates ATN, while fractional excretion of sodium < 1% favours HRS.

Absence of current or recent treatment with potentially nephrotoxic drugs, the absence of shock, and the absence of findings suggestive of parenchymal renal disease.

- Type 1: is characterized by a doubling of the serum creatinine concentration >2.5 mg /dL (221 µmol/L)in less than 2 weeks. Acute and rapidly progressive, and has extremely high mortality without liver transplantation.
- Type 2: follows a stable, less progressive course than does type 1. Mainly characterized by refractory ascites.

Management:

- Vasoconstrictor – eg. Terlipressin , noradrenaline or midodrine. Monitor for ischaemic complications with terlipressin.
- Albumin IV-1 g/kg body weight on day 1, followed by 20- 40 g/day thereafter

The combination of the above reverses up to 50% of Type 1 HRS

- Renal Replacement Therapy –if no response to vasoconstrictor and the underlying liver disease is treatable or are candidates for transplant. Avoid acetate and lactate buffers

Coagulation system

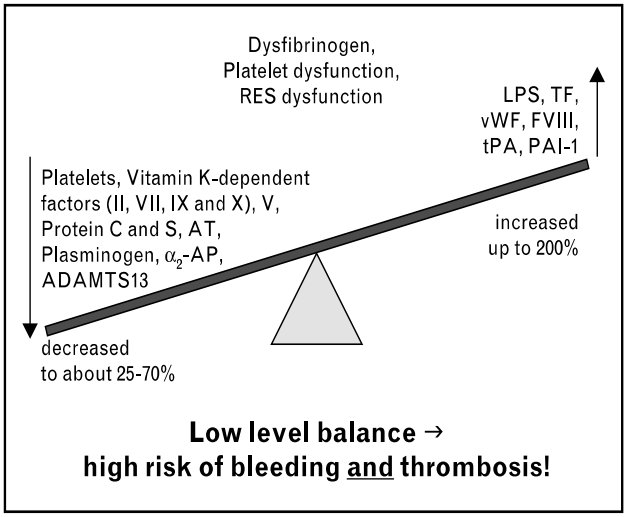
Haemorrhagic risk increased by:

- Reduced synthesis of vitamin-K dependent procoagulant factors II, V,VII,IX & X. Decrease in vWF cleaving enzyme ADAMTS13 which is normally synthesized in liver.
- Thrombocytopenia due to hypersplenism (portal hypertension) & decreased production of thrombopoeitin, platelet function defects,(uraemia from acute kidney injury; intrinsic defects of ADP, arachidonic acid)
- Dysfibrinogenaemia, increased tPA.

Thrombotic risk increased by:

- Decrease in anticoagulants protein C & S , antithrombin, α2 macroglobulin,plasminogen & heparin co-factor II
- The procoagulant factors produced by the vascular endothelium (Factor VIII and vWF) are increased.

The overall coagulation function depends on the balance between these pro-and anticoagulant changes



Assessment of coagulation: conventional coagulation tests include clotting time, PT, INR, and activated partial thromboplastin time measure only part of the process of thrombin generation.

Further tests that evaluate the function and interaction of plasma, blood cells, and platelets (including fibrinolysis) would be preferred. A viscoelastic test like thromboelastogram or thrombin generation assay modified by the addition of thrombomodulin can be used. The INR- liver is a modification of the standard INR where PT is calibrated using plasma from patients with cirrhosis instead of vitamin K antagonists and is thought to resolve variability of INR in these patients.

The fibrinogen level should be measured in patient planned for surgery and replaced appropriately if levels <100mg/dL with cryoprecipitate.

Ph**armacokinetic changes**

- Decreased hepatic metabolism
- Decreased renal excretion (HRS or other causes of renal dysfunction)
- Reduced synthesis of serum proteins eg .
  :Albumin –increased free fraction of drugs.
  :Cholinesterase – prolong duration of action of suxamethonium
- Increased total body water –increased volume of distribution of water soluble drugs . May require larger bolus doses

Hepatic metabolism takes place via two pathways:

- Phase 1: biotransformation via the cytochrome P450 system (which requires delivery of oxygen via hepatic perfusion) which is decreased in liver disease
- Phase 2: glucuronide conjugation is relatively spared when dysfunction begins

Volatiles:

- Enflurane (together with halothane) decreases the hepatic blood flow the most among volatile agents.
- Isoflurane : Biotransformation by cytochrome P450 ≈0,2% .Improves hepatic blood supply, possibly due to direct vasodilatation in the hepatic vascular bed & decrease in portal vascular resistance.
- Sevoflurane : 2-5% biotransformation .No fluoro-acetylated neo-antigens formed. Improves hepatic blood flow
- Desflurane: 0.02% biotransformation increases hepatic blood flow, but there is no significant difference between it and isoflurane.

Use of either one of the modern volatile anesthetics (Iso, Sevo or Desflurane) appears comparable until further data are available.

Benzodiazepines:

- Diazepam & midazolam metabolism is reduced causing prolonged duration of action and can worsen pre-existing hepatic encephalopathy by the stimulation of central GABA-receptors.
- Lorazepam, oxazepam and temazepam undergoes glucuronide conjugation and is less affected in hepatic dysfunction.

Opioids: Morphine glucoronidation is affected in mod-severe hepatic dysfunction. High hepatic extraction ratio therefore may accumulate if hepatic blood flow reduced or if co-existing renal dysfunction.

Fentanyl & sufentanil also have high hepatic extraction ratio but as a single dose seems well tolerated in liver dysfunction .Alfentanil, morphine, and oxycodone display a prolonged half-life. Remifentanil IVI does not have a prolonged duration of action.

Neuromuscular Blockers: Vecuronium and rocuronium have slower onset of action and longer duration of action. Cisatracurium– metabolism independent of liver

Propofol: Duration of action determined by redistribution therefore relatively unchanged. No change in clearance & minimal effects on pre-existing encephalopathy

Risk stratification

Patients with chronic liver disease have a reduced hepatic reserve capacity to cope with perioperative stress and are at increased risk for intra-& postoperative complications. Patient-specific risk factors, various scoring systems, and surgical procedures should be considered when stratifying risk for these patients. There are models that have been devised based on the liver-specific parameters (Child-Turcotte-Pugh) but these should be used in combination with other appropriate scoring systems eg. ASA for pre-operative or SOFA if critically ill. The combination of scoring systems may exponentially increase the perioperative risk.

Scoring Systems

Child-(Turcotte)-Pugh

Child-Turcotte score originally devised in 1964 to predict outcomes in cirrhotic patients undergoing porto-systemic surgery shunting for variceal haemorrhage. Subsequent studies have shown its usefulness in estimating risks for patients with liver disease undergoing hepatic or non-hepatic surgery This was modified(1984)with nutritional status being replaced with prothrombin time and renamed the Child–Pugh score .
It relies on a subjective assessment of ascites and encephalopathy and does not consider preoperative infection, aetiology of cirrhosis, or surgery type. Original studies suggested high mortality rates in Class A (10%), Class B (30%), and Class C (82%) patients who undergo abdominal surgeries. A newer study reports lower mortality rates after abdominal operations: Class A=2%; Class B=12%; Class C=12%.Improvements in surgical technique, anaesthetic management, and perioperative care might explain the difference in these findings.

Table 2. Child–Pugh classification and interpretation.

A. Classification			
Points	1	2	3
Albumin (g/dl)	>3.5	2.8–3.5	<2.8
Bilirubin (mg/dl)	>2.0	2.0–3.0	>3.0
INR	<1.7	1.7–2.3	>2.3
Ascites	None	Suppressed with medication	Refractory
Encephalopathy	None	Grades I–II (or suppressed with medication)	Grades II–IV (or refractory to medication)
B. Interpretation			
Points	Class	1-year survival (%)	2-year survival (%)
5–6	A	100	85
7–9	B	81	75
10–15	C	45	35

INR, international normalised ratio.

Model for End-stage Liver Disease (MELD)

Box 2
MELD score equation

MELD score = $(9.6 \times \log_e[\text{creatinine}]) + (3.8 \times \log_e[\text{bilirubin}]) + (11.2 \times \log_e[\text{INR}]) + 6.4$

Value of creatinine, bilirubin, or INR cannot be less than 1.0 for the equation.

Values greater than 40 assigned a value of 40.

MELD less than 10—consider low risk

MELD 10 to 15—intermediate risk

MELD greater than 15—high risk

Creatinine in mg/dL

Bilirubin in mg/dL

It was designed to overcome the ambiguity and inter-observer variability due to the subjective parameters (ascites & encephalopathy) of the Child–Pugh .It is objective, includes creatinine as indicator of renal dysfunction & has been validated across a number of liver diseases (alcoholic hepatitis and variceal bleeding) and surgeries (abdominal, orthopaedic, and cardiovascular). Initially aiming to predict 3-month mortality in patients with chronic liver disease, it has been used since 2002 by the United Network for OrganSharing (UNOS) to prioritise patients awaiting liver transplantation. Score ranges from 6-40, with a score of >15 being high risk for any surgery. When compared with CTP, MELD is a better predictor of 3 or 6-month mortality in patients with cirrhosis. A modified CTP score that included the serum-creatinine (CrCTP) predicted 3-month mortality better than CTP.

Preoperative Risk Stratification

Consider the scoring system, the patient's co-morbidities and the type of surgery.

Table 1 Perioperative risk factors associated with complications and mortality[1–33]

Scoring system
- Modified Child–Turcotte–Pugh (CTP)
- Model for end-stage liver disease (MELD)
- ASA-PS IV or V

Patient-specific risk factors
- Male gender
- Age >70 yr
- Preoperative infection
- Cirrhosis other than primary biliary cirrhosis
- Elevated creatinine
- Chronic obstructive pulmonary disease
- Intraoperative hypotension
- Upper gastrointestinal bleeding
- Ascites

High-risk surgeries
- Abdominal surgery
- Open cholecystectomy
- Cardiothoracic surgery
- Trauma laparotomy
- Oesophageal surgery
- Emergency surgery

High-risk patients with liver disease for any type of surgery

Child's C

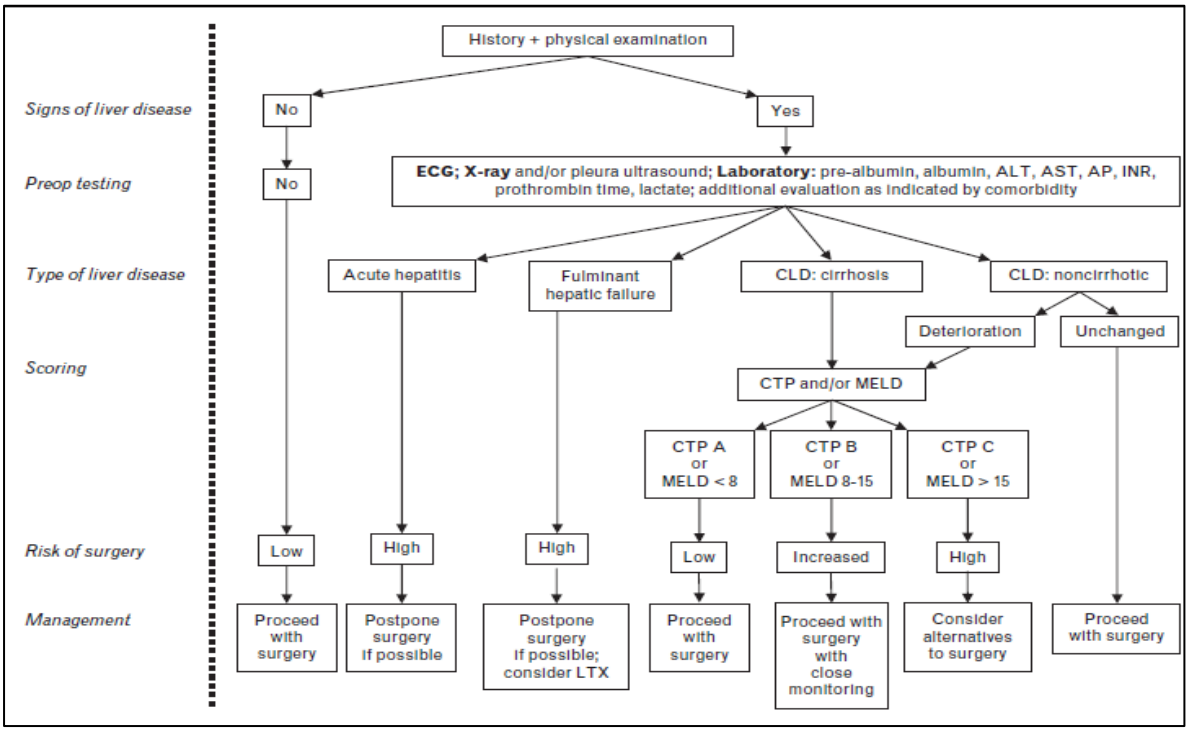
MELD score greater than 15

Acute liver failure

Acute alcoholic hepatitis

High serum bilirubin (>11 mg/dL)

Below is a proposed algorithmic approach to the patient with liver disease presenting for non-hepatic surgery. *Hoetzel A et al .Curr Opin Anesthesiol 2012;25:340-347*



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Notes

Liver Function Tests

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Anaesthetist in private practice

Classically, liver function tests (LFTs) referred to a battery of investigations that had little to do with liver function, and served more to distinguish between hepatocellular injury and cholestasis.

Traditional "LFTs"

Hepatocellular Injury

Alanine aminotransferase (ALT) is a mainly cytoplasmic liver enzyme

Aspartate aminotransferase (AST) is cytoplasmic and mitochondrial and found in many tissues other than in the liver, including heart, skeletal muscle, brain, kidney, pancreas, adipose tissue and blood.

Both are enzymes involved in gluconeogenesis, and are released into the blood as a result of hepatocellular damage.

Aminotransferase levels do not correlate well with the extent of liver damage or outcome. Generally though, high levels (>1000 IU/L) represent acute hepatitis of viral, drug or ischaemic origin.

Glutathione-S-transferase (GST) is a sensitive and specific test for some patterns of liver injury. While AST and ALT reside in the acinar zone 1, GST is more concentrated in zone 3, the centrilobular region, which is vulnerable to injury from hypoxia or reactive drug metabolites.

It is rapidly released, and has a short plasma half-life (90min), which means it can be used to track acute changes, but can miss peak effects.

Lactate Dehydrogenase (LDH) may reflect hepatocellular injury, but also hemolysis, rhabdomyolysis, tumor necrosis, renal infarction, CVA or MI. If due to hepatocellular injury, it is usually accompanied by ALT and AST, so rarely yields additional information.

Cholestatic Disorders

Alkaline Phosphatase (AP) is a family of enzymes widely located in the body, and so a nonspecific indicator of cholestasis. It has a half-life of nearly a week, so levels may remain raised for days after bile flow is restored.

It is also raised in the 3rd trimester (placenta), puberty, Paget's disease, rickets and osteomalacia (bone)

Extreme increases in AP suggest either a major block in biliary flow (primary biliary cirrhosis or choledocholithiasis), or hepatic malignancy compressing small intrahepatic bile ducts.

Gamma Glutamyl Transpeptidase (GGT) is a membrane-bound glycoprotein found in cells with high secretory/absorptive activity (liver, kidney, pancreas, intestines, prostate). It is sensitive, but not specific for hepatobiliary disease.

It can help distinguish between hepatic and extrahepatic sources of AP. (Bone, for instance, has very little GGT)

GGT can be induced by drugs like alcohol, anticonvulsants, and warfarin, which may confound interpretation.

In nondrinking, obese individuals, the most common cause of a raised GGT is a fatty liver.

Bilirubin is the end product of haem metabolism, and may be either unconjugated (water insoluble and bound to albumin) or conjugated. (water-soluble, normally excreted in the bile)

Unconjugated bilirubin may be raised in up to 10% of healthy individuals due to genetically low levels of glucuronyltransferase. (Gilberts Syndrome)

Increases in unconjugated bilirubin are otherwise generally due to the hepatocytes being presented with more bilirubin than they can handle e.g. haemolysis.

Increases in conjugated bilirubin result either because the flow of bile has been blocked, or because the hepatocytes produce more bilirubin conjugates than can be efficiently excreted. (Note: massive haemolysis can cause both conjugated and unconjugated hyperbilirubinemia)

The table below gives some common causes of hyperbilirubinemia. In brackets are examples of drugs that can cause jaundice.

Mechanism	Example
Unconjugated hyperbilirubinemia	
Increased bilirubin production	Hemolysis
Decreased hepatic bilirubin uptake	Heart failure (Chloramphenicol, Probenecid)
Decreased hepatic conjugation	Gilbert syndrome (Estradiol)
Conjugated hyperbilirubinemia	
Hepatocellular dysfunction	Viral hepatitis, drugs, toxins (Paracetamol OD, amiodarone, isoniazid)
Intrahepatic cholestasis	Alcoholic liver disease, viral hepatitis, drugs, toxins (augmentin, chlorpromazine, OCP)
Extrahepatic cholestasis	Common bile duct stone, pancreatic cancer

True liver function tests

Synthetic function

Albumin is largely synthesized in the liver, so albumin levels can be used as measure of synthetic function in stable, chronic kidney disease. It is also incorporated into prognostic scoring systems such as the Child-Pugh and Meld scores.

There are 2 important caveats:

1. There are many causes for a low albumin. (renal losses, plasma volume expansion, increased catabolism etc.)

2. Albumin has a long half-life (20 days), so it is days before a change in in hepatic protein synthesis can be detected by this measure.

Prothrombin Time/INR: The clotting factors, also proteins synthesized in the liver, have short half-lives compared to albumin, from 4 hours for factor VII to 4 days for fibrinogen. This makes them more suited to monitoring fluctuations in liver function.

Failure of prolonged PT to correct with IV vitamin K supplementation implies hepatocellular failure, and is one of the most reliable prognostic indicators of survival in acute liver failure.
Blood lactate concentration represents a balance between its production and elimination. Normally, the liver removes up to 60% of lactate.

Hypoperfusion, hypoxia and severe ischaemic damage, decrease lactate clearance, and increase its production, making it a marker of hepatic injury in acute liver failure. Blood lactate levels correlate with survival in paracetamol induced liver failure.

‘Dynamic’ tests of liver function

These test the ability of the liver to clear or metabolize an infused substance. They are relatively costly, time consuming, and do not confer additional diagnostic or prognostic value, so these are normally only used for research purposes.

Formation of monoethyleneglycine (MEGX), a metabolite of lignocaine:
1mg/kg lignocaine is injected intravenously, and MEGX measured after 15-30min.

However, because clearance of lignocaine is flow limited, rather than capacity limited, this probably reveals more about liver blood flow than functional capacity.

Indocyanine green (ICG) clearance: The elimination of 0.5mg/kg ICG has been used to assess liver function.

ICG has a high hepatic extraction ratio, so, in conjunction with the indirect Fick principle, measurements of blood levels after IV injection can be used to approximate liver blood flow.

The following table, adapted from Miller, illustrates how the liver function tests might help narrow one’s differential diagnosis:

Blood Test	Bilirubin Overload (Haemolysis)	Hepatocellular Injury	Cholestasis
Aminotransferases	Normal	Increased	Normal increase if advanced
Serum albumin	Normal	Decreased (unless ++ acute)	Normal decrease if advanced
Prothrombin time	Normal	prolonged	Normal prolongs if advanced
Bilirubin	Unconjugated	Conjugated	Conjugated
Alkaline Phosphatase	Normal	Normal	Increased
GGT	Normal	Normal	Increased
ICG (indocyanine green)	Normal	Retention of dye	Normal or retention of dye

References

1. Miller’s Anesthesia 7th edition: Chapter 17, Hepatic Physiology and Pathophysiology. pgs 424-428.
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3. Anaesthesia UK website ‘Laboratory tests in hepatic and renal failure.’

Notes

Recent advances in coagulation testing

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UCT and Groote Schuur Hospital

Introduction

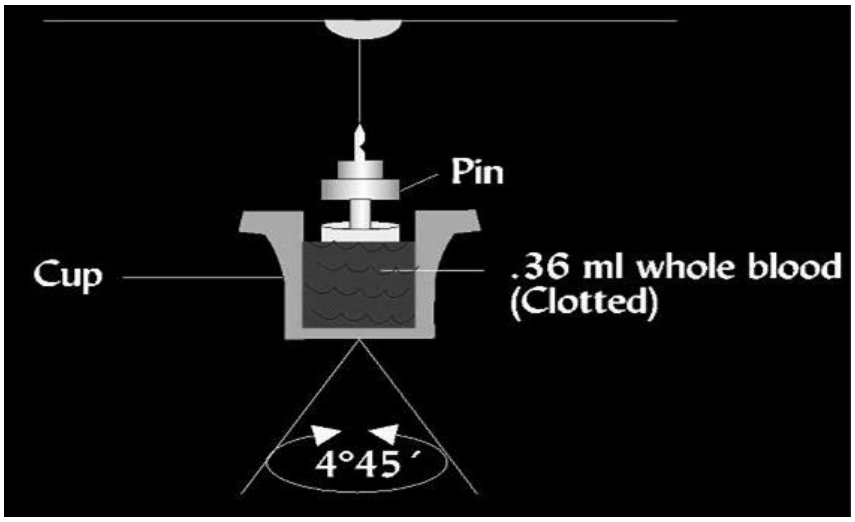
The value of conventional tests to evaluate coagulation such as INR and PTT have been questioned particularly in the peri-operative setting. These tests are done on plasma and citrated samples and have to be shuttled off to the laboratory for testing. A resurgence in point of care testing has brought renewed enthusiasm in Thromboelastometry, for the assessment of coagulation defects on whole blood samples.

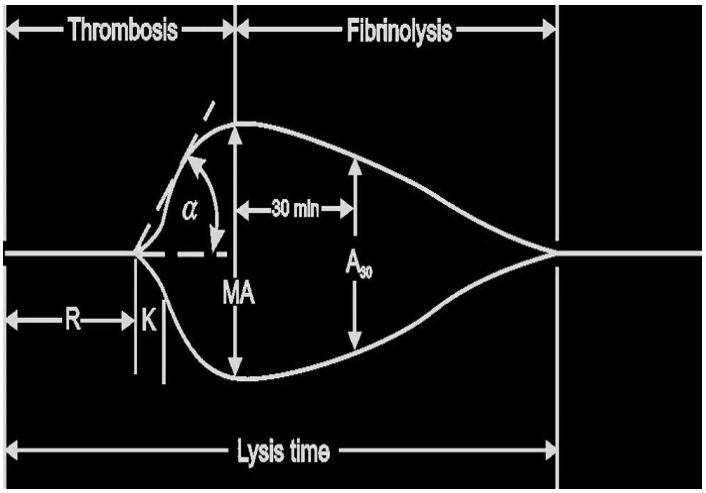
Visco-elastic coagulation devices

Thromboelastography was first described by Hartert in 1948 as a method to assess global haemostatic function from a single blood sample.
These devices assess the visco-elastic properties of blood samples under low shear conditions.
It represents a dynamic global assessment of coagulation from the point of clot initiation to clot stabilization and furthermore evaluates the breakdown of the clot.
The visco-elastic properties of clot formation represent the interaction of fibrin and platelets and are directly related to the strength of the clot formed. The clot then retracts and lysis which is also represented in terms of visco-elastic forces.
Important limitations of these devices are that they assess coagulation under static (no flow) conditions and in a cuvette which negates the effect of the endothelium.

Thromboelastography

TEG® is a registered trademark of Hemoscope Corporation and has been used exclusively to describe coagulation testing using their device.
The TEG measures the clot's visco-elastic properties using a cylindrical cup containing 0.36ml of whole blood that oscillates through an angle of 4^0 45'. Each rotation cycle lasts 10s. A delicate pin in immersed in the cup and the torque of the rotating cup is transmitted to the pin only once fibrin-platelet bonding takes place which links the cup and pin together. The strength of these fibrin-platelet bonds determines the magnitude of the pin motion. Thus the output is directly related to the strength of the clot formed. As the clot lyses, these bonds are broken and the motion transmitted through the pin is diminished. The rotation movement of the pin is converted by a mechanical-electrical transducer to an electrical signal, finally being displayed as a typical TEG tracing.



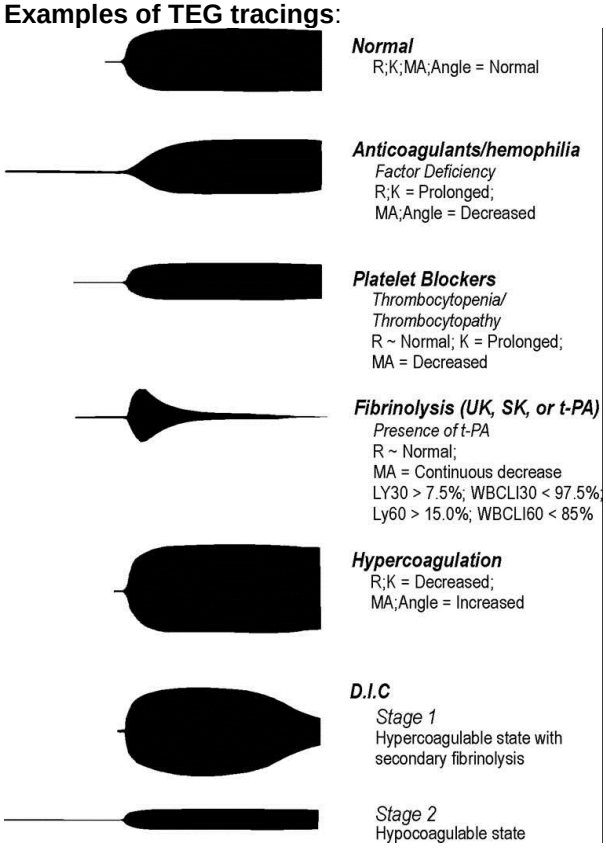


Nomenclature:

R-time: reaction time or time to clot initiation where tracing deviates by 2mm from the baseline
k-time: time from deviation of the tracing from 2mm to 20mm
MA: maximum amplitude
$MA_{30\text{-}60}$: amplitude at set time
G: clot elasticity(software derived value)
CI: coagulation index, an indication of clot integrity
CL: clot lysis usually at 30min and 60 min after the MA, expressed as a percentage
EPL: estimated percent lysis calculated 30min after the MA

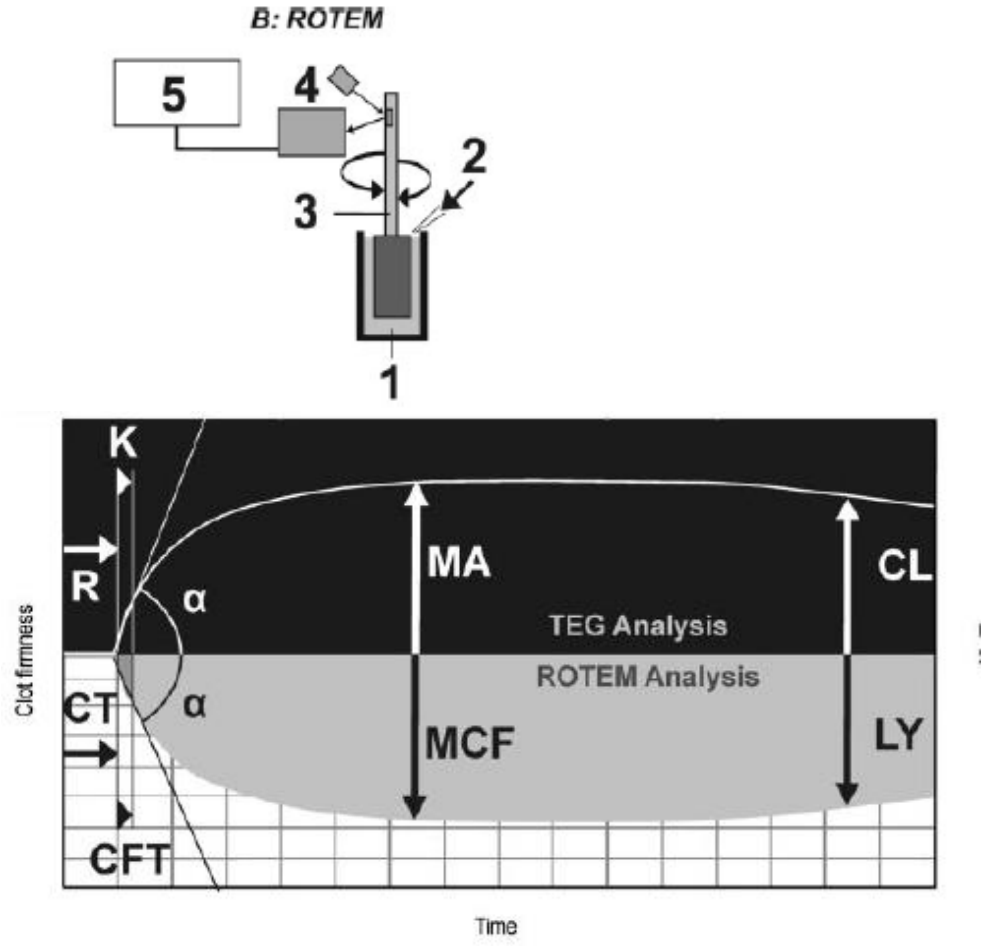
Importantly, TEG provides valuable information regarding both hypocoaguable states as well as prothrombotic states. Remember, clot formation is accelerated by the addition of kaolin to the whole blood sample and if heparin contamination is suspected, this can be neutralized by the use of a cup coated with heparinase.

Examples of TEG tracings:



ROTEM

The device has been commercially marketed as using rotational thromboelastometry as opposed to thromboelastography used by TEG but the technology is virtually identical. The ROTEM differs slightly from TEG in that the signal from the pin is transmitted via an optical sensor, not a torsion wire, and the movement is initiated from the pin, not the cup.



ROTEM nomenclature

CT: clotting time
CFT: clot formation time analogous to r-time plus k-time for TEG
MCF: maximum clot firmness
LY: lysis usually measured at 30min and 60 min

Assays available using ROTEM
EXTEM: clotting activated by addition of 20µl of tissue factor
Analogous to prothrombin time (PT)

INTEM: clotting activated by phospholipid
Analogous to aPTT

FIBTEM: evaluation of clot integrity by adding cytochalasin D, a platelet inhibitor, evaluating functional fibrin polymerization without platelet activity.

HEPTEM: heparinase added to inactivate the effect of heparin

APTEM: aprotinin added to evaluate the presence of fibrinolysis

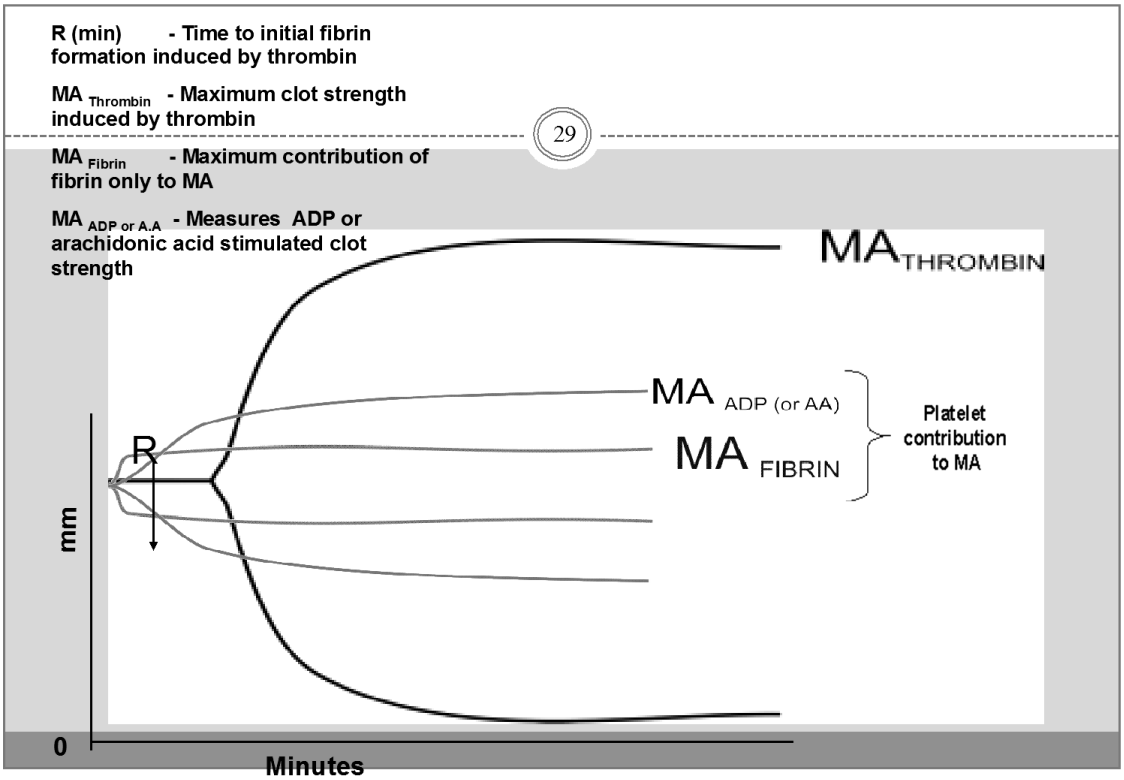
These assays provide a unique opportunity to evaluate the contribution of various factors in the causes of coagulation disorders and offer a distinct advantage over the TEG. However, the test, if all five assays are used, comes at a higher cost when compared to the TEG. The device is fully automated and comes with an electronic pipette making operator error less likely.

The future

Platelet mapping:

Platelet mapping measures the %inhibition present due to anti-platelet therapy. The assay uses two agonists i.e. ADP and Arachidonic acid to generate adjusted MA's that measure the inhibiting effect of the following anti-platelet agents:

TxA_2 inhibitors e.g. Aspirin
ADP inhibitors e.g. Clopidogrel, Ticlodipine
GPIIIb/IIa inhibitors e.g. Aggrastat, ReoPro, Integrilin



This new addition to the TEG repertoire requires at least 4 channels i.e. 2 machines and a computer to perform the analysis. This adds considerably to the cost.

Indications for Platelet mapping:

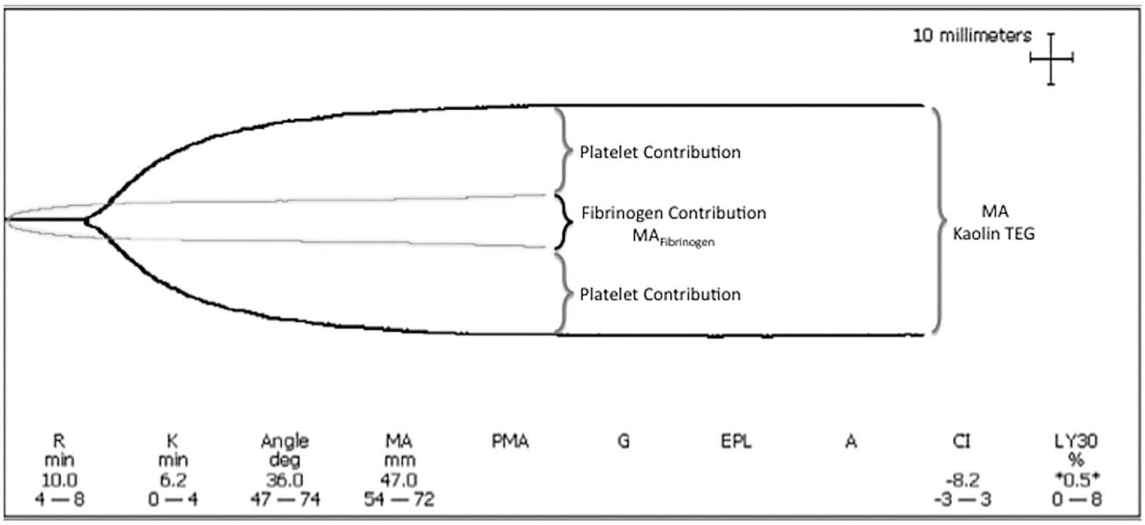
- Monitoring effectiveness of anti-platelet therapy
- Establishing possible resistance to therapy
- Assessing bleeding and ischaemic risk factors
- Planning surgical and prophylactic intervention

Rapid TEG

This is a quantitive in vitro diagnostic test intended to monitor anticoagulation in adult patients. The Rapid TEG delivers clot strength results (MA parameter) in 5 – 10 min. It also provides an ACT (derived from the R parameter) in less than 60seconds. Correlates with the Hemochron ACT and provides a rapid assessment of bleeding in anti-coagulated patients.

Functional Fibrinogen assay:

This test rivals the FIBTEM in many ways. It relies on evaluating a normal kaolin activated TEG and then superimposed on this TEG is another TEG which contains GPIIIb/IIa antagonist to eliminate the platelet contribution to clotting and thereby providing a MA fibrinogen value (see below). This MA fibrinogen correlates with a functional fibrinogen concentration in whole blood.



Conclusion

The newer point-of-care coagulation testing devices have emerged as worthy contenders to more conventional time-honoured tests of coagulation. They offer quicker results and might assist clinicians in targeting therapy more accurately when treating complex coagulation disorders. Areas where theses devices have been found to be particularly useful are in the trauma settting, cardiac surgical patients undergoing cardio-pulmonary bypass and in the peri-operative setting where major blood loss has occurred. It has been established as a discriminating test when considering whether patients have a surgical or medical cause for bleeding. Finally, these devices have shown cost benefit when managing patients with bleeding in the above settings by directing therapy and avoiding the empiric use of expensive blood products liberally.

References:

1. N. Salooja and D.J. Perry, *Thromboelastography: Blood coagulation and Fibrinolysis,2001,12:327-337*
2. M. Ganter and C. Hofer, *Coagulation monitoring: Current techniques and Clinical use of visco-elastic Point of Care coagulation devices; Anesth Analg, vol 106, No.5, May 2008.*
3. TEG Hemostasis Analyzer User Manual, Haemoscope Corporation, Niles IL USA.
4. Jeffrey N. Harr et al. *Functional Fibrinogen Assay Indicates that Fibrinogen is critical in correcting abnormal clot strength following trauma; Shock 2013 January, 39(1):45-49.*

Notes:

Pulmonary function tests

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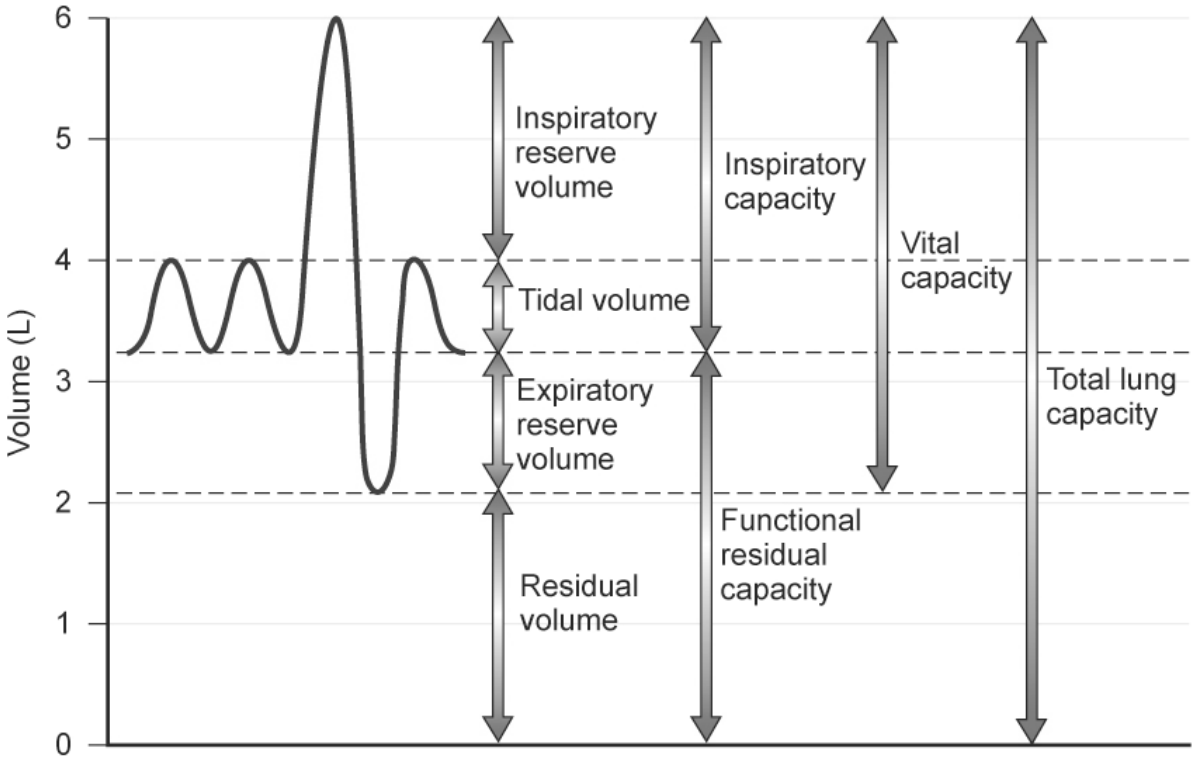
Pulmonary function tests is a term used to indicate a battery of studies or maneuvers that may be performed using standardized equipment to measure aspects of lung performance or lung reserve. It is useful and important in many clinical situations, including when the patient has a history or symptoms suggestive of lung disease, or when risk factors for lung disease are present. It's a quantitative, objective measure of normality or abnormality and, importantly, of improvement or deterioration in response to treatment.
However, it should always be interpreted in conjunction with other pulmonary assessment tools and never should it replace clinical evaluation.

Pulmonary function includes evaluating- 4 components

- Lung Mechanics (airflows and volumes)
- Ventilation perfusion interrelationship
- Diffusion and gas exchange
- Respiratory Muscle or bellows strength

Various diseases can affect each of these components

Lung volumes



Lung Physiology

Ventilation is the process of generating the forces necessary to move the appropriate volumes of air from the atmosphere to the alveoli to meet the metabolic needs of the body. Contraction of the diaphragm and other inspiratory muscles expands the thorax, generating negative pressure in the pleural space. One component of pleural pressure, known as transpulmonary pressure, causes a flow of air into the airways and lungs (inspiration). When the transpulmonary and alveolar pressures equilibrate, the airflow stops and the inspiratory muscles relax. The lungs and chest wall elastic recoil raise pleural pressure, forcing air out of the lungs (expiration).
With a forced exhalation, the early portion of the spirometry maneuver is characterized by high flows, mostly from large airways, and the latter portion is characterized by low flows with a larger contribution from the smaller airways. Forced inspiration is generally not flow limited and is a function of overall muscular effort. In contrast, a variety of factors affect expiratory flow, including the overall driving pressure, airway diameter and the dispensability of the lungs and chest wall, dynamic airway collapse (from a flow-limiting segment), and muscular effort. The overall driving pressure is the pressure head at the alveolus, or P_{ALV}, which is the difference between pleural pressure (P_{PL}) and negative transpulmonary pressure (P_{TP}).
$P_{ALV} = P_{PL} + P_{TP}$
The mechanism for the maximal expiratory airflow limitation seen in normal airways results from the gradual drop in pressure inside the conducting airways from the alveoli to the mouth, creating a transmural pressure gradient with the pleural pressure. This can cause dynamic airway compression and narrowing or closure of airways that have lost elastic recoil support from the lung parenchyma.

Specific pulmonary function tests

- Spirometry (measurement of flow)
- Formal lung volume measurement
- Diffusion capacity for carbon monoxide
- Measurement of respiratory muscle strength
- Pulmonary Exercise testing (not in the scope of this lecture)
- Arterial blood gases

Indications for lung function testing

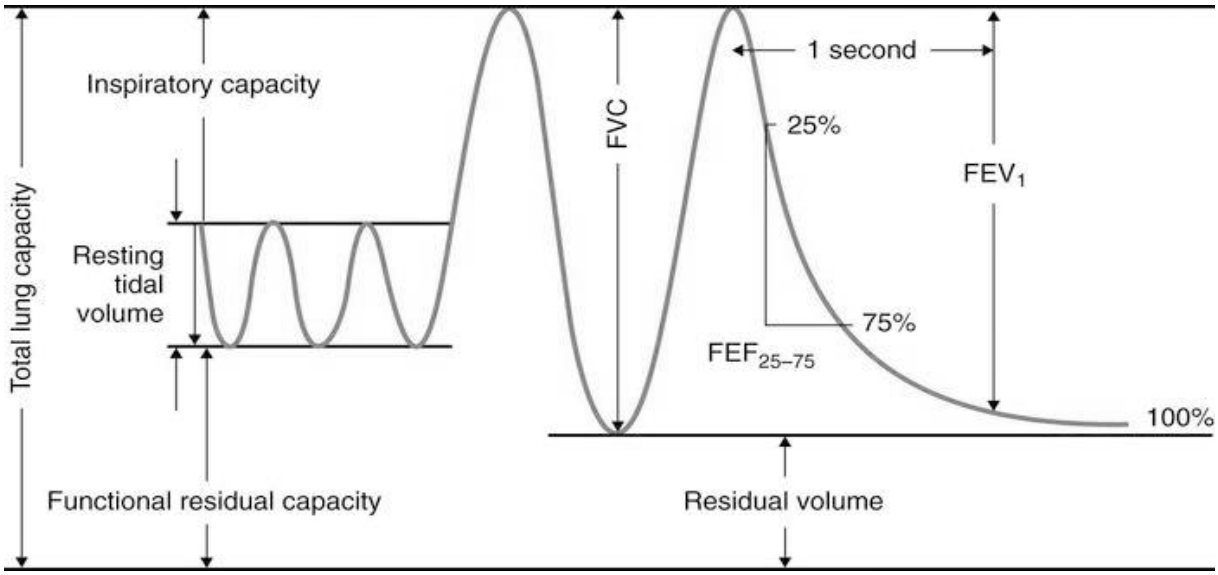
- As a work-up for suspected COPD and Asthma
- Analysis of a restrictive pattern of lung function
- Pre-operative assessment – including planning of lung reduction surgery
- Investigation of dyspnea in the absence of other respiratory symptoms
- Screening for pulmonary involvement in systemic diseases (connective tissue disease, vasculitis, sickle cell etc.)

Spirometry

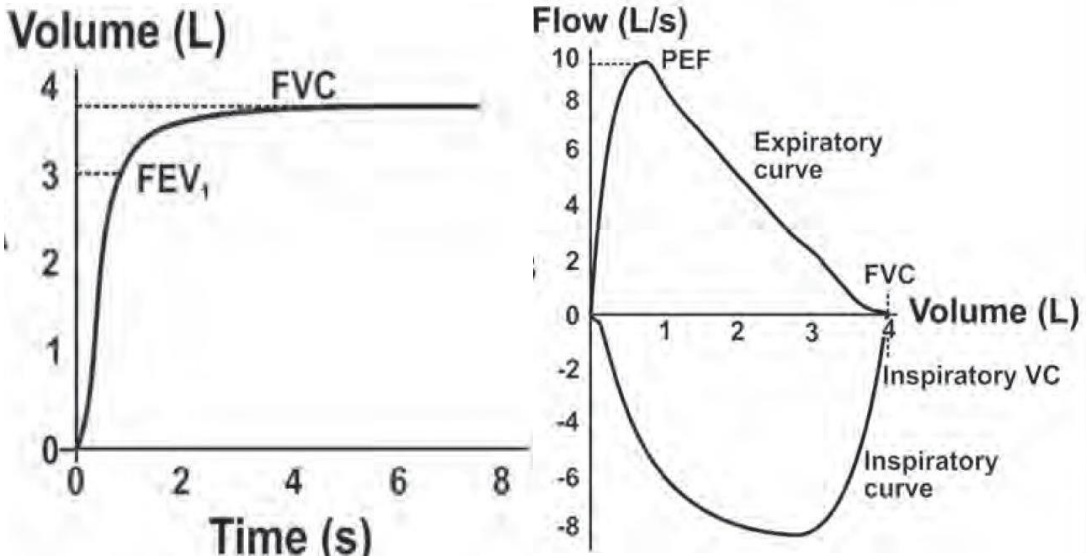
Spirometry is the most common used lung function test with the primary signal measured being airflow. It's an easy test to perform with the use of a spirometer. It requires a fully co-operating patient and a skilled operator.

The spirometer is an instrument that directly measures airflow using a flow-sensing device, such as a pneumotachometer or a tube containing a fixed resistance to flow. With modern technology, testing laboratories use a microprocessor-driven pneumotachometer to measure airflow directly and then mathematically derive volume.

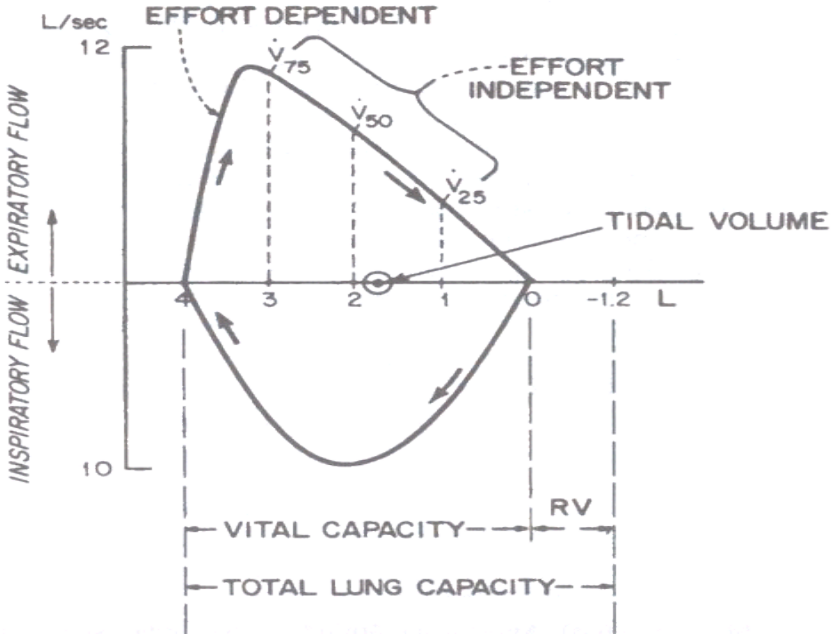
A voluntary maneuver is carried out where a patient inhales maximally from a tidal respiration to total lung capacity and then rapidly exhales to the fullest. This is usually performed in a forceful manner to generate a FVC or relaxed to produce a slow vital capacity (SVC). In normal patients the Inspiratory vital capacity the FVC and the SVC are equal. The percentage of predicted normal is used to grade the severity of the abnormality.



FVC (Forced Vital Capacity). This is the maximum volume of air exhaled with maximally forced effort from maximal inspiration (VC) The Maximally forced expiratory effort expressed in litres at body temperature and ambient pressure saturated with water vapour (BTPS The FVC correlates with the severity of parenchymal lung disease and respiratory muscle/chest cage mechanics.
FEV1 (Forced Expiratory Volume in 1 Second). This is the volume of air expired in the first second during maximal expiratory effort. The FEV1 correlates with effort tolerance, prognosis and the clinical status in obstructive lung disease. It's reproducible with a low coefficient of variation. The FEV1 is reduced in both obstructive and restrictive lung disease.
FEV1/FVC. This is the percentage of the vital capacity that is expired in the first second of maximal expiration. In healthy patients the FEV1/FVC is usually more than 70%. In patients with obstructive lung disease FEV1/FVC decreases and can be as low as 20-30% (severe obstructive airway disease) Restrictive disorders have a near normal FEV1/FVC.
FEF25-75% (Forced Mid-expiratory Flow Rate). This is the average rate of airflow during the midportion of the forced vital capacity. This is reduced in both obstructive and restrictive disorders. This is effort independent.



A spirogram produces a graphic representation of airflow depicted as volume-time or flow-volume tracing expressed in litres per second and corrected for body temperature and pressure of the gas that is saturated with water vapour.
The American Thoracic Society and the European Respiratory Society has published guidelines on the standardisation of spirometry. They cover definitions, equipment and patient related procedures.



Indications for spirometry

DIAGNOSTIC

1. To evaluate symptoms and signs
   - Cough, dyspnea, orthopnea, wheezing, chest deformity, cyanosis, diminished breath sounds, expiratory slowing, unexplained crackles

2. To evaluate abnormal lab tests
   - Abnormal CXR
   - Hypercapnea
   - Hypoxaemia
   - Polycythemia

3. Measure the effect of disease on pulmonary function

4. Screen the persons at risk for pulmonary diseases
   - Smokers
   - Occupational exposures

5. Routine physical examinations
   - Preoperative assessment
   - Assess prognosis
   - Assess health status before enrollment in strenuous physical activity

MONITORING

6. Assess therapeutic interventions
   - Bronchodilator therapy
   - Steroid treatment (interstitial lung disease)

7. Course of diseases affecting lung function
    - Obstructive lung disease (COPD)
    - Interstitial lung disease
    - Neuromuscular lung disease
    - Guillain-Barre syndrome

8. Monitor adverse reactions to drugs known with pulmonary toxicity

PUBLIC HEALTH

9. Epidemiology surveys
10. Comparisons of health status of populations living in different environments
11. Derivation of reference equations

Acceptability and reproducibility of spirometry

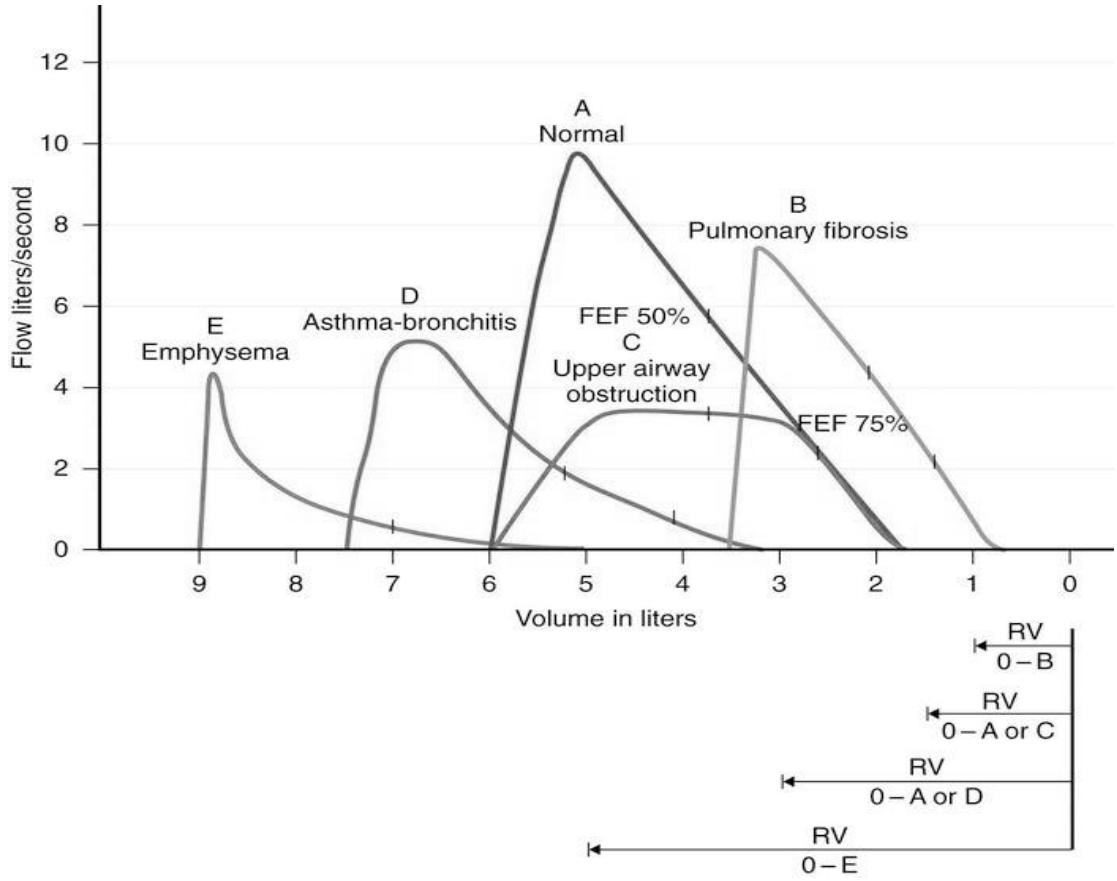
The technician should demonstrate the appropriate technique and coach the patient throughout the session. Ensure the correct posture, nose clip placement and the lips sealing the mouthpiece. Inhale completely and exhalation with maximum force until no more air can be expelled.
The spirometer must be able to accumulate volume for longer than 15s and measuring volumes of greater than 8 L with an accuracy of at least 3% of reading or within 50ml (whichever is greater) and with flows between 0 – 14L/s. The total airway resistance should also be less than 1.5cmH20/s.
While the manufacturers are responsible for demonstrating the accuracy and reliability of the systems, the user is still responsible for ensuring that the equipment's measurements remain accurate, thus, adherence to daily calibration, trained operators and infection control.

The patient needs to be sitting or standing, at least 3 acceptable reproductions with a maximum of 8 attempts. The 2 largest FVC's within 0.2L of each other and the 2 largest FEV1's within 0.2L of one another. There should be no artifacts such as pauses, coughing, glottis closures, leaks or obstruction of the mouthpiece.
There should be a sufficient exhalation for at least 6 seconds. If the patient does not exhale completely after 6 seconds, the volume accumulated may be used as an approximate surrogate for FVC. FEV6 = FVC this is considered a reliable surrogate. FEV6 is more reproducible and less physically demanding.

Performance errors will underestimate the true value. These measurements are referred to regression equations derived from normal populations which takes age, height and gender into account. There are discrepancies between different ethnic groups that may influence results as Caucasian-, Black-, Asian-, and other ethnic groups have different reference values
Other variable factors include muscle strength, BMI and the environment (pollution, altitude, climate, smoking)

Post bronchodilator spirometry

The performance of spirometry before and after a bronchodilator is used to determine the degree of reversibility of airflow limitation.
This is indicated if the baseline spirometry demonstrates airway obstruction or if asthma/COPD is suspected. Spirometry is repeated 10-15min after a bronchodilator administration. (short acting $\beta 2$ agonist)This also determines whether a patient's lung function can be improved with therapy in addition to their regular treatment. Reversibility is defined as an improvement of 12% and 200ml in FEV1 after bronchodilator administration. Bronchodilators should not be taken within 4hrs of testing.



Obstructive and Restrictive lung disease

Pulmonary Parameter	Obstructive lung disease	Restrictive lung disease
VC	N or □	□
TLC	N or □	□
RV	□	□
FEV1/FVC	□	N or □
FEF25%-75%	□	normal

Obstructive lung disease

COPD

Spirometry is the most reproducible and objective measurement of airflow limitation available and now required to make a confident diagnosis of chronic obstructive lung disease. The assessment is based of the level of symptoms, history of exacerbations and the severity of abnormality of spirometry.
The Global initiative for chronic obstructive lung disease has classified the airflow limitation into 4 grades. GOLD1(mild) – GOLD4(very severe)

The classification is based on the fixed ratio, post bronchodilator FEV1/FVC < 0.7, to define airflow limitation.

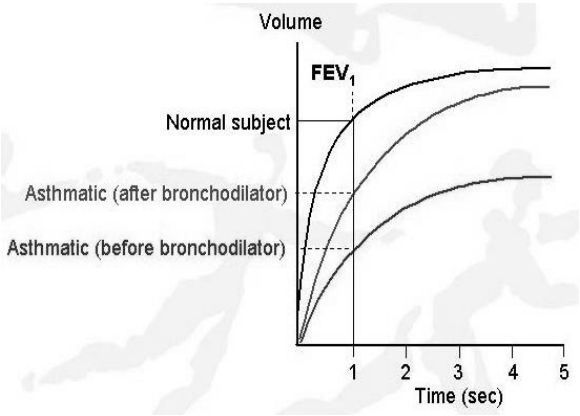
Patients with $FEV_1/FVC < 0.70$:

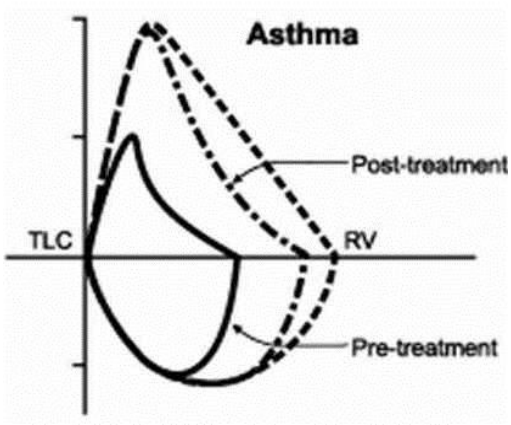
GOLD 1: Mild $FEV_1 \geq 80\%$ predicted
GOLD 2: Moderate $50\% \leq FEV_1 < 80\%$ predicted
GOLD 3: Severe $30\% \leq FEV_1 < 50\%$ predicted
GOLD 4:Very severe $FEV_1 < 30\%$ predicted

The FEV1 is reduced in obstructive lung disease because of increased airway resistance.

It is recognized that the use of the fixed ratio (FEV_1/FVC) may lead to more frequent diagnoses of COPD in older adults with mild COPD as the normal process of aging affects lung volumes and flows, and may lead to underdiagnosis in adults younger than 45 years.
The current guidelines suggest the use of statistically derived lower limits of normal values for FEV_1/FVC rather than a fixed ratio. The lower limits of normal is usually based on confidence intervals around the lowest fifth percentile of a reference population and is considered a potentially better way of identifying airflow limitation in elderly subjects. The use of lower limits of normal would, however, imply the availability of reference values for a specific population. Consensus has not been reached on whether a fixed ratio or lower limits of normal is more suitable for defining airflow limitation.

Asthma – is characterized by upper airway hyper-responsiveness, airway inflammation and variable airway obstruction. Airway narrowing limites airflow and therefore decreases the FEV1. The FVC may also be reduced because gas is trapped behind obstructed bronchi. An increase in intra-thoracic pressure compresses the airways causing early airway closure and gas trapping but this reduction is to a lesser extent than FEV1





PEFR/PEF

Peak expiratory flow is the highest flow achieved from a maximum forced expiratory maneuvre started without hesitation from maximum lung inflation. It is dependent on effort and lung volume. This can be obtained from flow-volume curve data expressed in L/s at BTPS or using portable monitoring instruments (Peak flow meter), expressed in L/min.
Peak flow readings has a high degree of variability and not used as a diagnostic test, but it useful to determine severity of symptoms and treatment of asthma. The measurement of PEFR requires training to correctly use a meter and the normal expected value depends on a patient's sex, age and height.
The measurements are recorded on a peak flow chart and compared to normal predicted values based on the normal population or specific calculators that have been developed to calculate predicted values.
The highest of 3 readings is used and now classified into 3 zones, based on these zones a asthma management plan can be developed by a health care practitioner.



Zone	Reading	Description
Green Zone	80 to 100 percent of the usual or normal peak flow readings are clear.	A peak flow reading in the green zone indicates that the asthma is under good control.
Yellow Zone	50 to 79 percent of the usual or normal peak flow readings	Indicates caution. It may mean respiratory airways are narrowing and additional medication may be required.
Red Zone	Less than 50 percent of the usual or normal peak flow readings	Indicates a medical emergency. Severe airway narrowing may be occurring and immediate action needs to be taken. This would usually involve contacting a doctor or hospital.

Restrictive Lung disease – diagnosed as a reduction in TLC. Because the RV is not always reduced in proportion to the TLC a low FRC can not always be relied on to diagnose restriction. A better diagnosis would be a reduction in VC without a increase in FRC or RV.

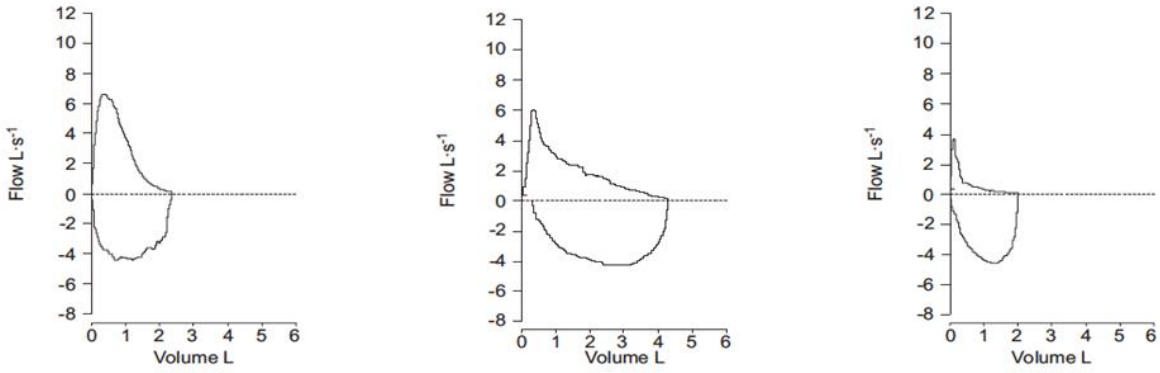
Full lung expansion is prevented by fibrotic tissue in the lung parenchyma and the FVC is reduced. Elastic recoil may be increased by fibrotic tissue and lead to an increase the airflow. Both FEV1 and FVC may be reduced because the lungs are small and stiff, but the peak expiratory flow may be preserved or even higher than predicted. This leads to tall, narrow and steep flow volume loop in the expiratory phase.

Flow volume loops

Normal subject
End expiratory curvilinearity
Seen with ageing

Moderate airflow limitation
Patient with asthma

Severe airflow limitation
COPD



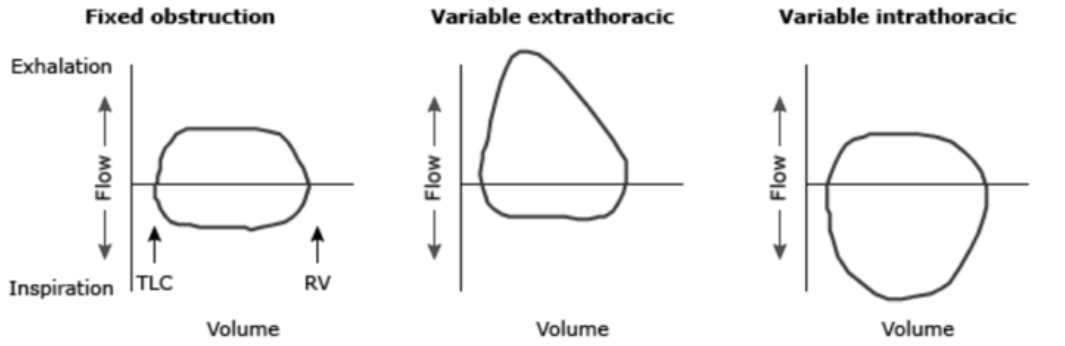
Flow volume loops

The patient has to make a full expiratory and inspiratory loop as a single maneuver.
One should appreciate the advantages of pattern regocnition from the flow volume loops, but the shapes must be repeatable before any interpretation can be made. The plateau effect on the expiratory and inspiratory limbs found in upper airway obstruction can be mimicked by poor effort which varies from blow to blow.

Upper airway obstruction

1. Fixed obstruction
2. Variable extra-thoracic obstruction
3. Variable intra-thoracic obstruction

Flow-volume loops in upper airway obstruction



The left panel shows fixed upper airway obstruction with flow limitation and flattening of both the inspiratory and expiratory limbs of the flow-volume loop. The middle panel shows dynamic (or variable, nonfixed) extrathoracic obstruction with flow limitation and flattening of the inspiratory limb of the loop. The right panel shows dynamic (or variable, nonfixed) intrathoracic obstruction with flow limitation and flattening of the expiratory limb of the loop.

TLC: total lung capacity; RV: residual volume.

Adapted from: Stoller JK. Cleve Clin J Med 1992; 59:75.

Fixed airway obstruction
1. Post intubation stenosis
2. Goiter
3. Endotracheal neoplasms
4. Bronchial stenosis

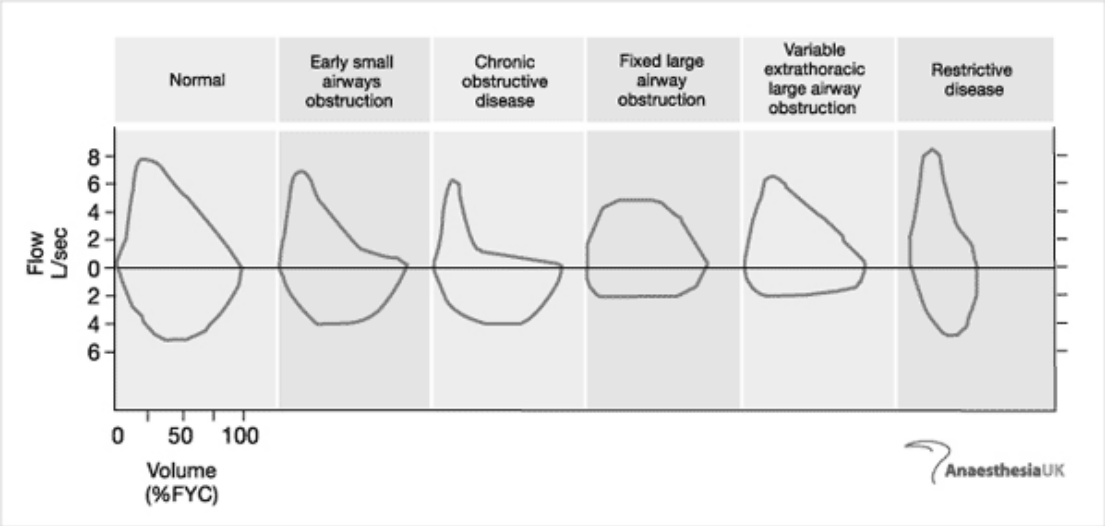
Maximum airflow is limited to a similar extent in both inspiration and expiration

Variable extra-thoracic obstruction
1. Bilateral and unilateral vocal cord paralysis
2. Vocal cord constriction
3. Reduced pharyngeal cross-sectional area
4. Airway burns

The obstruction worsens in inspiration because the negative pressure narrows the trachea and inspiratory flow is reduced to a greater extent than expiratory flow

Variable intra-thoracic obstruction
1. Tracheomalacia
2. Polychondritis
3. Tumors of the lower trachea or main bronchus.

The narrowing is maximal in expiration because of increased intra-thoracic pressure compressing the airway.
The flow volume loop shows a greater reduction in the expiratory phase



Lung Volumes

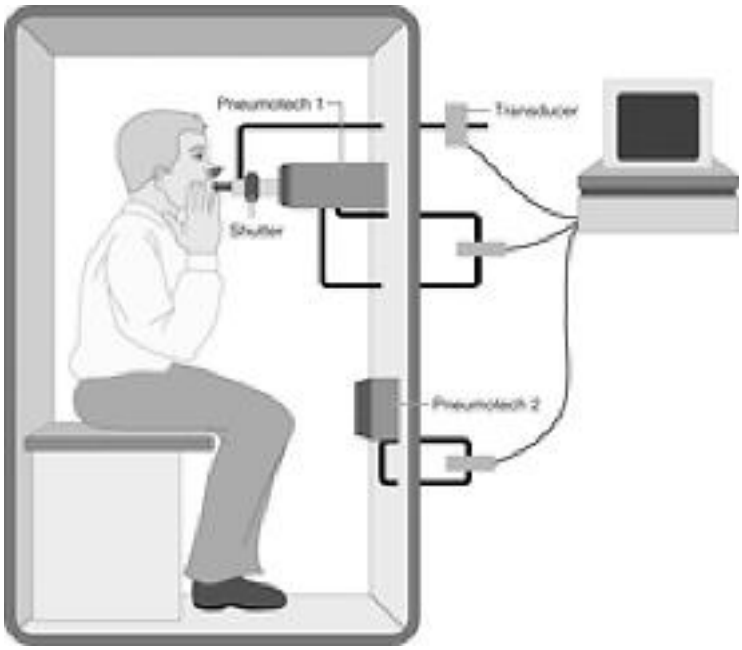
The measurement of total lung capacity may be helpful when the Vital capacity is decreased.
There are four methods of measuring TLC:

- Helium dilution
- Nitrogen washout
- Body plethysmography
- Chest radiograph measurements

a Reduction in vital capacity measured during spirometry should prompt the measurement of lung volumes to confirm the presence or absence of a true restrictive ventilatory disorder.
Gas dilution techniques provide a good measurement of all air in the lungs that communicates with the airways. A closed-circuit helium dilution technique or an open circuit nitrogen washout, this is based on the inhalation of a known concentration and volume of an inert tracer gas, such as helium, followed by equilibration of 7-10 min in the closed circuit with the helium dilution technique. The final exhaled helium concentration is diluted in proportion to the unknown volume of the air in the patients chest, the residual volume. If the patient is connected at the end tidal position of the spirometer this measures the FRC. The limitation of this technique is that it does not measure air in non-communicating bullae and can therefore underestimate the total lung capacity. In the nitrogen–washout technique the patient breathes 100% Oxygen and all the nitrogen in the lungs is washed out. The exhaled volume and the nitrogen concentration in that volume are measured. The difference in nitrogen volume at the initial concentration and at the final exhaled concentration allows a calculation of intrathoracic volumes, the FRC

Body plethysmography (gold standard)

Using boyles law, this method is an alternative method of measuring lung volume. The volume of gas at a constant temperature varies inversely with the pressure applied to it. Body plethysmography can measure the total volume of air in the chest including gas trapped in bullae. It's a quick test but the patient has to sit in a small enclosed space. The body box has a known volume, the patient sits in the box and pants with an open glottis against a closed shutter from FRC to produce changes in the box pressure. This is proportionate to the volume of air in the chest. The volume measured is referred to as the thoracic gas volume and represents the lung volume at which the shutter was closed – the FRC



The FRC is measured first, thereafter the IC, ERV and VC will follow. From these values the TLC and RV can be calculated.

Measurement of diffusing capacity (DLCO) (also called "Transfer Factor")

This test is designed to measure the properties of the alveolar-capillary membrane – the so-called diffusing capacity.
As haemoglobin has a strong affinity for carbon monoxide (CO) (200 times greater than for O_2), and there is such a large red cell mass available to absorb CO, the partial pressure of CO in the alveolar capillary stays low and diffusion occurs throughout the passage of blood through the alveolus (usually about 0.75s), with the partial pressures never equilibrating. This makes it an excellent gas to use to measure diffusing capacity, as its uptake is limited by **diffusion** alone. During the test, a known concentration of CO is inhaled; the breath is held for 10 seconds, and then the CO concentration in the expired air is measured. The uptake of CO is then calculated.
Limitations: expensive equipment; must have vital capacity >1500ml to be able to perform test. Any condition that impairs diffusion will decrease DLCO, however, any condition that increases pulmonary blood flow (and thus increases the amount of red blood cells available to bind CO) will increase DLCO. These conditions include left-to-right cardiac shunts, exercise, pulmonary haemorrhage and asthma.

Measurement of respiratory muscle strength (MIPs and MEPs)

Respiratory muscle weakness leads to hypercapnea and a reduced vital capacity due to hypoventilation. Unfortunately these are insensitive indicators, because they only become abnormal when muscle strength has fallen below 30-50% of normal. Other non-specific markers of muscle strength are maximum expiratory pressures (MEP) and maximal inspiratory pressures (MIP). Maximum mouth pressures are simple measurements that record pressures during maximal inspiratory or expiratory efforts against a closed airway (pressure gauge). All these tests require patient cooperation. Normal values vary considerably and are influenced by gender and age. References are as follows:
MIPs – 120cmH20
MEPs – 120cmH20
Disorders that weaken the muscles, such as muscular dystrophy and amyotrophic lateral sclerosis result in low pressures during inhalation and exhalation. Patients with low values have difficulty generating sufficient cough to clear secretions.

Exercise Testing (not in the scope of this lecture)

Spirometry, lung volumes and diffusing capacity tests remain the standards of evaluating subjects with dyspnea but they don't provide an explanation of the patient's symptoms or correlate with the level of impairment. Exercise testing should be implemented to distinguish between cardiovascular and pulmonary limitations to work. It also helps to assess perioperative risk in thoracic and abdominal surgery.

Perioperative risk

Numerous studies have reported on the pre-operative risk assessment of patients undergoing lung resection, and spirometry is indicated in such clinical scenarios in order to estimate postoperative FEV_1 and assess the functional outcomes of pulmonary resection.
Patients undergoing high-risk procedures such as abdominal, aortic or non-resective thoracic surgery, preoperative pulmonary function tests have a limited role. Some investigators have suggested that clinicians could identify patients who are at high-risk using clinical criteria and that the results of spirometry are unlikely to modify the clinical risk estimate.

Conclusion

Pulmonary function testing remains the cornerstone of diagnosis, assessment and monitoring of any patient with lung disease. It is also of great value in the peri-operative setting in patient's with COPD, asthma and interstitial lung disease. Spirometry is the most readily available test used and therefore important to understand and correctly interpret. It should always be evaluated in conjunction with other tools of functional reserve and never be used in isolation.

Abbreviations

TLC	Total lung capacity
VC	Vital capacity
RV	Residual volume
FRC	Functional residual capacity

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The intra-aortic balloon pump

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Intra-aortic balloon pump counter-pulsation is one of the therapies frequently used for the support of a compromised left ventricle. The principles were developed in the 1950s and have remained largely unchanged in the subsequent sixty years.

The device is placed in the descending aorta, using a Seldinger technique, just distal to the left subclavian artery and its pulsation is timed as follows:

- Inflation in diastole, immediately after aortic valve closure
- Deflation in systole, immediately prior to left ventricular ejection

The effects of the balloon are to increase aortic root pressure, and hence coronary perfusion pressure during diastole, and to reduce left ventricular afterload during systole. The net effects are an increase in coronary perfusion and a reduction in left ventricular stroke work.

Generally accepted **indications** for its use include:

- Unstable angina
- Acute left ventricular failure, usually with an EF of less than 30%
- Acute mitral regurgitation

Its use may also be considered in:

- High risk patients undergoing percutaneous translumimal coronary angioplasty (PTCA)
- Patients at high risk of cardiac decompensation undergoing non-cardiac surgery
- Ventricular arrhythmias refractory to conventional treatment

The use of a balloon pump is **contraindicated** in:

- Aortic regurgitation
- Aortic dissection
- Severe aorto-iliac disease
- Prosthetic aortic grafts

The drive unit for the intra-aortic balloon pump is exterior to the patient and can detect the timing of the cardiac cycle through a variety of means. These include:

- Central aortic pressure wave (measured from the tip of the balloon catheter)
- The ECG
- A peripheral arterial line tracing

Balloon catheters usually have a displacement volume of between 30 and 40 ml. The balloon is repetitively inflated and deflated with helium. The low density of helium facilitates the rapid movement of gas from the drive unit into the balloon.

The physiologic effect of the IABP on coronary blood flow

It has already been stated that the prime goals of the IABP are to improve coronary perfusion and to reduce myocardial oxygen consumption through a reduction in stroke work. Figure 1 introduces the concept of the Systolic Tension Time Index (STTI) and the Diastolic Pressure Time Index (DPTI). Inspection of the graphic reveals the effect of the IABP on the augmented beat. The DPTI is increased (increased coronary perfusion) and the STTI is reduced on the beat following augmentation (a reduction in myocardial oxygen consumption).

The balance of oxygen supply and demand DPTI/STTI has been described as the myocardial viability index.

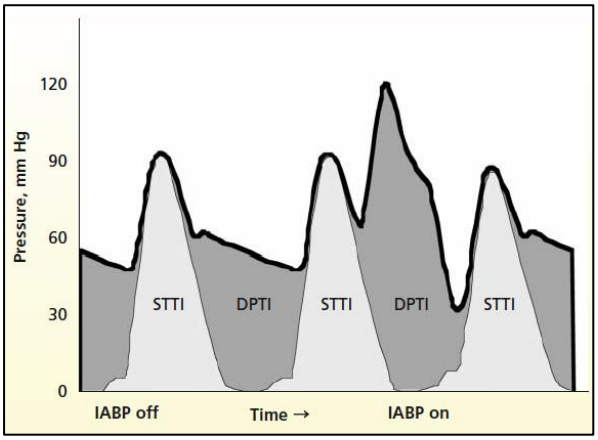


Figure 1.
The effect of the IABP on myocardial oxygen supply/demand balance

Timing of the balloon pump

The operation of the catheter is based on the fact that the interval between electrical and mechanical cardiac events varies with heart rate, both from patient to patient and in any given patient. In any particular patient the systolic time interval at a specific heart rate can be used fairly accurately to predict the systolic time interval at other heart rates. Aortic balloon pump drive units are preprogrammed with a variety of systolic time interval (STI)/ heart rate curves. These curves are used to adjust the balloon timing automatically as heart rate varies.

During the set-up of the catheter the operator sets, by estimation, the interval from the QRS complex to aortic valve opening and closure. The drive unit then selects a STI/heart rate curve that best fits the individual patient. This is subsequently used to calculate automatic balloon-timing parameters.

The ideal timing of the intra-aortic balloon pump (IABP) can be seen in figure 2, below.

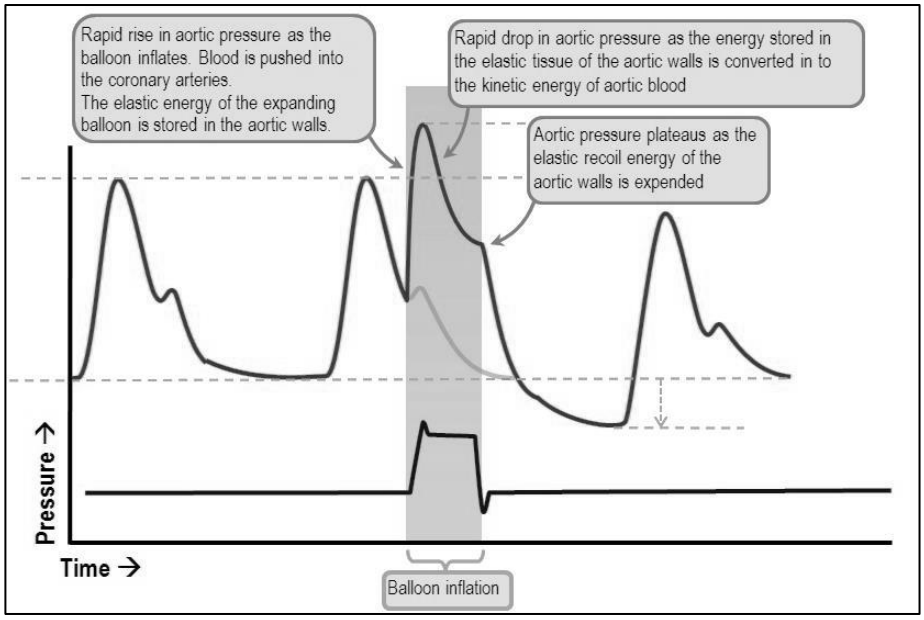


Figure 2.
The correct timing of the intra-aortic balloon pump

In the upper panel the aortic pressure waveform is visible, while the lower panel illustrates the inflation of the balloon. The time scale has been deliberately prolonged to illustrate the inflation and deflation of the balloon.

Note that balloon inflation is timed to occur immediately after closure of the aortic valve – right on the dicrotic notch! Balloon deflation is timed to occur immediately prior to ventricular ejection. Setting the pump to augment every 2nd beat of the heart, as in this diagram, allows for immediate comparison of augmented and non-augmented beats.

It is important to note that the augmented systolic pressure is higher than the normal systolic peak pressure and that the augmented diastolic pressure is lower than normal. These are the pressures that drive coronary flow and off-load the left ventricle respectively. Both of these are normal features of balloon counter-pulsation that should be confirmed on the monitor waveform.

ECG timing of balloon inflation and deflation

The ECG may be used to trigger the IABP. The drive unit monitors both QRS and T wave to ensure optimal timing. Note: the midpoint of the T wave triggers inflation, while the peak of the R wave triggers balloon deflation. This is demonstrated in figure 3, below.

While both ECG and arterial pressure may be used effectively to trigger both balloon inflation and deflation, the clinician should confirm appropriate balloon timing by inspecting the pressure/time waveform of either the peripheral arterial line, or preferentially the central aortic pressure. Again, the IABP should be set to a 1:2 or 1:3 ratio to facilitate the inspection of the pressure trace.

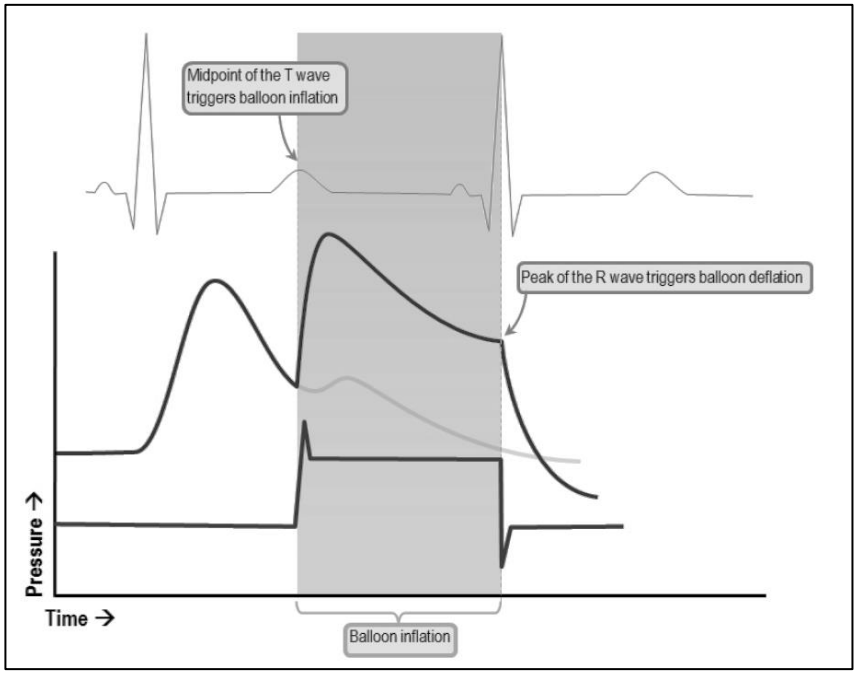


Figure 3.
The use of ECG pattern to trigger the IABP

Abnormal IABP waveforms

The pressure waveform, as described above, can be used to assess the effectiveness of the support and to troubleshoot timing issues. Poorly synchronized balloon inflation/deflation can lead to sub-optimal support of the left ventricle, and a reduction in coronary perfusion, at the expense of an increase in stroke work.

Early balloon inflation increases afterload

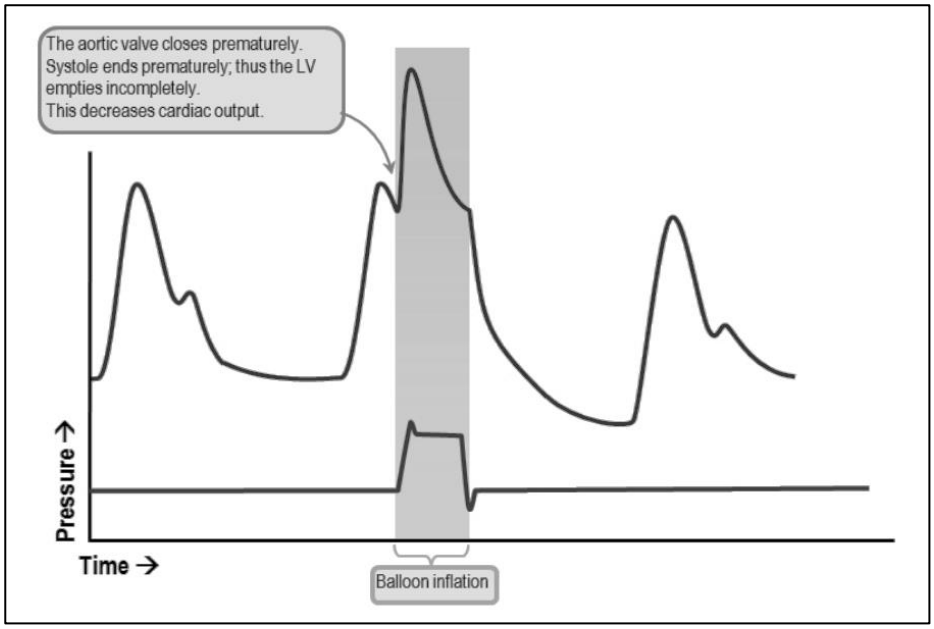


Figure 4.
The effect of early balloon inflation

Early inflation of the IABP leads to an increase in stroke work; the left ventricle is still ejecting as the balloon starts to inflate (figure 4). The left ventricle has to eject against an aorta that is now occluded by an expanding balloon. This leads to early closure of the aortic valve and a decrease in cardiac output. Note that inflation occurs before the dicrotic notch.

Early balloon inflation leads to:

- Increased left ventricular afterload and increased ventricular oxygen demand
- Decreased left ventricular diastolic perfusion and reduced oxygen supply
- Decreased cardiac output secondary to a reduction in stroke volume

Late balloon inflation decreases diastolic augmentation

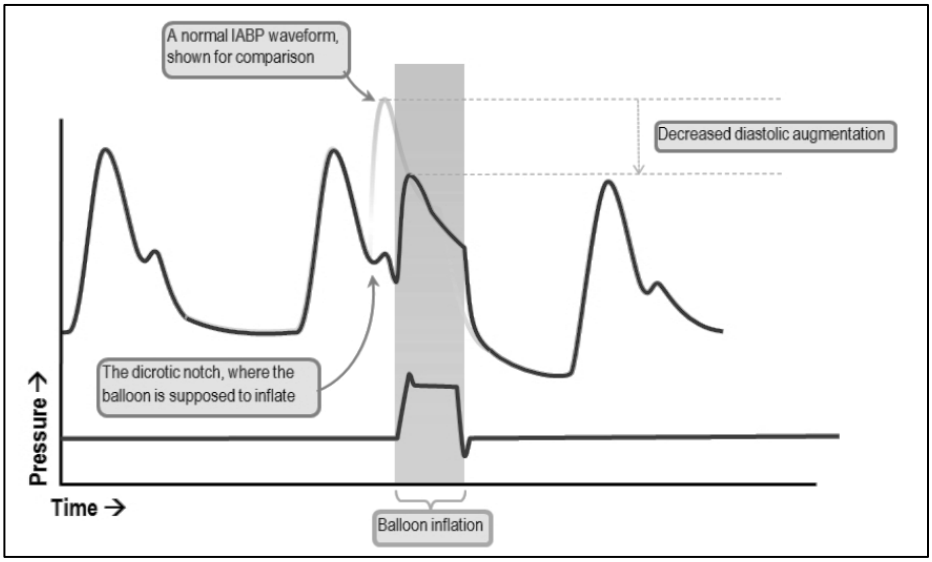


Figure 5.
The effects of delayed balloon inflation on diastolic augmentation

The balloon is usually timed to inflate just as the aortic valve closes – at the dicrotic notch. A delay in inflation misses out on the maximum augmentation of coronary perfusion. The blood that was supposed to be displaced by the balloon has “moved on” in the aorta. The elastic recoil of the aortic walls has already dissipated. This is seen in figure 5.

Delayed balloon inflation leads to:

- Decreased diastolic augmentation of coronary blood flow
- A reduction in coronary perfusion

Early balloon deflation does not decrease myocardial oxygen demand

If the balloon deflates too early, the aortic pressure has time to return to the unassisted pressure resulting in equalization of pressure between the aortic root and the distal aorta. There is subsequently no reduction in the duration of left ventricular isovolaemic contraction. As is seen later, isovolaemic contraction accounts for the majority of myocardial oxygen consumption.

The abnormalities associated with early balloon deflation are illustrated in figure 6. There may still be some diastolic augmentation benefit, but the IABP no longer assists with opening the aortic valve and so there is no reduction in afterload.

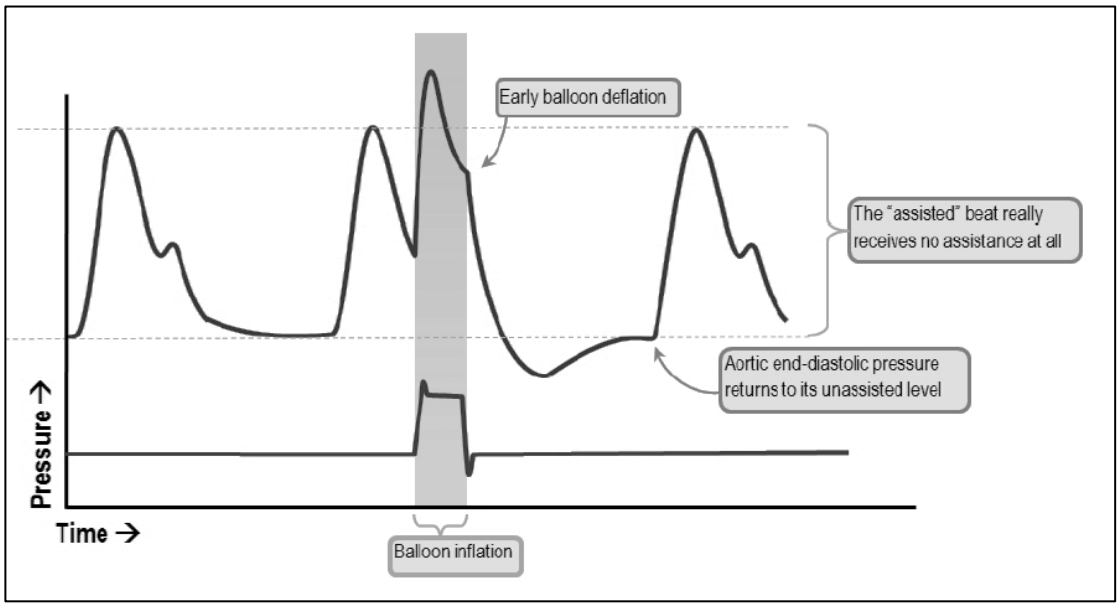


Figure 6.
The waveform of early balloon deflation

Late balloon deflation increases afterload

Late balloon deflation leads to an increase in aortic end-diastolic pressure immediately prior to ventricular ejection. The characteristically low diastolic augmentation is lost. The increase in aortic end-diastolic pressure is immediately noticeable in figure 7. The net effect of this abnormality is an increase in afterload and a consequent increase in left ventricular oxygen consumption.

During isovolaemic contraction the ventricle will be contracting against a closed aortic valve backed by an abnormally high end-diastolic pressure. Remember that isovolaemic contraction is ordinarily where more than 90% of oxygen consumption occurs.

Late deflation may be related to kinking of the drive tubing and obstruction to the flow of helium.

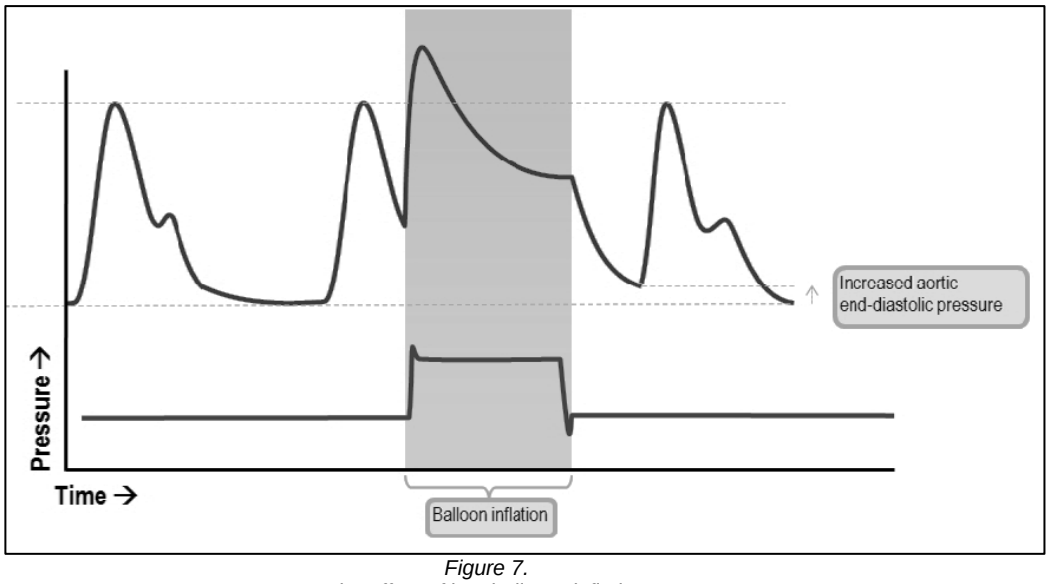


Figure 7.
The effect of late balloon deflation

Poor diastolic augmentation despite appropriate timing

It may happen that diastolic augmentation is not as good as may be hoped, despite setting the balloon timing dilligently. This is demonstrated in figure 8. Note that the diastolic augmentation peak is not as high as the ejection systolic peak. Although coronary filling will be better than normal, this is not ideal.

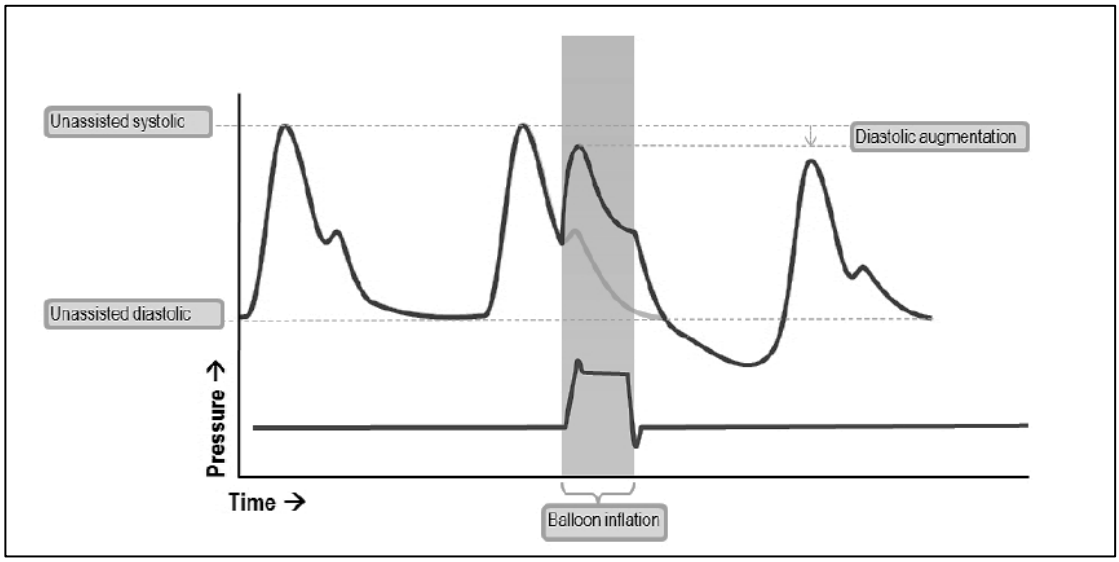


Figure 8.
Poor diastolic augmentation

Possible reasons for poor diastolic augmentation include:

- A low stroke volume and poor cardiac output
- Abnormally low systemic vascular resistance
- The balloon is too small for the patient
- The balloon is malpositioned (either too high, or too low)
- The helium pressure has dropped
- The balloon has not been fully deployed from its sheath
- The balloon has not unwrapped fully

Summary

For the purposes of the exam the candidate should be able to interpret the arterial pressure trace of a patient with an IABP in situ. Of particular importance are the identification of suboptimal balloon timing and the awareness of the implications of this. Strategies to improve the balloon timing need to be identified.

Further reading

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Notes

Enhanced recovery after surgery

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Definition
Evidence based interventions to allow early recovery

My plan for this lecture is to provide an **overview** of the topic without attempting an in depth discussion of each component. This set of notes will bring to focus the anaesthetist's potential role in promoting enhanced recovery.

Components of an ERAS programme:
A *system* reliant on evidence based interventions, assessed by measuring outcome and improving compliance and outcome through feedback loops.
It is a team approach incorporating surgeons, anaesthetists, nurses, hospital administrators and funders.

Recovery is a difficult concept to address particularly as different role players have different outcomes in mind. From an anaesthetic perspective, timely discharge from a recovery room may be a goal, whilst a surgeon would consider fewer complications eg. anastamotic leaks as important whilst a funder might be interested in a shorter length of hospital stay. Ultimately, to a patient, recovery signifies a return to normal functioning.

Table 1. Surrogate markers of outcome

Early recovery = Discharge from Recovery Room **Intermediate outcome** = Days in hospital **Late outcome** = Return to baseline function

Table 2. The Anaesthetist's role in an ESRA programme

Pre-operative
- Pre-operative assessment clinics
- Cardio-pulmonary exercise testing
- Pre-habilitation
- Starvation

Intra-operative
- Goal directed fluid therapy
  - -Monitors
  - -Fluids
- Analgesia
- Avoid hypothermia
- Anti-emesis
- DVT prophylaxis

Post-operative
- Managing
  - pain
  - N+V
  - DVT/early mobilization

Our role in the early recovery of patients is aimed primarily at decreasing the stress response.

Pre-operative interventions

Pre-operative assessment clinics:
These have been set up in many countries to risk stratify patients coming for surgery. Despite being labour intensive, they have the advantage of appropriately addressing co-morbidities prior to surgery by allowing timely multidisciplinary discussion of complex issues.

Cardio-pulmonary exercise testing can be utilized to determine:

1. anaerobic threshold as a tool to risk stratify patients – do we think this patient will 'get through' the intended surgery or should we consider alternatives eg. neoadjuvant radio/chemo therapy?
2. effect of
    a. pre-habilitation - endurance and strength training to improve cardio-respiratory capacity
    b. neoadjuvant therapy on cardiopulmonary reserve

Starvation
Avoid unnecessarily long starvation periods (not more than 8 hours)
Provide clear fluids up to 2 hours pre-surgery.
Provide a carbohydrate rich fluid to reduce insulin resistance

Intra-operative interventions

Antibiotic prophylaxis – single dose

Avoid hypothermia to decrease surgical site infection, coagulopathy, stress response and associated cardiac morbidity
Avoid T^{O} below $36^{O}C$ – measure oesophageal T^{O}
Use forced-air warmers

Goal directed fluid therapy

Current trend sees fluid administration based on context sensitivity ie. administering the correct fluid, in the correct amount for the correct indication. For the GIT surgeon too little leads to gut ischaemia with delayed function, bacterial translocation and ultimately sepsis, but more commonly, too much leads to delayed gut function, anastomotic leaks and associated cardio-pulmonary complications. On the other hand, a renal transplant or neuro- surgeon may be more interested in the type of fluid and an adequate perfusion pressure rather than 'too much or too little'. The recognition that 'just the right amount' is what's important has led the way towards a 'zero-balance' target.

GDFT is based on noninvasive cardiac output monitors to target fluid administration to specific empirically derived numerical values of stroke volume or pulse pressure variation.

What's the evidence?
Many trials and meta-analysis have shown the benefit of GDFT over 'standard treatment'. The problem with standard treatment is that it is not standard with no standard definition of what liberal or restrictive volumes are. Standard practice was different 10 years ago thus making already heterogeneous trials difficult to lump together in meta-analyses.

GDFT appears also only to make more of a difference outside an ERAS programme - if you are doing many things well than the effect of a single intervention is likely to make a smaller contribution to the overall effect.

In terms of absolute volumes given intra-operatively, GDFT tends to give +/- 200ml more colloid and +/- 500ml less crystalloid.

If done correctly GDFT does not appear to cause harm.

Useful definitions
Restrictive = <1.75 l/d
Zero-balance = 1.75-2.75 l/d
Liberal = >2.75 l/d
Sensible suggestion:
In higher risk patients or patients undergoing major surgery GDFT is more likely to be beneficial particularly if significant blood loss is expected particularly if performed outside an ERAS programme.

Aim for zero balance - avoid a weight gain of more than 2.5kg
Fluid responsiveness does not imply fluid is needed - clear stopping thresholds are needed to avoid unnecessary administration.

Monitors used in GDFT:

Oesphageal Doppler
The device (eg Cardio Q) measures velocity of descending aortic blood flow
Stroke volume variation is then calculated based on aortic cross sectional area using nomograms (weight, height and gender)
Limitations: needs sedated, non-moving, ventilated patient

Arterial waveform analysis
Estimate stroke volume using an arterial waveform and mathematical algorithms
Calibrated device – PiCCO (thermodilution), LiDCO^{+} (lithium)
Uncalibrated device – LiDCOrapid, Vigileo with FloTrac sensor
Calculates stroke volume and pulse pressure variation with each heartbeat over a respiratory cycle
Limitations: inaccurate with arrhythmias and aortic regurgitation

Other devices incorporate the use of bioimpedence, photoplethysmography and venous and tissue oxygen saturation

Other Limitations:
Stroke volume derived parameters are based on tidal volumes of 8-10ml/kg. These values are not necessarily applicable to the non-ventilated, non-paralysed patient.

Analgesia

The buzzphrase is *multimodal strategy*. Use of agents with separate mechanisms of action to minimize opioid side effects.

Specific therapeutics

Epidural analgesia

Advantages:

Attenuation of stress response: (limits sympathetic and pituitary activation, hyperglycaemia and protein breakdown)
Improved pulmonary function
Improved gut function
Fewer thromboembolic events
Less blood loss
Some evidence to suggest less myocardial infarction, renal failure and mortality

Disadvantages:

Significant failure rate
- Wrong site: lumbar and not thoracic
- Catheter migration
- Inadequate dose

Hypotension leading to excess fluid administration
Poor mobility: motor and or sensory block and hypotension
Neurologic injury: haematoma, wrong drug injection, direct trauma
Dural puncture
Urinary retention
Resource intensive

Therefore the need to weigh up the risks vs benefits for the individual patient and the type of surgery is paramount.

Because of resource constrains and complication rates, many centres rely on alternative techniques of local anaesthetic administration with good published results. These include paravertebral blocks, abdominal wall blocks (transversus abdominis plane, rectus sheath), and wound infiltration catheters.

Systemic drugs

Paracetamol – IV better kinetics than oral. Rectal unpredictable.
NSAIDS – short term for most patients to decrease opiate requirement. Be vigilant with non-specific COX inhibitors in the elderly, renal impairment, ischaemic heart disease and bleeding risk. Unknown validity of anastomotic leaks associated with NSAIDS.
COX-2 specific may impair bone healing but no clear evidence in humans.

NMDA – R antagonists
Ketamine – 0.5mg/kg IV prior skin incision + infusion 2mcg/kg/min
Magnesium – no consistent decrease in postop pain or opioid requirement

GABA analogues
Gabapentin 600-1200mg or pregabalin 150-300mg 1 hour before surgery

Intravenous lignocaine
1.5-2mg/kg IV prior to skin incision
Reduces opioid requirement, decreases PONV and ileus
Balance against the risk of toxicity

Intra-op analgesia for specific surgery:

Colorectal:
Thoracic epidural (T9/10) for max 48hours (bupivacaine 0.15% with 2mcg/ml fentanyl)
If no epidural then: TAP blocks
Paracetamol and NSAIDS (if no C/I)
Ketamine

Hepatobilary (liver resection):
Pregabalin/gabapentin pre-operatively
Thoracic epidural is the gold standard but concerns regarding epidural haematoma are a consideration in particular with extensive bleeding in a large resection. Haemodynamics may be a challenge, but can effectively keep CVP low and hence limit blood loss.
If no epidural placed, an attractive alternative is spinal morphine or subcostal TAP blocks.
Paracetamol – generally levels are not clinically significant to warrant omission.
Consider NSAIDS, but be cautious of renal impairment particularly where bleeding risk and hypotension are high.

Oesophagectomy:
Thoracic epidural still remains the gold standard in open oesophagectomy however a paravertebral block with catheter provides equivalent analgesia for thoracotomy, with fewer pulmonary complications and side effects.
Some evidence that intravenous magnesium and ketamine may reduce chronic pain.

Major Gynaecological:
Epidural anaesthesia – initially with LA only and then add epidural morphine if pain not managed adequately
No clear long term survival benefit with epidural anaesthesia
Spinal morphine 100-200mcg provides better analgesia than GA and systemic opioids
Pre-incision biltateral TAP blocks for open surgery decrease opioid requirement
LA infiltration with wound catheters: subcutaneous better than intraperitoneal placement. No effect if placed under muscle layer.
Pregabalin 600-1200mg or gabapentin 100-300mg preop stat dose to decrease opioid requirement + PONV
Use NSAIDS - reduce opioid usage. Ketorolac found not to increase bleeding
IV paracetamol

Major Urological:
Radical prostatectomy: pre-operative pregabalin; thoracic epidural. If no epidural then intrathecal morphine, IV paracetamol, NSAIDS, ketamine

Orthopaedics:
There is less clear evidence for epidurals for lower limb arthroplasties as the risk of epidural haematomas is real in the setting of post op pharmacological anticoagulation and with the equivalent analgesia offered through a multimodal approach.

Total Hip Replacement
Combination of the following: Pre-op gabapentin and dexamethasone; ketamine, spinal morphine, IV paracetamol, extended release oxycodone, tramadol, COX-2 inhibitors, fascia-iliaca block. Lumbar plexus block can be effective but carries significant risks.

Total Knee Replacement
Combination of the following: preop pregabalin; intrathecal morphine, NSAIDS, IV paracetamol, ketamine, periarticular injection, peripheral nerve blocks (femoral, adductor canal, fascia iliaca)

In conclusion:

The success of an ERAS programme is highly dependent on the implementation of as many evidence-based "bundles". Through meticulous data collection and its subsequent analysis it becomes possible to provide appropriate system interventions to complete a feedback loop of enhanced recovery. It is our responsibility as anaesthetists to be up to date with the latest evidence but to remember that individuals need individual care (context sensitive) in a protocol driven system.

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Aspects of spinal surgery

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Patients presenting for spinal surgery comprise a diverse group. They may share similar issues such as risk of neurological injury and need for special positioning but their management needs will vary depending on their co-morbidity, operative site, pathology and planned procedure.

The prone position [1]

This position is widely employed in spinal surgery and has both predictable physiological changes and complications.

Summary of cardio-respiratory changes from Edgcombe et al [1]

Cardiovascular

- ↓ CI
  - ↓ VR
  - Direct effects on arterial filling
  - ↓ LV compliance 2° to ↑ intrathoracic pressure
- IVC compression
  - ↓ CO
  - ↑ blood loss
  - Venous stasis → thrombotic complications
- ↑ sympathetic response to change in position

Respiratory

- Lung volumes
  - ↑ in FRC
  - FEV1 and FVC relatively unchanged
- Distribution of blood flow
  - Lung perfusion more uniformly distributed in prone position
- Distribution of ventilation
  - More even vertical distribution of ventilation in prone position

Suggested that pulmonary vascular and bronchiolar architecture may be more important than gravity in the prone position in determining ventilation and perfusion distribution

Complications associated with the prone position

CNS

- Occlusion of vertebral and carotid arteries
    - Avoid excessive extension or rotation of the neck when turning
- Venous occlusion.
- Air entrainment. Possible pneumocephalus
- Cervical spine injury. Avoid excessive neck flexion / extension

PNS

Peripheral nerve injuries may occur in any position and are thought to be the end result of nerve ischaemia from undue stretching or direct pressure. In patients at risk

- Diabetes
- Peripheral vascular disease
- Alcohol dependency
- Pre-existing neuropathy
- Anatomical variants
- Previous post-operative neurological problems

It may be prudent to assess them in the proposed operative position while awake.

The recommendation is that arms should be next to the side rather than abducted.

Pressure injuries

May be direct or indirect (when injury occurs as a result of pressure on, or occlusion of, vascular supply).

- Direct
    - Pressure necrosis of skin. Face, breasts, ears, genitalia, iliac crests
    - Contact dermatitis
    - Tracheal compression. Only reported in patients with underlying anatomical abnormalities
    - Salivary gland swelling. Postulated to result from stretching of salivary ducts, leading to stasis and acute swelling
    - Shoulder dislocation. Distribution of pressure may lead to anterior dislocation of the shoulder.

- Indirect
    - Macroglossia and oropharyngeal swelling. Thought to be caused by excessive flexion of the neck, obstructing the internal jugular vein which in turn obstructs the lingual and pharyngeal veins.
    - Mediastinal compression. Possible in patients with chest wall abnormalities.
    - Visceral ischaemia. Hepatic ischaemia and pancreatitis have been described.
    - Avascular necrosis of femoral head. Described in patients with osteoarthritis of the hip in the prone position subjected to a hypotensive anaesthetic technique
    - Peripheral vessel occlusion
    - Limb compartment syndromes and rhabdomyolysis

Embolic complications

- Venous gas embolism. Efforts to minimise abdominal compression and thus IVC pressure in the prone position can result in an increased negative pressure gradient between the right atrium and veins at the operative site. It is important to maintain intravascular volume to minimise the risk.
- Non-gaseous embolism. A few reports exist of fat, cement and bone fragment emboli.

Perioperative visual loss [2]

Perioperative visual loss (POVL) is a catastrophic complication for patients and healthcare providers because the common causes of POVL have no proven treatment and are associated with poor outcome.

Epidemiology

The major causes of POVL include:

- Anterior ischemic optic neuropathy (AION)
- Posterior ischemic optic neuropathy (PION)
- Central retinal artery occlusion (CRAO) / retinal vascular occlusion (RVO)
- Cortical blindness

AION	Cardiac bypass, major vascular surgery, spine surgery
PION	Assoc with ↑ venous pressures in head eg prone spine surgery, H and N surgery
CRAO / RVO	Injection of large emboli near facial vessels or prone operations
Cortical blindness	Cardiac bypass, profound hypotension

In a 10 year study from 1996-2005 Shen et al demonstrated an incidence in the USA of POVL of 8.64/10000 in cardiac surgery and 3.09/10000 in spinal fusion surgeries. [3] In this study factors that were independently and significantly associated with the development of ION after prone spinal surgery were:

- Male sex
- Obesity
- Use of Wilson frame
- Longer operative duration
- Greater estimated blood loss
- Lower percentage of colloid used in the non-blood replacement.

Other than the male sex factor listed above, these factors could be explained by the current pathophysiological mechanism that suggests that elevated venous pressure in the head damages the optic nerve via direct mechanical compression, venous infarction or compression of the thread-like pial vessels that feed the optic nerve.

Obesity is usually associated with increased abdominal girth, which elevates the central venous pressure in the prone position as well as reducing venous return and cardiac output. The Wilson frame places the patient's head significantly lower than the heart leading to increased venous pressure in the head. Greater estimated blood loss leads to inflammation, capillary leak, and lower oncotic pressure, which favours interstitial oedema formation. Using less colloid in fluid replacement will also result in lower oncotic pressure and favour interstitial oedema formation. The longer the surgery, the longer the more unfavourable pathophysiological conditions exist, the worse the injury. It must however be stressed that this is unproven theory. Furthermore other undetectable or unknown patient factors such as anatomy, auto-regulatory capacity of the optic nerve vasculature, or other genetic vulnerabilities may contribute to this complication. [2]

Low haematocrit and extended periods of low blood pressure have also been implicated as causative factors but did not achieve statistical significance in the multivariate analysis in this study. However it would be prudent to avoid extremes of physiologic disturbances.

Table 1 American Society of Anesthesiologists perioperative visual loss practice advisory consensus conclusions

There is a subset of patients who undergo spine procedures while they are positioned prone and receiving general anesthesia that has an increased risk for the development of POVL. This "high-risk" subset includes patients who are anticipated preoperatively to undergo procedures that are prolonged, have substantial blood loss, or both
Consider continuous blood pressure and central venous pressure monitoring in high-risk patients
Consider informing high-risk patients that there is a small, unpredictable risk of POVL
The use of deliberate hypotensive techniques during spine surgery has not been shown to be associated with the development of POVL
Colloids should be used along with crystalloids to maintain intravascular volume in patients who have substantial blood loss
At this time, there is no apparent transfusion threshold that would eliminate the risk of POVL related to anemia
High-risk patients should be positioned so that their heads are level with or higher than the heart, when possible. In addition, their heads should be maintained in a neutral forward position (without significant neck flexion, extension, lateral flexion, or rotation) when possible
Consideration should be given to the use of staged spine procedures in high-risk patients

From Nickels T et al. WJO 2014;5(2):100-106 [4]

There have been a few case reports of POVL in robotic and laparoscopic surgery where patients have been positioned in the head down position for prolonged periods of time resulting in facial oedema and presumably elevated intraocular pressures. Efforts aimed at reducing venous congestion and interstitial oedema formation in these patients would seem prudent.

Finally for completeness sake it is necessary to mention Posterior Reversible Encephalopathy syndrome (PRES) which is a constellation of neurological signs including seizures, visual changes, decreased level of consciousness, headaches, nausea and vomiting, brainstem symptoms, and hemiplegia. These occur in the setting of acute medical illness with hypertensive episodes, autoimmune disease, malignancy, immunosuppressant therapy, chemotherapy, infection, acute and chronic renal disease, vasculitis, preeclampsia, eclampsia and a number of other miscellaneous diseases. Unlike ION and CRAO, PRES has a good recovery for POVL if management is instituted expeditiously. [2]

Spinal cord monitoring (SCM)

Much of this section is taken from articles by Hetreed [(5)], Raw [(6)], DiCindio [(7)] and Mendiratta[(8)]. Since paraplegia is one of the most feared complications of spinal surgery some form of spinal cord monitoring is recommended and indeed some authorities say is mandatory.

The risk of permanent damage after surgery to correct idiopathic scoliosis is about 1:1000 procedures.

Most neurologic damage is due to ischaemia of the spinal cord caused by instrumental distraction, disruption of arterial blood supply and compression due to haematoma formation. Patients with severe deformity, congenital scoliosis, kyphosis or preoperative abnormal neurology are at increased risk. Any intraoperative compromise of spinal cord function needs to be detected as soon as possible and reversed immediately in order to improve neurological outcome.

SCM may be either clinical or neurophysiological.

6.1. Clinical

a) "Wake up" test.

As mentioned this involves advising the patient that during the operation anaesthesia will be "lightened" and they will be asked to move their hands and then their feet. They are reassured that they will feel no pain, will be re-anaesthetised immediately afterwards and will probably not recall the incident after surgery. The test is performed once the instrumentation has been applied. Anaesthesia is lightened until the patient responds to commands. The patient should not be awakened abruptly as bucking, coughing and sudden movement may result in tubes, lines and monitors being displaced. Sudden deep inspiration by the patient increases the risk of venous air embolism. One needs to be careful of suddenly discontinuing short acting anaesthetic agents. The exception to this is remifentanil as continued infusion will guarantee analgesia and the possible respiratory depression is of no consequence as one can continue to ventilate the patient. Indeed it may guard against sudden deep inspiration. Surgery should only continue once the patient no longer responds to commands.

b) Ankle clonus test.

This developed from the observation that ankle clonus can be elicited in normal people in a light plane of anaesthesia. During arousal this typically occurs before the patient is sufficiently responsive for the wake up test but it is a transient phenomenon which may be missed.

These two techniques have the advantage of requiring no specialized personnel or equipment and will continue to be used where resources are limited. They may also need to be used where electrophysiological monitoring techniques fail or yield equivocal results. However they only provide evidence of cord function at the time of the test. Furthermore the wake up test demonstrates only motor function and may miss a sensory deficit. It cannot be done in the very young, the mentally handicapped or deaf patient.

6.2. Neurophysiological or evoked potentials

a) Sensory evoked potentials (SEP)

Cortical sensory evoked potentials (CSEP) are most commonly used because they mimic SEP obtained in the awake state; they are non-invasive and can be used throughout the procedure. Stimuli are applied to surface electrodes and hence to peripheral nerves from which sensory fibres will pass through the surgical field. Typically the posterior tibial nerve at the ankle or the peroneal nerve at the fibular head (lower extremity) or the ulnar or median nerves at the wrist (upper extremity) are used for stimulation. Evoked potentials are then recorded from surface electrodes applied to the scalp over the relevant sensory cortex or they may be recorded at the level of the brainstem. At the brainstem level they are minimally affected by anaesthetic agents. They are however sensitive to changes in blood pressure and CO_2 tension. Recordings from the cortex are more sensitive to anaesthetic agents particularly inhalational agents.

The most widely used threshold for concern is a 50% reduction in amplitude compared with baseline preoperative records and a 10% increase in latency. However, some institutions are more conservative and others more lenient with regard to these figures. Interpretation of

changes close to the threshold may be difficult and confirmation of normal function by means of a wake-up test may still be indicated.

Spinal SEP are preferred in some institutions because although they require an invasive technique where recordings are made from an electrode inserted into the epidural space by the surgeon, they are more resistant to depressant effects of anaesthetics and physiological changes. Typically stimulation is applied percutaneously to the posterior tibial nerve at each knee and the evoked potentials are recorded from a bipolar electrode inserted into the epidural space in the high thoracic region.

b) Motor evoked potentials

Motor evoked potentials (MEP) are obtained by stimulating rostral to the site of surgery and recording the evoked signal distally. The stimulation is transcranial and the recording may be made from the spinal cord, from peripheral nerves or from a muscle in which a compound muscle action potential (CMAP) is generated.

Responses recorded from the epidural space consist of a direct or D wave representing the direct activation of the corticospinal tract (CST) by the transcranial stimulus. In awake or lightly anaesthetised patients, the D wave is followed by a series of I (indirect) waves generated by cortical synapses. These descending cortical volleys then summate to excite anterior horn cells and spinal alpha motor neurons, thereby inducing a compound muscle action potential. The requirement for electrode placement, either percutaneously or by laminotomy, precludes routine use of this form of MEPs.

Neurogenic descending evoked potentials elicited from epidural electrospinal stimulation and recorded over lower extremity peripheral nerves were previously thought to be mediated within spinal motor tracts and because of their technical simplicity and minimal alteration by anaesthetic agents were popular for a period. It is now recognised that these potentials are mediated through spinal cord pathways that are in common with pathways responsible for SEPs. It is therefore a mixed or pure sensory response.

c) Electromyography

SEPs are neither sensitive nor specific for identifying an injury to spinal nerve roots.

Spontaneous electromyography (spEMG) can be used to monitor for injury or neural trauma to spinal nerve roots. During a surgical procedure, microtrauma to a spinal nerve root will provoke ion depolarization, and the resultant muscle or motor unit potential can be recorded from a muscle innervated by that specific nerve root.

Stimulus evoked electromyography (stEMG) is another EMG technique that can be used to monitor injury during pedicle screw placement. stEMG allows the detection of a pedicle wall violation during and after pedicle screw fixation. An electrical stimulus is applied to the pedicle screw and EMG activity is recorded from the muscles innervated by the nerve root adjacent to the pedicle. If the pedicle wall is fractured, the nerve root will depolarise at a much lower current (≤ 7.0 *mA*) compared with a pedicle, causing muscle contraction that is recorded as an EMG response.

Effect of anaesthetic agents

Volatiles cause a dose dependent increase in latency and decrease in amplitude of somatosensory evoked potentials. The most potent in this regard is isoflurane, followed by enflurane and halothane.

Sevoflurane and desflurane are said to have a similar effect to isoflurane. At therapeutic concentrations the halogenated agents abolish TceMEPs.

The following table summarises the effects of the intravenous agents:

	SSEPs	**TceMEPs**
Opiates	Mild ↓	Mild ↓
Barbiturates	Variable	Profound
Midazolam	Mild	Marked
Ketamine	Enhanced	Enhanced
Etomidate	Enhanced	↓ amplitude
Propofol	Mild ↓	Mild ↓

Neuromuscular blockers have little effect on SEPs, but profound block precludes the recording of CMAPs.

In practice it is prudent to employ a TIVA technique using an opiate infusion together with a propofol infusion. In this regard sufentanil is a very useful agent. There is some controversy about the role of remifentanil in postoperative hyperalgesia and until more is known about this phenomenon, remifentanil should probably not be used as the main intraoperative opiate during corrective spinal surgery. [9, 10]

Non-anaesthetic intraoperative influences on evoked potential monitoring

- Spinal cord blood flow. Mean arterial pressure below the autoregulatory threshold will decrease SSEP amplitude.
- Haematocrit level. Levels below 15% will decrease amplitude and increase latency
- P_aCO_2. A tension less than 20 *mmHg* will also decrease amplitude and increase latency.
- Temperature. Moderate hypothermia will decrease amplitude, increase conduction time and latency, and increase stimulation threshold

Blood conservation strategies [11]

Spinal surgery, particularly corrective spinal surgery, may lead to massive blood loss.

For elective surgery patients histories of abnormal bleeding tendencies, abnormal family histories of haematological abnormalities, and drugs which may affect haemostasis should be elicited early on in the preoperative assessment period. Anaesthetists usually have a good understanding of drugs which may affect coagulation but herbal medicines such as ginko, ginsec and garlic should be considered as well.

Examination should show signs of increased bleeding tendency such as ecchymoses. petichiae and pallor. It is also necessary to look for evidence of organ dysfunction which may influence the trigger for blood transfusion.

Clinical evaluation will dictate which preoperative haematological special investigations will be needed.

Certain patients may benefit preoperatively from iron supplementation and erythropoietin therapy.

- *Preoperative autologous blood donation.* May be considered in patients likely to receive transfusions. The downside here is cost and wasted units.
- *Regional anaesthesia* has been shown to decrease blood loss but may not be practical for all spinal surgery.
- *Positioning.* May be critical in terms of blood loss particularly in the prone position. Pressure on abdominal wall should be avoided to decrease blood flow through collateral vertebral venous plexuses.
- *Ventilation.* Minimising mean intrathoracic pressure during controlled ventilation with minimal use of positive end expiratory pressures and using low tidal volumes will help in reducing blood loss.
- *Controlled hypotensive techniques.* In major cases may be risky unless employing continuous spinal cord monitoring, particularly in severe scoliosis patients where blood supply to the cord may be tenuous at best.
- *Maintenance of normothermia.* This is absolutely key to decreasing risk of transfusion. Even mild hypothermia increases blood loss by approximately 16 % and increases the relative risk of transfusion by approximately 22 %. Monitoring temperature and using warming devices is mandatory. [12]
- *Acute normovolaemic haemodilution* Dilution of circulating blood volume reduces the amount of red blood cells and plasma constituents during surgical bleeding.
- *Surgical technique.* One of the most important factors in reducing intraoperative bleeding is a skilled surgeon. Appropriate vasoconstrictor infiltration by the surgeon. Minimally invasive surgery where appropriate.
- *Cell salvage.* This process involves the collection of shed blood, processing it and reinfusion of autologous red blood cells lost during surgery. The pack infused usually has a haematocrit of 50-60 %. The biggest impediment to this process is the cost of the machine, consumables and technologist to run it. During surgery where one is returning the equivalent of at least 2 red blood cells packs it becomes cost-effective.
- *Antifibrinolytic agents.* The synthetic derivative of lysine, tranexamic acid (TA) is the most commonly used antifibrinolytic. There is much evidence that TA reduces intraoperative bleeding and therefore blood transfusion. [13] The optimum dose remains uncertain. The loading dose varies from 10-20 mg/kg in adults to 100 mg/kg in children and the subsequent infusion dose from 1 mg/kg/hr to 10 mg/kg/hr. The impression is that higher doses are more effective but further large scale studies are needed to confirm this. For the present thromboembolic side effects do not seem to be an issue but further studies in high risk patients and using higher doses are required before drawing firm conclusions.
- *Transfusion of blood components.* Indications for blood transfusion should be on merit depending on the situation and patient. In most patients a restrictive threshold (7-8 g/dL) is warranted rather than a liberal transfusion threshold (> 9 g/dL). [14] Transfusion of other blood products such as platelets, FFP, cryoprecipitate, fibrinogen and other clotting factors should be based appropriately on demonstrated abnormalities in monitored parameters.
- *Coagulation monitoring.* Point of care monitoring during surgery with TEG and Rotem machines is increasingly being used to guide blood product administration in a cost-effective manner

ETT vs LMA in the prone position

There have been a number of studies over the years looking at whether supraglottic airway devices may be used in place of the traditional endotracheal tube. Most of these studies have been descriptive, with only one RCT, the latter a study between the LMA supreme and the LMA ProSeal. Owing to the heterogeneity of the studies it has not been possible to do a meta-analysis yet. [15]

Current evidence suggests that using an LMA with a prone patient may be an acceptable alternative to endotracheal intubation in select patients. Advantages include reduced requirement of extra staff for positioning if the patient is induced in the prone position and consequently reduction in time to incision.

It is recommended that only anaesthetic providers skilled in the use of LMAs should consider using them in the prone position and that a plan must be in place to immediately turn the patient supine if problems are encountered during insertion. In view of the drain tube in the ProSeal and Supreme devices, they may offer advantages over other supraglottic devices.

Furthermore patients should not be obese, should have normal airway anatomy and be at minimal risk of aspiration. This practice should be considered only for short procedures. Further high-quality multicentre RCTs should be conducted before this practice can be widely recommended. [15]

GA versus regional anaesthesia for spinal surgery

There appears to be enough evidence in the literature to support the use of either general or regional anaesthesia for use in 1-2 level lumbar laminectomy or disc surgery. [16] Although there is no evidence to suggest that morbidity, mortality, or long-term complication rates differ between the two techniques, there is some evidence to suggest that spinal anaesthesia may confer a more favourable haemodynamic profile intraoperatively and reduce narcotic requirements. There is also evidence to suggest less blood loss and decreased nausea and vomiting.

Proponents of RA suggest that it may avoid brachial pressure injury and pressure necrosis of the face because of patient self-positioning and avoidance of general anaesthesia. This advantage may however be negated by using heavy sedation intraoperatively.

Suggestions that it may be advantageous in the elderly in terms of reducing dementia by avoiding GA, remain to be validated. [17]

There are a number of absolute and relative contraindications to RA. These include but are not limited to:

- Patient refusal
- Severe or multi-level spinal stenosis
- History of seizures
- History of intracranial hypertension
- Coagulopathy
- Infection at site of needle insertion
- Hypovolaemia
- Near complete-total myelographic block
- Myelographic demonstration of arachnoiditis

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Notes

Anaesthesia for shoulder surgery

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1. Introduction

Surgical procedures of the shoulder joint, whether minimally invasive (arthroscopic) or open are associated with considerable post-operative pain for up to 48 hours and beyond. Regional anaesthesia (RA) techniques, often combined with sedation or general anaesthesia, have become the mainstay of anaesthetic management for shoulder surgery. The most common procedures on the shoulder joint include hemiarthroplasty, total shoulder arthroplasty, arthroscopy, subacromial (SA) decompression, shoulder instability procedures including bankart and laterjet capsule tightening procedures, rotator cuff repair and frozen shoulder manipulations.

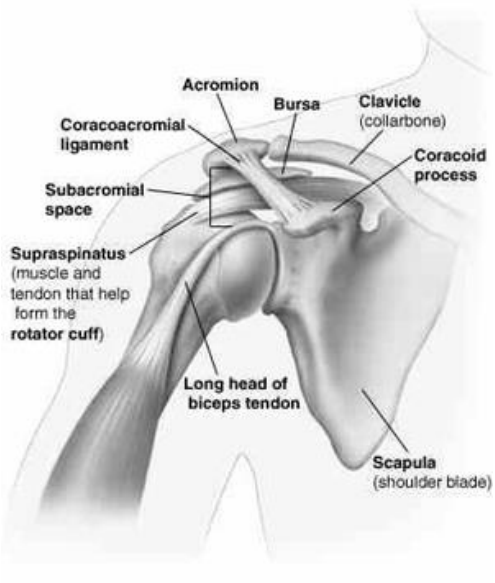
Interscalene brachial plexus blockade (ISB) is the RA technique of choice as it provides excellent and consistent intra and post-operative analgesia with minimal complications in expert hands. The use of RA for shoulder surgery has seen an increase in popularity, especially in ambulatory surgery, where it has shown to have a better profile than other analgesic interventions as regards quality of pain control, earlier discharge from the post-anaesthesia care unit, PONV, improved patient co-operation with rehabilitation and a reduced hospital length of stay.

2. History

In 1884, Halstead was the first to inject cocaine around the exposed roots of the brachial plexus (BP). But it was not until 1911 that Hirschel and Kulenkampff described a percutaneous approach to the supraclavicular BP. The posterior (paravertebral) approach to the BP at the level of the nerve roots was first described by Kappis in 1912 and subsequently reintroduced by Pippa et al in 1990. In 2003, Boezaart modified this approach to avoid the often painful needle passage through the posterior muscles of the neck. First performed in 1919 by Mulley, the anterior approach to the BP was perfected by Winnie in 1970 also using the transverse process of the 6th cervical vertebra as a reference for needle insertion.

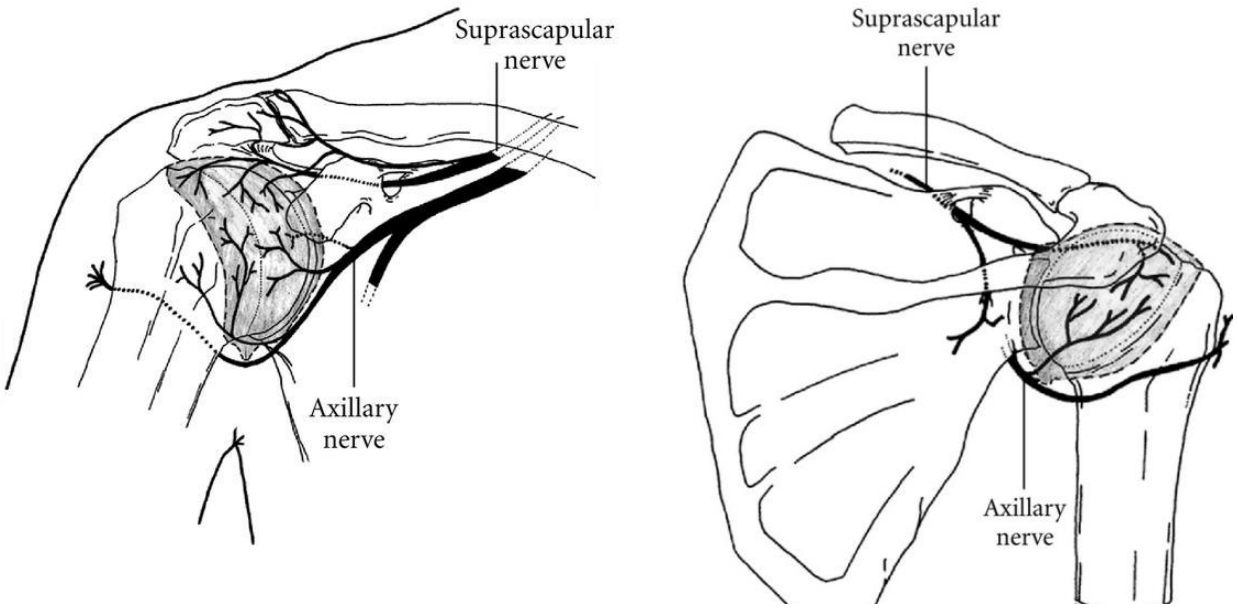
3. Anatomy and innervation of the shoulder joint

The shoulder girdle consists of three main joints: sternoclavicular, acromioclavicular and glenohumeral joints and the often unmentioned scapulothoracic joint. Static shoulder stability is provided by the labrum, capsule and glenohumeral ligament; dynamic stability by the the rotator cuff, the long head of the biceps tendon and the periscapular muscles.



Sensory and motor innervation to the shoulder joint are by the suprascapular (SSN), axillary and supraclavicular nerves that originate from the brachial and cervical plexi. The SSN originates from the C5 and C6 nerve roots of the superior trunk of the BP with variable contribution from C4. It is responsible for 70% of the sensory supply to the shoulder joint, the capsule, SA bursa, coracoclavicular ligament and makes variable contributions to the overlying skin. The axillary nerve originates from the C5 and C6 nerve roots with occasional contribution from C4. It arises from the posterior cord of the BP. The posterior branch of the axillary nerve teminates as the superior lateral cutaneous nerve that supplies the skin over the deltoid muscle; the anterior branch supplies motor innervation to the deltiod muscle. The supraclavicular nerves (anterior, middle and posterior) arise from the cervical plexus (C3 and C4) and supply the skin from the sternoclavicular joint antero-medially to the shoulder postero-laterally. They can be blocked as the emerge from under the posterior aspect of the sternocleidomastoid muscle.

Innervation of the shoulder joint



4. Pre-operative considerations

Due to advances in minimally invasive techniques and an increasing confidence in the use of RA by anaesthetists, the benefits of shoulder surgery have been extended to include patients with considerable co-morbidity and frailty. The spectrum of conditions that require surgery to the shoulder joint varies from simple trauma in relatively healthy individuals to shoulder arthroplasty in patients with rheumatoid arthritis that are often on a host of disease modifying and other drugs that may have significant anaesthetic implications. In these patients, a detailed assessment of organ reserve, in particular cardio-respiratory and renal function, should be investigated and optimisation effected as for any other surgical procedure. Severely affected patients may present challenges with IV or intra-arterial cannula placement as well as the performance of a RA block and positioning for surgery. The airway should be examined carefully for potential difficulties that may affect ease of mask ventilation, placement of a supraglottic device or performance of laryngoscopy (e.g. RA affecting cervical spine and TM joints, obesity).

Unless undergoing minor diagnostic arthroscopic procedures or manipulations under anaesthesia, all patients should be offered an anaesthetic that includes a BP block either as a sole anaesthetic or in combination with sedation or general anaesthesia. The risks and relative benefits of RA and other forms of anaesthesia should be clearly explained so that patients are able to make an informed choice regarding their anaesthetic care.

5. Anaesthetic options

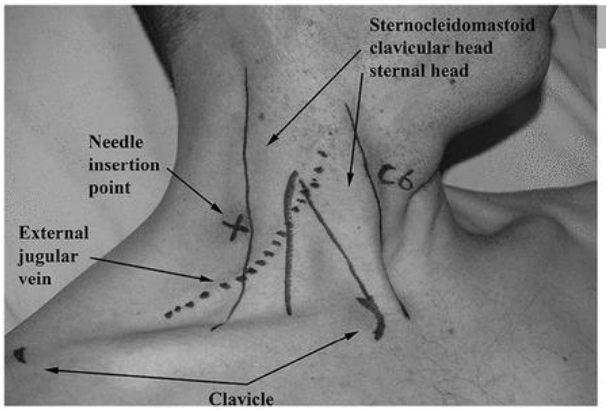
Patients may undergo shoulder surgery under GA alone, RA with or without sedation or a combination of RA and GA. The latter is the most common approach to shoulder surgery although RA with or without a degree of sedation is becoming more popular. RA only anaesthesia is associated with greater patient satisfaction, superior analgesia, less PONV, less cognitive dysfunction and earlier discharge from hospital. In awake shoulder surgery, patient selection is crucial with preparation starting long before the day of surgery. Obstacles to overcome include patient perceptions of RA to practical issues such as proximity of the patient's face to the surgical site (claustrophobia). Patients who are unable to communicate freely, sit still for prolonged periods, have multiple co-morbidities or potential airway problems are not suitable candidates RA only surgery.

It has been stated that an advantage of GA over RA for shoulder surgery is that any anaesthetic approach that incorporates RA takes longer and reduces efficiency. Good communication between anaesthesia, surgeon and nursing staff and a well organised regional anaesthesia team has been shown to reduce turnover time and improve efficiency.

- **Interscalene block (ISB)**

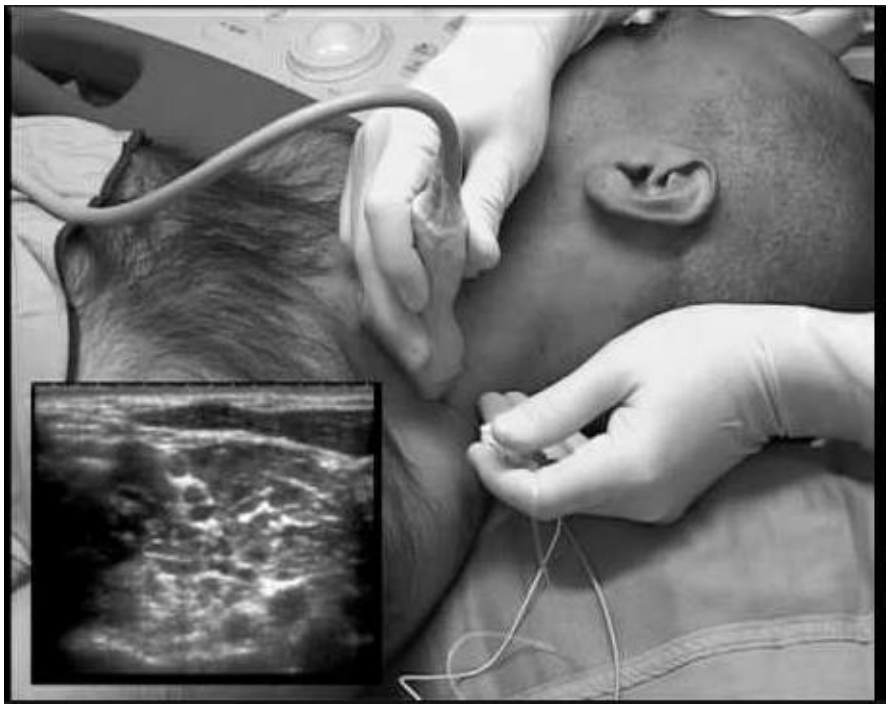
The ISB is considered the gold standard RA technique for shoulder procedures. ISB can be used for procedures involving the shoulder, including the lateral two thirds of the clavicle, proximal humerus and shoulder joint and is widely used both as the primary anaesthetic and as an adjuvant in post-operative pain management. Ulnar sparing (C8) is often seen with this block which limits its usefulness for more distal procedures. The ISB can be performed as a single injection or as a continuous nerve block with the placement of a perineural catheter. Localisation techniques range from 'blind' (paraesthesia and nerve stimulation) to the use of ultrasound guided (USG) nerve localisation and visualisation of LA deposition around nerves. With the ready availability of nerve stimulators and the evolving ubiquity of US machines, no patient should have to undergo ISB (or any other RA block, for that matter) using paraesthesia localisation techniques.

The classic interscalene approach as described by Winne (anterior approach) is still commonly performed, especially for single-injection blocks. Although Winnie used paraesthesia as an end-point for the block, most practitioners now use either NS or USG techniques.



Surface anatomy. The typical needle entry point (x) for an interscalene nerve block is shown in relation to the sternocleidomastoid muscle and its clavicular and sternal heads (solid lines) as well as the course of the external jugular vein (dotted line) and the ends of the clavicle.

Chan used US to directly visualise the nerve roots of the BP in the interscalene groove at the level of the cricoid. The needle can either be inserted using an in-plane or an out-of plane technique. Although the in-plane technique allows better visualisation of the needle, the out-of plane technique provides a shorter path to target tissues.



The use of US for ISB has been shown to have higher success rates than with NS (99,8% vs 91%) with better sensory and motor blockade than with NS. There is also a reduced number of needle passes with USG as compared with NS. In expert hands, ISB using USG or NS is highly effective with no significant difference in complications related to nerve injury.

Posterior approach to ISB: The cervical paravertebral block (CPB)

Over the past decade, the posterior approach to the BP has regained interest. Advantages of the posterior approach include avoidance of the eternal jugular vein, a greater distance between the catheter entry site and the surgical field, and a lower incidence of catheter migration. Disadvantages include pain on passing the needle through the posterior muscles of the neck (hence Boezaart's

modification), possible damage to the dorsal scapular and long thoracic nerves, as well as inadvertent needle entry into neuraxial structures.

The technique is performed with the patient either sitting or in the lateral position. After anaesthetizing the skin and subcutaneous tissue, an insulated 17- or 18-gauge Tuohy is inserted at the apex of the "V" formed by the trapezius and levator scapulae muscles at the level of C6 vertebra. The nerve stimulator is attached and the needle is advanced medially and approximately 30° caudally, towards the suprasternal notch until the short transverse processes or the pars intervertralis of C6 is encountered, typically at a depth of 4-6 cm from the skin. The loss-of-resistance syringe is attached to the needle and directed laterally until there is loss of resistance. A motor response of the shoulder muscles should immediately follow as the paravertebral space is entered 0.5 to 1 cm beyond bony contact. Supraclavicular nerve block or local infiltration by the surgeon is required if there is conversion to an open procedure as CPB does not block the superficial cervical plexus. Recently, Antonakakis and Mariano have each described their version of US guided placement of a continuous interscalene perineural catheter using a posterior approach.

Many institutions are discharging patients home with in-situ catheters and pumps with LA solutions with promising results. The cost effectiveness of this approach and potential for misadventure is still a subject for debate.

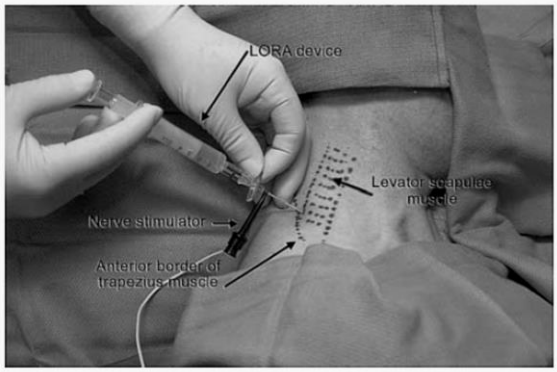


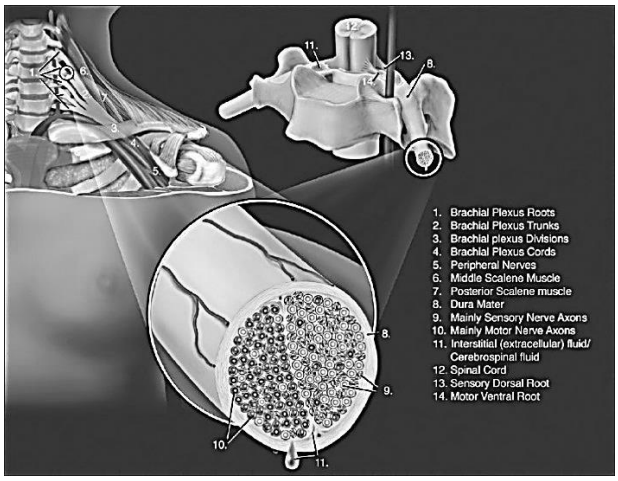
Fig 2. Needle entry. The nerve stimulator and the loss-of-resistance to air syringe (LORA) are applied to the needle. The needle enters in the "V" formed by the levator scapulae muscle anterior and the anterior border of the trapezius muscle posterior. The needle is aimed at the suprasternal notch and, in this way, penetration of the often-sensitive extensor muscles of the neck is avoided. Anterior = right side of figure.

Complications of interscalene block

The complications of ISB include phrenic nerve block (virtually 100%), recurrent laryngeal nerve block, horner's syndrome (stellate ganglion block), intravascular injection of LA, nerve injury,cervical spine injury, neuraxial spread of LA, pneumothorax, haemorrhage and sepsis.

The cervical roots (and possibly trunks in some patients) have *epineurium* that is continuous with the dural sheath of the cervical spinal cord. At this level, nerve fascicles are abundant, compact and easily detached from each other being poorly surrounded by *perineurium*. They appear as hypo-echoic structures, in contrast to peripheral nerves with more perineurium that appear hyper-echoic under US examination. Intra-neural (sub-epineurial but not intra-fascicular) injection of LA will likely track proximally epidurally or into the subarachnoid space resulting in a cervical epidural or cervical (total) spinal anaesthesia. Intra-fascicular injection will not only certainly cause severe nerve damage at the site of injection but also within the substance of the cervical spinal cord as the LA solution, injected under high pressure, tracks proximally. This is likely the mechanism of injury of several reported cases of paraplegia resulting from ISB carried out on patients under GA where diect damage to the spinal cord by the needle was deemed highly unlikely.

Micro-anatomy of brachial plexus at root level



Peripheral nerve injury (PNI) after surgery with ISB has been well described. In a retrospective study involving 1569 patients that underwent total shoulder arthroplasty (TSA) between 1993 and 2007, Sviggum et al reported an incidence of nerve injury of 2.2%, consistent with previous studies looking at nerve injury after TSA. The majority of patients (71%) recovered fully during the follow up period (2,6 years) and a further 26% had partial recovery. Considering that surgery itself can cause PNI due to positioning or stretching of the BP, they concluded that the use of ISB did not increase the risk for PNI.

Causes of surgery associated nerve injury

Anesthetic	Direct trauma with needle or catheter
	Direct nerve perforation, injury to fascicle and/or perineurium
	Pressure effect of local anesthetic injectate
	Nerve edema and/or hematoma
	Direct toxicity of local anesthetics and adjuvants
	Concentration and time dependent (in-vitro studies)
	Decreased neuronal blood flow
	Needle size and type
	Improper positioning (e.g. elbow flexion)
Patient	Diabetic mellitus, ulnar neuropathy, carpal tunnel syndrome, peripheral neuropathies, chemotherapy, vascular disease, multiple sclerosis, age, proximal nerve root compression, spinal canal stenosis
Surgical	Tourniquet pressure and duration compression, contusion, stretch, transection
	compressive dressings and casts
	Improper positioning (e.g. extreme abduction and external rotation of upper limb)
Other	Inflammatory-immune

Contraindications to ISB

1. Patient refusal
2. Allergy to LA (I have yet to see this)
3. Contralateral phrenic nerve block (realative in some cases, a risk benefit judgement call)
4. Contralateral recurrent laryngral nerve block
5. Sepsis at the site of injection
6. Peripheral neuropathy
7. Anticoagulation (controversial but a consideration if a breach of dural cuff occurs during ISB)

Volume and concentration of LA for ISB

There is no standard for the volume and concentration of LA that is maximally effective for intra and post operative analgesia for ISB. Higher volumes and concentrations are thought to lead to denser blocks and longer durarion of analgesic action (as well as motor block) but with an increased risk of complications (LA toxicty, LA associated nerve toxicity, phrenic nerve blockade etc.). Lower volumes of LA can be used in USG ISB with comparable analgesic effects to high volume techniques. Low volume ISB reduces the incidence of adverse events such as diaphragmatic paresis. In a study by McNaught et al using 0.5% ropivacaine, patients were randomised to receive either GA and ISB with 5 mL LA or 20 mL LA solution. There were no significant differences in pain scores, sleep quality and total morphine consumption for up to 24 hours after surgery. Most RA practitioners will agree that USG ISB rarely requires more than 20 mL of 0.25-0.5% ropivacaine or bupivacaine (the higher concentration if used as a sole anaesthetic)

Adjuvants

Numerous adjuvants have been used in combination with LA in an attempt to optimise block characteristics and improve clinical outcomes with variable success. Common additons to LA solutions are adrenaline and clonidine, with opiods, midazolam, ketamine and neostigmine also utilised. Recent research has focused on the addition of the glucocorticoid dexamethasone as an adjuvant in RA. Studies have shown that it can significantly prolong (up to 4 times) the duration of analgesia with minimal adverse events. The exact mechanism of action is unknown although it has been suggested that it acts by increasing the activity of potassium channels on nociceptive C-fibers or by causing vasoconstriction via glucocorticoid receptor mediated nuclear transcription modulation. However, recent studies have suggested a systemic effect may be responsible for its clinical effect and IV administartion may give similar results. Dosages range between 4 and 10 mg with 8 mg being the most common dose used.

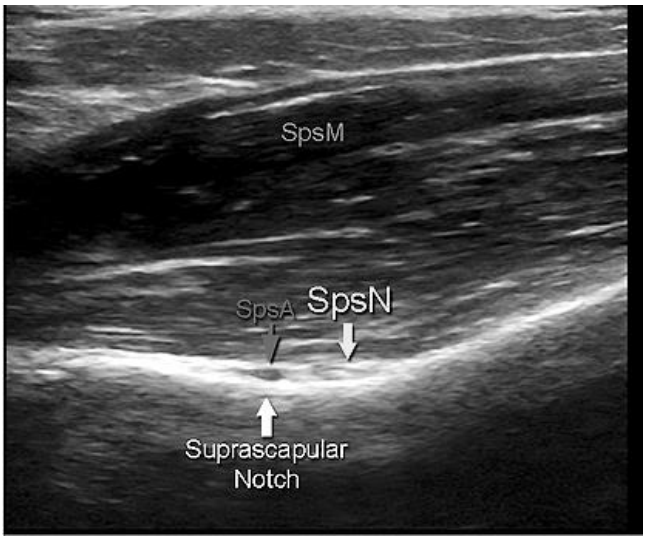
- **Supraclavicular block (SCB)**

SCB is a block at the level of the BP divisions between the anterior and middle scalene muscle and the first rib. USG has increased the popularity of this block as it visualises target tissues and surrounding structures in real time reducing common complications such as pneumothorax. SCBs have not been used for shoulder surgery because of concern that the block is too distal from the cervical nerve trunks and roots to provide satisfactory shoulder anaesthesia. However, anatomic studies with US and CT scanning demonstrate that LA injected for a SCB travels cephalad between the anterior and middle scalene muscles onto the trunks and roots within the paravertebral fascial covering. SCB for shoulder surgery has shown similar success to ISB in a recent study with no evidence of pneumothorax and an incidence of post-operative nerve symptoms at 0.4%. The investigators concluded that USG ISB and SCB are both effective for shoulder surgery.

- **Suprascapular and axillary nerve blocks (shoulder block)**

Patients in whom there is a contraindication to ISB e.g. those who would not tolerate a phrenic nerve block, may benefit from combined suprascapular and axillary nerve blocks for shoulder surgery. Although good intra and post-operative analegesia has been reported with these blocks, they are not comparable to ISB or even SCB and should probably be used as part of a multimodal analgesic approach in combination with GA.





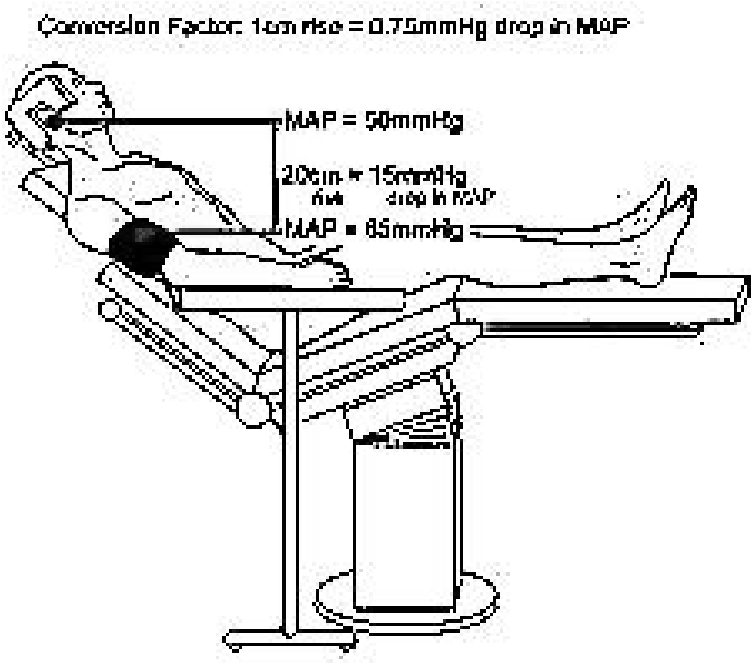
- **Intra-articular infiltration (IA) of LA and sub-acromial block (SAB)**

Many surgeons are enthusiastic proponents of IA and/or SAB for post-operative pain management for a variety of arthroscopic shoulder joint procedures claiming equal efficacy to ISB with a lower incidence of complications. Apart from the avoidance of anaesthesia related delay attributed to the performance of RA blocks, no studies have shown equivalence with ISB as regards quality and duration of post-operative analgesia. IA and SAB with indwelling catheters have been assoiciated with post-arthroscopic glenohumeral chondrolysis, a devastating complication that occurs mainly in young, healthy patients who have received IA boluses and infusions of high concentrations of bupivaciane.

6. Intra-operative management

On arrival in theatre the patient must be positively identified and asked to indicate the side that is to be operated upon. Hopefully, the surgeons have also made clear, unambiguous markings on the indicated limb. IV access is secured on the contra-lateral arm, or either a foot or ankle vein if none are available in the upper limb. Blood loss during shoulder surgery is not usually significant unless the patient is undergoing a revision arhtroplasty or open reduction of joint or upper humeral fractures. In these instances, a large bore IV cannula must be placed and a blood should be typed and screened if appropriate. RA is carried out in an awake (my preference), lightly sedated patient (a combination of midazolam and fentanyl) who is calm but able to communicate at all times.

Shoulder surgery can be carried out in the supine, lateral decubius position (LDP) or beach-chair position (BCP). Standard monitoring should be employed in all but the most compromised patients, with the NIBP cuff placed in the same arm as the IV in the BCP and the dependent arm or lower leg in the LDP. An NIBP cuff on the leg in the BCP is unacceptable as it falsely overestimates mean blood pressures compared to the upper arm. Mean pressure measurements at the level of the upper arm significantly overestimates that at the level of the carotid bifurcation. It must be noted that mean blood pressures fall 0.75 mmHg per cm rise above the upper arm NIBP cuff. There is no place for hypotensive anaesthesia, especially in elderly or patients with significant co-morbidities.



Invasive arterial monitoring should be considered in patients with significant cardiovascular co-morbidity. The transducer should be elevated to the level of the tragus of the ear as this will more accurately reflect cerebral perfusion pressure than NIBP. Cerebral perfusion monitoring using Near Infra-Red Spectroscopy (NIRS-INVOS) as a measure of regional cerebral oxygen saturation ($rScO_2$) is becoming standard monitoring for patients operated in the BCP under GA and mechanical ventilation.

Once surgery has commenced, it is extremely difficult to have access to the airway should it become compromised, hence most anaesthetists prefer to manage the aiway with an armoured ETT or south facing RAE as this ensures a more sucure airway. Use of LMA- with spontaneous ventilation or IPPV- is equally acceptable provided the patient is appropriately selected and the LMA well secured. The head and neck should be secure while care should be taken throughout the procedure to ensure that excessive stretching of the brachial plexus does not occur as a result of the excessive surgical traction. The eyes should be carefully taped and padded as the head is under drapes and surgeons will often use it as an arm rest during the procedure! Pressure points must be carefully padded (heels, elbows), the legs flexed with a pillow under the knees. An axillary roll must be placed when the patient is in the LDP as this protects the brachial plexus from compression between the rib cage and the head of the humerus. Sequential calf compressors must be utilised, not only to prevent thomboembolism, but to reduce venous pooling, particularly important in the BCP. Forced air warming is recommended as some procedures are lengthy and irrigation fluid used during arthroscopy is often well below body temperature. Antibiotic cover is mandatory for joint surgery and the use of tranexamic acid for more bloody procedures, such as TSA is recommended (1g infused over 20 mins).

Shoulder surgery is associated with grave complications related to positioning, particularly in the BCP. Visual loss as well as stroke and permanent post-operative cognitive dysfunction is an infrequent but devastating complication probably related to cerebral hypoperfusion. Cerebral autoregulation is well maintained in spontaneously breathing patients under GA, but becomes pressure dependent during IPPV, especially in older patients with systemic diseases such as hypertension, diabetes and peripheral vascular disease. All case reports of neurological misadventure in the BCP have occurred in patients under GA who have been mechanically ventilated. However, a recent article has shown that cerebral autoregulation is disordered in patients undergoing surgery in the BCP with no differences in post-operative cognition and brain injury biomarkers compared to the supine position.

Hypotension is a frequent occurrence in patients induced and then elevated into the BCP (elevations range from 30 up to 70 degrees from the horizontal). Mean pressures must be supported with vasopressors (ephedreine>>phenylephrine, or adrenaline) if they fall below 20 to 30% of baseline

values. rScO2 values that drop to 20% or below baseline (taken in an awake patient breathing room air) should alert the anaesthetist to pathological cerebral hypoperfusion. Interventions include reducing the angle of elevation, increasing end-tidal CO2 and using vasopressors (probably not phenylephrine as it is a vasoconstrictor that has been shown to decrease rScO2 saturations). The Bezold-Jarisch reflex may be activated during shoulder surgery in the BCP, especially when surgery is performed under interscalene block. This presents as sudden, profound bradycardia and hypotension, which can rapidly progress to cardiac arrest.

The aetiology of nerve injury has already been addressed. Extravasation of irrigation fluid into the subcutaneous tissues of the neck and head may lead to peri-operative airway compromise. Venous air embolism, pneumothorax, pneumomediastinum and sub-cutaneous surgical emphysema has been described.

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References on request

Anaesthetic considerations in chronic kidney disease

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Patients with chronic kidney disease (CKD) require careful evaluation and risk stratification in the perioperative period. The presence of renal dyfunction has been identified as an independent predictor of cardiovascular morbidity and mortality (Lee's Cardiac Risk Index & Euroscore in cardiac surgery patients).The co-morbidities that lead to the CKD may themselves confer increased perioperative risk eg. diabetes, hypertension and the medical management of these need to be optimized pre-operatively. Chronic kidney disease has multi-systemic effects that impact on the anaesthetic management of the patient.In addition, renal replacement therapy may lead to pathophysiological changes that are relevant in the peri-operative period.While these patients have estabilished renal disease, some may still have residual function that would require renal protective strategies .

For this refresher course lecture the organ system effects,pharmacokinetic changes and the impact of renal replacement therapy will be reviewed.

Definition and classification of Chronic kidney disease(CKD)

KDIGO 2012: Chronic kidney disease is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health.

Table 1. **Criteria for Chronic Kidney Disease***

Markers of kidney damage (≥1 for >3 mo)
- Albuminuria (AER ≥30 mg/d; ACR ≥30 mg/g)
- Urinary sediment abnormalities
- Electrolyte and other abnormalities due to tubular disorders
- Abnormalities detected by histology
- Structural abnormalities detected by imaging
- History of kidney transplantation

Decreased GFR (for >3 mo)
- GFR <60 mL/min per 1.73 m^2 (GFR categories G3a–G5)

ACR = albumin–creatinine ratio; AER = albumin excretion rate; GFR = glomerular filtration rate.

Table 2. **GFR and Albuminuria Categories in the New Classification**

Category	GFR, *mL/min per 1.73 m^2*	AER, *mg/d*	ACR Equivalent, *mg/g*	Descriptor
GFR		–	–	
G1	≥90	–	–	Normal or high
G2	60–89	–	–	Mildly decreased*†
G3a	45–59	–	–	Mildly to moderately decreased
G3b	30–44	–	–	Moderately to severely decreased
G4	15–29	–	–	Severely decreased
G5	<15	–	–	Kidney failure
Albuminuria				
A1	–	<30	<30	Normal to mildly increased
A2	–	30–300	30–300	Moderately increased*
A3	–	>300	>300	Severely increased‡

ACR = albumin–creatinine ratio; AER = albumin excretion rate; GFR = glomerular filtration rate.

The CKD-EPI formula is recommended to estimate GFR from serum creatinine as it has less bias, great precision and accuracy than The MDRD equation especially at GFR ≥ 60ml/min/1.73m^2. If patients have eGFR 45-59ml/min/1.73m^2 & don't have other markers of kidney damage, measuring cystatin-C is suggested.

The syndrome of uraemia is used to describe the illness accompanying kidney failure that cannot be explained by derangements in extracellular volume, inorganic ion concentrations, or lack of known renal synthetic products. It is thought to be largely due to the accumulation of organic waste products(eg. guanidines,phenols,aliphatic amines,nucleosides) that are normally cleared by the kidneys. While it does include some of the systemic effects of CKD, it does not fully encompass the pathology associated with CKD.

Risk factors for Chronic kidney disease

Globally ,Type II Diabetes accounts for up to 40% of chronic kidney disease. The other causes include hypertensive nephrosclerosis, glomerular disease ("nephrotic" and "nephritic" diseases), interstitial diseases, vascular diseases of the kidney autoimmune diseases or malignancy. Hypertension and glomerulonephritis were the major causes of end-stage renal disease (ESRD) among South Africans in previous registry data. A 2014 cross-sectional study of South African patients in a clinic in Northern Kwa-Zulu Natal showed that hypertension (77.8%) was the most common risk factor followed by diabetes (29.8%), HIV (28.5%), glomerulonephritis (7.0%) and tubulo-interstitial diseases (5.6%)

Organ system Effects

Cardiovascular

Chronic kidney disease increases the risk of cardiovascular disease & its associated outcomes.

Hypertension: could be both a cause and a consequence of chronic kidney disease. In CKD, activation of the renin-angiotensin–aldosterone system leads plasma volume expansion and vasoconstriction which contributes to hypertension. In addition, the use of erythropoietin which increases blood viscosity and vascular resistance may worsen hypertension. KDIGO recommends that both diabetic and non-diabetic adults with urine albumin excretion ≥ 300 mg/24 hours be treated with ARB (angiotensin receptor blocker) or ACE-I (angiotensin-converting enzyme inhibitor) to keep BP ≤ 130/80 mmHg.

Ischaemic Heart Disease (IHD): Accelerated atherosclerosis due to impaired endothelial function, inflammation, increased angiotensin II activity & dyslipidaemia (↓ HDL, ↑intermediate density lipoproteins). Left ventricular hypertrophy from volume overload, hypertension & arteriosclerosis.LVH is associated with myocardial fibrosis which can lead to diastolic dysfunction and arrhythmias. Calcified, stenotic atherosclerotic lesions due to the CKD or calcium supplements increase the risk of IHD.40% have symptomatic ischaemic heart disease (and likely many more are asymptomatic),32% have arrhythmias and 40% have evidence of cardiac failure(systolic and diastolic).

Conduction abnormalities: myocardial fibrosis & calcification of the conduction system increases the prevalence of second- and third-degree AV block which may require pacing. Hyperkalaemia,calcium channel blockers or the sympathectomy induced by an epidural could lead to a complete heart block.

Cardiac valves are also a site of abnormal calcification with the aortic being the commonest, followed by the mitral valve. As a result of these lesions, these patients may be more susceptible to bacterial endocarditis. Haemorrhagic uraemic pericarditis may be present in CKD before starting effective renal replacement therapy.

Fluid & Electroytes

Sodium excretion is a function of GFR.As the disease progresses,patients are unable to adapt to variations in salt intake with an impaired ability to concentrate/dilute urine.Impaired excretion of sodium load leads to a volume overload which is usually isotonic. If there is perioperative restriction of free water intake, the inability to concentrate urine will result in hypernatremia and hypertonicity.

In CKD a compensatory increase in the excretion of potassium per functioning nephron and secretion in the gut maintains a normal serum poatassium until late grade of CKD (usually grade 5).However if there is excessive exogenous potassium or transcellular potassium shifts, they are at risk of

developing hyperkalaemia. Avoid drugs that can cause an acute hyperkaelemia include β-blockers, potassium sparing diuretics(eg. amiloride, spironolactone),ACE-inhibitors and ARB's, NSAIDs, aminoglycosides, cyclosporine and succinycholine.Scoline causes an transient increase in potassium of 0.5-1mmol/L and it can be considered if the preoperative serum potassium is normal. Scoline has the advantage of being independent of renal metabolism and excretion. In acute acidosis, serum potasssium will increase by 0.5mmol/L for each 0.1unit decrease in pH.

Reduced magnesium excretion in CKD leads to hypermagnesaemia manifested by muscle weakness, hyper-reflexia and potentiation of non-depolarizing muscle relaxants.

Acidosis

Reduced clearance of hydrogen ions is caused by the inability to secrete protons & buffers(eg. phosphate) together with the limited bicarbonate generation . Reduction in glutamine utilization reduces ammonia production and secretion into the proximal tubule. Retention of organic anions will increase the anion gap and further decrease plasma bicarbonate level. All of these mechanisms lead to a chronic metabolic acidosis. Acute triggers that may worsen the acidosis include keto-acidosis, sepsis or infusion of large volumes of saline which will result in hyperchloraemic metabolic acidosis. The deleterious effects of metabolic acidosis include depression of myocardial contractility, reduced cardiac output and reduced renal blood flow.These patients have a reduced ability to compensate for a respiratory acidosis and drug distribution and efficacy is altered.Furthermore, hyperchloraemia can reduce renal blood flow and GFR.

Calcium, Phosphate and Parathyroid hormone

Calcium absorption from the gut is reduced due to the decline in renal production of calcitriol(1,25-$(OH)_2D_3$. As GFR falls below 20ml/kg/min phosphate excretion is impaired and hyperphosphatemia develops.This hypophosphatemia also suppresses the activity of 1-α-hydroxylase which is responsible for renal calcitriol production.Hypocalcemia and hypophosphatemia both stimulate the secretion of parathyroid hormone and causing hyperplasia of the parathyroid gland with secondary hyperparathyroidism.This increases osteoclastic and osteoblastic activity causing osteitis fibrosa cystica.Increased parathyroid hormone levels together with the hyperphosphataemia leads to metastatic calcium depostion in soft tissues like skin and blood vessels further lowering the serum calcium level.Medical management includes vitamin D analogues and phosphate binders.

Pulmonary

Fluid overload leading to pulmonary oedema, impaired cellular and humoral immunity predisposing to infection and decreased surfactant production causing atelectasis are some of the common pulmonary complications in CKD. Pulmonary hypertension may be present in up to 40% of CKD patients with an A-V fistula. It's presence is an independent predictor of increased 5-year mortality. It is suggested that pulmonary hypertension should be excluded before planning an A-V fistula formation.

Pathophysiology:

- Uremia-induced endothelial dysfunction resulting in lower basal nitric oxide levels .This reduces the ability of the pulmonary vasculature to accommodate the increase in cardiac output derived from the AV fistula
- Pulmonary injury resulting from chronic exposure to microbubbles originating in the dialyzer or it's tubing

Haematological

Anaemia : decreased renal parenchymal erythropoeitin production which reduces stem cell transformation into erythrocytes and uraemic toxins that reduce red cell life lead to a normochromic normocytic anaemia. Dialysis and chronic upper GIT losses may contribute while other forms of anaemia may follow the dietary deficiency of folate and iron.Compensatory mechanisms for the chronic anaemia include an increase in 2,3-DPG production and a right-ward shift of the oxy-haemoglobin dissociation curve.

When selecting haemoglobin targets in the perioperative period we should consider the critical role of blood viscosity in the maintenance of capillary density at tissue level .Blood viscosity and shear stress act on the capillary endothelium, inducing physiological nitric oxide (NO) release which increases capillary diameter thereby optimizing or recruiting the microvasculature. A ''viscosity trigger" is a point at which blood is required to recruit the microcirculation at haemoglobin levels that would not otherwise represent the conventional ''transfusion trigger''. Need to balance the beneficial effect of lower haematocrit on blood rheology and the detrimental effect of ''viscosity failure'' on perfusion. Unfortunately there has not been sufficient research done to make a recommendation on the "viscosity trigger" in CKD.

Coagulation

CKD patients can present with either episodes of severe bleeding (40–50% in chronic renal failure or haemodialysis) or thrombosis especially at sites of vascular cannula. Patients with renal insufficiency are prone to coagulation disorders due to the complex interactions of uraemic toxins, morphologically changed vessel walls (including the endothelium) the coagulation cascade and platelets. These mechanisms are further complicated by anticoagulants that may accumulate in these patients.

Bleeding disorders may present as gastrointestinal bleeding, bleeding from cannulation sites, retinal haemorrhage, subdural haematoma, epistaxis, haematuria, ecchymosis, purpura, bleeding from the gums, gingival bleeding, genital bleeding, haemoptysis, telangiectasia, haemarthrosis and petechiae. The components of the coagulation cascade increase the bleeding risk by various mechanisms:

Platelets:

Uraemic toxins influence platelet function eg. phenol, phenolic acid (impairment of primary aggregation to ADP), guanidinosuccinic acid (inhibition of the second wave of ADP-induced platelet aggregation).Dialysis may improve the platelet dysfunction but no correlation between the bleeding time and the concentration of the dialyzable uremic metabolites was detected. Platelet dysfunction may be due to:

- Platelet α-granules with an increased ATP/ADP ratio & reduced content of serotonin.
- Thrombin-triggered release of ATP together with an increased calcium content and a disturbed intracellular calcium flux
- Impaired synthesis and/or release of thromboxane A2 resulting in a reduced adhesion and aggregation of platelets
- Inhibited platelet-activating factor synthesis
- Circulating fibrinogen fragments that competitively bind to the glycoprotein (GP) IIb/IIIa receptor decreasing adhesion and aggregation

Platelet –wall interactions:

- High proteolysis of GP Ib results in decreased concentration on platelets
- Decreased function of the GP IIb/IIIa complex due to insufficient binding of vWF and fibrinogen to activated platelets. This defect may be related to a uraemic toxin interfering with binding since this defect improves with dialysis
- Functional defect in vWF–platelet interaction ,which can be corrected by cryoprecipitate(rich in vWF) and desmopressin (release of vWF from storage sites in platelets)
- Increased plasma levels of prostacyclin which modulates vascular tone
- Nitric oxide generation which inhibits platelet aggregation(reduced thromboxane and ADP) through the formation of cGMP

Anaemia: adequate haematocrit is necessary for coagulation because:

- Erythrocytes lead to a concentration of platelets along the vessel walls within the blood flow
- Stimulates platelet ADP release and an inactivation of PGI2
- Haemoglobin is a scavenger of nitric oxide.

While the administration of erythrocytes or erythropoietin reduced the bleeding time in uraemic patients, a normal haematocrit was associated with an increased incidence of myocardial infarction and a higher mortality.

Increased risk of Thrombosis due to:

- Increased levels of fibrinogen and plasma tissue factor with reduced activity of antithrombin
- Increased factor XIIa and VIIa, F VIII, activated protein C complex, thrombin–antithrombin complexes & D-dimers
- Platelets activity is increased by a reduced amount of vasoactive substances (i.e.NO) increased levels of phosphatidylserine, p-selectin and fibrinogen receptor PAC-1.
- Endothelium: hypoxia, shear stress, oxidants causing cytokine release
- Anti-phospholipid antibodies can also promote thrombosis in patients with renal insufficiency

Therapeutic interventions for Uremic Bleeding

Erythropoietin:

- Stimulates erythropoiesis thereby improving the margination of platelets.
- Increases the reticulated metabolically active platelets and platelet–subendothelial interaction.

Dose: 40-150U/kg three times a week to increase the Hct to above 30% and normalise bleeding time. The beneficial platelet effects start within 7 day, with the improvement in Hct taking up to 9 weeks. It therefore is not suitable for acute correction of coagulopathy.

Cryoprecipitate:

- Contains factor VIII, vWF and fibrinogen & may increase the proportion of functional clotting.
- Can be used in patients at high risk of or with active bleeding.
- Time to effect is within 4-12hrs

Desmopressin:

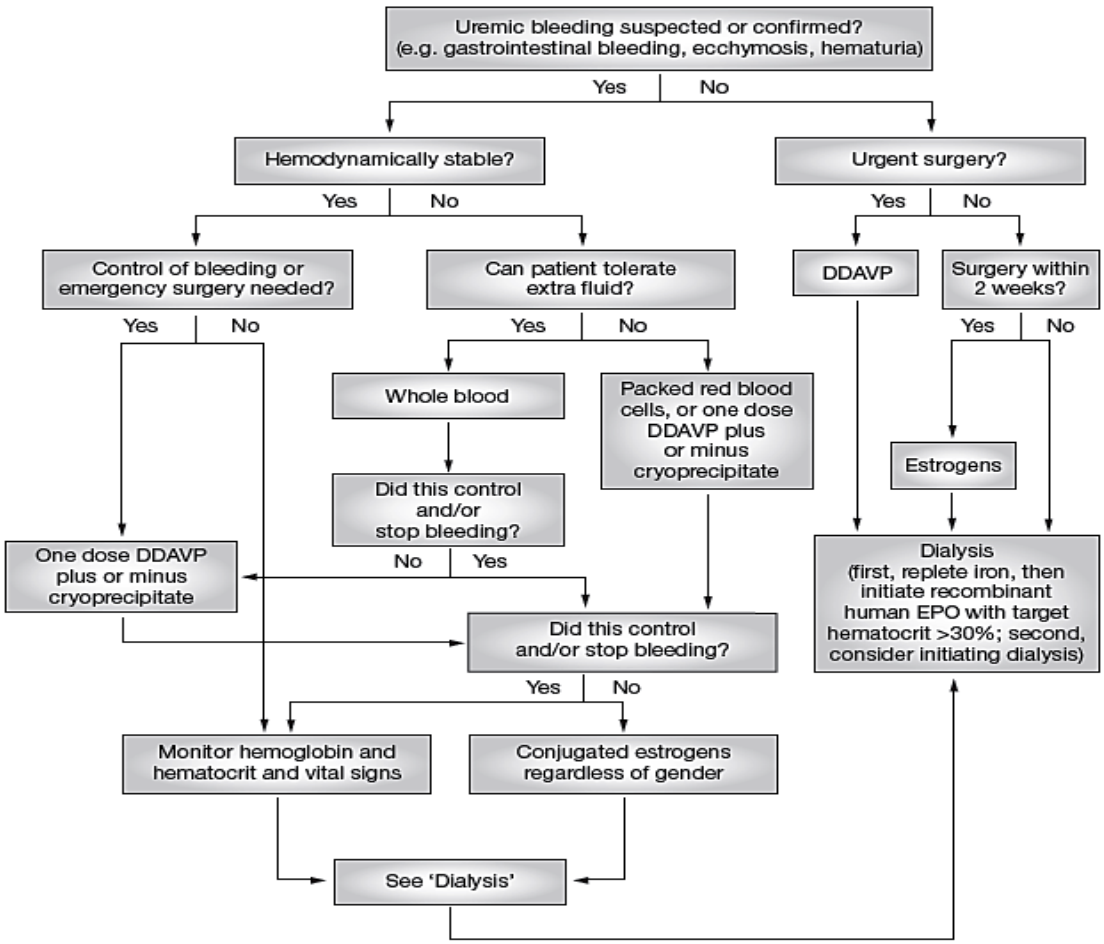
- Releases factor VIII from storage sites, potentially increasing the concentration of factor VIII and minimizing the effects of dysfunctional vWF.
- Desmopressin doses for uremic bleeding range from 0.3µg/kg- 0.4µg/kg intravenously or subcutaneously as a single injection.
- Its rapid onset of action of approx.1 hour makes it suitable for acute bleeding but due to a short duration of activity, bleeding time could return to baseline within 24 hrs.

Disadvantages of DDAVP include tachyphylaxis(may be due to depletion of vWF & Factor VIII from endothelial stores) after one dose, headache, facial flushing, and rare thrombotic events. If bleeding is not controlled after one dose of DDAVP, the risk of tachyphylaxis precludes a repeat dose. Use cryoprecipitate or conjugated oestrogens instead.

Oestrogens:

- Postulated that the hormones decrease production of l-arginine, which is a precursor of nitric oxide. Decreased nitric oxide leads to less guanylyl cyclase stimulation, less production of cGMP & potentially leads to increased production of thromboxane A2 and ADP.
- May also decrease antithrombin III and protein S levels, and increase factor VII concentrations.
- Conjugated oestrogens can safely improve bleeding time in both males and females not used for longer than 5 days.
- IV conjugated oestrogens are recommended and can be used for GIT bleeding associated with uremia
- The time to onset of action for conjugated oestrogens is about 6 h; maximum effect is evident at 5–7 days with duration of approximately 14–21 days.
- Dose: 0.6 mg/kg intravenously over 30–40 min once daily for 5 consecutive days.

Overleaf is an algorithm for uraemic bleeding. While there is limited data on the benefit of dialysis in active bleeding, one study showed improvement. (*Hedges SJ et al.Nature Clinical practice Nephrology 2007;3:3*)



Neurological

CNS effects: Defects in memory, ability to plan, attention and the performance of higher-order tasks are present. Patients experience impaired sleep with brief arousals and apnoeic episodes, which are often associated with bursts of repetitive leg movement. The cognitive impairment cannot be ascribed to co-morbidities & have been detected in patients with glomerular filtration rates between 30-60 ml/minute/ 1.73m^2 of body-surface area. As renal function worsens symptoms can progress to coma or catatonia that can be improved by dialysis.

Peripheral neuropathy: Sensori-motor neuropathy is common in untreated uraemia and effective renal replacement therapy aims to relieve the symptoms. While the neuropathy is often subclinical, it can still be detected with nerve function tests.

Autonomic neuropathy: Prevalent in 65$^{\%}$ in non-diabetic pre-dialysis CKD patients & between 38$^{\%}$ and 87.5$^{\%}$ of patients on haemodialysis. It is characterized by characterized reduced baroreceptor sensitivity, sympathetic over-activity and parasympathetic dysfunction and may increase the risk of perioperative arrhythmias & silent myocardial infarction. Delayed gastric emptying may be present in up to 69$^{\%}$ of patients.

Dialysis-associated neurological disturbances

Dialysis Dementia: usually in patients on dialysis for many years and thought to be related to aluminium toxicity. Short haemodialysis times are associated with early dementia in a chronic haemodialysis population with approximately 25% of patients having early dementia. Patients' age, nutrition status (BMI, serum albumin) and co-morbidity (diabetes, previous CVA) are independently linked to early dementia.

Dialysis Disequilibrium Syndrome: Clinical syndrome of neurologic deterioration that is more likely to occur in patients during or immediately after their first treatment, but can occur in any patient who receives haemodialysis. Symptoms include restlessness, headache, mental confusion and coma. Since these symptoms are non-specific other common differential diagnoses should be ruled out e.g. subdural hematoma, acute cerebrovascular event, metabolic(non-ketotic hyperosmolar coma, hypoglycaemia, hyponatremia) malignant hypertension & dialysis dementia. While the exact aetiology of the syndrome remains unknown, the underlying mechanism involves the development of an osmotic gradient. Current hypotheses to explain the osmotic gradient are the:

- "Reverse Urea Effect"- urea concentration in the CNS remains elevated because of the slower diffusion from the CNS to the blood compared to it's removal from blood into the dialysate.
- "Idiogenic Osmoles" - increase of brain osmolality was secondary to the new formation of organic molecules called "idiogenic osmoles" .

Both of these osmotically active molecules are affected by the decrease in brain intracellular pH and CSF pH which are significantly lower when patients are rapidly dialyzed. Acidosis of the CNS can alter the blood-brain barrier solute and water transport & displace cations from protein binding sites thereby affecting the intracellular osmolality.

Prevention should focus on avoiding the development of the osmotic gradient by:

- Using hemofiltration which relies on the convective removal of solute instead of diffusive removal. Thus, the osmolalities of the body fluid compartments will not change as rapidly as they do during standard haemodialysis.
- If using standard haemodialysis, slowly lower the blood urea concentration with the aim of reducing the urea concentration by 40% over 2hrs for the first treatment (URR of 0.4)This however has not been evaluated in RCTs.
- Adding an osmotic agent to the blood stream e.g. sodium which can be done in machines that allow sodium modelling. Other osmotic agents that have been used include mannitol and glucose

Treatment: Aimed at reducing the intracranial pressure of the patient and include mannitol or hypertonic saline to raise the blood osmolality and to hyperventilate the patient.

Gastro-intestinal

Anorexia, nausea and vomiting can lead to malnutrition. Urea is a mucosal irritant and together with the associated coagulopathy may lead to GI bleeding. Gastric emptying is delayed with high residual volumes and a lowered pH. Consider the need for a rapid sequence induction especially if there are co-morbidities that contribute to autonomic dysfunction e.g. diabetes.

Immune Function

An increase in pro-inflammatory cytokines leading to altered neutrophil & monocyte function .This together decreased number of lymphocytes & activation and abnormal pathogen recognition result in inhibition of cell-medited and humoral defence mechanisms. Patients are prone to colonization of vascular access and peritoneal catheter sites and often with multidrug resistance organisms eg. MRSA.

Pharmacokinetic Changes in CKD

Absorption affected by:

- Gastroparesis, delayed emptying and gut oedema
- Raised gastric pH: gastric urease converting urea to NH3.
- Reduced intestinal P- glycoprotein an apical cell transporter which usually moves toxic compounds to the intestinal lumen

Distribution

- Volume of distribution is affected by total body water, plasma protein binding & tissue binding
- Time since dialysis may reduce the volume of distribution & drugs given by continuous infusion will achieve an increased steady-state concentration

Protein Binding – if decreased it can result in an increased free fraction of the drug and increased volume of distribution.

- Albumin concentration may be reduced, with a conformational change in the binding site.
- Binding of acidic drugs to albumin are affected by organic acids (uric acid & lactic acid) which compete for binding sites on albumin.
- Basic drugs bind to α1-acid glycoprotein is an acute phase protein that is increased in CKD
- Local anaesthetics : high-affinity, low capacity binding site on α1-acid glycoprotein
  Low-affinity, high capacity binding site on albumin: reduced by acidosis

Elimination

Non-renal clearance of drugs is reduced eg. hepatic clearance is affected by changes in hepatic blood flow, free fraction of drug and metabolic capacity of liver enzymes. The kidneys are involved in conjugation reactions & up to $18^{\%}$ of cytochrome P450 activated drug metabolism. This enzyme system is differentially affected by the severity of renal disease and the plasma urea level.The enzyme system effect may be due to altered gene transcription or depletion of co-factors.

Pharmacokinetics of anaesthetic drugs

Volatile anaesthetics: Sevoflurane and enflurane have previously been highlighted as potentially nephrotoxic due to their production of fluoride ions. Retrospective studies comparing sevoflurane to iso- and enflurane did not show an increase in renal dysfunction following sevoflurane use, irrespective of the fresh gas flow or CO_2 absorbent. However case reports of enflurane use in patients with renal dysfunction suggest that it is best avoided.

Opioids: Most lipid-soluble opioids are metabolised in the liver to water-soluble metabolites before renal excretion. Some of these metabolites are more active than the parent compound e.g morphine-6-glucuronide (M6G) and nor-pethidine. M6G half-life is prolonged in renal failure from 2 hours to 27hrs but a significant fraction can be removed by dialysis.7% of fentanyl is excreted unchanged in urine and this clearance is reduced in CKD. Alfentanil's free fraction is increased due to reduced protein binding so a reduced dose may be required but the dosing interval is unchanged. Remifentanil has a reduced clearance & prolonged elimination half-life for which a lower infusion rate will be required.

NSAIDs: A major concern is of the platelet inhibition increasing the risk of GI bleeding in the CKD who is already at high risk.A retrospective study of aspirin in dialysis patients (DOPPS) found that it was not associated with increased risk of GI haemorrhage. There is a potential adverse effect on residual renal function in patients at earlier grades of CKD.NSAIDs can precipitate an acute decrease in GFR and cause an interstitial nephritis.They may also exacerbate hyponatremia and hyperkalemia in these patients are best avoided in this group of patients.

Neuro-muscular blockers : Suxamethonium chloride is not dependent on renal metabolism or excretion.The considerations of serum potassium level were discussed above. Patients with CKD may however have reduced levels of plasma cholinesterase which will prolong the duration of action of scoline and mivacurium.

Non-depolarising muscle relaxants that undergo Hoffman eliminationand non specific esterase metabolism e.g atracurium and cis-atracurium are preferred.Reduced clearance of amino-steroid agents, e.g.vecuronium & rocuronium prolongs the clinical effect and should be avoided. Sugammadex (2mg/kg) can be used to reverse the effects of rocuronium, if used for a modified rapid sequence induction. There is concern about renal accumulation of sugammadex-rocuronium complexes

Perioperative considerations for patient receiving renal replacement therapy (RRT)

The CKD patient is often on some form of renal replacement therapy via peritoneal dialysis or haemodialysis. These require particular access which can lead to complictions and the sites need noted pre-operatively. The intercompartmental fluid shifts and metabolic effects therof, use of anticoagulation and patient's exposure to an extracorporeal circuit and membrane need to be factored in the pre-operative assessment.

Renal replacement therapy itself can lead to particular pathophysiologocal changes in the CKD patient. Uraemic cardiovascular disease is characterized by a high prevalence of medial vascular calcification, arterial stiffness and altered left ventricular geometry.Intimal hyperplasia is common after either coronary angioplasty or the establishment of arterio-venous access. Calciphylaxis is a specific dialysis-related type of vascular calcification characterized by diffuse calcification of the media of small to medium arteries and arterioles with intimal proliferation and thrombosis.It results in skin ulcers and can lead to skin necrosis or acral gangrene.Pulmonary hypertension related to haemodialysis, as described above, will require intraoperative avoidance of triggers that will increase pulmonary vascular resistance eg.hypoxia, hypercarbia,acidosis and hypothermia.

In haemodialysis the options for vascular access include temporary non-cuffed catheters and long-term tunnelled cuffed catheters.When selecting the insertion site the risk of thrombosis and infection must be weighed. The subclavian site can complicate with stenosis in 40-50% of patients & this will lead to elevated dialysis pressures and oedema of the arm.The femoral route could also cause external iliac stenosis and is the site with the highest risk of infection.Other vascular access related

complications include aneurysm, limb ischaemia, pulmonary athero-embolism, steal syndrome & recirculation. A-V fistulae require a period of 1-4 months for maturation bfore it can be used. The site of the fistula must be noted and avoid cannulation or use of a blood pressure cuff on that limb.

Intermittent or continuous RRT exposes the patient to a foreign surface (membrane) which although these have improved to be more biocompatible, it still activates the coagulation & complement cascade, leukocytes and platelets. The subsequent release of inflammatory mediators induce oxidative stress, transforming lipids, proteins and causing endothelial injury.The activated platelets aggregate & stimulate thrombin formation. The oxidative stress and activation of the coagulation system may result in a counter reaction of enhanced activation of the fibrinolytic system.

The metabolic effects of RRT include the loss of amino acids,water-slouble vitamins, glutamine and trace elements (zinc, selenium) which are essential for anti-oxidant defence. Buffers that are used include bicarbonate, lactate and acetate. If the lactate load exceeds the capacity to metabolize it especially with tissue & hepatic hypoperfusion, it can cause impaired glucose tolerance & serum lactate will longer longer be a reliable marker of hypoperfusion or metabolic acidosis.

The anticoagulation that is used for RRT may impact on the timing of surgery.If therapeutic dose of low-molecular weight heparin is used as the anticoagulant, surgery would have to be delayed for 24hrs since the last dose. Alternatively anti-factor Xa levels can be monitored to assess the degree of inhibition & adjust the dose of LMWH. Systemic heparin effect can be monitored via APTT & for urgent surgery protamine for reversal can be considered. Other options include regional anticoagulation (pre-filter) & reversal (post-filter)with unfractionated heparin /protamine or citrate/calcium.

The dialysis disequilibrium syndrome was described above and there should be a period of at least 4-6 hours after a RRT session before surgery to allow the inter-compartmental shifts to stabilize & to monitor for disequilibrium.Take note of the patient's usual dry weight post dialysis and aim for that before anaesthesia.

Summary: CKD patient often present for surgical procedures related to the disease eg. catheter insertion, fistula formation or in emrgency situations laparotomy for peritonitis from infected peritoneal dialysis catheters.While they are inherently high risk patients ,the procedures are essential and as anaesthetists we need to consider the impact of CKD and adjust the anaesthetic management to optimize the outcomes for the patient.

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Evidence-based Anaesthesia for Renal Transplantation

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Introduction

The first kidney transplant was performed in 1950 and rejected 10 months later because immunosuppressive therapy was unavailable at the time. The first successful renal transplant followed in 1954 by Dr Joseph Murray on identical twins, which eliminated the problem of immune rejection.[1] Further progress was made with advances in immunosuppressive therapy with the use of azathioprine in 1959, coupled with prednisolone. This combination enabled transplantation with unrelated donor kidneys with around 50% still functioning at 1 year. A significant achievement in an era when renal failure was usually a death sentence, since dialysis was still in its infancy. Outcomes improved further with the introduction of antilymphocyte globulins in 1967 and organ preservation solutions in 1968, which enabled the use of allografts from remote organ donors.[2, 3]

The need for kidney transplantation results from end stage renal disease (ESRD) and has become the treatment of choice when the kidneys are functioning at 10 - 15% of their normal capacity and renal replacement therapy (RRT) becomes necessary. The mainstay of therapy for ESRD is chronic dialysis treatment, however this is extremely expensive and the 5 year survival rate is 30% vs. 70% in patients with transplanted kidneys.[4,5] Chronic kidney disease (CKD) refers to a decline in glomerular filtration rate (GFR) usually caused by diabetes mellitus (40%), hypertension (27%), chronic glomerulonephritis (13%), interstitial nephritis (4%), cystic kidney disease (3,5%) and other diseases such as obstructive nephropathy, lupus nephritis and HIV. CKD is categorized as mild (GFR 60 - 89 ml / min / 1.73 m^2), moderate (GFR 30 - 59), severe (GFR 15 - 29) or ESRD (GFR < 15). The progression of renal disease from one stage to the next has deleterious effects on multiple organ systems.[2]

The kidneys are essential for adjusting body fluid volumes, electrolyte composition, acid base balance and haemoglobin concentration. They receive about 25% of the cardiac output and function as filters for drugs and toxins in the blood.[2]

Renal transplantation options

Renal transplantation can be performed as an elective procedure with a living donor allowing optimal preparation of donor and recipient alongside minimizing organ preservation times.[5] Kidney donors in whom death has been certified by neurological criteria (donation after brain death, DBD) are taken to theatre on a ventilator with a beating heart still. This is an 'urgent' surgical procedure with poor results after > 18 hours of cold ischaemic time. After mobilization of the organs and administration of heparin, the circulation is stopped by cross-clamping the aortic arch, draining the vena cava, and immediately flushing ice-cold preservation solution through the distal aorta thus keeping warm ischaemia, and accompanying anaerobic metabolism, to a minimum. More recently, organ transplantation follows death after circulatory death (DCD). These organs are exposed to a more prolonged period of warm ischaemia, which has traditionally been assessed as the time interval between onset of irreversible asystole and subsequent cold perfusion. However, it is now recognized that organ hypoperfusion and warm ischaemia begin some considerable time ahead of asystole as cardiovascular and respiratory functions slowly collapse after treatment withdrawal. With the exception of the lung (which can be inflated with oxygen), all organs that suffer warm ischaemia tolerate subsequent cold ischaemia poorly. Despite this, in an effort to address the widening gap between demand and supply of donor organs, DCD has increased 10-fold in the last decade and now comprises one-third of all deceased organ donors.[3]

Pre-operative considerations

Patients undergoing renal transplant surgery should have had an extensive preoperative 'work-up' to assess and optimize the various concomitant medical diseases. This will allow both risk stratification and the development of a tailored perioperative treatment plan.

The 2014 ACC / AHA cardiac evaluation guidelines by Fleisher et al. classify renal transplant surgery as 'elevated risk' surgery implying the likelihood of peri-operative major adverse cardiac events (MACE) as > 1%.[21] Few studies have evaluated the predictive value of clinical risk factors during transplant surgery but a retrospective study of 2187 patients reported independent association of recipient age, diabetic

nephropathy, claudication and prior cardiac disease with increased risk of MACE within the first 3 months after transplantation. Studies show that even among high-risk candidates, patient survival is improved and the risk of developing congestive heart failure (CHF) decreased by transplantation compared with remaining on dialysis.[12]

Contra-indications to transplantation include active infection, untreated malignancy, predicted patient survival of less than 5 years, risk of transplant loss greater than 50% at 1 year, inability to comply with immunosuppression regimen and immunosuppression predicted to cause life threatening complication.[4]

Cardiovascular

Special attention needs to focus on the cardiovascular system as cardiovascular disease (CVD) is 10 - 30 times higher in dialysis patients than the normal population and accounts for over 50% of their deaths and as much as 30% of post-transplant deaths.[7, 8] ESRD is associated with an increased incidence of a wide range of CVDs including coronary artery disease (CAD) (25% incidence)[6], stroke, CHF, AF, sudden cardiac death, pulmonary hypertension, and valvular heart disease.[7] In addition, cardiovascular risk factors are common in patients with ESRD and most patients have multiple (≥ 3) risk factors: Hypertension (90%), age > 50 years (50%), diabetes mellitus (40%), hypercholesterolemia (25%), cigarette smoking (25%), and obesity (20%). Renal failure in itself is a significant cardiovascular risk factor.

Guidelines published in 2012 by ACC / AHA: "Cardiac Disease Evaluation and Management among Kidney and Liver Transplantation Candidates" focus on obtaining the following: a thorough history and accompanied by physical examination to identify active cardiac conditions and assessment of functional status. Special emphasis placed on assessment of intravascular volume, presence of hypertension and anaemia. A baseline 12-lead ECG and resting transthoracic echocardiography (TTE) should be used to assess heart function for evidence of dilated cardiomyopathy and concentric hypertrophy which develop in response to chronically increase intravascular volume and increased afterload usually present in these patients. In general, "functional status" is an indication of how well patients are coping with day-to-day activities despite ESRD and may reveal evidence of CVD given that ESRD patients are less likely to experience chest pain during myocardial ischaemia or infarction. Due to the relatively low prevalence of high-risk coronary anatomy (such as occlusive left main disease or severe 3-vessel disease) in asymptomatic patients, available evidence does not support the need for routine coronary angiography in all potential kidney transplant candidates. Non-invasive stress testing for further risk stratification should be considered in patients without active cardiac disease but have ≥ 3 factors associated with CAD regardless of their functional status. Relevant risk factors among transplantation candidates include diabetes mellitus, prior CVD, >1 year on dialysis, LV hypertrophy, age > 60 years, smoking, hypertension, and dyslipidaemia. The type of non-invasive testing (dobutamine stress echocardiography versus myocardial perfusion scintigraphy) is at the discretion of the perioperative evaluator.[4, 6]

Patients waiting on the transplant list beyond one year, should be screened annually with an ECG and possibly resting TTE, although the usefulness of periodic screening for resting LV function while on the transplantation list is uncertain, except in patients with moderate aortic stenosis who should be treated as rapid-progressors and therefore have yearly resting echocardiography. Recent studies have suggested that elevated pulmonary artery pressures are associated with adverse outcomes after renal transplantation. Renal transplant candidates found to have pulmonary hypertension on TTE should have right heart catheterization to confirm the diagnosis and full evaluation performed by a physician with expertise in pulmonary hypertension management.[4]

There are a number of studies of showing lipid-lowering therapy in patients with CKD and ESRD. The preponderance of the evidence favours use of statins for cardio protective effects. Statins lower cholesterol and also have antioxidant properties that reduce endothelial dysfunction, prevent plaque rupture in vessel walls, and inhibit platelet aggregation and thrombus formation.[9] A meta-analysis of 43 randomized controlled trials in CKD patients found a 19% relative reduction in fatal MACE with statin use, an effect approximating the benefit of statins in the general population. In the Study of Renal and Heart Protection (SHARP) clinical trial, 9,270 patients with CRD and no prior history of MI or coronary revascularization were randomly assigned to receive simvastatin plus ezetimibe or placebo. After a median of 4.9 years, there was a 17% reduction in the relative risk of MACE in the simvastatin/ezetimibe group. There was a low risk of myopathy, 2 per 10,000 patients per year of treatment. There was no evidence of excess risks of hepatitis, cancer, or excess death from any nonvascular causes.[8]

There are no large randomized controlled trials of aspirin or other antiplatelet agents to prevent MACE specifically in CKD or ESRD patients. As there is excellent evidence of benefit in the general population, low dose aspirin has been recommended in all patients with CKD who do not have a contraindication to its use.[8]

In general, transplant candidates should have individualized treatment for CVD and risk factors particularly hypertension, diabetes, hyperlipidaemia, smoking, and obesity. Anticoagulation therapy must be cautiously administered and carefully monitored in ESRD patients as they have an increased risk of bleeding.

Pulmonary
The respiratory challenges facing the anaesthetist during kidney transplantation surgery arise mostly from volume overload and pulmonary congestion. This usually results in hypoxaemia and occasionally hypercapnia. In patients undergoing peritoneal dialysis, diaphragmatic splinting may lead to basal lung atelectasis and result in arterio-venous shunting. Dialysis and fluid removal prior to surgery is helpful with alleviating pulmonary congestion. There are no specific indications for further pulmonary work-up in kidney transplant patients unless the patient has other co-morbid lung diseases.[4]

Gastrointestinal
Uraemia from kidney failure may lead to gastro paresis. Additionally, many ESRD patients suffer from diabetes mellitus and autonomic neuropathy and should therefore be treated with full stomach precautions. Pre-operative treatment with a Histamine^2 blocker and metoclopramide are recommended.

Endocrine
ESRD Patients with diabetic nephropathy are known to have higher mortality rates and increased risk of CVD than those with other causes for ESRD. Diabetic patients undergoing transplantation should be screened for CAD.[4] Good glycaemic control before and during transplant is associated with better outcomes.[13] Point of care glucose should be checked prior to surgery and then hourly. Glucose control between 6.6 - 11.1 mmol / L is recommended rather that tight glycaemic control.[16]

Hyperphosphataemia resulting from decreased excretion of phosphate and hypocalcaemia due to reduced absorption of Ca^{2+} from the GI tract and vitD deficiency are very common. This leads to a 2° hyperparathyroidism and demineralization of bone, possibly leading to pathologic fractures.[15]

Electrolytes & acid-base status
Patients with ESRD may present with electrolyte and metabolic abnormalities such as hyponatraemia, hyperchloraemia, hyperkalaemia, hypocalcaemia, hypermagnesaemia and metabolic acidosis. The severity of these electrolyte derangements is usually related to the timing of the patient's last dialysis session. Hyperkalaemia is most concerning in the perioperative period. Since these patients are usually chronically hyperkalaemic, the ECG changes usually seen in hyperkalaemia may not be present until much higher values are reached. Consequently, it is important to periodically check to detect hyperkalaemia. To avoid complications of hyperkalaemia, treatment should be considered if the potassium is greater than 5.5 mEq / L. Routine pre-operative electrolyte evaluation should be obtained prior to surgery.[4]

Na^+ and H_2O balance are closely related and in patients with CKD, the total body content of Na^+ and H_2O may be increased. This is due to glomerular disease promoting Na^+ retention leading to extracellular fluid expansion, which contributes to hypertension. The renal mechanisms for conserving Na+ and H_2O may also be dysfunctional and, especially if additional fluid loss takes place (vomiting, fever), these patients can be severely volume depleted.[14]

Metabolic acidosis is commonly noted when the GFR decreases to less than 25%. The decreased renal mass results in less NH_4^+ production and excretion of proton load. Chronic acidosis promotes muscle wasting, reduced albumin synthesis, impairs bone formation, and decreases insulin sensitivity.[14]

Haematologic
Patient with ESRD usually presents with normochromic, normocytic anaemia. Anaemia has been linked to cardiovascular morbidity and mortality, with the independent relative risk of mortality in dialysis patient to be 1.18 per 1.0 g / dl decrease in Hb level. Anaemia in ESRD results from impaired erythropoiesis from decreased EPO synthesis and release, and also decreased RBC life span. In addition, increased haemolysis, repeated blood loss during dialysis, uraemia induced bone marrow suppression and iron, folate & vitamin B_6 / B_{12} deficiencies all contribute to anaemia. Ideally patients should be treated with synthetic EPO to increase Hb.[4] Anaemia is well tolerated in most patients due to compensatory increases in cardiac output, 2,3-DPG and a right ward shift of O_2 dissociation curve, which results in improved tissue oxygenation.[14] The correction of decreased erythropoiesis with EPO, aids O_2 transport and decreases cardiac output, heart rate and cardiac workload, which leads to a decrease in LV hypertrophy and overall improvement in cardiac status. Exercise capacity, cognitive function and quality of life also improve. Ultimately, mortality is reduced.[4]

Patients may also have uraemia-associated thrombocytopaenia and thrombocytopathia. A thorough history should be obtained to detect possible platelet dysfunction requiring investigation. Routine preoperative

prothrombin time (PT), partial thromboplastin time (PTT), INR, full blood count (FBC), and liver function tests should be obtained during the pre-transplantation work-up.[4]

Nervous System
CNS manifestation such as malaise, fatigue, inability to concentrate, seizures and coma can be seen in patients who are uraemic. These complications are reduced with dialysis. Other manifestations such as prior stroke may be seen due to the vascular disease that often accompanies ESRD. Peripheral and autonomic neuropathies can lead to orthostatic hypotension and silent myocardial ischaemia.[16]

Intra-operative Considerations

Pharmacology
ESRD not only affects the pharmacokinetics and pharmacodynamics of drugs excreted by the kidneys, but also modifies the disposition of drugs through changes in protein binding or hepatic metabolism. Hepatic drug metabolism is influenced either through induction or inhibition of hepatic enzymes or by alteration of hepatic blood flow, and the production and elimination of metabolites. Changes in body fluid distribution and circulatory volume, which occur in patients with ESRD, also affect drug disposition. Anaesthetists should therefore be knowledgeable about the changes in the metabolism of each drug administered in the perioperative period. The distribution and clearance of the short acting benzodiazepine midazolam remains relatively unchanged making it a drug of choice for anxiolysis in this group of patients.[4]

Induction agents
Propofol and thiopental are safe for induction of anaesthesia in renal transplant surgery, as they are inactivated in the liver. The use of etomidate cannot be recommended as it induces adrenal insufficiency and increases mortality in critically ill patients.[6]

Neuromuscular blocking agents
Succinylcholine should be used with caution in patients with ESRD due to its potential to increase serum K^+ concentration, which can result in cardiac arrhythmias and even cardiac arrest. Long-acting nondepolarizing muscle relaxants (NDMR) are largely eliminated by renal excretion and their effects may be significantly prolonged in patients with ESRD, leading to a high rate of residual blockade at the end of surgery. Therefore, NDMRs that are not primarily dependent on renal function should be used for general anaesthesia. Cisatracurium is metabolized through Hofmann elimination and produces a metabolite, Laudanosine, which is partially eliminated through the kidneys hence, has a slightly prolonged elimination half-life in patients with renal failure. Overall, the duration of action of cisatracurium is slightly prolonged in CKD. The duration of action of vecuronium and rocuronium in patients with renal failure has been reported to be slightly prolonged and a cumulative effect has been noted with repetitive administration. Due to the 100% renal excretion of the sugammadex / rocuronium complex, its use is not recommended in patients with ESRD, although further studies are needed. Cisatracurium is the preferred muscle relaxant in patients with ESRD and neuromuscular monitoring is recommended in all patients undergoing renal transplant surgery.[4, 6]

Opioids
Peri-operative opioids should be administered with care in ESRD patients undergoing transplantation given that they and their active metabolites depend on renal excretion and may accumulate.[17] The effect of morphine is prolonged in patients with CKD as a result of the accumulation of its active metabolite morphine-6-glucuronide. Similarly, the administration of high or repeated doses of pethidine in these patients may lead to seizures due to the accumulation of its metabolite, norpethidine.[4] The elimination of oxycodone is also impaired in ESRD patients undergoing renal transplant.[17] Importantly, the pharmacokinetics of fentanyl, alfentanil, sufentanil are not altered in CKD, because the metabolites are inactive and are unlikely to contribute to the opioid effect even if they do accumulate. Remifentanil requires no change in dosing compared to patients with normal renal function.[4]

Inhalational agents
All potent inhalational agents cause a decrease in the renal blood flow and GFR in proportion to the dose. Many also release fluoride as a by-product and F^- has been linked to high output renal failure. Although F^- is a major metabolite of isoflurane, the extent of its metabolism is very small such that the amount produced is unlikely to cause renal damage and it can be used safely for renal transplantation. Sevoflurane is metabolised to compound A by standard CO_2 absorbents and can accumulate within the anaesthesia machine gas circuit when used at low gas flows. Compound A has been shown to be nephrotoxic in rats but has not been reported to cause renal dysfunction in humans. Sevoflurane has been found to be safe, even at low flows, and does not alter kidney function in patients with pre-existing renal disease. Similarly, desflurane is also safe to be used in patients with CKD.[14, 15, 17]

Diuretics
The use of furosemide for the treatment of acute renal failure is controversial. Two large randomised controlled trials did not show any benefit of furosemide on the recovery from renal failure in patients with oliguria.[22, 23] The effect of diuretics on renal function after transplantation requires further study. The administration of mannitol, immediately before reperfusion, has been shown to improve renal perfusion pressure. Three randomised controlled trials showed a significant, albeit transient, reduction in acute renal failure immediately after transplantation using mannitol,[24 - 26] and it is administered to nearly all patients undergoing renal transplant surgery.[6]

Avoidance of potentially nephrotoxic agents
Potential nephrotoxic agents should be avoided in any patient, but particularly in patients undergoing renal transplant surgery and in potential kidney donors. The nephrotoxic properties of drugs commonly used during anaesthesia warrant special consideration and are summarised below.

Table 1. Suitability of drugs commonly used during transplantation surgery[6]

	Use	Avoid
Volatile anaesthetics	Iso/Sevo/Desflurane	Enflurane
Neuromuscular blocking drugs	Cis/atracurium	Pancuronium Sugammadex
Rapid sequence induction	Rocuronium (1.2mg/kg) Succinylcholine (if K^+<5mmol/l)	
Analgesics	All fentanyl analogues	NSAIDS (Morphine)
Diuretics	Mannitol	Furosemide

Anaesthetic Management

Kidney transplantation is usually performed under general endotracheal anaesthesia (GETA) which provides stable haemodnamics, excellent muscle relaxation, and predictable depth of anesthesia.[17] Early kidney transplants were done under spinal anaesthesia and is still used by some transplant centres. The advantages of regional anaesthesia (RA), is the absence of the need for endotracheal intubation or the administration of neuromuscular blocking agents. These advantages are, however, negated if RA must be extensively supplemented with IV or inhaled anaesthetic drugs. Furthermore, the blockade of the peripheral sympathetic nervous system can complicate control of systemic BP, especially considering the unpredictable intravascular fluid volume status of many of these patients. Combined techniques using GETA and epidural analgesia can also be employed.[4, 6] Haemodynamics and renal function have not been reported to differ significantly between techniques.[18] The use of RA, particularly epidural anaesthesia, needs to be considered carefully in the presence of abnormal coagulation.[15] Another consideration is to avoid A-V fistula or future fistula sites when placing IV cannula.

Monitoring
Adequate monitoring is essential in patients undergoing kidney transplantation. Standard ASA monitors may be sufficient if the patient has no other co morbidities except ESRD. Most patients, however, will benefit from CVP insertion and possibly invasive arterial blood pressure monitoring given the expected large swings in hemodynamic parameters during surgery. Patients with severe CAD, LV dysfunction, valvular abnormalities, or pulmonary hypertension may also benefit from advanced intra-operative monitoring such as transoesophageal echocardiography (TOE).[4] Whether thermodilution or pulse contour-based cardiac output monitoring devices, such as the PiCCO or LidCO, can improve outcome after renal transplant surgery has not yet been studied. However, one limitation to the use of these devices is the need for an arterial line. Many of these patients have vascular disease and non-invasive devices, such as a recently introduced technique, which computes beat-to-beat cardiac output from radial artery pressure and capillary pulse, could be an alternative. The use of echocardiography to assess cardiovascular and fluid status during renal transplant surgery has also not yet been studied however, in patients with significant cardiac complications or valvular disorders, it may be useful.[6]

Haemodynamics
It has been shown that CVP does not correlate well with fluid status both in the general surgical patient and renal transplant patients.[4, 19] Despite this, current textbooks still advocate *"aggressive volume expansion to a target CVP of 10 - 15 mm 'Hg' is optimal"*. This management goal is based on evidence that volume

expansion is associated with increased renal blood flow and improved graft function.[4, 6, 14] CVP invariably declines in the late intra-operative and immediate postoperative period despite positive fluid balance and vigorous fluid resuscitation. The aetiology is unclear but may be due to increased vascular permeability and alterations in vascular tone accompanying surgery. Graft acute tubular necrosis (ATN) has been reported to be lower in patients who are vigorously hydrated. Although studies have found no correlation between the decrease in CVP and fluid balance, the fluid balance of recipients correlated strongly with immediate post-operative graft function.[4]

Normotension or slight hypertension (SBP 130 - 160 mm 'Hg')[14] should be maintained to help graft function, but one should be weary of using alpha agonists, as the vasoconstriction may interfere with renal perfusion.[20] Other agents used to promote renal blood flow such as dopamine, dobutamine and fenoldopam as well as osmotic and loop diuretics (mannitol and furosemide) have been proposed as aiding kidney function after reperfusion. Of these, only mannitol has been shown to decrease the incidence of ATN.[20] Two meta-analyses have shown a negative effect of dopamine on renal function in acute renal failure.[4] In addition, another study showed a higher mortality and prolonged length of ICU stay in patients receiving dopamine after renal transplant surgery. Therefore, the use of dopamine in renal transplant surgery cannot be recommended.[6] In contrast, dobutamine can be used as a positive inotrope for patients with a low cardiac output and these patients should receive advanced haemodynamic monitoring to optimise volume and drug therapy. When volume loading is not tolerated, such as in patients with pulmonary oedema, vasopressors should be considered despite the risk of renal vasoconstriction. The use of noradrenaline in donors does not have a negative effect on graft function in recipients. This is because the harmful effect of a low blood pressure outweighs the potential renal vasoconstriction caused by vasopressors. On the basis of the current data, a clear recommendation for the use of vasopressors cannot be made; however, it seems sensible to avoid hypotensive episodes, especially after reperfusion. The overall anaesthetic goal for the newly transplanted kidney is to maintain intravascular volume with optimal fluid therapy and avoid decreased perfusion to the new kidney.[4, 6]

Fluid Choice

In a survey performed in 2002, 'normal saline' was used in more than 90% of renal transplant surgery procedures in order to "avoid hyperkalaemia" and has historically been the fluid of choice.[4, 6] However, studies have shown that its use leads to a significant increase of serum K^+ when compared with Ringer's solution. This effect is likely due to an extracellular shift of potassium, caused by acute changes in serum H^+ concentration, which occurs in association with hyperchloraemic metabolic acidosis. Modern balanced crystalloid solutions are inexpensive and are a suitable hydration solution in renal transplant surgery. As larger volumes may be required and patients should be kept normothermic, fluids are warmed before administration. Although the risk of a significant increase in serum K^+ is small, continuous monitoring of serum electrolytes is essential during the operation, especially just before and after reperfusion of the transplanted organ.

Colloids may be considered in recipients with severe intravascular volume deficits who require high-volume resuscitation.[4] Although there is little evidence from clinical studies for the use of albumin in renal transplant surgery; many authors suggest an improvement in short and long-term outcome in these patients after volume expansion with albumin. These results were not confirmed in other investigations and, due to side effects such as anaphylactic reactions and potential contamination with infectious diseases, the routine use of albumin is not recommended in renal transplant surgery.[6] Artificial colloids such as gelatine, dextrans and hydroxyethyl starch (HES) have been developed more recently. Adverse effects have been reported with all of them. One problem is anaphylactic reactions, which are more common with dextrans and gelatine than for HES. Other side effects include bleeding complications, reticulo-endothelial system dysfunction and impaired renal function. An ideal HES solution combines the lowest in-vivo molecular weight above the threshold for renal elimination, with a low degree of hydroxyethyl substitution. The data on the use of HES 6% 200 / 0.625 to non-living kidney donors resulted in a negative effect on renal function. In more recent studies, medium molecular weight HES with a low molar substitution (HES 130 / 0.4) was shown not to affect the incidence of delayed graft function. In contrast to gelatine 4%, medium molecular weight HES shows a slight advantage regarding the recovery of renal function immediately after transplantation. However, concerns about the use of HES were highlighted by the VISEP trial, which reported a higher incidence of renal failure in septic patients when high molecular HES was used in doses greater than the recommended daily maximum dose. Even though these findings cannot be easily translated to the setting of renal transplant surgery, HES should be used with caution and reserved for special indications, such as the need for large volumes of fluid or for an increase in colloid osmotic pressure, until more data about the effect of medium molecular weight HES on graft function is available. Further prospective randomised trials are required to identify the ideal fluid for renal transplant surgery and to assess whether the incidence of delayed graft function can be reduced by an optimised volume therapy regime.[6]

Blood Transfusion
Although the immunomodulatory effects of blood transfusion were used in the 1970s to reduce organ rejection, later investigations showed a higher incidence of acute graft rejection due to HLA antigen sentization.[6, 15] As most patients have become accustomed to chronic anaemia and significant blood loss during the operation is rare, transfusion should be performed reluctantly; the transfusion trigger for these patients is not known, but is probably lower than in patients without renal failure.[6] Should replacing blood volume losses be required, transfusing with packed, washed and irradiated RBCs should be undertaken.[2]

Postoperative Care

- There are many important aspects regarding the postoperative management of renal transplant patients:
- These patients need close monitoring in a specialized ward. There are no recommendations as to whether all renal transplant patients should be admitted to the ICU, as their risk of hospital-acquired infection is increased. When they are treated in the ICU, for example if they require mechanical lung ventilation, their outcome is worse compared with other patients.[4, 6]
- Optimised volume therapy is essential with close monitoring of urine output. For example, a sudden decrease in urine output despite good intravascular volume status may require urgent surgical re-exploration. However, no recommendations or algorithms have yet been published or evaluated.[4, 6]
- Continue to avoid nephrotoxic agents.[6]
- Post-operative pain relief is essential after renal transplantation, as inadequately controlled pain can lead to agitation, tachycardia, hypertension and an increased risk of pulmonary complications. Postoperative pain can either be managed with epidural analgesia, if suitable, or by patient-controlled analgesia (PCA). Fentanyl (or if morphine used, beware of reduced clearance) delivered by PCA can provide sufficient pain relief. Epidural analgesia provides superior analgesia but may occasionally result in hypotension and decreased renal perfusion complicating graft survival. PCA while less effective for pain control is less likely to cause hypotension. Alternative methods such as wound infusion catheters may prove beneficial and require further investigation. The use of non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided. The use of high-dose NSAIDs in patients with CKD has been shown to increase the risk of rapid progression of the disease in the elderly age group. Cyclo-oxygenase[2] enzyme inhibitors have also been reported to be nephrotoxic in transplant recipients and in patients with impaired renal function.[4]

Immunosuppressive Therapy

Immunosuppression varies by centre and is usually protocol based. Regimens can be high dose conventional regimen or an antibody induction regimen. The conventional regimen consists of a calcineurin inhibitor (cyclosporine or tacrolimus), a corticosteroid, and an antimetabolite (mycophenalte mofetil or azthoprine). The antibody induction regimen, which has shown better graft outcomes, uses lower doses of the conventional medications with the addition of an antibody directed at T-cells antigens: anti-lymphocyte antibodies or interleukin-2 receptors antagonist. Induction of immunosuppression usually begins with the corticosteroid and an antilymphocyte administered shortly before reperfusion of the renal graft. As antithymocyte globulin can induce an anaphylactic reaction, it should be given carefully over a period of 60 min. Because of the use of immunosuppressive therapy, sterile conditions for invasive procedures is essential.[4, 6]

Summary

ESRD patients and kidney transplantation present significant challenges for the anaesthetist in the perioperative period. An extensive preoperative ‘work-up’ is required to identify risk factors, to improve cardiac conditions, to treat hyperkalaemia and acid–base disturbances and to develop individualised and tailored perioperative therapy regime. This, in combination with optimal care for the living donor, the avoidance of potentially nephrotoxic drugs, the implementation of goal-directed haemodynamic management and optimised postoperative care, may improve outcome after renal transplant surgery.

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ARDS : Evidence–based strategies to improve outcome

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Mortality and incidence

Acute respiratory distress syndrome (ARDS) literature refers to various different outcomes. Mortality has been suggested as the preferred primary outcome that does not require very large study sample sizes, if conducted in appropriately selected patient populations. It is also argued that measurable intermediate outcome variables do not exist for ARDS & that non-mortality outcomes are inconsistent, have variable external validity and may be subject to bias. Opposing views suggest that the mortality outcome itself is variably defined in studies and since survival is improving, other outcomes e.g. long-term cognitive and physical dysfunctions are becoming more clinically relevant.

In 1994 the first studies with lung protective ventilation showed improved survival which since has been 50-60%. Small percentage of deaths is due to hypoxemia (15%) with most being caused by multi-organ failure. Studies on ARDS incidence in adults published in the last decade using the AECC definition. The European studies reported a population-based incidence ranging from 5 to 7.2 new ARDS cases/100 000 population/year which is markedly lower than the 33.8/100 000/year reported in the USA. The presentation will focus on the interventions that have shown mortality benefit and those that have improved oxygenation and may require further, more robust studies to prove survival benefit.

Definition

Table 1. ARDS Berlin definition.

The Berlin definition of acute respiratory distress syndrome	
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities — not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mmHg < PaO_2/FIO_2 ≤300 mmHg with PEEP or CPAP ≥5 cmH_2O[c]
Moderate	100 mmHg < PaO_2/FIO_2 ≤200 mmHg with PEEP ≥5 cmH_2O
Severe	PaO_2/FIO_2 ≤100 mmHg with PEEP ≥5 cmH_2O

Abbreviations: CPAP, continuous positive airway pressure; F_IO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; [a]Chest radiograph or computed tomography scan; [b]If altitude is higher than 1,000 m, the correction factor should be calculated as follows: [PaO_2/FIO_2 (barometric pressure/760)]; [c]This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

Ranieri VM, Rubenfeld GD, Thompson BT, et al. ***Acute respiratory distress syndrome the Berlin definition.*** *JAMA 2012; 307.*

Risk factors

Table 2. Common risk factors for ARDS

Direct	Indirect
Pneumonia	Non-pulmonary sepsis
Aspiration of gastric contents	Major trauma
Inhalational injury	Pancreatitis
Pulmonary contusion	Severe burns
Pulmonary vasculitis	Non-cardiogenic shock
Drowning	Drug overdose
	Multiple transfusions or transfusion associated acute lung injury (TRALI)

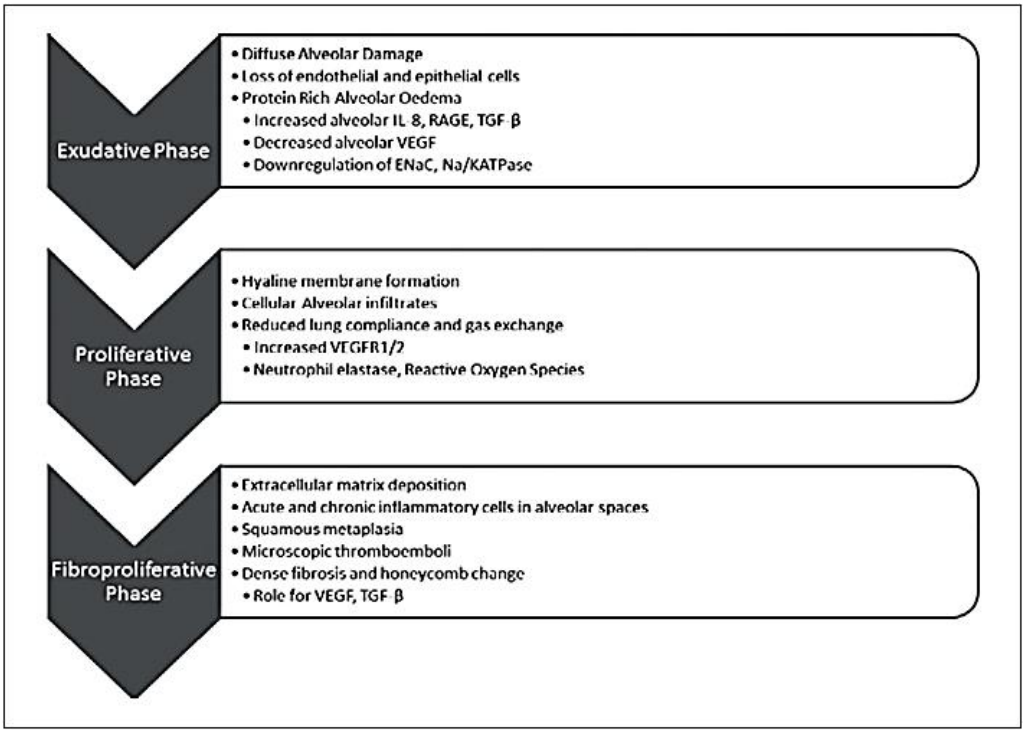
Ranieri VM, Rubenfeld GD, Thompson BT, et al. ***Acute respiratory distress syndrome the Berlin definition****. JAMA 2012; 307.*

Pathophysiology [(1)]

The progression of ARDS described as phases however, they can occur concurrently. The early, exudative phase demonstrates diffuse alveolar damage, with disruption of the alveolar-capillary membrane (ACM) which leads to changes in alveolar fluid transport and clearance. Alveolar epithelial cell apoptosis with altered endothelial-epithelial permeability lead to impaired physical barrier properties & alveolar proteinaceous oedema

In the proliferative phase there is formation of hyaline membranes on the epithelial side of the basement membrane, with a cellular infiltrate into the alveolar spaces comprising neutrophils, macrophages and erythrocytes. Increased neutrophil recruitment and activity together with altered patterns of chemokine expression [interleukin-8 (IL-8), transforming growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF) & receptor for advanced glycation end products (RAGE)] generates reactive oxygen and nitrogen species along with proteolytic enzyme release. These changes lead to a loss of lung compliance and impaired gas exchange.

If progressive, the fibro-proliferative phase follows and is marked histologically by extracellular matrix (ECM) deposition with acute and chronic inflammatory cells (fibroblast and type II alveolar epithelial cell) proliferation within the alveolar space with associated squamous metaplasia & microscopic thrombo-emboli. This phase of injury demonstrates remodelled lung architecture with dense fibrosis and ultimately honeycomb changes in the lung.



Ventilatory strategies

Lung Protective ventilation

The landmark ARDSnet study in 2000[(2)] which compared tidal volume (V_t) of 6ml/kg vs. 12ml/kg (predicted body weight) and Pplat ≤ 30 cmH_20 vs. ≤ 50cmH_2O, showed significantly improved in-hospital mortality 31 vs. 39.8[%](p= 0.007),ventilator free days 12 vs.10 (p=0.007) & non-pulmonary organ failure free days 15 vs. 12 (p=0.006). The criticism of this trial though is the injurious V_t and Pplat level used which could account for the worse outcomes in the conventional group.

The aims of lung protective ventilation is to reduce ventilator-induced lung injury(VILI):

- Vt : 6ml/kg (PBW)- avoid volutrauma
- Pplat : < 30cmH2O-avoid barotrauma
- PEEP ≥ 5cmH20- avoid atelectrauma
- Respiratory rate : 18-25/min (to achieve adequate minute ventilation with the lower V_t)
- Permissive hypercarbia (pH>7.2) & SpO2 : 88-92% : adjusting the targets to accommodate the changes above.

Evidence of survival benefit:

A Cochrane review & meta-analysis in 2013 looked at 6 RCT's till 2013 in ARDS which compared

- Low V_t <7ml/kg or Pplat < 30cmH_20 vs. V_t 10-15ml/kg. There was relative risk reduction of 26[%] in 28-d mortality. Did the low V_t or Pplat confer survival benefit?
- When conventional Vt (10-15ml/kg) with Pplat ≤ 31 cm H_20 was compared there was no mortality benefit.

Recruitment

The distending pressure of the lung (transpulmonary pressure) is the difference between airway pressure and pleural pressure. A recruitment manoeuver aims to overcome chest wall elastance and impart a distending pressure that opens collapsed alveoli. The length of time that a given distending pressure is applied may be less important as most recruitment occurs in the first few seconds of a sustained inflation but a longer duration of inflation can lead to haemodynamic compromise.

In ARDS both compressive and absorptive atelectasis occurs and the pressures required to open alveoli collapsed due to compressive atelectasis is usually moderate (below 35 cmH_2O) compared to those required for absorptive atelectasis. Reversal of atelectasis will decrease atelectrauma, as well as reduce the shear forces associated with ventilating heterogeneous lungs. Opening of collapsed alveoli decreases the strain ratio of tidal volume to FRC.

Assess the potential for recruitment to be a success. Conditions associated with better recruitment include: extra-pulmonary cause, diffuse parenchymal changes, higher chest wall & lower respiratory system elastance and if lower baseline PEEP needed.

There are various techniques of recruitment eg.sustained inflation pressures, 'sigh', stepwise increase in PEEP with fixed Pplat, prolonged stepwise increase in PEEP with constant driving pressure.Prone positioning and sponatanoeus respiratory activity also improve regional recruitment. Monitoring the recruitment response could be by the change in oxygenation, lung compliance, CT scan of chest or electral impedance tomography. End-tidal CO_2 can also be used to assess response to recruitment with some studies evaluating it as a better indicator than oxygenation, but it can be influence by other factors that affect the total body CO_2 stores.

PEEP

The most important aspect following a recruitment manoeuvre is to avoid decruitment by setting an appropriate PEEP. This can be done in many ways with a decremental PEEP titration commonly used.While adequate PEEP is necessary, excessive amounts of PEEP will lead to overdistension and barotrauma with worsening of dead-space ventilation due to compression of inter-alveolar capillaries.

There have been 5 RCT's that compared higher PEEP(10-15 cmH_2O) vs. lower PEEP(7-9cmH_20).The ALVEOLI, LOV and ExPress trials which used V_t of 6ml/kg in control and intervention groups showed a trend towards but not statistically significant improved in-hospital mortality. The studies by Villar et. al (2006) and Amato et al. (1998) used large V_t (9-12 ml/kg) in the control group and showed reduced ICU and 28-day mortality. This survival benefit was most likely not due to the experimental group's higher PEEP but rather their lower V_t compared to the control. An individual patient meta-analysis by Briel et al [(3)] in 2010 showed that in patients with a P/F ratio <200 the in-hospital survival improved & time to unassisted breathing was shorter with higher PEEP. A recent post-hoc analysis [(4)] of patients in ARDSnet trials assessed the driving pressure as an independent variable associated with survival. They postulated that driving pressure was a surrogate of cyclic lung strain which predicted lung injury better than the tidal volume.They found that 1 standard deviation (7cmH_2O) increase in driving pressure increased risk of in-hospital mortality(RR 1,36 $p<0.001$).Changes in V_t or PEEP were associated with improved survival only if reduced it this lead to decreased driving pressure. This was, however, a retrospective analysis and should for now be considered as hypothesis generating.

Prone Positioning [5]

During ARDS increased lung mass may develop a superimposed pressure four-five times greater than normal and collapse the most dependent lung regions (compression atelectasis) In addition, heart weight & abdominal pressure contribute to lung collapse. When patients are shifted into the prone position:

- Chest wall compliance decreases
- Lung density redistributes from dorsal to ventral due to recruitment of dorsal lung regions and collapse of ventral ones
- In dorsal regions (non-dependent when prone) the increased aeration and recruitment tend to exceed the decreased aeration and de-recruitment of the ventral regions (dependent when prone)
- The PaO_2 improvement may be due either to recruitment and aeration of perfused and previously collapsed lung regions or to diversion of blood flow from atelectactic regions to aerated ones. The most probable mechanism of oxygenation improvement is that the recruitment of perfused tissue in dorsal regions exceeds the ventral de-recruitment. The redistribution of blood flow as seen in animal studies and PET scans does not change substantially in the conversion from the supine to prone position.
- Impaired CO_2 clearance reflects structural changes of the lung parenchyma and strongly predicts outcome. Dead space and PaCO2 do not necessarily change but proning may improve CO2 clearance if repositioning causes dorsal recruitment to exceed ventral de-recruitment, and/or if hyperinflation & over-distension in ventral regions decreases to improve compliance. Both these decrease regional stress and strain which translates to improved outcomes
- Prone positioning relieves cardiac compression of the supporting lung and may improve lymphatic drainage as the heart moves inferiorly toward the sternum

Of the 5 large RCT's on prone ventilation, only one showed survival benefit. The **PROSEVA** trial [6] by Geurin et al. showed 28-day & 90-day mortality reduction in patients with severe ARDS. The study design and patient selection indicates why this trial showed better survival.

1. ARDS criteria confirmed after 12–24 h
2. ARDS with severity criteria:
   PaO_2/FIO_2 <150 mmHg with FIO_2 ⩾0.6 + PEEP ⩾5 cmH_2O + V_T 6 $ml \cdot kg^{-1}$ predicted body weight
3. Several noninclusion criteria
4. Strict lung protective mechanical ventilation (in both groups)
5. First prone position session started within 1 h after randomisation
6. Prone sessions of at least 16 h consecutively
7. Predetermined stopping criteria of prone position
8. Crossover not allowed except as a lifesaving procedure in the supine group
9. Neuromuscular blockade in both groups
10. Centres with expertise in prone positioning for many years

Patients were recruited early, with specified degree of severity (P/F ratio < 150 mmHg), lung protective ventilation & neuromuscular blockade was used in both groups. The prone ventilation sessions were started early and continued for at least 16 hours in centres with expertise .

- A meta-analysis in 2014 of 9 RCT's made similar conclusions .Here prone ventilation in patients with P/F ratio <100mmHg, for at least >12 hrs, with PEEP between 10-13 cmH_20 were associated with decreased 28, 30 & 60-d mortality.
- The Surviving Sepsis Campaign guidelines (2013) recommends (grade 2C) prone ventilation in patients with a P/F ratio < 100mmHg in facilities that have experience

HFOV

High-frequency oscillatory ventilation (HFOV) provides pressure oscillations around a relatively constant mean airway pressure (mPaw) at very high rates (3-15 breaths per second).This results in very small tidal volumes(1–3 ml/kg PBW), with active inspiration and expiration. HFOV is thought to be lung protective because it avoids zones of over-distension and de-recruitment /atelectasis provided an optimal mPaw is set and very small VTs are delivered.

In a systematic review and meta-analysis of 8 trials (2 paeds) in 2010 where 86% of the patients had moderate-severe ARDS, HFOV within 2-5 days of ventilation lead to reduction in hospital & 30-day mortality (Risk ratio: 0.77).But the mortality outcome was assessed 352 patients only with heterogeneity of physiological outcomes & the control group of the 3 largest studies were ventilated with V_t >6-8ml/kg. *Sud .S et al. BMJ 2010; 340:2327*

In 2013 the United Kingdom's **OSCAR** *(NEJM 2013; 368:806-813)* & North America's **OSCILLATE** (*NEJM 2013; 368:795-805)* trials were published.

OSCAR:

- Control group –"pragmatic" ventilation
- HFOV with a new ventilator , 9 centres with HFOV experience
- No difference in all cause in-hospital & 30-day mortality
- ? due to frequency being too low(7Hz) & lack of LPV
- Higher mortality than OSCILLATE control

OSCILLATE:

- Open lung approach in control
- Most centres had HFOV experience and had used that model of ventilator before
- In-hospital mortality reduced :HFOV 47% vs. 35% (p=0.005)
- mPAW higher :~38cmH20, Frequency 5,5 Hz
- BUT increased hemodynamic compromise : Vasoactive drugs used (66-73%) & higher positive fluid balance

There is still insufficient evidence of survival benefit with HFOV in adult patients with ARDS

Non-ventilatory Strategies

Neuromuscular blockers

The proposed mechanisms by which the use of neuromuscular blockers in ARDS confers benefit include improved thoracopulmonary compliance & ventilator synchrony. This may facilitate lung-protective mechanical ventilation & avoid asynchrony-related alveolar collapse and regional alveolar-pressure increases with over-distention. This may decrease intra-pulmonary shunt and protect against VILI, with possibly specific benefit in decreasing the pulmonary& systemic cytokine release.

The **ACURASY**S study by Papzian et al *(NEJM 2010;363:12)* randomised patients with severe ARDS (P/F ratio <150 mmHg) to receive cisatracurium within 48 hours & for 48 hours only.Primary outcome of crude 90-day mortality was not significantly different until the results were adjusted for P/F ratio, pPlat , SAPS II, then in the subgroup of P/F ratio<120 a survival benefit was found.Secondary outcomes of vent-free days & organ-failure free were better in the intervention group who also had less incidence of pneumothorax (due to barotrauma) and no difference in ICU paresis.

This study was combined with 2 others that used cisatracurium for 48 hours in severe ARDS in a meta-analysis (*Neto AS et al. Annals of Intensive Care 2012, 2:33)* which found :

- Reduced overall(ICU & 28d) mortality , NNT=7
- More vent-free days at day 28 with higher P/F ratios
- Less barotrauma & no difference in incidence of CINMA

Another meta-analysis of th same studies(*Alahazzani W, Alsharani M, Jaeshke R et al. Crit Care 2013;17(2))* also showed improved ICU, 28 d & in-hospital mortality , NNT=9. But both these meta-analyses extracted most of the patient numbers from **ACURASYS** and were done by the investigators of the primary studies.While there was no increase in critical illness myopathy, only cis-atracurium was used and not steroidal compounds (vecuronium, pancuronium, and rocuronium) which may carry the highest risk of myopathy. The risk of myopathy & diaphragmatic dysfunction has lead to suggestion that in mild-moderate ARDS, spontaneous respiration may be more beneficial by increasing dependent zone recruitment & reducing sedation and length of mechanical ventilation.

Steroids

Before LPV early animal & clinical studies of steroids in sepsis and ARDS showed improved physiological variables like oxyhaemoglobin dissociation, pulmonary vascular pressure & alveolar-capilary membrane permeability.In ARDS, the glucocorticoid-receptor complexes regulate the transcription of nuclear factor receptor-kb (NF-kb) which in turn modulates the transcription of many pro-inflammatory cytokines (including interleukins 1α, 1β, 2, 3, 5, 6, 8, and 12) TNF-alpha and interferon. They are synergistic with endogenous anti-inflammatory cytokines (interleukins 4, 10, 13, and interleukin-1 receptor antagonist) and inhibit fibroblast proliferation & decrease collagen deposition.

Factors affecting response to steroid treatment in ARDS include:

- Timing of initiation (Preventative or Therapeutic :early vs. late)
- Dosage (High vs. Low)
- Duration of Treatment (and if tapered)

Prevention of potential complications by infection surveillance, avoidance of paralysis and avoidance of rebound inflammation are essential.In the 4 studies used high dose (30mg/kg q6hrly) Methyl prednisone before the onset of ARDS, steroids did not prevent ARDS or reduce mortality once developed.(7)

Timing of initiation - Early:

Annane et al. CCM 2006;34:22-30

- Post–hoc analysis of steroids in sepsis(at study inclusion , hydrocortisone and fludrocortisone for 7 days)
- 28-d mortality reduced in the subgroup of non-responders to ACTH stimulation

Meduri G et al. Chest 2007; 131:954-963

- 91 patients low dose(1mg/kg/day IVI) methylprednisolone within 72hours,duration up to 28 days with taper
- 1°outcome : LIS score improved , more vent-free days
- 2°outcome: ICU mortality improved with (p=0.03)

Late *:* *Meduri G et al. JAMA 1998;280:159-16594-9624*

- ARDS patients low dose methylprednisolone after 7d on vent .Stopped early: cross-over of placebo to treatment

ARDSnet : Steinberg et al.NEJM 2006;354:1672-84

- Day 7-28 received low dose methylprednisolone with taper
- Subgroup of recruitment after day 14 had worse 60 day mortality but the baseline APACHE II in this group was higher than control

Evidence of survival benefit: The only recent study that showed mortality benefit *(Meduri G et al. Chest 2007; 131:954-963)* had small patient numbers & only ICU mortality (secondary outcome) was reduced. There is heterogeneity in the meta-analyses where cohort studies and RCT's are combined, patient selection (pneumonia without ARDS) and timing of initiation is variable. The mortality benefit therefore is disparate and relies on subgroup analysis which is inconsistent & imprecise eg.

Tang et al .CCM 2009; 37(5):1594-603

- Cohort and RCT low-dose steroids .Mortality RR 0.62
- The use of low-dose corticosteroids was associated with improved mortality and morbidity outcomes without increased adverse reactions. "Effective in treatment of ARDS"

Lamontagne F et al.J Crit Care 2010;25 (3);420-435

- 12 RCT's but only 6 ARDS- low-dose steroids before 14d
- OR 0.79: "Corticosteroids administered within 14 days of disease onset may reduce all-cause mortality".

Peter et al. (2008)[7]

- 8 RCTs for mortality analysis
- "A definitive role of corticosteroids in the treatment of ARDS in adults is not established"

Further RCT's are required in this area before a recommendation can be made.

Fluid therapy

Increased pulmonary capillary permeability together with increased hydrostatic pressure and decreased oncotic pressure can lead to increased extravascular lung water, which in some studies was an independent predictor of increased mortality. Positive intra-thoracic pressure during mechanical ventilation impedes the clearance of oedema via lymphatic flow and capillary reabsorption into the venous side of the pulmonary capillary network.

While a conservative fluid strategy may appear to be beneficial with regards to pulmonary outcome, there is concern about hypo-perfusion of other organs.

The **FACTT** trial (*NEJM 2006:354:24*) compared a liberal fluid strategy guided by CVP <8 cmH_2O & PAWP 14-18 mmHg vs. a conservative strategy where the CVP was maintained below 4 cmH_2O & PAWP <10-14 mmHg. There was no difference in 60d mortality (1°outcome) but:

- Conservative :28 days- improved oxygenation index & LIS
- More vent-free days, ↓ ICU LOS
- At 60 days- no↑ shock or dialysis requirements

A post-hoc analysis of the study patients *(Mikkelsen ME et al, Am J Respir Crit Care Med 2012; 185:1307-1315)* showed that hypoxemia & conservative fluid strategy was independently associated with long–term cognitive dysfunction.

FACTT Lite : *Grissom CK et al. CCM 2015;43(2):288-95*

Retrospective analysis of patients in ALTA (B_2 agonists) and EDEN (Early vs. Late feeding & omega 3 /antioxidants) trials. 1124 patients that were treated with a "Lite" fluid strategy (CVP4-8cmH_20) were

compared to the FACTT conservative strategy:

- No difference in 60 day mortality between groups
- Lite vs. conservative:vent-free days & AKI prevalence were equivalent
- Significantly less new shock in the Lite strategy

Adjusting the goals to those in the FACTT Lite strategy did not increase mortality but decreased other organ dysfunction and shock.

The contribution of the endothelial glycocalyx to the development of effective oncotic pressure decreases the influence of interstitial oncotic pressure on filtration rate. Most of the filtered fluid returns to the circulation as lymph. Diuretics, in addition to limited fluid intake, in haemodynamically stable patients did not affect 60-day mortality, oxygenation and the number of days without mechanical ventilation. Only patients that demonstrated elevated left ventricular filling pressures that contributed to pulmonary oedema were more tolerant of a negative fluid balance induced by diuresis and fluid restriction. Few studies investigated albumin added to diuretic therapy. Two studies in haemodynamically stable hypo-proteinaemic patients showed improvement of oxygenation with better fluid balance. The postulated mechanism of albumin's benefit in ARDS discounts the contribution of the glycocalyx and assumes an intact alveolar capillary membrane.

β_2 agonists have been used to decrease extravascular lung water via action of the Na^+/K^+/ATPase pump which would lead to sodium and water efflux. In the BALTI trial EVLW was decreased, oxygenation and lung mechanics improved. BALTI-2 was stopped early due excess mortality in intervention & the ALTA study was stopped early due to futility. Thus far there has not been evidence of survival benefit

ECMO

ECMO can be initiated when positive pressure ventilation cannot adequately maintain oxygenation or remove CO_2 or does so at the expense of VILI. ECMO facilitates the use of LPV by avoiding hypercapnia and allowing the reduction of tidal volumes while the PaO_2 is maintained.

Indications
Severe hypoxemia (e.g., ratio of PaO_2 to FIO_2 <80, despite the application of high levels of PEEP [typically 15–20 cm of water]) for at least 6 hr in patients with potentially reversible respiratory failure†
Uncompensated hypercapnia with acidemia (pH <7.15) despite the best accepted standard of care for management with a ventilator
Excessively high end-inspiratory plateau pressure (>35–45 cm of water, according to the patient's body size) despite the best accepted standard of care for management with a ventilator
Relative contraindications
High-pressure ventilation (end-inspiratory plateau pressure >30 cm of water) for >7 days
High FIO_2 requirements (>0.8) for >7 days
Limited vascular access
Any condition or organ dysfunction that would limit the likelihood of overall benefit from ECMO, such as severe, irreversible brain injury or untreatable metastatic cancer
Absolute contraindication
Any condition that precludes the use of anticoagulation therapy‡

Brodie D, Bacchetta M.NEJM 2011;365:1905-14

In observational studies survival rate of 47-66% was seen in selected patients with severe ARDS. The **CESAR** trial *(Peek GJ et al .Lancet 2009; 374:1351-63)* randomised 180 pts. with severe but potentially reversible respiratory failure. While they demonstrated a significantly reduced relative risk of death or disability at 6 months with ECMO, only 70% of the control group received LPV. The costs of

approximately £45000-54000/ 6 months-life & potential complications like hemorrhage, cannula thrombosis & infections need to be considered. The ongoing RCT,**EOLIA** investigating ECMO to prevent lung injury in severe ARDS may give more direction on the role of ECMO in ARDS.

Statins

The pleiotropic anti-inflammatory & endothelial modulatory effects of statins are potentially beneficial in ARDS. While early phase 1 & 2 RCT's showed some improvement of pulmonary function, this has not been supported subsequent trials. A multicentre study of rosuvastatin for sepsis associated ARDS was stopped early due to futility (*ARDSnet .NEJM 2014;370:2191-200).*

HARP-2:multi-centre RCT of Simvastatin within 48 hours of ARDS for 28 days
(McCauley DF et al. NEJM 2014:DOI:10:1056)

- No difference in 28-day mortality
- No difference in ventilator-free or non-pulmonary organ failure –free days

Future Therapies under trial:

Nebulized Heparin: decrease fibrin deposition. A small study showed more vent-free days and a longer term study is underway

Aspirin: to reduce platelet activation & micro-thrombi formation. Observational studies of pre-hospital antiplatelet use showed reduced incidence of ARDS & prompted a RCT of aspirin to prevent ARDS.

Immune-modulating:

Interferon beta treatment, TNF receptor 1 blockade, recombinant ACE-2 (blocks Angiotensin1 receptor-mediated vasoconstriction, inflammation & increased vascular permeability), keratinocyte growth factor and mesenchymal stem/stromal cells are being investigated.

Summary: The strategies in the table below have shown survival benefit

Ventilatory		**Non-ventilatory**
Lung protective ventilation especially Low Tidal Volume		Neuromuscular blockers • P/F <120 mmHg
Recruitment & PEEP • Individualize & Titrate		Fluid therapy –"lite"
Prone positioning • P/F <150mmHg • PEEP:10-13cmH20	• V_t <8ml/kg • >12hours /day	

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Notes

Postoperative pulmonary complications

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Dear reader…this is a lengthy, comprehensive foray into postoperative pulmonary complications (PPCs). I have reviewed over 60 articles in the preparation of these notes, trying to present the "best evidence" for the exam candidate. It's a difficult and complicated subject to approach due to all the factors that can play a role in the development of PPCs, heterogeneous patients and heterogeneous surgeries. Much of the evidence in the literature is conflicting. I have included a few salient studies in the notes, and in the references at the end, to try to highlight the controversies and conflicting findings. Remember, you're not going to be tested on the intricacies of studies, but you will be expected to formulate an approach based on the evidence. I think it's a good exam topic as it is a multifactorial problem that requires multidisciplinary input and will require you to draw your own conclusions from the literature, and think about how you will manage the "at risk" patient. Happy reading!

1. Introduction

1.1 Postoperative complications in general…

In the past 50 years, perioperative mortality has decreased (especially in developed countries), despite there being a concomittant increase in the patients' baseline risk, according to the ASA score. A large, multicentre study in Europe (EuSOS – Pearse R et al 2012), demonstrated that the post-operative mortality rate was 4%. This was higher than expected. The majority of deaths were attributed to cardiac and pulmonary morbidities. In addition to perioperative complications impacting on mortality rates, they also add a huge financial burden (long term hospital stays, long term follow up) as well as increasing morbidity in the survivors (repeated admissions, chronic illness, deterioration of function). Collaboration between multidiscilinary teams could result in planning for better perioperative care, leading to fewer medical errors and complications. Pulmonary complications differ from cardiac complications insofar as procedure-related factors are more predictive of pulmonary complications than patient-related factors - even healthy patients undergoing high-risk surgery are at risk for PPCs.

1.2 What are postoperative pulmonary complications?

There is no standard definition of a PPC, although the broad definition is "a condition affecting the respiratory tract that can adversely influence the clinical coutse of a patient after surgery". This includes conditions such as respiratory failure, the need for endotracheal intubation within 48 hours, weaning failure, atelectasis, pneumothorax, pleural effusions, aspiration pneumonitis, pneumonia, bronchospasm, laryngospasm, hypoxia, exacerbation of chronic obstructive pulmonary disease (COPD) as well as upper airway obstruction! No surprise then that such a broad definition means there is a huge range in the incidence of PPC (from 2-40%, although the commonly accepted range lies somewhere in the region of 2.5-5%), PPCs are at least as common as cardiovascular events. A suitable pathophysiological definition would be "a postoperative decrease in functional residual capacity and total lung capacity that results in ventilation-perfusion mismatch and hypoxaemia".

PPCs are a major contributor to the overall risk of surgery and anaesthesia, length of stay in hospital, admission into into an Intesive Care Unit (ICU), hospital readmission, quality of life after hospital discharge and mortality. They are the leading cause of death in both non-cardiac and cardiac surgery. They also impose a huge economic burden – the cost of surgery is between 2x and 12x higher when PPCs develop.

2. Risk factors for developing PPCs

The American College of Physicians has classifed risk factors for the development of PPCs, outlined below in Tables 1 and 2. They are categorised into modifiable and non-modifiable factors which are

- patient-related
- procedure-related (which may be surgical or anaesthetic)
- and factors pertaining to pre-operative testing.

Table 1. Modifiable risk factors for the development of postoperative pulmonary complications

Modifiable patient-related factors	Modifiable procedure-related factors	Modifiable preoperative tests
Low body weight	Prolonged surgery (>3h)	Low serum albumin
Obesity	General anaesthesia	Low preop S_pO_2
Smoking	Blood transfusion	Positive cough test
Alcohol consumption	Prolonged hospitalisation	Anaemia
Respiratory infection in the past month		
Sepsis		

Table 2: Non-modifiable risk factors for the development of postoperative pulmonary complications

Non-modifiable patient-related factors	Non-modifiable procedure-related factors	Non-modifiable preoperative testing
Congestive cardiac failure	High-risk procedures	Genetic variations
ASA ≥3	Aortic aneurysm surgery	Alterations in chest radiograph
Advance age	Thoracic surgery	High blood urea
COPD	Upper abdominal surgery	
Functional dependence	Abdominal surgery	
Impaired sensorium	Neurosurgical procedures	
GORD	Vascular surgery	
Diabetes mellitus	Head and neck surgery	
Obstructive sleep apnoea	Procedures with a high risk for ALI/ARDS	
Hypertension	Procedures with a high risk for UEPI	
Liver disease	Emergency surgery	
Cancer		

Key to Tables 1 and 2: ASA American Society of Anaesthesiologists; COPD Chronic Obstructive Pulmonary Disease; GORD Gastro-oesophageal reflux disease; ALI/ARDS acute lung injury/acute respiratory distress syndrome; UEPI unanticipated early postoperative intubation.

Let's look more closely at the evidence regarding some of these risk factors and the pathophysiology behind the development of PPCs.

3. Surgical related factors

3.1 Surgical site

Surgery a risk factor for PPCs in its own right. This arises due to inhibition of the function of respiratory muscles from:

- Incisional pain
- Functional disruption from the surgical insicion
- Reflex inhibtion of output from the phrenic nerve from traction on abdominal viscera.

The *surgical site is perhaps the most important risk factor for the development of PPCs.* Aortic, thoracic and upper abdominal surgery are associated with the highest risk of PPCs. Emergency surgery carries a high risk of PPCs, regardless of the site.

3.2 Laparoscopic vs. open surgery

The perioperative benefits of laparoscopic surgery include a decreased inflammatory response, and reduced postoperative pain. Minimally invasive surgical procedures *may* reduce the risk of PPCs (but much of this data comes from retrospective studies). There is a suggestion that lung function may be improved in higher-risk populations when laparoscopic techniques are performed (instead of open procedures) but definitive evidence regarding the development of PPCs is lacking. The EuSOS trial showed that mortality was lower following laparoscopic surgery (as compared to open surgery) but it did not specifically address PPCs.

Laparoscopic surgery has been shown to reduce the risk of PPCs compared to open procedures in patients undergoing bariatric surgery (OR 1.92; 95%CI: 1.54-2.38). The reported incidence of PPCs following laparoscopic cholecystectomy is 0.3-0.4%.

3.3 Duration of surgery

Surgical procedures of more than 3 hours duration are specifically associated with a higher risk of PPCs. Where feasible, shorter procedures should be considered in high-risk patients.

3.4 Nasogastric decompression

Routine use of nasogastric tubes after abdominal surgery is associated with an increased risk of aspiration and PPCs (OR=1.45; 95%CI: 1.08-1.93); however, *selective use* (e.g. in PONV, symptomatic abdominal distension) is appropriate.

3.5 Patient positioning during surgery

Positioning of the patient may negatively impact upon the functional residual capacity (FRC), in particular Trendelenberg, jack-knife and kidney rest positions. These positions may also cause a reduction in cardiac output which worsens ventilation / perfusion (V/Q) mismatch. Pulmonary vascular congestion is associated with the supine position and this may also contribute to a reduction in the FRC, patients who have experienced orthopnoea are particularly vulnerable.

In prolonged surgery, areas of the lung may be continually dependent in zone 3 or 4 (i.e. below the left atrium). The dependent areas are prone to fluid accumulation and, especially if coupled with aggressive fluid administration, will lead to transudation of fluid into the lung, pulmonary oedema and a decreased FRC.

4. Patient related-factors

4.1 Age

Elderly patients have an increased risk of PPCs even after adjustment for comorbidities. Advanced age is associated with:

- Decreased respiratory muscle strength
- Decreased chest wall compliance
- Decreased elastic recoil of lung parenchyma
- Decreased alveolar suface area

Age over 80 years appears to be the cut off at which the PPC rate dramatically increases (OR 5.6 after 80 years of age).

4.2 Asthma

The literature suggests that well-controlled asthma is not a significant risk factor for PPCs, although there are few studies specifically designed to look at this subgroup of patients. Patients with a peak flow within 80% of predicted / personal best have a similar risk to patients without asthma. Short acting bronchodilators, anticholinergis and anxiolytics may help to reduce bronchial tone, and short-acting corticosteroids may help to prevent PPCs, but these should only be used if there is a clinical indication, and must not be used routinely. There is no strong evidence to suggest that steroids impair wound healing or increase infection rates at the doses required to treat asthma. Previous concerns that the administration of neuraxial blockade increases bronchial tone and reactivity, due to unopposed parasympathetic effects, have not been borne out clinically. Bronchial motor tone is determined by β_2 stimulation rather than an imbalance between sympathetic and parasympathetic stimulation.

4.3 Chronic lung disease

COPD has been identified as an important risk factor for PPCs (OR 1.70; 95%CI: 1.44-2.22), however, restrictive lung pathologies have not been identified in the literature as putting the patient at risk for PPCs. Although the COPD itself is unavoidable, patients can be optimised for surgery with medication and pulmonary rehabilitation. The daily use of bronchodilators has been shown to be of benefit in COPD patients with lung cancer undergoing surgical procedures, and they should be maintained throughout the perioperative period in all COPD patients who take them routinely. All patients with symptomatic COPD should receive daily inhaled ipratropium bromide (or tiotropium bromide). β_2 agonists should be administered as necessary for symptoms and wheezing. Theophylline is a bronchodilator, a diaphragmatic inotrope and a respiratory stimulant, but the current recommendations

are that it not be used in the properative period, unless it would have otherwise been prescribed in the non-operative setting. Corticosteroids should be used in patients who, depsite the use of bronchodilators, have persistent wheeze or effort intolerance. Empiric antibiotics are not recommended in COPD, unless the patient has an acute exacerbation. These patients should have non-urgent surgery delayed until symptom resolution and for 4 weeks thereafter.

Respiratory muscle training has been demonstrated to modify the capacity of respiratory muscle fibre remodelling in noncardiac surgery and in coronary artery bypass graft (CABG) surgery. Incentive spirometry has not been universally shown to reduce PPCs for all surgical patients, but there is some evidence to suggest that it may improve the maximum oxygen consumption (VO_2 max) in patients with COPD, although evidence to suggest it improves pulmonary outcome is lacking.

4.4 Obstructive sleep apnoea (OSA)

There has been dissonance in the literature as to whether or not OSA itself confers risk of PPCs, or if the associated conditions (such as pulmonary hypertension, heart failure, arrhythmias, hypertension, metabolic syndrome and cerebrovascular disease) increase the risk for pulmonary events. There have been a few studies to support its role as a risk factor for PPCs, and others that find it to be unrelated. However – some of these latter studies applied prophylactic postoperative noninvasive continuous positive airway pressure (nCPAP) which may have mitigated the development of PPCs. The underlying message appears that to be that OSA ***is*** a risk factor for the development of PPCs, but its impact can be reduced by appropriate postoperative respiratory care such as the use of noninvasive ventilation devices. The risk for postoperative respiratory failure is probably reduced very quickly after initating nCPAP, and a week of nCPAP should be sufficient preoperatively, although there is no hard data to support this. Pulmonary hypertension has been identified as a risk factor for PPCs, although preoperative screening is not routinely recommended for asymptomatic patients with no clinical suspicion.

4.5 Congestive cardiac failure (CCF)

CCF is a significant risk factor for PPCs (OR 2.93; 95%CI: 1.02 – 8.43).

4.6 Smoking

Current smokers have an increase in 30-day postoperative respiratory events compared with former smokers. Cessation of smoking for >1 year prior to elective surgery seems to reduce PPCs although the exact duration of abstinence to reduce PPCs has not been established. A recent meta-analysis and systematic review of 107 studies (157 data sets) showed that preoperative smoking was associated with an increased risk of PPCs (RR1.73. 95%CI: 1.35-2.23), although only 16 data sets from the 157 specifically looked at PPCs and there was substantial heterogeneity (I^2=79.3%). In this meta-analysis, smoking was not associated with an increased postoperative mortality but there was an increase in admission to ICU. The highest risk of smoking related PPCs was observed after abdominal surgery (RR=3.35; 95%Ci: 1.54-7.29) and thoracic surgery (RR=1.98; 95%CI: 1.20-3.28).

Pathophysiological mechanisms include:

a. pre-existing tobacco-induced damage to organ systems
b. impaired immune function
c. small airway narrowing causing an increase in closing volume
d. reduced pulmonary capacity
e. increased secretion of hyperviscous mucus
f. reduced ciliary function

Effects d,e and f are seen even in young, asymptomatic smokers.

The incidence and severity of coughing during emergence from anaesthesia are significantly higher in smokers than non-smokers (50% vs. 17%). Sevoflurane anaesthesia in smokers is associated with 100% probability of coughing at extubation and this is independent of the estimated residual concentration of anaesthesia, (although the choice of halogenated anaesthetic agent is probably not important). Smokers are also at an increased risk of coughing at extubation on emergence from propofol anaesthesia, but the incidence is substantially less than with sevoflurane (Figure 1). This of particular importance where coughing and bucking on the tube is undesirable, such as seen in cervical spine surgery.

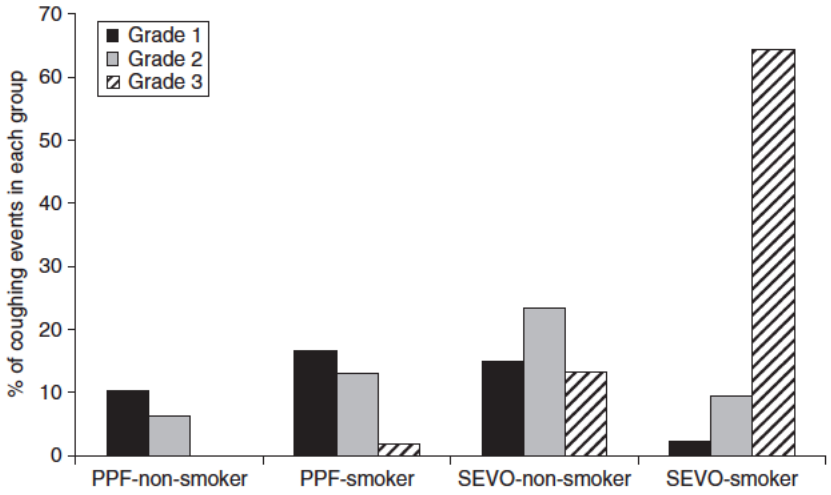


Figure 1. Occurrence of cough during anaesthesia for cervical spine surgery. Cough severity Grade 1-3 with 3 being most forceful. PPF = propofol, SEVO = sevoflurane.

The current literature recommends that at least 4 - 8 weeks of smoking cessation is optimal. A recent meta-analysis (Wong et al) showed that abstaining from smoking for <4 weeks prior to surgery had no effect on the risk of developing PPCs (earlier studies have showed a paradoxical increase in PPCs when smoking was stopped, probably related to the increase in coughing and sputum production after recent smoking cessation. In patients who quit for >8 weeks prior to surgery, the incidence of PPCs was comparable to nonsmokers. One should encourage patients to stop smoking as early as possible prior to elective surgery, but be reassured that even a short-term break, whilst it might not elicit positive effects on PPCs, will influence important parameters such as the reduction in carboxyhaemoglobin, tracheobronchial reactivity and will promote normalisation of ciliary activity.

PPCs in smokers are also related to the underlying condition of the lung. Smokers with normal spirometry have a 4% risk of PPCs, whereas heavy smokers have a PPC rate of up to 43%.

After smoking cessation, the physiological recovery follows the following pattern:

12-48 hours – reduction in carboxyhaemoglobin levels
this shifts the oxyhaemoglobin dissociation curve to the right and increases oxygen availability
2-3 days – ciliary function recovers, but sputum production increases
2 weeks – airway reactivity is reduced
6 weeks – sputum volume normalises
3 months – tracheobronchial clearance approaches normal
6 months – improvement in small airway narrowing.

4.7 Alcohol consumption

Habitual alcohol use or abuse has also been linked to PPCs, although not all studies corroborate this. A meta-analysis of 55 studies concluded that preoperative alcohol consumption was associated with a 1.80-fold increase in the risk of pulmonary complications (95%CI: 13.0-2.49) as well as general infections, wound complications, prolonged hospital stay and admission to ICU. Only high alcohol consumption (>60g/d) was associated with an increased risk of postoperative mortality. Subgroups in the meta-analysis with alcohol exposure (>24g/d for women and >36g/d for men, or AUDIT-C score >4, or classified as having alcohol dependency or abuse) reported higher relative risks of pulmonary complications (RR 2.15, 95%CI: 1.29-4.90), whereas light-moderate drinkers had a lower risk of PPCs (RR 0.86, 95%CI: 0.41-1.80) [NB there were very few studies looking at low-moderate alcohol intake included in this analysis]. The associations between alcohol intake and the development of PPCs were higher after thoracic surgery.

Pathophysiological mechanisms include a reduction in immunity associated with high alcohol intake and an increased stress response to surgery. In addition, acute alcohol withdrawal (Delirium tremens) may predispose to an altered level of consciouness and the risk of aspiration. It should be borne in

mind that there is a strong association between smoking and alcohol use, therefore the conclusions of the aforementioned meta-analysis could be confounded by the impact of smoking.

The current recommendations are that alcohol should be avoided for at least 2 weeks before surgery to avoid short-term abstinence syndrome and reduce complications.

4.8 Nutritional status

MaInutrition increases the risk of PPCs, as does weight loss of >10% in the past 6 months. Although theorectically some factors are modifiable (e.g. low body weight, low serum albumin), there is little evidence to confirm an effect of adequate preoperative nutrition on preventing PPCs; probably because it is impractical to delay surgery until adequate preoperative nutrition and weight gain has been achieved. It is difficult for highly catabolic patients to achieve weight gain until the underlying disease process has been addressed. There is minimal evidence to suggest that the routine use of parenteral nutrition modifies the risk.

Obesity is not a significant risk factor for developing a PPC, although it may be a factor in certain surgeries such as uvulopalatopharyngoplasty and thoracic surgery. Comorbidities associated with obesity do significantly increase the risk of PPCs, and severe obesity (morbid obesity, BMI >40kg/m^2) certainly increases risk and is associated with an increase in the occurrence of pneumonia, respiratory failure and unplanned tracheal intubation

4.9 Respiratory infections

Upper respiratory tract infection (URTI) within the last month increases bronchial reactivity and the risk of laryngospasm, bronchospasm and perioperative hypoxaemia. Elective surgery should be delayed in the presence of an URTI, 1 month is deemed a reasonable period of time to wait. Many recommendations include lower respiratory tract infections (LRTI) as a risk factor for PPCs, especially if accompanied by fever and the requirement of an antibiotic. Recent respiratory infections can also cause an impairment of immunity.

4.10 Functional dependence

Total dependence (where the patient is unable to perform any of the activities of daily living) is associated with an OR of 2.51 for PPCs (95%CI: 1.99-3.15), whereas partial dependence has an OR of 1.65 (95%CI: 1.36-2.01). The relationship between ASA status and rate of PPCs is illustrated in Table 3.

Table 3. ASA classification and the rate of PPCs

ASA Class	Class definition	Rate of PPCs by class (%)
I	Normally healthy	1.2
II	Mild systemic disease	5.4
III	Systemic disease not incapacitating	11.4
IV	Incapacitating disease that is a constant threat to life	10.9
V	Moribund and not expected to survive 24 hours	N/A

5. Perioperative testing

5.1 Serum albumin

Low serum albumin (<35g/L) is a predictor of PPCs and perioperative mortality. It probably reflects the underlying disease severity of the patient and there is no evidence to support its correction by the administration of intravenous albumin. The 2006 American College of Physicians (ACP) guidelines ranked albumin as an important risk factor, but this has subsequently been revised. A low serum albumin is now believed to be a minor risk factor in the development of respiratory failure.

5.2 Anaemia

Although a haemoglobin concentration of <10g/dl has been identified as a risk factor for PPCs, intraoperative transfusion has also been independently linked to PPCs! The cut-point of haemoglobin concentration that confers the greatest risk has still not been established in peri-operative patients, although some studies suggest that an Hb <10g/dl raises the risk of PPC by almost 3-fold.

However,preoperative blood transfusions are also associated with an increase in PPCs; specifically, patients who receive more than 4 units before surgery are at increased risk.

5.3 Preoperative peripheral oxygen saturation (S_pO_2)

Preoperative peripheral saturation should be measured. It reflects both respiratory and cardiovascular functional status and has recently been identifed as a predictor of unforeseen hypoxaemic events.

5.4 The "cough" test

The "cough" test can provide early warning of COPD exacerbation or an URTI. The patient should take a deep breath and cough once. The test is positive if the patient coughs more than once. A positive cough test has been linked to risk for PPCs.

5.5 Blood glucose

The ACP guidelines suggest that diabetes mellitus is not a risk factor for PPCs. Although the ARISCAT study (see section 7, table 4) found diabetes to be an independent predictor in bivariate analysis this was not so on multivariate logistic regression, and diabetes has only been described as a predictor in retrospective studies. In conclusion, diabetes mellitus may well be a risk factor for PPC, but its impact is modest at best.

5.6 Spirometry and chest X-rays

Perioperative spirometry and chest radiographs should not be used routinely to predict patients at risk for PPCs but may be appropriate in high risk populations, including those with pulmonary disease – an FEV1 of <60% of predicated has previously been identified as a risk factor for PPCs. The use of pulmonary function testing may be useful in thoracic surgical patients.

6. Anaesthetic factors

Although the ACP classification has scant mention of the impact of anaesthesia on PPCs, it is an important risk factor – with multiple facets that can be modified to reduce the occurrence of PPCs. I know I'm tackling it late in the notes – I just wanted to get all the other bits and bobs out of the way first so we can now concentrate on the nitty gritty.

6.1 "Pathophysiology" of general anaesthesia

General anaesthesia immediately reduces muscle tone which leads to a reduction in thoracic diameters, lung volumes and airway dimensions, this results in a decrease in functional residual capacity (FRC) which may fall below the closing capacity in disease states. Even in heatlhy, normal lungs, induction of general anaesthesia decreases the FRC by up to 20%. This drop in FRC is occurs immediately after intubation and is usually accompanied by airway closure and atelectasis, especially in dependent areas of the lung, leading to abnormal gas exchange with ventilaton-perfusion mismatching and shunt. The maximum decrease in FRC is usually seen within the first few minutes of anaesthesia and does not seem to progressively increase with time. The magnitude of drop in FRC is regardless of whether ventilation is spontaneous or controlled. Such a reduction in FRC can possibly be compensated for by the application of PEEP (or CPAP).

General anaesthesia has a significant effect on diaphragmatic movement, which may lead to increased ventilation of superior (nondependent) portions of the lung that are poorly perfused and decreased ventilation of dependant areas that are well perfused due to gravitational effects. The resulting V_A/Q inequalities cause an increase in shunt and dead space. Diaphragmatic dysfunction is not related to residual neuromuscular blockade or inadequate analgesia (although clearly these must be excluded). It is probably due to inhibition of neural output of the phrenic nerve as phrenic nerve stimulation reduces atelectasis.

Patients who breathe spontaneously under general anaesthesia tend to hypoventilate and have a reduced tidal volume (V_T). The reduction in V_T occurs because it is more difficult to breathe during general anaesthesia due to decreased compliance and increased airway resistance, these effects may be compounded by the presence of airway devices and breathing circuits. In addition, patients under GA have decreased chemical control of breathing. Shallow breathing will cause a decrease in FRC and may promote atelectasis.

Administration of opiates and other respiratory depressants can have effects that persist into the postoperative period, resulting in hypoventilation, atelectasis, pooling of secretions and impaired oxygen delivery. Additionally, tiny concentrations of intravenous and inhalational anaesthetics

(<0.1MAC) blunt the ventilatory response to hypoxaemia and hypercarbia. Such low levels of anaesthetic agents can persist for hours into the postoperative period and may worsen PPCs.
General anaesthesia has additional numerous biological effects on the respiratory system, which may contribute to PPCs. These include:

- Inhibition of alveolar macrophage activity
- Decreased production of surfactant
- Enhanced response of the pulmonary vasculature to neurohumoral mediators.

In addition, tracheal instrumentation alters mucociliary function and promotes retention of secretions. The presence of a cuffed endotracheal tube suppresses the flow of tracheal mucous, which is not seen if uncuffed tubes are used. Endotracheal intubation reduces the effective size of the trachea by 30-50% and adds to increased resistance and work of breathing. Many of the commonly used breathing circuits and airway devices impose an additional work of breathing that is 2-3 times normal.

Poor systemic hydration and low inspired humidity increase the viscosity of tracheobronchial secretions and slow the beating of cilia. A combination of these factors can lead to inspissation of tenuous secretions with increased V_A/Q mismatch and worsening hypoxia.

Atelectasis

Atelectasis occurs in up to 90% of patients perioperatively, but is usually self-limiting. However, it has been described as persisting for more than 2 days after abdominal surgery, with resolution only occuring by day 4 postoperatively. In some cases, atelectasis may not resolve, and other complications such as pneumonia may develop as a result. Causality between atelectasis and pneumonia has not been demonstrated, although experimental data suggest bacterial growth is promoted in atelecatatic areas of lung tissue. Atelectasis is seen both during spontaneous breathing and during positive pressure ventilation and occurs irrespective of whether intravenous or inhalational anaesthetics are used, its effects are probably dose related, since higher doses of anaesthesia causing more uncoordinated respiratory function. There is a decrease in pulmonary compliance, ventilation-perfusion mismatching worsens, gas exchange is impaired and hypoxaemia results. The total lung area involved can exceed 15-20%.

The mechanisms underlying the development of atelectasis are:

- Chest wall deformation due to a loss of the normal coordinatied activity of respiratory muscles during spontaneous breathing
- Absence of inspiratory muscle tone during positive pressure ventilation
- Absorption atelectasis behind closed airways
- Compression of lung tissue
- Loss of surfactant or impaired surfactant function

although the exact mechanism of atelectasis is still not completely understood.

Prevention of atelectasis includes the application of positive end-expiratory pressure (PEEP), which counteracts alveolar collapse and increases functional residual capacity. The administration of intraoperative PEEP is an attractive method to reduce PPCs, although a Cochrane review suggests there is insufficient evidence that it reduces post-operative death and PPCs in surgical “all-comers” (i.e. in a variety of different surgical procedures).

The use of a high inspired oxygen concentration can result in absorption atelectasis in those lung units with a low V_A/Q ratio, giving the effect of a right-to-left shunt. When breathing air, units with low V_A/Q ratio will have a low P_AO_2. With the inspiration of enriched oxygen, the P_AO_2 rises and oxygen rapidly moves from the alveolus into the capillary blood. If the oxygen flux increases to such an extent that the net flow of gas into the blood exceeds the inspired gas flow, the lung unit becomes progressively smaller and may collapse. Lowering the F_IO_2 during induction of anaesthesia reduces the amount of absorption atelectasis but reduces the margin of safety for the development of hypoxaemia, especially during periods of airway manipulation. A reduction of F_IO_2 from 1.0 to 0.8 may reduce absorption atelectasis whilst having minimal effects on the margin of safety or on oxygenation. Current recommendations are to pre-oxygenate with high enough F_IO_2 (between 0.8-1.0) to ensure a long safety time in the event of a difficult intubation or problem with the airway. 100% oxygen does reduce the time to desaturation but also is associated with significantly more atelectasis and should be reserved for patients who are at particularly high risk of developing hypoxaemia, it probably should be accompanied by a recruitment manoeuvre after intubation. Preoxygenation using CPAP has also been demonstrated to reduce atelectasis. Avoid an unnecessarily high oxygen fraction during

maintenance of anaesthesia. Prior to extubation, a combination of low F_IO_2 and CPAP during emergence decreases lung collapse and leads to better lung function in the early preoperative period.

Hypoxia

Hypoxia is common after general anaesthesia or sedation and may be exacerbated by pathologies such as pulmonary oedema, bronchospasm, laryngospasm and the residual effects of anaesthetic agents. Any decrease in p_aO_2 occuring under anaesthesia is frequently addressed by the administration of supplemental oxygen. However, high concentrations of oxygen (>80%) can result in absorption atelectasis, as described above.

Postoperative respiratory failure (PRF)

The development of postoperative respiratory failure (PRF) is determined largely by the respiratory muscle function, which is hampered under anaesthesia and in the postoperative period. In the early postoperative period the central stimulation of the upper airway (hypoglossal nerve) and diaphragm (phrenic nerve) may be depressed by the residual effects of opiates, sedatives and residual curarisation. This constellation has the effect of increasing upper airway collapsibility and predisposes patients to PRF; all of which may be compounded in the presence of other comorbidities such as COPD, smoking, obesity and OSA. Additive to these changes are issues such as functional disruption of the respiratory muscles and postoperative pain.

Postoperative ARDS

Postoperative ARDS is at the worst end of the spectrum of PPCs. It is classified according to the Berlin consensus: mild ($p_aO_2/F_IO_2 \leq$ 300mmHg and >200mmHg), moderate ($p_aO_2/ F_IO_2 \leq$ 200mmHg and >100mmHg), or severe ($p_aO_2/ F_IO_2 \leq$ 100mmHg). The incidence of ARDS in the postoperative period is around 0.2% (if high-risk surgical patients are excluded) to up to 10.2% in high-risk surgeries (cardiothoracic, aortic, abdominal, spinal surgery). Mortality associated with ARDS ranges from 17% in the mild form to 58% in severe ARDS.

6.2 ***Neuromuscular block and reversal***

Residual neuromuscular blockade after general anaesthesia is an important risk factor for the development of PPCs – it impairs breathing, hampers patency of the upper airway, protective airway reflexes, swallowing and coughing (and if you didn't know that….I suggest you defer writing the FCA for a while / lifetime ;)). The choice of a short acting neuromuscular blocking agent, in conjunction with the use of a peripheral nerve stimulator and the use of a cholinesterase inhibitor (neostigmine) reduces the risk of PPCs. Data highlight the negative impact of pancuronium: pancuronium has a higher rate of residual blockade than other neuromuscular blockers and the presence of residual blockade has a 3-fold increase in PPCs compared to patients without residual blockade. Longer acting neuromuscular blocking agents, such as pancuronium, can have residual effects for up to 7 days postoperatively!

Neuromuscular function must be monitored. Neostigmine is a cholinesterase inhibitor with parasympathomimetic effects that can impair respiratory function by precipitating bronchospasm and bronchorrhoea and has been implicated in contributing to PPCs. These effects are largely overcome by the use of a muscarinic antagonist (such as glycopyrrolate) and avoiding the use of anticholinesterases to reverse neuromuscular blocking agents is not to be recommended. Be aware that paradoxical bronchospam has been observed with low dose glycopyrrolate.

It is not yet determined if sugammadex is able to reduce the rates of PPCs.

6.3 Volatile vs. intravenous anaesthesia

Experimental studies suggest that volatile anaesthetics have protective properties in the lungs. Rodent studies show that isoflurane prevents ventilator induced lung injury via phosphoinositide 3-kinase/Akt signalling, and sevoflurane suppresses lung inflammation via $GABA_A$ signalling pathways. Human studies have showed that volatile anaesthesia (with sevoflurane and desflurane) reduces cytokine release observed in one lung ventilation when compared to propofol, although the clinical evidence has not yet been elucidated.

6.4 General anaesthesia (GA) versus neuraxial blockade (NAB)

There have been conflicting studies looking at the benefit of general anaesthesia vs. NAB, in **heterogeneous patient groups undergoing very different surgical procedures**. A meta-analysis

in 2000 (Rogers A et al. BMJ 2000; 321:1493) of NAB vs. GA with NAB revealed an incidence of pneumonia of 3% and 5% respectively (OR 0.61; 95%CI: 0.48-0.76) and respiratory failure 0.8% (OR 0.41; 95%CI: 0.23-0.73), but this meta-analysis was heavily criticised because of the heterogeneous group of patients and the inclusion of older anaesthetic techniques and agents. Although is appears that the risk of clinically important PPCs was higher when general anaesthesia was used, when compared to neuraxial blockade, the studies were underpowered to detemine whether it is the avoidance of general anaesthesia, or the neuraxial block itself, that conferred the benefit.

A recent study in patients with hip fractures (Neuman et al. Anesthesiology 2012; 117:72-92), showed that neuraxial blockade decreases PPCs when compared to GA by 25-29%, however, it should be borne in mind that these patients are at relatively low risk for PPCs!

In patients with COPD, however, the administration of general anaesthesia seems to be associated with more PPCs than neuraxial blockade +/- general anaesthesia. The majoriity of these studies are from retrospective propensity matched populations. Van Lier and colleagues in 2011 published retrospective data showing that epidural analgesia, in combination with general anaesthesia, reduced PPCs and mortality compared with general anaesthesia only, in a group of patients with COPD.

More recently, Hausman coauthored a retrospective propensity matched population study comparing outcomes in patients with COPD undergoing general anaesthesia +/- adjunct regional analgesia vs. regional anaesthesia alone. The most common operations performed were carotid endarterectomy, total knee arthroplasty, total hip arthroplasty and inguinal hernai repair (again, not those procedures associated with a high risk of PPCs). They found that the use of general anaesthesia in COPD patients was associated with a higher risk of pulmonary infection, prolonged ventilator dependence and risk of unplanned postoperative intubation but there was no difference in 30 day mortality. Nonpulmonary complications were similar between the 2 groups. Interestingly, subgroup analysis showed that when patients receiving general anaesthesia were compared to patients receiving epidural anaesthesia, there was no difference in pulmonary morbidity. The benefit of a reduction in PPCs was *only* seen in patients receiving spinal anaesthesia compared to general anaesthesia (+/- regional analgesia), but the study was underpowered to find a difference between different types of regional anaesthetics. In patients who had dyspnoea at rest, there were no differences in any of the outcomes by type of anaesthetic; but patients with moderate or no dyspnoea were found to have an increased incidence of prolonged ventilation if they received general anaesthesia compared to matched regional patients. Problems with this study included the fact that the postoperative analgesic regimens were not determined, and that intra-abdominal surgery was not included.

Trying to tease out the conflicting evidence….recent studies have found no mortality benefit for regional over general anaesthesia, and some have found an increase in cardiovascular morbidity with NAB. In patients with severe COPD there appears to be no benefit from avoiding general anaesthesia: the adverse effects of regional anaesthesia (such as loss of accessory muscles, phrenic nerve paralysis, and poor tolerance for supine positioning) may negate the proposed benefits of avoiding general anaesthesia. Patients with mild/moderate COPD may benefit from the avoidance of general anaesthesia, and in particular from the administration of spinal anaesthesia compared to epidural techniques.

This seems to confirm the excellent tip that has stood me in good stead throughout my career: the sicker the patient, the more likely you should be to give them a general anaesthetic (over neuraxial blockade). Remember that NABs are not blameless when it comes to PPCs – high levels of NAB are associated with impaired cough strength, reduced expiratory lung volumes and poor respiratory muscle force.

6.5 Intravascular volume management

During minor surgery, studies of liberal vs. restrictive fluid therapy does not have a major impact on the risk of PPCs, although liberal fluid therapy reduces forced vital capacity (FVC) 6 hours postoperatively. Liberal fluid therapy in minor surgery does, however, reduce the incidence of postoperative nausea and vomiting!

In major surgery, a liberal fluid strategy is associated with a higher incidence of acute lung injury (ALI) in the postoperative period. In adult patients, a positive fluid balance of >1.5L was associated with a significant increase in the risk of postoperative ALI (Evans RG and Naidu B Interact Cardiovasc

Thorac Surg 2012; 15:498-504). Targetting Goal Directed Fluid Therapy (GDT) rather than a "one-size-fits-all" approach is an attractive proposal. In GDT, fluid is administratered according to the individauls' requirements using haemodynamic parameters, and other markers of adequate tissue oxygenation, which are in a state of flux during a surgical procedure. Although this is an attractive proposal, RCTs looking at PPCs in patients managed with GDT are lacking.

6.6 Preoperative measures

Inspiratory muscle training (preoperative lung expansion, 20 minutes a day for 2 weeks before surgery) reduces PPCs in cardiac surgery patients (OR=0.52; 95%CI: 0.30-0.92).

Preoperative physiotherapy/pulmonary rehabilitation programmes for patients undergoing thoracotomy and lung resection have been shown to improve exercise capacity and preserve pulmonary function in patients with COPD. However, it is uncertain if these benefits translate into a reduction in PPCs, or if they are applicable to other patient groups.

6.7 Intraoperative ventilation

This is a very topical subject at the moment and the literature has been littered with articles and letters regarding the ideal way to ventilate normal lungs.

Traditionally, anaesthetists ventilated patients with V_T between 10-15ml/kg body weight (and minimal/no PEEP) in an effort to ameliorate atelectasis and hypoxia – we now know that this is a sure-fire way to cause lung damage. The ARDSnet trial in 2000 paved the way for the development of lung-protective ventilatory strategies in ARDS, many of which have spilled over into intraoperative ventilation in patients with normal lungs. High V_T (10-15ml/kg) initiates/aggravates an inflammatory response in the lung and is associated with poor outcomes. There have been many trials supporting the use of low V_T with moderate PEEP in healthy lungs in the belief that healthy lungs require protection from the detrimental efftects of high V_T. There is excellent evidence that this is protective in ARDS/ALI, and it doesn't require much of a leap of faith to assume that healthy lungs will also benefit…or will they?!

Experimental and clinical studies have suggested that lung-protective mechanical ventilatory strategies, as used in ARDS, may have relevance in non-ARDS lungs. Such techniques include limiting V_T to 6ml/kg of predicted body weight (PBW), use of moderately high PEEP (6-10cmH_2O) and recruitment manoeuvres. These strategies have been shown to reduce the incidence of postoperative ARDS, atelectasis, pulmonary infection, and even mortality (Hemmes et al 2013, Sutherasan et al 2014).

PEEP is probably important to "stabilise" the alveoli and prevent cyclical alveolar collapse (a risk factor for atelectrauma). A retrospective study revealed that the intraoperative use of low V_T with minimal PEEP (mean 4cmH_2O) was associated with an increase in 30-day mortality and hospital length of stay (Levin 2014). This suggests that low V_T in isolation are not superior to standard ventilation practices and that PEEP plays an important role.

The IMPROVE study (Intraoperative Protective Ventilation in Abdominal Surgery) investigated the effects of intraoperative low-V_T ventilation in abdominal surgery. It demonstrated that a lung-protective strategy with a V_T of 6-8ml/kg of predicted body weight (PBW) combined with PEEP of 6-8cmH_2O and recruitment manoeuvres performed every 30 minutes post-intubation was associated with a reduction in both PPCs and extrapulmonary post-operative complications, when compared to a V_T 10-12ml/kg with no PEEP and no recruitment manoeuvres (10.5% vs. 27.5% within the first 7 days). However, this is not a pragmatic study – few people today routinely ventilate patients without PEEP whilst using10-12ml/kg V_T PBW. What is does show is that poor ventilatory strategies damage the lungs, which can have far-reaching effects on distant organs.

It is difficult to know if the beneficial effects of "lung protective ventilation" are from the use of lower tidal volumes, or higher PEEP with or without recruitment. The recent PROVHILO study (PROtective Ventilation using HIgh versus LOw PEEP) tried to tease out the protective elements. They prospectively randomised patients at high-risk of developing a PPC (according to the ARISCAT score), undergoing intermediate and high risk abdominal surgery to ventilatory strategies of V_T 8ml/kg, with either high PEEP (12cmH_2O) with recruitment manoeuvres, or to low PEEP (2cmH_20) without recruitment manoeuvres. The results revealed that there was no difference in PPCs in the first 5 days postoperatively, but the patients in the lower PEEP group required more interventions for desaturation,

whereas and the higher PEEP group had more episodes of intraoperative hypotension and needed more vasoactive drugs.

The recommendations following the PROVHILO study are to use:

- low levels of PEEP (2cmH_2O) and
- low tidal volumes (6-7ml/kg)
- without the use of recruitment manouevres.

I have to admit, I'm not wild about this proposal. Whilst I support the use of low V_T ventilation in healthy lungs, studies have not addressed the benefit of combining this with moderate levels of PEEP (e.g. 5-8cmH_2O) instead of low PEEP. Maybe patients with low V_T and moderate PEEP will do even better, i.e. thereby avoiding the hypoxaemia and hypotension seen with low vs. high PEEP in PROVHILO. The place of recruitment manoeuvres (and they correct way to perform a recruitment manoeuvre) have also not been fully addressed in normal lungs. The literature remains horribly confusing when looking at how to ventilate the patient with normal lungs and the search for optimal intraoperative ventilation remains incomplete. My recommendations would be to continue with low V_T ventilatory strategies (6ml/kg PBW), use moderate PEEP (5-8cmH_2O), limit plateau pressures to <30cmH_2O, limit driving pressure (Ppeak – PEEP) to 20cmH_2O and probably avoid recruitment manoeuvres. What we do know is that, even in healthy lungs, high V_T and high airway pressures are harmful.

The PROBESE trial is an ongoing multicentre controlled trial focussing on the optimum ventilation of patients with obesity. So far, studies in obese patients suggest that recruitment manoeuvres and a PEEP of 10cmH_2O reduces atelecatsis, improves intra- and postoperative oxygenation and reduces PPCs compared to patients ventilated with lower levels of PEEP…although some studies suggest that the improvement in oxygenation is not sustained beyond 30 minutes postoperatively.

7. Stratifying risk

The use of scoring systems to predict patients at higher risk of developing a PPC has received much attention, these include: ARISCAT (a postoperative pulmonary complications risk score), SLIP (surgical lung injury prediction score) and SPORC (score for prediction of postoperative respiratory complications). The premise behind the scoring system is that patients who fall into high risk categories should undergo a multidisciplinary assessment, have modifiable conditions addressed, should be considered for intensive monitoring and for ICU / High care allocation where appropriate, or even look for a suitable non-surgical alternative. Even if the patient has non-modifiable disease, although the risk cannot be reduced before surgery, in-depth assessment is crucial in alerting care-givers and planning for admission to high care post operatively in high risk cases.

The ARISCAT score was developed in Catalonia as a 7-factor scoring system to assess risk for a composite PPC occurrence and has excellent discriminative ability (see Table 4). It divided patients into 3 levels of risk depending on the score they achieved: low risk <26 points, moderate risk 26 – 44 points and high risk ≥ 45 points. The ARISCAT study revealed the incidence of PPC as 5% in Catalonia.
Validation of the performance of the ARISCAT model for predicting PPCs yielded an area under the receiver operating curve of 88% (95%CI 85-94%). This regression model did not find an association between alcohol intake, obesity, intraoperative fluid therapy, postoperative pain and the development of PPCs. Male sex and a positive cough test were dropped off the final model – they may well have been included if the sample size was larger. Interestingly, the ARISCAT model found that current smokers had a lower risk of PPC compared to former smokers – this was probably due to the reason that current smokers were, on average, 17 years younger than former smokers, and that there was marked collinearity between smoking and COPD. Since smoking could not be separated as an independent factor, it was removed from the model. This is a fundamental problem with studies used to construct a predictive model – variable definitions of PPC, small sample sizes, heterogeneous surgeries and heterogeneous patients within the confines of a statistical model. I doubt that anyone would argue the impact of smoking and COPD on PPCs, even if they don't fit into a regression analysis looking at independent predictors.

Table 4. The ARISCAT score for the prediction of a composite of PPCs

Predictor	Score
Age (years) *	
≤50	
51-80	3
>80	16
Preoperative S_pO_2 **	
≥96%	
91-95%	8
≤90%	24
Respiratory infection in the last month***	17
Preoperative anaemia (Hb≤10g/dL)	11
Surgical incision	
Peripheral	
Upper abdominal	15
Intrathoracic	24
Duration of surgery (hours)	
≤2	
2-3	16
>3	23
Emergency procedure	8

Notes

- * Advanced age
  >80 years appears to be the cut off at which the PPC rate dramatically increases (OR 5.6 after 80 years of age)
- ** Low preoperative arterial oxygen saturation
  Breathing room air whilst supine – the strongest patient related risk factor for PPC
- *** Acute respiratory tract infection within the past month (both upper and lower airways)

The PERISCOPE study aimed to measure the predictive accuracy of ARISCAT for PPCs in a wider patient cohort (63 centres from 21 European countries). In PERISCOPE almost 6000 patients undergoing non-obstetric in-hospital elective or emergency surgery under anaesthesia (general, neuraxial, plexus block) were included. The incidence of PPC was 7.9%, occuring at a mean of 3 days following surgery. In-hospital mortality was 8.3% in the group of patients with ≥1PPC, compared to 0.2% in patients who did not have a documented PPC. PERISCOPE concluded that the ARISCAT score could accurately predict PPCs, but there were some differences in the performance of the score according to countries (i.e. the ARISCAT score showed better discrimination in Western Europe countries compared to countries in Eastern Europe).

7.1 Limitations of scoring systems

Scoring systems may define a composite PPC outcome or specific complications such as pneumonia or ARDS as the dependent variable. They may focus on specific surgical procedures such as thoracic surgery, upper abdominal surgery, colorectal surgery etc or they may have been developed from a large mixed surgical population (such as noncardiac surgery). It is important to consider the database used to develop the risk model, as the findings and attributable risk may not be generalisable to other populations or clinical scenarios. Often the risk factors are not able to be modified (such as age, and perhaps site of incision or duration of surgery). There are no validated pulmonary scoring systems developed for use in Africa or in lower-income countries.

7.2 Can ICU minimise complications?

The main reasoning behind scoring systems is to detect high risk patients and offer a mulitdisciplinary assessment and treatment for modifiable conditions if possible. This may include the perioperative provision of intensive monitoring and ICU / High care admission.

The EuSOS study looked at surgical outcomes in 28 European countries and was designed to describe postoperative mortality rates and the use of critical care in patients undergoing non-cardiac

surgery over a 7-day period in 2011. Over 46,000 patients were included and 4% died before discharge from hospital; this was higher than the predicted mortality of 1-2%. Only 5% of cases underwent a planned admission to ICU and 73% of patients who died in the postoperative period were not admitted to ICU. This suggests that there was either a lack of anticipation for planned admission into ICU and/or a lack of critical care resources. Unplanned ICU admission is associated with higher mortality rates. It may well be that the use of risk stratifying models to predict PPCs could reduce the mortality due to timeous (and preemptive) admission into critical care for those at the higher risk. I personally think that this approach is unsustainable in South Africa – preemptive admission into ICU is impossible in the governement sector due to a gross shortage of beds (ok, will get off my soap box now!).

ICU admission rates are between 9.5-91% higher in patients with PPCs.

8. The postoperative period

8.1 Postoperative pain: regional vs. systemic

Regional anaesthesia not only decreases pain (and thus improves pulmonary mechanics, coughing and mobilisation) but it may also reduce the reflex inhibition of respiratory muscles. The use of thoracic epidural analgesia may decrease PPCs, in particular, pneumonia, and postoperative ventilation (evidence from meta-analyses and systematic literature reviews). Randomised controlled trials have failed to demonstrate a benefit of epidural analgesia over systemic analgesia with respect to PPCs.

Analgesia with paravertebral blocks has been shown to reduce PPCs after thoracotomy and is associated with fewer side effects when compared to epidural analgesia (e.g. less urinary retention, hypotension, nausea and vomiting). However, continuous wound catheter analgesia was less effective as a post-thoracotomy pain management technique compared with paravertebral blockade and the implication is, therefore, that it would be less effective at reducing PPCs.

8.2 Physiotherapy

Early mobilisation, respiratory muscle training, breathing exercises and neuromuscular electrical stimulation have been shown to reduce radiographic changes, improve gas exchange, reduce postoperative length of stay and improve quality of life. No one physiotherapy technique has been shown to be more effective than any other, although incentive spirometry may be the least labour-intensive. However, there is low quality evidence regarding the effectiveness for incentive spirometry for the prevention of PPCs.

ICOUGH is an acronym for a programme developed by the Pulmonary Care Working Group that is easy and inexpensive to implement and has been shown to reduce postoperative pneumonia from 2.6 to 1.6% and unplanned intubation from 2% to 1.2%. ICOUGH stands for:

Incentive spirometry
Coughing and deep breathing
Oral care (twice daily tooth-brushing and mouth-washing)
Understanding (education for patient and family)
Getting out of bed frequently (>3 times a day)
Head of bed elevation.

Much of the evidence for the benefit of physiotherapy come from patients post-CABG surgery. Those receiveing physiotherapy had a shortened time to extubation, less PPCs and a shorter hospital length of stay. Fast-track surgery programmes (e.g. ERAS) have also incorporated early physiotherapy into their bundles of care.

8.3 Noninvasive respiratory support (NRS)

Noninvasive respiratory support (NRS) in the form of noninvasive positive pressure ventilation (nPPV) allows better unloading of the respiratory muslces, alveolar recruitment, oxygenation and CO_2 washout and relief from dyspnoea than noninvasive CPAP (nCPAP). In nPPV the patient's spontaneous inspiratory effort triggers the ventilator to provide gas flow that increases until the airway pressure reaches a preset level – i.e. during inspiration the patient receives a pressure-supported breath. In nCPAP, constant positive pressure is delivered in both inspiration and expiration.

NRS can be applied either **prophylactically** (to prevent postoperative respiratory failure in patients at risk), or as a **treatment** modality if respiratory failure occurs (it important to make this distinction). There is ***good evidence*** for NRS as a treatment modality in:

- pulmonary oedema
- hypercapnoeic respiratory failure, especially in the setting of exacerbations of COPD

NRS has also been used prophylactically in preoxygenation (especially in obese patients) prior to endotracheal intubation where it has been shown to reduce atelectasis. It has also been used immediately postextubation as prophylaxis against atelectasis and acute respiratory failure. A recent Cochrane Collaboaration Review of postoperative nCPAP concluded that postoperative nCPAP might reduce atelectasis, pneumonia and reintubation, although the effects on mortality, hypoxia and invasive ventilation were uncertain, it was acknowledged that the quality of evidence was very low.

NRS should not be applied if

- there is severe acute respiratory failure when minute ventilation is higher than 15l/min
- shock is present
- the base excess is more negative than -5mmol/L
- the p_aO_2 / F_IO_2 ≤120mmHg
- there are diffuse or patchy infiltrates on chest X-ray
- there is impaired ability to clear secretions and to swallow

Endotracheal intubation should not be delayed if the p_aO_2/ F_IO_2 <175mmHg after 1-4 hours of NRS treatment.

Prophylaxis can be provided with simple, stand-alone, nCPAP systems such as the Boussignac mask-valve system. Oxygen delivered through high flow nasal cannulae increase oropharyngeal pressure and lung volumes with an effect similar to low level nCPAP, although this is not considered a form of NRS.

The evidence outside of the above recommendations is scant and there have been numerous reports of NRS increasing mortality when used as treatment, rather than for prophylaxis. This is likely due to "pushing on" with NRS and delaying necessary intubation and ventilation, which then has to be performed as an emergency procedure. My opinion….be cautious of postoperative NRS **when used for treatment** – it can lull you into a false sense of security and delay necessary intubation, which can negatively impact on outcome. It should be performed in a high care setting only, on carefully selected patients, with close monitoring for signs of deterioration. If used to rescue patients with postoperative actue respiratory failure, it must be used early and be applied continuously for maximum benefit.

9. How to do it…

Preoperatively

- Use risk stratification tools such as ARISCAT to identify at risk patients
- Multidisciplinary involvement in high risk patients
- Consider preoperative physiotherapy for cardiothoracic patients
- Address modifiable parameters where possible
    - Reversible airway disease
        - ipratropium bromide to all wheezy COPD patients
        - β_2 agonists
        - corticosteroids
    - Postpone patients with URTI and LRTI for 1 month after symptom resolution
    - Nutritional aspects where appropriate
    - Target preoperative anaemia
    - Encourage stopping smoking for >4 (and preferrably 8) weeks
    - Encourage abstinence from alcohol for 2 weeks

Intraoperatively

- Limit surgery duration to <3 hours
- Consider minimally invasive / laparoscopic techniques
- Only use nasogastric tubes where clinically indicated
- Consider using F_IO_2 0.8 for preoxygenation in patients at low risk of desaturation

- Consider supraglottic airway devices if appropriate
- Titrate F_IO_2 (SaO_2 >92% / paO_2 >8kPa are probably adequate in most patients)
- Consider the use of neuraxial techniques as an adjunct to general anaesthesia
- Avoid long acting neuromuscular blocking agents
- Minimise "dose" of anaesthetic
- Avoid "lung damaging ventilation" with high V_T and plateau pressures (P_{plat})
- Ventilatory aims:
    - V_T 6ml/kg, modest PEEP
    - Unknown benefit of recruitment manoeuvres
    - Limit P_{plat}
- Judicious use of fluids
- Avoid blood transfusion if possible and apply blood saving strategies
- Use neuromuscular monitoring devices (peripheral nerve stimulator) and ensure complete reversal of neuromuscular blockade
- Consider low F_IO_2 0.4 and CPAP prior to extubation

Postoperatively

- Adequate analgesia, multimodal approach
- Consider NRS in high risk cases
- Consider physiotherapy and early mobilization.

…And good luck with the exam!

10. References…some of them!

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Anaesthesia for direct laryngoscopy and microlaryngeal surgery

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Microlaryngeal surgery is surgery performed on the larynx aided by a microscope. Direct laryngoscopy is performed either as part of the assessment for laryngeal pathology but also for laryngeal procedures such as laser ablation of localized laryngeal lesions, nodules or papillomatosis.

The need to share the airway with the surgeon and possible difficult intubation in many of these patients mandates a high level of co-operation between anaesthetist and surgeon. The anaesthetic should provide an adequate depth of anaesthesia or sedation, an unobstructed and immobile operative field, adequate oxygenation and carbon dioxide removal and a rapid return of airway reflexes after surgery.

Preoperative assessment and optimization of the patient is essential. Many of the patients, particularly those with a history of hoarseness or stridor are elderly with a history of heavy smoking and alcohol intake and have underlying cardiac or respiratory disease. A history of previous radiotherapy is important because the resultant fibrosis can make intubation more difficult than the Malampatti score or previous anaesthesia intubation experience prior to treatment would otherwise suggest.

In addition to the normal preoperative examination special attention should be given to the airway including the presence or absence of stridor, hoarseness or shortness of breath. Assessment of the Malampatti score, neck mobility and dental examination is vital. Poor dentition or gingivitis may require a gum guard and patients should be warned that their teeth may be damaged during the procedure.

Special investigations include looking at the most recent indirect or nasal fibreoptic endoscopy notes of the larynx, The CXR, CT scans (and possible MRI) of upper airway are important to assess the position of subglottic lesions. Important information may be gleaned from looking at the previous anaesthetic notes and the latest nasopharyngeal examination report.

Prior to the procedure the anaesthetist should establish from the surgeon exactly what he/she wants to achieve, whether intubation with a microlaryngeal tube (MLT) will provide satisfactory conditions for surgery and whether Laser will be used. It is imperative that the anaesthetist has a plan A,B and C in mind before induction.

If a difficult intubation is considered likely then the difficult airway trolley with a Sanders injector or high frequency jet ventilator (HFJV) should be in theatre prior to induction of anaesthesia. In the presence of critical airway stenosis an experienced surgeon should be present and should either first perform a tracheostomy under local anaesthesia, or be scrubbed and ready to perform an emergency tracheostomy should the need arise during induction of anaesthesia.

The best anaesthetic technique for patients with stridor has not been finalized and depends on experience and facilities. Positioning of the patient to facilitate intubation is important. Many anaesthetists prefer to keep the patient breathing spontaneously with a sevoflurane induction with intermittent spraying of the cords with 4% lignocaine via a Macintosh type spray until the larynx can be examined and the decision made as to whether or not to use a muscle relaxant to aid intubation. The use of suxamethonium as muscle relaxant is preferable. This technique has been criticized by some experts who feel that a preoxygenation, propofol, suxamethonium technique is preferable in that it will provide the best conditions for intubation whilst the patient is well oxygenated and that when the previous technique fails then propofol /suxamethonium is often used when the patient has already desaturated.

ANAESTHETIC TECHNIQUES

1. Intubation with microlaryngeal tube (MLT) and inhalational or TIVA anaesthetic
2. Techniques with no endotracheal tube (ETT) and TIVA
   a) Spontaneous ventilation with local anaesthesia & sedation
   b) Jet Ventilation (HFJV or LFJV) [Supraglottic, infraglottic or transtracheal]
   c) Apnoeic oxygenation with TIVA
   d) Intermittent apnoea with TIVA or inhalational anaesthesia

Conventional Anaesthesia after intubation using a Microlaryngeal Tube (MLT).
MLTs are longer than conventional endotracheal tubes (30cm). Sizes from 4.0 – 6.0 ID are available. The advantages are a secure airway with airway protection, the ability to monitor airway pressures, FIO_2 and ET CO_2, and used with muscle relaxants provide good operating conditions with immobile vocal cords. The disadvantage is that the posterior region of the larynx is obscured by the ETT. Either a TIVA technique or inhalational anaesthesia can be used. Remifentanil infusions are helpful to blunt the airway stimulation.

1. **Spontaneous ventilation** together topicalisation of airway with local anaesthetic and sedation. This should be thoroughly discussed with patients in whom this is considered the optimal technique, stressing the advantages which include rapid mobilization and discharge, less potential for PONV, avoidance of airway instrumentation and possibly increased likelihood of optimal voice outcome during vocal cord surgery. [(1)]
   Adequate airway topicalization of upper and lower airways takes 10 – 20 minutes and can best be achieved using nebulized 2% or 4% lignocaine in the holding area. Additional gargling of local anaesthesia without swallowing may be useful.
   Conscious sedation may be achieved using dexmedetomidine if available or midazolam or ketamine and supplemented with titrations of remifentanil. Capnometry via nasal specs should be used in patients receiving remifentanil. This topic is well covered in reference [(1)]

2. **Jet Ventilation** [(2,3,4)]
   using either low frequency ventilation (LFJV) or high frequency (HFJV), together with TIVA. Jet ventilation (JV) is achieved by the injection of gas under high pressure (1-3 Bar) through a catheter into the airway that is open to ambient air. Inspiration is an active process in which the tidal volume is supplemented by entrained ambient air whilst expiration is passive. Switching between inspiration and expiration is achieved either by either pneumatic or electronically controlled flow interruption devices.

   Low frequency jet ventilation
   In LFJV (6-30 bpm) oxygen is usually applied by a hand-triggered device such as the Sanders injector. The Oxygen from the piped supply (400 kPa) passes through a pressure reducing valve and can be further regulated by a control near the handset to a pressure that produces the desired chest-wall excursion. A short rigid pipe connects the injector to the laryngoscope or bronchoscope via a Luer lock connector. Gas exchange occurs primarily by *convective ventilation* or *bulk flow*.

   High frequency jet ventilation
   HFJV uses tidal volumes smaller than the dead space (1-2 ml/kg) usually at a frequency between 1-10 Hz. It is a form of time-cycled, pressure limited ventilation. If set ventilator parameters remain constant and the airway compliance decreases the minute volume will decrease. Driving pressure, frequency, inspiratory time and composition of the jet gas can be altered. *Bulk flow* plays only a minor role in gas exchange. More important mechanisms are: a) *Laminar flow* with a parabolic velocity profile that occurs in small airways whereby gas closest to the wall has a lower velocity than gas in the centre of the airway. The differences in flow rate become more exaggerated with each breath resulting in rapidly moving gas passing down the centre axis of the airway, whilst gas in the margins moves out of the lungs. b)*Taylor type dispersion* whereby further mixing occurs in smaller airways as a result of enhanced molecular diffusion (c) *Pendelluft or collateral ventilation* due to regional variations in airway resistance and compliance causing gas to flow from one alveolus to another due to different time constants; and d) *cardiogenic mixing* due to mechanical agitation of lung units close to the heart.
   HFJV requires a specialized ventilator such as the Acutronic Mistral. (see below)

- **Supraglottic LFJV, HFJV** with TIVA
  - the jet nozzle is located above the vocal cords in the trachea. This is an example of venturi in that the pressure drop as the jet exits the catheter tip entrains ambient air through the laryngoscope. Modified suspension laryngoscopes with a channel for the catheter providing gas are used. Jet ventilation is not possible before the suspension laryngoscope is in place, or after it has been removed. The surgeon is responsible for maintaining the airway and malalignment can cause gas to be blown into the oesophagus causing gastric distension. ETCO2 can not be measured with the supraglottic approach.

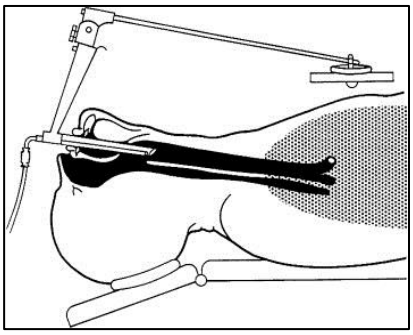


Fig. 1 Suspension laryngoscope with supraglottic jet ventilator [(2)]

- **Infraglottic LFJV, HFJV**
  - the jet nozzle is located below the vocal cords in the trachea via a thin jet catheter positioned by standard laryngoscopy with the tip in the mid trachea. Laser resistant double lumen tubes such as the LaserJet catheter (Acutronic MS, Switzerland) or the Hunsaker Mon-Jet catheter (seen if fig. 2) are available allow for jet ventilation through the one lumen and sampling of gases from the other or measurement of airway pressures through the other. The Hunsaker catheter is 33cm long and ends in a basket shape plastic cage which aligns the jet in the middle of airway, preventing direct trauma to the tracheal mucosa.

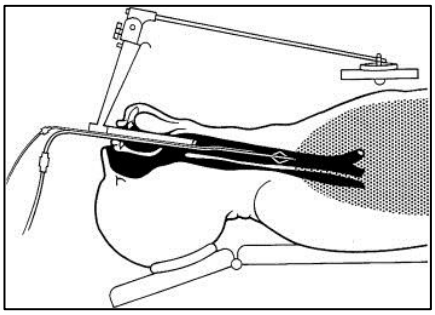


Fig. 2 Suspension laryngoscope with infraglottic tube for HFJV [(2)]

Transtracheal LFJV, HFJV with TIVA

This is usually performed using a short, narrow (1.0mm ID) catheter inserted via the cricothyroid space or the space between the cricoid cartilage and the first tracheal ring. Purpose made catheters include the Ravussin-type catheter demonstrated in fig 3. This technique can also be used to salvage a failed intubation scenario.

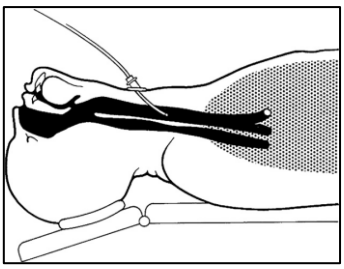


Fig 3. Transtracheal ventilation via a Ravusin-type canula [(2)]

Equipment necessary for Jet Ventilation

High frequency jet ventilators.
HFJ ventilators were introduced in the 1970's and first used during for percutaneous ventilation of patients undergoing fibreoptic bronchoscopy by Klain and Smith. In 1980, together with Babinski they described its use in patients undergoing laryngoscopy under general anaesthesia. Early ventilators were unable to humidify the inspired gases. Recent models such as the Acutronic Monsoon III ventilator can humidify and warm gases at a frequency between 1–10 Hz. Driving-pressure, frequency, inspiratory time, and the composition of the jet gas can be adjusted. Although the FiO_2 can be altered the delivered FiO_2 will depend on the amount of air entrained. End tidal carbon dioxide measurement requires a temporary cessation of HFJV and a normal tidal ventilation to be delivered for measurement.
JV can cause a dangerous increase in airway pressure if egress of gas is obstructed during expiration such as can occur with a tight airway stenosis.
The new ventilators display peak inspiratory pressure (PIP), mean airway pressure (MAP), plateau pressure (PP) and end expiratory pressure (EEP) and allow alarm limits to be set for PIP & PP. A high pressure cut off pressure can be set to reduce the problems mentioned in Table 2.

Jet ventilation catheters
Both Hunsaker Mon-Jet (Medtronic Xomed) and LaserJet catheters (Acutronic) are double lumen catheters made from non-flammable, fluoroplastic materials specifically designed for subglottic HFJV.

3. **Apnoeic Oxygenation**
This technique has been recommended for the performance of pan-endoscopy by Rudlof & Hohenhorst from Wuppertal in Germany. [5] Patients are preoxygentated for 3 minutes with 100% O_2, anaesthetized with propofol & remifentanil, paralysed with mivacurium and hand ventilated to a $FetO_2$ > 90%. An 8 French gauge catheter is then introduced into the trachea using a laryngoscope with the tip lying up to the carina and a flow of Oxygen 500 ml/minute administered through the catheter. In their retrospective study performed over a period of one year, satisfactory oxygenation for up to 45 minutes was reported in 44/47 patients. The one failure was in an obese patient. The technique relies on aventilatory mass flow.

4. **Intermittent ventilation** techniques rely on the MLT in patients under TIVA anaesthesia being removed intermittently from the larynx for short periods (< 5minutes) to allow surgery to take place. The MLT is re-inserted if SaO_2 fell below 90%. Laryngospasm was a major complication.[7]

Table 2. Complications of HFJV [7]

Barotrauma
- Pneumothorax
- Pneumomediastinum
- Pneumoperitoneum
- Sub cutaneous emphysema
- Air trapping can lead to decreased venous return, increased afterload for R ventricle resulting in decreased cardiac output and possible RV failure

Exposure to dry gases leading to:
- Damage to the tracheobronchial mucosa leading to:
- Decreased mucociliary clearance, infection, airway plugging, atelectasis
- Necrotizing tracheobronchitis.

Hypothermia

Malposition of catheters (with supraglottic approach)
- Gastric distension or rupture

Inadequate gas exchange
- Hypercapnia.
- Hypoxaemia

Laser Surgery [8]

CO_2 laser is widely used in ENT surgery for soft tissue ablation in the treatment of laryngeal pathology because it allows the application of a high amount of energy to a precise location that vaporizes cells. The high energy provided by the laser allows precision cutting, with little damage to nearby cells and provides good haemostasis. It can damage healthy tissue if misdirected and can cause airway or other fires if combustion occurs. CO2 laser radiation cannot be transmitted through fibreoptic cables and is transmitted via reflecting mirrors.

Airway fires

For a fire in theatre to occur three components need to be present viz. **Fuel** (ETT, drapes, alcohol prep), an **oxidizer** (O_2 or nitrous oxide) and an **ignition source** (laser, diathermy). These conditions frequently occur during laser surgery.

To reduce the risk of airway fires:

- the lowest possible FiO_2 commensurate with a satisfactory O_2 saturation should be administered and nitrous oxide avoided because it supports combustion.
- If infraglottic jet ventilation is to be used it should administered through a polytetrafluoroethylene catheter (LaserJet or Hunsaker Mon-Jet) as they are not flammable, (although they can be punctured by CO_2 laser).
- If the patient is to be intubated with a MLT, special precautions should be taken as both PVC tubes and red rubber tubes can be ignited. Mallinkrodt™ have developed their Laser flex tube to reduce the risk of airway fires whilst using laser. It has a flexometallic body with an external matte finish that defocuses laser beams; as well as a double cuff in case the first cuff is punctured during surgery.
- Many anaesthetists use water instead of air to obtain a cuff seal.
- Methylene blue is often added to the fluid in the cuff to facilitate recognition of airway puncture.
- If a laser resistant ETT is not used then wet pledgets should be placed around the PVC tube and kept moist during surgery.

All units using lasers should have a fire drill that should be discussed as part of the WHO Check List. A 50 ml syringe filled with saline should be immediately available in event of an airway fire.

Protocol for airway fire

As soon as an airway fire is recognized;

1) Remove the tracheal tube and have another member of the team extinguish it.
2) Remove pledgets and any pieces of the ETT that are left in the airway.
3) Pour saline or water into the airway to cool tissues
4) Care for the patient:
    - Reestablish the airway and resume ventilation with air until certain that nothing is left smoldering in the airway, then switch to 100% oxygen
    - Examine the airway to determine the extent of damage and treat accordingly

Prevention of Injury to Staff

- Protective eye glasses should be worn. (Because CO_2 laser is absorbed by glass and plastic ordinary eyeglasses will protect operating room staff from damage to their eyes).
- Warning notice should be placed on theatre doors when Laser surgery is in progress.
- Masks should be worn if papillomata are to be resected
- Non reflective instruments should be used to prevent reflection

Postoperative considerations following airway surgery

Problems of concern following airway surgery include airways obstruction, bleeding, laryngospasm, and laryngeal incompetence. Oedema can be reduced by the administration of dexamethasone or betamethasone intraoperatively. Patients should be nursed in the semi-sitting position and extubated either awake or under deep anaesthesia. Oxygen should be humidified and in patients with stridor, nebulized adrenaline should be administered. If available, heliox may be administered to reduce the work of breathing.

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EMERGENCY PROCEDURE
EXTINGUISHING A SURGICAL FIRE

Fighting Fires ON the Surgical Patient
Review before every surgical procedure.

In the Event of Fire on the Patient:

1. **Stop the flow of all airway gases to the patient.**
2. **Immediately remove the burning materials** and have another team member extinguish them. If needed, use a CO_2 fire extinguisher to put out a fire on the patient.
3. **Care for the patient:**
   - —Resume patient ventilation.
   - —Control bleeding.
   - —Evacuate the patient if the room is dangerous from smoke or fire.
   - —Examine the patient for injuries and treat accordingly.
4. **If the fire is not quickly controlled:**
   - —Notify other operating room staff and the fire department that a fire has occurred.
   - —Isolate the room to contain smoke and fire.

Save involved materials and devices for later investigation.

Extinguishing Airway Fires
Review before every surgical intubation.

At the First Sign of an Airway or Breathing Circuit Fire, Immediately and Rapidly:

1. **Remove the tracheal tube**, and have another team member extinguish it. Remove cuff-protective devices and any segments of burned tube that may remain smoldering in the airway.
2. **Stop the flow of all gases to the airway.**
3. **Pour saline or water into the airway.**
4. **Care for the patient:**
   - —Reestablish the airway, and resume ventilating with air until you are certain that nothing is left burning in the airway, then switch to 100% oxygen.
   - —Examine the airway to determine the extent of damage, and treat the patient accordingly.

Save involved materials and devices for later investigation.

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MS09445_1

Source: New Clinical Guide to Surgical Fire Prevention. *Health Devices* 2009 Oct;38(10):330. ©2009 ECRI Institute
More information on surgical fire prevention, including a downloadable copy of this poster, is available at www.ecri.org/surgical_fires

Notes

Awake Fibre-optic Intubation

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Awake fibre-optic intubation is an essential skill in the management of the patient with a known or suspected difficult airway. Despite technical advances in the field of airway management with new devices being added to the arsenal almost daily, AFOI remains the gold standard for the management of the anticipated difficult airway without airway obstruction. This should be seen as a core skill for which competence should be gained during your registrar time. It is our responsibility as 'airway experts' to ensure that we have the necessary skills to perform an AFOI safely. The single most common cause of a failed FOI is lack of experience and training.

Airway assessment continues to be an imperfect science but should be performed in every patient preoperatively to reduce the risk of patient harm. A strategy for airway management that preserves patient oxygenation and ventilation throughout the perioperative period should be used for every patient. The most recent version of the ASA guidelines for management of the difficult airway was published in 2013. (Appendix 1). Note the position of the awake fibre-optic intubation in the algorithm. In these guidelines there is no role for the fibre-optic bronchoscope if laryngoscopy and mask ventilation are impossible after induction of general anaesthesia. Unfortunately there is just not enough data to support every recommendation made concerning airway management; in the absence of hard evidence expert opinion and group consensus may fill the gaps.

The Fourth National Audit Project of the Royal College of Anaesthetists (NAP4) highlighted the underuse of AFOI in the management of difficult airways as well as a number of factors leading to its failure including lack of experience, inappropriate sedation, inability to view landmarks and endotracheal tube impingement during railroading. The audit identified numerous cases in which awake intubation with a flexible bronchoscope was indicated but was not used. Poor planning contributes to poor airway outcomes. It is also important to plan for failure of your primary airway plan.[1]

Advantages of the awake state for flexible fibre-optic intubation:

Spontaneous ventilation maintained
Oxygenation and ventilation maintained
Anatomy and muscle tone preserved, intubation therefore easier
Airway protection preserved
Safety
Options preserved

Miller's Anesthesia 7th Edition

Definition of a difficult airway:

ASA: A clinical situation in which a conventionally trained anaesthetist experiences difficulty with facemask ventilation, supraglottic device ventilation, tracheal intubation or all three. A more complete definition would include difficulty with tracheal access and a consideration of the airway at extubation.

Difficult intubation has been defined as outright failure, Cormack and Lehane grade 3 or 4 laryngoscopy, the need to use specialist equipment or more than 2 attempts at intubation. There is a lack of consensus for these definitions.

Indications:

The main indication for an awake intubation is a suspected or known difficult airway. In a case of easy mask ventilation but isolated difficulty with tracheal intubation, an asleep technique may be appropriate. The role of AFOI in a partially obstructed airway continues to be debated.

Another indication is to avoid iatrogenic injury e.g. a patient with an unstable C-spine. The overall incidence of secondary cervical injury attributable to intubation is very small. In an observational study of 327 patients with cervical spine disease, 39% were intubated with AFOI. Anaesthetists were more likely to use this technique if the patient had myelopathy, unstable or fractured vertebrae, or spinal canal stenosis. There is no published data to suggest that AFOI improves outcome in cervical spine injured patients compared to other intubation methods.[6]

Indications:

- Suspected or known difficult airway
- Anticipated difficult laryngoscopy and tracheal intubation
- Anticipated difficult mask ventilation
- Anticipated difficult rescue technique
- Avoidance of iatrogenic injury e.g. unstable C-spine

Contra-indications:

Absolute:

- Patient refusal or non-compliance

Relative:

- Lack of skill/equipment
- Critical airway obstruction
- Contamination upper airway
- Grossly distorted anatomy
- Local anaesthetic allergy
- Penetrating eye injury
- ??Aspiration risk
- Nasal route: Fractured base of skull
- Coagulopathy

The difficult airway with impending airway obstruction:

AFOI can be successful when done by experts in selected cases, depending on the site of obstruction and with nasendoscopy and radiological investigations to aid decision making. However, AFOI can also precipitate complete airway obstruction in this scenario. On the topic of the management of the obstructed airway I refer you to an article published in Anaesthesia in 2011 titled Progress in the management of the Obstructed Airway[9]. Successful use of an AFOI technique for an obstructed airway requires skill, an understanding of the nature and level or site of obstruction and recognition that with advanced glottic obstruction, fibre-optic techniques fail.

Patients at risk of aspiration:

Some debate exists about the use of airway topicalisation and AFOI in these patients but numerous reports of its success exist when relevant precautions are taken, e.g. aspiration prophylaxis, sitting /semi sitting patient position. In patients at risk of aspiration it may be best to avoid the transtracheal and possibly superior laryngeal nerve blocks. A spray-as-you-go technique might be safer. Postoperative oral intake should only be allowed once cough and swallowing reflex have returned to normal.

Requirements for AFOI:

It is essential to have a working knowledge of the anatomy of the normal upper and lower airways, from the nasal passage to the bifurcation at the carina. It is also important to know the mechanism of action and maximum doses of various local anaesthetics and vasoconstrictors used. Most importantly the anaesthetist must have a management plan A, B, C...

The flexible bronchoscope:

There are 2 types of flexible bronchoscopes, a fibre-optic bronchoscope and a video bronchoscope. Be familiar with your device. The fibre-optic scope contains bundles of optical fibres each with a diameter of 8-25um that transmit the image, a different group of fibres that transmit light to the distal end and cables from a control lever in the handpiece. The hollow channel can be used for aspiration of secretions or installation of local anaesthetic. The image can be displayed on a monitor by attaching a camera to the eyepiece. A video bronchoscope has a distal video chip from which the image is transmitted electronically to a video display.

The scope can be maneuvered in three planes: Tip flexion-extension, rotation of entire scope, advance-withdrawal of entire scope. The external portion of the scope should be kept as straight as possible during manipulation so that rotation of the hand piece is transmitted to the distal end.

Use the dominant hand to perform the finer movements of aiming the tip in the correct direction, rotating the tip and advancing/withdrawing the scope. Move the control lever and depress the suction valve with the non-dominant hand.[2]

Difficulty passing the tracheal tube over a correctly positioned scope is a common problem. The most common sites for hold up of the ETT are the inter-arytenoid notch and the right arytenoid cartilage and epiglottis. Hold up of the ETT is more likely if there is a significant size discrepancy between the diameter of the scope and the ETT. Try to advance the ETT through the cords with the bevel facing posteriorly. If hold up occurs withdraw the tube 1-2cm, rotate 90'anticlockwise and advance again. Never force the ETT. An alternative is to use a special ETT with a soft tapered end, e.g. the ETT of an intubating LMA.

Nasal vs oral intubation:

The type of surgery may dictate which route is chosen.

The nasal route is technically easier as there is a less acute angle to negotiate with the bronchoscope in the nasopharynx and on extubation a nasal tube is better tolerated and can be left in as a nasopharyngeal airway.

The Berman and Ovassapian airways are devices that facilitate the passage of a fibre-optic scope and endotracheal tube through the mouth into the oropharynx. Measure the distance from the corner of the mouth to the ear, this should be equal to the distance from the mouth opening to the glottis.

Airway Innervation:

Nasal cavity: Anterior third of nasal septum and the nares are innervated by the ethmoidal nerve, a branch of the olfactory nerve (CN 1). The posterior cavity is innervated by branches of the maxillary nerve (trigeminal nerve). Specifically the greater and lesser palatine nerves from the pterygopalatine ganglion innervate the turbinates and most of the nasal septum. The pterygopalatine ganglion is located posterior to the middle turbinate in the pterygopalatine fossa. .

Oropharynx: The oropharynx is mainly innervated by the glossopharyngeal nerve with both motor and sensory fibres. It enters the pharynx between the superior and middle constrictor muscles of the pharynx and provides sensory fibres to the posterior third of the tongue, vallecula, anterior surface epiglottis, walls of pharynx and tonsils.

Larynx: Branches of the vagus nerve innervate the larynx and trachea. The Internal branch of the superior laryngeal nerve provides sensation to vocal cords, posterior epiglottis, arytenoids and aryepiglottic folds. Essentially it is the sensory supply to the larynx above the vocal cords. It originates from the superior laryngeal nerve lateral to the greater cornu of the hyoid bone.

The recurrent laryngeal nerve is the sensory supply to the vocal cords and below, as well as motor function of all intrinsic laryngeal muscles except cricothyroid which is innervated by the external branch of the superior laryngeal nerve.

Anaesthetising the airway:

The aim here is to reduce sensation over specific regions that will be encountered by the scope and ETT and so reduce undesirable elevations in the patient's sympathetic and parasympathetic outflow as well as improve operator success.

There are many safe and effective ways of achieving suitable airway anaesthesia. Whichever method is chosen, adequate airway anaesthesia is the key to a successful awake intubation and should not be rushed.

Some techniques of airway anaesthesia:

Nebulizers: Entire airway
Topical sprays and gels: Upper airway
Spray-as-you-go: Larynx and trachea
Transtracheal injection: Larynx and trachea
Nerve blocks: Distribution of nerve supply
Combinations of the above

Miller's Anaesthesia, 7th Edition.

Topical anaesthesia:

Topicalisation of the airway involves spreading of local anaesthetic over a region of the mucosa to achieve local uptake and neural block of that region. Adequate time allocation is needed to provide optimal conditions. Topical anaesthesia reduces the calibre of a normal airway. Topicalising the airway in a patient with critical airway narrowing can lead to complete airway obstruction and should only be performed by experts when there is a team ready to perform an immediate surgical airway.

Lignocaine is the most widely used agent for topical airway anaesthesia as it has a favourable safety profile. It is available in a variety of concentrations and can be combined with a vasoconstrictor such as adrenalin or phenylephrine. The vasoconstrictor decreases local blood flow, slows the rate of absorption of local anaesthetic and prolongs its effect.

The use of cocaine has largely fallen out of favour in this setting. It has marked sympathomimetic activity and may cause cardiac dysrhythmias and myocardial ischaemia. (Maximum dose for topical anaesthesia is 1.5mg/kg.)

The maximum described dose for topical administration of lignocaine is 9mg/kg lean body mass in adults, with or without adrenalin, although this high a dose is seldom necessary. Calculate the maximum dose for your patient and do not exceed that. It is important to take note of further local anaesthetic that may then be used by the surgeon. Lignocaine has a narrow therapeutic range with toxicity being dose related and proportional to plasma levels. The accepted plasma threshold before signs of toxicity are seen is 5mg/L. However, factors such as hyperaemia and oedema of the airway caused by infection/trauma/tumour can enhance transmucosal systemic absorption of local anaesthetic. Hypercarbia and hepatic dysfunction can also facilitate the onset of neurotoxicity with serum concentrations lower than 5mg/L. Care should be taken in such patients and a lower total dose used. About 25% of the dose of lignocaine given is absorbed. Most of the lignocaine administered via sprays or gels is swallowed and undergoes first pass hepatic metabolism.

Lignocaine 2-4% should be used. A quicker and denser block can be achieved with a 4% solution.

Lignocaine can be nebulised, administered as a spray-as-you-go technique (SAYGO), gargled, via soaked pledgets judiciously placed or by airway blocks.

With nebulised lignocaine the density of anaesthesia throughout the airway may be variable and so this technique may need to be supplemented by a spray-as-you-go approach.

Spray-as-you- go technique allows supplementation of topicalisation as you advance the scope. It is particularly useful at the cords and below (recurrent laryngeal nerve). It does cause coughing and requires time for recovery after each application. Use an epidural catheter (cut off multihole tip) down side port of scope and advance until visible beyond scope, inject 1-2ml 4% lignocaine above and below the cords. Alternatively put 2 ml of 4% lignocaine in a 10ml syringe, fill the rest with air and inject directly via suction port of scope rapidly onto the vocal cords.

Lignocaine soaked swabs or cotton pledgets can be left for 5-15 minutes in the regions of mucosa that require anaesthesia e.g. nasal passages. Add adrenaline 1:200 000 or phenylephrine (0.05%). Alternatively use a vasoconstricting nasal spray (oxymetazoline) before applying the local anaesthetic.

Various other preparations include remicaine jelly to the nostrils with a pus swab, benzocaine oily foam via long spray nozzle, benzocaine lozenges, xylocaine spray (each activation of metered dose delivers 10mg lignocaine), amongst others.

Airway nerve blocks[10]:

Nerve blocks produce more profound and longer lasting anaesthesia than topical anaesthesia, however they are invasive, must be performed bilaterally and can be quite unpleasant for the patient.

Nose: Lignocaine soaked swabs to nose.

Oropharynx: Glossopharyngeal nerve block will block the gag reflex and facilitate the passage of the ETT through the posterior pharynx. It can be blocked most easily as it crosses the palatoglossal arch. It can be blocked by topical spray, direct mucosal contact of soaked pledgets in the tonsillar fossa or by injection infiltration.

Intraoral or extraoral approach:

Intraoral: Anaesthetise tongue with topical anaesthetic using a 22G needle. 5ml 2% lignocaine is given submucosally at the caudal aspect of the posterior tonsillar pillar (palatopharyngeal fold).

Extraoral: Peristyloid approach. With the patient supine draw a line from angle of the mandible to the mastoid process. Using deep pressure, palpate the styloid process just posterior to the angle of the jaw along this line. Use a short, small gauge needle and seat it on this process. Withdraw needle and direct posteriorly off the styloid process. As soon as bony contact lost 5-7ml 2% lignocaine injected after careful aspiration.

Both intra and extra oral approaches involve deposition of local anaesthetic close to the carotid arteries. The palatoglossal arch is a highly vascular area and so accidental vascular injection is an ever present risk. Significant absorption of the local anaesthetic can also be expected in this region. As with any injection in a highly vascular region this may be contraindicated in patients with coagulopathies or on anticoagulant medication.

Larynx: Superior laryngeal nerve block: The internal branch arises from the superior laryngeal nerve lateral to the greater cornu of the hyoid bone. The nerve should pass 2-4mm inferior to the greater cornu of the hyoid bone; from here it pierces the thyrohyoid membrane and travels under the mucosa in the pyriform recess.

Blockade of this nerve can be done by bilateral injections at the level of the greater cornu of the hyoid bone. Patient supine, head fully extended. Cornu of hyoid bone located below angle of mandible. Palpate outward from the thyroid notch along upper border of thyroid cartilage until greater cornu is encountered just superior to its posterolateral margin. Nondominant hand displaces hyoid bone with contralateral pressure bringing ipsilateral cornu and internal branch of superior laryngeal nerve toward anaesthetist. 25G inserted in an anteroinferomedial direction until lateral aspect greater cornu contacted. Needle walked off inferior border of greater cornu, thyrohyoid pierced and internal branch blocked. If needle retracted slightly after contacting hyoid bone both internal and external branches are blocked. 2ml lignocaine injected after aspiration.

If the patient is unwilling or unable to tolerate these injections due to distorted anatomy for example, soaked pledgets with right angle forceps can be placed in the pyriform fossa on either side of the root of the tongue for 5-10 minutes.

Recurrent laryngeal nerve block: The *transtracheal block* will prevent coughing as the endotracheal tube passes through the vocal cords.

Transtracheal block: Cricothyroid membrane located in midline. Small skin wheal of local anaesthetic. 22G needle on 10ml syringe with 4ml 4% lignocaine (or butterfly needle) passed perpendicular to trachea. Needle is advanced with continuous aspiration until air is aspirated. Rapidly inject on end expiration. The resultant coughing on injection of the LA disperses the LA solution and blocks sensory

branches of recurrent laryngeal nerve. Motor function is unaffected. This block can be done with a needle cannula and the cannula left in situ for rescue oxygenation and to provide a conduit for the passage of a guidewire for Seldinger tracheostomy, potential retrograde intubation or cricothyroidotomy.

Alternatively a spray-as-you-go technique with an epidural catheter down the side port of the fibre-optic scope can block this nerve.

Structure	**Nerve**	**Nerve Block**
Nose	Ethmoidal nerve Maxillary nerve	Lignocaine soaked pledges
Oropharynx	Glossopharyngeal nerve	Intraoral palatopharyngeal fold Extraoral peristyloid approach
Larynx	Superior laryngeal nerve, internal branch Recurrent laryngeal nerve	Greater cornu hyoid bone Transtracheal injection

Antisialogogue:

Oral secretions can make visualisation difficult and serve as a barrier to effective penetration of the local anaesthetic into the mucosa. Glycopyrollate 3-4ug/kg ivi 30 minutes preoperatively or atropine 0.5-1mg IMI/IVI.

Sedation:

Awake intubation can be achieved using local anaesthesia alone but sedation is often required to improve patient tolerance. The safety of AFOI lies in the ability to maintain spontaneous ventilation and the ability to stop and perform a different technique if intubation is unsuccessful. The use of sedation is generally accepted in a non-obstructed airway. Some argue that it should not be used as it is essential to maintain lower airway reflexes to avoid aspiration. It does however assist with patient compliance and so improves the chances of a successful intubation.

It is not easy to strike the balance between patient comfort and good intubating conditions on the one hand and maintaining spontaneous ventilation and a patent airway on the other. Oversedation can cause airway obstruction, respiratory depression, or apnoea which can result in significant morbidity or mortality (NAP4).

In order to provide safe sedation the following should be adhered to:

Patient selection: It has been said that sedation should not be used in a patient with airway obstruction or respiratory failure. The emergence of newer therapies may challenge this view.

Drug selection: The appropriate choice of drug(s) for the patient and the pathology.

Sedationist: If sedation is used for an AFOI a second anaesthetist must be present and be responsible for administering and monitoring the effects of sedation.

The goals of sedation for an AFOI would be a co-operative patient, maintaining his own airway with minimal respiratory depression.

Due to the relatively small numbers of AFOI performed, and the variable pathologies for which it is indicated, there are relatively few well-designed RCTs comparing different sedation regimes/drugs.

A recent review of the literature on this topic was published by Can J Anaesth 2013[4]. This looked at the evidence supporting the use of agents with regard to their efficacy, recommended doses, techniques and limitations to their use for AFOI. Benzodiazepines, opioids, propofol, alpha-2 agonists and ketamine have all been described to facilitate AFOI. From this review it appears there is good evidence to support the use of remifentanil and dexmedetomidine in particular.

A lot of these studies looked at patient recall of events as an indicator of drug efficacy. In this author's opinion recall is part of the definition of an AFOI. Ideally the recall should not be distressing but I do not think amnesia/hypnosis should be a primary target of the sedation regime used.

The ideal sedative for AFOI would provide anxiolysis, have analgesic properties, suppress the cough and gag reflex, be safe and easy to titrate with minimal respiratory and cardiovascular side effects, and have an antidote.

Drugs that are most suitable have both anxiolytic and analgesic properties and would ideally not depress ventilation. The ideal choice may vary depending on patient and pathology. For example the conditions for safe intubation of a patient with an oropharyngeal mass and respiratory distress are very different from those required for the management of a patient with an unstable cervical spine injury in whom coughing and straining should be avoided.

Psychological preparation of the patient is vital and contributes hugely to anxiolysis but this is sometimes not enough. The analgesic effects supplement local anaesthesia and may limit respiratory and cardiovascular responses to airway instrumentation.

The use of a combination of drugs during AFOI can result in synergistic or antagonistic effects between the drugs used. The effect of this could be over/undersedation as well as respiratory depression which could compromise the safety of the technique. While synergism may be desirable it can be unpredictable.

Benzodiazepines:

Midazolam is commonly used in combination with an opioid for AFOI. It might well be one of the most commonly used sedatives for AFOI. However a review of the literature with only a small number of studies available makes it difficult to arrive at a conclusion on its use. The advantages would be its wide availability, availability of an antidote (flumazenil) and user experience with the drug. However, a major disadvantage is the risk of oversedation with bolus injections and the wide inter-patient variability in response to the drug.[12]

Propofol:

Most studies using propofol use it as a TCI technique with or without remifentanil.

3 RCT's compared propofol with remifentanil and 1 RCT compared it with dexmedetomidine.

In all of these trials Remi/Dex was superior to propofol in terms of intubating conditions. The only benefit of propofol seems to be decreased recall. All of these trials show that the balance between underdosing (coughing and straining) and overdosing (airway obstruction and loss of co-operation) can be difficult to achieve. The use of propofol for AFOI is associated with a low incidence of recall at the expense of an increased risk of oversedation.

Propofol is definitely unsuitable for sedation for AFOI if airway topicalisation is not used.
There is no clear consensus on the dose range, however it does seem that the risk of oversedation increases with effect site concentrations greater than 3 ug/ml.
More recently case reports have described the use of propofol with remifentanil. The dose ranges used are TCI propofol Cet 0.8-2.0 ug/ml and remifentanil 1.5-3.2 ng/ml. Although there is no evidence to support the use of TCI propofol over fixed rate infusion it is safe to say that TCI has a more consistent pharmacodynamic effect and may allow for a more predictable level of sedation.

Opioids:

AFOI can cause intense nociceptive stimulation especially during passage of the endotracheal tube through the nose and larynx. Opioids can help to attenuate the coughing and haemodynamic changes associated with airway instrumentation. In situations where local anaesthesia may be inadequate e.g. mucosal inflammation, difficult anatomy, excessive secretions, opioids may be beneficial. In the history of AFOI most opioids have been administered as boluses. It must be noted that boluses of opioids combined with midazolam for sedation can result in significant hypoxaemia, apnoea and aspiration.

Remifentanil

Remifentanil is a potent, ultra-short acting synthetic u-opioid receptor agonist with a context sensitive half-time of 3 minutes and an elimination half-time of 6 minutes. It is metabolised by nonspecific plasma and tissue esterases. This makes it easy to titrate while providing profound analgesia and suppression of airway reflexes with little effect on cognitive function.

Initial studies used remifentanil as a fixed rate infusion in ug/kg/min. Even at doses of 0.25-0.5ug/kg/min where respiratory depression was common, it was always correctable by verbal commands to breathe. Further studies have shown that manual administration of remifentanil is more likely to be associated with overshoot, interpatient variability and accumulation than effect site targeting with TCI models. There is evidence to suggest that remifentanil administered by TCI is associated with a lower incidence of complications (apnoea, respiratory depression) compared with manual administration.

In the 3 RCT's comparing propofol to remifentanil all remifentanil patients were able to open their eyes and breathe on command if saturations fell; this was not the case in the propofol group.

The dose range for TCI remifentanil for AFOI is Cet 3-5ng/ml when used with midazolam 1-2mg or when combined with a small effect site concentration of propofol <1ug/ml. With adequate topicalisation and counselling of the patient remifentanil alone at <3ng/ml titrated to effect may be adequate.

3 studies have looked at the use of remifentanil for AFOI without topicalisation or any other sedation. Obviously the dose ranges here were much higher to achieve suitable intubating conditions. Cet 6-8ng/ml.

Remifentanil is commonly used in combination with propofol in order to reduce the high incidence of recall. However patients who do have recall when remifentanil is used alone don't describe the recall as unpleasant.

Dexmedetomidine

Dexmedetomidine is a highly selective alpha-2 agonist. It has numerous favourable characteristics for AFOI: It has sedative, antisialogoue and anxiolytic properties as well as moderate analgesic properties without having any respiratory depressant effect. In one study healthy volunteers were sedated to a degree that they were non-responsive to shaking and shouting but they still maintained spontaneous respiration.

Level 1 evidence for the efficacy and safety of dexmedetomidine for AFOI is provided by 5 RCT's. It provides good intubating conditions, high patient tolerance and high reported patient satisfaction. There is no evidence though in the form of well-designed randomised control trials demonstrating any clear benefit over remifentanil.

A Cochrane review on the use of dexmedetomidine for AFOI is awaiting further well designed randomised control trials.

Dose: 1ug/kg slow bolus over 10 minutes, followed by an infusion 0.3-0.7ug/kg/hr. The time to onset of the sedative effect is 10-15 minutes if a loading dose is used. The full sedative effect is seen in 20-30 minutes. Dexmedetomidine has a rapid distribution phase with a half-life of about 6 minutes. It has a terminal elimination half-life of 2 hours.

The main adverse effects are hypotension and bradycardia. Bradycardia is clinically not usually a problem provided the loading dose is administered over the recommended 10 minutes. There can be an initial transient hypertensive response with the loading dose followed by hypotension. Hypotension may be a problem after induction of general anaesthesia but it should respond to boluses of a vasopressor.

The real advantage of dexmedetomidine may be seen when presented with a patient at risk of airway obstruction or respiratory failure. The use of sedation in a patient with impending airway obstruction is controversial. Avoidance of drugs that depress consciousness level and ventilatory drive is recommended. However, application of topical anaesthesia can also precipitate complete airway

obstruction. There are no case reports to support the use of remifentanil in this situation but there is some evidence in case reports to support the use of dexmedetomidine.

Conclusion on sedation:

The benefits of sedation during AFOI are now widely accepted and include a greater success rate and ease of intubation as well as blunting of the haemodynamic response to intubation and an improved experience for the patient. The ideal drug would be predictable, short acting, titratable and reversible. It is still essential to have psychologically prepared the patient for the procedure with appropriate counselling and if possible to maintain verbal contact with the patient during the procedure.

The introduction of drugs such as remifentanil and dexmedetomidine, with unique pharmacokinetic properties as well as the availability of TCI infusion systems which allow for easy titration and maintenance of steady state drug levels, have made the prospect of sedation for AFOI safer. However, whether or not to use sedation, and which drug(s) to use should be decided based on patient and pathology features. A second anaesthetist 'sedationist' should be present to monitor and titrate the level of sedation.

There is enough level 1 evidence in the form of well-designed RCT's to support the statement that propofol is not very effective as a primary sedative agent for AFOI. Avoidance of benzodiazepines reduces the potential for pharmacodynamic interactions between drugs, so minimising adverse effects such as respiratory depression. At this point in time the literature supports the use of 2 drugs, remifentanil and dexmedetomidine, for sedation for AFOI.

Can J Anaesth 2013[4]

Table 4 Properties and adverse effects of remifentanil, dexmedetomidine, and propofol when used for conscious sedation for AFOI

	Remifentanil	Dexmedetomidine	Propofol
Patient satisfaction	High[10-12,28]	High[13,43-45]	High[9-11,13]
Recall of events	High[10-12,25,28,29]	Variable[29,45,48,50]	Low[10-13]
Risk of oversedation	Low[10-12,29,33,35,36]	Low[13,29,38,55,56]	High[11-13]
Airway obstruction	No[10,25,27]	No[13,27]	Yes[11-13]
Bradycardia	No[10-12,25,36]	Yes[44,50,61]	No[9-13]
Hypotension	No[10-12,25,36]	Yes[44,50,51,61]	No[9-13]
Respiratory depression	Yes[25,28,29,36]	No[13,29,38,46,49,50,52]	No[8,10-13]
Coughing	No[10,25]	Variable[13,45,48]	Yes[10,11,13]

Supplemental oxygen

The use of supplemental oxygen may be advocated in cases of critical airway obstruction either via nasal prongs or an upside down face mask over the mouth to provide a safety barrier for the rare time when awake intubation precipitates complete airway obstruction. However if this is a concern perhaps an awake tracheotomy would be the preferred choice of airway management. Be aware of the danger of using supplemental oxygen when using a sedative that can suppress respiration e.g. remifentanil, as the patient may be hypoventilating or apnoeic while maintaining oxygen saturations and becoming increasingly hypercapnoeic. When using remifentanil this author prefers not to use supplemental oxygen and rather rely on patient saturations as a warning to encourage the patient to breathe.

Complications of AFOI

Complications of AFOI include failure, bleeding, complete airway obstruction and oversedation. Laryngeal trauma and arytenoid dislocation is more common with multiple attempts and the use of force to pass the ETT through the cords. Local anaesthetic toxicity can also occur.

Training

Complications arising from airway management are an important cause of anaesthesia associated morbidity and mortality, and although they are not common, the outcomes are often severe, in the form of either hypoxic brain injury or death. Many training programmes don't offer a structured airway management programme and many trainees probably enter practice with limited skills to deal with difficult airways. A survey of delegates at the Group of Anaesthetists in Training (UK) meeting showed that although most felt that AFOI was a core skill, the majority of final year trainees failed to reach their minimum estimated competency target of 10 intubations. It has been shown that the time to complete FOI successfully by novice residents after only 10 patients each was in the region of 1.5min.

A stepwise approach to training would be as follows[7]:

1) Mannequins: Mannequins and simulators provide a safe validated introduction to the use of fibre-optic scopes and as little as 2-4hrs of manikin training has been shown to provide adequate scope skills to enable tracheal intubation in patients.
2) Asleep fibre-optic intubation with predicted normal anatomy.
3) Awake fibre-optic intubation with predicted normal anatomy.
4) Awake fibre-optic intubation with predicted abnormal anatomy.

Competence should be demonstrated at each stage before progressing to the next stage.

A needle-free technique for nasal AFOI:

Requirements:

Knowledge of indications and limitations of procedure.

Adequate equipment and skill available to perform the procedure.

Have an airway plan A, B, C....

Be patient! A properly conducted AFOI takes time.

Counsel and consent patient. Psychological preparation is essential.

As the patient arrives in the induction room, insert IVI and administer glycopyrollate 3-4ug/kg.

Prepare 4% lignocaine and calculate the maximum dose for the patient (9mg/kg).

Identify most patent nasal passage. Administer oxymetazoline vasoconstricting nose drops to both nostrils.

Nebulise 4 ml 4% lignocaine with 0.5-1mg 1:1000 adrenalin.

On completion of nebulised lignocaine, use remicaine jelly on a pus swab or lignocaine soaked pledgets (with 1:200000 adrenalin) into nasal cavity and posterior nasal space.

Allow patient to gargle with 1-2ml 4% lignocaine if possible.

Consider transtracheal injection.

Take patient into operating theatre and apply standard monitoring. Have drugs for GA drawn up.

Operating table as low as possible. Position patient semi sitting or supine with anaesthetist in front of or behind patient, depending on operator preference/patient convenience. Facing patient inverts FOI view.

Check scope, orientation, black notch at 12 o'clock, clear focus on written object, working suction, second wall suction with yankauer for oropharynx if needed. Prepare epidural catheter for SAYGO.

Decide on sedative: Remifentanil 1-3ng/ml TCI or dexmedetomidine 1ug/kg over 10 minutes then 0.3-0.7ug/kg/hr. Second sedationist present.

(Supplemental oxygen if indicated via nasal prongs or face mask.)

Mount the tracheal tube on the scope for the nasal route or within the oral airway for the oral route.

Use a 6-6.5mm warmed reinforced ETT with adequate lubrication between the scope and ETT and around tip/cuff of ETT for passage through the nose. (Alternatively use ETT from intubating LMA with tapered tip to avoid hold up at arytenoids). Secure ETT to top of scope

Pass scope along floor of nasal cavity directed inferiorly behind soft palate. Identify the nasal septum medially, turbinates laterally. Keep black hole (air cavity) in centre. Patient can assist in opening the airway by protruding tongue or deep inspiration. Pink out: mucosa (no cavity); white out: secretions; red out: blood. Suction or withdraw scope and reorientate.

Targets: Epiglottis, vocal cords, tracheal cartilages, carina.

Next landmark is epiglottis, advance scope into laryngeal opening, identify vocal cords and administer SAYGO lignocaine. Warn patient they may cough. Wait. Pass epidural catheter through the cords and administer further spray-as-you-go lignocaine. Advance scope into subglottic space and identify the tracheal rings.

Advance scope until see carina.

Advance ETT with gentle pressure and rotation, bevel laterally through nose (facing turbinates) and posteriorly through cords (facing arytenoids). Ask patient to inhale deeply just before you go through the cords. Do not force ETT, if resistance withdraw ETT rotate through 90' anticlockwise and advance gently. Keep carina in field of vision at all times.

Once ETT in trachea, remove scope and connect breathing circuit. Confirm ETT position with capnography, misting, auscultation. If concern about stability of cervical spine, assess neurology at this point. Induce anaesthesia with inhalational/IVI induction agent.

Inflate cuff after induction (intensely stimulating).

Confirm ETT placement with capnography and recheck position of ETT above carina.

Extubate awake with all equipment available for reintubation.

If fibreoptic intubation is not successful, options are preserved. Surgery can be postponed and an unhurried surgical airway can be performed.

The keys to success in AFOI include good topical anaesthesia, an excellent rapport with the patient, skill and patience.

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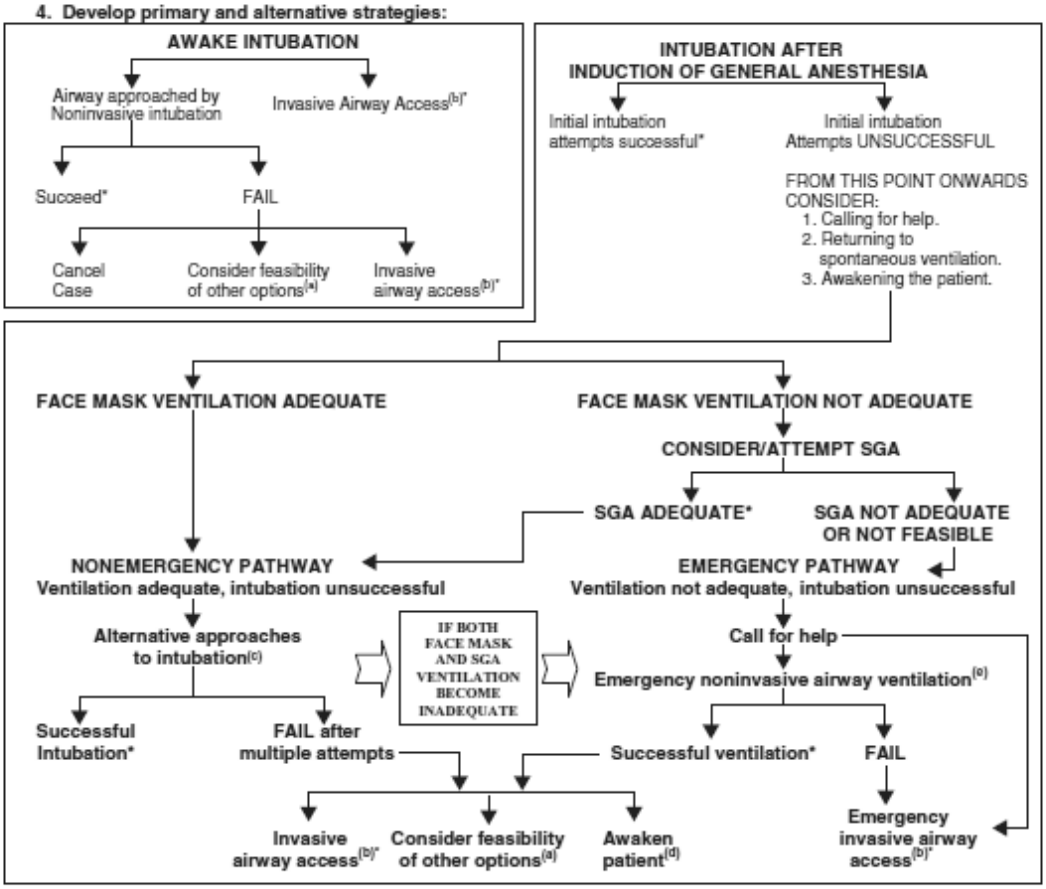
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Appendix A

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DIFFICULT AIRWAY ALGORITHM

1. **Assess the likelihood and clinical impact of basic management problems:**
   - **Difficulty with patient cooperation or consent**
   - **Difficult mask ventilation**
   - **Difficult supraglottic airway placement**
   - **Difficult laryngoscopy**
   - **Difficult intubation**
   - **Difficult surgical airway access**
2. **Actively pursue opportunities to deliver supplemental oxygen throughout the process of difficult airway management.**
3. **Consider the relative merits and feasibility of basic management choices:**
   - **Awake intubation *vs.* intubation after induction of general anesthesia**
   - **Non-invasive technique *vs.* invasive techniques for the initial approach to intubation**
   - **Video-assisted laryngoscopy as an initial approach to intubation**
   - **Preservation *vs.* ablation of spontaneous ventilation**
4. **Develop primary and alternative strategies:**



***Confirm ventilation, tracheal intubation, or SGA placement with exhaled CO_2.**

a. Other options include (but are not limited to): surgery utilizing face mask or supraglottic airway (SGA) anesthesia (e.g., LMA, ILMA, laryngeal tube), local anesthesia infiltration or regional nerve blockade. Pursuit of these options usually implies that mask ventilation will not be problematic. Therefore, these options may be of limited value if this step in the algorithm has been reached via the Emergency Pathway.

b. Invasive airway access includes surgical or percutaneous airway, jet ventilation, and retrograde intubation.

c. Alternative difficult intubation approaches include (but are not limited to): video-assisted laryngoscopy, alternative laryngoscope blades, SGA (e.g., LMA or ILMA) as an intubation conduit (with or without fiberoptic guidance), fiberoptic intubation, intubating stylet or tube changer, light wand, and blind oral or nasal intubation.

d. Consider re-preparation of the patient for awake intubation or canceling surgery.

e. Emergency non-invasive airway ventilation consists of a SGA.

Fig. 1. Difficult Airway Algorithm.

Anaesthesia for flap surgery

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History of Reconstructive Surgery

Free tissue transfer has become an almost essential part of reconstruction after major surgery where large defects exist, in order to reduce infection, maintain skin integrity and to restore aesthetic form. Since 1960, when microscopic anastomosis of blood vessels was perfected, the concept of free flap transfer was conceived. In 1972, McLean and Buncke successfully transferred an omental flap to reconstruct a scalp defect. Free flap surgery has become the gold standard of reconstructive surgery.

In the early days of free tissue transfer, flap failure rates were high – 40-50%. In more recent times, success rates have exceeded 90%. Total flap failure is rare nowadays, as we have a better understanding of the factors that influence flap outcome. The modern anaesthetist is therefore able to manipulate these factors in order to achieve optimal conditions for flap survival.

Hierarchy of reconstructive surgery for large defects

Skin grafts (full thickness, or split skin grafts). These can be painful. Adherence occurs due to fibrin production, and revascularization occurs as capillary buds grow from the recipient site into the graft.

Tissue expanders. Saline filled ballons are inserted under the skin, and are expanded gradually over time, in order to stretch the skin. The stretched skin can then be used to cover a neighbouring defect.

Local flaps. Used to cover an adjoining defect or surgical site. There is no disruption of vessels and nerves.

Pedicled flaps. These flaps keep their neurovascular supply, and are moved about their pedicle in order to cover a defect in a nearby region. e.g. LAT DORSI flap for breast reconstruction, or PEC MAJOR flap for head and neck reconstruction. No microvascular anastomosis is needed, but flap failure can occur if the pedicle is twisted, stretched or compressed.

Free flaps. They involve the transfer of skin, muscle,(bone) and vessels to a defect, with microscopic vascular anastomosis at the recipient site. The recipient site must be free from micro-organism colonisation in order to ensure flap success. The stages of free flap transfer are as follows –

1. Elevation of the flap, with vessels clamped once the flap is dissected.
2. Primary Ischaemic period. The severity of the ischaemic damage is proportionate to the duration of ischaemia. During this period, flap metabolism is anaerobic, with the accumulation of lactate and pro-inflammatory mediators. The capillaries are narrowed due to endothelial swelling, vasoconstriction and oedema.
3. Reperfusion. Once blood flow is re-established, the primary ischaemic changes are reversed as normal flow recommences through the flap. If flap conditions are poor (prolonged

ischaemic time, poor perfusion pressures), a reperfusion injury can occur, with inflammatory mediators causing flap damage.

4. Secondary ischaemia. Occurs after the reperfusion period. Usually due to poor flow determinants. Damage is more extensive than during the primary ischaemic period.

Why do flaps fail?

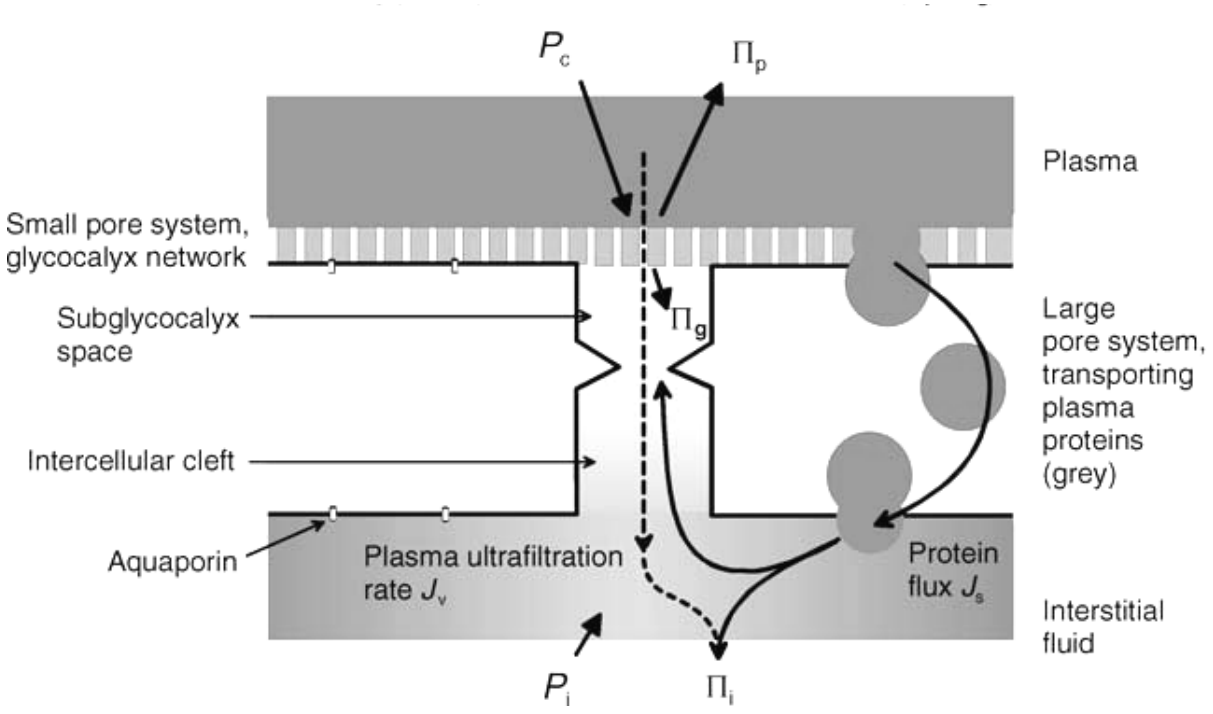
- Anastomotic failure – arterial or venous
- Vasospasm
- Thrombosis – patient predisposition, rheology (Hct , transfusion), secondary ischaemic insult.
- External compression – due to tight bandaging or poor patient positioning.
- Oedema – due to excessive crystalloid administration, excessive handling, or due to a prolonged ischaemic time.

Physiology of the Free Flap

The microcirculation is the conduit within the free flap, allowing blood flow through the flap, as well as the removal of waste products from the flap. Starling's revised equation describes the nett filtration of plasma throughout the arterial and venous end of the capillary bed, and nett reabsorption after the venous end of the capillary bed, largely by the lymphatic system. Adequate flow through the microcirculation is essential for flap survival. Poor flow at this level predisposes the flap to oedema.

Diagram 1: Revised Starling's forces; Filtration force= (Pc – Pi) – δ (πp – πg)

(πg = oncotic pressure within the Glycocalyx)



Flow through the microcirculation is regulated by distant and local factors which can cause either vasoconstriction or vasodilatation, which thus affects flow characteristics.

Distant factors include

- direct neural sympathetic effects on vascular tone
- humoral factors such as catecholamine release from adrenal medulla and sympathetic nerve endings

Local factors include

- Myogenic response - **low** hydrostatic pressure - causes **vasodilation** (and vice versa)
- Metabolic factors – vasodilation mediated by - increased levels of K+, H+, Osmolarity, Adenosine and PCO2 and by – low levels of PO2.

Flow through the microcirculation is also influenced by Rheology ie the flow behaviour of blood in the microcirculation. Rheology includes deformability of RBCs, Haematocrit etc. The Rheology of blood in the microcirculation is altered during general anaesthesia and surgery, largely due to hypothermia, making platelets more likely to aggregate, impairing RBC deformability and increasing whole blood viscosity. 2,3 DPG is required for optimal RBC deformability, and transfused blood contains minimal 2,3 DPG. Blood transfusions therefore impair RBC deformability, which hampers blood flow through the microcirculation.

Flow through the microcirculation is also determined by numerous factors, as summarized by the Hagen – Poiseuille equation for laminar flow

Diagram 2: The Hagen – Poiseuille Equation

$$\text{Blood flow } (\dot{Q}) = \frac{r^4 \cdot \Delta P}{\frac{8}{\pi} \cdot L \cdot \eta}$$

r	**radius of vessel**
ΔP	pressure gradient along vessel
L	**length of vessel**
η	**viscosity of fluid**

Thus an optimal perfusion pressure, vasodilation and low viscosity are crucial in the optimization of flow through the microcirculation.

In summary, there are certain identifiable physiological parameters and practices which can be manipulated in order to optimize flow through the microcirculation – these are:

- Patient Temperature
- Patient Fluid Status
- Vasopressor Usage
- Transfusion Thresholds
- Anaesthetic Agent Usage
- Anticoagulation
- Regional Blockade

A literature review revealed a paucity of randomized controlled trials to guide practice. However, a recent review article by Motakef et al, examined 106 articles which were relevant in guiding clinical practice.

Patient Temperature:

Normothermia should be maintained perioperatively in order to improve flap outcome. Evidence is conflicting, but infection rates at recipient sites are higher with intraoperative hypothermia. *Level of evidence 2b.*

Patient Fluid Status:

High volumes of intraoperative crystalloid infusion correlated with medical and flap complications. The ideal crystalloid infusion rate is proposed to range between 3.5 – 6ml/kg/hour. Similarly, high (> 2L) colloid infusions cause coagulation impairment, so colloids should be used judiciously intraoperatively, primarily to replace blood lost. Blood should be used when the Haemoglobin threshold for that patient has been reached, also to maintain a Haematocrit of 30%. *Level of evidence 2b.*

Transfusion thresholds:

Intraoperative blood transfusion is associated with higher overall complications, both medically and surgically. Cartain studies have suggested a link between transfusion and wound infections. In head and neck cancers, blood transfusions are associated with recurrence. A Haemoglobin level of 7g/dl is suggested as a transfusion threshold in appropriate patients. *Level of evidence 2b.*

Vasopressor usage:

In several clinical studies, intraoperative use of vasopressors affected neither the incidence of flap loss nor the rate of operation, with most evidence supporting the use of noradrenaline over other vasopressors*. Level of evidence 1b.*

Anaesthetic agent use/ Regional Anaesthesia:

Studies have shown that Sevoflurane protects the endothelium from ischaemia-reperfusion injury. Regional anaesthesia as an adjunct has been shown to be beneficial to flap survival*. Level of evidence 1b.*

Anticoagulation:

Dextran usage has been shown to have no effect on flap survival, yet significantly increases systemic complications. Thus its use is not recommended. *Level of evidence 1b*. Clinical studies comparing various different perioperative anticoagulation regimes have all shown equivalent reductions in anastomotic thrombosis and flap loss.

The Conduct of Anaesthesia

Free flap surgery is usually a long procedure (4-6 hours usually). It involves the institution of a hyperdynamic circulatory state with vasodilation and high cardiac output in order to maintain good flow through the flap, both at its original site, and at the recipient site. Vasoconstriction must be avoided, and optimal viscosity needs to be achieved.

Therefore the patient needs a thorough cardiovascular assessment. Those patients with risk factors associated with anaesthetic complications (smokers, diabetics, vasculopaths) need optimization preoperatively.

To prevent hypothermia, and thus vasoconstriction, the theatre temperature must be optimized to at least 20° C. The patient should be prewarmed and two temperature monitoring devices should be placed in order to measure the difference between core and skin temperature – less than 2°C indicates a well filled patient. Warm fluids should be used. Normothermia should be maintained into the postoperative period.

Positioning and pressure point protection is essential due to the prolonged nature of the surgery. Calf compressors should be used if possible, as part of the anticoagulation strategy. Preoperative heparin or other anticoagulants should be given as per protocol.

Sevoflurane based anaesthesia has been proposed, but there is no clear evidence to suggest a specific anaesthetic technique. When possible, regional anaesthesia should be used as an adjunct as it has been shown to improve regional flow characteristics, as well as to reduce opiate requirements. It also minimizes thrombotic incidents.

Invasive blood pressure monitoring is essential. Mean blood pressure should be maintained as close to the patient's preoperative baseline as possible, in order to achieve good flap flow. CVP lines are

sometimes necessary, especially if the need for certain vasopressors is forseen, however, in most patients, it is not needed, as fluid status can be measured by other means.

Fluid management should follow the principles mentioned earlier, ie 3.5 to 6 ml/kg/hr of an appropriate crystalloid to achieve a well filled patient. Monitoring of fluid status is crucial, and should be done at regular intervals (blood gas analysis, urine output, temperature differentials, continuous cardiac output monitoring devices). Colloids are used to achieve hypervolaemic haemodilution if the haematocrit is higher than desired, and also to replace blood loss. Transfusion of packed red cells should be considered when the patient approaches the Haemoglobin threshold deemed suitable for that patient – in otherwise healthy patients, a level of 7g/dl has been proposed as the transfusion threshold.

Ventilation should aim for good oxygenation and normocapnea, in order to minimize microcirculatory and macrocirculatory vasoconstrictor effects. Equally, hypercapnea must be avoided due to its sympathomimetic effects.

Postoperatively, the patient must be nursed in a high-care environment where attention to temperature control, fluid optimization and analgesic control is possible. Continued thromboprophylaxis is crucial. Flap observations must be scrupulous. At the earliest sign of flap compromise, a thorough assessment by the surgeon is needed, and an early return to theatre should be considered.

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Assessment, Management and Complications of Post-operative Pain

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Introduction

Pain is subjective and each individual patient's experience of pain is different. Pain is an individual, multifactorial experience influenced by culture, previous pain events, beliefs, mood and ability to cope. The IASP definition of pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey & Bogduk, 1994) This definition emphasises that pain is not a directly observable or measurable phenomenon, but rather a subjective experience that bears a variable relationship with tissue damage.

The psychological aspects of acute pain are extremely important and we know that

- Preoperative anxiety, catastrophising, neuroticism and depression are associated with higher postoperative pain intensity.
- Preoperative anxiety and depression are associated with an increased number of PCA demands and dissatisfaction with PCA.

The cornerstone of pain management post-operatively is **assessment** of pain. In order to optimise post-operative pain management, a preoperative evaluation and plan needs to be made.

a.) Preoperative patient evaluation:

Ask the patient and/or their carers to help establish **pain history**. (In particular use of analgesics, sedatives, anxiolytics, anti-depressants and opioids -oral, patches, and pumps-pre-operatively- dose and frequency)

Document in the patient's medical record, otherwise state that there are no relevant factors.

Discuss pain management strategies and expectations in the preoperative period. Document a pain plan for intra-and post-operatively.

Preoperative education improves patient or carer knowledge of pain and encourages a more positive attitude towards pain relief. Written information given to patients prior to seeing an anaesthetist is better than verbal information given at the time of the interview. Implementation of an acute pain service may improve pain relief and reduce the incidence of side effects.

Successful management of acute pain requires close liaison with all personnel involved in the care of the patient.

b.) Assessment of post-op pain

The pain measurement tool chosen should be appropriate to the individual patient; developmental, cognitive, emotional, language and cultural factors should be considered.
The measurement of pain should be considered the 5th vital sign.

Self-reporting of pain should be used whenever appropriate as pain is by definition a subjective experience.

In some instances it may not be possible to obtain reliable self-reports of pain (e.g. patients with impaired consciousness or cognitive impairment, young children, elderly patients or where there are failures of communication due to language difficulties, inability to understand the measures, unwillingness to cooperate or severe anxiety). In these circumstances other methods of pain assessment will be needed.

Scoring should incorporate different components of pain including the functional capacity of the patient. In the postoperative patient this should include static (rest) and dynamic (e.g. pain on sitting, coughing) pain.

Uncontrolled or unexpected pain requires a reassessment of the diagnosis and consideration of alternative causes for the pain (e.g. new surgical/ medical diagnosis, neuropathic pain)

Categorical scales:
Categorical scales use words to describe the magnitude of pain or the degree of pain relief.

The verbal descriptor scale (VDS) is the most common example (e.g. using terms such as none, mild, moderate, severe and excruciating or agonising) typically using four or five graded descriptors. These terms can then be converted to numeric scores (e.g. 0, 2, 5, 8, 10) for charting and easy comparison over time. There is a good correlation between descriptive verbal categories and visual analogue scales but the VDS is a less sensitive measure of pain treatment outcome than the VAS. Pain *relief* may also be graded as none, mild, moderate or complete using a VDS.
Categorical scales have the advantage of being quick and simple and may be useful in the elderly or visually impaired patient and in some children. However, the limited number of choices in categorical compared with numerical scales may make it more difficult to detect differences between treatments.

Numerical rating scales:

Visual analogue scales (VAS) consist of a 100 mm horizontal line with verbal anchors at both ends and no tick marks.
VAS ratings of greater than 70 mm are indicative of 'severe pain' and 0 to 5 mm 'no pain', 5 to 44 mm 'mild pain' and 45 to 74 'moderate pain'. A reduction in pain intensity by 30% to 35% has been rated as clinically meaningful by patients with postoperative pain acute pain in the emergency department, breakthrough cancer pain and chronic pain.

Verbal numerical rating scales (VNRS) are often preferred because they are simpler to administer, Patients asked to rate their pain using a VNRS prior to and after morphine administration were also asked to rate their pain relief on a 5-point standard Likert scale as 0 = no pain relief,
1 = a little pain relief, 2 = moderate pain relief, 3 = a lot of pain relief and 4 = complete pain relief.

Assessment of pain immediately after surgery can be more difficult and lead to greater inter-patient variability in pain scores because of transient anaesthetic-related cognitive impairment and decreases in visual acuity. A 'pain meter' (PAULA) which uses five coloured emoticon faces on the front of a ruler and has corresponding VAS scores on the back, allows patients to move a slider to mark the pain they are experiencing, resulting in less variance than pain scores obtained from a standard VAS.

Multidimensional measures of pain
Rather than assessing only pain intensity, multidimensional tools provide further information about the characteristics of the pain and its impact on the individual. Examples include the Brief Pain Inventory, which assesses pain intensity and associated disability and the McGill Pain Questionnaire, which assesses the sensory, affective and evaluative dimensions of pain.

Satisfaction is often used as a global indicator of outcome, however patients may report high levels of satisfaction even if they have moderate to severe acute pain.
Satisfaction may also be influenced by preoperative expectations of pain, effectiveness of pain relief, the patient–provider relationship (e.g. communication by medical and nursing staff), interference with function due to pain and number of opioid-related side effects.

Types of pain

Nociceptive pain: Most pain which we see postoperatively is nociceptive in nature- i.e. that which is associated with tissue damage and the peripheral inflammation secondary to cytokines and the "inflammatory soup". Nociceptive pain can be treated with paracetamol, NSAID's, local anaesthetics to prevent transduction and opioids to modulate ascending and descending transmission.

Neuropathic pain:
Neuropathic pain has been defined as 'pain initiated or caused by a primary lesion or dysfunction in the nervous system' (Merskey & Bogduk, 1994; Loeser & Treede, 2008).
Although commonly a cause of chronic symptoms, neuropathic pain can also present acutely following trauma and surgery-especially after surgery which has involved nerve damage e.g. amputation or

inguinal hernia repair. The incidence has been conservatively estimated as 3% of acute pain service patients and often it produces persistent symptoms.
Treatment of neuropathic pain acutely requires the use of local anaesthetics in order to prevent signal transmission or adjuvants such as the gabapentanoids (gabapentin and pregabalin) which block the alpha- 2-delta subunit of the calcium channel in the dorsal horn of the spinal cord. Alternatively NMDA antagonists such as ketamine may be used.

c.) **Management of post-op pain**

It is beyond the scope of this article to refer to every possible intraoperative pain management modality and drug which can be employed with the advantages and disadvantages for each. The reader is urged to consult the ANZCA Acute Pain guidelines for this information- this extensive 533 page document is freely downloadable- the reference is found at the end of this article.

Pre-emptive and preventive analgesia

Despite large meta- analysis largely refuting the benefit of pre-emptive analgesia- with lots of controversy with regards to what constitutes pre-emptive analgesia there is evidence that certain techniques may prevent post-operative pain.

Definitions of pre-emptive and preventive analgesia

Pre-emptive analgesia

Preoperative treatment is more effective than the identical treatment administered after incision or surgery. The only difference is the timing of administration.

Controversy about what constitutes pre-emptive analgesia

Two approaches have been used to try to demonstrate pre-emptive analgesia:

1) PRE versus NO: Tries to demonstrate a reduction in pain intensity and/or analgesic use beyond the expected presence of the drug. This approach uses a study design comparing pre-operative treatment and non-treatment groups
2) PRE versus POST: This approach attempts to prove that a treatment applied before surgery is more effective than the same treatment provided at the end of surgery.

The PRE versus NO approach was commonly used in the initial clinical studies on pre-emptive analgesia; the PRE versus POST approach was introduced later and has become the most common study design for pre-emptive analgesia.

Preventive analgesia

Postoperative pain and/or analgesic consumption is reduced relative to another treatment, a placebo treatment, or no treatment as long as the effect is observed at a point in time that exceeds the expected duration of action of the intervention. The intervention may or may not be initiated before surgery.

With regard to all these meta-analysis as shown in the table below the most recent analysis provided support for pre-emptive epidural analgesia (Ong et al, 2005).
The efficacy of different pre-emptive analgesic interventions (epidural analgesia, local anaesthetic wound infiltration, systemic NMDA antagonists, systemic opioids, and systemic NSAIDs) were analysed in relation to different analgesic outcomes (pain intensity scores, supplemental analgesic consumption, time to first analgesic).
The effect size was most marked for epidural analgesia (0.38; CI 0.28 to 0.47) and improvements were found in all outcomes.

Pre-emptive effects of local anaesthetic wound infiltration and NSAID administration were also found, but results were equivocal for systemic NMDA antagonists and there was no clear evidence for a pre-emptive effect of opioids.

Prior to the Ong et al (2005) study the Møiniche et al (2002) study had showed the following:

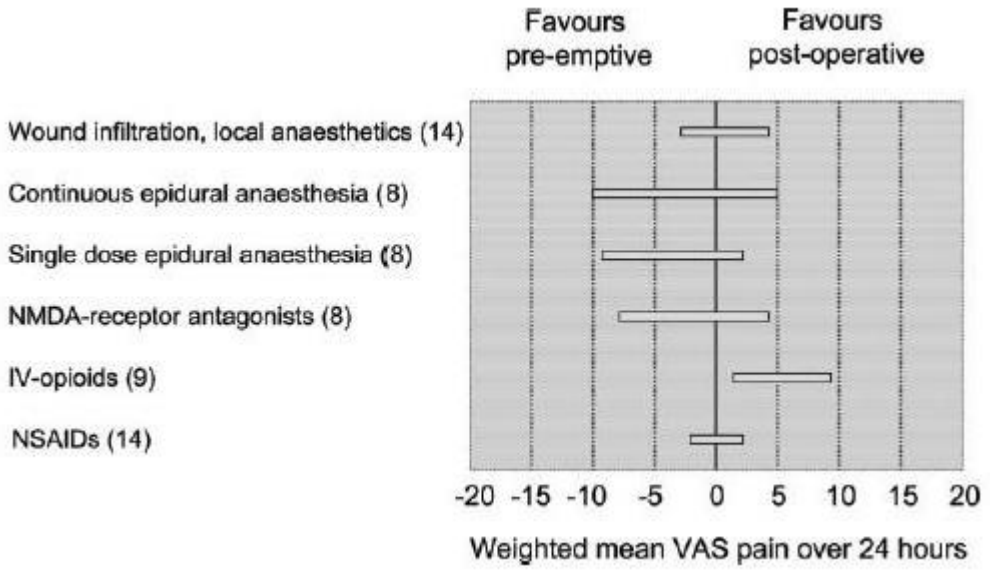


Figure 1.
Results from a meta-analysis of 80 RCTs with 3761 patients of whom 1964 received pre-emptive treatment. The figure shows a 95% confidence interval of the difference between intervention before and after incision. Numbers in brackets indicate the number of trials for each intervention. No clinical benefits were demonstrated with pre-emptive analgesia. For IV –opioids the weighted mean difference of the visual analogue score (VAS) significantly favoured postoperative administration.
*(*Reproduced from *Dahl J, Møiniche S*, **Pre-emptive *analgesia, British Medical Bulletin*** *2004; 71:13-27)*

Table 2. Preemptive analgesia: evidence from systematic reviews.

Reference	Included studies	Tested analgesic intervention	Conclusion
McQuay, 1995	15 RCTs 1987–1994	NSAIDs (oral, iv): 4 LA (epidural, caudal, infiltration): 7 Opioids (epidural, iv): 4 NSAIDs + LA + opioids: 1	No preemptive effect: paracetamol, NSAIDs, LA Weak positive evidence: opioids
Kelly et al, 2001	24 RCTs 1984–2000	LA (peripheral, intrathecal, epidural, intraperitoneal) +/− opioids: 15 Opioids (epidural, intraperitoneal, iv, im): 5 NSAIDs (oral, im): 4	No specific recommendation; privileges individual and multimodal approach
Møiniche et al, 2002	80 RCTs 1983–2000	NSAIDs (oral, iv, im): 20 Opioids (iv): 8 NMDA receptor antagonists (iv, im): 8 LA (infiltration, peripheral, intraperitoneal): 20 Epidural (opioids, LA): 18 Caudal (opioids, LA): 6	No effect: NSAIDs, iv opioids, ketamine; epidural, intrathecal, caudal block; infiltrational LA Insufficient data: dextromethorphan, intraperitoneal and peripheral LA Some reduction in analgesic demand: epidural opioids +/− LA Some evidence for improved pain scores at 3 and 6 months: epidural LA Timing of analgesia has no influence on postoperative pain
McCartney et al, 2004	40 RCTs 1989–2003	Magnesium (iv): 4 Ketamine (iv): 24 Dextrometorphan (iv): 12	No effect: magnesium Some evidence for reduction in pain, analgesic consumption or both: dextrometorphan, ketamine
Ong et al, 2005	66 RCTs 1989–2003	Epidural LA and opioids: 19 LA (infiltration): 15 NMDA antagonists (iv): 7 NSAIDs (iv): 17 Opioids (iv): 8	Some evidence for decreased pain intensity: epidural Slightly decreased analgesic consumption and longer time to first analgesic: LA wound infiltration, NSAIDs
Bong et al, 2005	6 RCTs 1996–2003	LA (epidural): 1 LA + opioids (epidural): 5	Significant reduction of acute pain Non significant reduction of chronic pain

LA = local anaesthetic; RCT = randomised controlled trial; NSAID = non-steroidal anti-inflammatory drug; NMDA = N-methyl-D-aspartat; iv = intravenous; im = intramuscular.

Figure 2: Evidence from systemic reviews
(Reproduced from *Grape S, Tramèr M*, Do we need pre-emptive analgesia for the treatment of postoperative pain? **Best Practice & Research Clinical Anaesthesiology** 2007; 21: 51-63).

In summary with regard to *pre-emptive* vs. *preventative* analgesia:

The timing of a single analgesic intervention (pre-incisional rather than post-incisional), defined as pre-emptive analgesia, has a significant effect on postoperative pain relief with **epidural** analgesia.
.
There is evidence that some analgesic interventions have an effect on postoperative pain and/or analgesic consumption that exceeds the expected duration of action of the drug, defined as **preventive** analgesia.

NMDA receptor antagonist drugs in particular show **preventive** analgesic effects.

The opioid dependent patient

The opioid dependent patient may pose a challenge but below are some key principles in their management:

- Opioid-tolerant patients report higher pain scores and have a lower incidence of opioid induced nausea and vomiting
- Ketamine improves pain relief after surgery in opioid-tolerant patients
- Opioid-tolerant patients may have significantly higher opioid requirements than opioid naïve patients and inter-patient variation in the doses needed may be even greater.
- Ketamine may reduce opioid requirements in opioid-tolerant patients
- Usual preadmission opioid regimens should be maintained where possible or appropriate substitutions made.
- Opioid-tolerant patients are at risk of opioid withdrawal if non-opioid analgesic regimens or tramadol alone are used.
- PCA settings may need to include a background infusion to replace the usual opioid dose and a higher bolus dose.
-Neuraxial opioids can be used effectively in opioid-tolerant patients although higher doses may be required and these doses may be inadequate to prevent withdrawal.
-Liaison with all health care professionals involved in the treatment of the opioid-tolerant patient is important.
-In patients with escalating opioid requirements the possibility of the development of both tolerance and opioid-induced hyperalgesia should be considered.

Table 11.7 Definitions for tolerance, physical dependence and addiction

Tolerance (pharmacological)	A predictable physiological decrease in the effect of a drug over time so that a progressive increase in the amount of that drug is required to achieve the same effect. Tolerance develops to desired (eg analgesia) and undesired (eg euphoria, opioid-related sedation, nausea or constipation) effects at different rates.
Physical dependence	A physiological adaptation to a drug whereby abrupt discontinuation or reversal of that drug, or a sudden reduction in its dose, leads to a withdrawal (abstinence) syndrome. Withdrawal can be terminated by administration of the same or similar drug.
Addiction	A disease that is characterised by aberrant drug-seeking and maladaptive drug-taking behaviours that may include cravings, compulsive drug use and loss of control over drug use, despite the risk of physical, social and psychological harm. While psychoactive drugs have an addiction liability, psychological, social, environmental and genetic factors play an important role in the development of addiction. Unlike tolerance and physical dependence, addiction is not a predictable effect of a drug.
Pseudoaddiction	Behaviours that may seem inappropriately drug seeking but are a result of undertreatment of pain and resolve when pain relief is adequate.

Recovering opioid dependent patients

Patients in drug treatment programs or in drug-free recovery may be concerned about the risk of relapse if they are given opioids for the management of their acute pain. However, there is no evidence that the use of opioids to treat acute pain increases the rate of relapse; a more likely trigger is unrelieved pain. Effective communication and planning, the use of multimodal analgesic strategies, reassurance that the risk of reversion to an active addiction disorder is small, and information that ineffective analgesia can paradoxically lead to relapses in recovering patients, are important and help avoid under treatment

Fast track surgery
A short note on Enhanced recovery (ER) pathways. These have become the established standard of care in many areas of gastrointestinal (GI) surgery in first world countries. The UK has established these programmed for urological, gynaecological and orthopaedics procedures too.
Although reduced length of stay (and therefore costs) were early drivers in ER, it is now understood that ER pathways reduce perioperative stress response, catabolism, and postoperative complications.

Laparoscopic surgery has facilitated this process for some operations, especially colorectal resections. Fluid therapy and **analgesia** are key areas of focus for anaesthetists.
The routine use of epidurals for these patients is increasingly debated.

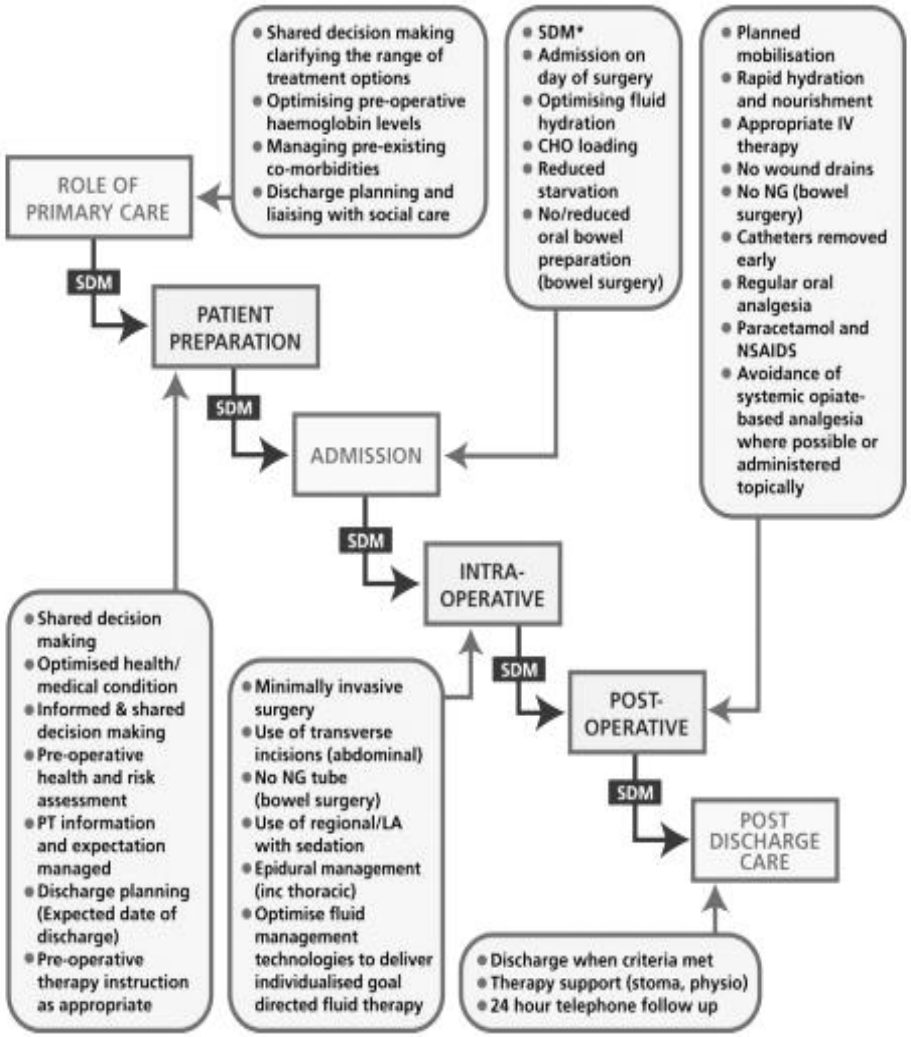


Fig 1 ER for gastrointestinal surgery (Department of Health). *SDM, shared decision-making. Reproduced with kind permission from NHS England (now NHS Improving Quality).

Opioid hyperalgesia (OIH)

Characterized by a paradoxical increase in pain on administration of opioids associated with allodynia and hyperalgesia. Pain may occur at a different location and can be widespread. It is usually poorly defined in terms of region and quality. OIH can manifest abruptly although its incidence in acute postoperative pain settings is not known. It is however usually associated with patients who have been on long term opioid therapy.
In the acute setting OIH has been shown to occur when remifentanil is used at dosages higher than 0.1 µg/kg/min either alone or with inhalation anaesthetics. Therefore, in these situations, one needs to be cautious for the possibility of the development of OIH, which may impair treatment of pain or even aggravate pre-existing pain. Suspect the manifestation of OIH when opioid treatment effect seems to decline in the absence of disease/injury progression, with unexplained pain reports or allodynia unassociated with the site of injury.
Co-administration of anaesthetic drugs, such as propofol and nitrous oxide, and using of TCI model seem to be helpful to modulate the development of OIH. Most importantly however an NMDA antagonist such as Ketamine is important in preventing its development.

The exact mechanism is poorly understood but central mechanisms involved include the glutaminergic system in the spinal cord, spinal dynorphins, opioid sensitive ON cells in the rostral ventral medulla may promote spinal pronociception together with changes in opioid receptor responsiveness.

Treatment options include:

- Increase the opioid dose and evaluate for tolerance.
- Reduce or discontinue the opioid and evaluate for OIH.
- Consider opioid rotation, by using opioids with unique properties that might mitigate OIH, for example, fentanyl, buprenorphine, methadone.
- Consider adding medication with NMDA receptor antagonist, for example, ketamine.
- Consider other opioid-sparing medications such as antidepressants, anticonvulsants, and NSAIDs.
- Consider non-pharmacological interventions, for example, physical therapies, therapies, or interventional therapies including spinal cord stimulators.

d.) Complications of post-op pain

1. **Acute physiological effects** (ANZCA **Acute Pain Management: Scientific Evidence**, Third edition 2010.)

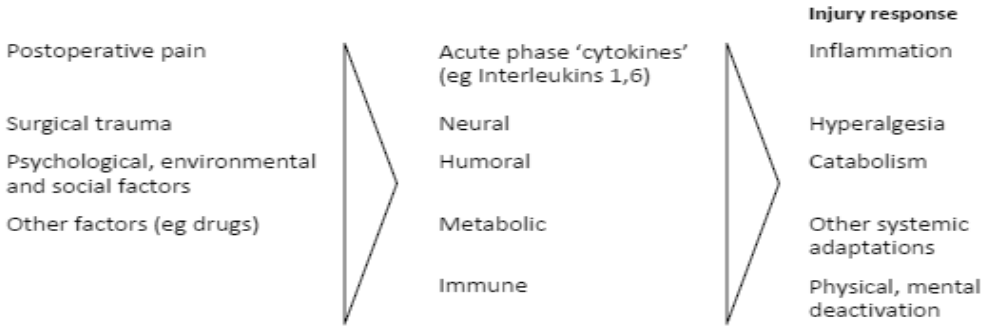
Acute pain is one of the activators of the complex neuro-humoral and immune response to injury and both peripheral and central injury responses have a major influence on acute pain mechanisms. Thus acute pain and injury of various types are inevitably interrelated and if severe and prolonged, the injury response becomes counterproductive and can have adverse effects on outcome.
Although published data relate to the *combination* of surgery or trauma and the associated acute pain, some data have been obtained with experimental pain in the absence of injury.
Electrical stimulation of the abdominal wall results in a painful experience (visual analogue scale [VAS] 8/10) and an associated hormonal/metabolic response, which includes increased cortisol, catecholamines and glucagon, and a decrease in insulin sensitivity.

Although acute pain is only one of the important triggers of the 'injury response' as the magnitude and duration of the response is related to the magnitude and duration of the stimulus, effective pain relief can have a significant impact on the injury response.
Clinically significant injury responses can be broadly classified as inflammation, hyperalgesia, hyperglycaemia, protein catabolism, increased free fatty acid levels (lipolysis) and changes in water and electrolyte flux. In addition, there are cardiovascular effects of increased sympathetic activity and diverse effects on respiration, coagulation and immune function.

Table 1.6 Metabolic and endocrine responses to injury

Endocrine	↑ Catabolic hormones	↑ ACTH, cortisol, ADH, growth hormone, catecholamines, angiotensin II, aldosterone, glucagons, IL-1, TNF, IL-6
	↓ Anabolic hormones	↓ Insulin, testosterone
Metabolic		
carbohydrate	Hyperglycaemia, glucose intolerance, insulin resistance	↑ Glycogenolysis, gluconeogenesis (cortisol, glucagon, growth hormone, adrenaline, free fatty acids) ↓ Insulin secretion/activation
protein	Muscle protein catabolism, ↑ synthesis of acute phase proteins	↑Cortisol, adrenaline, glucagons, IL-1, IL-6, TNF
lipid	↑ Lipolysis and oxidation	↑ Catecholamines, cortisol, glucagon, growth hormone
Water and electrolyte flux	Retention of water and sodium, ↑ excretion of potassium and ↓ functional ECF with shifts to ICF	↑ Catecholamine, aldosterone, ADH, cortisol, angiotensin II, prostaglandins and other factors

Note: ACTH: adrenocorticotrophic hormone; ADH: antidiuretic hormone; ECF: extracellular fluid; ICF: intracellular fluid; IL: interleukin; TNF: tumour necrosis factor.



Hyperglycaemia

Hyperglycaemia is broadly proportional to the extent of the injury response. Injury response mediators stimulate insulin-independent membrane glucose transporters glut-1, 2 and 3, which are located diversely in brain, vascular endothelium, liver and some blood cells.
Circulating glucose enters cells that do not require insulin for uptake, resulting in cellular glucose overload and diverse toxic effects. Excess intracellular glucose non-enzymatically glycosylates proteins such as immunoglobulins, rendering them dysfunctional. Alternatively, excess glucose enters glycolysis and oxidative phosphorylation pathways, leading to excess superoxide molecules that bind to nitric oxide (NO), with formation of peroxynitrate, ultimately resulting in mitochondrial dysfunction and death of cells served by glut-1, 2 and 3.
Myocardium and skeletal muscle are protected from this toxicity because these two tissues are served by glut-4, the expression of which is inhibited by injury response mediators.

Even modest increases in blood glucose can be associated with poor outcome particularly in metabolically challenged patients such as people with diabetes.
Fasting glucose levels over 7 mmol/L or random levels of greater than 11.1 mmol/L were associated with increased in hospital mortality, a longer length of stay and higher risk of infection in intensive care patients (Van den Berghe, 2004). Tight glycaemic control has been associated with improved outcomes following coronary artery bypass graft (CABG) in patients with diabetes but the risks and benefits of tight glycaemic control in intensive care patients continues to be debated.

Lipotoxicity

Free fatty acid (FFA) levels are increased due to several factors associated with the injury response and its treatment (see Table 1.6) and can have detrimental effects on cardiac function. High levels of FFA can depress myocardial contractility increase myocardial oxygen consumption (without increased work) and impair calcium homeostasis and increase free radical production leading to electrical instability and ventricular arrhythmias.

Protein catabolism

The injury response is associated with an accelerated protein breakdown and amino acid oxidation, in the face of insufficient increase in protein synthesis. Following abdominal surgery, amino acid oxidation and release from muscle increased by 90% and 30% respectively, while whole body protein synthesis increased only 10%.
After cholecystectomy 50 g of nitrogen may be lost (1 g nitrogen = 30 g lean tissue) which is equivalent to 1500 g of lean tissue. Importantly, the length of time for return of normal physical function after hospital discharge has been related to the total loss of lean tissue during hospital stay.

Protein represents both structural and functional body components, thus loss of lean tissue may lead to delayed wound healing reduced immune function and diminished muscle strength- all of which may contribute to prolonged recovery and increased morbidity.
An overall reduced ability to carry out activities of daily living (ADLs) results from muscle fatigue and muscle weakness. Impaired nutritional intake, inflammatory–metabolic responses, immobilisation, and a subjective feeling of fatigue may all contribute to muscle weakness
Such effects are broadly proportional to the extent of injury but there are major variations across populations, with durations also varying up to 3 to 4 weeks.

2. Transition from acute to persistent postsurgical pain (PPP).

Certain operations are associated with a higher incidence of PPP or CPSP (Chronic postsurgical pain). These operations tend to be areas in which nerve damage is often a feature.

Table 1.2 Incidence of chronic pain after surgery

Type of operation	Incidence of chronic pain (%)	Estimated incidence of chronic severe pain [>5 out of 10/10] (%)
Amputation	30–85	5–10
Thoracotomy	5–65	10
Mastectomy	11–57	5–10
Inguinal hernia	5–63	2–4
Coronary bypass	30–50	5–10
Caesarean section	6–55	4
Cholecystectomy	3–50	Not estimated
Vasectomy	0–37	Not estimated
Dental surgery	5–13	Not estimated

Sources: Adapted from Kehlet et al (Kehlet et al, 2006) and Macrae (Macrae, 2008)

Table 1.3 Risk factors for chronic postsurgical pain

Preoperative factors	Pain, moderate to severe, lasting more than 1 month
	Repeat surgery
	Psychologic vulnerability (eg catastrophising)
	Preoperative anxiety
	Female gender
	Younger age (adults)
	Workers' compensation
	Genetic predisposition
	Inefficient diffuse noxious inhibitory control (DNIC)
Intraoperative factors	Surgical approach with risk of nerve damage
Postoperative factors	Pain (acute, moderate to severe)
	Radiation therapy to area
	Neurotoxic chemotherapy
	Depression
	Psychological vulnerability
	Neuroticism
	Anxiety

Sources: Adapted from Kehlet et al (Kehlet et al, 2006) and Macrae (Macrae, 2008)

Mechanisms for the progression from acute to chronic pain

The pathophysiological processes that occur after tissue or nerve injury mean that acute pain may become persistent.
Such processes include inflammation at the site of tissue damage with a barrage of afferent nociceptor activity that produces changes in the peripheral nerves, spinal cord, higher central pain pathways and the sympathetic nervous system

After limb amputation for example, reorganisation or remapping of the somatosensory cortex and other cortical structures may be a contributory mechanism in the development of phantom limb pain. There is preclinical and clinical evidence of a genetic predisposition for chronic pain although one study found that an inherited component did not feature in the development of phantom pain in members of the same family who all had a limb amputation.
Descending pathways of pain control may be another relevant factor as patients with efficient diffuse noxious inhibitory control (DNIC) had a reduced risk of developing chronic postsurgical pain.

Table 1 Current evidence for use in perioperative pain and prevention of CPSP

Drug	Acute perioperative pain			Prevention of CPSP	Side-effects
	Pain intensity	Analgesia/opioid consumption	Opioid-related side-effects		
Ketamine	Decreased (20–25%; Level I)	Decreased (30–35%; Level I)	Decreased (Level I)	Inconsistent (Level II)	Psychomimetic—hallucination, dreams
Pregabalin	Decreased but inconsistent (Level I)	Decreased (Level I)	Decreased but inconsistent (Level I)	Yes (Level I)	Visual disturbance, dizziness
Gabapentin	Decreased	Decreased (20–62%; Level I)	Decreased (Level I)	Yes (Level I)	Dizziness, sedation
I.V. lidocaine	Decreased (Level I)	Decreased (Level I)	Decreased (Level I)	Possibly (Level II)	None but needs caution
Systemic α2 agonist	Decreased (Level I)	Decreased (Level I)	Decreased (Level I)	No data	Hypotension, bradycardia

Table 2 Summary of clinical benefits

Drug	Summary of clinical benefits
Ketamine	• Useful adjuvant in painful procedures: upper abdominal, thoracic, and major orthopaedic surgeries (Level I)[5] • Useful adjuvant to PCA analgesia (Level I)[1] • Patients with chronic pain issues and on high-dose opioids—decreases pain intensity and opioid consumption lasting much beyond the perioperative period (Level II)[17] • Opioid-resistant pain—rescue analgesia (mixed evidence; Level II)[1] • Has preventive but not pre-emptive analgesic effect (Level I). Studies looking at the role of ketamine in preventing CPSP have shown only mixed effects (Level II)[1]
Pregabalin	• Risk–benefits probably more acceptable for painful procedures resulting in acute neuropathic pain, requiring large doses of opioids (e.g. cardiothoracic surgery, arthroplasty, or spine surgery) in order for the reduction in opioid-related side-effects to outweigh the side-effects. The evidence for this is limited and needs further research. Risks for minor, laparoscopic, or day-care procedures probably outweigh the benefits[7] • Useful preventive analgesic effect[9]
Gabapentin	• Benefits similar to pregabalin, but being an older drug has more literature evidence • Improved analgesia at rest and movement (Level I) • Improved functional recovery with better range of movements and pulmonary function (Level II)[10] • Analgesic effect comparable and synergetic with NSAIDS and superior to tramadol[10] • Useful adjuvant to epidural analgesia—decreased pain scores, epidural analgesic consumption, and patient satisfaction despite an increase in dizziness[1] • In established acute postoperative pain, single-dose gabapentin is superior to placebo but worse than other commonly used analgesic. The NNT was 11 (Cochrane review)[18] • Useful preventive analgesic effect[9] • A small RCT (60 patients undergoing abdominal hysterectomy) showed gabapentin was superior to ketamine in preventing CPSP[9]
I.V. lidocaine	• Useful in visceral pain and improves postoperative bowel function after abdominal surgery—reduces pain and opioid requirements, nausea, vomiting, duration of ileus, resulting in decreased time to pass flatus, faeces and earlier intake of enteral food, rehabilitation, and discharge (Level I)[12,13] • Benefit seen even in patients undergoing laparoscopic colectomy as part of acute rehabilitation programme[12,13] • No proven use in non-abdominal surgeries[12] • Probably has a preventive effect after major abdominal and breast surgery (Level II)[14,15]
Systemic α2 agonist	• Moderate analgesic benefit—probably better than paracetamol but less than that of ketamine and NSAIDS as inferred from non-systematic indirect comparison[16] • All these beneficial effects may come at a price of significant hypotension and bradycardia[19] • Useful adjuvant in perioperative care in adults and children because of several useful extra analgesic benefits such as sedation, anxiolysis, analgesia, postoperative shivering, PONV, agitation, mitigation of stress response to surgery and tracheal intubation, anaesthetic-sparing effect, and as supplement to neuraxial and peripheral nerve blocks[16] • Decreased perioperative mortality and myocardial infarction especially in high-risk vascular surgeries[19] • No evidence for preventive analgesia[16]

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Managing complications of regional anaesthesia

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Although complications associated with regional anaesthesia remain extremely rare, they can be devastating for both patient and practitioner. This refresher course review will review the most common and serious complications of both neuraxial and peripheral nerve blockade, with emphasis on practical management.

A. SYSTEMIC LOCAL ANAESTHETIC TOXICITY

Local Anaesthetic Systemic Toxicity (LAST)

Local Anaesthetic Systemic Toxicity (LAST) ranges from mild, transient symptomatology to severe CNS toxicity and cardiovascular collapse. Although the mainstay of management is supportive, lipid emulsion therapy (LET) has been increasingly used. The first successful reported use of lipid emulsion therapy occurred in 2006.

In all cases of LAS, initial management is supportive. Attention should be given to airway compromise, severe hypotension, dysrhythmias and seizures. Lipid emulsion therapy is generally not necessary if CVS stability is maintained and seizures are controlled, but should be immediately available. Patients may present with either sudden, complete circulatory collapse, or the classic sequence of paraesthesia, perioral numbness, and altered cognition seguing into seizures. CNS signs typically occur before CVS signs, reflecting the sensitivity of sodium channels in the respective systems.

1. Early Recognition of Symptoms

LA toxicity may occur some time after the initial injection. The most important clinical signs and symptoms include

- Paraesthesias and peri-oral numbness
- Sudden alteration in mental status: agitation, loss or depression of consciousness
- Frank Tonic-clonic convulsions
- Cardiovascular collapse, hypotension (rarely hypertension)
- Arrhythmias (bradycardia, conduction blocks, ventricular tachyarrhythmias, asystole)

2. Immediate management

- Stop injecting LA if still busy with technique
- Call for help
- Maintain airway; give 100% oxygen; ensure adequate ventilation and intubate if necessary.
- Ensure adequate IV access, use fluids and vasopressor as indicated
- Control seizures: benzodiazepines are first line agents (midazolam; diazepam); incremental small doses of thiopentone or propofol may also be used. Should seizures be controlled with IV therapy and cardiovascular function not compromised, supportive management will usually be all that is needed.
- Assess CVS status throughout: if frank collapse, consider lipid emulsion treatment early.

3. Definitive treatment

- If CVS arrest: → Start CPR and institute lipid emulsion therapy
- If no CVS arrest, use supportive treatment and review response.
- Propofol **is not** a substitute for lipid emulsion
- **Do not** use lignocaine as an anti-arrhythmic agent

LIPID EMULSION THERAPY (AAGBI Guidelines)

Mechanism of lipid emulsion therapy

The first successful use of lipid emulsion therapy was in 2006, with case reports adding up ever since. LET is currently regarded as safe and may be lifesaving. Several bodies have drawn up protocols, the most well-known being the AAGBI guidelines. In all cases, the protocol should be well displayed in theatres and the location of freely available lipid emulsion known.

The mechanism of LET remains unclear. The most plausible theory is that the lipid emulsion provides a "lipid sink" into which the local anaesthetic will dissolve in preferentially. Animal evidence shows that the lethal dose of bupivacaine is significantly higher when lipid emulsion therapy has been employed. The availability of free fatty acids could also help reverse the ischaemia induced switch from lipid to glucose metabolism occurring in stunned myocardium.

The safety of large dose LET has yet to be established. Lipid infusions are typically emulsions of soybean oil made isotonic with glycerin. Egg yolk phospholipid acts as the emulsifying agent. The most well-known agent in South Africa is Intralipid ®

AAGBI Protocol

- Immediate: IV bolus of 1.5 ml/kg of 20% lipid emulsion over 1 minute (typical dose 100 ml for an adult)
- followed by IV infusion of 20% lipid emulsion at 15 ml/kg/hr (1000 ml / hr)
- Reassess after 5 minutes: give a *maximum* of two repeat boluses if CVS stability has not restored or circulation deteriorates; wait 5 minutes between boluses. The infusion should be continued at the same rate but the rate is doubled to 30 ml / kg / hr in these cases.

The infusion is to be continued until adequate circulation returns or the maximum dose is given (12 ml / kg), whichever comes first. Afterwards the patient should be monitored in a high care environment until stable.

ANAPHYLAXIS

Anaphylaxis following local anaesthetic administration is rare. Most reactions appear to be anaphylactoid (non-immune) presentations in the most of cases. Hypersensitivity to all LAs has been reported. Reactions may be due to the LA itself or preservative agents used in preparations. Management is as per standard anaphylaxis guidelines: immediate CVS and respiratory support, adrenaline, fluids and secondary measures such as antihistamine therapy. Immunology / allergology referral after stabilization is important as skin-prick and intradermal tests will help elicit the exact cause.

B. COMPLICATIONS OF NEURAXIAL ANAESTHESIA

The ASA Closed Claim Database

The ASA's Closed Claim Database, which excluded obstetric and pain management cases, reviewed cases from 1980 – 1999. The database suggested that neuraxial anaesthesia was associated with temporary nerve injury in 38% of the claims, with permanent injury occurring in 26%. Of the injuries believed to be directly block related, 45% were attributed to block technique (due to needle or catheter damage to nervous tissue.) Most injuries involved the lumbosacral nerve roots, or the thoracolumbar spinal cord. Over half of the neuraxial injuries were due to epidural haematoma.

1. Post-Dural Puncture Headache

Post-dural puncture headache (PDPH) was first described by August Bier in 1898 and classically presents as a postural headache following therapeutic or diagnostic interventions of the epidural or spinal space.

The incidence of PDPH is estimated to be between 30-50% following diagnostic or therapeutic lumbar puncture, 0-5% following spinal anaesthesia and **up to 81% following accidental dural puncture during epidural insertion in the pregnant woman.** PDPH varies in intensity from mild headache to intractable agony. Although PDPH usually resolves spontaneously, it is extremely unpleasant, may interfere with a new mother's ability to care for her infant and it may extend the length of hospital stay. More rarely, PDPH may be associated with serious complications such as subdural haematoma, seizures and sagittal sinus thrombosis. Effective treatment is limited so measures including the use of suitable needles and acquisition of appropriate skills in spinal and epidural placement are essential to reduce the development of PDPH.

PATHOGENESIS AND ANATOMY

The pathogenesis of PDPH remains unclear but is thought to be caused by CSF leakage into the epidural space via a tear in the dura. CSF loss leads to a reduction in intracranial pressure and downward traction on pain-sensitive intracranial structures, including veins, meninges and cranial nerves, resulting in a headache that is classically worse in the upright position. The fall in intracranial pressure may also cause compensatory cerebrovascular venodilation and this may contribute to the development of the headache.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The fundamental principle in the assessment of any patient – especially the parturient – with a post-partum headache is to carefully consider the differential diagnosis.

Differential Diagnosis

- Infective Meningitis
- Encephalitis
- Vascular migraine
- Cerebral vein thrombosis
- Cerebral infarction
- Haematomas (Subdural & Subarachnoid)
- Neoplasm
- Drugs
- Dehydration
- Pre-eclampsia
- Tension headache
- Benign intracranial hypertension
- Caffeine withdrawal

History and examination should be performed taking account of the **timing** of the headache in relation to the neuraxial procedure, the **nature** of the headache as well as other symptoms and signs. Since PDPH can present following an unrecognized dural puncture with an epidural needle or epidural catheter, details of the epidural insertion should be reviewed including the difficulty of the procedure and number of attempts. In the case of a headache following a spinal procedure, PDPH is more likely following dural puncture with a larger gauge 'cutting' tipped needle or after multiple attempts at spinal block which might result in a number of dural tears ('pepper -potting' of the dura), increasing the chance of a CSF leak.

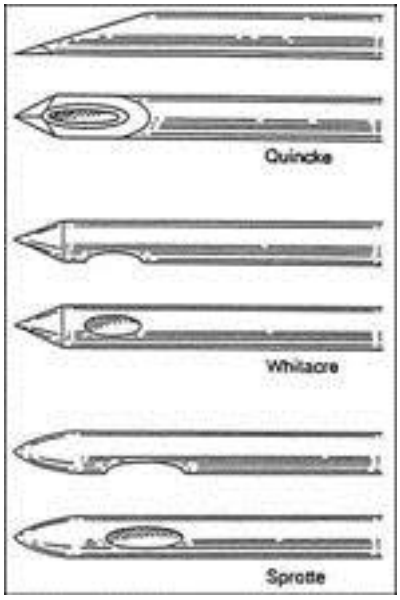
The cardinal features of PDPH as defined by the International Headache Society are a headache that develops within 7 days of dural puncture and disappears within 14 days; however, PDPH has been reported to occur later and continue for longer than these times. Classic features of the headache caused by dural puncture are listed below but presentation is often variable.

- Headache is often fronto-occipital
- Develops usually 24-28 hours after procedure; 90% will present in 3 days
- Headache worse in upright position; eases when supine
- May be associated with neck stiffness, photophobia, tinnitus, visual disturbances, rarely; cranial nerve palsies

*PDPH is primarily a **clinical diagnosis** however, if there is concern that the headache may be related to more serious intracranial pathology then diagnostic imaging should be considered early. In cases of PDPH, MRI may demonstrate diffuse dural enhancement and brain descent*.

Prevention of PDPH

- **Spinal Needle Selection:** Smaller gauge spinal needles with pencil point tips such as the Whitacre and Sprotte needle are associated with lower rates of PDPH. Pencil point needles part rather than cut the dural fibres, and so the hole in the dura closes more quickly. Ideally, spinal needles no larger than 25G should be used.
- **Epidural needles:** The loss of resistance to saline technique may have the effect of moving the dura anteriorly as the needle approaches, thereby reducing the likelihood of dural puncture, compared with an intermittent pressure technique with air. In addition, inadvertent dural tap while using LORA may result in pneumocephalus which itself a cause of headache.



Orientation of the bevel of the spinal or epidural needle during insertion has been suggested to influence PDPH in the event of an inadvertent dural tap. There is weak evidence to indicate a lower incidence of headache if bevel orientation is parallel to dural fibres; however the exact orientation of dural fibres is unclear.

Subsequent rotation of an epidural needle to allow catheter placement may itself be associated with higher rates of dural puncture so the benefits of a 'parallel' needle approach are unclear.

While there is no evidence that inadvertent dural puncture is less likely with an 18G Touhy needle compared with a 16G, in the event of a dural tap, the incidence of headache may be reduced with a smaller gauge.

Other precautions should include ensuring an optimal patient position, slow controlled advancement of the needle and limiting patient movement during the procedure (especially important during labour) by using adequate local anaesthetic infiltration and maintaining verbal contact throughout. Advancement of the needle should stop during labour contractions.

Operator experience is inversely related to inadvertent dural puncture and PDPH rates.

Diagnostic Lumbar Puncture: Following diagnostic lumbar puncture, replacing the stylet prior to removing the needle may reduce the risk of headache. Insertion of the stylet may prevent a strand of arachnoid that was trapped in the needle following CSF aspiration from being avulsed on needle withdrawal thereby reducing damage to the dura.

Management of PDPH

Conservative Management

- Most post-dural puncture headaches will resolve spontaneously.
- Conservative management has traditionally involved bed rest and fluids though there is little evidence to support either of these measures. A recent Cochrane review concluded that routine bed rest after dural puncture is not beneficial and should be abandoned. While routine administration of additional fluids may be unnecessary, avoidance of dehydration is advisable to help limit headache severity.

Pharmacological

- Many drugs have been recommended to treat PDPH, however in the vast majority of cases, evidence of effectiveness is limited.
- Simple analgesia should be instituted in all patients with PDPH; regular paracetamol and non-steroidal anti-inflammatory medications (if tolerated) may control symptoms adequately.

Caffeine

Caffeine is a central nervous system stimulant and is thought to influence PDPH by inducing cerebral vasoconstriction. Doses from 75 – 500 mg have been investigated and caffeine has been administered orally, intramuscularly and intravenously. There is low level evidence that caffeine confers a temporary benefit in PDPH, however a recent American consensus review concluded that the widely held opinion that caffeine is beneficial in PDPH is unwarranted. Caffeine is associated with adverse events including cardiac arrhythmias and maternal seizures. In high doses (probably >300mg) caffeine may enter breast milk and potentially lead to neonatal irritability.

Synacthen (synthetic ACTH)

Synthetic ACTH was first reported to be effective for treating PDPH in the 1990s. Postulated mechanisms include CSF retention through increased mineralocorticoid mediated sodium reabsorption, and a direct analgesic effect via its glucocorticoid activity. Most reports of its effectiveness stem from case reports and case series; however a randomised controlled trial in 2004 found no effect of a single intramuscular injection of Synacthen compared with an intramuscular injection of normal saline. It is unknown whether a larger or repeated dose of Synacthen may be beneficial.

Other Drugs

Numerous other reports exist in the literature with promising results for a variety of other pharmacological agents including: 5HT agonists (e.g.sumatriptan), gabapentin, DDAVP, theophylline, and hydrocortisone. To date there is insufficient evidence to support their use.

Invasive Management

Epidural blood patch (EBP)

Epidural blood patching involves injection of autologous blood into the epidural space under strict aseptic technique. It remains one of the few proven treatments of PDPH however the mechanism of action remains unclear. The resulting blood clot may have a “patch effect” on the dural tear while the volume of blood transfused into the epidural space raises intracranial pressure and reduces ongoing CSF leak.

Despite the early successes and long history of the epidural blood patch a number of controversies exist regarding the technique including its true effectiveness, the best technique and its safety.

Effectiveness

- Classically, it has been taught that 90% of patients will have at least some relief after epidural blood-patch, and of the remaining 10%, 9 out of 10 will benefit from a second blood patch.
- Reported success rates have fallen over time and current data suggest that permanent cure by a single blood patch can be expected in 50% of patients. To effect *complete* cure, recent data suggests that up to 40% of patients require a second blood patch.
- EBP still remains the *most effective treatment* for PDPH and has been shown in a randomised controlled trial to be more effective than conservative treatment in treating established PDPH.

Optimal Technique

- Epidural blood patch should be performed by two personnel under strict aseptic conditions, preferably in theatre. The patient should be seated and once the first operator is ready to perform the epidural blood should be taken by the fully scrubbed phlebotomist. A third operator is useful for applying a tourniquet to the arm.
- The operator should be an experienced anaesthetist and the second competent in taking a volume of blood from the arm.
- Contraindications include sepsis, coagulopathy and patient refusal.
- It is most effective when performed within 24 hours after headache onset.
- Which volume? Recommended volumes have varied from as little as 2 ml to 60 ml. Current recommendations suggest 10 – 20 ml should be injected.
- The procedure should be abandoned if the patient experiences severe discomfort during injection.
- The patient should lie flat for at least 2 hours after the procedure even if immediate relief occurs.

Safety & Complications

- The importance of strict asepsis cannot be overstated.
- FBC may be considered before the EPDP: it should not be undertaken if leukocytosis is present or the patient is pyrexial.
- Minor complications include backache, neck pain and transient bradycardia
- Major complications are rare but serious: meningitis, subdural haematoma, seizures, arachnoiditis and cauda equina syndrome.
- The procedure may be unacceptable to Jehovah's Witnesses.

Should an epidural blood patch fails to relieve a PDPH, it may be prudent to consider radiological imaging of the head to exclude other pathology prior to repeating the blood patch.

<u>Summary</u>

- PDPH will resolve spontaneously in the majority of cases
- Using appropriately sized and designed needles (pencil point spinal needles vs cutting beveled needles) greatly decreases the incidence of PDPH
- No specific medical intervention is more effective than another; simple analgesics should be implanted early.
- Epidural blood patch remains the most effective treatment; though not as effective as previously thought

2. Subdural Injection

The possibility of subdural injections in the setting of intentional spinal or epidural block is under-appreciated. These occur when LA is injected in the potential space between the dura and the arachnoid. Should fluid be injected here, it tends to ascend against gravity. It may become a permanent defect making it more difficult to find the subarachnoid space, either at the time of injection or subsequently.

Subdural injection can happen if either the spinal or Tuohy needle pokes through the dura, or if the epidural catheter is threaded or/and migrates there. In one series of over 2000 epidurals, the incidence was 0.82%. Because it is difficult diagnose, the true number is likely higher. Subdural injection may be the cause of failed spinals despite free aspiration of fluid: Existing arachnoid defects may allow flow of CFS into the subdural space. In contrast, subdural block may occur after apparent successful placement of an epidural catheter despite negative aspiration of CSF.

Classic presentation is delayed and gradual. The onset is in 10-30 minutes of a presumably successful epidural or spinal block. Following epidural catheter placement, it typically presents as an unexpectedly extensive sensory block after negative test dose/aspiration.

Motor block is typically minimal, though it can be extensive. Anteriolateral sympathetic fibres are hit, causing hypotension that is more than expected from epidural placement but less than a total spinal, and it is relatively easy to treat with fluids and small doses of vasopressor. If the subdural injection continues to track cephalad, it can pool intracranially and cause slow-onset dyspnoea and loss of consciousness.

A number of factors predisposing to the development of a subdural block have been identified. Accidental subdural injection is more likely with difficult block placement. Rough handling and rotation of an epidural needle in the epidural space may cause dural laceration, leading to a possibility of subdural placement of the catheter.

Leibinowitz et al suggested that patients who have had previous back surgery are potentially more prone to accidental subdural injection, because of altered anatomy secondary to scarring and retraction and possible obliteration of the epidural space. In their study, however, only 28% of patients had been identified as having previous back surgery.

A recent lumbar puncture may also predispose to subdural injections. In this situation cerebrospinal fluid

(CSF) may leak through the dural rent and distend the subdural space. Any attempt to inject local anaesthetics at the same intervertebral space may cause deposition in the subdural space. This fact is supported also by a study in the radiology literature, which indicates that once the subdural compartment is expanded, it is very difficult to place any subsequent injection into the subarachnoid space.

Subdural Injection: Characteristics and Symptoms

- Gradual/delayed onset (10-30 mins)
- Extensive sensory block with minimal motor block
- Hypotension (more than with epidural, less than with spinal)
- Intracranial tracking (worst-case scenario); dyspnoea and LOC

In all cases, supportive management should be implemented. If a subdural injection is suspected, the neuraxial block should not be repeated owing to the defect created by the first injection.

3. What About Backache?

A recent study by Howell et al concluded that the use of epidural analgesia was not associated with the development of chronic backache. In fact, the studies found no significant differences in the incidence of long-term back pain between women who received epidural pain relief and women who received other forms of pain relief. Instead, the backache, if any, developed because mothers receiving epidural analgesia were less sensitive to back stressing postures and hence allowed the poor back positions to remain for prolonged periods, resulting in back strains post-delivery. Another possible reason for the back pain experienced post-delivery could be trauma to the back muscles and ligaments during insertion of the epidural needle at the catheter site. However, this is relatively *uncommon* and usually the pain is *short-term*.

Based on studies conducted, there is no connection between back pain and epidural usage, and the epidural pain relief during delivery do not increase the risk of long-term back pain. Back pain post-delivery is more likely attributed to the pre-existing prenatal backaches due to mechanical and structural changes in the spine which are a result of normal physiological changes during pregnancy.

4. Epidural haematoma

Epidural haematoma following a neuraxial block can be a disaster, resulting in permanent nerve injury. The quoted incidence of epidural haematoma (EH) is 1:190 000 but may be underreported as this is based on case reports.

Classically, EH is related to the following symptoms:

- Radicular pain
- Motor impairment
- Sensory loss
- Urinary retention

However, these symptoms may not be useful in detection as the majority of patients under epidural care have sensory deficit secondary to the infusion of LA and are also catheterized. Not all haematomas are painful either. In a review of 61 cases of EH, only 38% of cases involved classic pain symptoms.

The most reliable sign of a developing EH is the development of a motor block. Literature also suggests that this is the most reliable prognostic indicator. The American Spinal Injury Association recommends the use of the modified Frankel Scale, which uses motor block as the principle variable assessed.

EH may occur at any time after insertion and removal of the epidural catheter. One review reported that 50% of EHs occurred after their removal. However, most units do not assess for motor function after removal. In the light of this, it would be prudent to continue assessments for 24 hours post catheter removal.

Investigations

The investigation of choice for detecting an EH is MRI scan – however this might prove unpractical, certainly in hospitals / units that do not have immediate access to an MRI scanner.

Regular CT scanning, however, may be useful especially if compression is suspected. If EH is suspected, prompt transfer to neurosurgical unit is mandatory.

Treatment

The definitive treatment for an EH is emergency surgical decompression by laminectomy. Key factors that determine outcome are (1) the severity of neurological deficit at presentation and (2) the time from presentation to surgery. If surgery is performed within 12 hrs of symptom onset, recovery rates exceed 60%; beyond 24 hrs, this drops below 10%

Prevention

A protocol by Meikle et al suggests the following:

- Patients in whom epidural infusions are running should be evaluated for motor block every 4 hrs;
- Observations should continue at least 24 hours after catheter removal;
- Motor block attributed to a recent bolus of LA should be reassessed within 2 hrs;
- A designated person should be assigned to provide cover for patients under epidural care;
- In established motor block; the epidural infusion should be discontinued, appropriate alternative analgesia established and a reassessment of motor block be made after a defined interval.
- If an epidural haematoma is suspected, an MRI scan should be organized immediately
- If MRI is not available or a delay is expected, direct neurosurgical referral should be instigated.

5. Epidural abscess

Epidural abscess (EA) after epidural catheter insertion is mercifully rare. A Danish study over a one-year period reported 9 cases in over 17 000 patients (0.48%) whereas no cases were found in a large Swedish study of 9232 patients.

A spinal epidural abscess threatens the spinal cord or cauda equina by compression and also by vascular compromise. If untreated, an expanding suppurative infection in the spinal epidural space impinges on the spinal cord, producing sensory symptoms and signs, motor dysfunction, and, ultimately, paralysis and death. Intervention early in the course of the disease undoubtedly improves the outcome. Frequently, diagnosis is understandably delayed because the initial presentation may be only nonspecific back pain. One half of cases are estimated to be misdiagnosed or have a delayed diagnosis. At times, radicular symptoms may lead to a chief complaint of chest pain or abdominal pain, mimicking a myocardial infarction or an acute abdomen.

Clinical presentation may be quite variable. The clinical triad of fever, back pain, and neurologic deficit is not present in most patients. Early presentations may be subtle, and atypical presentations are not unusual. A 4-phase sequential evolution has been described, with (1) localized spinal pain, (2) radicular pain and paraesthesias, (3) muscular weakness, sensory loss, and sphincter dysfunction, and finally (4) paralysis.

- The virulence of the infecting organism and the mode of infection contribute to the tempo of this progression. Abscesses from haematogenous spread tend to progress rapidly, while abscesses from osteomyelitis or discitis may evolve over weeks or months with slow progression of symptoms.
- Frequently the patient gives a history of back strain or mild injury.
- An evident source of infection in skin or soft tissue may be found.
- IV drug users are a high-risk group. Occurrences have been cited even in patients with a remote history of IV drug abuse.[7]
- Cases are frequently reported in patients with diabetes mellitus, which is a risk factor in 50% of reported patients; alcoholism; and conditions involving chronic immunosuppression.
- Haematogenous seeding of the epidural space with abscess formation may stem from intravenous lines, urinary catheters, or implantable devices. Direct inoculation of the epidural space may follow spinal surgery, epidural catheter placement, or epidural injections.

Symptoms may include the following:

- **Fever**, present in only about one third of patients. Leucocytosis is evident in two-thirds of cases.
- **Localized back pain** in most patients, often the first symptom.
- **Radiculopathy** with radiating or lancinating pain, including chest or abdominal pain. This may simulate myocardial infarction or other causes of chest or abdominal pain.

- **Spinal cord syndromes**, typically involving paraparesis with prospective progression to paraplegia (Epidural abscesses at the level of the cauda equina cause symptoms consistent with cauda equina syndrome rather than a spinal cord syndrome.)

- **Central cord syndrome** from epidural abscess has also been reported.

- **Sphincter dysfunction**, including incontinence or increased residual urine volumes

- **Headache and neck pain** may be present, especially with cervical epidural abscesses. (Of course, these symptoms might also suggest meningitis.)

Diagnosis and Treatment

Immediate imaging of the spine and spinal cord is imperative when the diagnosis is clinically suspected. If available, spinal MRI is the procedure of choice. If MRI is unavailable, CT myelography or conventional myelography can reveal an intraspinal extramedullary mass—a "surgical" lesion.

- Emergency surgical decompression of the spinal cord with drainage of the abscess is the usual surgical treatment.
- Successful conservative treatment with a combination of abscess aspiration and antibiotic treatment has been reported; although increasingly used, **it remains very controversial**. Should this be instituted the patient should have no neurologic deficits and a culture proven microbiological diagnosis be available. Stringent follow-up by both the primary and neurosurgical team must be available, with the option of emergency surgery at all times. Physicians must be aware that rapid deterioration may occur at any time especially in the first 72 hours.
- Risk factors for failure of medical therapy include neurological deficit, diabetes, bacteraemia, age > 65 and MRSA as causative organism.
- **Increasing neurologic deficit, persistent severe pain, or persistent fever and leucocytosis** are all indications for prompt decompressive surgery.
- Patients with spinal epidural abscess may be **clinically unstable** because of concomitant systemic infection, shock, complications of diabetes mellitus, or other complications. As a result, the increased surgical risk must be considered.

6. Prior back surgery and neuraxial techniques

Prior back surgery is not an absolute contra-indication to a neuraxial technique: however, placement of the block may be more difficult. Any existing neurological deficit should be very carefully recorded and a thorough neurological examination of the affected area undertaken. Reviews of case series of epidural placement in pregnant patients who had had previous back surgery showed no evidence of increased complications vs. patients who had not had prior back surgery; however, the number of cases studied was small.

3. COMPLICATIONS OF PERIPHERAL NERVE BLOCKS

Incidence

It is very difficult to obtain reliable data about the incidence of peripheral nerve injury secondary to regional anaesthesia, since neurological injury is (fortunately!) extremely rare. Retrospective studies have reported varying incidences depending on the specific definition of “nerve injury”. Auroy et al (2002) reported an incidence of 1.5 / 10 000 of major complications resulting in permanent nerve damage. Most injuries are *subclinical* or present as mild mononeuropathies. The incidence of transient neurological deficits is much more common: Up to 8% of blocks may be associated with **transient** paraesthesia in the days following the block.

Data form the ASA Closed Claim Database shows that, regarding peripheral nerve injury, 56% of claims were for temporary injury; yet only half of the deficits were block related. Improper patient positioning and the use of tourniquets were also associated with peripheral neurologic pathology. The brachial plexus was most commonly injured, whereas claims for lower extremity injuries were rare (possibly reflecting less frequent practice of these blocks.) In a more recent study of 7000+ plexus blocks (13% via US, 30% via nerve-stimulation, combined US with NS 50%) only 30 patients (0.5%)

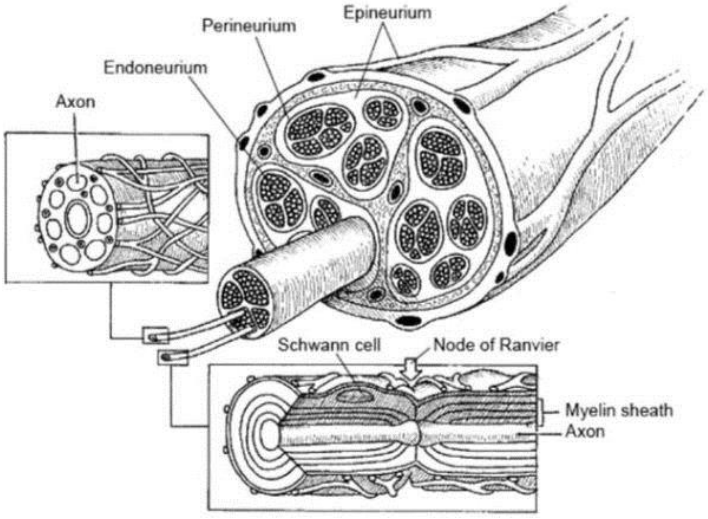
ended up with neurological referral, and of these 3 met criteria for nerve injury directly related to nerve block: an incidence of 0.04%.

Data from a recent review of published studies suggest that the incidence of neurologic symptoms following PNB varies depending on the anatomic location, the incidence ranging from 0.03% for supraclavicular blocks to 0.3% for femoral blocks to up to 3% for interscalene blocks (however, claims from the ASA database show that most claims were after upper limb blocks).

Anatomic considerations of nerves and nerve fascicles

Individual nerve fibres are enveloped by the endoneurium. These fibres are organized into *fascicles* in turn surrounded by the perineurium. Finally, groups of fascicles are embedded into stromal tissue and are collectively bound by the epineurium.

There is considerable variance: in the axilla, the nerves have almost no surrounding fascia and there is a large amount of stroma between fascicles: a blunt needle piercing the nerves would in theory be less likely to puncture a fascicle: less fascial constrainment implies lower pressure as they are allowed to swell. Proximally to distally, the number of fascicles increases and diameter decreases with a concomitant increase in stromal tissue.



Mechanisms of injury

Animal studies suggest it is intrafascicular injection in combination with high injection pressures that results in injury.

The crux of the intraneural injection problem appears to lie in the avoidance of penetrating the perineurium and entering the fascicle. The presence of a high opening injection pressure (>20 psi) in a canine model is a very sensitive (if not highly specific) sign of intrafascicular needle tip placement, whereas extrafascicular needle tip placement is associated with low (20 psi) pressures. High pressures are typically absent during extraneural injection.

Traditionally intraneural injection was considered the major cause of neural injury. It occurs despite ultrasound and/or nerve stimulatory guidance. Experience with US guidance has revealed that intraneural injection does not necessarily result in permanent injury. Interestingly, although increasing use of US guidance has improved the success, onset and quality of blocks, the incidence of neurological injury has stayed the same. This behoves the anaesthetist that neurological follow-up until resolution or stabilization of any peripheral neurologic symptoms post-block is mandatory.

Current evidence points to the fact that the mechanism of injury is multi-factorial and cannot be attributed to intraneural injection alone.

Needle choice

The tough, resistant nature of the perineurium renders it unlikely to be penetrated by a short, blunt-beveled needle. However, although long-beveled needles are more likely to pierce perineurium, animal studies also show that blunt-bevel penetrations cause more severe injuries that take longer to recover.

Pre-existing pathology

Patients with pre-existing nerve pathology are more susceptible to peripheral nerve block complications, though the exact mechanism of this remains unclear. They are also prone to prolonged duration of block. Already damaged nerves are likely to have increased sensitivity, such as in diabetic neuropathy or chemotherapy-induced damage.

Vascular injury vs. Neurotoxicity

Peripheral nerves have a dual blood supply: there are intrinsic exchange vessels in the endoneurium and an extrinsic plexus in the epineural space; this anastomoses with the intrinsic circulation. Ischaemia has been identified as one of the causes of nerve injury, while neurotoxicity due to the chemical nature of the agents themselves has also been investigated. In a rat model histological damage to nerves secondary to neurotoxicity included axonal destruction and Wallerian degeneration.

LA neurotoxicity

All LAs are potentially neurotoxic yet the mechanism remains unclear. Proposed mechanisms include increases in intracellular calcium concentration, disturbance in mitochondrial function, interference with membrane phospholipids, and cell apoptosis. The perineurium and blood vessel endothelium serve as a barrier to entry into the fascicle. However, even local anaesthetics placed within the epineurium have been shown to cause altered perineural permeability and fascicular oedema, leading to compression of the fascicle and reduced neural blood flow. This effect appears to be dose dependent.

Intraneural administration of local anaesthetics exposes the axons to higher concentrations of drug than extraneural application. One study comparing the extraneural, extrafascicular, and intrafascicular administration of ropivacaine 0.75% showed that histologic damage was least severe extraneurally and most severe intrafascicularly. (However, even when injected inside the epineurium, others have shown ropivacaine 0.75% to have no adverse effect on functional recovery. What is well known is that the injection of local anaesthetics *into the fascicle* results in widespread and immediate axonal injury.

Neural blood flow

Local anaesthetics alone are also capable of decreasing neural blood flow. Lidocaine 2% reduces neural blood flow in rat sciatic nerves by 20-40%, and this difference persists after washout of the local anaesthetic solution.

Adrenaline is a common adjuvant used to prolong the duration of blockade and to warn of intravascular injection/ absorption. At concentrations of 5 µg/mL and 10 µg/mL, adrenaline reduces neural blood flow by 20% and 35%, respectively. In contrast, at lower concentrations (2.5 µg/mL), neural blood flow increases by 20% transiently before returning to baseline, suggesting that at lower concentrations the β-adrenergic effects predominate. The effects of combining lidocaine and adrenaline are additive: A solution of 2% lidocaine plus 5 µg/mL of epinephrine reduced neural blood flow by 80%. Ropivacaine appears to be associated with the lowest incidence of neurotoxicity.

The clinical significance of the effects of various local anaesthetics and additives is unknown. The experimental data must be weighed within the context of clinical practice; countless of nerve blocks of blocks are performed in daily practice using a combination of local anaesthetic and adrenaline with no neurologic consequences. This reinforces the hypothesis that nerve injury is multifactorial, and one theoretical aspect may be insufficient to cause injury consistently.

Peripheral Nerve Catheters and Nerve Injury

Peripheral Nerve Catheters (PNCs) have demonstrable advantages over single-shot injections: fewer systemic side effects than systemic opioids, increased postoperative patient satisfaction, and in some cases, faster functional recovery of the affected limb. However, few studies exist regarding the prevention of complications regarding PNC placement.

Ideally, the PNC should be placed upon the 1st attempt. Clinically, this may be difficult. Both peripheral nerve stimulation and US guidance offer high success rates of PNC placement. Concerns exist regarding block failure, inadvertent catheter removal, kinking / knotting / looping of the catheter, infectious complications and complications associated with tunneling and suturing the PNC.

Infectious complications

Localized inflammation is infrequent; however, bacterial colonization of the PNC has a high rate of occurrence, usually by skin flora (esp. *Staphylococcus epidermidis.*) Despite asepsis, contamination can also occur at the time of block removal. Increased incidence of PNC infection include male sex, indwelling catheter > 48 hrs, immune-compromised patients and ICU admission.

Regarding prevention, strict asepsis must always be used when placing a PNC. Chlorhexidine as skin prep has been shown to be the most effective skin disinfectant currently available. Many studies support the administration of a dose of antibiotics to cover skin flora.

Vascular complications

Vascular puncture during PNC placement is not uncommon. The catheter may also migrate into a vessel. US guidance may reduce the risk of inadvertent puncture. Significant bleeding, however, occurs only rarely: in a study of 405 patients, only 1 patient developed a haematoma; the patient in question was also receiving heparin.

Regarding anticoagulation treatment, the American Society of Regional Anaesthesia recommends that patients undergoing deep plexus or PNBs be treated with the same guidelines as pertaining to those with neuraxial techniques.

Prevention and Management of Nerve Injury following Peripheral Nerve Blockade

- Contraindications should be carefully considered (sepsis, anticoagulation). Existing neurological symptomatology is not an absolute contraindication but may render the patient more vulnerable to peripheral nerve injury.
- While US guidance and / or nerve stimulation techniques do not appear to have decreased the incidence of intraneural injection, their use is prudent and has been shown to result in increased success rates and quality of analgesia.
- Any paraesthesia lasting beyond the expected length of the block (> 24 hrs) must be promptly investigated with neurological referral and follow-up.
- Simple reassurance may be all that is necessary as the majority of cases resolve completely and spontaneously.
- Good communication is essential. Counsel the patient that 95% of postoperative sensory deficits will resolve within 4-6 weeks; and that the majority of these reverse within the first week.
- Diagnostic challenges include residual sedation and blockade, pain limiting examination, casts / dressings / slings, movement restrictions and patient expectations regarding the block (e.g. not being told how long the block was supposed to last)
- Neuropathies can also be caused by prolonged tourniquets, casting, excessive intraoperative traction, or a misplaced surgical clip. Early involvement of the surgical team is prudent.
- **The presence of motor deficits is an ominous sign**, and a referral to a neurologist and/or neurosurgeon is indicated. **Neuropathies that are evolving, and those that are severe/ complete should be seen immediately by a neurologist and/or neurosurgeon**.

Referral for electrophysiological testing may be indicated when the symptoms are not purely sensory, or when the neuropathy is severe and/or long-lasting. Studies performed usually consist of the following:

Electromyography: This is undertaken to determine which muscle units are affected by a denervation lesion. Small needle electrodes are placed in various muscles and the pattern of electrical activity both at rest and with contraction is analysed. The results can help to localize a lesion, and, depending on the pattern, suggest a time frame for the injury.

Nerve conduction studies: In these tests, a device similar to the peripheral nerve stimulator used by anaesthesiologists to monitor the degree of neuromuscular blockade is attached over various nerves in the affected area. A characteristic waveform is generated following stimulation of the nerve, which may allow the neurologist to pinpoint a conduction block.

The optimal timing of these tests depends on the indication. An exam within 2-3 days of the onset of injury may give information regarding the completeness of the lesion (and therefore prognosis), as well as clues about the duration of the lesion, which often has medico legal ramifications, particularly if the lesion is deemed to predate the nerve block or surgical procedure. As such, this can be seen as a "baseline" exam. More information is obtained at approximately 4 weeks post-investigation.

Neuropathies that are evolving, and those that are severe/ complete should be seen immediately by a neurologist and/or neurosurgeon.

Conclusion

In conclusion, regional anaesthesia (both peripheral and neuraxial) remains safe with a rare incidence of serious complications. The management of systemic local anaesthetic toxicity has been augmented with the availability of lipid emulsion therapy, and this should be instituted early if cardiovascular collapse occurs. The most feared complications of neuraxial anaesthesia are epidural abscess and haematoma; careful monitoring of patients for signs of motor block is therefore mandatory after performance of these blocks. Regarding peripheral nerve injury, most injuries resolve spontaneously. Nerve damage appears to be multifactorial and most consistently related to intraneural injection under high pressures. Ultrasound guidance techniques have not appeared to decrease the incidence of peripheral nerve complications, but result in greater accuracy and improved patient satisfaction re. blind paraesthetic techniques.

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Troubleshooting in the recovery room

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Introduction

Though most patients will pass through the recovery room without incident, it is important to remain alert and prepared. Up to 25% of patients undergoing anaesthesia will present with postoperative complications. These complications contribute significantly to in-hospital morbidity and mortality and peri-operative costs. This talk aims to address the most common and the most serious complications the anaesthetist may encounter in the recovery room.

Incidence

The table below illustrates the most common complications encountered in the immediate post-operative period. Post-operative visual loss and awareness under anaesthesia may both present in the recovery room and, although they are rare, they receive considerable attention in both medical and lay press.

Complication	Reported incidence
Postoperative nausea and vomiting	**23 %**
Upper airway problems	**6.9%**
Hypotension	**2.7%**
Dysrhythmias	**1.4%**
Hypertension	**1.1%**
Altered mental status	**0.6%**
Major cardiac event / suspected cardiac event	**0.6%**

Postoperative nausea and vomiting (PONV)

PONV is the most common complication encountered in the recovery room. Since no patient may leave the recovery area until nausea and/or vomiting have been controlled, the major focus should be on prevention of PONV and then subsequent treatment.

PONV affects surgery in the following ways:

- PONV is the worst patient fear going into surgery (worse than the fear of surgical pain).
- Patient satisfaction is significantly decreased if PONV occurs.
- Severe PONV may necessitate an unplanned admission to the hospital, or in a South African setting, may delay hospital discharge – as many patients may not be able to return to hospital easily.
- Patients with severe PONV remain in the recovery room longer, delaying operating room turnover.
- Late onset PONV causes significant patient discomfort (especially during patient transport).

Risk factors for PONV
The following categories have the highest risk of PONV:

- Female gender
- Non-smokers
- Prior history of PONV or motion sickness
- Anaesthesia incorporating the use of volatile anaesthetics, nitrous oxide or opiods
- Type and duration of surgery (neurological, head or neck, abdominal, breast)

The *Apfel Scale* is easy to use and moderately predictive of PONV. The table below illustrates the mechanism to evaluate the risk of PONV and then which pharmacological modalities to consider. Prophylaxis before the development of PONV significantly reduces the incidence of PONV. Treatment of PONV in a patient who was not given prophylaxis or who developed PONV in spite of prophylaxis is termed rescue therapy.

Risk Factor	Number of risk factors	PONV incidence	Prophylaxis strategy
	0	9%	None
Female gender	1	20%	4mg dexamethasone ± 2nd antiemetic
Non-smoker	2	39%	Avoid inhalational agents if possible + 4mg dexamethasone ± 2nd antiemetic
History of PONV or motion sickness	3	60%	Avoid inhalational agents if possible + 4mg dexamethasone + 2nd antiemetic
Use of opiods (>100 mcg fentanyl or equivalent)	4	78%	Avoid inhalational agents if possible + 4mg dexamethasone + 2nd antiemetic + consider aprepitant (NK receptor antagonist) pre-emptive analgesia
Rescue strategy: antiemetic not used for prophylaxis, e.g. ondansetron 1mg IV			

Drugs from the following classes have been found to significantly reduce the risk of PONV when compared with placedbo:

PROPHYLAXIS ONLY

- Anti-cholinergics (scopolamine)
- Corticosteroids (dexamethasone)

PROPHYLAXIS AND RESCUE THERAPY

- Serotonin-receptor antagonists (ondansetron, granisetron)
- Anti-dopaminergic drugs (metoclopramide, droperidol)
- Anti-histamines (cyclizine)
- Neurokinin-receptor antagonists (aprepitant)

Respiratory complications

Supportive care of respiratory complications in the recovery room includes pain control, supplemental oxygen and positive pressure respiratory support. Analgesia for incisions to the chest or upper abdomen should be considered pre-operatively and may include the use of regional anaesthesia (epidural, paravertebral or TAP blocks) and non-narcotic intravenous analgesics (paracetamol, NSAIDs).

Hypoxaemia (low PaO_2) during the post-operative period may be due to hypoventilation (low PAO_2) or compromised alveolar oxygen exchange (increased alveolar to arterial oxygen gradient). Patients with significant comorbidities (neuromuscular, pulmonary or cardiac dysfunction) are at a higher risk for respiratory compromise.

The most common causes of respiratory complications post-operatively include:

HYPOVENTILATION

- Airway obstruction
- Effects of anaesthetic drugs
- Analgesics
- Sedatives
- Residual neuro-muscular block
- Poorly controlled pain – impairing respiration

IMPAIRED OXYGEN EXCHANGE

- Intrapulmonary shunting
- Pulmonary oedema
- Pulmonary embolus

The management of **airway obstruction** requires careful consideration of the patient, the surgery performed and the anaesthesia administered. Causes of airway obstruction that present in the recovery room include: pharyngeal muscle weakness, laryngospasm, vocal cord paralysis, airway oedema, cervical haematoma following surgery, foreign bodies and residual effects of anaesthesia. Relying solely on the patient's oxygen saturation as a marker of respiratory performance is imprudent, specifically when a patient is receiving supplementary oxygen. Rather, the patient's clinical condition should be carefully monitored, highlighting signs of respiratory distress (snoring, retraction of the sternal notch, paradoxical abdominal motion, etc.). The training of recovery room personnel to observe these signs is of critical importance.

Lung collapse (due to atelectasis or pneumothorax) leads to regions of lung that are perfused but not ventilated, causing **intrapulmonary shunting** and significant hypoxaemia. Supportive treatment for atelectasis includes adequate analgesia, deep breathing and coughing, incentive spirometry or even positive pressure ventilation.

Pulmonary oedema often manifests post-operatively in patients with pre-existing heart failure, but may also develop in otherwise healthy patients as a result of airway obstruction (negative pressure pulmonary oedema) or following drug administration, e.g. oxytocin or naloxone (flash pulmonary oedema). Treatment is supportive and includes supplemental oxygen and positive pressure ventilation if needed.

Although uncommon in the early post-operative period, **pulmonary embolus** can occur due to vein thrombus, fat or amniotic fluid. This possibility should be considered in patients with chest pain, tachycardia and hypoxaemia resistant to supplemental oxygen.

Cardiovascular complications

Cardiovascular complications during the post-operative period are related to the severity of underlying co-morbidities (hypertension, coronary artery disease) and the nature and course of the operation.

In patients with known cardiovascular co-morbidities, the surgery may cause complications by direct or indirect means e.g. INDIRECT: blood loss during surgery may lead to hypotension and hypoperfusion, with subsequent cardiovascular injury, or DIRECT: operations near the heart may cause cardiac irritability with post-operative arrhythmias.

Hypotension in the recovery room has numerous aetiologies. The most significant are:

- Hypovolaemia
- Myocardial ischaemia / heart failure
- Decreased vascular resistance
    - Pharmacological
    - Sympatholytic (spinal / epidural)
    - Sepsis
    - Anaphylaxis
    - Spinal shock

Patients that develop **hypertension** post-operatively in the recovery room are at a higher risk for post-operative complications (e.g. unplanned admission to ICU) than patients with an episode of hypotension. The most common causes of hypertension are inadequate pain control, hypoventilation, unrinary retention, anxiety and delirium (especially alcohol and drug withdrawal). Untreated hypertension increases cardiac workload and may lead to an imbalanced myocardial oxygen supply / demand relationship and subsequent cardiac failure. Patients with cardiac co-morbidities are at a greatly increased risk of this.

Cardiac arrhythmias in the post-operative period, particularly with uncoordinated cardiac contractions, can lead to marked hypotension. The aetiology may include for tachyarrhythmias: acute coronary insufficiency, hypoxia, electrolyte abnormalities (hypokalaemia, hypomagnesaemia), anaesthetic

agents or other pharmacological agents; and for bradyarrhythmias: excess antihypertensive agents, excess opioid dosing or high neuraxial anaesthesia (suppression of cardiac accelerator fibres).

Benign peri-operative arrhythmias, such as premature ventricular contractions (PVCs) and ventricular bigeminy, rarely degenerate into life-threatening arrhythmias and generally do not require treatment. The management of arrhythmias requires the identification and correction of underlying causes, i.e. hypoxia, hypercarbia, ischaemia and electrolyte imbalances. Should tachyarrhythmias cause haemodynamic instability, electrical cardioversion may be required, and similarly in cases of bradyarrhythmias, temporary pacing may be needed.

Hypothermia or Hyperthermia

A recent large observational study indicated that hypothermia occurred in 46% of patients admitted to ICU following elective non-cardiac surgery. Because of the adverse effects of hypothermia, the Joint Commission and the Surgical Care Improvement Project encourage warming of all patients to 36°C within 15 min of their arrival in the recovery room. Most frequently this is achieved by using forced air warming devices.

Causes of hypothermia in the recovery room include:

- A cold environment
- Administration of room temperature iv fluids
- Anaesthesia induced vasodilatation (due to medication, regional anaesthesia, etc.)
- Ventilation with unwarmed gases
- Anaesthesia-induced impairment of the hypothalamic thermostat
- Decreased basal metabolic rate
- Exposure of body cavities to room temperature air

Shivering in the recovery room can occur with hypothermia, hyperthermia or normothermia. Shivering causes patient discomfort and markedly increases myocardial oxygen consumption. Treatment is with a single dose of meperidine 12.5 to 25mg intravenously. Alpha-2 agonists (clonidine and dexmedetomidine) are used as second-line therapy.

Fever is defined as a core body temperature of more than 39°C. Potential causes are:

- Medication or blood products
- Trauma suffered pre- or intra-operatively
- Pre-operative infections
- Malignant hyperthermia (rarely)

Neuropsychiatric complications

Emergence delirium (also known as emergence agitation) refers to a prolonged (hours) change in mental status characterised by a dissociated state of consciousness in which the patient is irritable, uncooperative, uncompromising, thrashing, moaning, incoherent or crying. In children it may be as high as 30% (ages 2 – 4) and has been attributed to the increased use of rapid onset low-solubility inhaled anaesthetic agents. In adults it has an incidence of less than 5%, most commonly seen in elderly patients, especially following major orthopaedic procedures.

Reversible / Treatable causes are:

- Pain
- Hypoxia
- Hypercarbia
- Hypoglycaemia
- Urinary retention
- Electrolyte imbalance (especially hyponatraemia)
- Central, drug-induced anticholinergic activity

Pre-operative substance abuse and poor functional status are also risk factors for emergence delirium.

Visual disturbances in the recovery room are most commonly attributable to corneal abrasion. The patient complains of a foreign body in the affected eye. Staining the cornea with fluorescein makes the diagnosis. Topical antibiotics and an eye patch usually result in a full recovery.

Ischaemic optic neuropathy and retinal artery occlusion are debilitating, but fortunately very rare complications. Patients undergoing cardiac, spinal and head and neck operations are at the highest risk of these complications. Risk factors are prone positioning, prolonged procedure duration and significant blood loss or need for large volume resuscitation. All patients presenting with these complications should be sent for an urgent ophthalmology consultation, even though there may be very little to offer them in terms of treatment.

Epidural haematoma after neuraxial anaesthesia has a reported incidence of 1 in 150 000. The risk increases in the setting of systemic anticoagulation. Since epidural catheters are usually placed immediately before induction of anaesthesia, an epidural haematoma will not present until the patient awakens in the recovery room. Symptoms include back pain / pressure, progressing to muscle weakness, sensory loss and urinary or bladder dysfunction. If suspected, an emergency MRI and neurosurgical evaluation should be obtained as soon as possible, since permanent neurological injury can occur in as little as six hours from time of onset.

Intraoperative awareness enjoys a large amount of discussion in the professional and lay press. These patients may present in the recovery unit. Any patient that presents with post-operative recollection of intra-operative events should be offered psychiatric counselling.

Post-operative inability to void

Urinary retention following anaesthesia is common, with an incidence varying from 5 – 70%. In the absence of urologic pathology, post-operative inability to void is usually transient.

Risk factors:

- Patient
    - advanced age
    - male gender
    - pre-existing neurological disease (e.g. cerebral palsy, neuropathy, multiple sclerosis)
- Procedure
    - anorectal surgery
    - joint arthroplasty
    - hernia repair
- Anaesthesia
    - medications (anticholinergic agents, beta-blockers, sympathomimetics)
    - prolonged duration of anaesthesia
    - excessive fluid administration
    - mode of anaesthesia (neuraxial anaesthesia more likely than general anaesthesia)

History or physical evaluation may not be sufficiently sensitive to detect bladder overdistention. Ultrasound or aseptic “in-out” bladder catheterisation are the best ways to determine bladder volume, with ultrasound being the preferred method. Any patient with the above-mentioned risk factors and inability to void 4 hours post-operatively should have a bladder ultrasound performed. Should the bladder contain more than 600ml of urine a one-time catheterisation should be performed. Patients without risk factors and who have not voided post-operatively, may be discharged, but should be instructed to seek medical assistance if they have not spontaneously voided within 8 hours after discharge.

Conclusion

The recovery room is the perfect illustration of the old adage regarding anaesthesia: “90% boredom 10% blind panic”. Though many patients will pass through the recovery area without any concerns, it is those few that don’t, that caution us to remain vigilant at all times. Many complications are easily avoided with careful planning (PONV) or remedied with early intervention (hypotension, arrhythmias). When trouble wrangles into the recovery room it is best to be well prepared, with your six-shooter loaded and ammunition in reserve.

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New oral anticoagulants and anaesthesia

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Oral anticoagulants are widely used for long-term prevention or treatment of thrombosis. Until recently, the only available oral anticoagulants were the vitamin K antagonists, such as warfarin. In the past few years, however, the landscape has changed with the introduction of new oral anticoagulants (NOACs) that specifically target either factor Xa or thrombin. However, with the approval of new oral anticoagulants, such as dabigatran, rivaroxaban, and apixaban, clinicians now have a broader choice of anticoagulant and anaesthetists have more to worry about. These new agents do however have several advantages over warfarin. Warfarin's narrow therapeutic index and multiple drug and diet interactions affect its safety, compliance, and efficacy. The new agents produce such predictable anticoagulant effects that they can be given in fixed doses without the need for routine coagulation laboratory monitoring. Consequently, the new anticoagulants are more convenient to administer than warfarin. Furthermore, not only are they as effective as warfarin, but the new agents also cause less intracranial bleeding. Given the recent approval and availability of these medications, several questions arise on how to manage these patients peri-operatively.

The cell-based model of coagulation

The cell-based model explains the mechanism of haemostasis in vivo and includes the important interactions between cells directly involved in haemostasis (i.e. tissue factor [TF]-bearing cells and platelets) and coagulation factors. This model more accurately represents the interaction between cellular activity and coagulation proteins that leads to thrombus formation and haemostasis. The cell-based model identifies the membranes of TF-bearing cells and platelets as the sites where activation of specific coagulation factors occurs. This model is described in a three-phase process:

Initiation

All evidence to date indicates that the sole relevant initiator of coagulation in vivo is TF. Cells expressing TF are generally localized outside the vasculature, which prevents initiation of coagulation under normal flow circumstances with an intact endothelium. Once an injury occurs and the flowing blood is exposed to a TF-bearing cell, FVIIa rapidly binds to the exposed TF. FVIIa is the only coagulation protein that routinely circulates in the blood in its active enzyme form, with approximately 1% of total FVII circulating as FVIIa. The TF-FVIIa complex then activates additional FVII to FVIIa, allowing for even more TF-FVIIa complex activity, which then activates small amounts of FIX and FX. FV can be activated directly by FXa. The FXa generated by TF-FVIIa binds to the few generated molecules of its cofactor FVa to form the prothrombinase complex, which subsequently cleaves prothrombin and generates a small amount of thrombin. Due to rapid inactivation by antithrombin the FXa generated is effectively restricted to the surface of the TF-bearing cell on which it was generated. However, the FIXa generated can dissociate and move to the surface of nearby platelets or other cells.

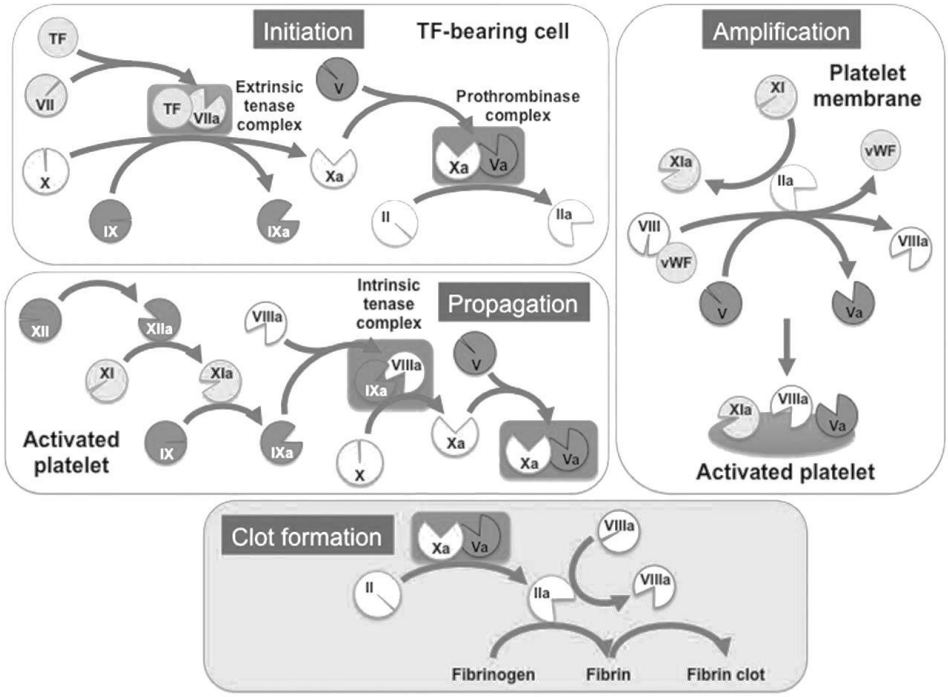
Amplification

Once a small amount of thrombin has been generated on the surface of a TF-bearing cell (the initiation phase), that thrombin diffuses away from the TF-bearing cell and is available for activation of platelets at the site of injury. Binding of thrombin to platelet surface receptors causes rapid changes in the surface of the platelet, resulting in shape change, reorganisation of membrane phospholipids to create a procoagulant membrane surface, and release of granule contents that provide additional fuel for the reaction. The thrombin generated in the initiation phase also cleaves FXI to FXIa and activates FV to FVa on the platelet surface. Furthermore thrombin cleaves von Willebrand factor off FVIII (they circulate bound together), releasing it to mediate platelet adhesion and aggregation. The released FVIII is subsequently activated by thrombin to FVIIIa.

Propagation

The propagation phase occurs on the surface of the activated platelets. FIXa that was generated by TF-FVIIa in the initiation phase can bind to FVIIIa (generated in the amplification phase) on the platelet surface. The intrinsic tenase complex (FIXa – FVIIIa) on the activated platelet surface rapidly begins to generate FXa on the platelet. The FXa generated on platelets then rapidly binds to FVa (generated

by thrombin in the amplification phase) and cleaves prothrombin to thrombin. This prothrombinase activity results in a burst of thrombin generation leading to cleavage of fibrinopeptide A from fibrinogen. When enough thrombin is generated with enough speed to result in a critical mass of fibrin, these soluble fibrin molecules will spontaneously polymerise into fibrin strands, resulting in an insoluble fibrin matrix. Thrombin also activates Factor XIII, which stabilizes the thrombus by cross-linking fibrin. The resulting fibrin mesh traps and holds cellular components of the thrombus (platelets and red blood cells).



The central role of Factor Xa and Thrombin in clot formation

According to the cell based model of coagulation factor Xa and factor IIa (thrombin) play central roles in the coagulation processes that lead to haemostasis. One molecule of Factor Xa has the ability to catalyse the formation of approximately 1000 thrombin molecules. Furthermore factor Xa, with activated Factor V as a co-factor, propagates coagulation by converting prothrombin (Factor II) to thrombin. Factor Xa is a crucial site of amplification in the coagulation process. Development of medications that inhibit Factor Xa and thrombin generation are, therefore, attractive areas of coagulation pharmacology research.

NOACs targeting Factor Xa and Thrombin

NOACs were developed to overcome the limitations of Warfarin. In contrast to Warfarin, which lower the levels of multiple coagulation factors, NOACs only have a single target; dabigatran inhibits thrombin, whereas rivaroxaban and apixaban inhibit factor Xa. Selective targeting endows these drugs with a wider therapeutic window than Warfarin, thereby enabling administration in fixed doses without coagulation monitoring. Consequently, NOACs are more convenient to administer than Warfarin. When compared with warfarin in patients with atrial fibrillation or venous thromboembolism, NOACs were at least as effective for prevention of stroke and recurrent venous thromboembolism, respectively, but were associated with a significant reduction in the rate of intracranial haemorrhage, the most feared complication of anticoagulation therapy. Rates of extra cranial bleeding with NOACs were similar or lower than those with warfarin, providing additional evidence of the safety of NOACs.

Clinical pharmacology - Factor Xa inhibitors – Rivaroxaban and Apixaban

Direct factor Xa inhibitors, are small molecule synthetic oral drugs capable of inhibiting not only free factor Xa with high selectivity but also pro-thrombinase-bound and clot-associated factor Xa in a concentration-dependent manner. They are called “direct inhibitors” because unlike heparin, LMWH and fondaparinux, they do not require antithrombin to inhibit their target.

The oral bio-availability of these drugs is high (rivaroxaban 80 - 100% and apixaban 50%) and is not affected by food intake and both have a rapid onset of action (within2 - 4 hours).
Compared to warfarin they have relatively short half-lives apixaban 7 - 8 hours and rivaroxaban 11 - 13 hours. The longer half-life of rivaroxaban means that it can be given as a once daily dose which may improve patient compliance. (Apixaban is usually given as a twice daily dosing). Both drugs are partially renally cleared so half-life will be prolonged in patients with renal impairment and dosing adjustments will be required.
Rivaroxaban has a dual mode of excretion with the renal route accounting for one-third of the overall elimination of unchanged active drug. Rivaroxaban is a substrate of CYP3A4 and P-glycoprotein and therefore not recommended for concomitant use with strong inhibitors of both pathways, e.g. most azole antimycotics and protease inhibitors.
The favourable pharmacological properties underpin the use of rivaroxaban and apixaban in fixed dosing regimens, with no need for dose adjustment or routine coagulation monitoring. Since the drugs inhibits factor Xa, PT/INR and aPTT may be variably affected. The PT / INR and aPTT are not useful for monitoring the pharmacodynamic effects of rivaroxaban in clinical practice, because the prolongation of these parameters varies significantly depending on the clotting assays and conditions used. These drugs efficacy can however be monitored, if required, by using an anti-Xa assay.
Pharmacologically, the 2 factor X inhibitors are for all practical purposes the same. However, rivaroxaban's once-daily dosing schedule may be preferable to many patients. As there no direct comparative studies we have to rely on indirect comparisons between drugs, which is not ideal. One needs to look at all the nuances from the trials and select the drug that is most appropriate for each individual patient.

Clinical pharmacology - Thrombin inhibitor Dabigatran

Dabigatran etexilate is an oral reversible direct thrombin inhibitor that is rapidly absorbed and converted to its active form, dabigatran. Dabigatran has been shown to be a potent, competitive, and reversible inhibitor of thrombin, inhibiting both thrombin activity and generation.
The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate is approximately 3 - 7%. In healthy volunteers, peak plasma concentrations of dabigatran are reached approximately 2 hours after oral administration.
The elimination half-life is 12 - 14 hours, with clearance predominantly occurring via renal excretion of unchanged drug. Dabigatran is not metabolized by cytochrome P450 isoenzymes, has no interactions with food, and also has a low potential for drug—drug interactions. The pharmacokinetic profile of dabigatran is consistent across a broad range of different patient populations and is unaffected by gender, body weight, ethnic origin, obesity, and mild-to-moderate hepatic impairment. Small differences in dabigatran pharmacokinetics associated with age are attributable to variation in renal function. The half-life will be prolonged in patients with renal impairment and dosing adjustments may be required. 80% of the drug is excreted unchanged by the kidneys; it is contraindicated in patients with end stage renal failure.
At recommended therapeutic doses, dabigatran etexilate prolongs the coagulation markers such as aPTT, ECT, and TT. INR is relatively insensitive to the exposure to dabigatran and cannot be interpreted the same way as used for warfarin monitoring. The aPTT provides an approximation of dabigatran's anticoagulant effect. Dabigatran etexilate produces a predictable pharmacodynamic effect and usually requires no coagulation monitoring.

Clinical uses of the NOACs

In the United States, Europe, Canada and many other countries, dabigatran rivaroxaban and apixaban are licensed as alternatives to warfarin for prevention of stroke or systemic embolism in patients with atrial fibrillation and prevention and treatment of acute VTE.
In South Africa dabigatran and rivaroxaban is licensed for the prevention of VTE in patients undergoing major orthopaedic surgery and dabigatran is also licensed for risk reduction of stroke and systemic embolism in patients with atrial fibrillation.

Settings in which a heparin or warfarin may be preferable. There are several settings in which warfarin may be preferable to one of the target-specific oral anticoagulants, or in which a target-specific oral agent is contraindicated (e.g. prosthetic heart valve, pregnancy). In addition, patients who are receiving warfarin with excellent stable INR control and minimal bleeding side effects may have little to gain by switching to a different agent. In many inpatient settings, heparins are preferable because of similar efficacy to parenteral direct thrombin inhibitors, availability of an antidote, and substantially lower costs.

- **Prosthetic heart valves** – The direct thrombin inhibitors and direct factor Xa inhibitors are not used in patients with prosthetic heart valves, due to greater risk of valve thrombosis, which may be fatal.
- **Pregnancy** – Direct thrombin inhibitors and direct factor Xa inhibitors are not used during pregnancy, due to lack of clinical experience in this setting; LMW heparin is preferred in most pregnant women who require an anticoagulant. If a patient taking a one of these agents becomes pregnant, she should be switched to LMW heparin immediately.
- **Renal impairment** – Renal insufficiency is a common setting in which heparin or warfarin may be preferable to the target-specific agents. Product labelling for dabigatran and rivaroxaban states that the agents are not to be used in individuals creatinine clearance <15 mL / min. Heparin, warfarin or dose-adjusted low molecular weight (LMW) heparin should generally is used in patients with renal insufficiency
- **Compliance** – The lack of routine monitoring and short half-lives of these agents make it more difficult to determine if a patient is taking them appropriately. In addition, missing one or two doses can leave the patient inadequately anti-coagulated; in contrast, missing a couple of doses of warfarin is unlikely to substantially increase the time outside the therapeutic range. Dabigatran and apixaban require twice daily dosing, which may also reduce patient compliance.
- **Gastrointestinal disease** – Patients with gastrointestinal diseases, especially those with a history of bleeding, may prefer to avoid the target-specific oral agents because of the lack of a reversal agent.
- **Cost** – Vitamin K antagonists are typically much less expensive than target-specific oral anticoagulants.

Anaesthetic management of the NOAC anti-coagulated Patient

Elective surgery recommendations
Creatinine clearance should be assessed in all patients receiving NOACs and being scheduled for elective surgery.

NOACs should neither be interrupted for skin surgery, dental and other oral procedures and endoscopies, nor for most anterior chamber ophthalmic surgery.

Low risk (CHADS2 score < 2, treated for > 3 months for a non-recurrent VTE) patients with a high risk of bleeding, requiring normal coagulation intraoperatively, should have their NOACs stopped 5 days before surgery and no bridging therapy is needed.

In high-risk patients (CHADS2 score > 2, patients with recurrent VTE or treated for < 3 months). NOACs should be stopped 5 days prior to surgery and bridging therapy with a LMWH started at therapeutic doses 3 days before surgery.

In patients on dabigatran with a creatinine clearance between 30 and 50 mL / min, stop drug 5 days before surgery with no bridging therapy.

UFH or LMWH should be restarted > 6 h after the procedure, taking the bleeding risk into account. NOACs may be resumed when surgical bleeding risk is under control.

Major Bleeding
Data from the Dresden NOAC registry indicate that, rates of NOAC related major bleeding is lower, and that the outcome may be better than that of major warfarin associated bleeding. The present lack of a specific reversal agent does however remain a concern for anaesthetists managing these patients intra-operatively or in the ICU.

Supportive care remains the mainstay of treatment in the event of haemorrhagic complications. The drug must be discontinued, the source of bleeding investigated and general supportive measures should be adopted, including mechanical compression, surgical or endoscopic haemostasis, and replacement of fluids and blood products. Activated charcoal can be used if recent ingestion of the medication has taken place (<2 hours). Haemodialysis can also be considered for patients on dabigatran, especially in patients with renal impairment.

Haemostatic agents should be considered in life threatening bleeding. Although there are no human clinical trials demonstrating the efficacy of these agents several animal models and in vitro testing have demonstrated an improvement in coagulation with prothrombin complex concentrates (PCC) and recombinated activated factor 7 (rFVIIa). Antifibrinolytics appear to offer no benefit for these patients.

	Warfarin	**Dabigatran**	**Rivaroxaban & Apixaban**
General measures	Drug discontinuation, mechanical compression, surgical haemostasis, transfusional support	Drug discontinuation, mechanical compression, surgical haemostasis, transfusional support	Drug discontinuation, mechanical compression, surgical haemostasis, transfusional support
Activated charcoal	Consider if last dose <2 h	Consider if last dose <2 h	Consider if last dose <2 h
Haemodialysis	No benefits (highly protein bound)	Removes 62–68% of circulating drug	No benefits (highly protein bound)
Coagulation factors	PCC (25 U/kg, repeat if necessary) FFP (10–15 ml/kg) rFVIIa (90 ug/kg)	PCC (25 U/kg, repeat if necessary) rFVIIa (90 ug/kg)	PCC (25 U/kg, repeat if necessary) or FEIBA (50 IE/kg, max 200 IE/day) rFVIIa (90 ug/kg)
Specific inhibitors	Vitamin K (5–10 mg IV)	Idarucizumab (Phase 1) Ciraparantag (preclinical)	Andexanet alfa (Phases 1–3) Ciraparantag (Phase 1)

Specific reversal agents
One of the potential drawbacks of NOACs since their introduction has been the absence of an antidote to reverse anticoagulation in case of life-threatening bleeding or emergency surgery. This will soon change as specific agents that counteract the effects of NOACs are under development and promising results in clinical trials have recently been announced.

Andexanet alfa is structurally very similar to native Factor Xa, but it has a number of limited modifications intended to restrict its biological activity to reversing the effects of Factor Xa inhibitors. Andexanet alfa acts as a Factor Xa decoy that binds to Factor Xa inhibitors in the blood. Once bound to Andexanet alfa, the inhibitors are unable to bind to and inhibit native Factor Xa. The native Factor Xa then becomes available to participate in the coagulation process and restore haemostasis, or normal clotting. Andexanet alfa also binds to LMWH or pentasaccharide-activated ATIII and modulates the activity of these indirect fXa inhibitors. Andexanet alfa has successfully completed phase 3 clinical trials and is expected to be licensed by both the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) before the end of the year.

Idarucizumab (BI-655075) is a fully humanised monoclonal antibody fragment which has a highly specific binding affinity with dabigatran etexilate, and acts as a reversal agent for the anticoagulant activity of dabigatran and its metabolites. Idarucizumab has been submitted for approval of marketing authorisation to the EMA, FDA and Health Canada.

Aripazine is the least developed, but potentially the most promising of these reversal agents. Aripazine (PER997) is a small (512 Da), peptide-like molecule was specifically created to bind to the charged sites on UFH. Pre-clinical in vitro testing demonstrated PER977 binding to the NOACs (dabigatran, edoxaban, apixaban, rivaroxaban), as well as to LMWH and fondaparinux.

Neuraxial Anaesthesia and NOACs

The decision to perform spinal or epidural anaesthesia/analgesia and the timing of catheter removal in a patient receiving thromboprophylaxis should be made on an individual basis, weighing the small, though definite risk of spinal haematoma with the benefits of regional anaesthesia for a specific patient. Alternative anaesthetic and analgesic techniques exist for patients considered to be at an unacceptable risk. The patient's coagulation status should be optimised at the time of spinal or epidural needle / catheter placement, and the level of anticoagulation must be carefully monitored during the period of epidural catheterisation. It is important to note that patients respond with variable sensitivities to anticoagulant medications. Indwelling catheters should not be removed in the presence of a significant coagulopathy, as this appears to significantly increase the risk of spinal hematoma. In

addition, communication between clinicians involved in the perioperative management of patients receiving anticoagulants for thromboprophylaxis is essential in order to decrease the risk of serious haemorrhagic complications. The patient should be closely monitored in the perioperative period for signs of cord ischaemia. If spinal haematoma is suspected, the treatment of choice is immediate decompressive laminectomy. Recovery is unlikely if surgery is postponed for more than 10 - 12 hours.

For the NOACs, the time between drug discontinuation and neuraxial injection is based on the drug's pharmacokinetic half-life.

In high risk patients (CHADS2 score > 2) it has been recommended that two half-lives are an adequate compromise between safety - avoidance of spinal haematoma and prevention of VTE. The presence of residual anticoagulation facilitates transition to full anticoagulation after the procedure and having residual anticoagulant might prevent perioperative VTE. Residual anticoagulation will naturally increase the risk of spinal haematoma formation, and extra care should be taken particularly in the elderly (who typically have total joint surgery) or in patients with renal disease or other co-morbidities as drug half-lives may be prolonged. When neuraxial procedures are performed under these conditions, safety measures should be observed including avoidance of multiple catheter insertion attempts and cessation of the procedure if excessive bleeding is noted. The conscientious follow-up of these patients and a high index of suspicion for bleeding complications should be observed. Alternatively, five half-life intervals can be observed in conjunction with LMWH bridge therapy.

For low risk patients (CHADS2 score < 2), five half-life intervals between discontinuation and neuraxial procedure are recommended.

The incidence of spinal haematoma is the same with both catheter placement and catheter removal, so it has been recommended that the same guidelines apply to both neuraxial injection or epidural catheter placement and catheter removal.

As it is assumed that it takes 8 hours for a for a platelet plug to become a stable clot, resumption of NOACs should take place no earlier than 8 hours minus the time it takes for the drug to reach peak effect (about 6 hours for the NOACs).

Conclusion

All anticoagulants increase bleeding risk. The agents discussed herein generally do not appear to increase bleeding risk more than heparins or vitamin K antagonists. The present lack of a specific antidote for these agents is a concern; however, their half-lives are short, and reversal agents are in development. Knowledge of relevant pharmacokinetics of the anticoagulant drugs provide the foundation for safe perioperative use in terms of perioperative drug interruption, management of intraoperative bleeding, neuraxial injections and epidural catheter placement and removal.

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The assessment of effort tolerance

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Coronary artery disease (CAD) is the most common morbidity and mortality worldwide. The two most common complaints are chest pain and dyspnoea. These patients form the largest group to be recruited for exercise testing, mostly using the Modified Bruce Protocol.

Assessment of effort tolerance and functional capacity are an integral step in pre-operative cardiac risk assessment and are usually measured in metabolic equivalents (METs). One MET equals the basal/resting metabolic rate (3,5 ml O_2.kg^{-1}.min^{-1}).

Exercise testing provides an objective assessment of functional capacity. Functional capacity can be estimated by abilities to perform activities of daily living. Preoperative assessment of functional capacity predicts the individual's ability to increase oxygen delivery in the peri-operative period.

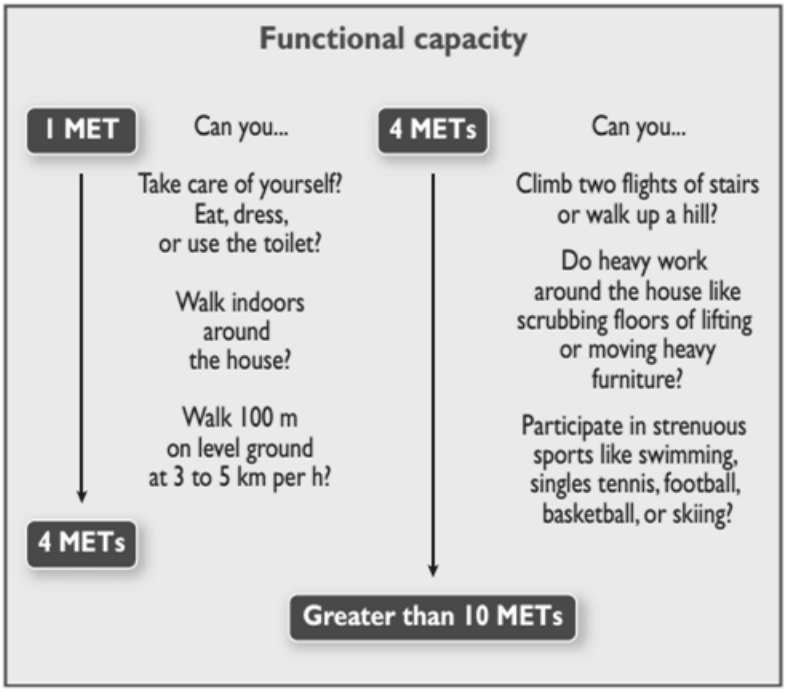


Figure 1 Estimated energy requirements for various activities. Based on Hlatky *et al.* and Fletcher *et al.*[36,37] km per h = kilometres per hour; MET = metabolic equivalent.

Examples of poor prognostic indicators are an inability to climb two flights of stairs or run a short distance (< 4 METs). An anaerobic threshold of less than 11 ml/kg/min and a VO2 max<15ml/kg/min are also frequently quoted values specifically used in thoracic surgery. Poor indices are associated with an increased incidence of post-operative cardiac events. Poor functional capacity in thoracic surgery has been directly linked to increased mortality (RR 18.7; 95% CI 5.9-59). Poor functional capacity has not been associated with an increased mortality after other **non-cardiac** surgery (RR 0.47; CI 0.09-2.5).

The opposite of this is also true. When functional capacity and effort tolerance are high, the prognostic value is excellent, even when cardiac risk factors and stable IHD are present. When functional capacity if poor or difficult to determine (unknown), the presence of risk factors along with the surgical risk involved will determine the pre-operative risk stratification and peri-operative management.

Exercise testing

Physical:

- Submaximal or "constant work rate: Stair climbing, shuttle walk test, 6MWT
- Maximal or "incremental work rate": Aerobic exercise with progressively increasing intensity to maximal tolerance (CPET).

Pharmacological: Pharmacological stress agents (Dobutamine, Atropine, Adenosine/Dipyridamole) monitoring cardiovascular response to physiological stress.

Indications:

1. Detection of CAD in patients with chest pain (mean test sensitivity 68%, mean test specificity 77%)
2. Evaluation of anatomic and functional severity of CAD
3. Prediction of cardiovascular events
4. Evaluation of physical capacity and effort tolerance
5. Evaluation of exercise-related symptoms
6. Assessment of chronotropic competence, arrhythmias, and response in implanted device therapy
7. Assessment of response to medical intervention

Endpoints:

Maximal oxygen uptake (VO_2 max): Peak oxygen uptake achieved during performance of dynamic exercise. Product of maximum cardiac output (stroke volume, heart rate) and maximum arteriovenous oxygen difference. (VO2 max>15ml/kg/min)

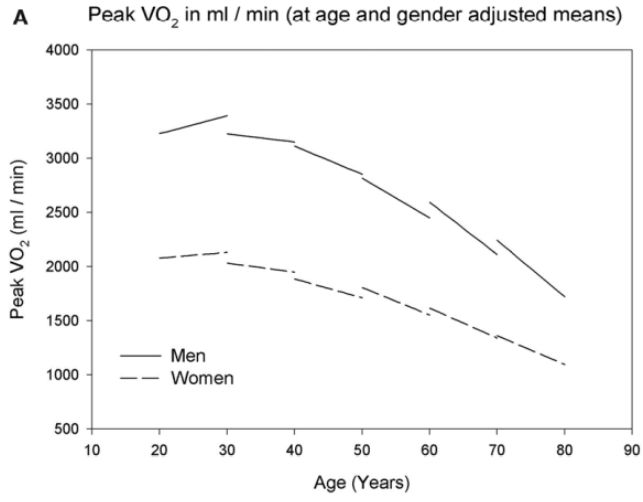


Figure 1. Progressive and accelerating decline in peak $\dot{V}o_2$ according to age decades in clinically healthy men and in women. Reprinted from Fleg JL et al.[21] Copyright © 2005, the American Heart Association, Inc.

Anaerobic threshold (AT): Point during progressive exercise beyond which muscles cannot derive all required energy from oxygen utilisation. (AT>11 ml/kg/min)

Chronotropic index: Increase in HR during exercise is due to decrease in vagal tone followed by increase in sympathetic outflow. HR increases linearly with workload and oxygen demand. Chronotropic incompetence (inability to reach >85% of age predicted maximum HR) is predictive of cardiac events and all-cause death.

$fc_{(max-rest)}/VO_{2\ (max-rest)}$

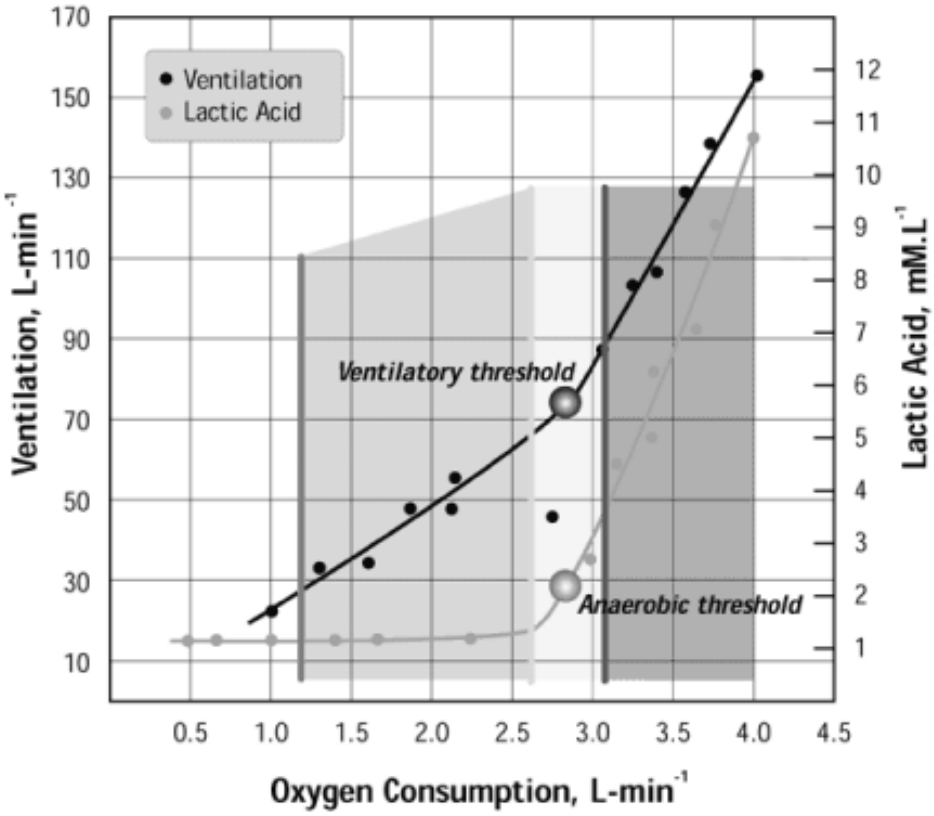
Max HR=220-age.

(HR response depends on: anaemia, metabolic disorders, intravascular volume, peripheral resistance, ventricular dysfunction. These conditions DO NOT affect max HR.)

Inadequate HR response: sinus node dysfunction, cardiac disease, drugs (beta-blockers), miscellaneous.

HR recovery: Fast decline during first 30 seconds, followed by slower return to baseline. Abnormal HR recovery demonstrated prognostic value in recent years.

Ventilatory threshold: Point at which ventilation abruptly increases in response to increasing carbon dioxide production (V_{co2}).VE/VCO2 has a linear relationship until near maximum, i.e. ventilator compensation point. After this point the slope becomes steeper. VE/VCO2 slope becomes steeper in cardiac patients according to severity of heart failure, reflecting severity of ventilation perfusion mismatch.



Oxygen pulse=Vo_2/fc

Contraindications:

Absolute: Acute myocardial infarction (< 2d)

Ongoing unstable angina

Uncontrolled cardiac arrhythmia

Active endocarditis

Symptomatic severe aortic stenosis

Decompensated heart failure

Acute pulm embolism, pulm infarction, DVT

Acute myocarditis or pericarditis

Acute aortic dissection

Physical disability

Relative: Obstructive left main coronary artery stenosis

Moderate to severe aortic stenosis (asymptomatic)

Tachyarrhythmias with uncontrolled ventricular rates

Advanced/complete heart block

Hypertrophic obstructive cardiomyopathy

Recent stroke/TIA

Mental impairment, limited cooperation

Resting HPT (>200/110 mmHg)

Uncorrected medical conditions (electrolytes, hyperthyroidism…)

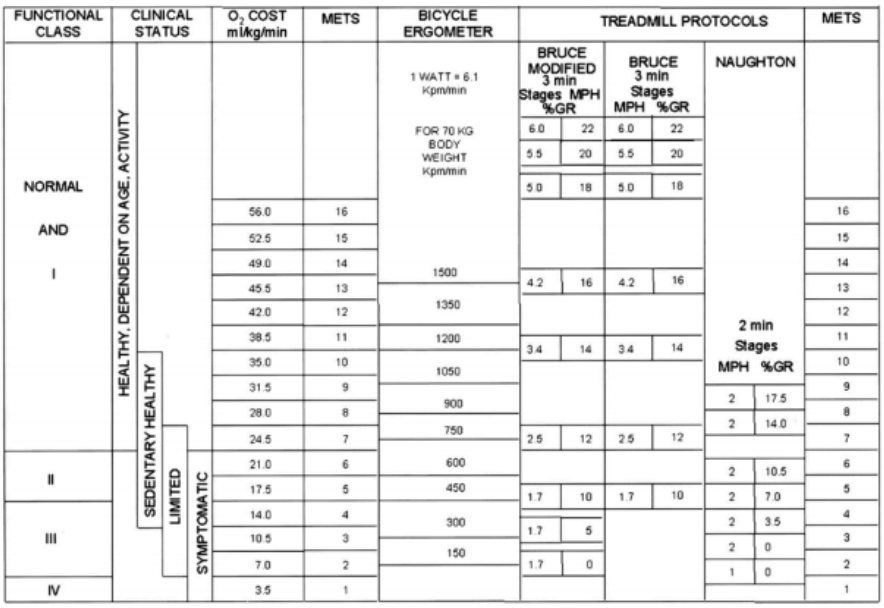
Exercise tests/protocols

1. Cardiopulmonary exercise testing (CPET):

- Gold standard: Most accurate noninvasive quantification of VO_2 max
- Provide information about respiratory, cardiovascular, metabolic and muscular responses to physical activity (breath-to-breath gas analysis, ABGs, pulse oximetry, haemodynamic monitoring)
- Most important measures: VO_2 max, AT
- Specialised equipment and highly trained personnel required (ventilatory expired gas analysis)
- Not feasible in immobile patients

2. Exercise testing with Modified Bruce Protocol: Treadmill and cycle ergometers

- Many published studies
- Widely available and relatively inexpensive, most commonly used
- Exercise duration powerful predictor of prognosis



FUNCTIONAL CLASS	CLINICAL STATUS	O_2 COST ml/kg/min	METS	BICYCLE ERGOMETER	TREADMILL PROTOCOLS						METS
					BRUCE MODIFIED 3 min Stages		BRUCE 3 min Stages		NAUGHTON 2 min Stages		
				1 WATT = 6.1 Kpm/min	MPH	%GR	MPH	%GR	MPH	%GR	
NORMAL AND I	HEALTHY, DEPENDENT ON AGE, ACTIVITY	56.0	16	FOR 70 KG BODY WEIGHT Kpm/min	6.0	22	6.0	22			16
		52.5	15		5.5	20	5.5	20			15
		49.0	14								14
		45.5	13	1500	5.0	18	5.0	18			13
		42.0	12	1350							12
		38.5	11	1200	4.2	16	4.2	16			11
		35.0	10	1050							10
	SEDENTARY HEALTHY	31.5	9	900					2	17.5	9
		28.0	8	750	3.4	14	3.4	14	2	14.0	8
	LIMITED	24.5	7								7
II		21.0	6	600	2.5	12	2.5	12	2	10.5	6
	SYMPTOMATIC	17.5	5	450					2	7.0	5
III		14.0	4		1.7	10	1.7	10	2	3.5	4
		10.5	3	300					2	0	3
		7.0	2	150	1.7	5			1	0	2
IV		3.5	1		1.7	0					1

Figure 3. Relation of exercise workload ($\dot{V}o_2$ and metabolic equivalents [METs]) to stages of the standard Bruce protocol and other treadmill protocols and to stationary bicycle ergometry. Completion of Stage 4 of the Bruce protocol (4.2 mph at a 16% grade) approximates 1500 kpm/min on the bicycle. Functional class refers to New York Heart Association class. kpm indicates kilopond-meters; MPH, miles per hour; and %GR, percent grade. Reproduced with permission from Fletcher et al.[1] ©2001 American Heart Association, Inc.

3. 6-minute walk test: Evaluate submaximal exercise capacity

- Walk down 100 foot (30m) corridor at own pace for 6 minutes
- Distance and symptoms recorded (Normal 450-600m)
- Direct correlation with VO_2 max (6 MWT/30) and peak O_2 pulse, inverse relation with minute ventilation/CO_2 production
- Simple, easy to perform, reproducible and well standardised (not to be considered as a surrogate for CPET)
- Currently represents the most used exercise endpoint for trials assessing response to therapy

4. Incremental Shuttle Walk Test:

- Walk between two cones (10 metres apart) in time to a set of auditory beeps played on a CD
- 12 levels of speed (0.5 m/s – 2.37 m/s)
- Each minute the required walking speed progressively increases
- The patient walks for as long as they can until they are either too breathless or can no longer keep up with the beeps at which time the test ends
- The number of shuttles (laps between the cones) is recorded

5. Stair climbing:

- More than 2 flights of more than 12m in vertical height > 4 METs
- Decrease in saturation > 4% with 2 flights is abnormal (thoracic surgery)
- Poorly standardised

6. Duke Activity Status Index:

- Structured questionnaire, developed in medical patients with cardiac disease (predictive value in surgical population undetermined)
- Grades exercise ability on basis of questions related to exercise equivalences (ability to wash/dress without breathlessness strenuous activity as swimming/tennis...)
- Score above 11.6 roughly equivalent to oxygen consumption of 14 ml $O_2.kg^{-1}.min^{-1}$ (4 METs)

- ESC and ACC/AHA recommend using metabolic equivalent task

Table 4 Estimated energy requirements for various activities (modified after ref. 1). MET, metabolic equivalent task. 1 MET, oxygen consumption of 3.5 ml kg^{-1} min^{-1}

Can you ...
1 MET
• ... take care of yourself?
• ... eat, dress, or use the toilet?
• ... walk indoors around the house?
• ... walk a block or two on level ground at 2–3 mph (3.2–4.8) km h^{-1}?
• ... do light work around the house like dusting or washing dishes?
4 METs
• ... climb a flight of stairs or walk up a hill?
• ... walk on level ground at 4 mph (6.4 km h^{-1})?
• ... do heavy work around the house (e.g. scrubbing floors)?
• ... participate in moderate recreational activities (e.g. dancing, doubles tennis)?
>10 METs
• ... participate in strenuous sports (e.g. swimming, singles tennis, skiing)?

<u>Complications secondary to execise testing:</u>

Cardiac: Bradyarrhythmias

Tachyarrhythmias

Acute coronary syndrome

Heart failure

Hypotension, syncope, shock

Death (rare, 1:10 000)

Non-cardiac: Musculoskeletal trauma

Soft-tissue injury

Miscellaneous: Severe fatigue (malaise); dizziness; body aches; delayed feeling of illness

Indications for termination of exercise testing:

Absolute: ST-segment elevation (>1.0mm)

Drop in Systolic blood pressure > 10mmHg

Angina

CNS syncope

Signs of poor perfusion (cyanosis/pallor)

Sustained VT or other arrhythmias

Technical difficulties

Subject request to stop

Relative: ST displacement (horizontal/down sloping>2mm)

Drop in Systolic BP>10mmHg

Increasing chest pain

Fatigue, shortness of breath, wheezing, leg cramps, claudication

Arrhythmias other than above, bundle-branch blocks

Exaggerated hypertensive response (systolic BP>250 mmHg, diastolic BP>115mmHg)

Stress Imaging Modalities and Exercise Testing

Provides greater diagnostic accuracy than ECG testing alone:

- Location and amount of ischemic myocardium and LV function
- Relative lack of increase in perfusion in myocardium supplied by stenotic coronary arteries relative to areas with normal flow augmentation
- Metabolic or functional consequences to mismatch between oxygen supply and demand (exercise induces ischemia)
- Helpful if angina or potential angina occurs as a limiting symptom in patients during exercise testing with subthreshold HR

Pharmacological agents:

1. Dobutamine:
- Adrenergic agents: increase myocardial oxygen demand (contractility, HR, BP)
- Monitoring: ECG, HR, BP
- Primary endpoints: target HR 85% of age predicted maximum
- Dobutamine stress echocardiography (DSE) where transthoracic echocardiography is used to detect stress induced myocardial ischaemia in the form of new or worsening ventricular wall motion abnormalities. The test has a sensitivity of 85% and specificity of 80%. (A myocardium that shows no response to dobutamine has a very poor prognosis)
- DSE compared to thallium imaging: DSE superior in predicting cardiac events, better predictor of uneventful peri-operative period, favoured test for detection of LV dysfunction

2. Adenosine/Selective A2a adenosine receptor agonists (Dipyridamole):
- Coronary vasodilation in normal epicardial arteries

- Coronary arteries with metabolically significant stenosis already recruit vasodilator reserve at rest due to autoregulation, therefore cannot increase flow as much as normal coronaries
- Relative lack of increased perfusion visualized with nuclear myocardial perfusion agents (mostly dipyridamole-thallium imaging) (sensitivity 85%, specificity 80%)

3. Nuclear Myocardial Perfusion Imaging:

- Stress myocardial perfusion imaging: single-photon emission computed tomography (SPECT) or positron emission tomography (PET) (sensitivity 87-90%, specificity 73-89%)
- Myocardial perfusion images at rest and during stress displayed as tomographic slices in 3 different views to visualise all myocardial segments
- Perfusion defects present during exercise but not at rest indicate myocardial ischemia
- Perfusion defects present during exercise and persist at rest suggest previous MI

4. Cardiac Magnetic Resonance Imaging and Computed Tomography:

- Increased usage due to technological advances
- With or without pharmacological agents (vasodilator to assess perfusion or dobutamine stress to assess regional myocardial function)

Prognostic value of exercise capacity

Exercise capacity is the most powerful predictor of survival. In addition to assisting with the diagnosis of CAD, assessing myocardial viability before revascularization and prognostication post-MI, it is extremely valuable in evaluating cardiac risk before noncardiac surgery.

Many regard CPX as a superior means to assess exercise performance, because gas exchange measurements provide detail about VO_2 max, ventilator responses and level of effort.

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Epidural (& other neuraxial) labour analgesia

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Currently, we can offer no better form of pain relief to labouring parturients than neuraxial analgesia. But in 2015, there should be no such thing as a "one-size-fits-all", generic approach. The specific technique and choice of drugs should be individualised for each parturient, taking into account factors including her parity, stage and phase of labour, use of intravenous oxytocin, the presence of any coexisting disease(s), as well as the status of the fetus.

The nature of labour pain:

1st stage	- distension of lower uterine segment and cervix - transmission by *visceral* afferents accompanying sympathetic fibres - spinal cord entry at T10, 11, 12, L1
Late 1st stage & 2nd stage	- as above, but superseded in severity by vaginal and perineal distension, ischaemia & frank injury - *somatic* impulses transmitted via pudendal nerve - enter spinal cord at S2-4

Benefits of epidural labour analgesia

- pain relief & birth satisfaction greater than with nonpharmacologic methods, TENS, systemic opiates, Entonox
- lower maternal plasma catecholamines- may improve uteroplacental perfusion & uterine activity
- blunting of maternal "hyperventilation-hypoventilation" cycle, with better fetal oxygen delivery
- better neonatal acid-base status compared with systemic opiates, and less respiratory assistance required at birth
- lower paternal anxiety, & greater paternal involvement & satisfaction with birth process
- facilitation of rapid establishment of epidural *anaesthesia* for emergency caesarean delivery (CS); safer overall than emergency GA for CS

Indications for epidural labour analgesia

- maternal request for pain relief in labour, including early labour, is a sufficient medical indication, in the absence of contraindications
- facilitation of atraumatic vaginal delivery of breech presentation, twins, the preterm infant
- blood pressure control in pre-eclamptics
- blunts haemodynamic effects of contractions (e.g. sudden preload increase) and pain response (↑HR, ↑SVR, ↑BP, ↑RR) which is beneficial for patients with comorbidities e.g. mitral stenosis, SCI, asthma, intracranial neurovascular disease)

The analgesia plan *must* be a collaborative effort between anaesthetist, obstetrician, patient and midwifery staff.

Contraindications

Patient refusal or lack of cooperation
Raised ICP
Infection at site of needle entry
Frank coagulopathy
Recent pharmacologic anticoagulation
Uncorrected maternal hypovolaemia
Inadequate training or experience
Inadequate resources- monitoring & resuscitation

Most cases of properly-treated systemic infection, pre-existing neurologic disease and cardiac disease (including stenotic valvular lesions) do not preclude epidural analgesia, though they are regarded as relative contraindications by some. An individual risk-benefit assessment must be performed for each patient.

Preprocedural assessment and informed consent

The evaluation must include;

1) review of obstetric history, medical history and past anaesthetic history
2) focused physical examination (vitals, CVS, resp, airway, back)
3) review of relevant lab tests (routine platelet count not necessary) & radiological studies
4) assessment of fetal well-being with obstetrician
5) ascertaining availability & competence of attending nursing staff
6) checking routine and emergency resuscitation equipment

Informed consent must comprise an honest explanation of the procedure(s), impact on labour and delivery, the risks and benefits, and financial implications. Most pregnant women want to know about the possible complications, including the rare ones. The OAA (Obstetric Anaesthetists' Association) has published a patient information booklet called Pain Relief in Labour (also available as a smartphone app) which includes what information to convey and the risk of complications.

There has been concern that labouring parturients, who may be anxious, in extreme pain or sedated by recent opiate administration, are not able to understand the information being conveyed. Whilst such information is best provided in the antenatal period, adequacy of consent may be assumed if there is written documentation of what was discussed, the patient has signed her consent in the presence of two witnesses, and has cooperated with the procedure without objection.

Types of neuraxial labour analgesia

Continuous epidural and combined spinal-epidural labour analgesia are by far the most widely used in modern practice.

1) Epidural analgesia
- Continuous lumbar epidural analgesia is most well-established technique
- Catheter placement allows for conversion to epidural anaesthesia for CS
- Initiation is by bolus injection of drug(s); maintenance is by anaesthesia provider- or patient- administered intermittent bolus injections or continuous infusion, or both
- Catheter removed after delivery when there is no further analgesic or anaesthetic requirement

2) Combined spinal-epidural analgesia (CSE)
- Growing popularity over past 15 years; analgesia initiated with an intrathecal injection of opiate alone or opiate combined with a small dose of local anaesthetic (LA), and maintained via the epidural catheter
- Most common CSE technique is needle-through-needle technique in a midlumbar interspinous space (note that the tip of the small non-cutting spinal needle must protrude 12-17mm beyond the end of the epidural needle when the two are fully engaged); alternately, the spinal needle and epidural needle and catheter are introduced sequentially at two different interspaces
- <u>Advantages</u>: (a) Significantly faster onset of complete analgesia than with lumbar epidural (2-5 mins vs 10-15 mins)
  (b) Rapid onset of sacral analgesia vs lumbar epidural- useful if initiating analgesia late in the first stage or in a parous patient whose labour will progress quickly
  (c) Allows provision of complete analgesia in the early first stage of labour with the sole use of a lipid-soluble opiate; no LA, so no motor block & less hypotension- allows safe ambulation & ideal for patients with preload-dependent cardiac lesions
  (d) Lower maternal, fetal, and neonatal plasma concentrations of anaesthetic agents
  (e) May lower the incidence of failure of epidural analgesia, and increases the likelihood of successful epidural anaesthesia for CS fivefold compared with pure lumbar epidural catheter placement

- Disadvantages: (a) concern for higher risk of postdural puncture headache; no apparent increased risk if small-gauge pencil-point needle used
  (b) small risk of meningitis with dural puncture in labour
  (c) intrathecal opiates cause more pruritus than epidural opiates
  (d) inability to test correct placement & functionality of epidural catheter for first 1-2 hours whilst spinal component working- not the best technique if a functioning epidural catheter is critical to the safe care of the patient (e.g. difficult maternal airway, non-reassuring fetal heart trace)
  (f) possible higher risk of fetal bradycardia- aetiology may be related to an acute reduction in circulating maternal catecholamines esp. adrenaline which is a tocolytic, resulting in uterine hypertonicity

3) Continuous spinal analgesia
   - Seldom employed because available catheters require dural puncture with a large-gauge introducer needle, resulting in a high risk of PDPH, but a potential strategy when there has been accidental dural puncture.
   - Possibility of overdose and total spinal anaesthesia if epidural doses are accidentally administered through the spinal catheter
   - FDA withdrew approval for the use of spinal microcatheters less than 24-G after a series of 11 non-obstetric patients developed cauda equina syndrome after their use (possibly due to the pooling of hyperbaric lignocaine)

4) Continuous caudal analgesia
   - Technically more difficult than other neuraxial techniques, with possible higher infectious risk
   - In advanced labour, there is the risk of accidental rectal or fetal injection
   - Large volumes of LA are required to achieve low thoracic blockade, with resultant higher maternal plasma concentrations achieved
   - Allows access to the lumbar spinal canal in patients who have had lumbar vertebral fusion

5) Single-shot techniques
   - Whether spinal, epidural or caudal, the major disadvantage of single-shot techniques are their limited duration
   - They may be considered when vaginal delivery is imminent

Side effects of neuraxial labour analgesia

Hypotension - incidence of 14% after initiation of analgesia
- no difference in incidence between low-dose EA and CSE
- preload administration is not helpful as prophylaxis
- usually easily treated with IV fluid, positioning & vasopressors

Pruritus - common after neuraxial opiate; worse via intrathecal than epidural route
- dose-dependent; mediated through central μ-opioid receptors
- usually self-limiting & reduces dramatically over 1st hour
- if treatment required, naloxone, naltrexone or nalbuphine effective

Nausea and vomiting - common in labour; must exclude neuraxial analgesia-induced hypotension
- nausea incidence 1.0% with epidural opiate & 2.4% with intrathecal opiate
- metoclopramide, droperidol & ondansetron used prophylactically

Fever - a small subset of women receiving epidural analgesia show a rise in core temperature within an hour of epidural initiation, and go on to develop fever
- likely an inflammatory process; often histological placental inflammation
- associated with higher rates of CS & instrumental vaginal delivery
- associated with more neonatal sepsis work-up but no increase in sepsis

- growing evidence that maternal inflammation, manifesting as fever, may damage the neonatal brain (risk of seizures, encephalopathy, CP)

Shivering - may occur more commonly after epidural analgesia

Urinary retention –

Recrudescence of herpes simplex virus –unknown whether epidural or intrathecal opiate use in labour increases the incidence of oral HSV reactivation after vaginal delivery, as has been observed after caesarean section

Delayed gastric emptying - this can occur with 25µg intrathecal fentanyl, or with an epidural *bolus* of fentanyl (50-100µg) or after prolonged epidural infusion

Complications of neuraxial analgesia

Inadequate analgesia - failure rate varies according to definition of failure
- rate of failed analgesia significantly lower after CSE than epidural analgesia (10% vs 14%)

Unintentional dural puncture - occurs at a rate of 1.5%
- choice of re-siting the epidural at another interspace, or threading a catheter into the subarachnoid space and providing continuous spinal analgesia

Respiratory depression - time to onset, and duration, of any respiratory depression following neuraxial opioid administration depends on whether the drug is lipid- or water-soluble
- dose is a major determinant of risk
- previous parenteral opioid administration is a risk

Intravascular injection of local anaesthetic - occurs at a rate of 1:5000 labour epidurals
- ASRA & AAGBI include lipid emulsion in their guidelines for managing LAST

High block and total spinal anaesthesia - published series suggest an incidence somewhere between 1:1400 and 1:16,200 attempted labour epidurals

Extensive motor blockade – may occur after repeated bolus doses or after a prolonged infusion of LA;
- commoner when adrenaline added to the LA solution
- tends not to be a problem when very dilute LA + opioid solutions are used

Prolonged block - again, usually a feature of prolonged infusions of high concentrations of LA with adrenaline; epidural haematoma & peripheral nerve injury must be excluded

Sensory changes -reported after the sole administration of intrathecal opiate for CSE; the opiate causes neither sympathectomy nor motor block, but may block afferent information from A-delta and C-fibres to the spinal cord, resulting in unpleasant symptoms for the patient, e.g. the feeling of being unable to breathe or swallow

Back pain -a number of prospective studies have shown no causal relationship between epidural analgesia and long-term postpartum backache; patients may suffer short-term backache for a few days related to needle trauma at the site of epidural placement

Pelvic floor injury -although epidural analgesia increases the risk of instrumental vaginal delivery (see later), which might be expected to heighten the risk of pelvic floor injury & dysfunction, the very few studies done thus far have not shown this to be the case.

Impact of neuraxial analgesia on labour outcomes

Effect on the duration of labour:

The effect on the duration of the **1st stage of labour** seems variable. Any prolongation is short, has no adverse maternal or fetal effects, and is likely to be clinically insignificant.

There is definitely a prolongation of the **second stage of labour**, with a mean duration 15-20 minutes longer for women receiving epidurals rather than systemic opiates or no analgesia. This is more pronounced in nulliparous than parous parturients. The American College of Obstetricians and Gynecologists has recognised this effect in developing guidelines for the management of delayed second stage of labour: second-stage arrest is defined as no descent or rotation of the fetal head for ≥ 4 hours in nullipara with EA, ≥ 3 hours in nullipara without EA, ≥ 3 hours in parous women with EA and ≥ 2 hours in parous women without EA. Sometimes the anaesthetist is asked to stop the epidural because the woman is fully dilated but is not experiencing the urge to bear down. If the fetal head has not yet descended, there is no sense in doing so. Once the fetal head is on the perineum with the mother still not feeling the urge to push, it is reasonable to slow the epidural maintenance rate. It is very unusual to need to stop the epidural entirely, and it may then be very difficult to re-establish the block quickly if CS becomes necessary.

Epidural analgesia does not prolong the **third stage of labour**.

Effect on caesarean delivery rate

There has been a strong perception amongst gynaecologists, midwives (and also anaesthetists) that epidural analgesia leads to a higher caesarean section (CS) rate. A number of large RCTs have examined the effect of neuraxial (mainly epidural) analgesia and systemic opiate (mainly pethidine) analgesia on the CS rate. Methodology and inclusion criteria differed in a number of ways, but the vast majority of these studies found no significant difference in the caesarean delivery rate between women randomised to receive either epidurals or systemic opiates. When the data was analysed on an intention-to-treat basis, any difference in the caesar rates between groups was eliminated. Impact studies, where an epidural service is upscaled from a particular date, whilst all other aspects of obstetric practise remain unchanged, have also shown no difference in the CS rate before and after the change.

The COMET (Comparative Obstetric Mobile Epidural Trial) study published in The Lancet in 2001 showed no significant difference in the CS rate between three groups of patients receiving neuraxial labour analgesia: (1)traditional “high-dose” epidural with 0.25% bupivacaine, (2)“low-dose” epidural with bupivacaine 0.1%/ fentanyl 2mcg.mL^{-1}, and (3)“low-dose” CSE (intrathecal bupivacaine/fentanyl followed by intermittent epidural boluses of bupivacaine 0.1%/fentanyl 2mcg.mL^{-1}. So, the mode and density of the neuraxial block does not affect the risk of CS.

There is high-quality evidence showing no difference in caesarean section risk whether epidural labour analgesia is initiated early in labour (before 4-5 cm of cervical dilatation) or later on in labour.

So why is/was there this perception amongst our colleagues? Studies suggest that women who experience severe pain from early on in labour, and who require a lot of analgesia, are at higher risk for abnormal labour, fetal heart trace abnormalities and CS. These women are more likely to request epidurals or be identified by their caregivers as needing the best form of analgesia on offer, namely an epidural. They already have risk factor(s) for CS and epidural administration can unfortunately not alter this risk.

Effect on instrumental vaginal delivery rate

The many studies into this subject have provided conflicting results. The density of the neuraxial block probably does have a bearing on the outcome of labour. The higher the concentration of epidural LA and dose of LA received, the greater is the maternal motor blockade. Motor block results in pelvic floor muscular relaxation which may impair the rotation of the fetal head as it descends. Weakness of the mother’s abdominal muscles will also negatively impact on her ability to push. An *effective* block during the second stage increases the risk for instrumental vaginal delivery (forceps or vacuum extraction).

Impact of neuraxial analgesia on fetal outcomes

Effects of neuraxial anaesthesia on the fetus may be direct, indirect, or both. *Direct effects* occur by maternal systemic absorption of the drugs used and their transplacental transfer. They include intrapartum drug effects on the fetal heart rate (FHR) and possible neonatal respiratory depression.

Published data suggest that epidural local anaesthetics and opioids have little, if any, direct effect on FHR. Epidural opioids administered by continuous infusion seldom accumulate and as a result neonatal respiratory depression is rare and adverse effects on neurobehavioural scores have not been encountered.
Indirect effects occur as a result of the effects of neuraxial blockade on the mother, and these are neuraxial analgesia. With rapid onset of analgesia, the concentrations of circulating catecholamines, that usually have a uterorelaxant effect on uterine β_2-adrenergic receptors, are reduced. This may result in increased uterine tone (uterine tachysystole), with decreased uteroplacental perfusion and fetal hypoxia. This effect appears to be more marked with CSE than with epidural analgesia.
Fortunately, fetal bradycardia after labour analgesia does not seem to increase the overall risk for poor outcome nor the need for caesarean delivery. The FHR must be monitored during and after the administration of intrathecal or epidural labour analgesia.
Effects on breastfeeding: Two recent studies have shown that low-dose LA /low-dose fentanyl epidural labour analgesia regimens do not clinically affect either the initiation of, or the duration of, breastfeeding.

Drug choices for neuraxial labour analgesia

Contemporary epidural labour analgesia practice usually incorporates low doses of a long-lasting local anaesthetic combined with a lipid-soluble opioid. This allows lower doses of each to be employed, thus reducing the side-effects of each. The addition of the opioid decreases latency, prolongs the duration of analgesia, improves the quality of analgesia and reduces shivering.

Local anaesthetics
Different drugs may be compared with respect to potency:- *MLAC (minimal local anaesthetic concentration)* = median effective concentration of LA solution when administered as a 20-mL epidural bolus; increases as labour progresses; lowered by addition of a lipid-soluble opioid. Bupivacaine is more potent than ropivacaine.
The same drug may be compared at different concentrations:- *MLAV (minimal local anaesthetic volume)* and *MLAD (the minimal local anaesthetic dose)* are the median effective volumes and doses of two different concentrations of the same epidural local anaesthetic given as the first bolus to women for analgesia in labour, e.g. bupivacaine 0.125% produces equivalent analgesia to bupivacaine 0.25%, with a 50% increase in required volume and a 25% reduction in dose, i.e. there is a dose-sparing effect when one administers a more dilute solution.
Epidural analgesia and safety are improved when low concentration-high volume LA solutions are used for initiation and maintenance.

Opioids
Lipid-soluble opioids such as fentanyl and sufentanil are preferred over water-soluble drugs like morphine because of their much more rapid onset. Their action is primarily at the spinal level. The potency ratio of epidural sufentanil to fentanyl is approximately 6:1. The major maternal side-effect is pruritus. There is no adverse effect on neonatal outcomes with the use of lower doses.

Adjuvants: limited role currently

1) Epinephrine – shortens latency, reduces MLAC & prolongs duration of epidural LA analgesia
   - systemic absorption may ↑ maternal HR & transiently ↓ uterine activity
   - no adverse effects on intervillous blood flow
   - disadvantages: *increases intensity of motor block* & risk of drug errors
2) Clonidine – potentiates both quality & duration of epidural LA analgesia, with no additional motor block; may be useful for breakthrough pain with a functioning catheter
   - In the US, its epidural use in obstetrics carries a black box warning because of the risk of bradycardia and hypotension

- maternal sedation is a side-effect
- FHR changes with higher doses

Neostigmine – no real benefit as epidural adjuvant, unless combined with clonidine

- further studies needed to elucidate its role, if any

The epidural test dose:

This is an initial dose of LA and/or adrenaline used to help identify unintentional placement of the epidural catheter in an epidural vein or the subarachnoid space. Enough must be given to allow the recognition of intravenous or subarachnoid injection but not so much as to cause systemic toxicity or total spinal anaesthesia. Intravascular placement of the epidural catheter may occur in as many as 7% to 8.5% of obstetric patients.

A suggested combined intrathecal and intravenous test dose comprises 3 mL of a lignocaine 1.5% + adrenaline 5 mcg/mL (1: 200,000) mixture. An alternative is 3 mL of a bupivacaine 0.25% + adrenaline 5 mcg/mL mixture. A positive intravascular result is a heart rate increase of 20 bpm within one minute. A positive intrathecal result is motor blockade with weakness in hip flexion at 3-5 minutes.

The argument against using an adrenaline-containing test-dose:

1) Possibility that I.V. injection of adrenaline may decrease uteroplacental perfusion and precipitate fetal compromise. However, there has been no report of adverse neonatal outcome after intravenous injection of an epinephrine-containing test dose
2) .Aspiration of multi-orifice catheters is 98% sensitive in identifying their intravascular location. (The sensitivity of aspiration is significantly lower for single-orifice catheters.)
3) The epidural test dose contributes to undesirable motor blockade.
4) Because modern epidural labour analgesia involves the infusion of a low concentration of LA solution, unintentional intravascular or intrathecal administration is not likely to result in cardiovascular collapse or total spinal anaesthesia.
5) A single test dose cannot exclude subsequent migration of the catheter into a vessel or the CSF. For that reason, one should aspirate before giving each dose of local anaesthetic, and never inject more than 5 mL of LA as a single bolus.

The argument for using a test dose:

1) Large volumes of a concentrated LA solution are still routinely administered for emergency caesarean delivery.
2) It is easier for the parturient and anaesthetist to identify a misplaced catheter at the time of initial placement and to replace the catheter at that time rather than identify the misplaced catheter after the sterile field has been breached and the parturient repositioned.

If an adrenaline-containing test dose is used, it should be given immediately after a uterine contraction so there is less confusion as to whether tachycardia is caused by pain or intravenous adrenaline. In labouring women, cyclic changes in maternal heart rate may complicate interpretation of its effects.

Drugs used for initiation of epidural and spinal labour analgesia

Drug	**Epidural analgesia***	**Spinal analgesia**
Local anaesthetics		
Bupivacaine	0.0625% - 0.125%	1.25 – 2.5 mg
Ropivacaine	0.08% - 0.2%	2.0 – 3.5 mg
Levobupivacaine	0.0625% - 0.125%	2.0 – 3.5 mg
Opioids		
Fentanyl	50 – 100 mcg	15 – 25 mcg#
Sufentanil	5 – 10 mcg	1.5 – 5 mcg#

***The volume required to initiate epidural labour analgesia is 10 – 15 mL of LA solution

Opioids may be administered without local anaesthetics when spinal analgesia is induced in early labour. Women in active labour need a higher dose than women in latent labour.

Anaesthetic solutions used for maintenance of epidural analgesia: Continuous infusion or PCEA*

Drug#	**Concentration**
Local anaesthetics	
Bupivacaine	0.05 – 0.125%
Ropivacaine	0.08 – 0.2%
Levobupivacaine	0.05 – 0.125%
Opioids	
Fentanyl	1.5 – 3 mcg/mL
Sufentanil	0.2 – 0.4 mcg/mL

*Local anaesthetic is usually combined with an opioid

#Continuous infusion rate into lumbar epidural space = 8- 15 mL/hr

Administration techniques for maintenance of epidural analgesia

1) Intermittent bolus (manual top-ups): This was the first means by which epidural analgesia was maintained & predated the development of infusion pumps. Its major disadvantage is that regression of pain relief is the trigger for further top-ups, & severe pain may be experienced if there are delays in further drug administration
2) Continuous infusion (CEI). This popular technique is advantageous in a busy labour ward, as it lengthens the time between bolus rescue injections and leads to greater patient satisfaction. A CEI technique leads to a larger total dose of LA being given than the intermittent bolus technique, but an advantage is that over time reasonable perineal analgesia usually develops. The downside of a prolonged infusion is possible development of a significant motor block, unless very low LA concentrations are employed.
3) Patient-controlled epidural analgesia (PCEA) PCEA is a mode of epidural drug delivery that allows patients to administer intermittent boluses of epidural maintenance solution. This provides individual flexibility to accommodate the escalating analgesic requirements as labour progresses or with the commencement of labour augmentation regimens. PCEA programme settings such as demand bolus, lockout interval, basal infusion rate and hourly maximum dose limits are set by the anaesthetist. The use of PCEA has been shown to reduce the total volume of LA solution used without compromising the quality of analgesia, resulting in a lower incidence of side-effects and greater maternal satisfaction with labour analgesia than with CEI.
4) PCEA with basal infusion: Various studies and a large meta-analysis show that PCEA with a basal infusion results in better analgesia and patient satisfaction than PCEA alone, and may reduce the incidence of breakthrough pain requiring the anaesthetist's intervention. A high-rate basal infusion (≥5mL/hr) appears to be more effective than a low-rate (≤4mL/hr) basal infusion.

Sample PCEA settings (using anaesthetic solutions shown in above table)			
PCEA technique	**Basal infusion rate (mL/hr)**	**Bolus dose (mL)**	**Lockout interval (minutes)**
Without background infusion	0	8-12	10-20
With background infusion	4-8	5-8	10-15

5) Automated intermittent bolus techniques: Automated intermittent mandatory boluses (AMB) or continuous intermittent boluses (CIB) are automated systems regulated to administer an epidural bolus (5 to 10 mL every 30-60 minutes) at programmable intervals. The hourly total amount of LA solution normally used in a CEI is administered as intermittent boluses. Studies have shown that PIEB resulted in longer duration of analgesia, higher maternal satisfaction,

less need for unscheduled rescue boluses and a reduced consumption of L.A. when compared with CEI. Some reasons may explain these findings:
• The high-driving pressure generated to inject a bolus may result in a more uniform spread of the solution in the epidural space.
• With the use of multi-orifice epidural catheters, solutions injected as a bolus exit the catheter through all the orifices resulting in a wider spread, as opposed to solutions injected as infusion, which exit only through the proximal orifice.
Some clinicians have combined PCEA with AMB or CIB.

6) Computer-integrated PCEA
This is a new technique, described by described by Sia et al. They have developed a clinical algorithm which allows a PCEA pump to automatically adjust its basal infusion rate based on the patient's PCEA requests over the past hour. CIPCEA has been developed to meet the requirement for higher doses of anaesthetic solution as labour progresses. It has been found that women receiving CIPCEA have similar LA consumption compared with demand-only PCEA, but have a lesser incidence of breakthrough pain and are more satisfied.

Despite numerous epidural regimens to alleviate labour pain, there are no definitive regimens that have been shown to be the optimal system to reduce breakthrough pain or clinically significant outcomes such as instrumental or caesarean delivery. Individualized analgesic regimens utilizing modern drug delivery systems, especially the use of programmed or automated boluses, may have a significant impact in improving patient satisfaction with epidural analgesia.

The concept of the "walking epidural"

"Walking epidurals" were first described by Collis and Morgan from Queen Charlotte's Hospital in London in 1993. By using low-dose CSE opioid analgesia, motor function was maintained and the ability to walk was not impaired. In fact, the term applies to *any* neuraxial technique where the parturient can ambulate safely. This was popularised in the lay press, despite ambulation having no impact on the progress or outcome of labour, and studies showing that most women prefer to rest in bed once their CSE or low-dose epidural is working!

Studies employing computerised dynamic posturography, a sophisticated method of individually assessing the relative contributions of somatosensory, visual and vestibular inputs to maintain accurate balance, have shown that pregnancy in itself affects balance, but that low-dose CSE analgesia has no further negative impact in the majority of women, provided that a concentrated test-dose of local anaesthetic is avoided. As the cumulative dose of LA given through the epidural component increases over the course of labour, a significant motor block may develop, and that is the reason why the ability to walk safely should be tested each time before the woman gets out of bed. The following criteria must be met before ambulation during labour with neuraxial analgesia is permitted:

1) Reassuring fetal status
2) Engagement of fetal presenting part
3) Stable orthostatic vital signs (within 10% of baseline)
4) Ability to perform bilateral straight-leg raises in bed against resistance
5) Ability to step up on a step stool with either leg taking the first step, without assistance
6) Satisfactory trial of walking accompanied by a nurse or midwife
7) Patient to be accompanied by a companion at all times
8) Intermittent FHR monitoring (every 15 minutes)

The benefits of a walking epidural lie in the minimisation of motor blockade, as a dense motor block may adversely affect the likelihood of spontaneous vaginal delivery. Giving the patient the least

possible motor block should be an important goal whenever neuraxial labour analgesia is provided, whether or not the patient has expressed the desire to walk about.
Some typical CSE regimens are given below:
- Spinal dose = 2.5 mg bupivacaine + 25 mcg fentanyl; epidural dose = 0.1% bupivacaine + 2mcg/ml fentanyl (15 ml intermittent bolus or 8-15 ml/h infusion) / **Queen Charlotte's Hospital Regimen**

- Spinal dose = 2.5 ml of epidural mixture (0.1% bupivacaine + 2 mcg/ml fentanyl) = 2.5 mg bupivacaine + 5 mcg fentanyl; epidural dose = as above / **Royal Free Hospital Regimen**

- Spinal dose = 2.5 mg bupivacaine + 5 mcg sufentanil; epidural infusion of 0.0625% bupivacaine + 0.25 mcg/ml sufentanil at 10-12 ml/h

Epidural labour analgesia in women attempting vaginal birth after caesarean delivery (VBAC):

There were 2 concerns related to the provision of epidural analgesia to women attempting VBAC:

1) EA might mask the pain of uterine scar separation or rupture and thereby delay the diagnosis of uterine rupture
2) The sympathectomy associated with EA might attenuate the maternal compensatory response to the hemorrhage associated with uterine rupture.

Consensus now exists that these concerns do not preclude administration of neuraxial analgesia during attempted VBAC, for several reasons:

1) Pain, uterine tenderness, and tachycardia have low sensitivity as diagnostic symptoms and signs of lower uterine segment scar dehiscence or rupture. Scar dehiscence may be painless.
2) Pain, uterine tenderness, and tachycardia have low specificity as diagnostic symptoms and signs of lower uterine segment scar dehiscence. Also, it has been suggested that the unexpected development of breakthrough pain during previously successful epidural analgesia might be indicative of uterine rupture, and this phenomenon is called the "epidural sieve."
3) Most cases of lower uterine segment scar dehiscence do not lead to severe haemorrhage. However, if significant bleeding should occur, epidural anaesthesia may attenuate the maternal compensatory response to haemorrhage, and so prompt intravascular volume replacement is required in this instance.
4) Several published series have reported the successful use of epidural analgesia in women undergoing VBAC. There is little evidence that epidural analgesia either decreases the likelihood of vaginal delivery or adversely affects maternal or neonatal outcome in women who have uterine scar separation or rupture.
5) Some obstetricians favour the use of epidural analgesia because it facilitates postpartum uterine exploration to assess the integrity of the uterine scar.
6) Epidural analgesia provides rapid access to safe, surgical anaesthesia if caesarean delivery or postpartum laparotomy should be required.
7) Adequate pain relief may encourage more women to choose VBAC. Thus, the availability and use of neuraxial analgesia may decrease the incidence of unnecessary repeat caesarean delivery.

The ACOG's position is that good scientific evidence supports a conclusion that epidural analgesia may be used during VBAC.

Assessment and management of inadequate neuraxial analgesia (from Chestnut, 5th ed. pg. 485)

1) Assess progress of labour:
   - Rule out other causes of pain (distended bladder, ruptured uterus).
2) Perform an honest evaluation of the anaesthetic:
   - Is the catheter really in the epidural space?
   - If in doubt, replace the catheter.
3) If the catheter is in the epidural space, but the extent of neuroblockade is inadequate (does not extend from T10 to S4, as is required for late labour):
   - Inject a dilute solution of local anaesthetic (5 to 15 mL), with or without an opioid.
   - Alter maintenance technique (e.g., increase volume, decrease concentration).
   - If this manoeuvre is unsuccessful, replace the catheter.
4) If catheter is in the epidural space, but the block is asymmetric:
   - Inject a dilute solution of local anaesthetic (5 to 15 mL), with or without an opioid.
   - Alter maintenance technique (e.g., increase volume, decrease concentration).
   - Place the less-blocked side in the dependent position.
   - If this manoeuvre is unsuccessful, replace the catheter.
5) If the catheter is in the epidural space, but the patient has breakthrough pain despite adequate extent of neuroblockade:
   - Inject a more concentrated solution of local anaesthetic, with or without an opioid.
   - Alter maintenance technique (e.g., increase concentration of local anaesthetic).

Anaesthesia/analgesia for vaginal delivery

A more concentrated solution or larger volume of epidural local anaesthetic is required to provide sacral analgesia/anaesthesia for the second stage, especially if the obstetrician needs to perform an episiotomy and instrumental delivery, but this unfortunately comes with the price of more extensive motor blockade just when the mother needs to be able to push. If epidural analgesia is not adequate for the second stage of labour and delivery, the anaesthesia provider can give additional doses of local anaesthetic to augment perineal analgesia, as suggested below:

1) Lumbar epidural catheter already in situ:
   - Supplement existing analgesia with 5 to 10 mL of 1% or 2% lignocaine
2) Spinal Anaesthesia
   - Intrathecal injection of hyperbaric bupivacaine 6 to 8 mg or hyperbaric lignocaine 25 to 50 mg.
   - Administer a larger dose for a “trial of forceps” in case caesarean delivery is necessary.
3) Combined Spinal-Epidural Anaesthesia
   - Intrathecal injection of bupivacaine 2.5 to 5 mg with fentanyl 15 to 25 mcg.
   - Follow with administration of additional drug(s) via epidural catheter if anaesthesia is inadequate.

Extension of epidural labour analgesia to surgical anaesthesia for caesarean delivery

The choice of LA agent used will depend on the urgency of the case. Lignocaine 2% with adrenaline gives a more rapid onset than bupivacaine/levobupivacaine 0.5%, or ropivacaine 0.75%. Extension of epidural analgesia can be initiated as preparations are being made to move the patient from the labour ward to the operating room, but this practise is controversial. One of the factors in deciding whether to use the in situ epidural catheter for anaesthesia is the quality of the existing labour analgesia. If analgesia has been suboptimal with a unilateral or patchy block, replacing the catheter and using a

spinal or CSE technique may be a better method to attain rapid and effective anaesthesia. The incidence of failed conversion of labour analgesia to surgical anaesthesia is greater when a number of epidural boluses have been required to produce sufficient labour analgesia, a greater urgency for caesarean delivery exists, and a nonobstetric anaesthetist is managing the case.

Extension of a T10 level of analgesia to a T4 level of anaesthesia typically requires a volume of 15 to 20 mL of local anaesthetic with one or more adjuvants. Alkalinisation of the local anaesthetic solution not only increases the speed of onset but also improves the quality and prolongs the duration of neuroblockade, and is of particular value when a short-acting local anaesthetic like lignocaine is used.

Bupivacaine 0.5% may be used in increments of 5 mL; 15-20 mL is usually sufficient. This will take slightly longer (on average 20 minutes) to establish an effective block.
An alternative is to draw up 17mL 2% lignocaine, plus 50mcg fentanyl, 1mL 8.4% sodium bicarbonate, and 1mL 1:10,000 adrenaline (i.e. 1mL of an ampoule which has been diluted 10 times). This makes a total of 20mL, with approximately 1:200,000 adrenaline. Administer 5mL boluses after a test dose.

Unless the initial dose of epidural bupivacaine has been administered within the previous hour, treat as though the patient has no block at all. Conversion to spinal anaesthesia may result in a high block if there has been an unsuccessful attempt at a top-up with a large volume of local anaesthetic. A poorly functioning epidural catheter is best re-sited, and then CSE is a useful strategy, or spinal anaesthesia may be performed using a reduced dose (unpredictable, with the risk of a high spinal), or general anaesthesia may be preferred.

Newer techniques for localisation of the epidural space: Ultrasonography

Ultrasonography has an established place in peripheral nerve block placement, but is still less widely used for neuraxial labour analgesia. The reasons for this include the effectiveness of a landmark-based technique in the majority of patients, and the impracticality of ultrasound usage in real-time for epidural placement- there is the risk of contaminating the aseptic field, the procedure becomes unwieldy, and it is unknown whether U/S coupling jelly might have a harmful effect on neuraxial tissues.
It is useful for imaging epidural anatomy *prior* to epidural placement in situations of morbid obesity, abnormal spinal anatomy, previous spinal instrumentation or when specific interspaces must be avoided. It may help to identify the midline, locate the epidural insertion site, estimate the needle angle, and measure the skin-to-epidural space distance.
A low-frequency (2-5 Hz) curvilinear probe is used to achieve adequate depth of penetration, and to allow lateral structures to be visualised. Both transverse, median sagittal and paramedian sagittal views are used.

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The rational use of vasopressors and anti-cholinergics during spinal anaesthesia for caesarean section

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Haemodynamic instability during single shot spinal anaesthesia (SA) for caesarean delivery (CD) is the result of sympathetic blockade in a pregnant patient predisposed to aortocaval compression.

The splanchnic vasculature provides a major reservoir for venous return in the parturient. This blood returns to the inferior vena cava via the hepatic vein, above the level of potential aortocaval compression. During a state of hypovolaemia, typically after blood loss in obstetrics, the transmural pressure of the compliant splanchnic veins is predominantly above zero, due to activation of the sympathetic nervous system. The sympathectomy associated with SA would inhibit these compensatory changes, resulting in a marked decrease in venous return, due to a precipitous decrease in mean circulatory filling pressure.[1] This may result in cardiovascular collapse. SA is thus absolutely contraindicated in this situation. Even in the healthy parturient with her expanded blood volume, SA for CD is associated with hypotension, due to a combination of increased venous capacitance and decreased systemic vascular resistance (SVR). Since uterine blood flow is pressure dependent, hypotension results in a decrease in uterine blood flow and potential compromise to fetal oxygenation. Hypotension is commonly associated with unpleasant symptoms such as maternal nausea and vomiting, and cardiovascular collapse may rarely occur.

Potential haemodynamic responses to SA are:

- Hypotension and increase in heart rate.
- Hypotension and bradycardia.
- Persistent refractory hypotension.
- High motor block with cardiorespiratory failure.

These responses are influenced by:

- Aortocaval compression.
- The baricity and dose of local anaesthetic and opioid employed.
- The rational use of fluids.
- The goal-directed use of vasopressors.

For rational use of fluids and vasopressors, the practitioner should understand the maternal physiology and the haemodynamic effects of SA for CD.

Haemodynamic effects of aortocaval compression and spinal anaesthesia

Aortocaval compression

The association between arterial hypotension and the supine position in late pregnancy was first recognised by the Swedish obstetrician Ahltorp in 1931, as described in a review of the subject. The correct aetiology was described in 1951, and classic case reports alerted anaesthetists to the importance of avoiding this complication. Whilst cardiac output (CO) may be reduced in the supine position, most women respond with compensatory increases in systemic vascular resistance (SVR) and heart rate (HR). The result is that less than 20% of women experience arterial hypotension and the “supine hypotensive syndrome”.

Positioning during spinal anaesthesia

During SA for CD, CO has been shown to be greatly improved by a change from the supine to the left lateral position. CO is 5% higher if the patient is tilted >15 degrees, but as much as 34 degrees of lateral tilt may be necessary to completely eliminate the effects of aortocaval compression.

Haemodynamic effects of spinal anaesthesia

1 The typical response: hypotension and an increased heart rate

During SA, sympathetic blockade diminishes the compensatory mechanisms and results in a high incidence of clinically significant hypotension. Recent studies using continuous minimally invasive CO, have demonstrated a marked decrease in SVR and a baroreceptor- mediated increase in heart rate and partial compensatory *increase* in CO following SA, using pulse wave form analysis. In most women, the baroreceptor response is well preserved soon after induction of SA, despite sympathetic blockade. In keeping with findings in the non-obstetric population, where sympathovagal balance usually does not alter to complete vagal dominance during the sympathetic block associated with SA, sinus bradycardia is infrequent during SA for CD.

2 Hypotension and bradycardia

Sudden severe bradycardia may occur in a small percentage of patients, and occasional cardiac arrest has been described. The cause of the profound vagal activity that occurs in a small proportion of women is unknown, but it may be triggered by several different causes such as aortocaval compression, high block, emotional stress, peritoneal manipulation, or sudden haemorrhage. Reflex phenomena such as the pacemaker stretch-, Bezold-Jarisch (BJR)- and the “reverse” Bainbridge reflex may be causatory, but there is no strong evidence to support this theory. The BJR was initially described as a chemo-reflex: precipitous bradycardia followed the injection of toxic steroidal alkaloids into dogs’ coronary arteries. More recently,it has been postulated that there may be mechanical stretching during contraction of the poorly filled left ventricle, which results from a sudden decrease in venous return following induction of SA for CD, or in severe hypovolaemia. This may result in increased afferent input into the vasomotor centre via C-fibres in the inferoposterior wall of the left ventricle, followed by profound bradycardia and peripheral vasodilatation. The Bainbridge reflex was described in 1915. An infusion of saline into anaesthetised dogs produced tachycardia, on the basis of activation of stretch receptors in the atria. The “reverse” Bainbridge reflex has been proposed to explain slowing of the HR when venous return decreases. Whatever the mechanism, the final common efferent pathway is the vagus nerve, and the result is occasional profound bradycardia.

3 Persistent refractory hypotension

Having ensured adequate uterine displacement, hypotension resistant to vasopressors should raise the suspicion that either an error has been made concerning the volume status of the patient, or there is undiagnosed cardiac pathology. In low resourced areas, the diagnosis of valvular heart disease and cardiomyopathy may be missed in patients presenting close to term.

4 High motor block

This scenario is fortunately rare, of the order of 1/3000, or lower with currently used spinal doses of local anaesthetic. Therefore, when teaching SA for CD, it should be emphasised that cardiovascular instability requires immediate treatment, and is by far the more common scenario than high spinal

block. High motor block results in increasing dyspnoea and weak respiratory effort, followed by apnoea. Concomitant sympathetic block may result in cardiovascular collapse.

An editorial discusses the relative contribution of the venous and arterial circulation to spinal hypotension during CD. The point is made that despite careful attention to fluid management and positioning in order to minimise aortocaval compression, significant hypotension still occurs in a large percentage of patients, due to the effects of SA on the *arterial* circulation. The authors suggest that there is a "lesson" to be learned "from preeclampsia", in that one would expect greater haemodynamic instability in these patients if intravascular depletion and decreased venous return were the predominant contributor to spinal hypotension.[2] Research employing continuous pulse wave form analysis supports the contention that spinal hypotension is usually in large part due to effects on the *arterial* circulation during SA for elective CD.

As regards fluid administration during SA for CD:

- Crystalloid preload is not effective.
- Preload with crystalloid or colloid increases cardiac output but this does not reduce the incidence of arterial hypotension.
- Crystalloid coload is partially effective, and superior to crystalloid preload, however the benefit most likely depends on the volume of fluid infused (higher volume best) and the rapid administration of the fluid over the first 5-10 minutes after induction of SA, timed with the onset of the sympathectomy.
- Colloid coload is as effective as colloid preload.
- Colloid coload is equally effective – and possibly more effective – than crystalloid coload.
- Rapid, high volume crystalloid co-loading in combination with early administration of the appropriate vasopressor, is the favoured method of management of spinal hypotension.

Vasopressor use

Fluids alone are inadequate to treat spinal hypotension in 40 – 60% of cases. The most commonly used vasopressors worldwide are ephedrine and phenylephrine. The choice of vasopressor should be based upon a knowledge of the maternal haemodynamic effects of the agent, efficacy (preferably rapid onset and short duration), maternal and fetal side-effects.

Ephedrine is a slow onset and relatively long-acting, non-catecholamine, direct-acting β-receptor agonist, with indirect α-effects via noradrenaline release. The exact mechanism of action remains controversial; one study in a rat model suggested mainly indirect effects via noradrenaline release, and another supported direct α-effects. In either case, the fact that the uteroplacental circulation is relatively devoid of sympathetic innervation, suggests a resistance to uterine arterial vasoconstrictive effects of this agent. A dose response meta-analysis of prophylactic IV ephedrine for the prevention of spinal hypotension, suggested a dose of 12 mg as a balance between benefit as a vasopressor and risk of causing hypertension. Clinical disadvantages in terms of haemodynamic effects include a low efficacy for vasopressor effect, the development of tachyphylaxis to the pressor effects, and tachycardia and arrhythmias. The rapid onset α-1 agonist phenylephrine is also more effective for the reduction of nausea and vomiting during SA.

The basis for the long-established use of ephedrine as a first-line drug for the management of spinal hypotension in obstetrics, was a paper showing reductions of uterine blood flow in pregnant ewes following administration of α-agonists. However it has been shown in ewes that in pregnancy the uterine artery is less responsive to α-1 agonist stimulation than in the non-pregnant state. In the human haemochorial placental system, flow is very dependent upon pressure in the uterine arteries;

thus phenylephrine maintains flow by its predominant effect on the systemic arterial pressure, while causing relatively little uterine arterial constriction.

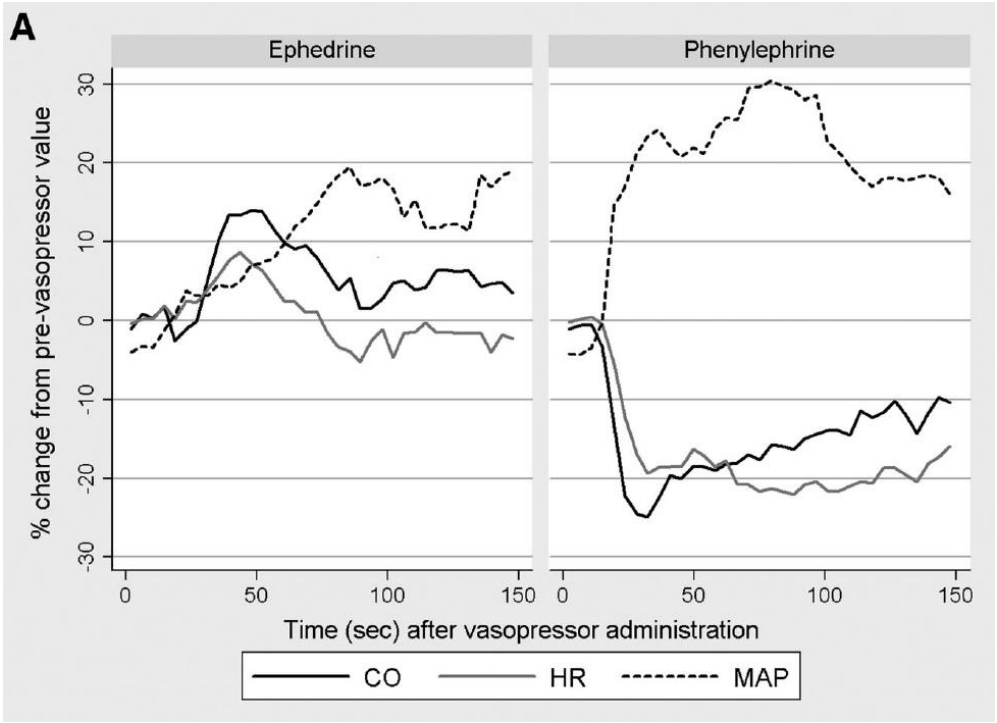
One of the further chief objections to ephedrine is the fetal acidosis associated with its use. The decreased umbilical arterial pH and increased base deficit have been attributed to an ephedrine-generated increase in fetal metabolic rate, evidenced by an increase in an umbilical arteriovenous PCO_2 difference in patients receiving ephedrine when compared with phenylephrine. Ephedrine also increases fetal catecholamine concentrations. Transplacental transfer of ephedrine is more efficient than that of phenylephrine. When large doses are used, umbilical arterial pH is lower, and base deficit and lactate significantly higher when ephedrine is used. Some neonates may have a genetic predisposition to fetal acidosis, based upon their ß-2 adrenoreceptor haplotype. Overall, both ephedrine and phenylephrine have been demonstrated to be safe for the fetus when used in healthy pregnant women in normal clinical doses. Minor increases in fetal metabolic rate may even be beneficial to the normal fetus; one investigation showed that neonatal respiratory rates were higher, and airways resistance lower in patients randomised to placebo than the β agonist terbutaline prior to elective CD. In non-elective caesarean sections, there are no significant differences in fetal acid base status after randomisation to phenylephrine or ephedrine. It is however possible that in compromised infants already at risk of acidosis and intrapartum hypoxia, large doses of ephedrine may have a clinically deleterious effect, particularly by virtue of increased fetal oxygen consumption.

Phenylephrine is a potent direct-acting α-1 agonist which has a rapid onset and is shorter acting by virtue of metabolism by monoamine oxidase. An excellent recent review discusses the effects of phenylephrine during obstetric SA.[3] A study comparing infusions of phenylephrine and ephedrine suggested a potency ratio of 80. Phenylephrine has a significantly shorter time to peak pressor effect than ephedrine (median 27 seconds vs. 78 seconds). A further study employing the LiDCO pulse wave form analysis system showed that baseline MAP was restored in approximately 40 and 90 seconds by phenylephrine and ephedrine IV boluses respectively. Two investigations employing noninvasive BP monitoring have examined the ED95 and ED90, respectively, of bolus phenylephrine, using up-down sequential allocation. The ED95 of phenylephrine has been found to be 137 and 159 µg for preventing hypotension and nausea respectively, but these doses are higher than those used by most clinicians.

Overall, the selection and method of administration of a vasopressor to prevent hypotension should therefore be based on the efficacy in preventing *maternal symptoms*, and the maternal *haemodynamic changes in response to SA*.[4]

There are few available data comparing maternal CO responses to ephedrine and phenylephrine during SA for elective CD. Two studies employing infusions of vasopressors, suggested that phenylephrine may depress maternal CO. A further study has demonstrated the effects on CO of bolus ephedrine and phenylephrine administered for spinal hypotension during elective caesarean section. Vasopressor was administered in response to a 20% decrease in mean arterial pressure, at which point SVR had decreased by 35% and HR and CO had increased from baseline pre-SA values (approximately 12 and 20% respectively). Phenylephrine reduced CO and HR to values approximating pre-SA baseline measurements, by reversing the SA-induced decrease in SVR and increase in CO (Figure 1). The study suggested that HR could guide phenylephrine dosing, in that HR correlated strongly with CO.[5] In most cases, simply titrating phenylephrine to maintain the baseline HR will thus restore BP and CO. When this typical response to SA is observed, it is not logical to use ephedrine to further increase CO, which in most cases is already elevated as a response to SA. A further disadvantage of ephedrine is that the peak pressor effect occurs later than in the case of phenylephrine.

Figure 1: Haemodynamic changes in response to ephedrine and phenylephrine administered for spinal hypotension.



The effect of vasopressors on the venous circulation is difficult to study in humans. In this regard an animal study has been performed, which if translated to the human circulation, may add new insights into the effects of alpha agonists on CO. It was shown that phenylephrine boluses increased CO in fluid-depleted pigs under general anaesthesia, in a dose-dependent fashion. In fluid-replete pigs phenylephrine induced a dose-dependent decrease in CO. The authors postulated that these effects were due to alpha-adrenergic effects on the splanchnic circulation, resulting in increased venous return when the animals were fluid-depleted, as opposed to the predominant effect of an increase in SVR in fluid-replete pigs.

Several investigators have examined the advantages of bolus versus infusion or a combination of these methods of administration of phenylephrine. A comparison of a prophylactic infusion of 100 µg/min phenylephrine with the administration of 100 µg boluses in response to a decrease in blood pressure to < 80% of baseline, showed a greater number of hypotensive episodes in the latter group, with no benefit in terms of cord blood gases. A closed-loop feedback computer controlled infusion has been used to maintain baseline blood pressure, using an on-off algorithm for a phenylephrine infusion at 100 µg/min. No patients were symptomatic, and umbilical arterial pH was above 7.2 in all 53 cases; however hypertension occurred in 38% of patients. Closed-loop feedback computer-controlled phenylephrine infusion has been shown to provide better arterial pressure control with fewer interventions required than with manual controlled infusion. This is however not a readily practicable method in most units. The well preserved cord gas values after high dose phenylephrine, suggest that phenylephrine is effective in sustaining uterine blood flow during SA by its effects on uterine artery perfusion pressure.

Initiation of a phenylephrine infusion immediately after induction of SA, rather than treating established hypotension, may be beneficial. In one study using a suprasternal Doppler flow technique to measure changes in CO, 3 different phenylephrine infusion rates were administered after crystalloid preload in 75 patients. An infusion rate of 100 µg/min resulted in a clinically significant reduction in both HR and

CO. A further investigation compared placebo with 4 different fixed rates of phenylephrine infusion in combination with a crystalloid coload, using noninvasive BP measurements in 101 patients. Overall, an infusion rate of 25-50 µg/min has been found to be optimal, but some authors have suggested that variable rate infusions would be more effective. A recent editorial summarises the various options and the rationale for the choice of infusion technique.[6] Combinations of ephedrine and phenylephrine have also been studied, but there is no apparent benefit over phenylephrine alone.

Overall, the studies confirm the finding from research pioneered by Ngan Kee et al, that phenylephrine is the first line drug for the prevention or treatment of spinal hypotension in obstetrics. Many investigations show that the dose should be tailored to prevent hypertension and bradycardia. A review on vasopressor use during CD, points out that the increase in blood pressure due to excessive doses of phenylephrine, is to some extent limited by a baroreceptor mediated slowing of the heart rate. Blocking the vagus nerve by the use of anticholinergic agents in this situation, may therefore result in dangerous hypertension. In addition, administration of glycopyrrolate prior to induction of SA for CD, does not reduce the severity of hypotension, or vasopressor requirements.

In summary

- Hypotension and an increased heart rate is the typical response to SA for CS.

This response reflects a decrease in SVR, and a partial compensatory increase in CO, via an increase in HR and stroke volume. Therefore, appropriate management is left lateral tilt, rapid crystalloid or colloid coload, and the administration of IV phenylephrine. Given that this haemodynamic response is so common, many practitioners administer the vasopressor prophylactically. Since the haemodynamic response varies between patients, it is also reasonable to administer phenylephrine in immediate response to an increase in the heart rate. Current evidence is that the best approach is to titrate the rate of phenylephrine administration in order to maintain the baseline *heart rate*, since this restores SVR, CO and blood pressure to baseline values. The initial dose should be a 50-100 µg bolus, followed by intermittent 50 µg boluses or infusion (25-50 µg/min), or both as required. There is no evidence to support the use of anticholinergic agents in the setting of a normal or raised blood pressure and a decreased HR in response to phenylephrine. This can cause tachycardia and hypertension. Noradrenaline infusions have recently been compared with phenylephrine and found to maintain CO and heart rate better, but this may be a dose-related phenomenon, and the routine use of noradrenaline via a peripheral line is currently not recommended.

- Hypotension and bradycardia.

Since the final common pathway is the vagus nerve, anticholinergics should be administered, preferably atropine 0.25-0.5 mg if bradycardia is severe, together with attention to maternal position, and accelerated fluid administration. Ephedrine may also be used in conjunction with anticholinergic agents, but theoretically it may worsen bradycardia if the Bezold-Jarisch reflex is involved, since β -1 agonist-induced mechanical stretch of an empty left ventricle may initiate the reflex.

- Persistent refractory hypotension.

Since a possible misdiagnosis has been made with respect to fluid balance or underlying cardiac pathology, adequate uterine displacement should be ensured, larger doses of vasopressor and/or small bolus doses of positive inotropes such as adrenaline (10 µg) may then be necessary, together with close attention to fluid balance.

- High motor block.

This results in increasing dyspnoea and weak respiratory effort, followed by apnoea, requiring tracheal intubation. Concomitant sympathetic block may result in severe haemodynamic disturbance, and may necessitate full cardiopulmonary resuscitation.

Preeclampsia

Detailed recent investigations employing transthoracic echocardiography, have shown that the cardiac abnormality in patients with severe preeclampsia, is diastolic dysfunction. Inotropy is usually well preserved or increased, and an "inovasoconstrictor" state is accepted as the usual response in severe disease. The resistance to hypotension during regional anaesthesia may thus be due to a combination of factors. Firstly, there is an imbalance between pro-and anti-angiogenic factors in preeclampsia, due to vascular endothelial damage caused by the release of proteins derived from the placenta. This results in vasoconstriction. Secondly, the increased inotropic state of the myocardium results in adequate compensation for any decrease in SVR induced by SA. In complicated cases with established pulmonary oedema and hypoxia, there may be severe systolic dysfunction, and regional anaesthesia is relatively contraindicated.

SA usually induces only modest afterload reduction. This suggests that vasopressor therapy during SA should be conservative in patients with severe preeclampsia, and a modest lowering of blood pressure should be allowed before treatment is initiated. There are no randomised trials comparing the maternal or fetal effects of phenylephrine and ephedrine in this patient population. In one study, phenylephrine 50 µg effectively raised SVR in cases in whom hypotension required treatment.

Cardiac disease

Several case reports describe the use of titrated regional anaesthesia in high risk patients with cardiac disease, including congenital heart disease, acquired valvular heart disease, pulmonary hypertension, and cardiomyopathy. Patients with high risk for morbidity and mortality during pregnancy are those with Eisenmenger's Syndrome, pulmonary hypertension, severe aortic and mitral stenosis, hypertrophic obstructive cardiomyopathy (HOCM), and poor ventricular function with NYHA functional class > II, independent of underlying cause.

A suggested approach to the prevention of haemodynamic instability and tachycardia during regional anaesthesia in pregnant women with moderate and high risk cardiac disease, is as follows:

- Position.
    - Cardiac compromised pregnant women are more vulnerable to aortocaval compression and must be placed in left lateral tilt.
- Monitoring.
    - An arterial line is mandatory to detect rapid haemodynamic changes, after preoperative transthoracic echocardiographic assessment.
- Titrated anaesthesia.
    - Single-shot spinal, combined spinal-epidural anaesthesia (CSE), epidural, or continuous spinal anaesthesia should be chosen according to the specific lesion and NYHA-classification. NYHA Class III-IV patients with severe ventricular failure are especially vulnerable to rapid haemodynamic changes and tachycardia, and continuous spinal anaesthesia has been described, with small titrated doses of IV phenylephrine to counteract vasodilatation; however most practitioners prefer general anaesthesia in these

cases. In cases with moderate/severe mitral or aortic stenosis or HOCM, CSE may be tolerated, with coload and initial more aggressive use of phenylephrine to compensate for the SA-induced induced vasodilatation.

- General anaesthesia still has a significant role to play, especially in complex urgent or emergency cases with poor ventricular function. Phenylephrine should be used cautiously in this setting, and inotropic support is often required.

In summary

- Cardiac disease is no longer an absolute contraindication for spinal anaesthesia for CD. The exact haemodynamic status should however be determined preoperatively, and judicious use of alpha agonists and/or inotropes may then be employed during SA, CSE, or epidural anaesthesia, in carefully selected cases.

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Anaesthesia for the bleeding tonsil:
How I do it

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Tonsillectomy and adenotonsillectomy are among the most common surgical procedures, especially in children. Post-tonsillectomy bleeds occur in 0.5-2.5% of cases and many of these will need to return to theatre. Anaesthesia in these patients carries a significant risk of complications including failed intubation and haemodynamic instability. Pre-operative resuscitation and thorough theatre preparation are important.

The anaesthetic considerations specific to patients with a post-tonsillectomy bleed are listed in Table 1.

TABLE 1: Anaesthetic consideration with a post-tonsillectomy bleed

- Hypovolaemia
- Aspiration (full stomach)
- Anaemia
- Difficult airway (blood obscuring vision, oedema)
- A second general anaesthetic(in the case of primary haemorrhage)

Bleeds may be primary, occurring within 24 hours of surgery and necessitating immediate return to theatre or secondary, occurring up to four weeks after the initial surgery. The latter is usually due to sloughing of the surgical eschar or a secondary infection (which may respond to rest, antibiotics and fluids alone) or loosened surgical ties.

Factors increasing the risks of post-tonsillectomy bleed include male sex and advanced age and are listed in Table 2. A history of recurrent tonsillitis, which causes fibrosis distorting tissue planes and making surgical dissection more challenging, makes post-operative bleeds more likely. Surgical technique at initial surgery contributes to the risk of post-tonsillectomy haemorrhage. The use of diathermy, while associated with less intra-operative bleeding, is directly linked with an increased risk of post-tonsillectomy bleeding compared with the use of "cold steel". Patients with coagulation abnormalities are more likely to bleed. In adults this may be related to medication while in children, particularly males, inherited coagulopathies may need to be considered.

TABLE 2: Risk factors for post-tonsillectomy bleed

- Male
- Increasing age
- History of recurrent tonsilitis
- Surgical technique
- Coagulation Abnormalities

Surgery will involve suspension in the Boyle-Davis gag and haemostasis by means of (and in order of escalation) compression with tonsil swabs, ties, diathermy, suturing of tonsillar pillars, embolization and external carotid artery ligation. On average surgery may be anticipated to take around an hour but this depends on the cause of the bleed.

Pre-Operative Considerations

It is impossible to assess the amount of blood lost as much of it will be swallowed. In the case of late bleeds, patients may have been oozing for an extended period and swallowing the blood. Clinical assessment of haemodynamic status is critical, Table 3 considers signs to look for on examination.

TABLE 3: Clinical assessment of volume status

PARAMETER	NOTES
Heart rate	Tacchycardia, due to hypovolaemia and/or anxiety; Bradycardia is a late sign of cardiac decompensation
Capillary refill time (CRT)	Particularly useful in children
Blood pressure	Hypotension is a late sign in children
Tacchypnoea	Due to anxiety, acidosis and/or anaemia
Pallor	Reduced with hypovolaemia
Urine output	
Mental state	Confusion may result from reduced cerebral perfusion

Signs of airway obstruction should be sought on examination and may be due to post-operative swelling (in primary haemorrhage) or the presence of clots in the pharynx. Other pre-operative assessment should include checking the previous anaesthetic chart for endotracheal tube (ETT) size, evidence of previous difficult intubation and analgesia administered (especially if surgery took place in the preceding hours, when opiates administered may still be active).

Pre-operative resuscitation is essential where clinical evidence of hypovolaemia is detected. IV (intravenous) access should be established rapidly, consider intraosseous (IO) access if IV access is not easily achieved. Blood should be sent for full blood count (FBC), clotting screen (if a coagulopathy is suspected) and a cross match. A bolus of 20ml/kg of isotonic crystalloid solution should be given immediately and the volume status reassessed after this. If the Hb is </= 7g% blood should be ordered urgently. Transfusion of O- blood should be considered if bleeding is brisk and ongoing with haemodynamic instability despite ongoing fluid resuscitation while awaiting matched blood.

Theatre Preparation

Prepare for a difficult airway, obscured by bleeding. Laryngoscopes should have appropriately sized blades and bright lights. It is useful to have double sets of laryngoscopes in case blood obscures the light on insertion. Two yankauer suckers should be in hand’s reach in case clots block one and a wide bore nasogastric tube (NGT) should be ready for suctioning the stomach at the end of the procedure. Cuffed ETT's are preferable, two of each size should be available in case blood clots obstruct the first tube inserted. Children may require a half size smaller if swelling from the initial surgery is suspected to be present. Equipment for a surgical airway (cricothyroidotomy) should be in theatre and checked.

Temperature monitoring (can be nasal if the initial surgery did not include adenoidectomy), a forced air warmer and blood warming device (effective at high flows) will help with temperature management in the perioperative period.

An extra pair of hands and an experienced anaesthesia assistant (nurse) are highly recommended.

Intraoperative Technique

Anaesthetic induction technique is controversial with advantages and disadvantages to both inhalational and intravenous techniques (Table 4). I prefer an intravenous technique but arguments for both can be supported and practitioners should choose the technique they are most comfortable with performing.

TABLE 4: Inhalational vs. intravenous induction

TECHNIQUE	**Inhalational in the lateral position**	**IV Rapid sequence +/- cricoid pressure**
ADVANTAGE	- Maintain spontaneous ventilation and oxygenation - Drain blood clots by gravity - Spontaneous ventilation, can intubate by "aiming for the bubble"	- Decreased risk of aspiration - Muscle relaxation improves intubating conditions - Less stressful for the child
DISADVANTAGE	- May be difficult in a bleeding, anxious child - Cardiovascular instability in the face of hypovolaemia will be exacerbated by volatiles - Easy to get too deep fast - Intubating in the lateral position may be difficult	- Adequate pre-oxygenation is very difficult to achieve, hypoxaemia may occur during induction necessitating PPV which will increase the risk of aspiration - No "bubble in the blood" to indicate larynx
NOTES	- Do not use halothane for induction in the presence of hypovolaemia	- If haemodynamic instability persists despite pre-operative resuscitative efforts consider the use of etomidate or ketamine for induction - Unless a contraindication exists suxamethonium is the muscle relaxant of choice until suggamadex is readily available.

Notes: IV intravenous, PPV Positive Pressure Ventilation

Failed intubation and/or aspiration was the cause of 43 deaths or severe disability in a study of devastating outcome after adenotonsillectomy bleeds, illustrating that adequate airway management is essential. Pre-oxygenation is difficult and hypoxia may be seen with IV induction necessitating PPV. Careful, thorough airway suctioning will improve visualization but brisk bleeding may continue to obscure the airway. Early recourse to a surgical airway (cricothyroidotomy) should be considered in such situations.

Analgesia should be provided with opiates and paracetamol (cognisant of time intervals from previous doses in the case of primary haemorrhage). The use of non-steroidal anti-inflammatories is somewhat controversial with inconclusive evidence of an increase in post-operative haemorrhage due to platelet dysfunction. Consider avoiding these drugs if adequate, safe analgesia can be achieved without them. Patients with obstructive sleep apnoea in whom opiate use should be minimised may be candidates in whom the use of NSAID could be considered on a risk *vs.* benefit basis.

Peri-operative transfusion management should be individualised. In the face of ongoing haemorrhage despite surgical control thromboelastography (TEG) may provide useful information to guide the administration of coagulation products. In patients suffering from known or suspected coagulation disturbances (e.g. haemophilia) a haematologist should be involved in management early and will guide the transfusion of clotting factors. In children, injudicious use of FFP may cause a dilutional coagulopathy to exacerbate an already precarious situation.

At the end of surgery a wide-bore NGT should be passed under direct vision and the stomach thoroughly suctioned.

Awake or deep extubation? Whatever you do the tonsillar bed should be examined under direct vision after removal of the Boyle-Davis gag and before extubation. My preference is for deep extubation in the tonsillar position on the trolley. In such cases recovery staff should be warned to allow the patient to wake undisturbed while also monitoring for bleeding. Awake extubation reduces the risk of laryngospasm in the recovery room but is associated with an increased risk of bleeding.

Post-Operative Management

Patients should be managed in a well-lit area where bleeding can be easily seen. Blood transfusions may be continued pre-operatively as required according to haemoglobin measurements. Discharge may be contemplated when there is no more bleeding, pain is easily controlled with oral analgesics and normal eating and drinking has resumed without incident. Patients should be monitored for at least 24 hours.

Conclusion

The patient with a post tonsillectomy bleed presents anaesthetic challenges in the form of significant hypovolaemia, risk of aspiration and a difficult airway. Pre-operative resuscitation and careful planning are essential for safe management. Controversies in management include the methosd of induction and extubation. A calm, focussed manner, experienced surgical hands and good preparations are keys to success.

RECOMMENDED READING

Windfuhr JP *et al*. A devastating outcome after adenoidectomy and tonsillectomy: ideas for improved prevention and management. *Otolaryngology-Head and Neck Surgery;* 2009. 140:191-196

Fields RG, Gencorelli FJ and Litman RS. Anesthetic management of the pediatric bleeding tonsil. *Pediatric Anesthesia*; 2010. 20:982-986

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Gorham AP. The role of the anaesthetist in the management of post-tonsillectomy haemorrhage in children*. Anaesthesia*; 1964: 19(4): 565-569 (For an interesting historical perspective)

How I do it: Anaesthesia for Whipple Procedure

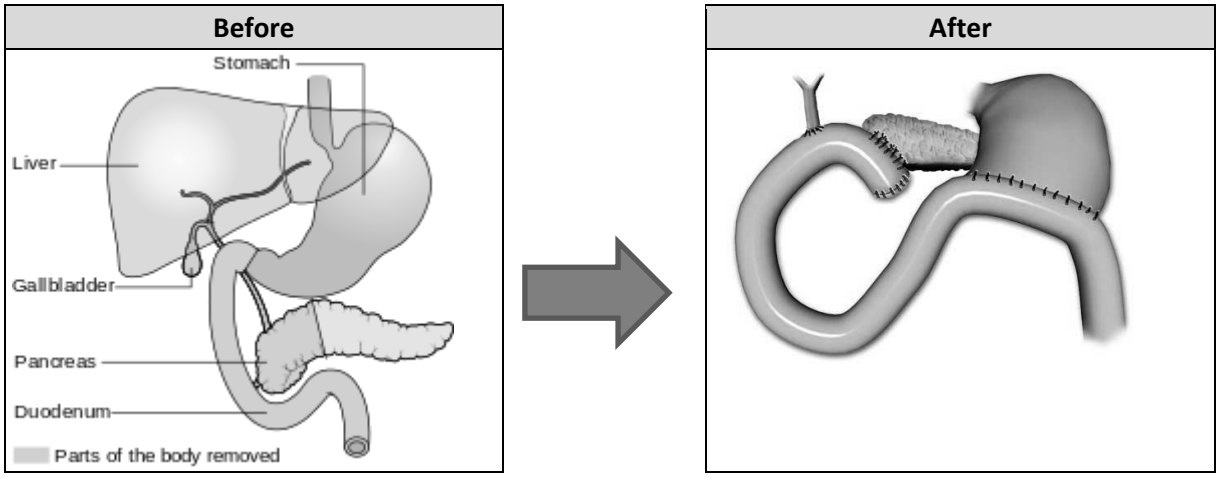
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Definition: A Whipple procedure (named after Allen Whipple, 1935) is a Pancreatoduodenectomy which may or may not be pylorus sparing and may or may not be duodenum sparing. The usual indication is to remove pancreatic cancers, but it may also be done for some benign pancreatic conditions e.g. cysts and for bile duct or duodenal cancers.

Pancreatic cancer in general has a poor prognosis. It is often detected late by which time it is unresectable with a 1-year survival rate under 10% and 5-year survival rate less than 5%. It typically also spreads rapidly. Several patients will already have had laparoscopic staging to confirm resectability before coming for the Whipple.

Anatomy:



The procedure: Is usually done via a subcostal incision or a longitudinal laparotomy incision, but some institutions do offer a laparoscopic approach. It involves removal of the head of the pancreas ± duodenum + common bile duct + gall bladder ± part of the stomach. A significant number of patients will prove to have unresectable disease which may result in a) nothing done b) simple bypass procedure or c) triple bypass procedure. Sometimes it takes considerable dissection and time before a final decision is made as to whether to proceed. The duration of the procedure with our surgeons is generally 4 to 12 hours with an average of 6 hours – depending on technical difficulty. Pylorus sparing resection does not appear to provide any advantage or disadvantage. Rarely the dissection includes a section of portal vein which does make for increased complexity. When that happened to my patient I was able to persuade them to get the transplant surgeons to do the vascular repair rather than the vascular surgeons. After all, they do portal vein anastomoses for their liver transplants, whereas the vascular surgeons do not often deal with portal veins.

Preoperative: Weight loss of 10-20% common, jaundice, abdominal pain, fatigue. Most of our jaundiced patients have had an endoscopic retrograde cholangio-pancreatography (ERCP) and placement of biliary stents and so are no longer jaundiced at the time of the procedure. This means we no longer have to consider the complications of anaesthesia related to jaundice e.g. the hepato-renal syndrome. On the other hand pancreatitis or cholangitis may follow the ERCP. The procedure is best done in centres that do more than 20 per year so beware of the occasional surgeon doing the procedure in an institution that does not know how to look after them perioperatively.

Preoperative investigation: Full blood count, urea, creatinine and electrolytes and ECG, chest radiograph, glucose and lung functions for patients at risk. Blood group and screen is usually adequate unless antibodies are present – then I get two units cross-matched. This is also the time to ensure an ICU or PAHCU bed is available. (My surgeons usually prefer the former as usually we can then get 2 days of epidural and high care).

Premedication: According to patient requirement. Usually patients selected for resection are reasonably well. If the patient is to have an epidural, low molecular weight heparin is omitted for the appropriate time interval.

Preinduction: I start with a good IV just in case of blood loss (generally the incidence of transfusion is low, but damage to the portal vein, splenic vein or hepatic or superior mesenteric artery may need control and transfusion). This is followed by epidural insertion at about T8 as this is a good level for covering the segments required for analgesia. If you have the time and the monitoring, establishing the block beforehand would be ideal. Generally I do not have the time so I give the test dose as I transfer the patient onto the table. Standard monitoring (ECG, pulse oximeter, temperature) is placed prior to induction.

Positioning: The patient is placed supine on the table as high up the table as possible in case the C arm is required for cholangiography (uncommonly) so that the hepatic area is not over the table leg. Because there are usually several surgeons and the scrub nurse to accommodate around the table the arms should be tucked in by the sides to prevent brachial plexus injuries. I place a screen at about the T4 level mainly to prevent the surgeons from leaning on the patient's nose as they tend to migrate upwards. If you place the clamp for the screen on the left, it leaves the Gabler rail on the right for the surgeon's Omnitrack or Thompson's retractor. A rotatable clamp will allow the rail position to be adjusted later if required.

Induction and maintenance: Generally straightforward with preoxygenation, propofol and muscle relaxant of choice depending on whether there is gastric outlet obstruction or not and whether airway difficulties are anticipated followed by intubation. Since the odd patient has had unexpected peritoneal or liver metastases on opening, we now often do a laparoscopy beforehand on separate occasion, to make better use of the theatre time. Even so, occasionally we do get a nasty surprise. Be judicious with your choice of relaxant and dosage. Maintenance is with air/oxygen/isoflurane or sevoflurane and relaxant top-ups. I avoid nitrous oxide, but many centres use it without problems. I don't use intravenous anaesthetic techniques as I do not see any advantage with them.

I usually place an arterial line after induction because most patients do not enjoy the insertion and most of them do not need it prior to induction. The cuff becomes quite traumatic over a long time which makes the arterial line very convenient during the long period of anaesthesia anticipated. It also provides information during the phases of dissection of the porta hepatis so that one can warn the surgeon if the retraction is a little too hard (they normally deny it but let go anyway and the pressure comes up nicely) and is useful for the measurement of blood glucose and haemoglobin where it becomes necessary. A nasogastric tube is not essential, but may be needed if there is gastric outlet obstruction or the stomach is hyperinflated during induction. I generally just ask the surgeon if he needs it and at the end ask if it needs to stay. While busy with the induction, I encourage the surgeons to catheterize (long procedures) the bladder and we place a forced air warmer, temperature probe and calf stimulators. I used to do all of these cases with a central venous catheter, but found them not very useful in the majority of patients as they are not a good guide to fluid therapy – one tends to "over fill" patients. I now only use them if the patient has poor venous access, significant cardiac disease or a specific indication. Fluid-wise, I aim at normovolaemia and use a colloid/ balanced salt mix. Patients with an epidural generally need a little more fluid than those without. Oedematous bowel makes for a difficult anastomosis and may be a result of overhydration or a poor surgical harvesting technique. Antibiotic prophylaxis is usually with a cephalosporin (as dictated by our antibiotic policy makers).

I generally run my epidural with 0.25% plain bupivacaine (0.5% gives me more sympathetic block and a higher incidence of the ICU physician calling me because the patient cannot move their legs) and give a 3 mg morphine bolus in 10 ml saline after establishing my block (usually takes around 9 to 12 ml bupivacaine in aliquots of 3ml) which I find, makes my block less level sensitive. I also find that because I then use a little less bupivacaine, I need less phenylephrine to keep the pressure stable. I top up with about 3 to 5 ml bupivacaine hourly depending on the patient response. I avoid systemic fentanyl as I find it makes it harder to assess how well my block is working. I may be old-fashioned, but I still think morphine epidurally makes good pharmacological sense, which is why I choose it, but I have used fentanyl/bupivacaine mixes equally successfully – very convenient and safe where the premix bags are available. I find the bupivicaine1% mix gives quite a bit of intraoperative breakthrough so only convert to that at the end, prior to transferring the patient to the ICU. If epidural placement is refuses or unsuccessful, I have found spinal morphine (300 micrograms) quite effective and intravenous morphine via patient controlled systems or continuous infusions quite satisfactory – especially in patients who are already on morphine anyway. Even with a good epidural, paracetamol IV near the end is worthwhile, but if you have a medical aid that won't pay for more than 24 hrs, then save that for later.

The emergence phase: Generally the patient can be extubated at the end after routine reversal of the relaxant. Occasionally patients have a marked SIRS response presenting mainly with tachycardia and a low systemic vascular resistance. These patients are better off in the ICU and I usually insert a CVP line before or at the end of the procedure. This can often be done while the surgeons are still busy with the anastomoses if you want to save some list time (another reason to have the surgical screen in place).

In General: These procedures tend to be long and rather boring for most of it, so be prepared. It is useful to listen to the surgical conversation during the initial several hours of dissection as you often get an idea of the resectability of the lesion before they formally voice their decision (helpful in planning the rest of the list and your day). Most of the patients do not require a blood transfusion.

Post-operative:

Generally around 2 days in the ICU or high care unit then about 10 days in all before going home if there are no delaying complications like anastomotic leaks.

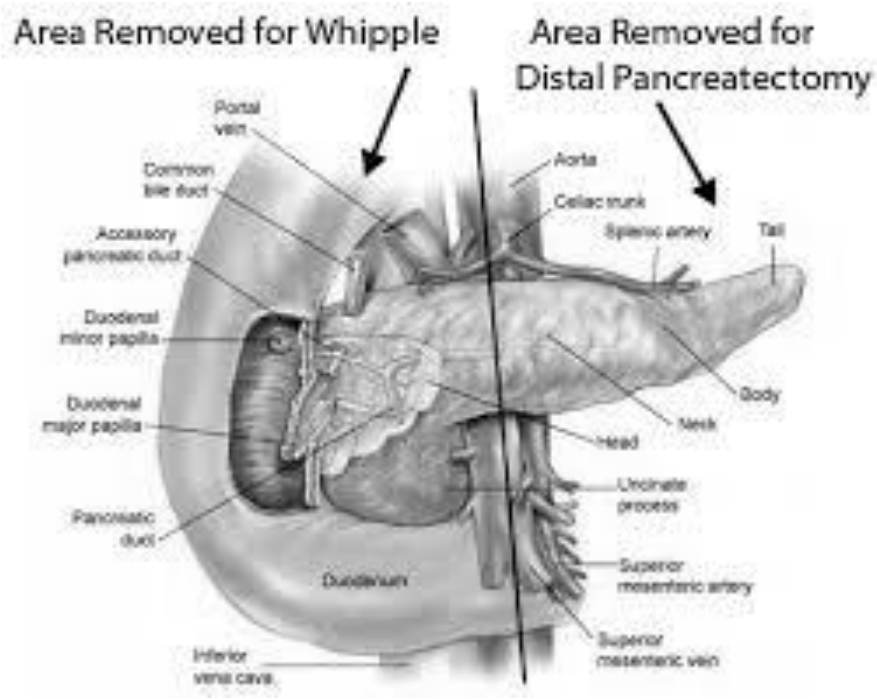
Complications:

In hospital: The most common post-operative complication is an anastomotic leak from the various surgical connections (10-15%incidence). About 10% of patients develop new diabetes which may improve later. Infections, gastric emptying difficulties and bleeding may occur. One of our patients developed mesenteric artery occlusion and bowel infarction. Short term perioperative mortality varies from 4 -15%. Overall 5 year survival post resection is ± 20% with some centres reporting up to 40%. Rapid growth of liver metastases which were not seen to be present at resection may occur (within 6 weeks!) after what looks like a complete resection.

Later: Continued weight loss after the operation is a frequent complication. Some patients experience bloating, fullness, nausea or vomiting.

Just a thought before on embarking on all this: It is important to realize that patients may not benefit from the procedure and operative mortality is not insignificant when accepting a patient for the procedure. Discussion with the patient and surgeons may be necessary.

Some additional useful information:



A good description of the Whipple procedure surgical steps can be found at:

tinyurl.com/WhippleProcedure

(https://www.froedtert.com/upload/docs/services/liver-pancreas-bile/whipple-illustrations.pdf)

There are some good you tube clips which are mainly for prospective patient information but give a good idea of the surgery. These are easy to google.

Awake craniotomy

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The awake craniotomy technique was originally introduced for the surgical management of epilepsy but has subsequently been used in patients undergoing surgery for supratentorial tumours, arteriovenous malformations, deep brain stimulation, and mycotic aneurysms near eloquent brain regions. The surgical aims are to maximise lesion resection while sparing important areas of the brain (motor, somatosensory, and language areas). Awake craniotomy offers great advantages with respect to patient outcome. Here, the anaesthetist's goal is to make the operation safe and effective, while reducing the psychophysical distress of the patient.

Now, in the era of functional neuro-oncology, the primary aim of the modern neurosurgeon should be two-fold: to have a positive impact on the natural history of disease, especially by increasing overall survival, and to preserve, or even improve quality of life. To accomplish this goal, neurosurgeons should aim to achieve the best extent of resection, while obtaining optimal functional outcome. This implies not only the avoidance of severe disabling neurological deficits (such as aphasia or hemiplegia) but also the preservation of high-order neurocognitive functions, which are crucial for the enjoyment of normal social and professional lives.

It is for this reason that awake mapping has been shown to represent the most reliable method of optimising 'onco-functional balance', which was recently defined as 'a compromise between achieving maximum tumour resection together with preservation of maximum function'. Indeed, a recent meta-analysis comparing outcomes of glioma surgery with or without intraoperative functional mapping (8,091 patients) demonstrated that electrical stimulation allowed a significant increase in the extent of resection, as well as a significant decrease in permanent severe neurological deficits.

There is a paucity of literature detailing the best way to achieve optimal awake conditions. Personal experience, careful planning, and attention to detail however, form the basis for obtaining good awake craniotomy results. Additional studies are still necessary in order to optimise the procedure, reduce complications, and improve patient tolerance and outcome.

Anaesthetic types

The primary goal of the anaesthesia is always patient safety. However, the provision of effective surgical conditions and the reduction of psychophysical distress of the patient is also of paramount importance here. Added to this, in an environment where trained neuropsychologists are not easily on hand to carry out functional testing intra-operatively, this responsibility falls on the anaesthetist as well. Multiple authors have described different protocols for anaesthetic care during awake craniotomy based on monitored anaesthesia care (MAC) or general anaesthesia (the so-called asleep-awake-asleep technique [AAA]).

Since 1959 when the concept of 'neurolept anaesthesia' first originated, there have been a myriad of described techniques to facilitate functional neuro-anaesthesia; from haloperidol and phenoperidine to Innovar (droperidol with fentanyl) to alfentanil infusions to propofol sedation. Despite these different anaesthetic strategies, modern anaesthetic approaches may be generally divided as follows: MAC and AAA.

> **MAC**: The patient is sedated, can breathe spontaneously and is responsive to name calling (Observer's Assessment of Alertness/Sedation Scale [OAA/S] score of ≥3 or BIS ≥60).
>
> **AAA**: This technique is comprised of deep sedation or general anaesthesia, and return of spontaneous breathing is possible (OAA/S score <3 20 or BIS score <60). Oxygen administration and airway control are obtained with devices that allow for mechanical

ventilation. The patient is awakened at some stage throughout the procedure as needed (for example, for brain mapping and/or tumour resection).

What both anaesthetic techniques have in common, however, are these three specific aims:

1. Maintaining patient cooperation - optimal analgesia, appropriate sedation and anxiolysis during the different surgical steps, comfortable positioning, and nausea, vomiting, and seizure prevention.
2. Physiological homeostasis - safe airways, adequate ventilation, haemodynamic stability and the maintenance of normal intracranial flow and pressure.
3. Most important for epilepsy surgery - limited interference with electrophysiological recordings.

Throughout these procedures, it is extremely important for the anaesthetist to remember that sedatives and opioids may interfere with electrophysiological recordings. Neuroleptic and propofol administration must be discontinued well prior to cortical mapping in order to obtain accurate interpretation of the ECoG (electrocorticography) recordings and to avoid suppression of inter-ictal spike activity. Opioids are particularly effective in selectively activating inter-ictal epileptiform activity. Such opioid-induced activation may assist the surgeon in selecting an appropriate resection location during epilepsy surgery, but this activation is a negative interference during tumour surgery. Opioids may also promote signs of neuro-excitation such as nystagmus, muscle rigidity, myoclonus, and seizure-like activity.

Pre-operative evaluation

Preoperative evaluation is of course necessary in order to evaluate the patient's health, likelihood of co-operation, and to seek any medical contra-indications to awake surgery. The anaesthetist must explain in detail the advantages, benefit/ necessity, and nature of the awake craniotomy experience. A specific and focused clinical evaluation is extremely important, and particular attention should be paid to:

1. Upper airways - prediction of difficult tracheal (or supraglottic) intubation (physical confirmation and past intubation), obstructive and central apnoea risk (obesity, sleep apnoea).
2. Epilepsy - pharmacotherapy, antiepileptic drug serum concentrations, type and frequency of seizures. Interestingly, according to Szelényi, patients with symptomatic epilepsy do not appear to have a higher risk of intraoperative stimulation-associated seizures than patients without symptomatic epilepsy during awake tumour resection.
3. Nausea and vomiting - past anaesthesia, kinetosis.
4. Intracranial pressure estimation - type of lesion, radiological and clinical signs.
5. Haemorrhage risk - type and localisation of lesion, therapy (antiplatelet drugs), medical history.
6. Patient cooperation - anxiety, pain tolerance, neurological deficits.

Prior to surgery, the patient must be informed about all potential risks, safety measures, stages of the procedure, and what will likely occur while he/she is in theatre. The anaesthetist must not try to conceal sounds (monitor alarms, cranial drilling, electroknife, ultrasonic surgical aspirator) or minimise potential discomforts (unchangeable position, aphasia during cortical mapping) to the patient. The patient must also understand that these discomforts are necessary in order to successfully expedite the procedure. The anaesthetist must gain the patient's confidence, as the patient will depend on him or her during the procedure. It is of utmost importance (perhaps in the case of awake craniotomy more than other procedure) to establish a good, trusting rapport with the patient.

Absolute contra-indications to awake craniotomy include:

1. Respiratory pathology - severe asthma, heavy smokers with evidence of obstructive airways disease, active respiratory infections, OSA, cardio-respiratory pathology.
2. Patient uncooperative, obtunded or unable to comprehend the procedure.
3. Young age. (The youngest successful case completed in this country to date was a 12 year old female).

Premedication

There is still no consensus regarding premedication, and decisions should be made based on the patient's clinical condition, the anaesthetist's experience and hospital protocols and standards. Midazolam is the most frequently used benzodiazepine before awake craniotomies; it is a short-acting, rapid-onset drug which is twice as effective as diazepam. Midazolam is sometimes combined with opioids such as fentanyl, but this may increase the respiratory depressive effects of each drug. Benzodiazepines, may however have some negative effects during awake craniotomy such as respiratory depression, paradoxical agitation or delirium, and interference with ECoG recordings. Clonidine is a good alternative to benzodiazepines, and the author's choice of premedication if available: several studies have proved it to be effective in neurosurgery when it is necessary to control the haemodynamic response to tracheal intubation, and in application of the Mayfield clamp. In some centres, clonidine is administered at a dose of 2-3 µg/kg orally one hour before arrival in theatre.

Analgesia

Anaesthetic care for an awake craniotomy ALWAYS includes a Scalp Block. The local anaesthetic must ensure an eight-hour duration of block. A 40 to 60mL anaesthetic volume is used for infiltration in an average sized adult. The combination of high local anaesthetic volume and a well-vascularised area may predispose to local anaesthetic toxicity. The use of adrenaline with the bupivacaine both minimises acute rises in plasma anaesthetic concentration and maximises the duration of the block. Clinical vigilance is particularly indicated within 15 minutes or so after the blocks are performed.

Local anaesthetic blocks are performed to include six nerves (Figure 1):

1. The supraorbital nerve is blocked just above the supraorbital notch and local anaesthetic is deposited just superficial to the periosteum.
2. The supratrochlear nerve (root of frontal nerve which originates from the ophthalmic branch of the trigeminal nerve) is infiltrated together with the supraorbital nerve.
3. The temporal branch of the auriculotemporal nerve is blocked immediately posterior to the superficial temporal artery at the level of the auditory meatus. Injection is superficial and subcutaneous. Too deep an injection will produce facial nerve block.
4. The main branch of the zygomaticotemporal nerve emerges from the temporalis fascia near the lateral border of the orbit, although many smaller deep branches ramify within the temporalis muscle. These small branches are especially important to block so as to cover temporally based flap incisions. Field infiltration above the zygoma through the temporalis muscle and almost down to the periosteum of the temporal bone will give a good result without causing a facial nerve block. Up to 5 ml can be used on the operative side.
5. The lesser occipital nerve can be blocked either deep or superficial to the fascia at the upper, posterior border of sternocleidomastoid.
6. The greater occipital nerve is blocked subcutaneously by injecting along the middle third of a line between the mastoid process and the external occipital protuberance along the superior nuchal ridge. This injection will also reinforce the lesser occipital nerve block as it becomes subcutaneous.

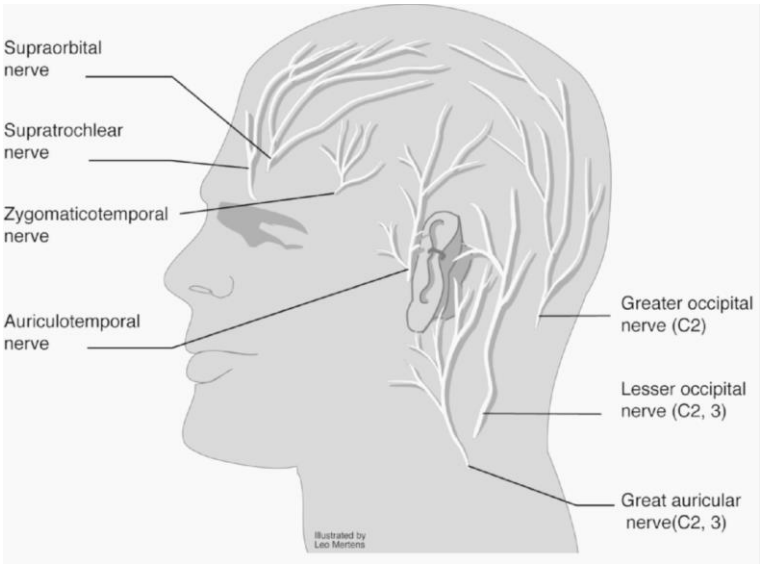


Figure 1. Innervation of the scalp

Positioning

The main objective of positioning is to ensure access to the airway and adopt a comfortable position for the patient, while avoiding airway obstruction if sedation is necessary. To achieve this, a lateral or semi-lateral position is preferred with minimal rotation of the neck. Other (often competing) considerations are the visibility of the patient to the anaesthetist during intraoperative functional testing and allowing the surgeon and assistant adequate surgical access. One such set up is depicted in Figure 2.

Of note is the closed circuit video monitoring (a luxury not available in our centre), which allows the surgeon and neurologist to clearly see and hear the patient during testing.

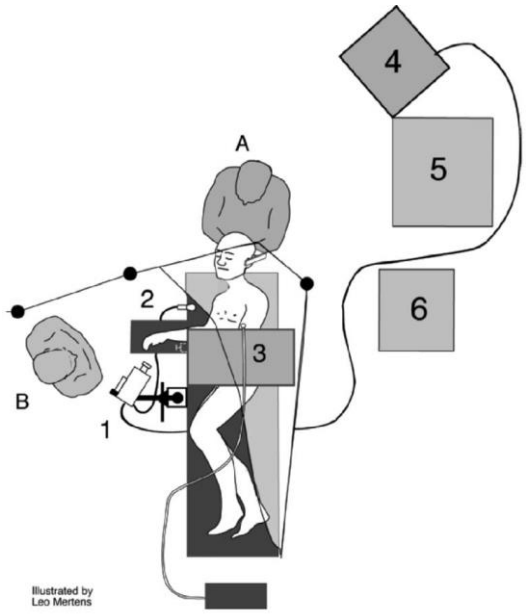


Figure 2. Suggested positioning for awake craniotomy. A: Surgeon; B: Anaesthetist; 1: Camera; 2: Microphone; 3: Fibreoptic light; 4: Television monitor; 5: Frameless stereotactic monitor; 6 Microscope base.

Asleep-awake-asleep

Dexmedetomidine as a background infusion is run. Loading standard with 1mic/kg, then infused at 0,2 - 0,5mic/kg/hr. The preference in our unit is to then run a Propofol and Remifentanil TCI, guided by haemodynamic parameters and BIS monitoring. Propofol, compared with volatile anaesthesia, increases cerebral perfusion pressure, decreases neurophysiologic monitoring interference, appears to ensure neuroprotection and decreases the incidence of nausea and vomiting. Once anaesthesia has been induced, VERY careful placement of a Classic LMA (the author's choice) to maintain airway patency and facilitate positive pressure ventilation. If possible, the avoidance of lubricants and other airway devices is advised so as to minimise secretions.

Once the highly sensitive dura has been infiltrated, the paitent is woken up on a background of dexmedetomidine. The dura is only opened once full cognitive faculties have been regained. Appropriate intraoperative testing can then be reliably performed.

Once the surgeon is satisfied with the mapped eloquent areas, the patient is either put back to sleep (epilepsy surgery) or kept awake (tumour resection).

Intraoperative events

Problems that may arise during the course of the anaesthetic include, but are not limited to;

1. Seizures. Relatively common. An Ojemann stimulator is used to map the functional areas of the cortex and it is during this phase, particularly when in the vicinity of the motor cortex, that intraoperative seizures can occur (up to 15% in one series). Iced saline lavage must be readily available for the surgeon to apply to the brain. This is usually effective in seizure termination.
2. Anxiety. Reassurance, excellent pre-operative preparation and full theatre staff support is manadatory
3. Pain. Scalp blocks usually suffice, and with a small amount of dexmedetomidine this is a rare complaint. Dura close to the saggital sinus or the middle meningeal artery is particularly sensitive to traction. Attempts to topicalise these areas are used in some centres, but gentle surgical technique and a little sedation can overcome any brief discomfort quite easily.
4. Nausea and bradycardia. This is usually associated with deep cortical resection close to the midline. Asking the surgeon to reduce traction and administration of anticholinergics might be more effective than antiemetics in these cases. However, Propofol TCI and combination prophylaxis in the form of dexamethasone and ondansetron usually suffice in combatting this problem.
5. Airway obstruction. Suctioning of secretions, placement of a nasopharyngeal airway, thereafter placement of an LMA. If no improvement, endotracheal intubation; this is facilitated by the surgeon de-clamping the head with the brain covered by a sterile drape and holding it in an appropriate position. Again here, experience and excellent communication between surgeon and anaesthetist is vitally important.

Deep Brain Stimulation (DBS)

DBS electrode implants are used in the treatment of medically refractory movement disorders such as Parkinsons disease, Essential tremor, Dystonia as well as severe depression and Obsessive Compulsive Disorder. Anatomical as well as physiological information of each individual patient is vital prior to trajectory planning.

Anatomical: MRI, CT, MRI-CT merge, 3D computer mapping transposition.

Physiological: For micro-electrode reading one needs an awake, alert, attentive and cooperative patient.

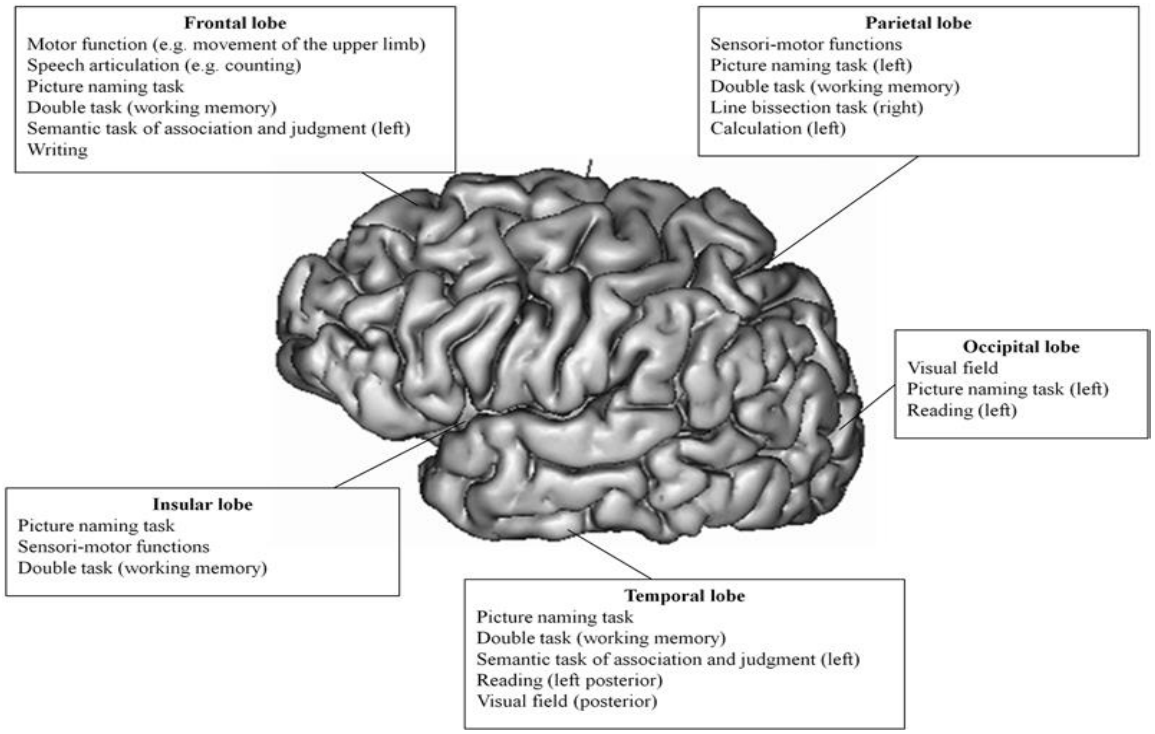
DBS can be an extremely long procedure (often lasting up to six hours for bilateral electrode placement). Stereotactic equipment is attached with pins placed under local anaesthetic on the morning of the procedure. High resolution MR images with volumetric echo imaging and T2 weighted sequences are obtained and transferred to the Stealth Planning Station for trajectory aiming using the target coordinates. For this the patient is usually in a semi-recumbent position to ensure optimal comfort, limit CSF loss and brain shift, and to minimise the chances of VAE. The literature is vague in its recommendations for the best method of anaesthesia for DBS. Most authors hesitate to advocate for the use of sedation in patients requiring microelectrode recordings (MER), and some surgeons request termination of the dexmedetomidine infusion if cognition and arousal are at all affected.

Anti-hypertensive medication may be required because of the release of Dopamine and Noradrenaline on electrode stimulation. Nifedipine 5-10mg sublingually has been described. Our practice is to use intravenous magnesium boluses of 1-2g. On rare occasions, labetalol may be required. Whichever agent is used, intraoperative hypertension must be promptly managed as it may predispose to intracranial haemorrhage (1.7 - 4% incidence).

Intraoperative tasks

A full description of intraoperative neuro-functional testing is beyond the scope of this lecture. The goal though is to develope a personalised, practical, and efficient intraoperative protocol based on relationships between tumour location and functional networks.

Examples include language mapping (peri-sylvian regions in the left dominant hemisphere), and reading and writing have been used to map the superior and posterior parts of the temporal lobe, the inferior parietal lobule, and the lateral part of the frontal gyrus.



The figure above crudely illustrates what tasks might aid in localising vital structures within the brain.

Conclusion

Awake craniotomy for tumour resection involving functional areas is a surgical approach that offers great advantages with respect to patient outcomes. This is a complex technique that requires great patient and equipment engagement. In this type of procedure, the anaesthetist's goal is to provide a safe and effective operating environment and to reduce the patient's psychophysical distress. The choice of the anaesthetic technique, MAC or AAA, must be related to the anaesthetist's capability and experience. AAA, even if more complex, allows the advantages of avoiding respiratory depression and access to airway protection, consequently decreasing intraoperative complications. The AAA technique may be preferred for delicate and more complex patients. However to date all of these ideas have not yet been demonstrated by any one study. The large number of different airway control techniques performed during awake craniotomies in the literature confirms that an optimal *modus operandi* does not exist. Dexmedetomidine appears to be the best drug for sedation without interference with respiratory function. For the moment, propofol and remifentanil are the most-used adjunct anaesthetic agents.. Particularly, TCI infusion systems allow better drug titration, avoiding oversedation and respiratory depression. Depths of anaesthesia monitoring systems, like BIS, are useful in this kind of surgery even if clinical observation of vital signs and specific sedation scores are adequate to manage these patients. International studies indicate that awake craniotomy is generally well-tolerated and only moderately burdened by intraoperative complications. Personal experience, careful planning, and attention to detail are the basis for obtaining good results.

Notes

Neuroprotection in anaesthesia

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INTRODUCTION

The endpoint of all cerebral injuries is the inadequate supply of the brain with oxygen and glucose which triggers a characteristic pathophysiologic *cascade* leading to neuronal death.

Perioperative brain damage is among the most serious adverse complications of surgery and anaesthesia, resulting in new postoperative neurological deficits including transient ischaemic attack (TIA), cerebrovascular accidents and postoperative cognitive decline (POCD).

The risk of perioperative stroke is increased in cardiovascular and neurovascular procedures and in patients with predisposing risk factors such as previous stroke, carotid stenosis, patent foramen ovale, atrial fibrillation, infective endocarditis, diabetes, renal failure, and older age > 62.

Neuroprotection is defined as any strategy that antagonizes, interrupts, or slows the sequence of injurious biochemical and molecular events, which have the potential to cause irreversible cell death. Many methods and agents have been investigated to produce neuroprotection from cerebral ischemia. Essentially none of the pharmacological approaches were identified as useful in humans although most agents have been successfully tested in animal models. Multiple clinical trials have shown that maintenance of cerebral homeostasis appears to be the most important neuroprotective strategy.

This review discusses essential physiological mechanisms to warrant adequate supply of glucose and oxygen to the brain. In addition, neuroprotective strategies in cardiac surgery are reviewed.

REVIEW OF PHYSIOLOGICAL VARIABLES

Cerebral metabolic rate of oxygen ($CMRO_2$)

Neurons have a high metabolic rate and use more energy than other cells. Although the brain accounts for 2% of the total body weight, it uses 20% of the body's total oxygen consumption. The major proportion of energy is generated by oxidative phosphorylation of glucose. The cerebral metabolic rate of awake young adults is 3.5 mL O_2/100 g/min (Table 1) Neuronal metabolic integrity accounts for 45% and neuronal function for about 55% of total $CMRO_2$. Both anaesthetic agents and hypothermia have been shown to decrease functional $CRMO_2$.

Anaesthetic agents:
The decrease in $CMRO_2$ is most profound at burst-suppression of cortical activity (e.g. 20–40% reduction in $CMRO_2$ by Propofol or Thiopentone).

Temperature:
$CMRO_2$ is reduced by more than 50% if the brain temperature decreases from 37 °C to 27 °C. With a further 10 °C reduction to 17 °C, cerebral function is abolished. At this point the total oxygen consumption is reduced to less than 8% of the normothermic value.

Table 1 Age-dependent physiological variables.
Age-dependent physiological variables.

Age	MAP [mmHg]	ICP [mmHg]	CBF [mL/100 g/min]	$CMRO_2$ [mL/100 g/min]
Premature	35–45	<3	5–30	1–2
Newborn	45–55	2–5	30–40	2–3
Nurseling	55–65	2–5	40–60	3–4
Infant	70–75	3–7	50–80	4–5
Schoolchild	75–80	5–12	85–100	3.5–5
Adult	90–100	8–15	45–50	3.5

Cerebral blood flow (CBF)

The rate of CBF is largely determined by the regional $CMRO_2$. Regional CBF may vary in dependency to brain region, cortical activation and age. The gray matter, where the neuronal cell bodies and synapses are located, has a blood flow of 60 – 80 mL/100 g/min. In contrast, the white matter, which consists mainly of fibre tracts, has a blood flow of 20 – 25 mL/100 g/min. The global blood flow to the brain remains fairly stable for a given physiologic state.

Neurovascular coupling

Regional CBF adapts to maintain regional $CMRO_2$. This relationship is defined as neurovascular coupling of metabolism and flow. This profound mechanism is developed by birth and maintained during lower cerebral energetic states (e.g. hypothermia, anaesthesia) and higher cerebral energetic states (e.g. hyperthermia, seizure).

Cerebral perfusion pressure (CPP)

CPP = MAP (mean arterial blood pressure) - ICP (intracranial pressure)

In order to interpret anaesthetic effects on CPP, the effects on MAP and ICP must be considered. In general, anaesthetic agents (Barbiturates, Propofol, Benzodiazepines, Opioids, Dexmedetomidine, Sevoflurane, Desflurane and Isoflurane) decrease MAP in a dose dependent fashion (Table 2). Their potential to decrease systemic haemodynamics is related to the speed of application and the pre-existing volume status of the patient. The only drug with stimulating potential on systemic haemodynamics is Ketamine. Barbiturates and Propofol decrease ICP while Benzodiazepines, Ketamine, Dexmedetomidine and Sevoflurane (< 1 MAC) have limited impact on ICP. Desflurane, Isoflurane and Nitrous oxide increase ICP due to increases in cerebral blood volume (CBV) secondary to potent vasodilatation. Therefore, and in balance of effects on MAP and ICP, Barbiturates and Propofol may increase CPP if the administration is not associated with the decrease in MAP but only with a decrease in ICP. While Benzodiazepines and narcotic agents have little effect on CPP, Ketamine increases CPP. Dexmedetomidine, Desflurane and Isoflurane decrease CPP because they either decrease MAP or do both decrease MAP and increase ICP.

Table 2 Effects of anaesthetic agents on vasodilation/constriction and associated determinants such as cerebral perfusion pressure (CPP), cerebrovascular autoregulation and CO_2-reactivity.

	Vessel tone	CPP	Autoregulation	CO_2-reactivity
Propofol	Vasoconstriction	↑↓	Intact	Intact
Thiopental	Vasoconstriction	↑↓	Intact	Intact
Desflurane	Vasodilation	↓	Impaired	Intact
Isoflurane	Vasodilation	↓	Impaired	Intact
Sevoflurane	Vasodilation	(↓)	(Impaired)	Intact
Ketamine	Vasodilation	↓	Intact	Intact
Dexmedetomidine	Vasoconstriction	↓	Intact	Intact

Cerebrovascular autoregulation

Cerebrovascular autoregulation refers to the ability of brain vessels to vasoconstrict and vasodilate between 50 and 150 mmHg CPP.

If CPP increases within these limits, cerebrovascular constriction occurs with the effect of decreasing cerebral blood volume (CBV) and a resultant constant CBF (Fig. 1). Similarly, increases in CPP induce autoregulatory vasodilation, which increases CBV and maintain CBF constant.

If cerebrovascular autoregulation is impaired, changes in cerebral blood flow occur in a pressure-passive fashion with an inverse effect on cerebral blood volume. That is, with increasing CPP, CBV increases because the vessels get passively dilated and with decreasing CPP there is vascular collapse and decreases in CBF and CBV.

Studies in laboratory animals and humans have shown that intravenous anaesthetic agents (Hypnotics, Ketamine, and narcotic agents) maintain cerebral autoregulation. In contrast, drugs with

vasodilating potential such as Desflurane, Isoflurane and high-dose Sevoflurane impair the dynamic and static autoregulation response. Autoregulation may be impaired or fully abolished in some patients with intracranial pathology (e.g. subarachnoid haemorrhage, intracranial bleed, traumatic brain injury, and stroke).

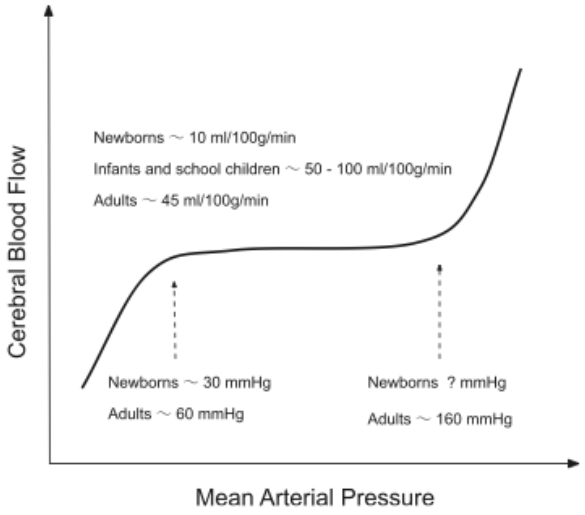


Fig. 1. Cerebral autoregulation: cerebral blood flow is maintained during decrease or increase in mean arterial pressure within age-dependant limits.

Intracranial pressure (ICP)

The volume of the various intracranial components (brain tissue volume 80%, blood volume 10%, cerebrospinal fluid volume 10%) determines ICP. Because the cranium has a fixed volume, an increase of any component must be compensated by a decrease in the volume of another component (intracranial compliance 1 mL/mmHg, Fig. 2). Otherwise, the pressure in the cranium will increase (Monroe–Kellie hypothesis). The normal value of ICP is 8–15 mmHg in adults. ICP values > 20 mmHg are associated with higher probability of cerebral ischemia and hypoxia and therefore must be treated using current clinical guidelines.

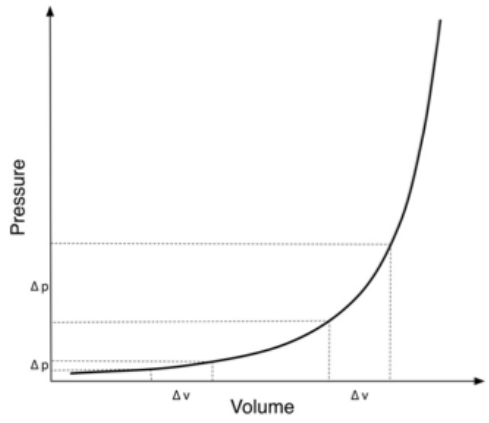


Fig. 2. Intracranial pressure–volume relationship: additional intracranial volume is accommodated with minimal change in intracranial pressure. Once this capacity is exhausted, minimal increase in volume leads to exponential rise in intracranial pressure.

Carbon dioxide and Oxygen vasoreactivity

CO_2 vasoreactivity refers to the ability of brain vessels to vasoconstrict in the presence of hypocapnia and to vasodilate in the presence of hypercapnia.

This most important physiological regulatory mechanism affects CBF in a linear manner within a range of 2,7 – 10,7 kPa $PaCO_2$ (4% increase in CBF per 0,13 kPa increase in $PaCO_2$) in order to remove cerebral CO_2 (Fig. 3).

CO_2 vasoreactivity is mostly maintained during anaesthesia but may be impaired or abolished in patients with intracranial disease.

Unlike the response to CO_2, CBF does not change significantly during small alterations of oxygenation. However, when the PaO_2 falls to below 6,7 kPa, CBF increases in an exponential manner up to 400% of baseline to ensure metabolic needs are met. In contrast, profound hyperoxia (e.g. PaO_2 > 53,3 kPa) results in a 10 – 30% reduction in CBF.

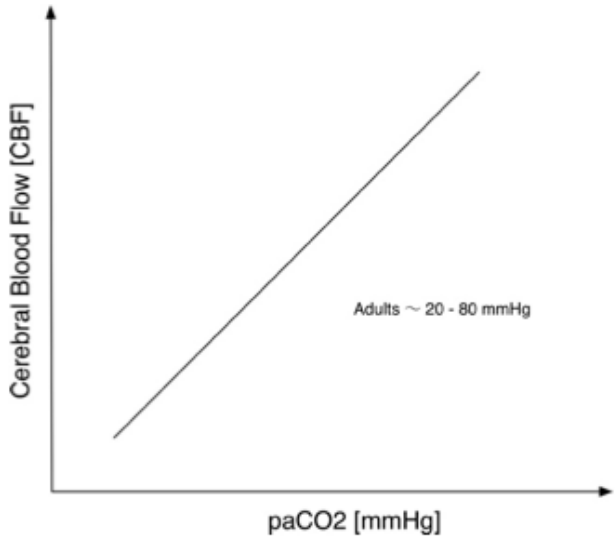


Fig. 3. CO_2-vasoreactivity: linear relationship between arterial partial pressure of carbon dioxide ($paCO_2$) and cerebral blood flow.

PATHOPHYSIOLOGY OF BRAIN ISCHAEMIA

The extent of cerebral injury depends on whether ischemia is global (e.g. circulatory arrest) or focal and whether its duration is temporary or permanent.

Cells die as a consequence of energy and metabolic failure, leading to ionic imbalance and membrane rupture. Dead cells release glutamate, which causes excitotoxic damage and activates a cascade of events in neighbouring cells (Fig 3). The extent of the infarcted area will depend on the length of time that the supplying blood vessel is occluded, the degree of reperfusion and the underlying metabolic rate of the tissue.

Brain energy stores are rapidly depleted during ischemia which leads to

- depolarization
- release of Glutamate, an excitatory neurotransmitter which causes excitotoxic damage
- ionic imbalances
- membrane rupture
- altered calcium homeostasis
- free radical production
- activation of proteases
- and initiation of apoptosis

Vulnerability to injury varies between cell subtypes. The neurons located in the hippocampus, cortex, cerebellum, corpus striatum, and thalamus are particularly susceptible to injury.

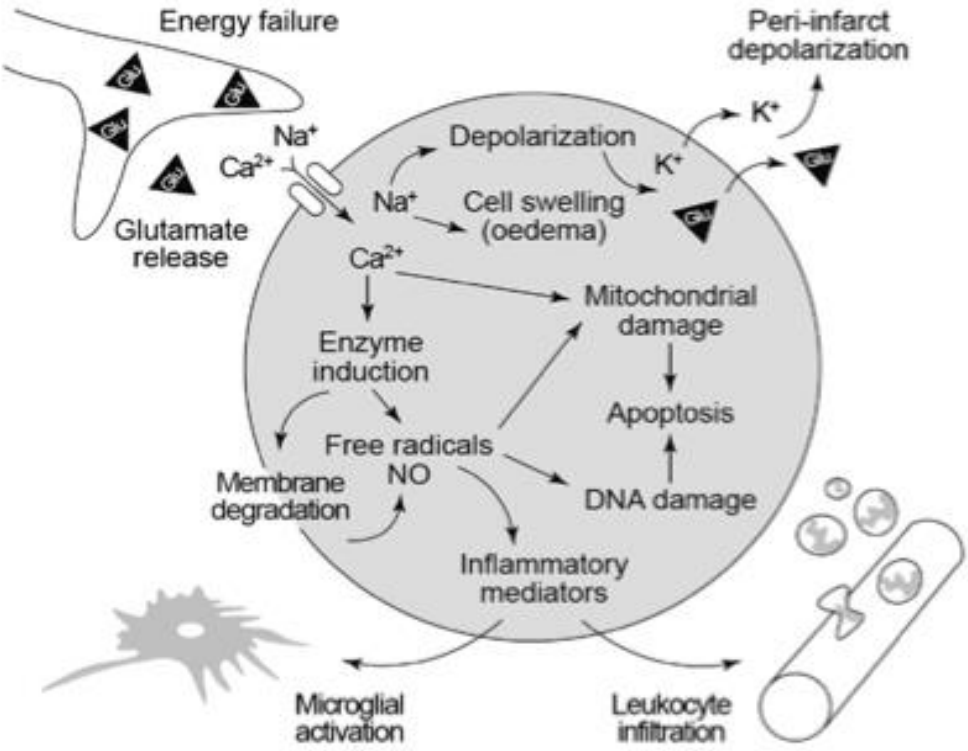


Fig 4. Simplified overview of pathophysiological mechanisms in the focally ischaemic brain. Energy failure leads to the depolarizations of neurons. Activation of specific glutamate receptors dramatically increases intracellular levels of calcium (Ca^{2+}), sodium (Na^{+}), and chloride (Cl–) while potassium (K^{+}) is released into the extracellular space. Diffusion of glutamate and potassium in the extracellular space can propagate a series of spreading waves of depolarization (peri-infarct depolarizations). Water shifts to the intracellular space via osmotic gradients and cells swell (edema). The universal intracellular messenger calcium activates a number of enzymes such as proteases, lipases, endonucleases etc. Free radicals and nitric oxide (NO) are generated which in turn damages membranes, mitochondria and also DNA itself, all of which may trigger apoptosis by intrinsic mechanisms. Inflammatory mediators are released to attract and activate immunocompetent cells such as microglia and blood-borne inflammatory cells.

NEUROPROTECTION DURING CARDIAC SURGERY

Cerebral injury related to cardiac surgery continues to be a focus of intense investigation not only because of its devastating clinical nature but also because of its strong association with mortality, long hospitalization, health resource utilization, and impaired quality of life after surgery.

Incidence of cerebral injury post-cardiac surgery

Rates of CNS injury vary between studies, but a large multicentre study found an overall 6.1% incidence of adverse cerebral outcomes. Other studies, examining only neurocognitive dysfunction, have reported incidences approaching 60%. A large European study involving more than 16,000 patients reported the following injury rates:

OPCAB	1.9%;
CABG	3.8%;
Aortic valve operations	4.8%;
CABG combined with valve procedures	7.4%
Mitral valve operations	8.8%
Multiple-valve procedures	9.7%.

Mechanisms of cerebral injury related to cardiac surgery

The two main sources of cerebral injury from cardiac surgery are **cerebral embolism** and **cerebral hypoperfusion**. Investigators using sensitive diffusion-weighted magnetic resonance imaging methods have reported that 30 – 45% of patients develop new cerebral ischemic injury after cardiac surgery. These lesions typically have an embolic and/or hypoperfusion imaging signature.

The clinical manifestations likely depend on the size and location of the injury (e.g. motor areas vs areas involved with cognition). Primary cerebral hemorrhage is a rare cause of cerebral injury despite the high levels of anticoagulation used during cardiopulmonary bypass (CPB). Inflammatory processes resulting from CPB and organ ischemia/reperfusion may further contribute to injury.

1. Cerebral embolism

Brain imaging studies suggest that 30 – 50% of strokes that occur after cardiac surgery result from cerebral macroembolism, likely arising from atherosclerosis of the ascending aorta in many patients. Cerebral microemboli (< 200 µm) occurring in the cerebral circulation have been demonstrated by retinal fluorescein angiography at autopsy and with transcranial Doppler (TCD) monitoring of the middle cerebral artery (MCA).

Cerebral microemboli may be gaseous or composed of particulate material. Sources of gaseous emboli include an open left-sided cardiac chamber or air entrained into the CPB circuit.

Particulate emboli have multiple sources:

- Atherosclerotic burden of the aorta has been found to be associated with the number of TCD-detected cerebral micro embolic signals during CABG surgery.
- Lipogenous emboli detected at autopsy on non-surviving cardiac surgical patients are caused by fat arising from the cardiotomy suction aspirate which gets returned to the CPB reservoir. Current CPB filters are inefficient at removing fatty material.

It is likely that the *composition* and not the *number* of cerebral microemboli are more important for determining the manifestations of cerebral injury.

2. Cerebral hypoperfusion

Data show that as many as 27 – 43% of patients experience regional or global cerebral O_2 desaturations during CPB, which indicates cerebral O_2 demand/delivery mismatch. The importance of cerebral hypoperfusion as a cause of perioperative stroke is emphasized by Gottesman et al[1]

- They found that 68% of 98 strokes after cardiac surgery were hypoperfusion-type watershed strokes based on diffusion-weighted MRI findings.
- A decrease in mean arterial pressure (MAP) during CPB ≥ 10 mmHg from baseline was associated with a 3-fold higher risk for watershed stroke.

Cerebral hypoperfusion might be of particular concern during “off pump” surgery. In this situation, displacement of the heart may lead to systemic hypotension and cerebral venous hypertension. Episodes of cerebral hypoxemia were found with EEG and cerebral oximetry monitoring in 15% of 550 patients undergoing off-pump CABG surgery.

1. Stroke. 2006; 37:2306-2311.

NEUROPROTECTION STRATEGIES: CPB MANAGEMENT

Conduct of CPB

1.Membrane oxygenator

Oxygenators have undergone considerable development over the years. Early studies compared the two types of oxygenators (bubble versus membrane). Padayachee and colleagues demonstrated that membrane oxygenators produced fewer cerebral microemboli on transcranial Doppler when compared with bubble oxygenators.[2] Studies have also suggested that postoperative cognitive dysfunction (POCD) is reduced when membrane oxygenators are used compared with bubble oxygenators. The almost universal use of membrane oxygenators these days is likely to have a beneficial effect on neuropsychological test outcome

2. Arterial line filter

A 2.40 µm arterial line filter is considered the standard of care for CPB. Arterial line filters are designed to prevent extraneous matter in the circuit from entering the patient.
Studies in favour for usage of arterial line filters:

- Two studies found that the number of microemboli detected in the middle cerebral artery was significantly reduced when an arterial line filter was used.
- Pugsley and co-workers found less POCD in the filter group[3]
    - 46% POCD in the filter group versus 71% POCD in the nonfilter group 8 days after surgery.
    - 8% POCD in the filter group versus 27% POCD in the nonfilter group 8 weeks after surgery.

3. pH management

Management of pH during hypothermia can be carried out as pH-stat or α-stat
Evidence: In adult patients, several independent, prospective randomized trials have shown that using alpha-stat management during moderate hypothermia produces better neurologic outcomes than observed with pH stat management. These data have led to an evidence based recommendation (ACC/AHA class I, level A) that alpha-stat management be used in adults undergoing moderate hypothermic CPB.
It is unclear which strategy is superior in adults when deep hypothermia is used with or without circulatory arrest. In paediatric CPB, however, several human and animal studies suggest that pH-stat management may be more beneficial than alpha stat management for infants. These studies showed that pH stat management produced more homogeneous cooling, less oxygen consumption and better cerebral metabolic recovery than did alpha-stat management.

4.Surface modifications of the CPB circuit

Heparin bonding aimed at reducing inflammatory reactions during surgery have not been conclusively shown to improve postoperative neurocognitive endpoints.

5.Pulsatile versus Nonpulsatile Flow

Although nonpulsatile CPB is the most commonly practiced form of perfusion, pulsatile flow has been recommended for being more physiologic.
Evidence:

- Murkin and colleagues examined the neuropsychological benefits of pulsatile over nonpulsatile flow and found no significant differences in outcome.[4]

2.Padayachee TS et al: The detection of microemboli in the middle cerebral artery during cardiopulmonary bypass: A transcranial Doppler ultrasound investigation using membrane and bubble oxygenators. Ann Thorac Surg 44:298-302, 1987
3.Pugsley W et al: the impact of microemboli during cardiopulmonary bypass on neuropsychological functioning. Stroke 25:1393-1399,1994
4.Murkin JM et al: A randomized study of the influence of perfusion technique and pH management strategy in 316 pts undergoing coronary artery bypass surgery. J Thorac Cardiovasc Surg 110:346-362,1995

Maneuvers to reduce cerebral emboli during CPB:

1.Epiaortic ultrasound

Manipulations of the atherosclerotic aorta during surgery may dislodge atheroemboli and lead to stroke, new brain MRI lesions, TCD-detected cerebral emboli and possibly neurocognitive dysfunction. In patients presenting with stroke, aortic atherosclerosis is associated with blood hypercoagulability, which increases the risk for recurrent stroke and death. Two clinical issues related to atherosclerosis of the aorta are its detection and its surgical management.
Epiaortic ultrasound is more sensitive than direct palpation or TEE for detecting atherosclerosis of the ascending aorta. This method allows the surgeon to identify and avoid atheroma during aortic cannulation and cross clamping. Approaches to surgical management of patients found to have an atherosclerotic aorta include:

a) converting to off-pump surgery

b) using alternative sites for CPB cannulation

c) using the single-cross clamp technique to avoid partial aortic occlusion clamping for proximal bypass graft anastomosis

d) using fibrillatory arrest rather than cardioplegic arrest to avoid cross-clamping

e) avoiding proximal anastomosis by using arterial grafts

f) replacing the ascending aorta under circulatory arrest

Improved neurological outcomes are reported with epiaortic ultrasound-guided surgery and with practices that minimize the risk for embolization.

2.The use of in-line leukocyte-depleting filters

There is limited data available to support a benefit from using in-line leukocyte depleting filters

3. Modified aortic CPB cannulae

There is limited data available to support a benefit of modified aortic CPB cannulae for reducing cerebral injury.

4. Mediastinal insufflation with CO_2

The aim with CO_2 insufflation is to increase the rate of absorption of intravascular emboli by substituting the more soluble CO_2 for air in the surgical wound. This may reduce the number of arterial emboli.
Evidence: In a study of 80 patients undergoing open chamber cardiac surgery, flooding of the surgical field with CO_2 resulted in preserved P300 auditory evoked potentials compared with patients not receiving this intervention (P300 auditory evoked potential is a sensitive marker for subtle cognitive changes)
…However, neurocognitive outcomes did not differ between the CO_2 insufflation and control groups.

5.Cardiotomy suction aspirate

Cardiotomy suction aspirate is high in lipid content and is a source of cerebral lipid microemboli in experimental canine CPB. Many centers adopted a practice of either discarding or processing cardiotomy suction aspirate before returning the blood to the CPB circuit. As platelets and coagulation factors are lost with either approach, this practice might increase the frequency of blood transfusions when the suction volume is high. This is an important consideration as transfusion of allogeneic packed red blood cells and platelets are associated with increased risk for stroke after cardiac surgery.

Evidence against processing of cardiotomy suction aspirate:

- Rubens et al [5] reported no difference in the frequency of neurocognitive dysfunction 1 week or 3 months after CABG and/or aortic valve surgery when cardiotomy blood was processed with a cell saver compared with direct return to the CPB circuit.

Evidence in favor of processing of cardiotomy suction aspirate:

- Djaiani et al [6] found that processing cardiotomy blood with a continuous-flow cell saver led to a significantly lower rate of neurocognitive dysfunction 6 weeks after CABG surgery compared with controls. These benefits were not sustained after 1 year of follow-up.

Neither study showed a difference in the number of TCD embolic signals between cell-saver and control groups. In both studies, patients in the cell-saver group had higher rates of transfusion than controls. Thus, the data are conflicting on whether the routine processing of cardiotomy suction aspirate with a cell saver improves neurological outcomes. Any benefits might depend on the volume of aspirated blood and/or the type of device used. Thus, in situations where large blood loss is not expected, avoiding the return of unprocessed cardiotomy suction aspirate to the CPB circuit is reasonable.

Blood Pressure Management:

Most centers target MAP during CPB to > 50 mmHg, but lower pressures frequently occur, particularly during CPB initiation. This practice is based on the fact that CBF-MAP autoregulation is intact using □□α stat management and based on a concern that higher MAP might increase CBF and embolic load. Whether this low MAP target is appropriate for the rising proportion of patients with impaired autoregulation (e.g., those with diabetes, prior stroke, and hypertension) is not clear.

Evidence:

- Gottesman et al [7] has shown a relationship between a decrease in MAP during CPB ≥ 10 mmHg from baseline and a risk for watershed stroke detected by MRI.
- Gold et al [8] randomized patients to either a target MAP on CPB of 50 – 60 mmHg or 80 – 100 mmHg. Fewer combined endpoints of myocardial infarction and stroke were recorded in the "high" than in the "low" MAP group (p=0.026), but there were no differences in the frequency of neurocognitive dysfunction.
- Other data suggest that higher MAP during CPB might improve neurological outcomes for patients with atherosclerosis of the aorta.

Red Cell Transfusion Triggers:

Blood conservation strategies have led to acceptance of anemia during CPB in order to avoid risks from allogeneic blood transfusion. On the other hand, retrospective analyses have linked both preoperative and intraoperative anemia with adverse outcomes, particularly when hematocrit is < 21% during CPB. Nonetheless, transfusion targets during or after CPB have not been prospectively defined, particularly with regard to reducing adverse neurological outcomes. The Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists clinical practice guidelines recommends the following: *"For patients on CPB with risk for critical end-organ ischemia/injury, it is not unreasonable to keep hemoglobin level at 7 g/dL or more.*

5.Circulation. 2007; 116 [suppl I](I-89-I-97).
6.Circulation. 2007; 116:1888-1895.
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Blood Glucose Control:

Diabetes is recognized as a risk factor for stroke and delirium after cardiac operations.

Hyperglycaemia is extremely common during cardiac surgical procedures because of the

- stress response to surgery and CPB
- the resultant increases in circulating catecholamines and cortisol
- hypothermia induced reductions in insulin effectiveness.

Experimental evidence has revealed a relationship between hyperglycaemia and worse outcome after

different types of neurologic injury. However, attenuating the hyperglycemic response to cardiac surgery or CPB has proved difficult. Furthermore, concerns exist regarding inducing even a single episode of severe hypoglycaemia with aggressive attempts to control glucose levels. In a randomized, prospective study of 400 cardiac surgical patients managed with either tight glucose control (the use of intravenous insulin to maintain intraoperative glucose levels at 80 to 100 mg/dl) or conventional management (glucose level < 200 mg/dl), the investigators found a significantly higher incidence of stroke in the tight control group. More recent guidelines recommend that in both diabetic and nondiabetic patients, blood glucose levels should be maintained at 140mg/dl or lower. The mechanisms by which normoglycaemia may protect neuronal tissue include decreases in intracellular lactic acidosis along with decreases in membrane permeability and reduced oedema of endothelial cells, neuroglia, and neurons.

Temperature Management:

Since the early days of cardiac surgery when it was shown that hypothermia could prolong the safe period of circulatory arrest, hypothermic perfusion has been used routinely by the majority of surgeons for both valve and coronary artery bypass graft (CABG) surgery.

Protective effects of hypothermia and deleterious effects of hyperthermia during cerebral ischemia	
Hypothermia	Hyperthermia
Favorable balance between oxygen supply and demand - ↓ $CMRO_2$	Imbalance between oxygen supply and demand - ↑ $CMRO_2$
↓ Excitotoxic neurotransmitter release	↑ Excitotoxic neurotransmitter release
↓ Blood brain barrier permeability	↑ Blood brain barrier permeability
↓ Inflammatory response	↑ Inflammatory response
	↑ Free radical production
	↑ Intracellular acidosis
	Destabilized cytoskeleton

Evidence:
Despite its widespread use, there is little evidence that hypothermia is neuroprotective during cardiac surgery. The ineffectiveness of hypothermia might be explained by the absence of hypothermia during all periods of cerebral risk or inadvertent hyperthermia with re- warming during CPB. The latter might result from the proximity of the aortic cannula (returning warm blood) to cerebral vessels and/or inaccurate patient temperature monitoring that underestimate brain temperature. Rapid re- warming and postoperative hyperthermia are associated with risk for neurological complications. Neurons may be injured by rewarming to 38 °C and it has been suggested that rapid rewarming may force anesthetic and other gases out of solution and thereby produce microemboli.

Deep hypothermic circulatory arrest
DHCA involves reducing the patient's core temperature to profoundly hypothermic levels (15 °C – 22 °C) before globally interrupting blood flow to the body, draining all the blood out of the patient and collecting it in the extracorporeal circuit reservoir. In adults this procedure is primarily used during surgical repair of the aorta, especially in cases of dissection or aneurysm involving the transverse arch. Deliberate hypothermia with systemic cooling is the only reliable method of neuroprotection during complete global ischemia. Some clinicians also put ice bags on the patient's head to augment or to maintain cerebral cooling. Pharmacologic approaches to neuroprotection, such as administering steroids to reduce inflammation or Barbiturates or Propofol to induce burst suppression are used in some centres although evidence to support their efficacy in the setting of complete global ischemia is scant. Furthermore, if the EEG is monitored, it is important to induce EEG isoelectricity with hypothermia before commencing the period of circulatory arrest rather than relying on supplemental Barbiturates or Propofol to provide neuroprotection.

NEUROPROTECTION: AVOIDING CPB

The resurgence of off-pump coronary artery bypass (OPCAB) surgery as a common technique for multivessel revascularization has paved the way for research into isolating the role that CPB plays in neurologic and neuropsychological decline after CABG surgery. Although many of the early studies conducted were retrospective in design and therefore potentially biased in that the patients were specially selected to undergo OPCAB surgery, they provided some evidence that OPCAB surgery may lead to a reduction in microemboli and strokes. The majority of the evidence are however not conclusive on the matter.

Evidence:

- Three meta-analysis studies show a trend toward an advantage for OPCAB over conventional CABG for incidence of stroke but failed to find a significant difference.
- Studies reporting neuropsychological outcome are equally inconsistent.
    - Poorer cognitive outcome at both 1 and 10 weeks was reported in patients undergoing on-pump surgery compared with OPCAB.
    - A large (*N* = 281) randomized study found that neuropsychological performance at 3 months after surgery was better in patients undergoing OPCAB; however, these differences had disappeared by the 12 month and 5-year follow-up assessments.
- Subjective accounts of cognitive outcome have also been found to be similar at 1 year after surgery.

NEUROPROTECTION: PHARMACOLOGICAL MEASURES

Multiple drugs have been tested as neuroprotectants during cardiac surgery with mostly disappointing results. Agents that have shown neuroprotective effects in vitro via multiple mechanisms include: Volatile agents, Barbiturates, Propofol, Calcium channel blockers, NMDA receptor antagonists, GABA receptor blockers, Anti-inflammatory agents, Anti-oxidants,17β-estradiol, Magnesium and Lignocaine.

Important limitations with existing trials of neuroprotection during cardiac surgery must be considered in interpreting the mostly negative results. These include:

- evaluation of drugs with marginally positive pre-clinical data,
- the reliance on laboratory models for data may not replicate clinical injury,
- often small study size,
- neurological assessments are limited to only one aspect of cerebral injury (e.g. cognitive function).

A systematic literature review, nonetheless, concluded that evidence was insufficient to choose one anaesthetic over another for the purposes of cerebral protection.

Volatile anaesthetics

The proposed mechanisms of neuroprotection from inhalational agents include:

- Reduction of cerebral metabolism and ICP
- Suppression of seizures and sympathetic discharge
- Inhibition of synaptic Glutamate release
- Activation of inhibitory gamma-amiobutyric acid (GABA) and glycine receptors
- Minimization of intracellular Ca^{2+} accumulation
- Minimization of free radical accumulation

Evidence: There is general agreement that volatile anesthetics reduce ischemic cerebral injury. Isoflurane neuroprotection has been demonstrated in a variety of experimental models of ischemia, including hemispheric, focal and near complete ischemia. The available data also suggest that both Sevoflurane and Desflurane can reduce ischemic cerebral injury. There does not appear to be a substantial difference among the volatile agents with regard to neuroprotective efficacy. In terms of duration of the neuroprotection acquired from inhalational agents, the available data suggest that long-

term neuroprotection may be provided, provided that the severity of injury is of mild to moderate intensity. In the setting of severe ischemia, infarct expansion will preclude long-term neuroprotection.

The noble gas Xenon, which is currently undergoing trials as an anaesthetic agent in patients, reduces the extent of cerebral infarction in rodents subjected to focal ischemia possibly by NMDA-receptor blockade. However, clinical trials investigating the neuroprotective potency of Xenon are still lacking.

Hypnotics

Studies in laboratory animals have shown that Barbiturates as well as Propofol reduce infarct size and improve neurologic outcome following focal or incomplete global cerebral ischemia as long as physiological variables were controlled during the experiments.

In contrast Etomidate worsens neurologic outcome.

While experimental data support the preventive neuroprotective effects of hypnotic agents, there is no clinical evidence to support the convincing positive data.

Barbiturates:

- Infusion of Thiopentone (total dose during extracorporeal circulation: 39.5 ± 8.4 mg/kg iv) in patients undergoing cardiac surgery with normothermic cardiopulmonary bypass insignificantly reduced postoperative neuropsychological deficits.
- Barbiturates infused to comatose patients within the first hour following cardiopulmonary resuscitation were ineffective to reduce mortality as well as neurological deficits in survivors compared to standard ICU treatment.
- Barbiturates may be beneficial in patients with severe head injury and refractory intracranial hypertension as long as systemic hemodynamic stability was maintained.

Propofol

- Suggested as an alternative to Barbiturates in patients undergoing cardiac surgery or sedation following head injury due to a favorable context-sensitive half time.

Calcium channel blockers

The proposed mechanisms of neuronal protection by Ca^{2+} channel blockers include

- cerebral vasodilation
- prevention of vasospasm
- reduced Ca^{2+} influx
- modulation of free fatty acid metabolism.

Evidence:

Unfortunately, the results in animal models are rather contradictory. While several studies found decreases in neuronal injury and improved outcome following focal ischemia, others have failed to produce protection with Ca^{2+} channel blockers.

Magnesium

The potential neuroprotective mechanisms of magnesium include reduction of the presynaptic Glutamate release, blockade of NMDA-receptors, improvement of mitochondrial calcium buffering, blockade of calcium entry via voltage-gated channels and relaxation of smooth muscles.

Evidence:

- Magnesium was investigated as a neuroprotectant in a randomized, blinded, placebo-controlled trial in 350 patients undergoing cardiac surgery in a dose that increased serum

levels 1½ to 2 times normal. Magnesium use was associated with improved cognitive performance 24 to 96 hours after surgery compared with placebo, but these benefits were not present 3 months after cardiac surgery.

- Recently, Mathew et al [9] reported the results of a prospectively randomized, placebo controlled blinded trial showing Magnesium did not reduce the frequency of neurocognitive dysfunction after cardiac surgery.

Lignocaine

Lignocaine has multiple neuroprotectant properties: ↓ Glutamate release, ↓ ischemic ion flux, preservation of cerebral blood flow and ↓ cerebral metabolism.
Evidence: Two prospectively randomized placebo-controlled studies failed to show improvements in the frequency of neurocognitive dysfunction after cardiac surgery.

Erythropoietin

Cerebral erythropoietin is produced in the hippocampus, internal capsule, the cortex, endothelial cells and astrocytes. Neurons, microglia, astrocytes and cerebral endothelial cells express erythropoietin receptors. Hypoxia and ischemia have been recognized as important driving forces of Erythropoietin expression in the brain, suggesting that Erythropoietin is part of a self-regulating physiological protection mechanism to prevent neuronal injury. Systemic application of the growth factor Erythropoietin stimulates neurogenesis, neuronal differentiation, and activates brain neurotrophic, anti-apoptotic, anti-oxidant, and anti-inflammatory signaling. These multiple protective approaches were confirmed in animal models of focal and global cerebral infarction.

9.Abstract 10 SCA Annual Mtg 2009

Glucocorticoids

The proposed mechanisms by which glucocorticoids reduce neuronal injury include increased order of lipid bilayers, free radical scavenging, and prevention of free fatty acid-accumulation by inhibition of lipid peroxidation.

Evidence: Studies in patients with acute stroke or following cardiac arrest could not demonstrate a significant reduction in infarct size or improvement in neurologic outcome with the infusion of glucocorticoids (e.g. Dexamethasone or Methylprednisolone) despite some positive effects in experimental preparations.

Anti-excitotoxic interventions

Glutamate and Aspartate are known as excitatory neurotransmitters that stimulate NMDA- and AMPA-receptors. Since the activation of these receptors initiates catabolic intracellular processes, blockade of NMDA and AMPA receptors may protect cerebral tissue.

NMDA receptors are hyper activated during neuronal injury. Ketamine and Magnesium represent non-competitive NMDA receptor antagonists. In animal models of focal cerebral ischemia and in head injury, Ketamine reduced neuronal injury and improved outcome. This was not shown in global cerebral ischemia.

Another approach to minimize excitotoxic damage is the blockade of the AMPA receptor. However, in a phase-III trial the AMPA antagonist YM872 (ARTIST þ trial) was abandoned after failing an interim futility analysis.

Decreased excitotoxicity might also be achieved by activation of the inhibiting GABA receptor. However, the GABA agonist, Clomethiazole has failed to improve neurologic outcome when administered within 12 h after the onset of stroke.

In summary, until today no anti-excitotoxic drug was effective in clinical multicenter trials.

Anti-inflammatory interventions

Post stroke inflammation is associated with progression of neuronal damage. Therefore, anti-inflammation represents a neuroprotective strategy, which includes inhibition of inflammatory mediators like cytokines (IL-1, IL-6, NF-$k\beta$) and of adhesion molecules (ICAM, VCAM, integrins).

Despite many successful experimental studies, only few clinical studies have been performed. Until today no multicenter trial was able to prove the validity of anti-inflammatory therapeutic strategies in patients with neuronal injury.

Antioxidants

High concentrations of free radicals cause cellular degeneration and the disruption of brain–blood barrier. Antioxidants have been neuroprotective in several in vitro models of oxidative cell damage and in vivo models of cerebral ischemia. However, none of them have been successfully translated into clinical practice.

NEUROPROTECTION: NEUROMONITORING

Near infrared cerebral oximetry (NIRS)

- NIRS is increasingly used to identify episodes of cerebral hypoperfusion during cardiac surgery with and without CPB.
- The FDA has approved two NIRS devices.
  - The INVOS device is a dual-channel continuous wave spectrometer designed to measure changes in regional O_2 saturation of the frontal lobe.
  - The Foresight device monitors phase shifts at 754 nm, 785 nm, and 816 nm in reference to 780 nm to measure absolute brain tissue oxygenation.
- NIRS provides an estimate of oxyhaemoglobin saturation that is weighted toward venous blood, thus indicating the adequacy of regional cerebral O_2 supply vs demand.
- Cerebral O_2 desaturations detected with NIRS are associated with postoperative cognitive decline and stroke.
- Evidence:
  - In a randomized study of 200 CABG surgical patients, NIRS-guided interventions were associated with less major organ injury (death, MI, stroke) and shorter ICU length of stay compared with the non-monitored group.
  - Interventions for improving regional cerebral O_2 saturation are:
    - ensuring adequate CPB flow or cardiac output when not on CPB
    - increasing the MAP
    - avoiding hypocarbia (reducing gas-inflow during CPB)
    - deepening anesthesia
    - increasing the FiO_2
    - instituting pulsatile CPB flow
    - consider transfusion if indicated
    - administer anti-convulsant if indicated
    - consider hypothermia

EVIDENCE BASED STRATEGIES FOR CEREBRAL PROTECTION DURING CARDIAC SURGERY

Strategies Supported by Clinical Investigations

- Epiaortic ultrasound for detection of atherosclerosis of the ascending aorta
- Avoidance of hyperthermia during CPB re-warming

Strategies With Reasonable Level of Clinical Evidence

- The use of a membrane oxygenator and an arterial line filter (≤40 µm) during CPB
- α-stat pH management during CPB
- Single cross-clamp technique for proximal CABG anastomosis patients at risk for atheroembolism
- NIRS monitoring especially in high-risk patients
- Arterial blood pressure kept >70 mmHg during CPB in high-risk patients

Strategies That Are Acceptable and Considered Reasonable Treatment by Most Experts

- Serum glucose should be kept <140 mg/dL with an infusion of insulin
- Consider processing cardiotomy suction aspirate with a cell-saver device
- Transfusion of packed red blood cells should be considered in high-risk patients when hemoglobin
- Is ≤ 7 g/dL or higher depending on other patient-specific considerations

PRE AND POSTCONDITIONING

An unconventional way to protect the brain seems to enhance its tolerance to ischemic or anoxic insults by preconditioning. By a brief sublethal episode of ischemia, cells become resistant to subsequent lethal events, which has first been proven for the myocardium and later for the brain. Shortly after preconditioning the brain develops tolerance towards the same or even different subsequent injury.

The preconditioning cascade includes stimuli that via sensors and transducers activate downstream transcription factors, which ultimately modulates gene expression. Novel proteins may then act to enhance the resistance of neurons to ischemia.

Tolerance induced by preconditioning changes the expression of genes involved in the suppression of metabolic pathways, immune responses, ion-channel activity and blood coagulation. These protection concepts include the antagonisation of mechanisms of damage, the increase in substrate delivery, the decrease in energy use and the improvement of recovery. Besides the classical preconditioning of using short sublethal ischemia, drugs like anaesthetic agents, molecules like glutamate, inflammatory cytokines, caspases and adenosine triphosphate-sensitive potassium (KATP) channel openers can also precondition brain tissue and increase their tolerance towards injury.

If the concept of preconditioning is clinically valid, patients with transient ischemic attacks should have an attenuated severity of subsequent stroke and an improved outcome compared to patients without a preceding event. Most of pro- and retrospective clinical studies were able to show this improvement.

The clinical benefit of pharmacological preconditioning might include patients undergoing cardiovascular surgery, neurosurgery or patients who sustained a SAH (with possible delayed ischemic deficits due to vasospasm). These patients are at risk of developing brain injury in the near future.

Of particular clinical and pharmacologic interest are the mitochondrial KATP channel openers, erythropoietin, and volatile anaesthetics.

CONCLUSIONS

Cerebral injury from cardiac surgery remains an important source of patient morbidity and mortality that will likely persist in light of the continuing aging of surgical patients. A comprehensive approach to neuroprotection that includes interventions to reduce cerebral embolism and ensure cerebral perfusion is associated with improved neurological outcomes. Future developments will likely involve improved patient monitoring, refinement of equipment and perioperative care and hopefully novel compounds that interrupt neuronal ischemic injury pathways.

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Anaesthesia for interventional neuroradiology /neuroendovascular procedures

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There are several excellent reviews covering the anaesthetic implications of this new field (1, 2, 3, 4), although relatively little literature exists to support specific anaesthetic techniques.

What lesions are INR techniques used to treat?

The lesions treated via the endovascular route include:

1. Aneurysms

Common lesions in adults with a population prevalence between 1-5% although it is estimated that 50-80% never rupture. Aetiology is mostly sporadic although there is a rarer familial form.They are strongly associated with autosomal dominant polycystic kidneys and up to 40% of them have an aneurysm with up to 30% having multiple aneurysms. Also associated with high flow vessels to brain AVM's; and thought to be associated with a collection of "Collagen-vascular disorders" (Fibromuscular dysplasia, Marfan's syndrome, Ehlers Danlos syndrome type IV). There is no clear understanding of what causes their formation, growth and rupture but hypertension (OR 1.51) and smoking (OR 1.57) induced vascular changes thought to play a role. Their combined OR is 2.28 (CI 1.29-4.02).

Patients who have had a recent Sub-arachnoid haemorrhage will have the CNS and systemic consequences as would a patient having open craniotomy for clipping, and these need to considered when planning and performing anaesthesia. Especially important is the presence of cerebal vasospasm.

The vast majority can be treated endovascularly and in the UK currently 85% are treated endovascularly. In Cape Town we see about 220 aneurysms per year and 87% are treated endovascularly. The Cape Town group have published their results showing less ICU requirements, decreased ALOS and decreased cost.

Ruptured aneurysms have a 30% risk of rebleeding in first month, highest in first 7 days, and rebleeding carries a 60% risk of death. Medium term analysis of the ISAT trial showed INR to be equivalent or slightly better than open clipping. The probability of death or dependency was significantly greater in the neurosurgical group than in the endovascular group. There remains a centre-dependent variation in treatment practices, with the endovascular approach used in 85% of SAH patients in the UK, and between 36 and 98% of patients, in different in centres in the USA.

2. Arteriovenous Malformations (AVM's).

Are the most common pathology after aneurysms, often occurring in young patients. The ARUBA trial demonstrated better outcome in unbled AVM's from medical management over endovascular treatment, decreasing the indication for treatment. The best treatment for ruptured AVM's has not been established in randomized trials. Endovascular treatment is achieved by flow obliteration using N-butyl cyanoacrylate (superglue), Onyx, coils or emboli particles. Procedure related death/severe disability rate is about 7%.

3. Less common pathology treated via the endovascular route includes:
    - Pre-operative embolisation of cerebral and spinal tumours
    - In South Africa we see a lot of carotid cavernous fistulae, following both blunt and penetrating trauma.
    - Embolisation for epistaxis
    - Investigation and treatment (venous angioplasty/venous stenting) of Idiopathic Intracranial Hypertension (IIH)

- Balloon angioplasty for carotid stenosis and vasospasm
- Treatment of acute thromboembolic stroke

There have been interesting developments in thrombotic stroke prevention and treatment. Stroke is 2nd commonest cause of death after IHD, and accounts for 10% of deaths worldwide. 3 recent papers have shown that endovascular treatment for acute ischaemic stroke (either using highly selective tPA or mechanical devices to re-establish flow are no better that systemic tPA given via peripheral vein. So the recent blush of literature describing endovascular treatment is currently put to bed, but from that work has come several papers describing the anaesthetic choices that could be used, and the issues include:.

i) Hypotension:
Retrospective and prospective studies show that for acute ischaemic stroke, that general anaesthesia is associated with a worse outcome. Previous stroke trials have shown that a systolic pressure less than 140mmHg is worse for outcome, and general anaesthesia may be contributory.

ii) Control of ventilation**:**
Carbon dioxide control may be an important element of clinical care. In stroke patients low carbon dioxide may be a more important determinant of outcome than low blood pressure.

4. Tests looking for eloquent areas of the brain, in particular carotid occlusion and Wada and/or SAFE tests.

What is different that you need to know or be aware of?

Equipment
Angiography suites are often not in daily use for anaesthesia provision, or have the older equipment placed in them, so additional care needs to be paid to the checking the anaesthetic equipment.

Remote environment
Fluoroscopy suites are often in a location, far removed from all the clinical and health technology support of the operating room suite, leading some anaesthetic departments to ensure that there are extra anaesthesia staff on hand for the induction and recovery from anaesthesia.

Environment is not always anaesthetic friendly
Radiology suites often make little allowance for placement of anaesthetic equipment and drip stands, and frequently have banks of ceiling mounted screens for the procedure, creating an obstruction in the very area that they wish the anaesthetic personnel to work in.

Temperature control
Fluoroscopy suites are cool due to the computer hardware's temperature requirements, and active measures need to be taken ensure that patients do not cool down excessively, and that if they do that they are returned to normothermia.

Positioning
For neurointervention procedures, the gantry of the image intensifier is required to move around the patient's head, with the two elements close to the head. The patients head typically is on a narrower extension off the top of the bed, and unless the head is carefully placed, the intensifier's movement can catch on the anaesthetic tubing or simply displace the head. Some attention must be given to limiting unneccesary points that could snag, and to strapping the head to the narrow extension.

Anti-coagulation
Once highly selective catheters are used down vessels off the carotid, heparin is frequently used to limited thrombotic complications. ACT is typically targeted close to twice baseline, and usually allowed to reverse spontaneously at the end of the procedure.

Fluid load
Fluid administration requirements are not high due to 2 factors:

- Constant infusion of heparinised crystalloid down intervention catheters
- Contrast used has a very high osmotic load

Recent evidence that endovascular treated patients require less post-op fluids to maintain normovolaemia. Urinary catheters are not obligatory. Hyperglycaemia is considered deleterious and glucose- containing solutions should be avoided. Diabetics should have strictly controlled blood sugar. It is considered prudent to avoid blood glucose above 8.5mmol/L (7.1-8.5mmol/L is target range).

Low stimulation and rapid recovery
Anaesthesia is required to maintaining immobility during the procedure to facilitate imaging and there is minimal stimulation. Often there is a requirement to maintain blood pressure (especially in the vasospasm period post SAH) so anaesthesia without the balance of surgical stimulation makes cardiovascular stability a challenge. Then rapid recovery from anaesthesia is required at the end of the case to facilitate neurologic assessment and monitoring; placing additional pressure on the anaesthetic techniques to match the requirements of the interventional team.

Road mapping
Technique uses injection of radiocontrast media so that vessels are identified on a contrast "run". The images of the vessels' positions is saved and this "Road-map" used to guide the advancing catheter. Any head movement makes the procedure difficult, and dangerous.

Recovery
Many require post-procedure ICU admission and patients must be recovered locally until they are safe to transport to an ICU or must be accompanied by a doctor.
Standard recovery facilities and trained staff need to be available for patients returning to a normal hospital ward and they require recovery to standard discharge criteria.

Transfer to theatre
Indications for direct transfer, usually under anaesthesia, to the operating theatre are usually either due to a procedural complication or failed INR then being followed by open surgery. Both these scenarios need prior planning especially for consent, staffing of theatre; and equipment and staffing requirements for the transfer.

Staff safety and radiation
Studies suggest that the anaesthesiologist on average, may get more than three times the exposure of the interventional radiologist, the differential being due to the configuration of the fluoroscopy beam that results in the anaesthesiologist being exposed to more scatter radiation as well as the interventional team leaving the vicinity for each major 'run" of images..
Recommend that anesthesiologists follow the practice of radiologists and wear leaded glasses to prevent cataracts when monitoring patients during neurointerventional cases.
Three principles should be applied to protect staff from radiation:

i. Maximise distance from the radiation source.
ii. Limit the exposure time, imaging should be stopped when physical attendance to the patient is required
iii. Utilise adequate radiation protection. Lead aprons and thyroid shields must be worn in the procedure rooms.

Complications and managing them
Treating and managing sudden unexpected procedure-specific complications during the intervention (eg, haemorrhage or vascular occlusion), which may involve manipulating systemic or regional blood pressures or reversing heparin. Reported intra-procedural complications rates are in the region of 2.6% for haemorrhage and 13.6% for thromboembolic events 13.6% although only about 6% of those are symptomatic.

i. Vascular perforation/haemorrhage
   Usually presents as an obvious blush on angiography, or the catheter can be seen to be outside of where the vessel is thought to be. Management includes increasing coagulability by reversing heparin with protamine and consider keeping arterial blood pressure low using β-blockers or propofol/thiopentone. The interventional team can then attempt control of the bleeding using a balloon, glue, or coils. When bleeding is controlled then arterial pressure can be raised again.
   If ICP is thought to be significantly raised then hyperventilation and/or osmotic diuresis can be utilised.
ii. Vascular occlusion
   Due to emboli, thrombosis, vasospasm or arterial dissection. In the event of occlusion the goals are to raise the mean arterial pressure (MAP), remove 'hardware" and the interventional

team can consider angioplasty, thrombolytic therapy, Clopidogrel or a intravenous IIb/IIIa inhibitor.

iii. Movement

iv. Air embolism
Open ended catheter is placed into the arterial system with a pressurised flush, creating conditions for air embolism. Some consider it prudent to avoid nitrous oxide.

v. Contrast related
- Allergic
- Hyperosmolar nephropathy
  Contrast media have an osmolality of around 672mOsm. A nephropathy is described with their use, and the risk factors are diabetes, volume depletion, high doses of contrast, nephrotoxic drugs and pre-existing renal failure. Prevention consists of risk stratification, possible avoidance of endovascular treatment, limiting the dose of contrast and considering the prophylactic use of N-acetyl cysteine.

Are there any guidelines or evidence to help guide anaesthetic techniques?

Anaesthetic techniques described include:
- Awake
- MAC/sedation
- General anaesthesia

Choice of anaesthetic technique has mainly been on institutional experience and individual preference. Surveys have shown a preference for general anaesthesia due to eliminating patient movement, and perceived safety and efficiency.

Evidence for specific anaesthetic drug choices:

i. Sevoflurane vs Propofol maintenance:
Isoflurane vs Propofol - INR treatment of AVM's. Oral pre-meds, standard induction, alfentanil. Early wakening not different. Medium term assessment better with Isoflurane. Up to 2 hours worse with propofol.

ii. Sevoflurane vs Propofol (INR "procedure")
Standardised induction. 1-3% sevoflurane, propofol, fentanyl or alfentanil analgesia. 50% rise in inspired sevoflurane or 20-50mg bolus propofol. Sevo had shorter time to spontaneous breathing, eye opening and extubation

iii. Sevoflurane vs Propofol - "unruptured aneurysms".
Alfentanil + rocuronium. Sevoflurane group showed faster recovery in spontaneous ventilation, eye opening, extubation, and orientation. Propofol groups received more vasopressors.

Summary: Anaesthetic techniques:
We have a few randomised studies (few hundred patients), tending to show a small early recovery benefit of sevoflurane over propofol TIVA and currently anaesthetic technique is decided by local experience and patient assessment as there is no work demonstrating a better outcome with any one technique.

Extracts from published guidelines from profession bodies

Guidelines for subarachnoid haemorrhage (SAH) published by the American Heart Association and the American Stroke Association (5)

a) On the medical measures to prevent rebleeding after Acute SAH:
- Between the time of aSAH symptom onset and aneurysm obliteration, blood pressure should be controlled with a titratable agent to balance the risk of stroke, hypertension-related rebleeding, and maintenance of cerebral perfusion pressure
- The magnitude of blood pressure control to reduce the risk of rebleeding has not been established, but a decrease in systolic blood pressure to **<**160 mm Hg is reasonable.
- For patients with an unavoidable delay in obliteration of aneurysm, a significant risk of rebleeding, and no compelling medical contraindications, short term (**<**72 hours) therapy with tranexamic acid or aminocaproic acid is reasonable to reduce the risk of early aneurysm rebleeding.

b) On hospital characteristics and systems of care:

- Low-volume hospitals (eg, <10 aSAH cases per year) should consider early transfer of patients with aSAH to high-volume centers (eg, >35 aSAH cases per year).
- Annual monitoring of complication rates for surgical and interventional procedures is reasonable
- A hospital credentialing process to ensure that proper training standards have been met by individual physicians treating brain aneurysms is reasonable.

c) On anaesthetic management:

- "Little information …on anaesthetic management "
- "Choice of technique depends on the institution and the most common techniques are conscious sedation and general anaesthesia" and "general anaesthesia with tracheal intubation is often preferred"
- "General principle that apply to open treatment should apply to endovascular"
    - Avoid hypotension and induced hypotension
    - Little evidence for cardiac pause to control intraop bleeding or decompress a large aneurysm
    - No evidence for hypothermia
    - Avoid high blood glucose (7.1-8.5mmol/L is target range)

Guidelines for acute ischaemic stroke from Society for Neuroscience in Anaesthesiology and Critical Care (SNACC) (6)

"Literature on the anaesthetic management is ….limited"

- Preprocedure evaluation for anesthesia should be done as quickly as possible with the understanding that the risk benefit ratio of proceeding with a limited preoperative anesthetic evaluation for these urgent procedures is not known
- The choice of anesthetic technique and pharmacological agents should be individualized based on clinical characteristics of each patient.
- GA may be preferable in uncooperative or agitated patients or patients with elevated neurological severity who cannot protect their airway
- Local anesthesia with sedation and GA are feasible options for patients with anterior circulation stroke who can protect their airway and are cooperative

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Pituitary surgery

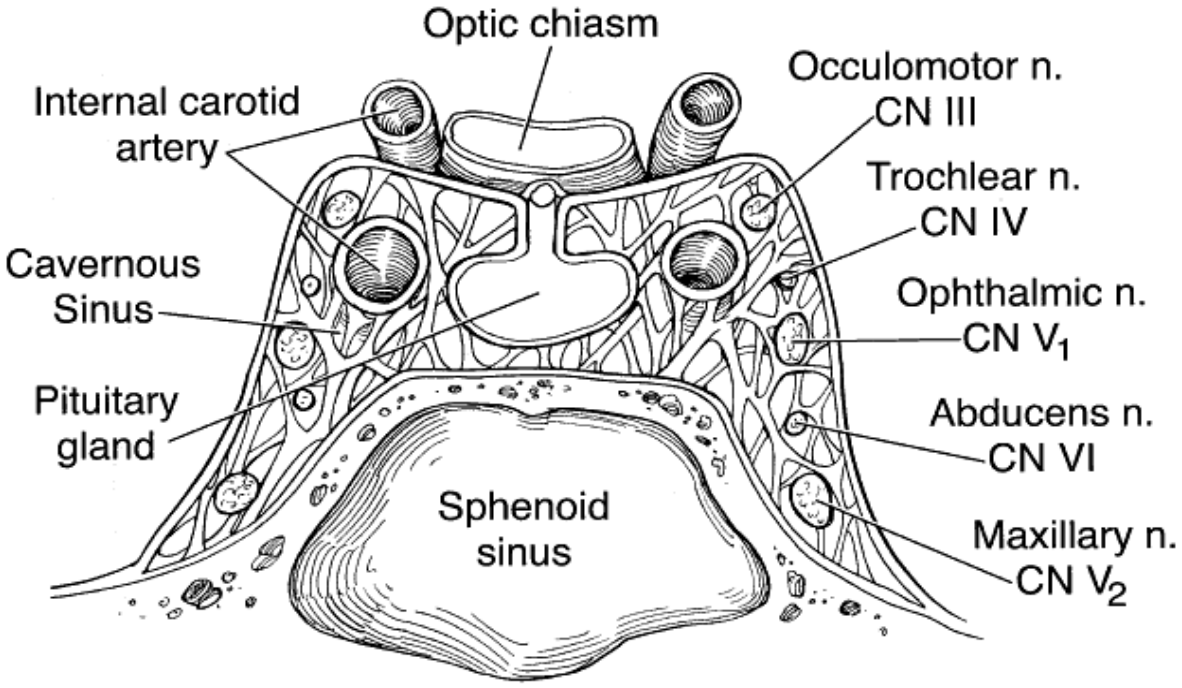
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The pituitary gland has been labeled the 'master gland' within the physiological hierarchy of the endocrine system. It is under the control of the hypothalamus and secretes multiple substances that act either directly or indirectly, via the regulation of other hormones, on the organ systems. The pituitary has far-reaching control over many metabolic pathways, and its dysfunction has similar widespread ramifications.

Anatomy

The pituitary gland is small, weighing about 500-900mg, with a diameter of approximately 10mm. It lies within the *sella turcica* (Turkish saddle/chair) that is itself within the sphenoid bone of the skull. Superiorly, it is in close proximity to the optic chiasm, and is attached to the hypothalamus via the pituitary stalk that passes through an orifice in the diaphragm above the *sella*. Posteriorly, it is limited by the clivus of the sphenoid bone. Laterally, it is surrounded by the cavernous sinus: a plexus of veins containing the carotid arteries and cranial nerves III, IV, VI and the first two branches of cranial nerve V (V_1 ophthalmic, V_2 maxillary). On average, the distance between the pituitary gland and carotid arteries is about 2 to 7mm.



The pituitary gland is divided into two main regions: the anterior *adenohypophysis*, supplied by the superior hypophyseal artery; and the posterior *neurohypophysis,* supplied by the inferior hypophyseal artery. Both arteries are branches of the internal carotid artery. Venous drainage of the gland is via the petrosal sinuses to the internal jugular vein and cavernous sinus. Despite numerous similarities, the anterior and posterior lobes of the pituitary are as structurally and functionally different as their unique embryological origins would suggest.

The **adenohypophysis** has both secretory and non-secretory *(null)* cells. The secretory cells synthesize, store and release hormones in response to upstream hormonal stimulation from the hypothalamus. The hypothalamic hormones reach the anterior pituitary gland via an arterial capillary network surrounding both the hypothalamus and pituitary, and connected via portal vessels that traverse the pituitary stalk. The advantage of this discrete portal system is the strict control of the

release of the pituitary hormones it affords – the concentration of the hypothalamic hormones is far higher in these vessels than in the rest of the body; in other words: a small amount travels a short distance and exerts a precise effect at its target gland, the pituitary.

This hypothalamic stimulation of hormone release by the pituitary is, itself, regulated by negative feedback control by the end-point hormone in a classical long and short loop. For example, rising thyroid hormone levels secreted by the thyroid gland as stimulated by pituitary TSH and hypothalamic TRH, will consequently inhibit the further production of both TSH at the pituitary level and TRH at the hypothalamic level.

In the anterior pituitary:

- The *somatotrophic* cells make up half the cells of the anterior pituitary and produce **growth hormone.**
- *Corticotrophs* secrete **adrenocorticotrophic hormone (ACTH).**
- *Lactotrophs* secrete **prolactin.**
- *Gonadotrophs* secrete **follicle stimulating hormone (FSH) and luteinising hormone (LH).**
- *Thyrotrophs,* less than 5% of the adenohypophyseal cells, secrete **thyroid stimulating hormone (TSH).**

Anterior Pituitary Hormone	Hypothalamic Hormone	Target Organ	Primary Target Organ Hormone or Mediator
GH, somatotropin	Growth hormone-releasing hormone (GHRH) (+) Somatostatin (–)	Liver, muscle, bone, kidney, and others	Insulin-like growth factor-1 (IGF-1)
TSH	Thyrotropin-releasing hormone (TRH) (+)	Thyroid	Thyroxine, triiodothyronine
ACTH	Corticotropin-releasing hormone (CRH) (+)	Adrenal cortex	Glucocorticoids, mineralocorticoids, androgens
FSH & LH	Gonadotropin-releasing hormone (GnRH) (+)[2]	Gonads	Estrogen, progesterone, testosterone
Prolactin	Dopamine (–)	Breast	—

The **neurohypophysis** consists of unmyelinated axons, fenestrated capillaries and glial cells; it remains anatomically continuous with the hypothalamus via the hypothalamo-hypophyseal nerve tract. The axonal cell bodies are in the supraoptic and paraventricular nuclei of the hypothalamus; these neurons synthesize and store oxytocin and anti-diuretic hormone (ADH)/vasopressin, and release them into a similar capillary network associated with the posterior pituitary.

The pituitary gland lies outside the blood-brain barrier, but retains anatomical and functional connections with the brain.

Tumours of the pituitary gland

These are rarely symptomatic with an annual incidence of approximately 1 in 50 000; but are reported as incidental findings in up to 14% of autopsies and 23% of radiological studies requested for unrelated reasons. Although these tumours seldom cause symptoms, their resection (due to primary pituitary adenomas – the most common cause of primary pituitary dysfunction) makes up a fifth of all intracranial neurosurgical procedures.

The pituitary adenoma comprises about 85% of all pituitary tumours, with the other 15% consisting of craniopharyngioma, carcinoma, meningioma, metastasis and even more rarely: astrocytoma, sarcoma etc. The syndrome of multiple endocrine neoplasia 1 (MEN1) is diagnosed in patients with a combination of tumours: pituitary, parathyroid and pancreas (usually an insulinoma) – "all the P's".

About half the adenomas present with symptoms due to the over-secretion of a single hormone, dependent on the original *secreting cell*-type of the adenoma; whilst the other half present due to growth of the *null* cells with symptoms of compression of the normal gland (hormone under-secretion) or compression of the structures adjacent to the *sella*. It is uncommon for the adenoma to result in the over-secretion of more than one hormone, but when this does occur, it is likely to be a combination of growth hormone and prolactin. Tumours resulting in hormone over-secretion are much more likely to be overtly symptomatic early on as the over-secretion plays havoc with multiple metabolic pathways – these tumours tend to be diagnosed relatively early and so are often small in size; whereas the opposite is true of tumours of *null* cell origin – these tend to be larger, the onset of symptoms occurs later and is due to adjacent structure compression and raised intracranial pressure:

- Superior compression affects the **optic chiasm** and the medial retinal fibres, in particular. Remember: the medial retinal fibres 'see' the lateral visual fields. This compression and dysfunction results in **bitemporal superior quadrantanopia** early on, and the classic **bitemporal hemianopia** later.
- Further superior extension may compress the **third ventricle**, obstructing the normal flow of cerebrospinal fluid and resulting in **hydrocephalus** and symptoms and signs of raised intracranial pressure: headache, nausea and vomiting, papilloedema.
- Lateral compression may affect the cavernous sinus and associated **cranial nerves**, resulting in isolated **nerve dysfunction**; or may cause compression of the carotid artery.
- Compression of the whole **pituitary gland** from within may result in gland failure and **pan-hypopituitarism** due to obstruction of the cells, or the pituitary stalk and its portal vessels.

Therefore, pituitary adenomas can be classified according to whether they are functional or non-functional; and whether they are large *macro-adenomas* (>1cm diameter at presentation) or small *micro-adenomas* (<1cm diameter at presentation).

ANTERIOR PITUITARY

Growth hormone-secreting tumours

Growth hormone acts systemically via GH-specific receptors and target cells. It directly stimulates protein synthesis, chondrocyte proliferation, muscle hyperplasia and bone mineralization – it stimulates the growth of long bones and all internal organs except the brain.

Metabolically, it stimulates hepatic gluconeogenesis (whilst inhibiting hepatic glucose uptake), and hepatic and tissue production of *insulin-like growth factor 1.* ILGF-1 is a potent stimulator of cell growth and proliferation throughout the body.

The symptoms and effects of growth hormone over-production manifest differently depending on the ossification state of the epiphyseal plates of the long bones: pre-adolescent GH excess results in **gigantism**; and adult GH excess, after fusion of the growth plates, results in **acromegaly**. If the tumour persists through childhood to adulthood, untreated, the clinical picture changes from gigantism to that characteristic of acromegaly. This serves to remind us that although these are different disorders, they share many aspects of their pathophysiology and characteristics.

Features of acromegaly include:

- **Bone hypertrophy:** Growth of the hands and feet. Coarse facial features and prognathism. Kyphoscoliosis.
- **Airway manifestations:** Thick tongue. Large tonsils, epiglottis and larynx. Splayed teeth. Vocal cord dysfunction due to stretching of the recurrent laryngeal nerve, and crico-arytenoid dysmobility.
- **Cardiovascular disease:** Hypertension and eccentric left ventricular hypertrophy. Diastolic dysfunction with preserved systolic function at rest, but poor functional response to stress with a falling ejection fraction. Cardiomyopathy. Dysrhythmias. Coronary artery insufficiency due to increased demand from the hypertrophied myocardium and decreased supply due to diastolic dysfunction.
- **Peripheral neuropathy:** in particular, carpal tunnel syndrome.
- **Endocrine disturbances:** glucose tolerance or frank diabetes mellitus due to hepatic gluconeogenesis. Some patients may have tumours secreting both GH and prolactin resulting in hyperprolactinaemia. Proximal myopathy.
- **Compressive symptoms:** if the tumour is large enough, it may result in the symptoms discussed previously.

Peri-operative management of growth hormone over-production

1. Airway assessment
   Pre-operative airway assessment, particularly a Mallampati class 1 or 2 score, may provide false comfort to the anaesthetist, and the practitioner may easily under-estimate the potentially difficult acromegalic airway.

   Mask ventilation may be difficult due to facial bone and soft tissue hypertrophy. Jaw hypertrophy may increase the distance from the lips to the larynx. The large tongue, soft palate and epiglottis may obstruct the airway during bag-mask ventilation and may obscure the view during direct laryngoscopy. Hoarseness may indicate recurrent laryngeal nerve injury and a smaller diameter endotracheal tube should be considered.

   Consider: large facemask, long laryngoscope blade, smaller ETT, difficult airway equipment including gum elastic bougie, exchange catheter, video-laryngoscope and fibre-optic scope. A second pair of hands!

2. Obstructive sleep apnoea
   OSA occurs in up to 70% of these patients and is due in part to both the hypertrophied pharyngeal and laryngeal structures, and centrally mediated respiratory drive dysfunction. Monitor post-operatively for hypoxia and apnoea in a high care or ICU setting. Non-invasive ventilation is usually not an option after transsphenoidal pituitary tumour resection as the high upper airway pressures will be transmitted through the sphenoid sinus and may disrupt the surgical site, and result in tension pneumocephalus. Meticulous care must be taken with head positioning and an oral airway device may be necessary.

3. Positioning
   Great care needs to be taken when positioning these patients due to both their abnormally large size, possible kyphoscoliosis and high incidence of peripheral neuropathies. Ensure the theatre table is an appropriate size and has appropriate padding to accommodate the acromegalic patient. Position the limbs in such a way as to avoid tension on peripheral nerves. Theoretically, there is a risk of arterial insufficiency with radial artery cannulation and concomitant carpal tunnel syndrome. The radial artery does not run within the carpal tunnel and should not be affected by tissue hypertrophy and oedema within the tunnel – there is no increased risk of ischaemic complications. However, almost half of these patients *do* have ulnar artery insufficiency as it *does* traverse the carpal tunnel; and so they are radial artery dominant. It may be prudent to consider arterial cannulation at another site.

4. Cardiovascular evaluation
   Assess hypertension and degree of pre-operative control to guide peri-operative mean arterial pressure goals. Enquire about effort tolerance and symptoms of current or previous congestive cardiac failure, and symptoms of ischaemic heart disease. Deteriorating effort

tolerance and cardiac function will necessitate pre-operative echocardiography. A history of angina will direct possible stress testing. Dysrhythmias such as heart block are common and a 12-lead ECG should be a standard investigation.

ACTH-secreting tumours – Cushing's disease

An ACTH-secreting tumour of the pituitary results in overproduction of adrenal corticosteroid and is the primary characteristic of Cushing's disease (as opposed to the syndrome of the same name which applies to strictly to patients who have the classic cushingoid features due to adrenal steroid overproduction, ectopic ACTH-producing tumours or exogenous steroid administration).

Features of Cushing's disease include:

Sign/symptom	Frequency (%)
Truncal obesity	97
Moon face	89
Hypertension	76
Skin atrophy and bruising	75
Diabetes or glucose intolerance	70
Gonadal dysfunction	69
Muscle weakness	68
Hirsutism, acne	56
Mood disorders	55
Osteoporosis	40
Fungal infections	10

Peri-operative management of ACTH over-production

1. Fluids and electrolytes
   Patients should be managed pre-operatively with an aldosterone antagonist such as spironolactone to ameliorate the fluid excess, hypernatraemia and hypokalaemia of excess glucocorticoid production. Evaluate glucose and blood pressure control and optimize as far as possible within the constraints of the ongoing tumour hormone production; investigate potential target organ damage; in particular, ischaemic heart disease – a leading cause of mortality. The glucose intolerance may resolve rapidly after tumour resection – it may be easy to induce hypoglycaemia if pre-operative hypoglycaemic agents are continued without alteration post-operatively.

2. Airway assessment
   Although these patients do tend to be overweight, that in itself is not a risk factor for a difficult airway: the 'moon face' is not associated with difficult bag-mask ventilation; however, the increased neck circumference and posterior 'buffalo hump' may make positioning and intubation difficult. Investigate potential obstructive sleep apnoea and gastro-oesophageal reflux. Proximal myopathy may result in impaired respiratory function post-operatively, especially when paired with OSA.

3. Positioning and asepsis
   Pay careful attention to positioning and padding of these patients as their atrophic skin may be easily damaged by adhesive dressings or tight NIBP cuffs or inadequate padding. Their tendency towards bruising makes this especially important. Their habitus can make intravenous access challenging and their friable skin and thin veins may result in early venous cannulation extravasation. Osteoporosis may be severe with likely pre-existing pathological fractures that can be aggravated by injudicious positioning. Up to a third of all cushingoid patients may have exophthalmos due to increased fat deposition in the retro-orbital space. Special care must be taken when protecting the eyes to avoid corneal abrasion. They are immunologically compromised and so strict asepsis must be adhered to, particularly when placing central lines.

Pituitary hyperthyroidism

A TSH-secreting tumour is rare, often large at presentation with local invasion, and seldom metastasizes. Although this is a secreting tumour, diagnosis can be delayed as the symptoms of hyperthyroidism are often mistakenly ascribed to Graves' disease – that is, primary thyroid gland disease. A pituitary adenoma should be suspected in any patient with elevated T_4 or T_3 **AND** elevated or normal, unsuppressed TSH.

Peri-operative management of pituitary hyperthyroidism

1. Thyroid hormone over-production
   The patient should be physiologically euthyroid unless mass effect symptoms dictate emergency decompression. Octreotide, a somatostatin analogue, is first-line treatment and is started at 50mcg SC injection twice daily. This may be increased to up to 500mcg SC three times daily as required and as tolerated. A beta-blocker can be added to control peripheral conversion of T_4 to T_3 and to reduce some of the symptoms of hyperthyroidism.

2. Hypothyroidism
   Some patients may be rendered hypothyroid at presentation after surgical thyroidectomy or radioactive-iodine based ablation therapy due to a previous incorrect diagnosis of Graves' disease. These patients will need thyroid hormone supplementation with eltroxin, which must be continued until they are euthyroid.

   Consider: large bore intravenous access, invasive arterial monitoring and having treatment on hand for thyroid storm – an unlikely complication, but with a high mortality rate if untreated.

Pituitary hyperprolactinaemia

Although various pituitary diseases can cause elevated serum prolactin levels, the most common cause is a prolactin-secreting pituitary adenoma. Surprisingly, a non-secreting tumour is also likely to increase serum prolactin levels as it compresses the pituitary stalk and prevents one of the prolactin inhibitory factors, hypothalamic dopamine, from reaching the pituitary and exerting its effect. Prolactin is vital for milk production after pregnancy and modulates aspects of reproduction, such that, if in excess, will suppress the gonadotropin-stimulating hormone production resulting in infertility in both men and women.

Symptoms of hyperprolactinaemia are more overt in women with galactorrhoea, amenorrhoea and loss of libido. The latter is likely the most obvious sign in men, associated with oligospermia and erectile dysfunction. Some men may experience galactorrhoea but this is less common due to the smaller amount of breast tissue. A prolactin-secreting adenoma is far more likely to present late in men with symptoms similar to that of a non-secreting tumour; that is, mass effect.

Peri-operative management of pituitary hyperprolactinaemia

1. Dopamine agonist
   Medical management of a prolactinoma is essentially a dopamine agonist, such as bromocryptine, carbergoline or pergolide. Patients prescribed these drugs may suffer some of the long-term complications such as nausea and vomiting, and orthostatic hypotension. All of these symptoms may be exacerbated by general anaesthesia. This needs to be taken into account and compensated for or treated appropriately.

2. Cardiovascular evaluation
   The latter two dopamine agonists mentioned, carbergoline and pergolide, at high doses, are associated with valvular lesions similar to those found in carcinoid syndrome. New onset murmurs or evidence of cardiac failure warrant further investigation. Both drugs have been withdrawn from the US market in 2007.

Gonadotropin-secreting tumours

These tumours are relatively common amongst pituitary adenomas, making up about 25% of all adenomas. They secrete FSH and LH, which affect their target organs, the ovaries or testes; and usually result in symptoms of sexual dysfunction or reproductive disorders. Unfortunately, the differential diagnosis of the constellation of symptoms is long and varied, and the over-production of the hormones leads to little discernible metabolic effect on immediately life-sustaining pathways, so the gonadotropin-secreting tumours tend to present late with symptoms of mass effect.

POSTERIOR PITUITARY

The posterior pituitary secretes **anti-diuretic hormone (ADH)** in response to changing serum osmolality. Osmoreceptors sense increased *serum osmolality* above 285mOsm/kg body water and stimulate the secretion of ADH, which acts via vasopressin receptors to:

- Mediate vascular smooth muscle vasoconstriction.
- Increase renal collecting duct permeability to water, allowing increased water re-absorption from the urine, falling urine output and increasing urine osmolality.

ADH has a short half-life of about 15 minutes and so circulating levels fall quickly as serum osmolality decreases, and its secretion by the posterior pituitary is suppressed.

ADH is also secreted in response to falling *blood pressure and volume* as sensed by aortic arch and carotid sinus baroreceptors, and baroreceptors in the atria and pulmonary vasculature. Its release is, however, much less sensitive to pressure and volume than to osmolality – blood pressure must fall by 10% before ADH levels start to rise. Thereafter, the ADH levels increase exponentially.

Abnormal ADH secretion, both too much and too little, has many causes. Both under- and over-secretion do have some causes in common; namely pituitary tumours (although seldom adenomatous tumours – more likely craniopharyngioma, germinoma or carcinoma) or mass lesions, and destruction/resection of the pituitary gland.

SIADH Syndrome of inappropriate ADH secretion

This describes the clinical situation where ADH secretion continues abnormally in the face of falling serum osmolality. It is characterized by low serum osmolality (<275mOsm/kg body water) and sodium, and high urine osmolality (>100mOsm/kg body water) and sodium, in the presence of clinical euvolaemia and normal salt and water intake. It is the most common cause of euvolaemic hypo-osmolality.

Mild SIADH may be asymptomatic, but as the disease progresses patients will complain of nausea, headache, lethargy and confusion. Seizures and coma may occur when serum sodium falls below 120mmol/l. Mild disease can be managed with limiting water intake and increasing water loss with the use of loop diuretics. A high salt diet can be added to encourage the kidneys to excrete more free water. Medical treatment for severe SIADH favours sodium replacement with 3% hypertonic saline and increases of the serum sodium by 0.5-2mmol/l per hour depending on the severity of the symptoms. Rapid correction may lead to cerebral pontine myelinosis.

Required volume of 3% hypertonic saline *(ml/hr)* = body weight *(kg)* x
desired Δserum sodium *(mmol/l/hr)*

Diabetes insipidus

This describes the clinical situation where either the brain cannot produce enough ADH (central DI), or the kidney cannot respond to normal ADH levels (nephrogenic DI), and there is excessive production of hypo-osmolar urine (<300mOsm/kg water) in the face of rising serum osmolality (>295mOsm/kg water).

Medical management aims to limit ongoing water losses and replace the free water deficit. In severe diabetes insipidus, this can be done with intravenous normal saline; in more mild disease, oral free water replacement is preferred. Again, normalization must occur slowly over two to three days as rapid correction can cause cerebral oedema when water enters the brain's relatively hypertonic intracellular compartment. Sodium levels need to be corrected at a similar rate to that prescribed for SIADH.

Free water deficit *(litres)* = total body water *(litres)* x (serum sodium – 140) / 140

Ongoing losses can be prevented with the oral hypoglycaemic agent, chlorpropamide, which potentiates ADH in the kidney; and/or supplementing circulating ADH with vasopressin or desmopressin, a synthetic ADH analogue.

PITUITARY FAILURE

Hypopituitarism

Pituitary failure describes the impaired synthesis of one or more of the pituitary hormones. The causes are many, but the one of the most common is a pituitary tumour (and, unfortunately, post-pituitary surgery for tumour resection). Failure may be acute or chronic. Pituitary tumours cause gland failure by:

- Compression of the gland, directly obstructing the cells
- Compression of the pituitary stalk or portal vessels, obstructing the flow of hypothalamic releasing hormones to the pituitary and so being unable to exert their effect on the cells of the gland
- Loss of pituitary tissue mass following resection or radiation
- Resultant haemorrhagic infarction and necrosis of the tumour, so-called *pituitary apoplexy*

Presenting signs and symptoms may be vague and seem multi-factorial; they will also depend on the particular hormone deficiency and the cause of the failure. In acute pituitary failure, perhaps due to apoplexy, the hormone effects felt first are those with the shortest half-lives such as ACTH, which manifests as acute adrenal insufficiency. Patients will experience nausea and hypotension, with hyponatraemia and may progress to shock.

In chronic pituitary failure, growth hormone deficiency occurs early in the disease course with ACTH and TSH levels dropping much later. Prolactin seldom falls as it is mainly under inhibitory control from the hypothalamus. Anti-diuretic hormone levels may decline and will result in diabetes insipidus.

Peri-operative management of pituitary failure

1. Resuscitation
   A patient with pituitary apoplexy and acute pituitary failure may present for emergency surgery to decompress the tumour and prevent vision loss. They may well be profoundly shocked with low levels of ACTH and corticosteroids, resulting in a severe hypotension unresponsive to vasopressors. Control of the airway, ventilation and circulation are paramount. Instigate corticosteroid therapy immediately with 100mg hydrocortisone IV, followed by 50mg six hourly thereafter. Low vasomotor tone may cause relative hypovolaemia and should be treated with colloid intravascular volume expansion. Continue inotropic circulatory support and consider vasopressin – although diabetes insipidus is rare, the vasopressin can supplement the ADH deficiency and improve inotropy.

Consider: large bore intravenous access, invasive arterial and cardiac output monitoring. Not immediately urgent: possible hormone supplementation – fortunately T_4 has a long half-life and acute growth hormone deficiency is not imminently life threatening.

2. Evaluation of hormone deficiencies and supplementation
   Non-emergent management of pituitary failure entails evaluation of hormone levels and supplementation of deficiencies; and postponement of elective surgery until these approximate normal. Patients already receiving corticosteroid therapy will need standard peri-operative steroid supplementation, eltroxin should be continued until the day of surgery and desmopressin/vasopressin may be needed to treat diabetes insipidus throughout the peri-operative period.

PITUITARY SURGERY

This may be either the first-line treatment of some pituitary tumours; or become indicated later due to failure or intolerance of medical management

Surgical approach

The vast majority of surgical resections of pituitary adenomas are performed extra-cranially via the transsphenoidal approach. Transcranial resection via craniotomy is reserved for patients in whom the transsphenoidal route has failed, the tumour is large or is located mostly outside of the *sella.* The transsphenoidal route offers some **advantages**:

- Minimal surgical trauma and blood loss
- Direct access to the gland
- Avoidance of craniotomy and its associated complications

But it is not devoid of its own fair share of **complications**:

- Persistent CSF leak and increased risk of post-operative meningitis
- Pan-hypopituitarism
- Transient diabetes insipidus
- Vascular and cranial nerve injury
- CVA due to vasospasm or thromboembolism

The direct endo-nasal approach is favoured over the sublabial trans-septal approach as it requires less dissection and removal of bone. The endoscopic guidance, alone, has improved tumour visualization and therefore resection and ultimately, remission rates. It has also minimized the risk of dental complications and septal perforation.

Computer-assisted navigation has further improved results. MRI images and facial markers are synchronized pre-operatively; intra-operative co-registration aids in directing the angle of approach allowing better, more complete resection.

Anaesthetic technique

A standard **preoperative evaluation** should be performed, as usual, with special attention paid to possible endocrinopathies (and their associated co-morbidities), the appropriate medical management and hormone supplementation; and investigations should be guided by these findings. MRI is the preferred imaging for surgical planning; CT can be used to exclude hydrocephalus. Visual field defects need to be mapped and documented.

The **general aims** of anaesthesia for transsphenoidal pituitary surgery are optimization of cerebral oxygenation, haemodynamic stability and rapid, smooth emergence. Invasive arterial pressure monitoring is required in all cases. More advanced monitoring is decided upon according to the needs of the individual patient.

A **lumbar drain** may need to be inserted pre-operatively to allow later injection of a small volume of saline or air to encourage downward displacement of the tumour into the surgical field. Intra-operative controlled hypercapnia targeting $PaCO_2$ 40-45mmHg will give similar results; but the lumbar drain has the added advantage of being left in place post-operatively to assist the management of potential persistent CSF leak. It is important to exclude raised ICP before insertion of the drain.

The various difficulties associated with 'endocrine' **airways** have been discussed. The patient needs to be intubated and ventilated. The ETT of choice is likely the south RAE or oral armoured ETT, as the airway is obscured with the surgical approach. Airway access later is also limited by the operating microscope, sinus endoscope and portable imaging C-arm. A throat pack is necessary to protect the oropharynx from accumulation of blood due to the trans-nasal approach.

Deliberate nasal bone fracture is required for the trans-nasal, transsphenoidal approach. To minimize bleeding, mucosal vasoconstrictors (adrenaline) and/or topical local anaesthetic agents (cocaine) have been used - these may exacerbate any conditions associated with co-morbid hypertension. It may be safer to use phenylephrine and/or lignocaine.

Surgery is typically performed with the patient supine, with a head-up angle of less than 40° which minimizes the incidence of venous air embolism (<10%) whilst improving venous drainage to prevent engorgement of the surgical site.

Maintenance of anaesthesia will depend on the restrictions of the patients' underlying diseases and target organ damage. Both inhalational and intravenous TCI agents are acceptable. Intravenous antibiotics and steroid are administered at induction. There are two periods of intense surgical stimulation: deliberate nasal septal fracture, and breaching of the sphenoid bone to access the fossa. This can clearly disrupt tight haemodynamic control, and a short-acting, potent analgesic such as Remifentanil may be ideal to manage the potential hypertensive response.

After tumour resection, a Valsalva manoeuvre may be used to test for a CSF leak. If such a leak is observed, most surgeons will pack the *sella* with an autologous fat graft.

Analgesia is multi-modal: intravenous paracetemol is ideal due to its relative potency and thus its opiate-sparing effect. Long-acting opiates may be required later and can be titrated to effect. It is important to consider the performance of an accurate post-operative neurological assessment, and to optimize respiratory care in the face of OSA and possible compromise. Non-steroidal anti-inflammatory agents have been associated with post-operative haematoma. Anti-emetics are necessary as PONV is common after neurosurgery. Although vomiting is highly undesirable in any circumstance, it is particularly detrimental in the setting of raised ICP and should be prevented (and treated promptly, if present).

Post-operative care

These patients require a minimum of high care placement in the post-operative period. This is mainly to monitor them for airway obstruction, ongoing neurological assessment and further endocrine dysfunction.

1. Airway obstruction:
   Exacerbated by possible pre-existing obstructive sleep apnoea, and post-operative nasal packs. Patients should be warned pre-operatively of the nasal obstruction. Non-invasive ventilation is not an option, for reasons mentioned previously.

2. Neurological assessment
   Level of consciousness, cranial nerve fallout (eye movements, facial sensation), visual field defects and visual acuity need to be tested regularly. Any change or deterioration needs to be discussed with the surgeon; the patient may need further radiological investigations or exploratory surgery.

3. Endocrine dysfunction
   Diabetes insipidus may develop within the first 24 hours and usually resolves within the first week. It is treated with desmopressin, which may then cause subsequent hyponatraemia. This may also be due to SIADH but this is uncommon. Hormone replacement therapy will be required in all patients – how much will obviously depend on the degree of dysfunction and this will need to be quantified by endocrinologists.

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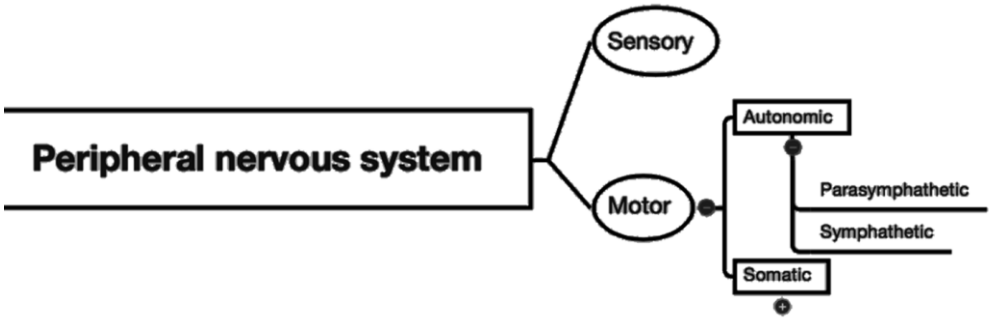
Autonomic neuropathy

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Introduction

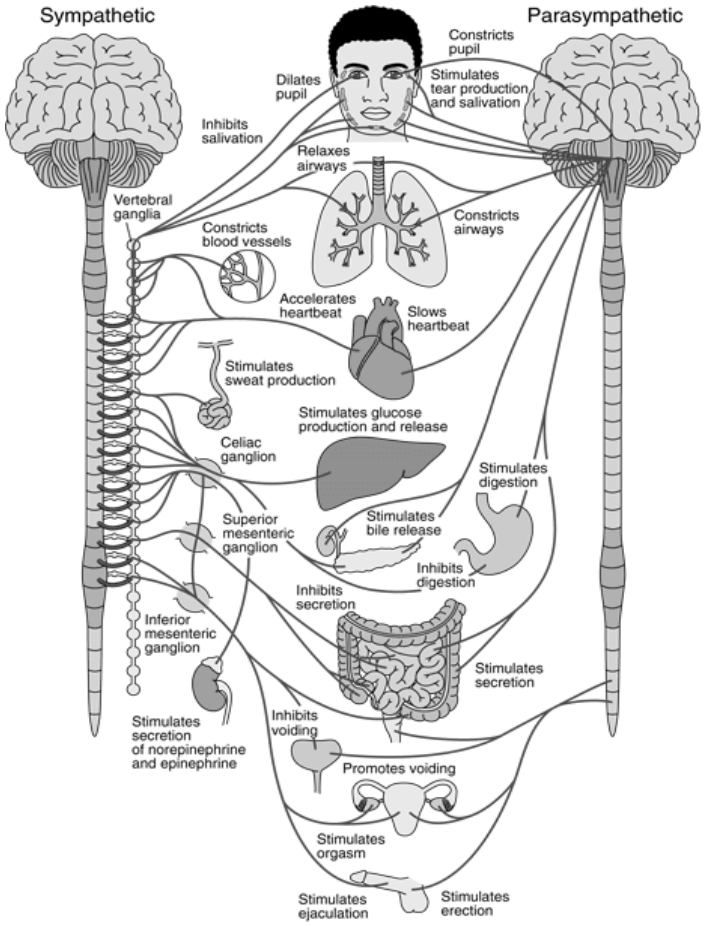
The autonomic nervous system (ANS) regulates homeostasis and innervates all the organs except the skeletal muscle, which receives its innervation from the somato-motor nervous system. It is an unconscious and involuntary control of the automatic bodily functions that can be influenced by the hypothalamus as the central control and integration of the systems.



The Peripheral Nervous System is divided in sensory and motor divisions. The motor system is subdivides into autonomic and somatic and the two divisions of the autonomic nervous system is the parasympathetic system with cranio-sacral outflow and the sympathetic system with thoraco-lumbar outflow.

Definition

Autonomic neuropathies are disorders of peripheral nerves and include the parasympathetic and sympathetic systems. It may be hereditary or acquired and often occur with somatic neuropathies. It is important to keep in mind that when a certain portion of the autonomic nervous system is affected, there might be other parts involved as well.
The degree and type of system involvement can differ widely from subclinical to clinically relevant. It is however a diagnosis of exclusion



Aetiology

The aetiology of autonomic neuropathy is vast. Some diseases that is of concern to the anaethetist include:

Acquired neuropathies	1°: Parkinson's disease, Spinal cord trauma, aging patient 2°: Diabetes Mellitus, Uremic autonomic neuropathy and Hepatic neuropathy
Autoimmune disease	Guillain-Barré syndrome, Rheumatoid arthritis, SLE and other connective tissue disorders
Drug-related	Alcohol, chemotherapeutic agents
Infectious diseases	HIV, syphilis
Inherited autonomic neuropathies	Variegate or Acute intermittent porphyria
Neoplastic disease	Eaton-Lambert syndrome, Paraneoplastic neuropathy

*Due to the vast spectrum of diseases affected by the autonomic nervous system, the most common sympathetic **hypo-responsive** circulatory disorder- DAN (Diabetic autonomic neuropathy) with specific focus on Cardiovascular autonomic neuropathy (CAN) and the **hyper-responsive** sympathetic disorder of autonomic dysreflexia will be discussed here.*

Diabetic Autonomic Neuropathy (DAN)

Diabetes Mellitus is a disease frequently encountered by anaethetists. This is a high-risk population with the major factors affecting these patients peri-operatively being cardiovascular dysfunction, renal insufficiency, joint collagen abnormalities and neuropathies. Autonomic neuropathy in Diabetes can occur within a year of the diagnosis of type 2 DM and within two years in type 1 diabetes.

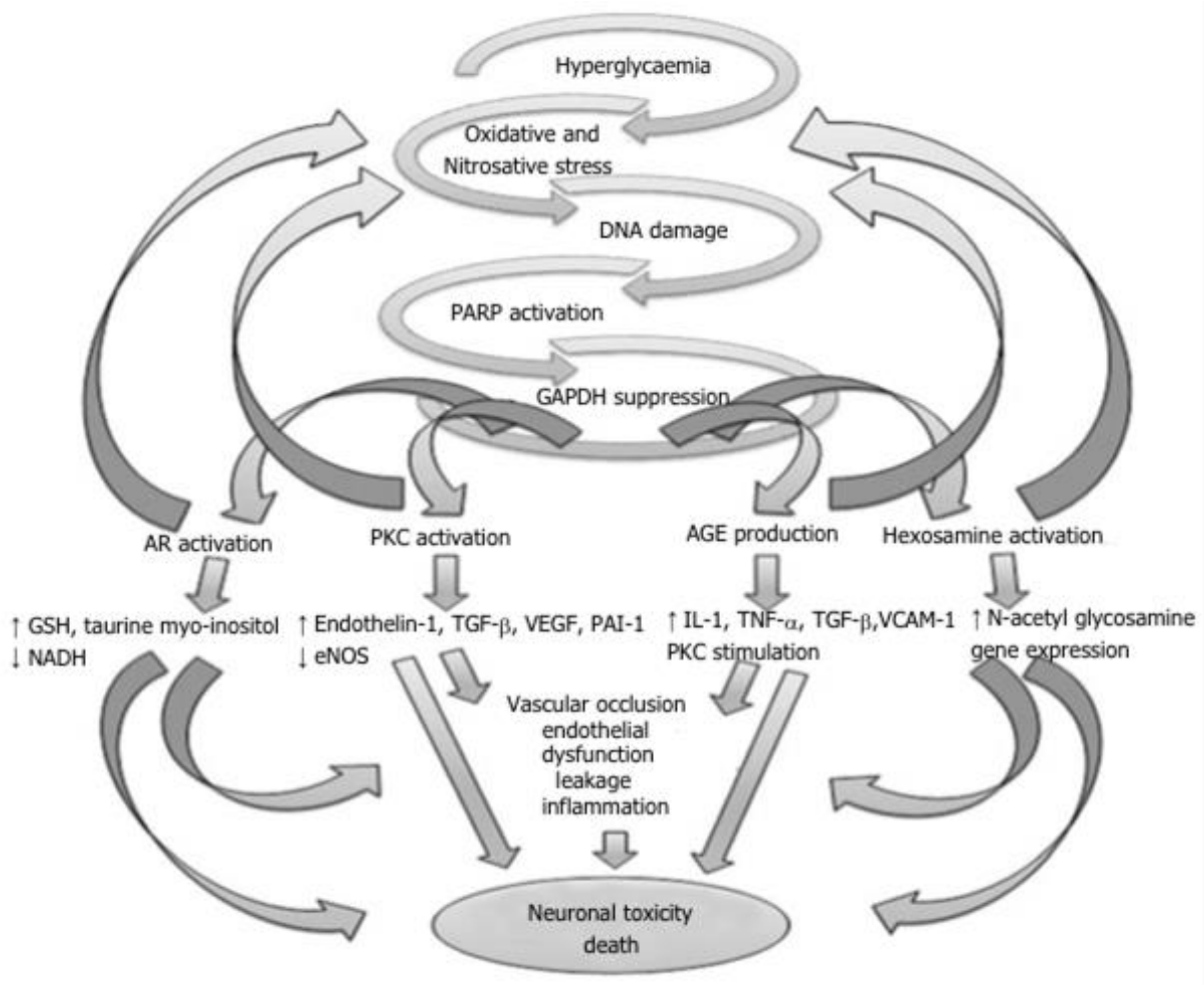
Clinically the most important complication of diabetes is the cardiovascular autonomic neuropathy (CAN). CAN is a diagnosis of exclusion and is the impaired cardiovascular autonomic control in patients with DM. Clinical predictors of CAN include Diabetic nephropathy, retinopathy and polyneuropathy.

Damage to the autonomic nerve fibers, innervating the heart and blood vessels result in abnormal control of the heart rate and hemodynamics at vascular level. The perioperative implications of CAN include an association of sudden death (long QT), LVH and intra-operative hypotension

Pathophysiology

To understand the pathophysiology, it is important to keep in mind the normal physiology of the autonomic control of the heart. The SA node in the posterior wall of the right atrium determines the intrinsic heart rate. It contains specialized cells that generate action potentials that equates to 100 – 120. Change in the heart rate is balanced between the sympathetic and parasympathetic system and the normal heart rate in adults at rest in determined by vagus tone that decrease the heart rate to 60-80 bpm.

The pathogenesis is multifactorial and complex. It involves a cascade of pathways initiated by hyperglycaemia and oxidative stress with neuronal ischemia and death as end result. Autoimmune and genetic factors may also play a role.

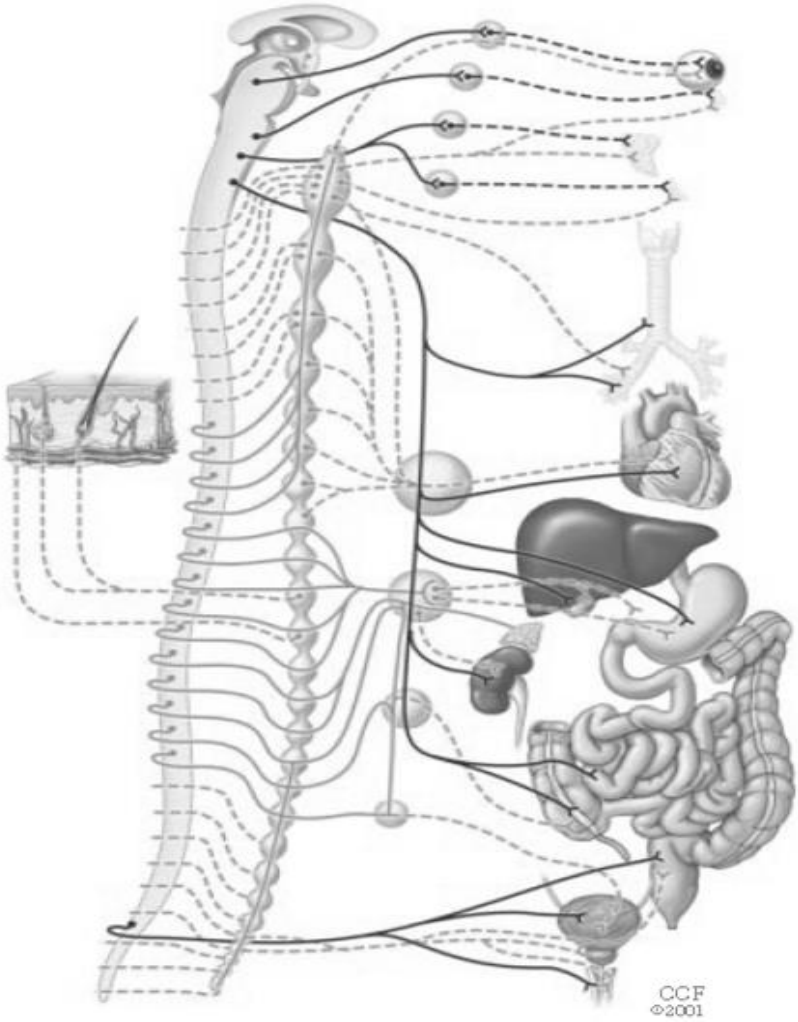


Diabetes involves not only the autonomic but also other divisions of the peripheral nervous system. The vagus nerve is the longest nerve and responsible for approximately 75% of the parasympathetic activity, is involved early in the development of CAN.

In the subclinical and early phases of CAN there is sympathetic predominance. As the disease progresses, the increased sympathetic tone continues till the severe stage of CAN, where sympathetic denervation occur from the apex to the base of the heart. The time span of progression from the subclinical phase till severe CAN is variable, but can occur within 5 years.

Clinical manifestations of autonomic neuropathy

Diabetes can cause dysfunction of any or all parts of the automomic nervous system, leading to a wide range of disorders. (Sympathetic fibers are shown in orange, parasympathetic in blue, preganglionic solid, and postganglionic dashed.)



Pupillary
Decreased diameter of dark-adapted pupil
Argyll-Robertson type pupil

Metabolic
Hypoglycemia unawareness
Hypoglycemia unresponsiveness

Cardiovascular
Tachycardia, exercise intolerance
Cardiac denervation
Orthostatic hypotension
Heat intolerance

Neurovascular
Areas of symmetrical anhydrosis
Gustatory sweating
Hyperhidrosis
Alterations in skin blood flow

Gastrointestinal
Constipation
Gastroparesis diabeticorum
Diarrhea and fecal incontinence
Esophageal dysfunction

Genitourinary
Erectile dysfunction
Retrograde ejaculation
Cystopathy
Neurogenic bladder
Defective vaginal lubrication

The spectrum and natural progression of CAN is divided into 3 phases: subclinical, early and advanced. There may be several years in between the development of the subclinical stages and advanced CAN. Poor glycemic control plays a major role in the progression of CAN.

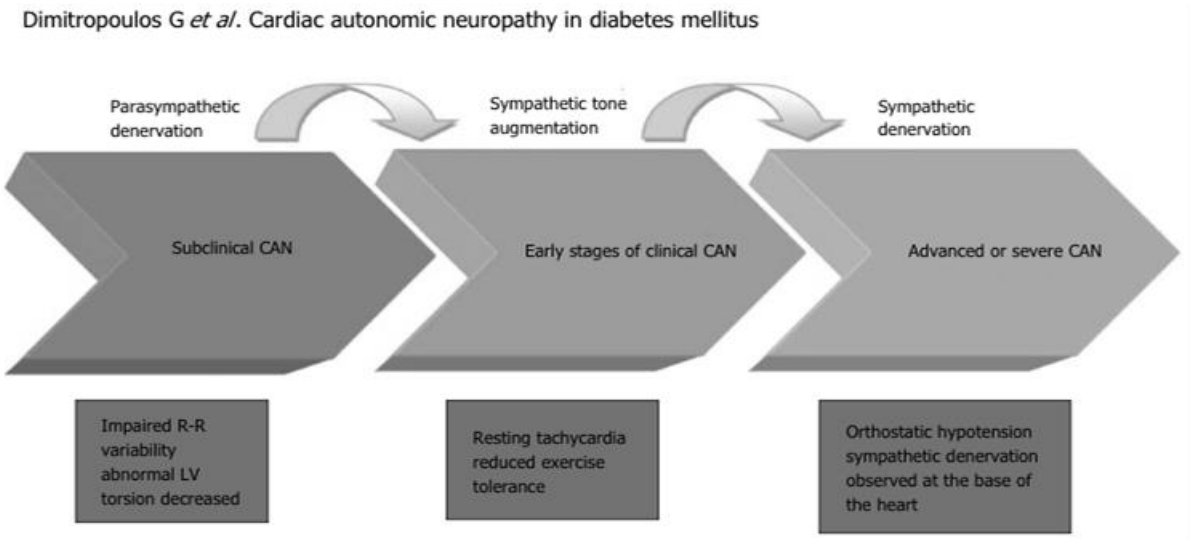


Figure 2 Natural progression of CAN and correlation with clinical signs and symptoms. CAN: Cardiac autonomic neuropathy; LV: Left ventricle.

Diagnosis

Why should we screen for CAN? The Toronto Consensus Panel on DAN stated that screening for CAN is good clinical practice and enable accurate and clinical relevant diagnosis and assists in detection and treatment of CAN. It also provides a clinical tool for risk stratification of complications and modulates treatment targets in diabetes.

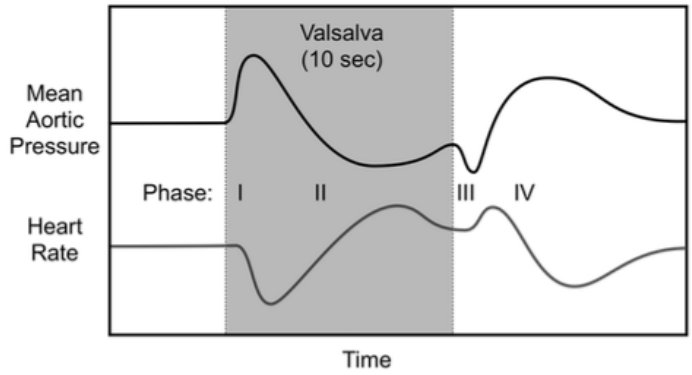
DIAGNOSTIC TESTS - Cardiac autonomic reflex testing (CART)

Five diagnostic tests for CAN was developed by Ewing and Clarke. The 5 tests include 2 sympathetic tests that are related to Blood pressure (BP) and 3 parasympathetic tests that are related to the heart rate (HR). To be able to establish a clinical diagnosis of CAN, you need 2 abnormal tests.

1. HR response to Valsalva

A basic knowledge of the normal phases of valsalva is discussed first.

Physiology of Valsalva



The Valsalva maneuver is a forceful expiration against a closed glottis that increases the intra-thoracic pressure and subsequently affects the cardiac output as well as venous return and hemodynamics.

There is 4 phases of the Valsalva maneuver:

Phase I

- ↑ intra-thoracic pressure lead to compression of organs against rib cage →↑ external pressure on heart and thoracic blood vessels → ↑ aortic pressure transiently
- ↑ RAP (right atrial pressure) from venous compression impedes venous return →↓preload and filling→↓cardiac output (Frank-Starling)
- Baroreceptor reflex control changes in heart rate (HR) - ↓HR with ↑ aortic pressure

Phase II

- Aortic pressure ↓ due to ↓ CO and HR ↑

Phase III

- When normal respiration starts: ↓ aortic pressure (external compression removed) and reflex ↑ heart rate

Phase IV

- Rapid ↑ cardiac filling →↑ aortic pressure and ↓HR
- Aortic pressure overshoots sympathetic-mediated ↑SVR

1. HR response to Valsalva

- Patient sits and blows into mouthpiece at 40mmHg for 15 sec
- Immediate HR ↓ during ↑ sBP and dBP at onset of straining observed
- Ratio of the longest R-R after and the shortest R-R interval during the maneuver is observed
- Mostly confirmatory information

2. HR response to standing (30:15 ratio)

- Patient lies on couch and then stand up unaided
- Normal stat ↑ HR maximal at 15th beat followed by relative bradycardia maximum at 30th beat.
- This 30:15 ratio is the ratio of the longest R-R interval around 30th beat to the shortest R-R around the 15th beat.

3. HR response to deep breathing (maximum-minimum HR)

- Patient sit and breathes deeply and evenly at 5 breaths/minute
- Maximum and minimum HR during each breath cycle is measured and mean difference during 3 successive breathing cycles give the max-min HR.
- Sensitive to assess vagal heart control for cardiac vagal neuropathy

4. Postural BP change

- Orthostatic hypotension is a ↓ sBP of ≥ 20 mmHg or dBP of ≥ 10 mmHg within 3 min of standing.
- Sometimes symptomatic
- It is a sign and not a disease
- Systolic and Diastolic BP ↓ without corresponding reflex ↑ HR
- ↓ sBP without ↓ dBP suggests a non-neurologic disorder like central hypovolemia

5. BP response to sustained handgrip

- In normal patients the response would be ↑ BP due to ↑ HR with no change in peripheral resistance.
- BP measured 3x before testing
- Handgrip maintained at 30% of maximum for as long as possible to maximum of 5 minutes
- BP measured at 1 min intervals
- Result is difference between highest dBP during handgrip and mean of 3 dBP readings before test

Values for tests of Cardiovascular Autonomic Function

	Normal	Borderline	Abnormal
Parasympathetic function			
HR – Valsalva ratio	> 1.21	1.11-1.20	<1.10
HR (R-R) – deep breathing (max-min HR bpm)	> 15	11-14	< 10
HR - standing (30:15 ratio)	>1.04	1.01-1.03	<1.00
Sympathetic function			
BP - standing (↓ sBP) mmHg	< 10	11-29	>30
BP - sustained handgrip (↑ dBP) mmHg	> 16	11-15	< 10

Interpretation of results:

- Normal - if no tests abnormal
- Early parasympathetic damage – 1 test abnormal
- Definite parasympathetic damage – 2 tests abnormal
- Combo of parasympathetic and sympathetic damage – abnormal tests in both categories

Differential diagnosis of DAN

Idiopathic orthostatic hypotension	
Endocrine disease	• Panhypopituitarism • Pheochromocytoma • Addison's disease
Fluid imbalance	• Hypovolemia – poor glycemic control • Diuretics
Drug related	• Insulin • Vasodilators (CCB, nitrates) • Sympathetic blockers (Clonidine, prazosin, TAD)
Others	• Orthostatic hypotension caused by alcoholic neuropathy • GIT dysfunction • GU dysfunction
Peripheral autonomic neuropathies	• Amyloidosis

A short note on:

Gastroparesis

Gastorparesis is delay of gastric emptying without mechanical obstruction. Symptoms that the patients might experience include early satiety, nausea, vomiting and bloating. Gastroparesis in diabetic patients usually occur after 10 years of the disease and is concurrent with retinopathy, neuropathy and nephropathy. In the process of gastric emptying, the proximal stomach is the reservoir and distal the grinder. The particle size, fat and caloric content and physical nature determines the rate of emptying as seen in the figure below. Non-nutrient liquids empty rapidly and the rate is fastest if there is a large volume. Solids are retained for churning in the stomach and once broken down to 2mm diameter particles empty during 2 phases over 3-4 hours.
Glucose regulating hormones act in different regions in the gut. In diabetic patients where the vagus is affected, there is a reduction in the motor coordination and numbers of cells. The patient with diabetic gastroparesis is thus at risk for aspiration.

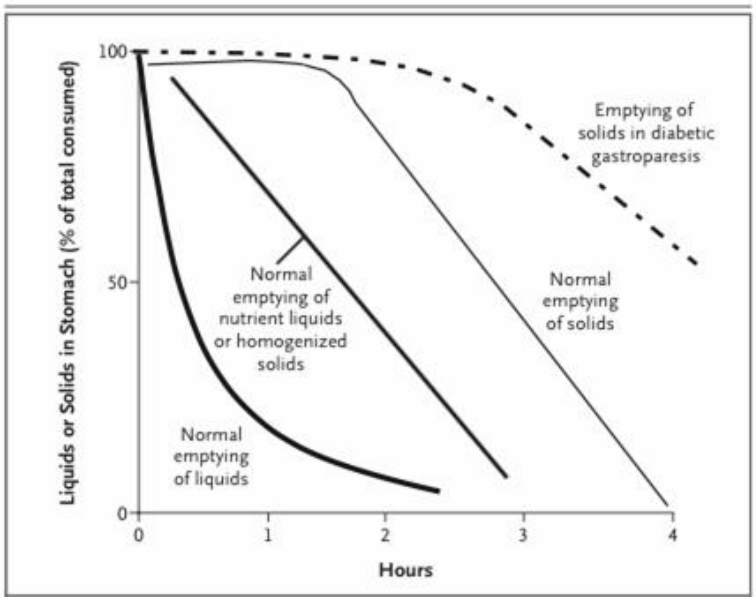
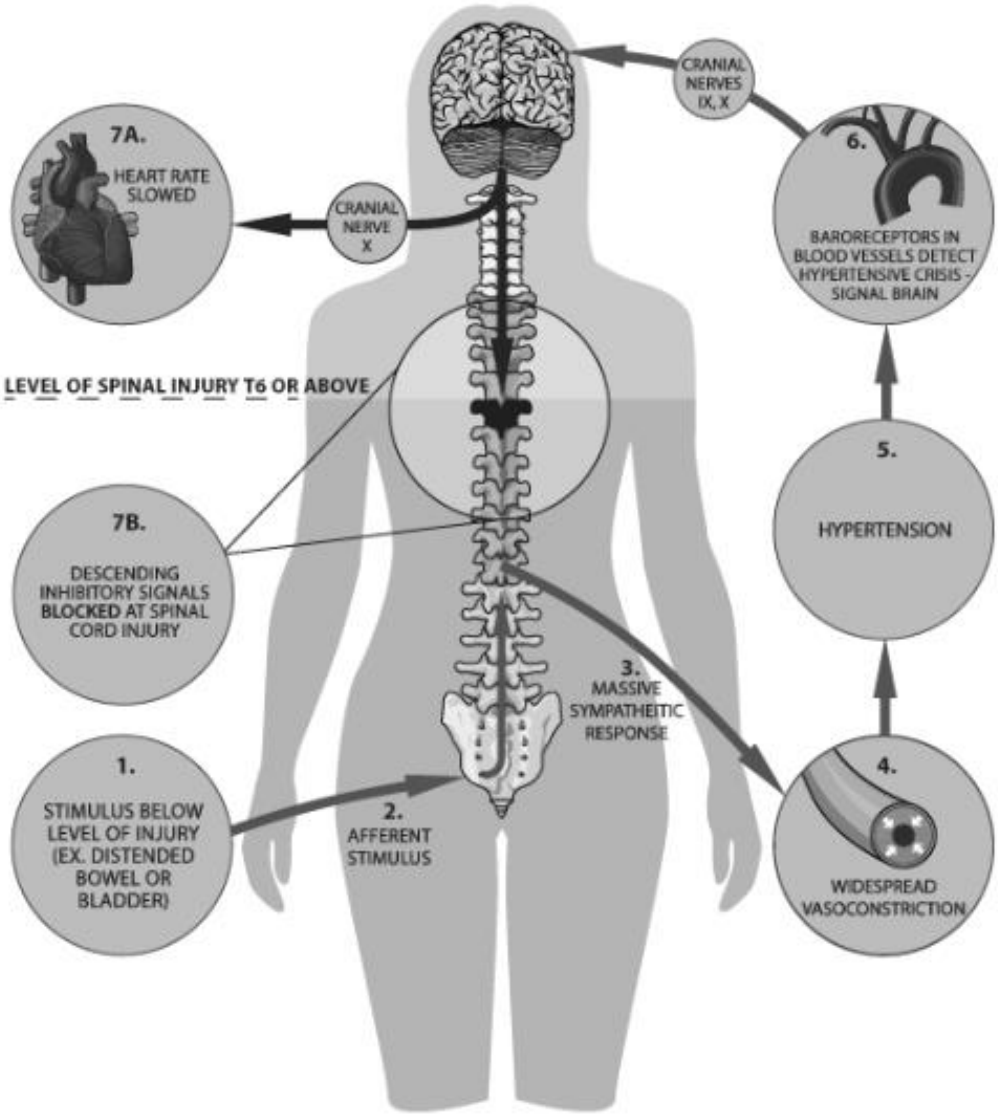


Figure 1. **Patterns of Gastric Emptying in Healthy People and in Patients with Diabetic Gastroparesis.**

Sympathetic HYPERfunction

Autonomic Dysreflexia (AD)

Autonomic dysreflexia is an acute life-threatening syndrome of uninhibited sympathetic discharge in patients with spinal cord injuries above T6 level. The triggering response can be any noxious stimuli but most commonly bladder or bowel distension under the lesion.



Pathophysiology

Autonomic dysreflexia occurs after a spinal cord injury due to dysfunctional sympathetic regulation, reorganization in the spinal cord and disconnection between parasympathetic and sympathetic tracts.

- A stimulus (distended bowel/bladder) ➔afferent stimulus to spinal cord
- The stimulus unable to ascend past lesion ➔exaggerated sympathetic reflex
- Widespread vasoconstriction of blood vessels below injury
- Hypertension and sympathetic stimulation
- 2 vasomotor brainstem reflexes to ↓ BP
  1. ↑ parasympathetic stimulation ➔bradycardia
  2. ↑ sympathetic inhibitory outflow from vasomotor centers above injury ➔sweating and vasodilated skin above injury (impulses can't pass below injury level and can't dilate splanchnic bed to accommodate extra circulating blood due to ↑ peripheral resistance

Treatment options

- Remove the trigger of the stimulus
- Pharmacological management: Magnesium, Clonidine, Vasodilators (Nifedipine, Nitroglycerine)
- Anaesthetic management options:
  - Spinal anaesthesia: blocks visceral afferents to spinal cord
  - Epidural: lumbar block with sacral sparing can still trigger AD
  - General anaesthesia: not completely obtund the sympathetic response, pain relief important

Summary of Anaesthetic considerations in autonomic failure

Pre-operative	• Orthostatic hypotension • Gastroparesis and aspiration risk • Blood volume status • Anemia (↓ erythropoiesis)
Intraoperative	• GA vs. RA (type of procedure) • Monitoring and vigilance!! • Poor thermal regulation (control) • Positioning effect on hemodynamics • TNT, prone or reverse Trendelenberg if supine hypertension • Sudden blood volume changes precipitate untoward BP response • Pneumoperitoneum with extreme caution • Vasopressors and inotropes resistance or sensitivity • Electrolyte imbalance
Post-operative	• Expect volume changes and need for higher care facility • Orthostatic hypotension requires good volume assistance esp. on first ambulation • Abnormal electrolyte values affect responses to medication • Thermal regulation continues • Ileus worsened by opiate use post-operative • Restart normal meds before discharge

Conclusion

Cardiovascular autonomic neuropathy (CAN) is associated with increased morbidity and mortality and if often undiagnosed.

Exercise tolerance is not accurate in these patients at risk for diabetic cardiomyopathy and silent ischemia. Patients can have subclinical CAN for years before it become clinically evident.

Disease modifying treatment lacks despite the improved understanding of the pathogenesis of CAN. Further research for the development of disease modifying treatments is still necessary. The progression of CAN can't be reversed but is slowed by improved glycaemic control, lifestyle changes and management of cardiovascular risk factors.

The relationship between obstructive sleep apnea (OSA) and microvascular complications of DM need to be clarified to identify new treatment targets in future.

Autonomic dysreflexia is an acute life-threatening syndrome of uninhibited sympathetic discharge in patients with spinal cord injuries above T6 level.

The triggering response can be any noxious stimuli but most commonly bladder or bowel distension under the lesion.

Regional anaesthesia is the preferred method cause spinal anaesthesia blocks visceral afferent impulses to spinal cord and prevents AD.

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New in anaesthetic literature 2015

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Review Article

The impact of autonomic dysfunction on peri-operative cardiovascular complications

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Organ transplantation, death and brain death in South Africa

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Background

Transplantation is an established life-saving procedure for selected patients with end-stage heart, liver and lung disease. For kidney (and potentially simultaneous pancreas) transplant recipients, there is a markedly improved life expectancy, quality of life and financial saving over long-term dialysis. The waiting list for organ transplants however continues to grow while the numbers of deceased donors are actually decreasing. This has led to the acceptance of marginal donors (termed extended criteria donors) being used since transplantation with such an organ still offers a marked survival benefit over no transplant at all.
South Africa has a deceased donor rate of 1 per million population (pmp) compared to a rate of 36 pmp in Spain. This is driven by the failings of our two health care systems to adequately identify, refer and manage potential donors. This text will hopefully allow you as the anaesthetist to fulfil your part in the system as knowledgeably as possible.

Dead donor rule

The increased need for transplantable organs has not changed the ethical standard of the dead donor rule which stipulates that a donor must be certified dead prior to organ procurement. However with continued medical advances (eg. use of therapeutic hypothermia) and efforts to improve the process of organ donation (eg. involving transplant co-ordinators earlier in end-of-life care discussions) it is important to be familiar with all aspects of the determination of death in various contexts as well as some of the issues that may arise.

Legal requirements of death

Various definitions of death have been used over the years with some cultures and religions considering the heartbeat or respiration to be central to the preservation of life. The medical definition of death however is accepted as the irreversible absence of brain function. The loss of the integrative function of the entire brainstem mean that all capacity for consciousness and involuntary physiological functioning are lost. This can be from a primary brain insult or secondary to irreversible cessation of circulatory and respiratory function.
In South Africa, Chapter 8 of the National Health Act defines death as “brain death”. Specific standards for determination are not stipulated in law and this allows for the natural evolution of medical standards as treatments advance.
The regulations regarding organ transplantation do stipulate that in the case of organ transplantation brain death must be determined by two doctors, one with more than 5 years experience and neither of whom may be members of the transplant team.[1]

Brain death certification

Brain death certification offers the rare entity of absolute certainty in medical care. It must however be performed rigorously and when done so any and all doubt about prognosis is removed. When all brainstem reflexes are absent and there are no confounding factors the patient is 100% dead. This is the time that is filled in on the death certificate as the time of death. It offers the family closure in a complicated situation where machines and medications are often supporting organ systems.

Brain death is a purely clinical diagnosis however it is important to follow sequential steps when evaluating a patient for brain death. These can be divided into ensuring that certain preconditions

have been met and that the entire brainstem has been adequately assessed. If even one of the criteria is not met then one cannot pronounce the patient brain dead on purely clinical grounds.

Before commencing brain death testing ensure that: (prerequisites)

1. The cause of brain death is specifiable and irreversible.
2. The effects of CNS depressing drugs and muscle relaxants have been excluded.
3. The rectal temperature is > 35°C and systolic BP is >90mmHg.
4. There is no endocrine or metabolic cause of coma.

Brainstem testing:

1. Pupillary reflex: Pupils should be fixed (unreactive to light), not necessarily dilated.
2. Corneal reflex: No response to light touch with cotton wool. Don't damage the cornea.
3. Gag reflex: Absent on stimulating the back of the pharynx.
4. Cough reflex: No response to suctioning via endotracheal tube.
5. Pain response in facial distribution: Supra-orbital compression must not elicit any response in a *facial* distribution. Spinal and tendon reflexes may be present.
6. Oculo-cephalic reflex (Doll's eye movement): Ensure there is no cervical fracture. Lift the head to 30°. Turn the head to one side and open the patient's eyes. Keeping the eyes open turn the head rapidly through 180° to the opposite side. Any movement in relation to the head indicates an intact reflex. In the brain dead donor the eyes will stay fixed looking forward and move with the head.
7. Oculo-vestibular reflex (Cold caloric test): Confirm the tympanic membrane is intact and free from wax with an otoscope. Inject 20ml of iced water onto ear drum while holding the eyes open and look for any eye movements or nystagmus. In a brain dead patient there won't be any movement.
8. Apnoea test (Done last): Ventilate the patient fully on 100% oxygen for 10 minutes. Do an arterial blood gas to check the pCO_2 is within normal limit(4.0 – 5.3kPa or 35 – 45 mmHg). Then disconnect the ventilator and place patient on a T-piece with O_2 flow rate of 15l/min. One of three things may take place:
    a. The patient may show some respiratory effort. The patient is not brain dead, although he may become brain dead at a later time. Replace on the ventilator. Consider for donation after circulatory death if decision is still to withdraw support and death is expected.
    b. After 10 minutes there may be no signs of spontaneous respiration. A blood gas is done to confirm a raised pCO2 of >6.6 kPa (50mmHg). In this setting the patient may be certified brain dead.
    c. The patient may desaturate or become haemodynamically unstable. Reconnect the ventilator but do a blood gas to see if the PCO2 is adequately raised. If it is and there was no spontaneous respiration then the patient may be certified brain dead. If not consider ancillary testing.

    At the end of the test it is essential to reconnect the ventilator as breathing or not breathing through an ET tube unsupported by ventilation hastens cardiac arrest.
9. Some transplant centers request an atropine test. This is done by administering 2mg of atropine and noting that the heart rate does not change(< 10 beats / minute). This is not used by the majority of brain death determination guidelines.

Confounding situations[2]

1. Potentially reversible circulatory, metabolic and endocrine disturbances

Major disturbances can accompany brain death. These may be the effect of brain death rather than the cause of the coma and it is therefore important to know the proximate cause. It may

be detrimental to correct such abnormalities too rapidly and targeting absolute electrolyte concentrations can delay brainstem testing unnecessarily.
The effects of hypo- and hypernatraemia depend on the rate of its development. A raised sodium frequently accompanies brain death. A patient is unlikely to be unresponsive with a sodium level above 115mmol/L. A sodium above 160 mmol/L can be associated with coma and this must be considered if the primary cause of the coma is unknown.
Low potassium can cause a flaccid paresis and a level lower than 2.5 mmol/L should be corrected. Similarly a phosphate or a magnesium < 0.5 or > 3.0 mmol/L may cause significant weakness. A peripheral nerve stimulator can be used to check for neuromuscular transmission and muscle response.
Hyperglycaemia in diabetic ketoacidosis or hyperosmolar non-ketotic coma may cause an unresponsiveness mimicking cessation of brainstem reflexes. A level > 3.0 mmol/L and lower than 20mmol/L is accepted and an HGT should be done prior to brainstem testing.
A thyroid storm, myxoedematous state or an Addisonian crisis may cause coma. These conditions are extremely rare and unlikely to co-exist in the presence of known primary pathologies. Hormonal assays are only indicated where there is a clinical suspicion.

2. Sedatives

The prolonged action of narcotics, hypnotics and neuromuscular blockers can be of concern especially when there is hypothermia or renal or hepatic impairment. Some sedatives (eg. benzodiazapines) and analgesics are also markedly cumulative.
An accurate drug history is essential and any possibility of intoxication contributing to the patient's clinical condition precludes the diagnosis of brain death. Length of time between the last dose and brain death testing is dependent on several factors including the total dose, duration of treatment, underlying renal and hepatic function and the availability of drug level testing. Residual effects of drugs should be predicted along pharmacokinetic principles. Drug antagonists such as naloxone and annexate can be used if benzodiazapines or opiates are thought to be contributing to the decreased level of consciousness.
In the setting of preserved renal and hepatic function a waiting period of more than 5 drug half-lives is accepted.

3. Paediatrics

Guidelines vary internationally about the assessment of brain death in children. Some countries advocate retesting after a period of 24 hours following the initial testing and specify that tests must be carried out by two consultants.
It is important that testing be approached in an unhurried manner and it may be prudent to measure drug levels given the altered pharmacokinetics in children. Adult criteria for brain death are valid in children older than 2 months. Under this age the clinical validity of brain stem testing is not clear and ancillary testing is recommended.

4. Spinal reflexes

Spinal reflexes can be preserved in brain dead patients. It is important to be clear about this with the family as their presence can be misleading. The most dramatic presentation of a reflex arc through the spinal cord is the Lazarus reflex where the arms seem to rise-up and fall back across the body. Ancillary testing (or repeated brain stem testing) may be warranted to reconfirm the diagnosis of brain death in such a situation.

5. Persistent vegetative state

Brain death must not be confused with persistent vegetative state. In this situation the loss of brainstem function is not complete and although the reticular system is affected such that there is complete loss of consciousness (unawareness of self and the environment) some autonomic functions remain, namely breathing, a stable circulation and a simulated sleep and waking cycle.

Ancillary testing[3]

In the majority of cases clinical determination of brain death is possible however there may be certain clinical situations where ancillary tests can be of use. For example if one is not able to complete the apnoea testing due to haemodynamic instability.

Cerebral angiography is the gold standard of ancillary testing. A 4-vessel angiogram will demonstrate a complete lack of brain perfusion from both the anterior and posterior cerebral circulation. Radionuclide imaging techniques with a lipid soluble radio-isotope which easily crosses the blood brain barrier (such as technetium-99) will demonstrate a complete lack of uptake by the brain. Such studies are the preferred ancillary test at Red Cross Children's Hospital.

Transcranial doppler ultrasonography can demonstrate cerebral circulatory arrest however it requires clinical expertise and is not always technically possible.

Electroencephalography is the most commonly used supplementary test for brain death. (NB. Status epilepticus precludes the diagnosis of brain death.) There are technical guidelines relating to its use in determining brain death however it cannot be used as an isolated test (unlike a cerebral angiogram) due to its limitations from electric interference. And some authors argue that an isoelectric EEG does not preclude deep thalamic function.

Consent for transplantation

Without consent from the family there is no possibility of transplantation. There are very good evidence based guidelines for how to approach a family in order to maximize the chances of getting informed consent for transplantation.

The approach for consent must be made by the transplant co-ordinator and not the treating doctor. Consent rates are much higher if these specialists make the approach to the family. Discussions should be held away from the bedside in an appropriate setting.

The approach for consent must be decoupled from the discussion about the prognosis of the patient. Families require time to come to terms with the situation and are more likely to refuse if approached about transplantation too early. Open ended questions are essential to be able to gauge the families' level of understanding. Terms used to describe the clinical situation must be clear and direct. Gentle words can confuse the situation with a family clinging to any optimistic words.

Early discussion with the transplant team in end-of-life care is important. This does seem to conflict with the dead donor rule, however there is no involvement at this stage in patient management. In cases of donation after circulatory death all consent discussions have to take place prior to death certification. The transplant coordinator is experienced in these situations and offers end-of-life care and counselling regardless of the decision to donate.

Additional consent

Following brain death certification and family consent, permission is also obtained from the medical superintendent of the institution where the donor operation takes place. In all cases of unnatural death consent is obtained from the state pathologist. The procuring surgical team includes their operative findings into the post mortem request form.

Improving transplantation in South Africa

This requires identification of all potential donors and appropriate referral and handling of the family.

Extended criteria donors include

1. HIV positive donors- can be transplanted into HIV positive recipients
2. Treatable infections – recipient can be treated with antibiotics
3. Older donors - organs can be assessed individually and allocated to older recipients
4. Younger donors – allocated to younger recipients
5. Malignancy – primary brain tumours have a low risk of metastatic spread
6. Donation after cardiac arrest

Donation after cardiac arrest

Although the role of the anaesthetist is very limited with such a donor it is important that you are familiar with the process. One third of deceased donors in the UK now come from donors after circulatory arrest. Consent for donation is given by the family prior to withdrawal of futile life supporting care. All eventualities are discussed.

Upon withdrawal of care if the patient arrests within an hour of being extubated and the procurement operation takes place immediately following certification of the death then it is possible to donate kidneys, liver and lungs.

The operation must take place immediately as the organs suffer irreparable damage if they are warm and ischaemic. The setting where withdrawal of care takes place will vary depending on the hospital. The transplant team is however scrubbed and waiting in the theatre for the body in order to cold perfuse the organs as rapidly as possible.

Not all patients will arrest within the specified hour and in this case the theatre team stands down, the patient is transferred to a palliative care ward and the family informed that organ donation was not possible.

Brain dead donor management[4, 5]

The degree of monitoring and interventions required to maintain a stable donor vary considerably between donors. The various transplant teams also have different preferred means of resuscitating their particular organs. The transplant co-ordinator is responsible for managing these sometimes conflicting objectives. The time frame involved in organizing everything can also vary markedly (12 – 24 hours for a multi-organ donor).

Some of the general considerations of the management of a brain dead donor will be considered here:

Basic standard monitoring

Fluid intake and output, hourly urine output
Pulse oximetry, temperature and ECG
Arterial blood pressure
For donors requiring vasopressor support invasive arterial monitoring and a central line.

Laboratory investigations

4 – 6 hrly U/E, Blood glucose, ABG
8 – 12 hrly FBC, Liver enzymes, INR

Work-up of the donor for infection and tissue typing is handled by the transplant co-ordinator

A minimum is HIV, syphilis, CMV, EBV, Hepatitis B, C, CXR, Sputum MC&S, Urine protein creatinine ratio, Blood group

General targets

Heart rate: 60 -120 / min
Blood pressure: MAP > 65 mmHg
Urine output: 50 – 100 ml / hour

Hypotension

Donors are frequently under resuscitated and adequate volume expansion may be necessary. Typically a crystalloid (not normal saline due to concerns of hypernatraemia affecting liver transplant outcomes). An Hb of between 7 – 10 is adequate in a stable donor. Too much fluid can adversely affect the potential for a lung transplant.

Loss of vasomotor control often occurs (following an initial hypertensive episode related to raised intracranial pressure) and vasopressors can be required. Adrenaline is not favoured due to its adverse effects on cardiac transplant outcomes. The renal team prefer dopamine/dobutamine as an initial agent and this is often sufficient. International guidelines suggest vasopressin or phenylephrine as first line agents because of their pure vasomotor activity.

Dynamic indicators of volume status such as pulse pressure variation and response to a passive leg raise are the best way to assess volume status.

Respiratory

A tidal volume of 6 – 8 ml /kg and a PEEP of 5 cm water is recommended targeting a saturation of > 95%. Routine suctioning, head up 30º and cuff pressure > 25 mmHg. Avoid fluid overload.

Diabetes Insipidus

Features include a high urine output (> 4 ml / kg / hr), and increasing sodium (>145 mmol/L) and decreasing urine osmolarity / specific gravity. Formal testing is not required and can be suspected clinically. An appropriate initial replacement fluid is 0.45% N/S switching to 5% Dextrose water if sodium control is an issue. DDAVP can be used if the urine output is greater than 300 ml / hr for 3 hours.

Hypothermia

The body loses thermoregulation and active rewarming may be required.

Steroids

Steroids are given routinely. Methylprednisolone 1g / 24 hrs. (eg Solucortef 100 mg 2 hrly). T3 is no longer available.

DIC

Occurs in up to a third of patients and may need to be corrected if there is active bleeding.

Intra-operative management (anaesthetic role)

For a brain dead donor a full anaesthetic is required with paralysis. It is important to keep all organs functioning as optimally as possible right up until the point of cross clamping and cold perfusion.
A multi-organ donor of heart, liver and kidneys will take approximately 3 hours. Ongoing resuscitation is often required through the operation. Prior to clamping and insertion of perfusion cannulas a large dose of systemic heparin is given (30 000U) to help prevent clot formation within the organs. At the time of cross clamping ventilation and all other active management can be stopped.

The cold perfusion of the organs occurs in situ before further dissection of the organs prior to removal.

Psychological support

These cases can be demanding both clinically and in managing the family and fellow staff members. Communication and questions should be encouraged and support given where required.

It is important to realise that the moral, ethical, legal and clinical principles are not always well understood and vary between individuals.

Conclusion

In South Africa transplantation depends on a completely altruistic system of identification, referral, consent and management of deceased donors. All doctors and health care staff play an important role in the process.

By adhering to the dead donor rule transplantation is on ethically sure ground and the appropriate use of brain death criteria allows absolute clarity in an often confusing and emotional situation. Transplant co-ordinators are the backbone of the transplant service and are the go to contact person between family, ICU, theatre, transplant teams, laboratory etc.

They are highly specialized and experts in handling the family, getting informed consent and sorting out all the logistics.

Thank you

Sisters Fiona McCurdie and Maryn Reyneke (Groote Schuur transplant co-ordinators) for proof reading this document.

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Western Cape Government
Health

BRAINSTEM DEATH CERTIFICATION

Issued by Department of Surgery, Groote Schuur Hospital - November 2014

Doctor 1	Prerequisites	Doctor 2
	Coma, irreversible and cause known	
	Normothermia (> 35^{0}C)	
	Systolic blood pressure > 90mm Hg	
	Significant metabolic, electrolyte, endocrine abnormality excluded	
	Sedative/analgesic/neuromuscular drug effect excluded*	

	Examination**	
	Pupils fixed and non-reactive	
	Absent corneal reflex	
	No gag reflex	
	Absent cough reflex on deep suctioning down tracheal tube	
	No facial grimace to supra-orbital pain	
	Absence of motor response in all limbs (spinal reflexes may persist)	
	Oculovestibular (cold caloric) reflex absent	
	Apnoea testing - no spontaneous respiration	

Doctor 1

Name: _____

HPCSA Number: _____

Signature: _____

Date and time: _____

Doctor 2

Name: _____

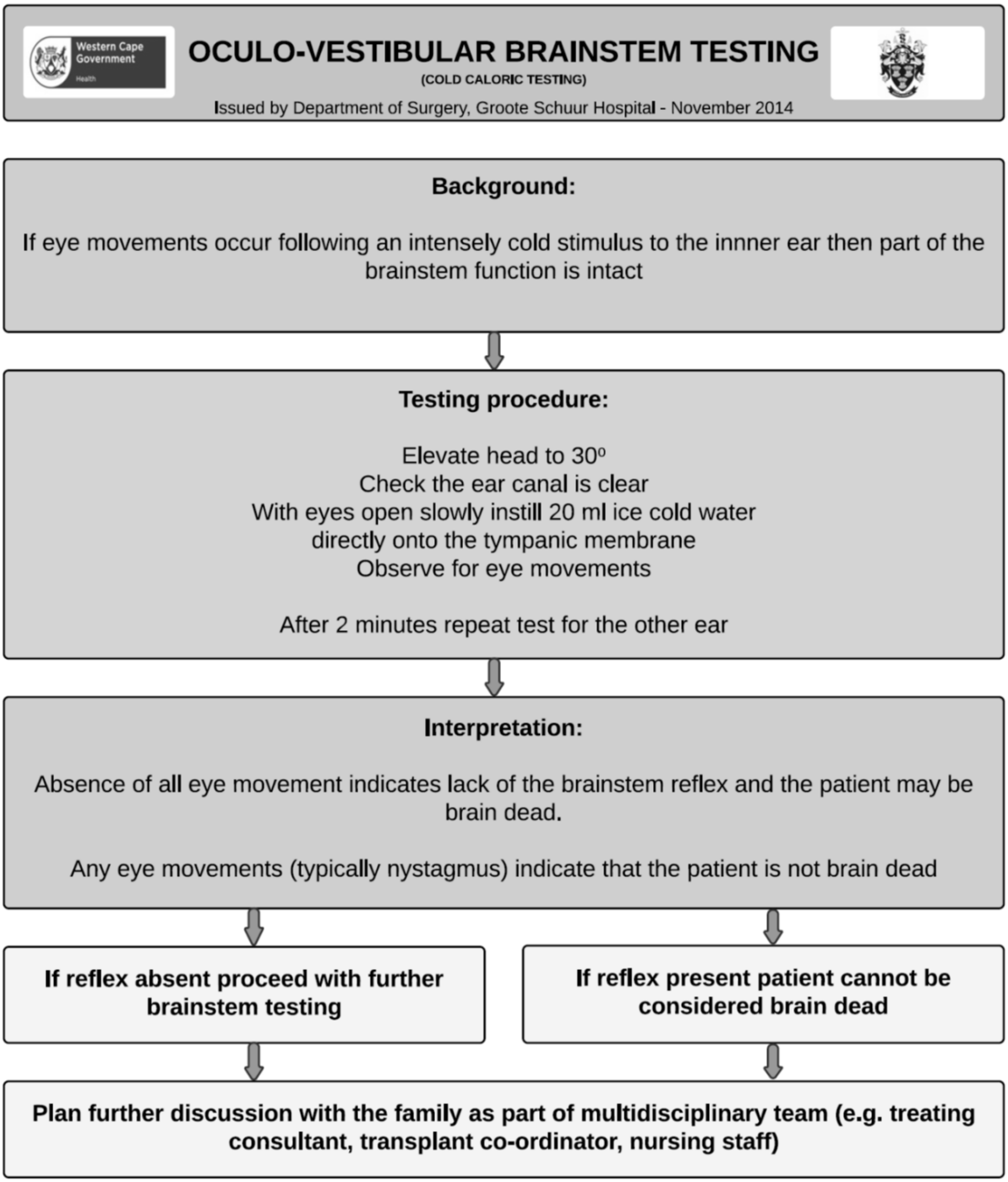
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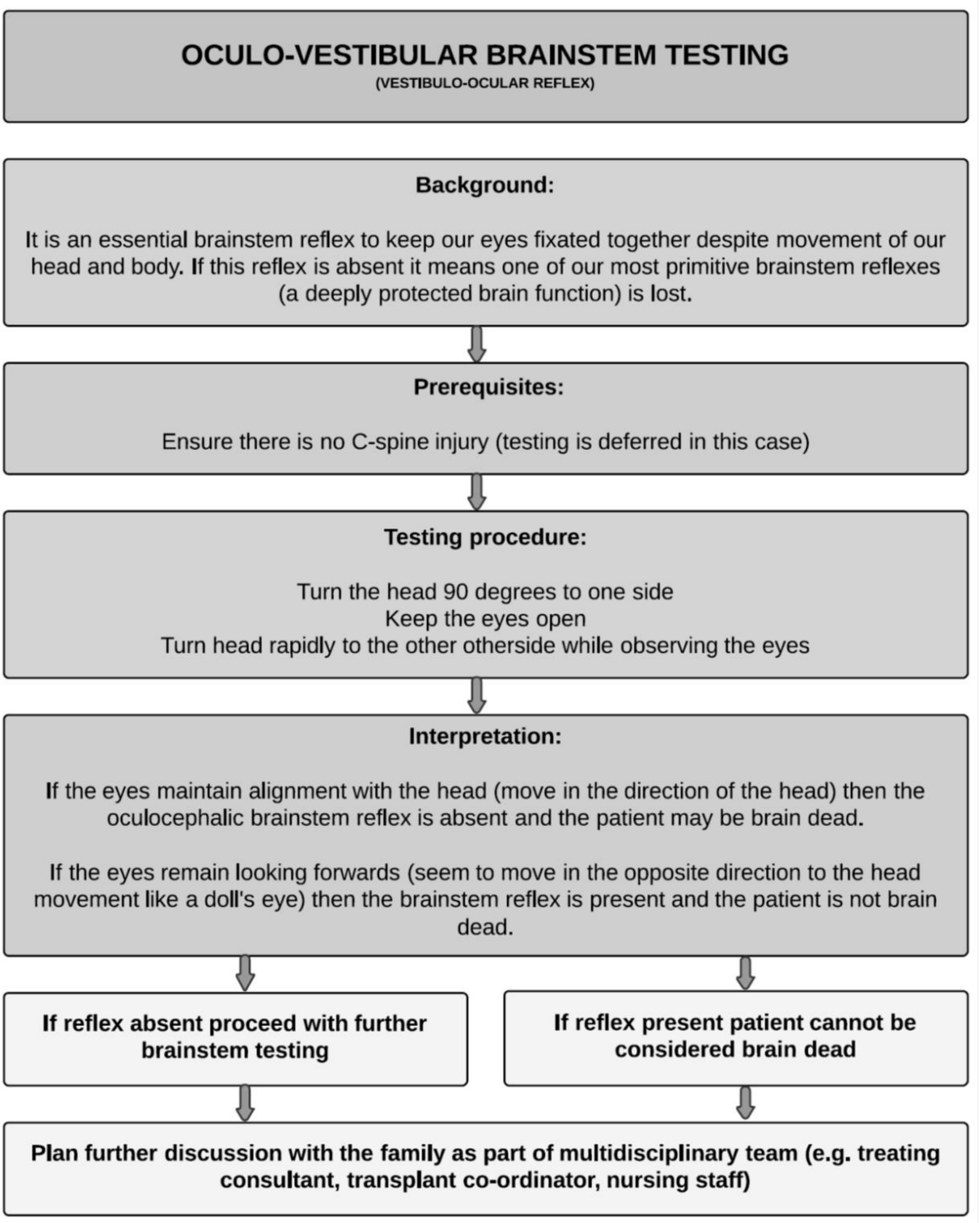
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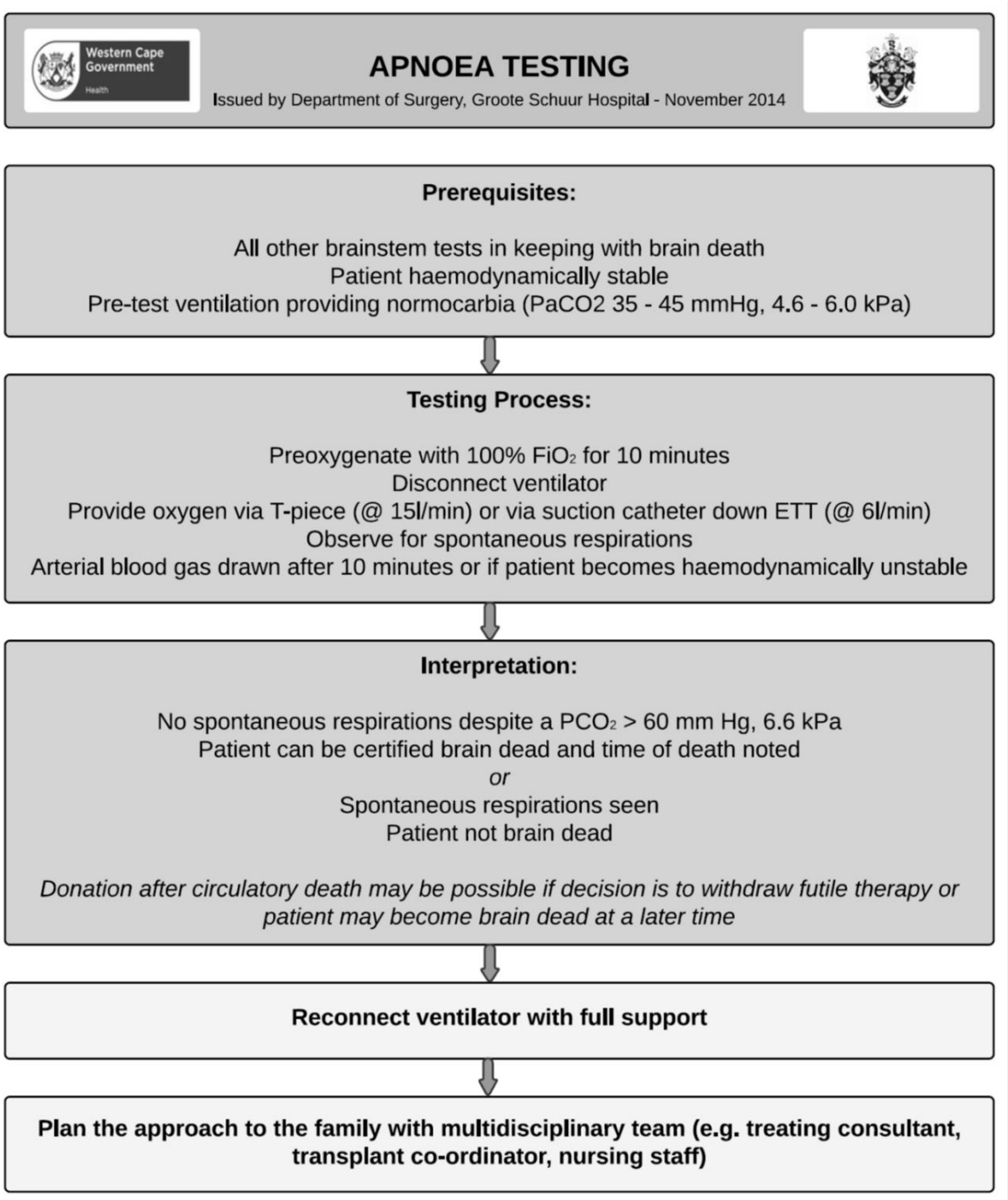
Date and time: _____

*In donors with preserved organ function 12 hours free from sedation is adequate

** One doctor with more than 5 years experience, tests may be done by both doctors simultaneously, no doctor may be involved with the transplant team


OCULO-VESTIBULAR BRAINSTEM TESTING
(COLD CALORIC TESTING)
Issued by Department of Surgery, Groote Schuur Hospital - November 2014
Background:
If eye movements occur following an intensely cold stimulus to the innner ear then part of the brainstem function is intact
Testing procedure:
Elevate head to 30º
Check the ear canal is clear
With eyes open slowly instill 20 ml ice cold water directly onto the tympanic membrane
Observe for eye movements
After 2 minutes repeat test for the other ear
Interpretation:
Absence of all eye movement indicates lack of the brainstem reflex and the patient may be brain dead.
Any eye movements (typically nystagmus) indicate that the patient is not brain dead
If reflex absent proceed with further brainstem testing
If reflex present patient cannot be considered brain dead
Plan further discussion with the family as part of multidisciplinary team (e.g. treating consultant, transplant co-ordinator, nursing staff)


OCULO-VESTIBULAR BRAINSTEM TESTING
(VESTIBULO-OCULAR REFLEX)
Background:
It is an essential brainstem reflex to keep our eyes fixated together despite movement of our head and body. If this reflex is absent it means one of our most primitive brainstem reflexes (a deeply protected brain function) is lost.
Prerequisites:
Ensure there is no C-spine injury (testing is deferred in this case)
Testing procedure:
Turn the head 90 degrees to one side
Keep the eyes open
Turn head rapidly to the other otherside while observing the eyes
Interpretation:
If the eyes maintain alignment with the head (move in the direction of the head) then the oculocephalic brainstem reflex is absent and the patient may be brain dead.
If the eyes remain looking forwards (seem to move in the opposite direction to the head movement like a doll's eye) then the brainstem reflex is present and the patient is not brain dead.
If reflex absent proceed with further brainstem testing
If reflex present patient cannot be considered brain dead
Plan further discussion with the family as part of multidisciplinary team (e.g. treating consultant, transplant co-ordinator, nursing staff)


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APNOEA TESTING
Issued by Department of Surgery, Groote Schuur Hospital - November 2014
Prerequisites:
All other brainstem tests in keeping with brain death
Patient haemodynamically stable
Pre-test ventilation providing normocarbia (PaCO2 35 - 45 mmHg, 4.6 - 6.0 kPa)
Testing Process:
Preoxygenate with 100% FiO2 for 10 minutes
Disconnect ventilator
Provide oxygen via T-piece (@ 15l/min) or via suction catheter down ETT (@ 6l/min)
Observe for spontaneous respirations
Arterial blood gas drawn after 10 minutes or if patient becomes haemodynamically unstable
Interpretation:
No spontaneous respirations despite a PCO2 > 60 mm Hg, 6.6 kPa
Patient can be certified brain dead and time of death noted
or
Spontaneous respirations seen
Patient not brain dead
Donation after circulatory death may be possible if decision is to withdraw futile therapy or patient may become brain dead at a later time
Reconnect ventilator with full support
Plan the approach to the family with multidisciplinary team (e.g. treating consultant, transplant co-ordinator, nursing staff)

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DONATION AFTER CIRCULATORY DEATH

Issued by Department of Surgery, Groote Schuur Hospital - November 2014

Procedure

Discuss case with transplant co-ordinator prior to withdrawal of support

Potential for donation assessed

Consent from family

Transplant team scrubbed and ready in theatre

Withdrawal of futile life supporting measures (extubate and stop inotropes)

No spontaneous respiration or cardiac output for 5 minutes

Death certified by treating doctor*

Organ procurement operation to begin directly

Certifying Doctor

Name: _____

HPCSA Number: _____

Signature: _____

Date and time: _____

If patient does not arrest within one hour of withdrawal of therapy transplantation of the organs is not possible. Transplant team stands down, family informed and patient transferred to end of life palliative care ward

Management of massive blood transfusion

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Massive blood transfusion (MBT) is a response to massive and uncontrolled hemorrhage. It is often a challenging clinical scenario, and optimal management, regardless of aetiology, requires a well-coordinated approach involving clinical teams, laboratory and transfusion services. Managing a MBT includes the selection of appropriate quantities and types of blood products to be administered, as well as consideration around alternative strategies, the timing of interventions, appropriate monitoring and addressing a number of hemodynamic and metabolic issues in the patient.

Definition

MBT refers to a large volume of blood products transfused over a short period of time.

It is traditionally defined in adults as:

- The replacement of the **total blood volume (TBV)** of an average patient /**10** red blood cell (RBC) units within **24 hours**.

Patient	Fat	Thin	Normal	Muscular
Male	60	65	70	75
Female	55	60	65	70

Table 1: TBV estimation (ml/kg body weight) based on Gilcher's rule of 5.

This is largely impractical in the short term and so other definitions have arisen, more appropriate in a dynamic setting:

- Transfusion of > **4 RBC units in 1 hour**, with anticipated continuing need for blood products.
- Transfusion of > **50% of the TBV in 3 hours**

Due to age and weight differentially affecting TBV in children, suggested definitions for pediatric MBT include:

- Transfusion of > **100% TBV in 24 hours**
- Transfusion of > **10% TBV/ min**
- Transfusion of > **50% TBV within 3 hours**

Patient	**Estimation of TBV (ml/kg body weight)**
Neonate (0-4kg)	85
Infant (5-9kg)	85
Young child (10-24kg)	75
Older child (24-49kg)	70
Young adult (>49kg)	Same as for adult

Table 2: TBV estimation in paediatric patients (ml/kg)

Regardless of the absolute numbers the aim of the definition is the same: rapid identification of patients with a life threatening bleed.

Epidemiology and history of transfusion

Blood transfusion has been utilized for centuries as a well established practice in order to save lives and prevent illness. Today in the US every 3 seconds a patient receives blood, and 4.5 million lives are saved by transfusions annually. The first recorded human transfusion was performed by James Blundell in 1818. He treated a patient with postpartum hemorrhage using her husband as a donor. Karl Landsteiner discovered the first blood types (A, B, O) and received the Nobel Prize for Medicine in 1930 for his breakthrough work in this field. Most of the changes in transfusion practice over time have occurred during the first and second world war (WW II) and were thus developed in a military setting based on trauma patients. By WW II freeze dried plasma as well as whole blood were used to achieve balanced resuscitation, and component therapy was introduced in the 1970's in order to reduce infectious transmission and preserve resources. This however led to the underuse of clotting factors and inadvertent hemodilution with resultant failure to control bleeding. Complications due to initial large volume crystalloid infusion subsequently led doctors to return to the balanced resuscitation theory used in WW II, and thus we have come full circle in our approach to the management of massive hemorrhage.

Currently in South Africa, trauma-related injuries are the second leading cause of death and disability. About 60 000 deaths per year are due to interpersonal violence, injuries from traffic accidents, fires and falls. Acute exsanguination is the leading cause of death in such trauma patients. In the US, unintentional trauma alone accounts for +/- 120 000 deaths per year. 40% of these are due to uncontrolled hemorrhage.

Various **etiologies** of MBT include:

- Obstetrics and gynaecology (post partum haemorhage, ectopics and septic miscarriage)
- General surgery (acute abdomen, upper gastrointestinal bleed)
- Orthopaedic surgery (polytrauma)
- Cardiothoracic surgery (stab heart, valve replacement)
- Neurosurgery (head injury)
- Liver transplant
- Vascular surgery (ruptured aortic aneurysm)

Pathophysiology

Oxygen delivery

At rest oxygen delivery (DO_2) is normally 4 times oxygen consumption (VO_2). Indicating a large reserve. Therefore mild anemia has few symptoms. During massive hemorrhage RBC volume is rapidly lost from the circulation. If this is replaced with clear fluid and cardiovascular status remains unimpaired, oxygen delivery will remain adequate until the hematocrit decreases to <10%, as sympathetic stimulation causes cardiac output (CO) as well as oxygen extraction to increase, allowing for this compensation. However, the critical point where VO_2 becomes delivery dependent is then higher, as increased cardiac work requires more oxygen delivery. Therefore RBC replacement becomes paramount in maintaining oxygenation.

DO_2 = $CO \times CaO_2$
= $CO \times ((\mathbf{Hb} \times SpO_2 \times 1.34) + PaO_2 + 0.03$ (mmHg)

The transfusion requirements should always be based on the individual patient's physiological need and improving in oxygen delivery.

Recent evidence supports the use of a restrictive transfusion strategy. This was associated with a reduced incidence of hospital acquired infections (pneumonia, wound infection, sepsis). What the hemoglobin (Hb) value should be adjusted to in patients with specific risk factors (ischaemic heart disease) is less clear, but should take clinical symptoms and signs of ischaemia into account in the bleeding patient. The ASA recommends that a Hb of 6 be avoided in healthy adults. Studies of Patients in ICU, undergoing cardiothoracic surgery, hip fracture repair and with acute upper GIT bleed have been shown to tolerate Hb of 7-8 g/dl. The TRICC trial also showed that there was no change in mortality in ICU patients with restrictive transfusion to an Hb of 7-9g/dl.

Coagulopathy

Tissue injury and hypoperfusion due to trauma and massive hemorrhage cause 2 different types of hemostatic defects. They are dynamic, and have a multifactorial pathogenesis. They are integral in causing ongoing hemorrhage resulting in the need for MBT.

Acute trauma coagulopathy (ATC) / Trauma induced coagulopathy (TIC)

- Present within 30 minutes of injury in 24% - 56% of severely injured patients.
- Correlates with poor clinical outcomes
- Associated with systemic anti-coagulation and hyperfibrinolysis
- Hypoperfusion leads to thrombomodulin (TM) expression on endothelial cells.
- Thrombin-TM complexes formed:
    - **activate protein C, causing inhibition of F V and VIII**.
    - Depletes **PAI-1**, enhancing fibrinolysis, and accelerating plasmin formation.
    - Decreased activation of thrombin-activatible fibrinolysis inhibitor, further causing hyperfibrinolysis (as thrombin is diverted from cleaving fibrinogen).

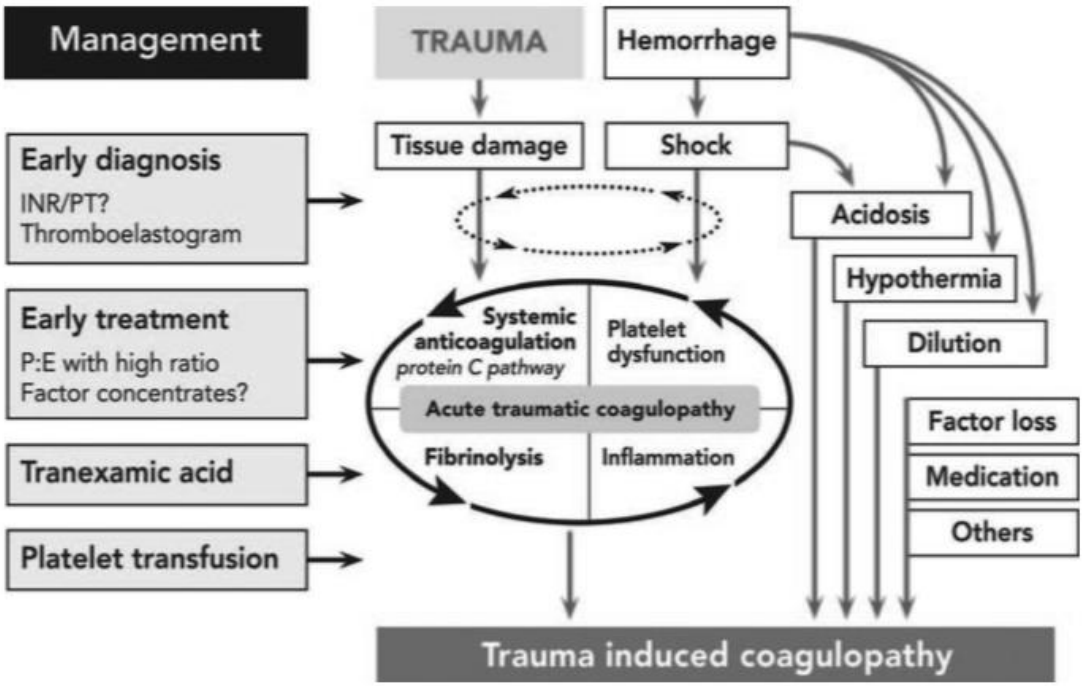


Figure 1: Mechanism of trauma induced coagulopathy. INR = international normalized ratio.PT = prothrombin time.

Further coagulopathy

- Develops due to resuscitation related factors.
- Clotting factors and platelets lost during hemorrhage.
- Tissue injury releases tissue factor (TF).
- TF activates coagulation pathways causing **consumption** of clotting factors.
- Tissue injury causes hormonal (adrenaline and vasopressin) and cytokine release, which activates the endothelium.
- Hypothermia reduces enzymatic activity of CF, and prevents activation of platelets. The onset of this effect is seen at core temperatures of 34'C and at 30'C it stops functioning in 50% of patients.
- Acidosis interferes with assembly of CF complexes involving calcium and negatively charged phospholipids. Xa/Va prothrombinase complexes are reduced by 50, 70 and 80% in pH's of 7.2, 7.0, and 6.8 respectively.

- Dilution due to interstitial fluid moving intravascularly and fluid deficits replaced via IV infusion.
- Immune system activation amplifies hemostatic activation.

Early recognition of the need for a MBT

Various **models and scoring systems** have been developed to ensure early recognition and prompt treatment initiation in trauma patients. They combine clinical, laboratory and demographic data.

- TASH (Trauma Associated Severe Hemorrhage) score incorporates 7 variables.

Variable	Value	Points	Score
Haemoglobin (g/dl)	< 7	8	
	< 9	6	
	< 10	4	
	< 11	3	
	< 12	2	
Base excess (mM)	< –10	4	
	< –6	3	
	< –2	1	
Systolic blood pressure (mmHg)	< 100	4	
	< 120	1	
Heart rate (bpm)	> 120	2	
Free intraabdominal fluid (e.g. by FAST)		3	
Clinically instable pelvic fracture		6	
Open or dislocated femur fracture		3	
Male gender		1	
TASH > (sum of score points)			

Probability for massive transfusion (MT)	
TASH	P
1–8	< 5%
9	6%
10	8%
11	11%
12	14%
13	18%
14	23%
15	29%
16	35%
17	43%
18	50%
19	57%
20	65%
21	71%
22	77%
23	82%
24 +	>85%

Table 3: The updated TASH score.

- Nunez et al used simple rapidly available parameters where 2 or more positive parameters correlated with an increased likelihood of MBT:
  - Penetrating trauma
  - SBP < 90mmHg
  - HR > 120bpm
  - Positive FAST (focused abdominal sonography for trauma) scan.

Similar scores are also now being developed in other fields such as cardiac surgery.

Identifying **clinical risk factors** elevating the risk of hemorrhage is also important. For example: history of coagulation disorders, medications such as antiplatelet and anticoagulant agents, type of surgery, etc. The transfusion plan should then be modified accordingly.

It can be difficult to predict who will need a MBT, and overuse of the MTP (massive transfusion protocol) can also pose unnecessary risks to the patient and cause significant harm, as well as wastage for the blood bank. In non-trauma studies, plasma transfusion is associated with a 3 times increased in risk for acute lung injury. In one study by Dente and colleagues, 27% of trauma patients for whom the MTP was activated never received a MBT. Trans pelvic and multi-cavity gunshot wounds, SBP < 90mmHg, and base deficit > -10 were identified as strong predictors necessitating a MBT. Consequently, a universal set of activation triggers may not always be appropriate in all settings, and the final decision will ultimately depend on the judgment and experience of the clinical team

Clinical management

The management of the bleeding patient as a whole is integral in managing a MBT. The first goal is to restore and maintain arterial blood pressure and blood flow via circulating blood volume, and oxygen carrying capacity and therefore tissue oxygenation. Subsequently oncotic pressure and viscosity, coagulation function and biochemistry should be addressed.

Damage control resuscitation is now a widely accepted approach in trauma patients. This consists of permissive hypotension (SBP 90mmHg), damage control surgery, active warming and **hemostatic resuscitation**. One of the core tenets of hemostatic resuscitation is the use of early, balanced transfusion. This represents a change in clinical management from the previous approach of initial crystalloid volume expansion in the 1970's. It has largely been driven by the identification of ATC, and the multiple complications of large volume crystalloid infusion, such as: abdominal compartment syndrome, ARDS, multi-organ failure and sepsis.

Since 2006, where the original observational data showed increased survival, with aggressive use of plasma in US military casualties, there have been at least 30 other studies examining the same subject (high ratio's of plasma to RBC usage) in military and civilian trauma units. The majority of them have shown the same outcome, with less use of blood products and less acute coronary syndrome (ACS). Although survivor bias is a consideration, the observations make physiological sense. This has also led to 2 different approaches: that adopted by the US, and that by the Europeans.

- The US favour early fresh frozen plasma (FFP) transfusion, with an empiric replacement of RBC, plasma and platelets, in a ratio close to that of whole blood itself. Their rationale is that it is universal, easy to apply, and that the complexity of coagulation may require the pleotropic properties of plasma, rather than only individual factors. Plasma has been shown to better preserve the endothelial glycocalyx during hypovolaemia, and contains a synergistic balance that preserves vascular integrity.
- The Europeans favour early factor specific replacement, based on the measurement of the specific deficit (eg: prothrombin or fibrinogen factor concentrates). Their rationale is that there is almost always a delay in receiving and transfusing the plasma, due to the need for thawing and blood bank preparation. Where as factor concentrates can be ready for immediate dispatch. Few blood banks maintain a readily available supply of pre-thawed plasma due to supply and resource considerations. Their concern is also that any extra unneeded components will contribute to late inflammatory and septic complications of transfusion.

The need for more and better quality data on the early plasma transfusion issue has led to further investigations:

- The **PROPPR** study (pragmatic randomized optimal platelet and plasma ratios) - provides more evidence with regard to optimal plasma transfusion ratio.
    - 680 hemorrhaging trauma patients received ratios of 1:1:1 or 1:1:2 (plasma:platelet:RBC).
    - There was no difference in the 24hr or 30 day mortality.
    - But death from exanguination, which was the predominant cause of death in the first 24hours, was significantly decreased in the 1:1:1 group (9.2% vs 14.6%).
    - No difference in the amount of pre-specified transfusion complications
    - More patients in the 1:1:1 group achieved hemostasis.
- The **PROMMT** (Prospective, observational, multicenter, major trauma transfusion) study related in hospital mortality to early plasma/platelet transfusion.
    - Increased plasma: RBC ratios were independently associated with a decreased 6-hour mortality when hemorrhagic death predominated.
    - In first 6 hours, patients with a 1:2 ratio were 3-4 times more likely to die than 1:1 ratio's.
    - Among survivors at 24hours 30 day mortality risk was not associated with plasma or platelet ratios.

In preparation for massive bleeding and MBT management one should consider and note the following:

Pre-operative:

- History (anticoagulants), physical examination, vital signs, activation of the MTP, assisting with communication and acquiring extra personnel.

Intraoperative:

- large bore IV access (14/16G), warming devices (fluid and patient), rapid infusion devices, and pressure bags, continuous temperature monitoring, invasive arterial pressure monitoring, point of care testing (ABG and TEG/ROTEM), assessment of blood loss volume, cell salvage technique

Post-operative:

- intensive care (ICU) arrangements for completion of late resuscitation, when the active bleeding has been controlled and the aim is restoration of homeostasis. The Gold standard is an acid base status and serum lactate returned to normal.

In other clinical settings there is less evidence available regarding set ratios for transfusion. It is more difficult to conceptualise in patients who undergo extensive elective surgery and develop ongoing microvascular bleeding. These patients are dissimilar in that they may be warm, normotensive and have a normal acid base balance, but do have a common final pathway of coagulopathy and may also require MBT. What about transfusion and ratios of blood products in these patients?

Blood Products

It is important to consider the composition of blood products you are going to use. The characteristics of blood components are summarized in the table below.

	Red Cells	**Pooled platelets**	**Apheresis platelets**	**FFP**	**MB-FFP**	**SD-FFP (Octaplas)**	**Cryoppt pool**
Volume (ml)	220 - 340	295.3 (24.5)	179.5 (14.9)	275 (14)	229.5 (12.7)	200 (standardized)	204.9 (21.4)
Storage temp	4 ± 2°C	22 ± 2°C with agitation	20 - 24°C with agitation	< - 25°C	< - 25°C	< - 18°C	< - 25°C
Anti-coagulant	CPD	CPD	Acid citrate dextrose	CPD	CPD	Sodium citrate	CPD
Shelf-life	Up to 35 days	5 days (7 if bacterial screening)	5 days (7 if bacterial screening)	36 months (24h after thawing if stored at 4 ± 2°C)	36 months (24h after thawing if stored at 4 ± 2°C)	4 years	36 months (4h after thawing if stored at ambient)
Specific-ation	Hb >40g/unit	Platelet count ≥240x10^9/ pool	Platelet count ≥240x10^9/ unit	Factor VIII:C >0.70IU/ml	Factor VIII:C >0.50IU/ml	Factor VIII >0.50IU/ml	Fibrinogen >700mg/pool and Factor VIII:C >350IU/pool
Typical values	Hb 0.41 (9.52)	Platelet count 300 (45)	Platelet count 261 (35)	Factor VIII:C 0.85 (0.2)	Factor VIII:C 0.65 (0.18)		Fibrinogen 1753 (398)mg/pool and Factor VIII 435(112) IU/pool

Table 4: Blood product characteristics

Whole blood:

- < 5 days or 96 hours old
- no F V and VII
- no functioning platelets after 6 hours
- volume: 500mls
- Hb 10-12
- Considered useful in MBT

Fresh whole blood would be the closest to the ideal solution to replace acute blood loss.

- 500ml
- warm
- Hct 38-40
- Platelets 150 – 400
- Full coagulation function
- 1500ml fibrinogen
- used in the military setting with good outcomes

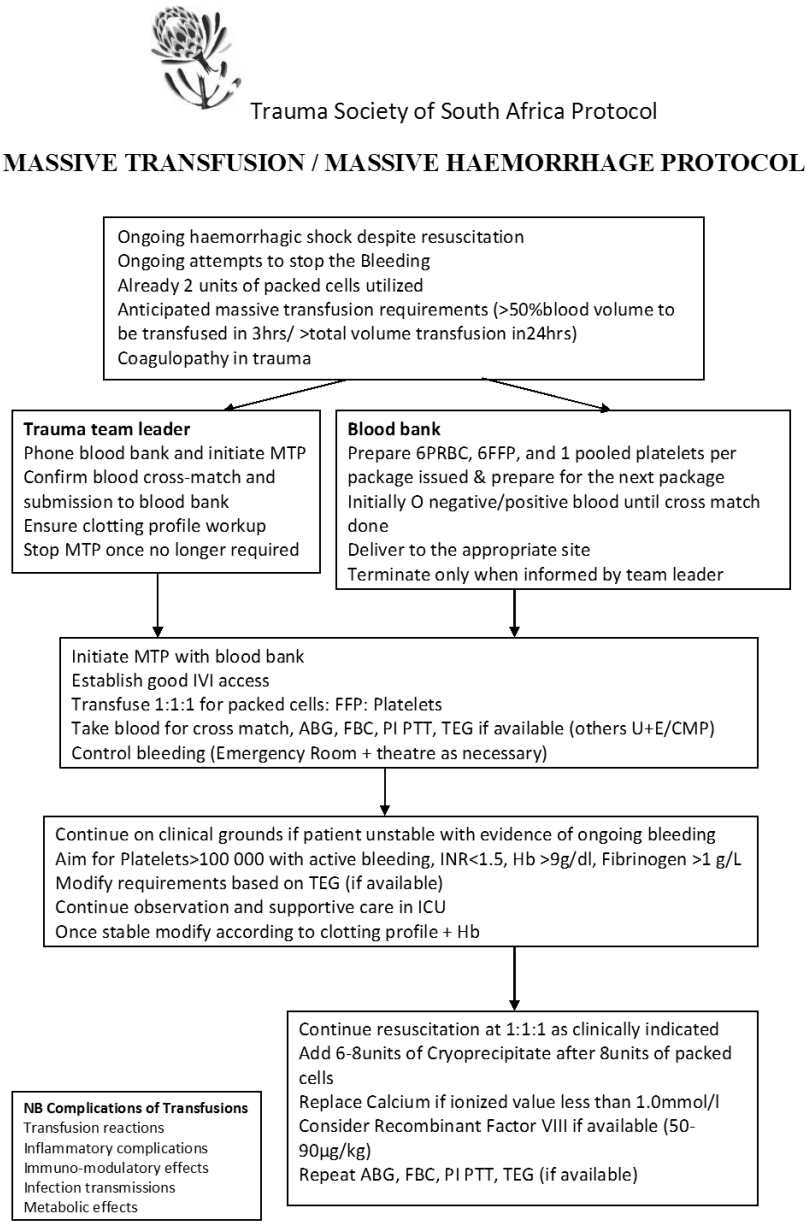
1 MBT unit: 1 RBC, 1 FFP, 1 platelet, 2 cryoprecipitate together will have a total composition of:

- 660mls
- Hct 29%
- Platelets 87000
- 65% of coagulation function (due to dilution by volume of others)
- 750mg fibrinogen

Prothrombin complex concentrate (PCCP):

PCC are purified form pooled plasma, and contain F II, VII, IX, X and coagulation inhibitors protein C and protein S. They may have some antithrombin III and small amounts of heparin. They are licensed for urgent reversal of the effects of warfarin and congenital coagulation defects in actively bleeding patients or those undergoing surgery. In Europe it replaces FFP's in the management of major bleeding in many centers, although there is a lack of clinical data and it may be associated with thromboembolic risk.

MBT Protocols



A MBT Protocol (MTP) describes an empirical standardized treatment, which optimizes the management of resuscitation and complications arising from massive hemorrhage.

"*A well designed MTP is a valuable tool which delineates how blood products are ordered, prepared and delivered, determines laboratory algorithms to use as transfusion guidelines, and outlines duties and facilitates communication between involved personnel*."

Figure 2: The Massive Transfusion Protocol for the Trauma Society of South Africa

In South Africa, MTP are not regularly used. A prospective audit at a tertiary South African hospital in 2010, looking at blood product utilization during massive transfusions included 30 cases during 2 months, in both emergency and elective situations. A MTP was not used once and varying amounts of blood products were used. In order to provide good patient care we should try and improve this.
The benefits of a MTP include the following: facilitation of communication between different services (trauma, nursing, transfusion, laboratory), avoidance of delay in clinical services, laboratory testing,

blood product supply and transfusion. MTP's have demonstrated improvements in patients survival, decreased incidence of organ failure and post trauma complications.
An MTP should have the following components:

- When and who should initiate the protocol
- Notification of involved parties of start and stop instructions.
- Laboratory testing algorithm
- Blood product preparation and delivery
- Other patient care needs (blood warmers etc.)

Laboratory Monitoring

MBT requires good laboratory support in monitoring of oxygen carrying capacity, hemostasis and metabolic status, in order to correct abnormalities and in a timeous manner. Traditional laboratory monitoring includes prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen level, blood gas and complete blood count. These tests are not available in real time, and so do not assist in rapid management of coagulopathy. Point of care (POC) tests such as thromboelastography (TEG) or thromboelastometry (ROTEM) may be better for a number of reasons. Coagulation system tests should be carried out after each 5 units of RBC.

The advantages of TEG\ ROTEM are:

- The graphic representation is received in a shorter turnaround time (15-30min).
- Hyperfibrinolysis can be detected.
- All phases of coagulation are assessed (such as the contribution of platelets to primary hemostasis, and FXIII to linking the fibrin clot).
- It can be performed at the patient's true temperature.

However, a Cochrane review suggested that there is no evidence that it reduces morbidity or mortality in MBT patients, and so there is no universal agreement on its use in MBT.

Coagulation targets in MBT:

- PTT < 1.5
- Platelets > 75000
- Fibrinogen > 1
- Normal TEG

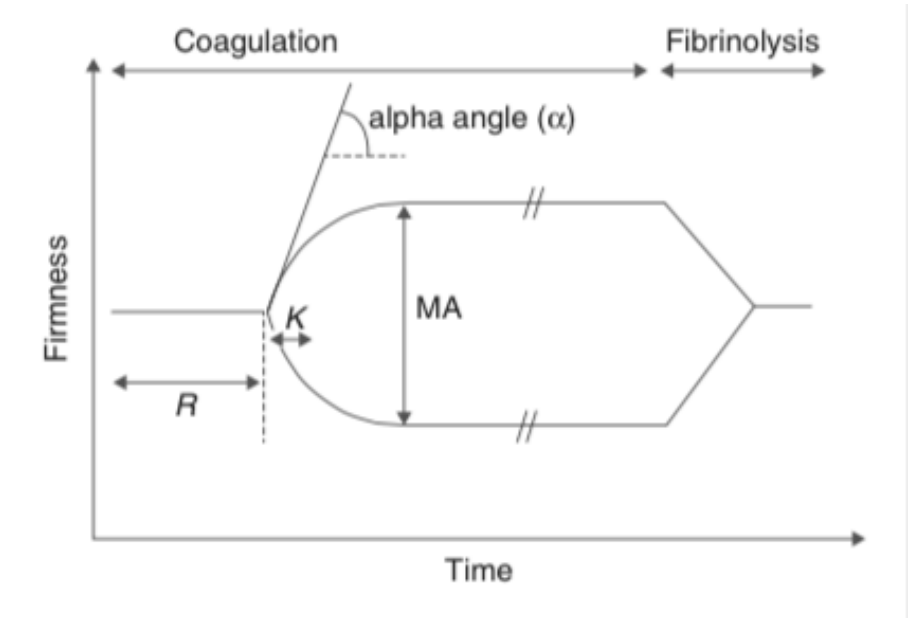


Figure 3: Thromboelastogram

TEG parameter	ROTEM parameter	Definition	Haemostatic phase	Aetiologies for abnormalities	Potential management
R	CT	Time from the start of the test till the first sign of clot formation	Initiation of coagulation	Prolonged *R*/CT: factor deficiencies or anticoagulants. Shortened *R*/CT: plasma hypercoagulability	Plasma for prolong *R*/CT
K	CFT	Time from the start of clot formation to the time when the curve reaches amplitude of 20 mm	Amplification of coagulation	Prolonged *K*/CFT: factor deficiencies, hypofibrinogenaemia, dysfibrinogenaemia, thrombocytopenia, or platelet dysfunction	Cryoprecipitate
α	α	Angle between the baseline and the tangent to the curve through the starting point of coagulation	Propagation of coagulation (i.e. 'thrombin burst')	Low α: factor deficiencies, hypofibrinogenaemia, dysfibrinogenaemia, thrombocytopenia, or platelet dysfunction	Cryoprecipitate
MA	MCF	Amplitude measured at the maximum curve width	Propagation of coagulation (i.e. 'platelet=fibrin interaction')	Low MA/MCF: factor XIII deficiency, hypofibrinogenaemia, dysfibrinogenaemia, thrombocytopenia, or platelet dysfunction	Platelets might consider plasma or cryoprecipitate for factor XIII if ongoing bleeding and persistently low MA/MCF
LY	ML	Reduction in area under the curve (LY) or in amplitude (ML) from time MA/MCF is achieved until 30 or 60 min after MA/MCF	Fibrinolysis	Increased LY/ML: hyperfibrinolysis	Anti-fibrinolytic medication

Table 5: TEG/ROTEM parameters, interpretations, and management of hemostatic abnormalities

Fibrinogen:
Fibrinogen levels should be closely monitored in patients with obstetric hemorrhage, and if necessary early fibrinogen transfusion given. It has been shown that obstetric patients with that above 400mg/dl do not develop PPH. In neuro- and cardiac surgery, data has shown an increased bleeding tendency if the fibrinogen is <150-200mg/dl.

Alternative agents/ adjuncts

Tranexamic acid (TXA):
This antifibrinolytic has been shown to reduce mortality in trauma patients if given early in the resuscitation process (<3hrs form injury, preferably in the 1st hour) in the CRASH-2 trial. It has also been seen to reduce bleeding by a third in surgery and obstetric patients post caesarean section and vaginal delivery. The WOMAN trial is a study looking at outcomes in obstetric patients with PPH due to report in 2016/7.

Recombinant factor VII:
rFVIIa is not recommended for use. It has not been shown to improve outcomes and is associated with thrombotic risk.

Complications

There are significant complications to transfusion of blood products. The risk versus benefit balance should always be weighed up and the best decision made for the patient. Massive blood transfusion however is a life saving intervention, in a situation where transfusion itself is unavoidable. Transfusion reactions, infection and immunological reactions may occur in any transfusion circumstances. Metabolic complications, hemostatic defects, transfusion associated circulatory overload and air embolism are more specific to MBT due to the large volumes transfused. The patient should be monitored closely for these, and pediatric patients,, patients with cardiac, hepatic and renal disease are more at risk. Evidence also shows that increased storage time of RBC's is associated with a worse outcome. The complications that may be encountered with MBT are discussed in the table below.

Adverse events	Comments and potential treatments
Transfusion reactions	
Allergic	Range from simple urticarial to anaphylaxis. Steroid and diphenhydramine might be given to patients with allergic transfusion
Haemolytic transfusion reaction (acute and delayed)	Might be reduced by giving group O RBCs and AB plasma for emergency release of blood products
Febrile non-haemolytic transfusion reaction	Diagnosis of exclusion
Immunological reactions	
Transfusion-related acute lung injury (TRALI)	Incidence can be reduced by transfusing male-only plasma
Transfusion-related immunomodulation (TRIM)	Might be responsible for increased risk of bacterial infection
Transfusion-associated graft *vs* host disease (Ta-GVHD)	Irradiation of cellular blood products in patients at risk (such as neonates and immunosuppressed patients) to prevent Ta-GVHD
Post-transfusion purpura (PTP)	Can be treated with IVIg infusion, steroid, or plasma exchange
Metabolic complications	
Hypocalcaemia*	Because of citrate overload from rapid transfusion of blood products. Neonates and patients with pre-existing liver disease are at risk for hypocalcemia. Monitor ionized calcium level and correct if necessary
Hypomagnesaemia*	Because of large volume of magnesium-poor fluid and citrate overload. Monitor ionized magnesium level and correct if necessary
Hyperkalaemia*	Because of haemolysis of RBC from storage, irradiation, or both. Neonates and patients with pre-exisiting cardiac and renal diseases are at risk for hyperkalaemia. Monitor potassium level and correct if necessary. Fresh RBCs (<5–10 days old), irradiated <24 h before transfusion or washing may decrease risk
Hypokalaemia*	Because of re-entry into transfused RBCs, release of stress hormones, or metabolic alkalosis. Monitor potassium level and correct if necessary
Metabolic alkalosis*	Because of citrate overload. Monitor acid–base status
Acidosis*	Because of hypoperfusion, liver dysfunction, and citrate overload. Monitor acid–base status
Hypothermia*	Because of infusion of cold fluid and blood products, opening of body cavities, decrease heat production, and impaired thermal control. Neonates and infants are at increased risk. Blood warmer should be used
Other adverse events	
Haemostatic defects*	Result from complex mechanism (discuss in the pathophysiology section)
Infection	Can result from blood products or other resuscitated procedures, such as surgeries
Transfusion-associated circulatory overload (TACO)*	Should be differentiated from TRALI. Infants and patients with pre-existing cardiac disease are at increased risk. Oxygen and diuresis can be used
Air embolism	A rare fatal complication. Instructions and/or protocols on how to use rapid infuser must be followed

Table 6: Complications of Massive Blood Transfusion

Conclusion

The management of a patient who requires massive blood transfusion needs consideration of a number of complex physiological relationships. It is a life saving intervention, whether in an emergency trauma or elective surgical setting. There is no clear threshold for Hb, platelet count or coagulation factor deficiency below which use of blood products is futile. Massive transfusion protocol implementation has proven to increase survival and should be followed. It is advocated that ratios of plasma:platelets:RBC of as close1:1:1 as possible, be implemented in trauma patients, with consideration of adjuncts such as tranexamic acid in appropriate cases. The patient should be monitored closely for known complications such as coagulopathy and acid-base disturbance, and appropriate interventions initiated. Follow up care once the hemorrhage is controlled should aim to restore homeostasis and prevent long term sequelae.

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Management of the severely injured patient:

Current concepts

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These notes will aim to cover current concepts and controversies regarding the severely injured adult patient and some of the important anaesthetic considerations. The management of multiple injured patients, burns and the injured pregnant or paediatric patient will not be addressed. Please e-mail me f.roodt@uct.ac.za, if you would like a pdf copy of the power point presentation.

Introduction

Trauma is the leading cause death and disability worldwide, despite improvements in trauma care. Half of trauma deaths occur immediately, another 30% within a few hours of injury and up to a third of all trauma deaths are due to exsanguination.

In South Africa the burden of injury is significant and in a recent trauma surveillance in Cape Town, alcohol was implicated in 30% of trauma admissions, with the following injuries; assault with sharp objects (68%), blunt objects (23%), motor vehicle accident (16%), and 2% with falls. Age distribution was heavily weighted toward patients 40 years of age or younger. [1]

Battlefield lessons have been transferred to civilian trauma care as well as our understanding of the pathophysiology of resuscitation. These and other conceptual changes necessitates consideration of current concepts and controversies regarding the management of the individual severely injured patient (SIP):

Major trauma network.[2, 3]

Organization of trauma care and optimal triage of patients is aimed to provide optimal management of severely injured patient, reducing morbidity and mortality. This has led worldwide to a change establishing specialized major trauma centers (MTC) with supporting trauma units (TU) that have adequate facilities, staffing and organisation to receive and manage trauma patients.

Major trauma can be defined as an injury severity score of >15. Triage pre-hospital and on arrival to hospital, is essential to direct the right patient to the right place in the shortest time. SIPs are identified and taken directly to the MTC if journey is < 45 minutes. In the event of immediate life threatening injury or journey > 45 minutes away from the MTC, patients are taken to the nearest TU for resuscitation, evaluation and triage. Secondary transfers will take place to MTC if required. Hospitals that due not have the facilities to receive major trauma are by-passed by the pre-hospital system. Transporting trauma patients directly to trauma center reduces time to definitive treatment (trauma bypass). There is growing evidence that providing trauma care with-in a well-organized system saves lives and prevents long-term disability.

MTC criteria
• level 1 Hospital • 24/7 availability of all services • sufficient numbers of patients treated • co-ordinated multidisciplinary team • adequate staff, equipment and facilities

Trauma team. [4]

Effective care of SIP requires the skills of clinicians of several specialities and the introduction of multidisciplinary trauma teams has improved patient outcome independently.
Importance of handover by paramedics should not be underestimated as they have knowledge of the scene, mechanism of injury, patient condition and pre-hospital management that affects assessment and further care. MIST structure for handover and forward communication:

M - Mechanism of injury
I - Injuries sustained or suspected
S - vital Signs @ scene/on transport
T - Treatment and response

There is much variation in trauma team composition. In a basic setup it should consist of emergency physician, surgeon/orthopaedic surgeon, 2x nurses, anaesthetist and some include a radiology technician/radiologist and or neurosurgeon. Many hospitals have a tiered trauma team call out response. The goals of a trauma team are to rapidly resuscitate and stabilize the patient, reduce the time to diagnosis and treatment with the overall improvement of survival rates.

It also allows early mobilization and involvement of more experienced medical staff. The ATLS principles are followed and utilize a horizontal distribution of tasks between team members, reducing the time of injury to critical interventions. Tasks are carried out in parallel rather than sequentially.

Leadership skills have been shown to be of particular importance. The quality of leadership is paramount to the safe and efficient trauma scenario, as well as clear communication. The team leader, maybe any member of the team, and oversee the resuscitation and intervene as necessary.

The role of the anaesthetist in the team –
As airway specialist, positioned at head of patient presents unique overview of the patient and situation, ideally situated to recognise and manage any acute physiological derangements.
Provides direct continuity of care through the early part of the patient treatment pathway.
The Anaesthetic Non-Technical Skills (ANTS) systems are all the critical determinants of successful trauma resuscitation. (task management, team working, situation awareness and decision-making)

Damage Control Concepts:

The concept of damage control has spilled over from military medicine to clinical practice and expanded to from damage control surgery to damage control resuscitation and radiology.

Damage control surgery (DCS)

Damage control surgery is not new. It denotes the application of early and aggressive life saving techniques while avoiding reconstructive surgery. It describes the surgical practice of quickly controlling haemorrhage and containing contamination, with delayed definitive surgical repair of such injuries. It may be part of the resuscitation effort, by stopping bleeding, and prevent further damage while minimizing the surgical insult.

Time to DCS is a key determinant of outcome and the transfer to surgery should only be delayed for life-saving interventions.

The sequence followed is essential surgery, “pit stop” resuscitation and catch-up; this may be repeated several times.

Damage control resuscitation (DCR)[5]

The lethal triad of coagulopathy, hypothermia and acidosis compounds morbidity and mortality associated with traumatic haemorrhage.

DCR describes the rapid correction of hypothermia and acidosis, as well as the direct treatment of coagulopathy. It involves early transfusion of trauma patients, the use of permissive hypotension and minimization of crystalloid use, massive transfusion protocols, tranexamic acid and damage control surgery.

Coagulopathy of trauma

The pathophysiology is not just a result of resuscitation (dilution of clotting factors), hypothermia or both. The coagulopathy of trauma is a multifactorial and early phenomenon, often present even prior to the dilutional effects of resuscitation. There are 6 key interacting mechanisms that lead to this coagulopathy: tissue trauma, shock, haemodilution, hypothermia, acidaemia and inflammation. The SIRS response associated with severe injury results in activation of cellular and humoral mediatators much earlier than previously thought. Shock is an independent contributor to early coagulopathy, demonstrated by dose dependant association between tissue hypoperfusion and degree of coagulopathy. Tissue damage cause activation and depletion of clotting factors and hyperfibrinolysis through endothelial injury. Hypothermia and acidaemia inhibit protease activity decreasing platelet function.

Time limited permissive hypotension (controlled fluid resuscitation)

The aim is to limit fluid resuscitation until haemorrhage control has been achieved, thereby reducing clot disruption and the dilutional coagulopathy. This strategy is applicable to the pre-hospital and hospital phase of care. Pre-hospital fluid resuscitation implemented a strict fluid resuscitation protocol of 250ml fluid bolus, titrated to a palpable radial pulse (estimated SBP ~70 mm Hg). In hospital the fluid resuscitation should be targeted to a BP that will almost produce adequate vital perfusion. This target is dependant on age, co-existing disease. It’s controversial especially in SIP with TBI and active bleeding. In TBI recommendation is to avoid SBP <90 mm Hg.

The key is promptly recognizing the bleeding source with earliest possible control (surgery or interventional radiology) and limiting the time of permissive hypotension, after which definitive resuscitation becomes the goal.

Fluid

Fluid in trauma is controversial, and as with all drugs, it must be regarded as context sensitive. It should only be administered in the context for which they are intended and volume to be used should be guided by goal-directed fluid therapy.[6] Colloids rapidly restores circulatory goals although no survival benefit have been shown for colloids. Crystalloids, on the other hand are cheaper but large volumes are associated with complications of tissue oedema and increased abdominal compartment syndrome. Current evidence supports the use of colloids solutions in the context of perioperative and trauma medicine, when acute plasma volume expansion is appropriate and when haemodynamic stabilisation is under taken in the acute phase. The FIRST trial demonstrated in penetrating trauma that HES provides significantly better lactate clearance and less renal injury than saline. No firm conclusions could be drawn for blunt trauma.[7]

Massive transfusion protocols (MTPs)

Several studies demonstrated a survival benefit as well as reduction in organ failure and other complications with implementation of MTPs. It migate blood bank delays with timely release of products. Multiple scoring systems have been developed to identify patients at risk of massive transfusion or coagulopathy, but most lack clinical utility, their sensitivity is too low to effectively rule-out the condition.

Optimal blood product ratio

Literature from military trauma showed a mortality benefit from earlier use of plasma and platelets in addition to RBC in massive transfusion resuscitation strategies with an optimal ratio of 1:1:1. Early aggressive transfusion improves outcome and using higher plasma to RBC transfusion ratios have been associated with lower overall blood product usage. With regard to military medicine, massive transfusion protocols have moved into the pre-hospital phase.
1:1:1 is not universally advocated. There is a U-shaped curve with respect to optimal ratio of plasma to RBC, with a ratio of 1:2 associated with the lowest mortality rates, ratios both higher and lower demonstrate increased mortality.

Recombinant factor viii

It offers compartmentalized activation of coagulation cascade at the site of injury rather than systemic. It is usefulness as adjunct to treatment of surgical bleeding and binds exposed tissue factor, amplifying factor X conversion promoting thrombin generation, platelet activation and fibrin clot formation. In a randomized control trial it showed a reduction for massive transfusion in blunt and penetrating trauma.

Tranexamic acid (TXA)

CRASH-2 demonstrated early treatment with TXA, within 1-hour of surgery, significantly reduced the risk of death from bleeding. It is more effective in penetrating than blunt trauma.
Its use is associated with few adverse events and no increase in thromboembolic events.
Current recommendations are in all trauma patients with evidence of haemorrhage and

a) early presentation (within 3 hours of injury)
b) systolic blood pressure <110 mm Hg or
c) heart rate > 110 bpm
d) or both

Point of care tests:

Coagulation monitoring: TEG, ROTEM, and Sonoclot

These are bedside tests assessing viscoelastic properties of whole blood measuring changes in clot development, strength and resolution. It is a more physiological real time quantification of coagulation than conventional tests and allows more rapid individualized focused management of coagulation abnormalities from early on in the management path. Its use is associated with a more effective resuscitation, improved lactate clearance and mortality.

Arterial blood gas and bedsides electrolyte testing; I-stat

Hypocalcaemia is real danger with MTP and calcium levels should be monitored.

Damage control radiology.[8]

The term is used parallel to DCS and DCR from patient retrieval, transfer and appropriate primary treatment.

The aims are:

- rapid identification of life-threatening injuries,
- identification/exclusion of head or spinal injury,
- accurate triage of patients to theatre for thoracic and/or abdominal surgery or angiography suite for endovascular control of haemorrhage.

Early CT (within 30 minutes of arrival) has become the investigation of choice for the severely injured adult patient and indicator of quality and efficiency of the trauma team. The most severely injured patient benefits most from early diagnosis and life saving therapy with a number needed to treat of 17:1 for patients with an ISS score >15.

There is increasing evidence to support the use of CT in haemodynamically unstable patients. It is the quickest and most accurate way to establish sites and extent of injury in order to plan and prioritize management, as it is more comprehensive, sensitive and specific than clinical examination, X-rays or ultrasound in identifying injuries. It is transforming the diagnosis and management of major trauma patients. Interventional radiology techniques have become a key component of the management and the addition of hybrid theatres facilitating combined surgical and endovascular treatment.

Early Management of SIP:

Treatment of seriously injured patients requires rapid and clinical assessment of injuries; institution of immediate life-saving treatment; the use of this clinical information and that learned from imaging to decide most appropriate patient pathway; with safe and timely patient transfer and clear communication.

ATLS (advanced trauma life support) provides a framework on which immediate management of trauma patient is based. Initial management can be considered in 4 phases; the primary survey, resuscitation, secondary survey and definitive care. The first 2 phases are done simultaneously.

Primary survey aims to identify immediately life-threatening injuries.

A. Airway and cervical spine control takes priority but with management in of ABC's in parallel rather than sequence. Trauma intubations are more difficult evidence from NAP4 with higher failed intubation rate, surgical airways and complications from emergency airway management. Risk benefit of securing definitive airway vs. not doing so, its urgency and best intubation strategy requires experienced clinical assessment. RSI most commonly practiced and drug choices should balance the risk. NAP4 also highlighted the higher failure rate and complication rate of needle cricothyroidotomy as a rescue option. It is important to identify and mark the cricothyroid membrane prior to start of RSI, and have appropriate staff and equipment available to rescue the airway. (video laryngoscopy, 2nd generation LMAs, bougie, FOB)
One exception to ABCDE approach is in the context of penetrating wounds, when exsanguinating external haemorrhage poses most immediate treat and must be controlled as priority. Immediate control of bleeding can be achieved with direct pressure on the wound and pneumatic tourniquet.

B. Breathing: Consider and exclude immediate life threatening injuries and employment of lung protective ventilation strategies in positive pressure ventilated patients. Two exception to this rule are i) permissive hypercapnoea in lung injury and 2) temporary hyperventilation in presence of impending brainstem herniation.

C. Circulation and haemorrhage control: Haemorrhage continues to be a cause of preventable trauma deaths. A deteriorating conscious level due to hypovolaemia implies at least 40-50% loss of blood volume. (see text on fluid, permissive hypotension and resuscitation targets)

D. Disability – rapid assessment of neurological function. Brain injury is common in polytrauma patients and remains a leading cause of death. Early recognition of TBI is essential to determine resuscitation targets and timeous evacuation of mass lesions. There is clear evidence that a single episode of hypotension doubles the morbidity and mortality and hypoxia should be avoided to prevent secondary brain injury.

E. Exposure - prevent hypothermia. Hypothermia (core temperature <35'C) is an independent predictor of mortality.

Other anaesthetic considerations:
Prolonged surgical procedures, multiple surgical teams, large fluid loss, acute lung injury, and causes of unexplained hypotension, hypoxia, and hypertension.

On going patient care

Resuscitation targets

No single parameter provides adequate indication to end points of resuscitation.

Currently lactate is used as a surrogate marker of adequacy of resuscitation. Lactate coupled with acid base status may also be a useful marker of resuscitation with improving lactate and resolution of acidosis. Serial measurement of lactate levels have also been described to aid decision to DCS or ECT in the first 12-24 hours

Alveolar dead space may aid as indicator of adequacy of resuscitation. This is tracked by arterial-end tidal CO2 difference, and a change in dead space may reflect pulmonary perfusion.

Non-invasive cardiac output monitors may be of benefit and seems intuitive but there is little evidence to its use.

Point of care Ultrasound (POCUS)

Assessment of cardiac pathology by point-of-care ultrasonography performed by a novice examiner is comparable to the gold standard.[9] and a full FATE examination can be performed in 70 seconds. It is important to note that the POCUS is goal directed ultrasound and aim to simply answer a specific question with a simple yes or no, and not to be a fully diagnostic examination. It can be repeated as often as needed and importantly the information should relate to the clinical context.

POCUS can also help identify cricothyroid membrane and trachea, confirm tracheal intubation, LMA placement[10] and potentially help determine aspiration risk, with gastric content and volume assesment.[11]

DCS *vs.* Early total care (ETC).

DCS has been described above and consists of 4 components
i) haemorrhage control
ii) decompression of compartments (thorax, abdomen, limbs, cranium)
iii) decompression of wounds and ruptured viscera
iv) fracture splints

ETC is defined as definitive surgery with fixation of all long bone fractures within 24 hours of injury, but only once the patient has been stabilized.

The decision between DCS and ETC (definitive surgery) may be difficult. The decision to continue with ETC instead of DCS should be made with close communication and co-operation between surgical teams, ICU and Anaesthesia.

Rehabilitation
All care from the point of injury affects the quality of patient rehabilitation. It is directly affected by early resuscitation and surgery. Early and appropriate pain management is a key component to care and rehabilitation affecting the patients' long-term physical and psychological recovery.
Subsequent repeated evaluations are essential. Missed injuries and consequences on patient clinical condition should be avoided with subsequent repeated evaluation. (2-50% missed injuries) The secondary evaluation is head to toe evaluation and starts once the primary survey and resuscitation has been completed and the patient stabilized. Tertiary surveys are advocated by many trauma centers usually within 24 hours or prior to discharge to reassess and confirm known injuries and identify occult ones.

Good rehabilitation is key to making optimal recovery after trauma and there is a drive to improve this. Advocate that all MTC have rehabilitation coordinators, with rehabilitation medicine being involved in patient management within 72 hours of injury.

Conclusion

Care of the trauma patient has quietly undergone a revolution in the past few years. The aim of this abstract was to provide an overview of current concepts and controversies regarding the management of the severely injured patient. Our understanding of the pathophysiology of resuscitation and trauma is evolving and changing along with lessons from the battlefield transferred to trauma care, that have conceptually changed the management of these individual patients. Effective care of the SIP requires the skills of clinicians of several clinical specialities, teamwork, leadership and communication is of the essence for effective quality patient care. Radiology plays an increasingly important role in patient management and rehabilitation of trauma patients should not be an afterthought. The anaesthetist plays an important role in the management of SIP, as he/she is often the unique position of providing direct continuity of care through the early part of the patients treatment pathway.

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Management of the patient with a coronary stent:

How to do it

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Outline of this talk:

1. Coronary stents & stent advancements
2. Antiplatelet therapy after coronary stent placement
3. Stent placement prior to elective noncardiac surgery
4. Perioperative management following percutaneous coronary intervention
5. Perioperative antiplatelet therapy
6. Management of bleeding on dual antiplatelet therapy
7. Management of perioperative stent thrombosis
8. *In summary: How to manage the patient with a coronary stent perioperatively*

1. Coronary stents & stent advancements

Percutaneous Coronary Intervention (PCI) has advanced significantly since the first successful balloon angioplasty (BA) in 1977. Unfortunately this procedure, in which a balloon-tipped catheter is inflated in an area of coronary narrowing, is limited by two major complications: (a) acute vessel closure during or immediately after the procedure secondary to thrombosis or vessel dissection (occurs in 4-8% of cases, of which 20% require emergency CABG); and (b) re-stenosis due to a combination of elastic recoil, smooth muscle proliferation, and neointimal hyperplasia. Re-stenosis rates vary from 30-50% by 6 months.
The 1990's saw the emergence of coronary stents which are deployed over a balloon at the site of an atheromatous narrowing. The use of stents has reduced the complications associated with angioplasty, and ongoing improvements in safety and efficiency have resulted in an exponential rise in the number of procedures being performed.

There are two major types of coronary artery stents:
Bare metal stents (BMS) and drug eluting stents (DES)

- *BMS* reduce the frequency of symptom recurrence and need for repeat procedures due to re-stenosis when compared with angioplasty, but the rate of re-stenosis remains unacceptably high in the region of 10-20%. Acute and subacute stent thrombosis rate is reduced with the use of dual antiplatelet therapy (DAPT) for 4-6 weeks after which re-endothelialisation should be complete.
- *DES* were designed to prevent re-stenosis by coating stents with a polymer containing an antiproliferative substance which inhibits smooth muscle proliferation and neo-intimal hyperplasia. They have successfully reduced re-stenosis rates to below 10%. The drawback is that metal surfaces are exposed for longer as re-endothelialisation takes longer. This prolongs the risk for stent thrombosis, and DAPT should be continued for at least a year following their placement.

Types of DES: First generation DES are sirolimus-eluting and paclitaxel-eluting stents (SES and PES). SES are no longer available in the United States and Europe, and PES use has been overtaken by second generation products.

Second generation DES are everolimus-eluting or zotarolimus-eluting stents (EES or ZES). These have been in use since 2008. There are two versions of ZES: the Endeavor and the Resolute, however Endeavor manufacturing has stopped. Resolute-ZES and EES have comparable efficacy and safety. Second generation stents have improved outcome benefits as compared with the first generation stents; namely a 38% lower risk of clinically significant re-stenosis, a 43% lower risk of stent thrombosis, and a 23% lower risk of death. Despite second generation DES having better biocompatibility and generating less of an inflammatory response than first generation products, DAPT is still recommended for a minimum of 12 months.

Newer stents in development include those with a bioresorbable polymer, stents that are polymer free, and bioabsorbable products. These products are being developed in an effort to deal effectively not only with re-stenosis but also stent thrombosis. These are either in development or have had early clinical trials performed.

2. Antiplatelet therapy after coronary stent placement

DAPT significantly lowers the risk of stent thrombosis as demonstrated by the PCI-CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) study and the CREDO (Clopidogrel for the Reduction of Events During Observation) study. Stent thrombosis is a platelet-mediated process that occurs through progressive platelet activation and aggregation, leading to thrombus formation. It usually manifests as ST-segment elevation myocardial infarction, malignant arrhythmias, or death. The recommended DAPT regimen is aspirin 75-100mg daily plus a platelet $P2Y_{12}$ blocker (usually clopidogrel 75mg daily) for a period of 4-6 weeks following BMS placement and for a minimum of 12 months following DES placement. Aspirin monotherapy provides inadequate antiplatelet action in the face of exposed thrombogenic metal stent struts. The STARS trial randomly assigned 1653 patients to receive aspirin alone or in combination with ticlopidine or clopidogrel, and demonstrated that aspirin alone is inferior to DAPT. The thienopyridines alone are also inferior to DAPT, as is the combination of aspirin and warfarin.

Following the desired period of DAPT, aspirin should be continued indefinitely if possible. DAPT may be continued for longer periods in patients deemed to be at prolonged or increased risk for stent thrombosis. These can be divided into clinical risk factors and angiographic risk factors as indicated in Table 1 below:

Clinical Risk Factors	Angiographic Risk Factors
• Cessation of platelet blockade • Advanced age • Diabetes • Low ejection fraction • Renal failure • Acute coronary syndrome • Perioperative period • Malignancy • Peripheral arterial disease • Smoking	• Thrombus-containing coronary lesions • Multiple coronary lesions • Overlapping coronary stents • Coronary ostial lesions • Small-calibre coronary vessels • Complicated stent deployment • Coronary bifurcation lesions • Inflow lesion proximal to coronary stent • Outflow lesion distal to coronary stent • Neoatheroma development within the stent

Table 1: Identified risk factors for coronary stent thrombosis

It is thought that the benefit of DAPT following PCI may also be attributable to the prevention of plaque rupture at sites distant from the stented lesion, leading not only to a reduction in stent thrombosis but also reduced major adverse cardiovascular and cerebrovascular events. This was ammunition for promoting prolonged DAPT beyond 1 year. However, prolonged DAPT is not without risk and is associated with bleeding complications and an increased all-cause death rate (due to an increase in non-cardiac deaths). The CHARISMA (Clopidogrel for High Atheromatous Risk and Ischaemic Stabilisation, Management and Avoidance) study showed no significant benefit of continuing clopidogrel beyond 1 year, and a higher risk of bleeding. Another retrospective cohort study of over 41 000 patients having surgery within 2 years of stent placement concluded that major adverse cardiac events were associated with emergency surgery and advanced cardiac disease but not stent type or timing of surgery beyond 6 months after stent placement.

$P2Y_{12}$ blockers include clopidogrel, ticlopidine, prasugrel and ticagrelor. Ticlopidine and clopidogrel have similar clinical efficacy in the setting of DAPT, but clopidogrel is most often the drug of choice in randomized trials and clinical practice because of the haematological side effects of ticlopidine such as agranulocytosis and thrombotic thrombocytopaenic purpura.

Prasugrel is a novel orally administered thienopyridine prodrug metabolised via cytochrome P450 in the liver. It has similar action to clopidogrel, binding selectively and irreversibly to the platelet $P2Y_{12}$ receptor, but has a more rapid, potent, and consistent antiplatelet effect at much smaller doses. The problem, however, is an increased risk of bleeding including fatal bleeding. Ticagrelor is an adenosine diphosphate $P2Y_{12}$ receptor antagonist with REVERSIBLE antiplatelet action. It has a relatively short half-life of 6 to 13 hours and a rapid onset of action (2 to 4 hours). It could possibly be a favourable drug to use in the perioperative setting as patients would only need to discontinue 1 day before surgery and could restart soon after, but it has not been extensively evaluated in patients with stable coronary artery disease undergoing PCI. We have neither of these agents available at our institution.

Triple therapy has evolved to manage various groups of high risk stented patients, for example, those with concomitant atrial fibrillation or a cardiac valve. In these cases, warfarin is added with the INR kept between 2.0 and 2.5.

Stent placement prior to elective noncardiac surgery

The evidence outlined below ultimately points towards limiting preoperative PCI as patients with stable coronary artery disease (CAD) will often not benefit from revascularisation before noncardiac surgery (NCS).

In the Coronary Artery Revascularisation Prophylaxis (CARP) Trial, in which 510 patients with CAD were randomised to revascularisation or medical management before elective major vascular surgery, there was a similar incidence of postoperative myocardial infarction and 27-month survival in both groups. DECREASE II demonstrated that preoperative coronary revascularisation did not significantly improve the 30-day outcome in patients with extensive ischaemia, and DECREASE V also failed to demonstrate significant benefit of preoperative coronary revascularisation over best medical therapy.

Recommendations for PCI before NCS are as follows:

(2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery)

- PCI before NCS should be limited to:
    - Patients with left main disease whose comorbidities preclude bypass surgery without undue risk
    - Patients with unstable CAD who would be appropriate candidates for emergency or urgent revascularisation
    - Patients with ST-segment elevation myocardial infarction or non-ST-elevation acute coronary syndrome
- Patients requiring PCI for myocardial ischaemia who need surgery within the following 12 months should have BA or BMS placement followed by DAPT for 4-6 weeks

3. Perioperative management following percutaneous coronary intervention

Up to 20% of patients with coronary stents will require NCS within 3 years of stent placement. Because surgery induces hypercoagulability through platelet activation, stent thrombosis is a major perioperative risk. Major cardiac complications in the perioperative period occur in about 2% of patients with DES placed within the preceding year. The mortality rate due to stent thrombosis is in the region of 30%. This coupled with an increased surgical bleeding risk in patients remaining on DAPT makes for interesting perioperative patient management.

Regardless of whether a patient has had a BMS or a DES inserted, evidence supports that the two most important perioperative factors that significantly increase perioperative risk are interruption of DAPT for more than 5 days before NCS, and surgery within 30 days of stent deployment. Also,

emergency NCS is associated with a higher incidence of adverse events than elective procedures in both groups.

Balloon Angioplasty

Studies indicate that elective NCS following BA is safe if the surgery is carried out at least 2 weeks (14 days) after the intervention (class I recommendation; level C evidence). This allows for vessel wall healing at the site of the angioplasty. Unfortunately, because of the limitations of BA, significant coronary restenosis may be apparent as soon as 8 weeks after the procedure. For this reason, it is recommended that elective NCS is safest in a limited time period of 4-8 weeks following BA (class III recommendation; level B evidence).

A new technique, namely drug-eluting BA, may change this scenario in the future.

BMS

Two retrospective studies independently demonstrated perioperative mortality rates of 3 and 20% if surgery was carried out within 6 weeks of BMS placement. Further studies indicate that the risk of stent thrombosis decreases exponentially over the 6 week period following coronary intervention.

The recommendation is to wait 30 days for elective NCS following BMS placement (class I recommendation; level B evidence).

DESs

Regardless of the generation of DES, elective NCS should not be carried out within 365 days of stent placement (class I recommendation; level B evidence). In emergency NCS where clopidogrel must be discontinued, it is advisable to continue with the aspirin and restart DAPT as soon after surgery as feasible (class IIa recommendation; level C evidence).

A new recommendation from the 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery is that elective NCS after DES implantation may be considered after 180 days if the risk of further delay is greater than the expected risks of ischaemia and stent thrombosis.

4. Perioperative antiplatelet therapy

The aim of perioperative antiplatelet therapy is to maintain stent patency. The caveat is that DAPT is associated with an increased surgical bleeding risk. Perioperatively, the risk of stent thrombosis needs to be carefully weighed against the risk of bleeding.

With regards to antiplatelet agents and surgical bleeding, a meta-analysis of patients undergoing NCS by Burger et al in 2005 showed that although aspirin alone increased surgical bleeding by a factor of 1.5, it did not increase the severity of bleeding complications or fatal bleeding except in intracranial surgery. Withdrawal of aspirin was associated with a higher incidence of cardiac, cerebral, and peripheral vascular events. In another study, the addition of 75mg of clopidogrel to 150mg of aspirin in healthy volunteers increased the bleeding time 3.4-fold. Despite an increased risk of surgical bleeding and need for transfusion in patients on DAPT, it has not been shown to increase morbidity or mortality.

There are ultimately 3 options for managing patients on DAPT in the perioperative period:

1. *Continue DAPT throughout the perioperative period: here the usual clinical scenario would be that of bleeding risk being lower than the risk of stent thrombosis; a potential surgical bleed would not be life-threatening.*
   DAPT may be continued in cases where the surgical bleeding risk is deemed to be very low. This option is excluded in closed space surgery including brain, spinal cord and eye surgery.

2. *Discontinue clopidogrel preoperatively and recommence after surgery: usual clinical scenario would be that of high bleeding risk or catastrophic consequences of a bleed; stent thrombosis is not a major consideration.*
   This is deemed to be safe after stent endothelialisation is complete, i.e., 30 days after BMS placement and more than 180 to 365 days after DES placement depending on individual risk. Restart clopidogrel postoperatively with a loading dose of 300-600mg before continuing with maintenance therapy. Aspirin should be continued throughout if possible.
3. *Discontinue clopidogrel preoperatively and bridge perioperatively: usual clinical scenario would be that of relatively urgent surgery with a high or catastrophic bleeding risk; surgery can wait 5 days but cannot wait for endothelialisation of stent; risk of stent thrombosis high.*
   An acceptable option for bridging is as follows:
   Stop clopidogrel 5 days before surgery. Admit to hospital 3 days before surgery and start tirofiban or eptifibatide (intravenous GPIIb/IIIa blocker) and heparin infusions, then discontinue the infusions 6 hours preoperatively. Restart clopidogrel with a loading dose on day 1 post surgery if the bleeding risk is acceptable, and then continue with maintenance therapy.
   What about bridging with aspirin and heparin alone?
   Heparin, although commonly used as a substitute for aspirin or thienopyridines, is not an antiplatelet agent but rather an antithrombotic. Given that stent thrombosis is platelet mediated, and that heparin has not been proven to be effective in perioperative prevention of stent thrombosis, unfractionated heparin and low molecular weight heparin are not ideal agents for bridging.

New advances in antiplatelet bridging therapy: Cangrelor is a short-acting intravenous $P2Y_{12}$ blocker with a half-life of 3-6 minutes. Platelet function returns to baseline within an hour. A randomized controlled trial published in 2012 that looked at bridging therapy with cangrelor in patients undergoing cardiac surgery showed no significant increase in surgical bleeding risk. The study was underpowered to sufficiently comment on reducing stent thrombosis during NCS.

5. Management of bleeding on dual antiplatelet therapy: a few points

The antiplatelet effect of clopidogrel is irreversible. The half-life of the drug is 8 hours. In cases of major haemorrhage in a patient who has taken clopidogrel, platelet transfusion after 16 to 24 hours from the last intake should result in minimal inhibition of the transfused platelets.

Following tirofiban and eptifibatide administration, 90% of normal platelet function should be restored by 6 hours after the infusion is stopped.

Monitoring platelet function on antiplatelet agents: The best measure of the effects of antiplatelet agents on platelet function is ‘bleeding time’, but this is unfortunately not a practical test in the clinical setting. The standard tests of coagulation, namely prothrombin time (PT) and partial thromboplastin time (PTT), do not allow assessment of platelet function. Optical light transmission platelet aggregometry is considered the gold standard of assessing platelet function, but it is laboratory-based and time consuming. With regards to point-of-care techniques, the maximum amplitude (MA) of conventional thromboelastography (TEG) is not sensitive enough to detect the presence of thienopyridines or salicylates. TEG may, however, be used to monitor the effects of GPIIb/IIIa inhibitors. Modified TEG (mTEG) is sensitive to thienopyridines and salicylates and would be a useful monitor of platelet function in this setting.

6. Management of stent thrombosis in the perioperative period

Perioperative stent thrombosis has a high mortality and needs prompt recognition and management. Perioperative monitoring should focus on early recognition of myocardial injury with ECG, echocardiography, and troponin assay. Stent thrombosis usually manifests as ST-segment elevation

myocardial infarction necessitating primary PCI as soon as possible to reduce morbidity and mortality. Thrombolysis is contraindicated in the setting of recent surgery.

Patients should, if at all possible, be closely monitored in an appropriate high care facility postoperatively depending on their individual risk, not only for stent thrombosis but also catastrophic bleeding. It is recommended to monitor these patients until antiplatelet therapy has been reinstituted and antiplatelet action confirmed.

7. In summary: how to manage the patient with a coronary stent perioperatively

Key points:

- Surgery should be planned by a multidisciplinary team including anaesthetist, surgeon, cardiologist & intensivist
- Know your patient (cardiac for NCS)
- Know your medications (medical optimisation of the cardiac for NCS)
- Know your stents and antiplatelet agents
- Know your cardiologist (identify patients at increased risk of stent thrombosis)
- Know your surgeon (bleeding risk and urgency/timing of surgery)
- Plan your management of antiplatelet therapy to minimise the risks of both stent thrombosis and catastrophic bleeding in the perioperative period
- Plan an appropriate anaesthetic technique for the patient and the surgery:
    - Both regional and general anaesthesia have been used to manage stented patients
        - Neuraxial techniques are often limited by antiplatelet agents
    - Apart from standard monitoring, additional monitoring should be individualised and aim to detect myocardial ischaemia
- Plan appropriate postoperative placement to ensure adequate monitoring for a cardiac event and ensure appropriate reintroduction of antiplatelet agents
- Ensure prompt access to an interventional cardiology facility in the event of stent thrombosis

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Anaesthesia for infantile pyloric stenosis

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Pyloric stenosis is one of the most common gastrointestinal abnormalities that occur in infancy. Gastric outlet obstruction occurs due to pyloric smooth muscle hypertrophy and the etiology remains largely unknown. The incidence is 1-3 per 1000 live births and has a 4:1 male predominance.

Term infants mostly present between the 2nd and 6th week of life with progressive, non-bilious vomiting that can become projectile after large feeds. Infants are typically ravenous and can even become slightly jaundiced due to glucuronyl transferase deficiency as a consequence of starvation.

The progressive vomiting leads to a distinctive pattern and sequence of electrolyte and acid/ base disturbances. It results in a chloride-responsive, hypochloraemic, hypokalaemic, hyponatraemic, metabolic alkalosis:[1]

- Vomiting leads to a loss of water, H+, Cl-, K+ and Na+ ions
- A net increase in HCO3+ ions secreted by the duodenum leads to plasma alkalosis.
- The increased HCO3+ reaching the glomerular filtrate, overwhelm the renal resorptive capacity in the proximal convoluted tubule, and leads to alkaline urine, pH > 7.
- A protracted ECF volume increase Aldosterone secretion with Na+ and water retention via renal Na+/K+ exchange, at the cost of K+ loss.
- K+ is further lost from the glomerular filtrate in exchange for H+ in an attempt to restore the acid/ base disturbance.
- K+ is also shifted intracellular in response to plasma alkalosis. All these factors lead to profound hypokalaemia.
- When potassium drops to a critical level, too low to maintain renal Na+/K+ exchange in the distal tubule, Na+ is exchanged for H+ in a last attempt to conserve Na+ and water. This leads to acidic urine (paradoxical aciduria) and worsening of the metabolic alkalosis.
- A large amount of Cl- is lost through vomiting. An adequate glomerular filtrate Cl- concentration is needed to facilitate renal HCO3+ secretion via Cl-/HCO3+ exchange. Acid/base disturbance can only be corrected once Cl- concentration is corrected.
- Urine Cl- concentration >20mmol/l is the best indicator of a corrected ECF volume.

Resuscitation

When pyloric stenosis are diagnosed, an intravenous line should be sited and blood samples taken. A size 8 Fr nasogastric tube should be inserted and losses replaced 1:1 with an isotonic solution such as normal saline or ringer's lactate. Some centres replace nasogastric losses with 0.45% saline. If dehydration is severe, give a bolus of 20ml/kg of normal saline or a suitable colloid on top of continued infusion. Fluid replacement must be started with 5% dextrose, 0.45% normal saline with added KCl (20mmol/l) at 6-8 ml/kg/hr. 6-8 hourly electrolyte measurements are recommended.

Resuscitation should continue until the following parameters have been achieved:[1]

Serum Cl^-	>106 mmol/l
Serum Na^+	>135 mmol/l
Serum HCO_3^-	< 26 mmol/l
Urine Cl^-	>20 mmol/l
Urine output	>1 ml/kg/hr

Haemoglobin measurement will be needed before surgery.

Anaesthetic management

When the above parameters have been achieved, the patient can proceed to theatre for surgery. The main considerations include need for ongoing correction of electrolyte disturbances, safe induction with the prevention of aspiration and adequate analgesia without increasing the risk of postoperative apnoea.

General principles of anaesthesia apply to the young infant with special consideration for temperature control and glucose.

Standard monitoring includes ECG, saturation, temperature, non-invasive blood pressure and CO2 monitoring.

Fluid maintenance and electrolyte correction should continue with an isotonic solution such as normal saline with added glucose and KCl as directed by electrolyte measurement.

The stomach must be emptied prior to induction with a large bore orogastric or nasogastric tube with the patient in the right lateral, left lateral and supine positions respectively. A vented tube with a sump (eg. Salem, Replogle) works best. Some anaesthetists advocate lavage with normal saline until the gastric content is clear. I would advocate this practice when Barium swallow was used to diagnose the stenosis.

Induction of anaesthesia has evolved over the past 2 decades with awake intubation still advocated in the late 90's to reduce the risk of aspiration. Awake intubation has since completely fallen out of favour although it is still mentioned in recent textbooks.

Rapid sequence induction (RSI) was favoured before 2010 but the support for RSI with regards to its efficacy and safety in children has declined rapidly in the past 5 years.[4]

A retrospective cohort study of 252 infants at a South Hampton, UK hospital, receiving gas inductions for pyloromyotomy showed no evidence of aspiration. Gas induction is now the preferred method of induction and may provide safer intubating conditions than RSI. Intravenous inductions are also safe in the child that is adequately resuscitated and can be intubated promptly. The use of propofol could however increase the risk of apnoea post operatively.

The patient should be intubated and ventilated with care not to over ventilate as a low carbon dioxide level could worsen postoperative apnoea and hypokalaemia. Infants are at increased risk of apnoea due to the metabolic alkalosis even after it has been corrected. This is due to central chemoreceptors that lie within cerebrospinal fluid that takes a lot longer to correct HCO_3^+ balance. Inhalational agents

and opioid use will add to the risk and infants should be monitored for apnoea in a high care setting for 12 hours post-surgery.

Open pyloromyotomy is not a very painful procedure as the incision can be kept small. Surgical approach can be via a small right sided subcostal incision, short supra umbilical midline incision or para-umbilical incision. Analgesic options, to minimize the use of opioids, include intravenous paracetamol, analgesic doses of Ketamine (0.25 – 0.5mg/kg), local wound infiltration or ultrasound guided rectus sheath block.

Breschan et al analysed a case series of 26 infants that received ultrasound guided rectus sheath blocks and found it to provide excellent analgesia in most infants without the need for supplemental analgesia. Only 4 infants needed added analgesia.[6]

Willschke & Marhofer et al did a retrospective analysis of 20 neonates treated with single shot epidural in an attempt to reduce the incidence of postoperative apnoea, by avoiding intubation and general anaesthesia. They still gave Propofol at 1-2mg/kg as sedation.[5]

We do not advocate the use of spinals or epidurals for pyloromyotomy as most infants are adequately analgesed with local infiltration and paracetamol. The risk of a neuraxial block in this age group outweighs the marginal benefit.

An audit of postoperative analgesia after pyloromyotomy in 72 cases at a hospital in Perth, showed that all infants except 3 were adequately analgesed with bupivacaine local infiltration and paracetamol. The other 3 infants received supplemental opioids.[3]

Laparoscopic pyloromyotomies are gaining popularity and benefits mentioned include reduced analgesic requirements, smaller scars and decreased hospital days. Laparoscopic surgery in neonates has it's own risk associated and the open procedure leaves a small scar and require little analgesia as well. The benefits will only be relevant with very experienced laparoscopic teams.

The surgical team will often ask for air inflation into the stomach via the nasogastric tube to test integrity of the mucosal layer. Take care to use the correct port for air inflation and remove air after they have confirmed integrity. Empty any residual gastric content prior to extubation.

Infants must be reversed upon completion of surgery and extubated awake on their side. Maintenance fluids should be continued until oral feeds are fully established.

Patients should be monitored for 12 hours post surgery for apnoea in a high care setting. Infants are usually discharge after 24-48 hours once oral feeds are established without further vomiting.

The mortality of hypertrophic pyloric stenosis has dropped from 10% to less than 0,3% in the past 20 years due to better resuscitation guidelines.[1]

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The fractured neck of femur

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Fractures involving the proximal femur have become increasingly prevalent as a result of our aging global population, and high incidence of osteoporosis.
These fractures are associated with significant postoperative mortality as well is a major cause of morbidity, resulting in loss of function and independence in the geriatric patient.

¾ hip fractures occur in *women*, with an average age of *80 years*,
80% of patients being above 75 years of age.
Simple mechanical falls from a standing height in an osteoporotic patient is the most common aetiology.
It is important to note too that "falls" may have been as a result of co morbid pathology and this needs to be sought and excluded, for example

- CVS: atrial fibrillation, Aortic Stenosis
- CNS: TIA, CVA

Surgical management

98% of patients are managed surgically, as fixation provides analgesia and facilitates earlier mobilization and better rehabilitation and nursing.
Depending on the nature of the fracture, surgical preference, patients' pre-existing functional capacity and life expectancy; surgical intervention may take the form of:

1. Fracture fixation (Cannulated Hip Screw, DHS, Richards Screw) or
2. Cemented or Uncemented Hemiarthroplasty.

It is important to determine what the surgical plan involves, as this would have direct impact on intraoperative planning, anaesthesia, choice of analgesia, as well as post operative placement and degree of care anticipated.
For the severely surgically unfit patient, one might consider prolonged skin traction but this is unpopular as nursing and rehabilitation is impeded, so patient outcome is consequently poor.

Mortality

Femoral neck fracture is associated with a *30-day post operative mortality of 5-10%*, and a *1 year mortality* of about *30%,* all unchanged for the last 20 years, despite protocols, guidelines and intervetions.[2]
30% of elderly patients suffer at least one post operative complication, and only 30% of patients return to their pre fracture level of function.
The mean length of hospital stay remains around 20 days.
To address this issue, multiple guidelines were formulated, all emphasising:

- Early pre op assessment and if needed optimization
- Minimising system delays
- Early surgery
- Multimodal analgesia, commencing in pre operative period
- As well as early involvement of a multidisciplinary team, consisting of orthopaedic surgeons, anaesthetists, geriatricians, phyisotherapists, dieticians.

Pre operative patient assessment and planning

As neck of femur fractures are more common in the **elderly** population, the anaesthetist has to be cognisant of the *aging physiology, common co morbidities, possible pharmacological interactions, altered pharmacokinetics/dynamics;* as well as specific issues pertaining to this population such as *cognitive impairment.*
(Kindly refer to appropriate courses on the elderly patient, as this is not within the scope of this talk)

Pre-habilitation (implying patient optimisation before theatre) should commence in casualty as soon as the diagnosis is made.

*A **multi team approach***, consisting of orthopaedic surgeons, physicians, geriatricians, physiotherapists, as well as anaesthetists should plan facilitate efficient, all encompassing care. Appropriate discharge and rehabilitation planning should commence from the time of admission. The British Orthopaedic Association recommends casualty to ward transfers occur within 4 hours of admission, and surgery before 36 hours.

Timing of surgery

Most literature supports *early surgery within 24- 48 hours of admission*, showing reduced mortality at 1 year, but not at 30 day or 3-6 months post operatively. [3]
Mortality risk reduction with early surgery was still evident even when analysing studies corrected for ASA grade, age, and gender.[4]

Early surgery had been associated with

Decreased mortality
Shorter length of hospital stay -> decreased POCD for patient at risk
Earlier patient mobilization -> less: Pneumonia
Pressure sores
Severe pain
DVT risk
Muscle loss[4]

Two meta analysis involving 27500 patients confirmed that *delays beyond 48 hours was associated with a higher 30 day mortality to 41% and the one year expected mortality was as high as 32%.*[5]
The possible controversy is that the delay to surgery may be as a result a confounding factor affecting survival rather than an independent aspect. I.e. patients, for whom surgery was delayed, might have been sicker on admission, requiring more investigations and stabilisation pre operatively. However, a prospective case matched cohort study, which defined delay as >24hours, indicated that the poor prognosis remained even when patients who had were medically in-optimal were removed from this study.

Recommendations therefore suggest:
Early surgery within 24-48 hours in a patient medically fit for an anaesthetic.
Despite this emphasis on expedient surgery, ***serious co morbidities may benefit from 48 hours of medical optimization or further investigation,*** as the risk of suboptimal anaesthesia would outweigh the risk of delaying surgery.

Correctable Problems include

- Severe anaemia
- Electrolyte imbalances Na, K
- Uncontrolled diabetes, DKA
- Acute or decompensated CCF
- Acute coronary syndromes
- Poorly managed, correctable arrhythmias, e.g. AF
- Severe chest infection, with systemic sepsis
- Exacerbations of chronic lung diseases, requiring nebs
- Correctable renal dysfunction
- Reversible co-agulopathy
- Emergency resuscitative efforts as result of other co existing injuries!
- Guidelines all suggest that *investigations be chosen appropriately*, and delays be limited to those that are *clinically relevant to patient*, which *alter proposed anaesthetic management* or improve patient outcome or influence immediate post operative placement (PACU)

Preoperative Assessment

As per UK audit, the mean ASA score for hip fracture patients is ASA III
A thorough *history and examination* are an essential part of any pre op assessment. Often third party information from a caretaker is invaluable, especially in the presence of cognitive dysfunction.
It is important to *enquire about events pertaining to the fall* as this may provide clues as to the presence of undiagnosed co-morbidities. Determine/ exclude the presence of *concurrent injuries.*
The patient's *pre-fracture baseline* provides means of assessing clinical functional reserve, degree of post op care required, as well as rehabilitative placement.
Co morbidities, as well as their management need to be determined.
Common co morbidities involve the CVS, as well as COAD, diabetes, hypothyroidism, renal impairment and cerebrovascular diseases.
Poly-pharmacy is common and has direct impact on analgesic drug choices and anaesthetic planning.

Other aspects worth assessing include:

Dehydration
Patients maybe intra-vascularly depleted as a result of poor oral intake, haemorrhage from fracture site or diuretic use. Determine if fluid replacement is required, and do so judiciously, preferably monitoring its effects on cardiorespiratory system, as elderly patients may not cope with fluid overload as a result of over enthusiastic IV replacement. This in itself may then worsen outcome with consequential pulmonary oedema and CCF. (Refer to courses on choosing the optimal fluid for patients, colloid vs. crystalloid controversies, as well as measuring intra vascular endpoints for fluid resuscitation.)
Avoid long periods of fasting and encourage oral clear fluid intake until 2 hours preop. (The consequences of prolonged starvation and benefits to clear oral fluid intake perioperatively have been well publicised)

Anaemia
Most patients present to hospital with anaemia as a result of:

- Haemorrhage from the fracture site (consider haemo-concentration if dehydrated)
- Pre existing anaemia as a result of chronic illness or nutritional deficiencies

Variable from 200-500ml. Average *expected decline in Hb ~ 2.5gm/dl* for hemiarthroplasty, less for a simple fixation.
Establish *transfusion triggers* based on patient profile pre operatively, then decide whether G&S is sufficient, or anaemia requires pre operative correction; bearing the consequences of blood product administration in mind.
Plan to measure Hb intraoperatively.

Nutrition
Malnutrition is common in geriatric patients
Perioperative supplementation is essential. Enteral supplementation is always the preferred route.
Serum albumen<3 g/dl associated with poor healing.
Get the dietician involved from the start.

Basic special investigations

Hb, as discussed
Coagulation (platelets and INR), patients may be on anticoagulants for co morbid dx
U&E- high incidence of renal insufficiency esp. pre renal states dt dehydration
CXR- CXR does not exclude pathology completely but provides means of assessing cardiac architecture, possibility of fluid overload, presence of infection as well as clues as to atelectasis
ECG- essential to exclude arrhythmias, ischemia, etc.

Analgesia in preoperative period

Adequate analgesia is essential from the time of admission, to prevent the physiological disruption associated with the stress response. Inadequate pain relief may also exacerbate co existing disease processes, e.g. myocardial ischemia.
Extra-capsular fractures are more painful than intra-capsular fractures due to the extent of periosteal damage.
At rest, $\frac{1}{3}$ patients have no pain, $\frac{1}{3}$ moderate ans the remaining $\frac{1}{3}$ severe pain. On movement, however, at least $\frac{2}{3}$ experience moderately severe pain. *Pain should so be assessed in both, static and dynamic states*.
Also, *25% of patients have a cognitive deficit*, and are so unable to communicate discomfort effectively.
Initial pain management, preferably pre-hospital, includes temporary immobilization. Analgesic regimes aim to be *multimodal*, utilising a combination of drugs/ techniques to manipulate the pain pathway at various stages and different receptor sites, so as not to burden the patient with severe side effects of one drug class.
Simple analgesics (Paracetamol) administered at regular intervals, as well as limited use of opiates are a commonly adhered to regimen.
Limiting high doses of opiates or opiate only analgesic regimens are associated less unwanted side effects (confusion, sedation, constipation, pruritus and apnoea.)
Also, *40% of elderly patients with femur fractures have some degree of renal impairment* and so opiate effects last longer than predicted. Furthermore, with poly-pharmacy, one needs to *consider drug interactions*, e.g. Tramadol and Amitryptaline.
NSAIDs are best avoided, due to adverse effects especially in this patient population. (Renal impairment, gastric mucosal damage.)

Increasingly, local anaesthetic peripheral nerve blocks are being administered by casualty staff in UK to facilitate multimodal opiate sparing analgesia, that may or may not be continued during the operative or post op period.

Anticoagulation

Hip fractures patients are high risk factor for VTE and PE, and this is a major cause of mortality. Thromboprophylaxis is recommended for 10-35 days, in accordance with ACCP guidelines. LMWH is commonly prescribed, with fondaparinux, LDUH and VIT K antagonists possible alternatives. Enoxaparin is usually prescribed from admission, omitted preoperatively, with meticulous timing to allow for 12hour window, thereby allowing for safe neuraxial anaesthesia. LMWH therapy is then re commenced in the postoperative period, once adequate surgical haemostasis has occurred.
Patient may also be on anti coagulant therapy for co morbid illness, Clopioigril for DES, Warfarin for artificial heart valve. The risk, benefit of interrupting therapy needs to be individualised for each patient's condition. Interdisciplinary discussion and planning required. (Kindly refer to notes with regards to stopping anti coagulant therapy, bridging and ACCP/ AZRA guidelines for thromboprophylaxis)
Consider dosing intervals, prior to establishment regional anaesthesia and Psoas compartment blocks. The literature is less clear with regards to peripheral nerve blocks in presence of VTE prophylaxis.
Mechanical prophylaxis with sequential pneumatic calf compression devices and graduated compression stockings should also be utilized.

Cardiology consult and echocardiography

Aortic stenosis, often an aetiological factor in the fall, has 20-40% prevalence amongst hip fracture patients. Traditionally anaesthetists are reluctant to deliver an anaesthetic in the presence of an undiagnosed systolic murmur in this patient profile, without echocardiographic determination of ejection fraction, Ao valve area and pressure gradient. Previous recommendations and guidelines insist that surgery be delayed until cardiology consultation. In practice, UK audits suggest that practically this is not what happens, due to limited access to cardiology consultations, with consequential lengthy delays to time of surgery. It was also found that most anaesthetists had decided to manage patients with general anaesthetic, assuming a moderately severe AS; thereby choosing the safer option. (Information the echo had shown hence not changing immediate management).
With the advent of FATE scans, skilled anaesthetist may be better equipped to make an efficient assessment of a valvular lesion in the immediate perioperative period. While clinical exam and patient history may be suggestive of a valvular lesion, accurate diagnosis cannot be assumed. The safest option would be to wait for cardiologist consult.
Consultation may also be required for assistance in optimising decompensated CCF, unstable coronary syndromes and stabilisation of poorly managed arrhythmias, severe valvular heart disease, as well as patients with pacemakers or ICD's that had not been recently assessed or interrogated. In these instances, surgical delay is warranted.

Pulmonary Optimisation

Aside from pre existing pulmonary co morbidities, *4% of hip fracture patients* are *at risk of perioperative pulmonary complications* (PPC), including;

- Atelectasis
- Pneumonia
- Pulmonary venous thrombo-embolism
- Exacerbation of pre existing lung disease
- Respiratory failure requiring prolonged ventilation
- Acute respiratory distress syndrome

Prevention involves early identification of patients at risk

Risk factors for developing PPC

Patient factors

- Poor general health state
- (impaired sensorium, functionally dependant, ASA≥ 2)
- Age >60 years
- Smoking
- LRTI
- COAD
- Poorly controlled asthma
- OSA
- CCF
- Low albumin

Procedure related risk factors

- Emergency surgery
- General anaesthesia
- Operative duration >3 hours
- Long acting neuromuscular blockade

Spirometry, CXR and ABG should not be considered routine investigations but ordered only in presence of unexplained respiratory symptom, or suspected LRTI or to assess extent or exacerbation of chronic disease.
No evidence suggests preop Spirometry is useful in risk stratification in this instance.
Respiratory physician consultation is rarely required, though should be considered when room air saturation <90%, acute severe chest infection, or exacerbation of chronic disease. Chest infections and exacerbations are common and delaying surgery may only worsen this as consequence of prolonged immobility. The decision as to whether to proceed or not depends on patients' functional reserve, the severity of the infection and the degree of post op support available.
Improve outcomes by attempting to optimise pre existing baseline if possible, smoking cessation, incentive spiromerty with physiotherapist involvement pre and post op, and where needed, even delaying surgery to manage severe pneumonia (vs. simple RTI) with antibiotics.

Risk assessment
The presence of co morbid disease is a predictor of mortality and degree of potential rehabilitation. There are a variety of scoring systems available to predict outcome and risk; though they are practically difficult to institute.
The ***Nottingham Hip Fracture*** score has been used to predict 30day mortality
Predictors of mortality from that scoring system include: age (66-85, over 86 years), male gender, two

or more co-morbidities, mini-mental test score 6 or less out of 10, malignancy, living in an institution and anemia (admission hemoglobin concentration <10 g/dl). Other predictive factors include preoperative mobility, cognitive state, preoperative residence, abnormal sodium and renal dysfunction.

Intra Operative Management

Regional vs. General anaesthesia: Does it matter?
Audits and met analysis have failed to indicate a significant mortality benefit of one technique above the other.
Studies are unable to come to definite conclusions, possibly as a result of:

- Inter institutional and inter individual variation of anaesthetic technique
- Difficulty defining an appropriate end point, as 30day mortality and length of hospital stay are seemingly remote from time of anaesthesia.

Parker et al and colleagues' Cochrane review 2004, looked at 22trails/ 2567 patients, (all methodologically flawed), found that regional anaesthesia only marginally (not statistically significant) had a lower mortality at 30days but was **no different** from GA at the 3month and 1-year mark. [6]
Current literature suggests regional anaesthesia is associated with reduced morbidity [6,7]
Regional anaesthesia was found to be associated with less acute postoperative cognitive dysfunction, however this was only in the immediate post op period. [6,7]
It may be argued that **regional anaesthesia advantages**:

- Decreased incidence of DVT- however this is less of a significance if thromboprophylaxis is already instituted
- Less intra op blood loss, less chance of requiring transfusion
- Less bleeding at operative site, improved cement bonding, faster operating times
- Less pulmonary complications,
- Adequate analgesia (albeit short immediate post op term),
- Earlier mobilization and probable faster rehabilitation efforts. [6,7]

This has to be balanced against the greater tendency of spinal anaesthesia to produce hypotension requiring subsequent management with vasoconstrictors and fluid (judiciously).
Advantages of general anaesthesia

- More suited to patient unable to lie flat
- Safer for cardiac patients, AS
- Safer in presence of co agulopathy
- Patient preference and co operation

Neuraxial anaesthesia is often used in combination with *sedation. TCI of propofol* offer better recovery than benzodiazepines which may precipitate a disinhibitory effect.
General anaesthesia, whether intubated or LMA, is often combined with peripheral nerve blocks or neuraxial anaesthesia foe better pain relief.
Currently both regional or general anaesthetic acceptable, in all its varieties, as long as it tailored for the individual patients requirements, and combined with adequate multimodal analgesia to obliterate physiological stress.

Other Intra Operative Considerations

Monitoring
Despite this patient profile being amongst the sickest in hospital, elderly hip patients are seldom monitored extensively intra operatively. Consideration should be given to *invasive arterial pressure monitoring*, *5 lead ECG's* where necessary and point of care *Hb* samples done in theatre rather than solely post operatively. Where possible, it is suggested a means to measure *cerebral function or perfusion* by means of BIS or INVOS respectively, may offer additional pertinent information.

Positioning
With *fracture fixation*, the patient will be positioned on a *hip prop*, feet fixed in shoe supports, with only the upper body supported by the theatre table. It is imperative to assess pressure points and to be aware that patients easily *slide off* this structure, before during and after the operation!
Hemi arthroplasties are positioned *supine or lateral on the operating table*. Pressure care padding is important, to prevent peripheral nerve injuries. Furthermore, cemented arthroplasties may be associated with a drop in BP, heart rate and ETCO2. (Please see cement implantation syndrome.)

Antibiotics
Elderly patients are high risk for the development of infections. This is enhanced with the reduced mobility.
Single dose prophylaxis administered pre incision, for prevention of deep and superficial wound infections. Follow up doses as per protocol of institution.
Other common infection sites include chest and urinary tract.

Analgesic Options Intra Operatively
Analgesia should provide stable operative conditions, optimal pain relief with minimal side effects such as excessive sedation, PONV, hypotension or motor block.
A Multimodal approach to analgesia, by combining various drug classes, affecting different aspects of the pain pathway, has become standard of care. Regular administration of Paracetamol in conjunction with long acting opioids is usually commenced in the pre op period.
Well-conducted regional techniques have been found to facilitate earlier mobilization and so rehabilitation. This may be achieved by single shot techniques or continuous peripheral nerve blocks.

Epidural anaesthesia/analgesia
Remains a useful technique for lower limb arthroplasty, provided anaesthetist is fully aware of caveats wrt side effects and timing of anticoagulant drugs, as well as post op PACU placement
Cochrane review however found that analgesic benefits of continuous epidural analgesia compared to PCA with morphine was limited to the early post operative period (3-4days)
Lumbar epidural is also associated with some undesirable side effects

- Hypotension,
- Urinary retention
- Bilateral motor block, delaying mobilization

Spinal anaesthesia with intrathecal opiates
Spinal anaesthesia offers a quick, reliable means of anaesthesia and analgesia, with the advantages of regional techniques already mentioned.
The favourable recovery profile and analgesia post operatively, that may be prolonged by administration of low dose intrathecal opiates, makes this the most optimal technique utilised by many. Low dose intrathecal morphine provides prolonged analgesia, owing to its low lipid solubility (and therefore slower clearance from the dorsal horn as compared to fentanyl) Optimal doses for hip arthroplasty were found to be 100-200ug (opposed to knees that require higher doses), providing pain relief for up to 21 hours.

Undesired side effects of intrathecal morphine include but are not limited to:

- PONV- seen in up to35% of patients not receiving prophylactic anti emetics.
- Pruritus and urinary retention as common as 30%, managed with opiate antagonists and catheterization respectively.
- Respiratory depression due to the rostral spread, albeit rare with administration of low doses. Respiratory depression may occur as early as 30 min post administration, or as late as 24 hours. Hence adequate postoperative observation in a PAHCU remains crucial for first 24 hours.

Peripheral nerve blocks

The hip joint is innervated by

1. Femoral nerve via nerve to rectus femoris (L2,3,4)
2. Sciatic nerve via nerve to quadric femoris (L4,5 S1,2,3)
3. Obturator nerve from its anterior division (L2,3,4)

Cutaneous innervation is supplied by the lateral cutaneous nerve of the thigh

Peripheral nerve blocks

Single shot or *continuous peripheral nerve blocks* have become increasingly popular for preop pain control, an adjunct to anaesthesia for intraoperative analgesia as well as postoperative pain management.

Current evidence supports improved rehabilitation where PNB are utilised post operatively as they provide adequate analgesia with minimal impingement on motor function. Furthermore they avoid the undesired side effects of continuous epidural analgesia (hypotension, urinary retention) and PCA morphine (sedation, PONV)

Continuous nerve blocks provide prolonged analgesia, especially demonstrated for femoral nerve, lumbar plexus and sciatic nerve blocks.[13]

There is debate as to whether patients should be awake or sedated or under anaesthetic for catheter insertion. Various schools of thought exist with regards to safety of practice.

Insertion of catheters requires a *level of expertise* and can *be time consuming* and *technically challenging*.

Ultrasound guidance has been shown to improve accuracy.

All continuous nerve blocks performed under strict aseptic techniques with adequate monitoring application.

To minimise the motor deficit, low concentrations of local anaesthetic should be used (<0.1%) targeting rates of 5-10ml/hr. infusions usually established in PACU, and continued for 48-72 hours.

Motor block and altered proprioception may still be a problem, and patients may require support to mobilize

Serious complications of this technique:

- Systemic toxicity of local anaesthetic
- Haematoma development
- Infection
- Catheter impinging on surgical site
- Dense motor deficit
- Minor complications: catheter knotting, kinking, obstruction, dislodgement.

Useful Peripheral Nerve Blocks to consider (single-shot or continuous)

1. Lumbar plexus block
2. Femoral nerve 3 in one block
3. Fascia iliaca block
4. Sciatic nerve block

Post operatively

Postoperative placement is dependant on the patient's pre existing co morbidities and baseline function, as well as the degree of surgery incurred and anaesthetic techniques employed. Arthroplasties and patients requiring epidural care or post op care as after intra thecal morphine administration are admit to high care units. Meticulous detailed attention to fluid balance is important in the elderly population. Ensure that formal Hb levels are tested and transfusion administered if necessary. A well thought out analgesia plan is essential. Commencement of regular Paracetamol, and alternative pain relief (opiate, tramadol, PCA) needs to be considered ahead of time, as intrathecal morphine, if used, will eventually become ineffective. Pain-teams are invaluable in accessing adequacy of pain relief and re adjusting analgesia to patients needs.
Anti emetics are vital to patient well-being.
Thromboprophylaxis needs to be continued.
Consider re commencement of patients regular medication when appropriate.
Elderly patients will require regular orientation to assist with/ prevent cognitive decline.
Early rehabilitation, mobilization and physiotherapy are encouraged, as this facilitates better overall recovery and a shorter hospital stay.
Re commence oral intake as soon as possible and consider nutritional supplementation.

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Emergence delirium

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Eckenhoff et al. were the first to report hyper-excitation on emergence from anaesthesia in the 1960's. These findings were in relation to ether, cyclopropane or ketamine anaesthesia; and were noted to occur more often after tonsillectomy, thyroidectomy and circumcision. With the advent of halothane use in clinical anaesthesia, the incidence decreased, but with the arrival of sevoflurane and desflurane, it became a major clinical problem again.

Definition

Emergence delirium (ED) is also known as emergence agitation, or post-anaesthetic excitement. It can be described as a **dissociated** state of consciousness during *early* recovery from anaesthesia. The patient (child) is crying, *inconsolable*, and *thrashing*. Children typically *do not recognize* familiar objects or people such as parents or caregivers. Altered perceptions include **disorientation** and **hypersensitivity** to stimuli, and **hyperactive** motor behaviour is usually present.
(Some define emergence *agitation* as a state of mild restlessness and mental distress without a significant change in behaviour, as opposed to *delirium*. Most do not discriminate between the two terms, though.)

Agitation does not always indicate ED, however, agitation and thrashing *requiring restraint* are parameters used commonly to define ED in children.

Motor activity significantly associated with ED includes *non-purposefulness,* **averted eyes, staring,** or closed eyes. Absence of *language* or irrelevant language*, non-responsivity*, *back arching*, and *tilting the head* backward are also significantly associated with ED.

Tantrum, as opposed to ED, may be indicated by screaming and combativeness, and pain is indicated by communicating pain verbally, or by touching the surgical site. In one study, the majority of children who presented with ED transitioned into tantrum, pain, or unsettled behaviour.

Emergence delirium presents most commonly in pre-school children (2 - 5 years), but can present in adult patients. Although it is usually self-limiting and resolves spontaneously within 15 - 30 minutes, it can be very distressing to staff and family alike, and it may be associated with injury, removal of intravenous lines, removal of urinary catheters, etc. There have been reports of ED lasting hours, and even up to two days. There is currently no *clear* evidence that it affects post-operative behaviour after resolution, or future interactions with healthcare (one study found an increased odds ratio of negative behavioural changes after emergence delirium). This is despite the association between pre-operative anxiety and ED on the one hand, and pre-operative anxiety being an independent predictor of postoperative negative behaviour (including nightmares, waking up crying, separation anxiety and temper tantrums) on the other hand.

Delirium

"Emergence delirium" differs from the "delirium" defined by the DSM-IV criteria. According to DSM-IV criteria, delirium is a disturbance in consciousness or awareness, causing reduced awareness of one's environment and impairment of the ability to sustain, focus or shift attention. There are changes in cognition (such as impaired memory, language disturbance and disorientation) or perceptual disturbances (such as misinterpretations, illusions or hallucinations). These disturbances develop over a short period and fluctuate over time. ED can be distinguished by the absence of fluctuation, and its short duration.

Patients with delirium may have hypo-active, hyperactive, or mixed psychomotor behaviours.
Subtypes of delirium include:

- Delirium due to a general medical condition
- Substance-induced delirium
- Substance withdrawal delirium

- Delirium due to multiple aetiologies
- Delirium not otherwise specified

Delirium is associated with cortical dysfunction, and shows diffuse slowing of background activity on the electroencephalogram (EEG). Serum anticholingeric activity has been associated with delirium, as well as other mediators like melatonin, noradrenaline and lymphokines.

Apart from **ED**, which is acute and usually short-lived, other disturbances of behaviour and cognitive function may be found postoperatively:

- Postoperative negative behaviour (mostly in children, comprised of nightmares, separation anxiety, tantrums).
- Postoperative delirium (more common in the elderly, starting on day 1 - 3, fluctuating).
- Postoperative cognitive dysfunction (defined in terms of pre-operative function, which would need to be assessed formally. Includes learning and memory, verbal abilities, perception, attention, executive functions, and abstract thinking.)

Hyperactive and hypo-active ED

Although ED is defined as a phenomenon with hyperactivity, some describe a hypoactive form of ED, and some scales for measuring ED (or delirium) include hypoactive sections. This hypoactive ED has been associated with longer surgery, higher opiate use (in some studies), and intra-abdominal surgery, high-risk surgery, more crystalloid administration, decreased core temperature and residual neuromuscular block. It was associated with a longer hospital stay in one study.

Incidence

Incidences of ED quoted range between 5% and 80%. This wide variation in reported incidence may reflect different patient populations (e.g. adult versus pre-school), different surgeries and anaesthetic techniques, and the use of different criteria for diagnosis of ED. Studies including mostly adults, found incidences around 5%, going up to about 21% for surgeries of the head and neck (e.g. ENT, neuro).

Assessment scales

More than 16 scales have been described to diagnose ED. Some large studies involving / including adult patients used **RASS** (The Richmond Agitation-Sedation Scale) – described for patients in ICU – and **Riker's SAS** (sedation-agitation scale).

Richmond agitation sedation scale (RASS)		
+ 4	**Combative**	Overtly combative, violent, immediate danger to staff
+ 3	**Very agitated**	Pulls or removes tube(s) or catheter(s); aggressive
+ 2	**Agitated**	Frequent non-purposeful movement, fights ventilator
+ 1	**Restless**	Anxious but movements not aggressive or vigorous
0	**Alert and calm**	
- 1	**Drowsy**	Not fully alert, but has sustained awakening (eye-opening / eye contact) to voice (>10 seconds)
- 2	**Light sedation**	Briefly awakens with eye contact to voice (<10 seconds)
- 3	**Moderate sedation**	Movement or eye opening to voice (but no eye contact)
- 4	**Deep sedation**	No response to voice, but movement or eye opening to physical stimulation
- 5	**Unrousable**	No response to voice or physical stimulation

Riker's sedation-agitation scale (Riker's SAS)		
7	**Dangerous**	Pulling at endotracheal tube, trying to remove catheters, climbing over bed rail, striking at staff, thrashing from side to side
6	**Very agitated**	Does not calm down despite frequent verbal reminders of limits, requires physical restraints, biting ET tube
5	**Agitated**	Anxious or mildly agitated, attempting to sit up, calms down with verbal instructions
4	**Non-agitated**	Calm and co-operative or awakens easily, follows commands
3	**Sedated**	Difficult to arouse, but awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands
2	**Very sedated**	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	**Unrousable**	Minimal or no response to noxious stimuli, does not communicate or follow commands

The **PAED** (paediatric anaesthesia emergence delirium) scale is used for young children. It tests five psychometric items:

- Whether the child makes eye contact with the caregiver
- Presence of purposeful movement
- Awareness of the surroundings
- Restlessness
- Whether the child is inconsolable

Each is scored 0 - 4, with 12 (some use 10) being diagnostic. A decreased ability to make **eye contact** and inadequate awareness of **surroundings** reflect disturbances in consciousness with a reduced ability to focus, sustain, or shift *attention*. Less **purposeful** actions suggest cognitive changes that include *perception and memory impairment* as well as disorganized thinking patterns. **Restlessness** and **inconsolable crying** reflect a disturbance in *psychomotor behaviour* and *emotion*, but they may also reflect pain or fear.

The PAED scale has fair sensitivity but a high false-positive rate. It includes items that can be confounded with symptoms of pain, tantrum, hunger, or distress, and high scores on these items (restlessness and inconsolability) along with low scores on other items can produce a score within ED classification. It has the advantage of being a validated scale.

PAED scale		
Points assessed		**Score**
1	The child makes eye contact with caregiver	**4** = not at all **3** = just a little **2** = quite a bit **1** = very much **0** = extremely
2	The child's actions are purposeful	
3	The child is aware of his/her surroundings	
4	The child is restless	**0** = not at all **1** = just a little **2** = quite a bit **3** = very much **4** = extremely
5	The child is inconsolable	

To its credit, the PAED scale tests for more specific symptoms than some other scales, like the Watcha scale. The Watcha scale is very practical to use, and it may be more sensitive and specific than many other scales.

Watcha scale	
1	Calm
2	Crying, but can be consoled
3	Crying, cannot be consoled *ED
4	Agitated and thrashing around *ED

Associated factors

Age:
As mentioned, ED is more common in **young** children. Only one study also managed to find an increased incidence in the youngest and oldest of three *adult* age groups (18–39, 40–64, and >65 years), but this has not been confirmed by other studies.

Anxiety:
Emergence delirium in children (and possibly adults) is associated with preoperative anxiety, and in children it responds to behavioural preparation and preoperative sedation. Character traits may also play a role in children. Children who are emotional, impulsive, or withdrawn, and children with low adaptability have a higher risk for developing ED.

Studies have different findings, but it seems possible that parental anxiety, parental presence, and difficult separation of children from their parents may influence emergence behaviour.

A study showed that the induction and emergence behaviours of children undergoing general anesthesia significantly correlated with maternal salivary amylase activity (an indicator of increased noradrenaline) during the pre-anesthetic period. The children of mothers with higher pre-operative salivary amylase activity, had more severe the induction anxiety and emergence agitation.

Type of surgery:
Surgeries strongly associated with ED include ENT surgery, and surgery to the head (including ophthalmic, neurosurgery, oral surgery) and neck. Other surgeries implicated include abdominal, breast, urologic, orthopaedic and vascular surgeries. Endoscopy is protective.

Other factors:
Long duration of anaesthesia, long fasting times, the presence of an endotracheal tube (during emergence), urinary catheterization, and recent smoking have been implicated as associated factors.

Pre-operative medication:
Long-term use of anti-depressant drugs or benzodiazepines, as well as premedication with benzodiazepines (see discussion under prevention) have been implicated as associated factors. In another study, long-term treatment by antidepressants decreased the risk, though.

Patients on neuroleptic medication seem to be protected against ED. Hydroxyzine premedication decreases ED.

Pain:
Pain is associated with ED, but it may also be confused with ED. Although peroperative analgesia decreases the risk of ED, painless anaesthetics (for MRI and EUA eyes) are also associated with ED. Pre-emptive caudal epidurals don't abolish ED either.

FLACC pain scale			
	0	**1**	**2**
Face	Smile or no particular expression	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Leg	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moved easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or talking to, distractible	Difficult to console

Anaesthetic technique:
General anaestheisa (as opposed to regional anaesthesia) is associated with ED.

The use of neuromuscular blockers have been reported to be associated with ED. This may be on the basis of inadequate reversal of neuromuscular block.

The insoluble inhalational agents (sevoflurane and desflurane – probably to a similar extent) are strongly associated with ED, while halothane is protective. In children undergoing magnetic resonance imaging (MRI), the incidence of ED after use of sevoflurane may be up to 7-fold greater than with halothane.

Total intravenous anesthesia and balanced anesthesia with short duration are protective factors.

Prevention and treatment
It is advisable to warn parents of the possibility of ED in pre-school children, especially if other risk factors are present.

Hypoxaemia, hypotension and hypoglycaemia need to be excluded.

Measures to prevent ED may include extubation pre-emergence, removal of urinary catheters, reversal of neuromuscular block, treating pain, and relieving peri-operative anxiety (which includes measures like distraction during induction). Holding an upset child, and recovery in a quiet, dark environment have also been proposed.

Medications proven to be of benefit were described in two analyses (listed in table below).

Meta-analyses BJA 2010	Cochrane review 2014	RR
Propofol	Profol maintenance	0.35
Alpha-2 agonists	Dexmedetomidine	0.37
Ketamine	Clonidine	0.45
Fentanyl	Fentanyl	0.37
Peri-operative analgesia	Halothane	0.51
Midazolam and 5-HT3 inhibitors **not** protective		

The Cochrane review could not find evidence for decreased risk of ED with desflurane or isoflurane when compared to sevoflurane. Nitrous oxide may be used at the end of anaesthesia while sevoflurane washes out, in an attempt to prevent ED.

Propofol infusion in addition to inhalation agent, or as bolus at the end of surgery is also effective in preventing ED, and a dose of 0,5 - 1 mg / kg can be used in the treatment of ED.

Fenatanyl is protective, as are other opioid drugs, and a bolus of fentanyl (1 - 2,5 mcg / kg) may be used in treatment of ED.

Ketamine has protective effects. Oral ketamine has also been shown to protect against ED – the sedative effects of the hepatic metabolite, nor-ketamine, may be very useful when using oral preparations. Although ketamine was reputed to cause ED, the converse is true, and a pleasant emergence phenomenon has been described with the intravenous and intramuscular use of ketamine for procedural sedation.

Midazolam has a controversial role in ED. While several studies report a reduced incidence of ED after midazolam premedication, others report no effect or an even increased incidence and longer duration of agitation. The Cochrane review found no evidence for improvement in ED with oral midazolam premedication, but midazolam bolus at the end of anaesthesia had moderate evidence for efficacy. Adding diazepam (0,25 mg / kg) to a midazolam premedication may decrease ED.

Alpha-2 agonists' *sedative* effect is mediated via post-synaptic alpha-2 receptors in the locus coeruleus (LC), where they reduce noradrenergic output and thereby facilitate the firing of inhibitory neurons (most importantly, the gamma-aminobutyric acid (GABA) system). They also have an *analgesic* action through binding to alpha-2 receptors in the dorsal horn of the spinal cord and in supra-spinal sites (reducing the release of substance P). Dexmedetomidine may additionally have *neuroprotective* effects, and can therefore attenuate neurocognitive impairment (mainly delirium and agitation).

Both clonidine and dexmedetomidine prevent ED (dexmedetomidine with a better odds ratio than clonidine, and clonidine associated with longer PACU stay). Dexmedetomidine has been used in a dose of 0,5 mcg/kg to treat ED in the PACU. Clonidine used caudally is more effective in prevention of ED when used in higher doses (2 - 3 mcg / kg). Oral clonidine (4 mcg / kg), when compared to midazolam, not only prevents ED, but also decreases pain scores in the PACU and may provide better sedation.

Other medications used, but with too little evidence at this stage to be proven remedies, include the neuroleptics, haloperidol and droperidol, melatonin, intra-operative magnesium infusion, and pre-operative gabapentin.

Haloperidol and droperidol are used in psychiatry as sedatives, and two very good case reports exist for the effectiveness of droperidol in a dose of 100 mcg / kg. This is 10 times the dose used for prevention of nausea and vomiting. Droperidol has no ventilatory depression, and in stead, intravenous droperidol increases the ventilatory response evoked by hypoxaemia (by blocking inhibitory neurotransmitter actions at the carotid body).

Gabapentin has been given as a premedication for tonsillectomy at 15 mg / kg, and not only decreased the incidence of ED, but also improved post-operative pain for the first 24 hours.

Proposed mechanisms for ED

The cause of ED is unknown. What follows here is a discussion of some theories.

Rapid emergence:
Traditionally it was thought that the sudden emergence from anaesthesia produced by insoluble agents, combined with children's poor ability to respond to a strange environment could contribute to the development of ED. This theory is refuted by the fact that propofol also causes rapid emergence, but is protective against ED, and that a step-wise reduction in sevoflurane concentration to prevent ED did not manage to protect patients.

Differential regional emergence:
Inhalation anaesthetic agents (IAA) inhibit different parts of the central nervous system (CNS) in a non-uniform manner. These different areas may therefore recover at different rates, e.g. audition and locomotion usually recovers early. Parts of the cerebral cortex and reticular activating system may still be depressed during emergence, which is usually evidenced by drowsiness, but it may be expressed by disorientation.

The brain is described to have two states that do not function simultaneously (men only?):
The "resting functional connectivity network" (i.e. when thinking), and the "executive control network" (i.e. when focused externally, like on motor function). Sevoflurane blocks the "resting functional connectivity network" at low concentrations.

Neuronal imbalance:
The EEG changes observed during the administration of sevoflurane, desflurane and isoflurane, differ from those of halothane. This may support the idea that ED is due to an imbalance between neuronal synaptic inhibition and excitation associated with the newer IAA.
(Interestingly, the EEG seen with ED is similar to the EEG of night terrors).
Sevoflurane is also associated with higher brain lactate and glucose levels than propofol - lactate and glucose correlate positively with ED.

Sevoflurane has a biphasic effect on GABA-A mediated inhibitory currents: it potentiates these currents at high concentrations, but blocks them at low concentrations. A study of currents in the locus coeruleus (LC) of rats showed that IAA directly activate an inward current that *excites* the LC neurons. This inward current is activated earlier than the outward (*inhibitory*) current, accounting for transient excitatory effects at low concentrations.

Another study in "NMDA GluRe1 subunit knockout mice", when compared to "wild mice", and sevoflurane, when compared to isoflurane and halothane, indicated that sevoflurane at 0,1 MAC reduced activity in wild mice, while increasing activity in knockout mice. This emphasizes the differential effects at low concentrations of IAA in susceptible organisms.

Children may be more susceptible due to their immature CNS. They have low levels of neurotransmitters, immature cholinergic centers, and an immature hippocampus. It has even been suggested that the GABA-A receptor could be excitatory rather than inhibitory in early infancy. It is actually known that the switch from excitatory to inhibitory transmission of GABA transmission takes place before the birth of a term human baby, while ED is a problem of 2 - 6 year old children.

There were some interesting findings in a study of rat pups, though:
1. Sevoflurane induced *hyperactive behaviours* in post-natal day 1 - 15 rats, but failed to do so in older rats.
2. GABA-ergic transmission produced *excitation* rather than inhibition the neocortex of day 5 - 10 rats, but produced inhibition in adult rats.
3. Sevoflurane at concentrations less than 1 MAC potentiated excitatory GABA-ergic potentials.

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Update on the Management of Postoperative Nausea and Vomiting

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Introduction

In recent years due to advances in modern Anaesthetic technique, the risk of major mortality and mortality with elective and emergency surgery has decreased significantly. Attention has now shifted to address and improve other factors that may influence patient satisfaction and morbidity, with the aim to improve patient outcome. Postoperative nausea and vomiting (PONV) have proven to be one of the most important patient morbidities after surgery, often quoted by patients as the worse possible post-operative anaesthetic complication. It has been described as the final therapeutic challenge to our anaesthetic speciality as well as the major problem with ambulatory surgery. Postoperative nausea and vomiting (PONV) are common, the incidence of vomiting is about 30% in the general surgical population; and the incidence of post-operative nausea about 50%. In a subset of high-risk patients, the PONV complication rate can be as high as 70 - 80%, without the use of PONV prophylaxis. Unresolved PONV may result in prolonged recovery, hospital or post-anesthesia care unit (PACU) stay or unanticipated hospital admission that will result in a significant increase in the overall health care cost. The goal of PONV prophylaxis is to decrease the incidence of PONV and therefore also reduce morbidity, complications, patient-related distress as well as health care cost resulting in improved patient outcome and satisfaction.

Though generally non-fatal and self-limiting, PONV may occasionally lead to serious medical consequences. This may include dehydration, electrolyte imbalances, venous hypertension, bleeding, haematoma formation, suture dehiscence, oesophageal rupture, blindness as well as aspiration. PONV therefore has a profound impact on patient satisfaction, quality of care and estimated health care costs. This could be as a result of delayed discharge, prolonged nursing care, and unanticipated hospital admissions. Patients in a first world health care system have reported willingness to incur expenses of up to $100 for an effective anti-emetic. In one study by Macario et al, patients were asked to allocate $100 to avoid undesirable outcomes after surgery, and it was found that PONV was allocated the largest amount and therefore considered to be one of the most undesirable postoperative complications of general anesthetic. It is therefore crucial to consider the need for prophylactic anti-emetics in every surgical patient.

Nausea and vomiting due to surgery may also occur beyond the immediate post- operative period. Although not as well studied, in recent years the later problem of postdischarge nausea and vomiting (PDNV) has received increasing attention from health care providers. The issues of PONV and PDNV are especially important in the context of rising health care costs and the increasing diversity and volume of surgical procedures that are performed as ambulatory or day case procedures. This may comprise up to 60% of the combined 56.4 million surgical procedures performed in the United States in a year. Patients who experience no PONV immediately after surgery may develop PDNV after discharge to such a degree that they may need readmission. In one study, approximately 36% of patients who experienced PDNV had not experienced any nausea or vomiting before they were discharged. Surveys of patients following ambulatory surgery have found PDNV to range between approximately 20% and 50%, resulting in increased difficulty in performing daily activities and also prolonged time to return to work with longer recovery times before resuming normal activity. Although the incidence of PONV and PDNV in ambulatory surgeries may be slightly lower due to the general shorter duration of the procedures than that of inpatient surgeries, it is still believed to be

underreported. Because of the relatively short period that ambulatory patients spend in health care facilities, it is of particular importance to identify, prevent and treat PONV and PDNV effectively.

Background on the developments of PONV management guidelines and publications

Several guidelines, management protocols and new developments have aided in the prevention and management of PONV. The present guidelines as published in 2014, in the journal of Anesthesia and Analgesia are compiled from the most recent data on postoperative nausea and vomiting (PONV) and constitutes an update on the 2 previous sets of guidelines published in 2003 and 2007. This latest update sets out new information on PONV risk factors,and includes a new risk scoring system for post- discharge nausea and vomiting (PDNV). This is important in a setting of rising health care cost and a drive to perform more surgical procedures as day case ambulatory surgery. These guidelines were compiled by a multidisciplinary international panel of individuals with interest and expertise in PONV management under the Society for Ambulatory Anaesthesia. The panel members critically evaluated the current medical literature on PONV to provide an evidence-based management tool for the risk assessment and management of patients who are undergoing surgery and are at increased risk for PONV.

These guidelines identify individuals at risk for PONV in adults and peadiatric patient population groups and recommend approaches to reduce baseline risk as well as identifying the most effective anti-emetic single therapy and combination therapy regimens available for PONV prophylaxis. It also includes the non-pharmacologic therapies and recommends strategies for the treatment of PONV. It provides an algorithm for the management of individuals at increased risk for PONV as well as steps to ensure PONV prevention and treatment are implemented to minimize the risk of PONV occurring or effectively treating the complication if it does occur. The present guidelines include new information on PONV risk factors; a risk scoring system for PDNV, recommendations on new anti-emetics, for example the neurokinin-1 receptor antagonists; changes in recommendations from previous guidelines based on new published information on efficacy and risks of anti-emetics. One of these risks often quoted is the prolongation of the QT segment and possible dysrythmias associated with certain anti-emetics. The significance of QT prolongation and drugs that cause this as a side-effect also gets discussed in greater detail.

Several new developments have also occurred in the field of the pharmacological agents available for prophylaxis and management of PONV. The 5-hydroxytryptamine type 3 receptor antagonists continue to be the mainstay of anti-emetic therapy. Newer pharmacological agents such as the neurokinin-1 receptor antagonists and the long-acting serotonin receptor antagonist have been added to the Anaesthetist's arsenal for the prevention and treatment of this important post-anaesthetic complication. Furthermore, risk assessment protocols, multimodal management strategies, non-pharmacological therapies and novel techniques for the management of high-risk patients should always being kept in mind and practised.

Mechanism of nausea and vomiting

Most of our current understanding of basic neuro-anatomy as well as the physiology of emesis comes from the work of Wang and Borison in the 1950s. Prior to the research of Borison, it was believed that the chemodetection, coordination and conduction of emesis was controlled solely by the dorsal vagal nucleus. This was inconsistent with the observation that emesis could be induced by GIT toxins and irritants. Borison showed the existence of two brain areas involved in the emetic response. The first centre is the chemosensor for vomiting with no co-ordinating function, located in the floor of the fourth ventricle. The second centre, which have a co-ordinating function for vomiting, but no chemosensory

function, is located in the lateral reticular formation of the medulla obligatea. Borison and Wang then concluded that the chemosensor area acts as a vomiting trigger zone in the brain stem and they named the area the chemoreceptor trigger zone (CRT) for emesis. By using animal models they have shown that by removing the trigger zone from the brain, emesis can be prevented when emetic agents are injected into the blood stream. This demonstrates the relationship between the trigger zone and the act of emesis. Borrison received a doctorate from the University of Columbia for his work on studying the function of the CRT zone, located in the area Postrema of the medulla obligate. This area was already anatomically identified 60 years earlier by Swedish anatomist Magnus Retzius, but its function was never been studied before the work that was done by Borison. The central co-ordinating site for nausea and vomiting is therefore located in an ill-defined area of the lateral reticular formation in the brainstem. This ‘‘vomiting center,’’ as it is traditionally called, is not so much a discrete centre of emetic activity as a functional pathway of neuronal connections involved in generating the emetic response. It can be explained as a a central pattern generator (CPG) that sets off a specific sequence of neuronal activities throughout the medulla which will then result in vomiting.

Four major pathways have been identified, that are responsible for activation of CPG:

- **Vagal pathway**: chemical or mechanical activation of the vagal afferent fibers innervating the gastrointestinal tract.
- **Vestibular pathway**: activation of the vestibular system by motion
- **CPG mechanism**: direct chemical action on or near the brainstem CPG or closely associated nuclei, such as the area of postrema
- **Forebrain**: stimulation via descending pathways from the forebrain including the cerebral cortex. This last pathway is the least understood and likely plays an important role in the modulation of emesis by learning, for example the anticipatory vomiting seen before cancer chemotherapy.

Although the inputs and outputs for emesis are well described, the final common pathway for the emetic response are not that well defined. It seems as if the nucleus of the solitary tract in the lower brainstem acts as a potential site for the common inputs from the vagus, vestibular system, AP and cerebral cortex. The chemical receptors involved in transduction of signals in the area of postrema and vomiting centre include dopaminergic, cholinergic, histaminergic, serotinergic and opioid neurotransmitters.

Multiple inputs may therefore arrive from different areas such as the higher cortical centers, cerebellum, vestibular apparatus, vagal, and glossopharyngeal nerve afferents which then feeds into the so called vomiting centre. This neuronal afferents then serve to trigger a complex efferent motor response that will result in emesis. It was also shown that direct electrical stimulation of the CPG causes emesis whereas electrical stimulation of the CRT zone will not result in vomiting.

The chemoreceptor trigger zone is a particularly important afferent, located at the base of the fourth ventricle in the area postrema. Anatomically it lies outside of the blood-brain barrier but functionally it plays an important role in detecting neurotransmitters and emetogenic agents in the blood and cerebrospinal fluid (CSF). The CRT zone communicates with the adjacent nucleus tractus solitarius (NTS), which in turn projects into the central pattern generator (CPG). Signals between these anatomically distinct areas are mediated through a variety of neurotransmitters and neurotransmitter receptor systems. These includes the histaminergic, serotonergic, dopaminergic, cholinergic and neurokininergic systems. The neurotransmitters bind to their respective receptors in the CRT zone which is densely populated by different receptor types involved in the emetic response. Anti-emetic prophylaxis or therapies block one or more of the associated receptors, which may include; histamine H1, serotonin 5-HT3, dopamine D2, muscarinic cholinergic and neurokinin NK1 receptor. The neurokinin-1 pathway may represent the final common pathway in the emetic response, and the understanding of its role will be paramount to the further development of novel pharmacological therapies.

RISK - AND PROTECTIVE-FACTORS FOR PONV AND PDNV

A patient risk assessment for PONV should form a very important componant of the pre-operative assessment of every surgical patient. The assessment of patient risk factors is the fundamental key component in guiding anti-emetic prevention and management strategies. Various risk factors have been proposed associated with an increased risk and incidence of PONV. However, some may be simple associations and may not be directly linked to increased incidences of PONV. For objective risk assessment, it is recommended to focus on those factors that independently predict PONV after accounting for all other confounding factors.

Risk factors that remain significant in multivariate analyses of large cohort studies represent such independent factors. The most likely of these independent PONV factors/triggers are volatile anesthetics,nitrous oxide and postoperative opioids. It should be noted that the effect of volatile anesthetics on PONV is dose-dependent and depends on the duration of the anaesthetic. Volatile anaesthetics are of particularly importance in causing early PONV, causing nausea and vommiting in the first 2 to 6 hours after surgery.

Irrespective of the specific opioid used, postoperative opioids also increase the risk for PONV in a dose-dependent manner. The problem with opioids is that its effect appears to last for as long as it is used for pain control, into the postoperative period. This also explains why the incidence of PONV is lower with opioid-free regional anesthesia and reduced opioid consumption through the use of non-opioid analgesics and perioperative alpha-2 agonists. Opioids is a major cause of late PONV, and may cause emesis for up to 24 – 48 hours after surgery.

Many patients do not experience PONV, despite being exposed to triggering agents such as volites or opioids. This can be explained by the fact that the risk of developing PONV will also depends on the individual patient's susceptibility, which forms part of the baseline risk. Patient-specific risk factors for PONV in adult surgical parients include female sex, a history of PONV and/or motion sickness, nonsmoking status, and young age. Type of surgery is still strongly believed to be a risk factor for PONV, yet it is difficult to prove as an independent risk factor. Certain types of surgery may be associated with a higher incidence of PONV, but it may also be explained by the longer exposure to volatile anesthesthetic agents as well as higher doses of opioids. More recent studies implicate cholecystectomies, laparoscopic and gynecological surgery as risk-associated procedures that independently increase the risk for PONV.

Like all drugs, anti-emetics carry some risk for adverse effects, which range in severity from mild headache to clinically significant QTc prolongations, which may rarely be associated with cardiac arrythmias and sudden cardiac arrest. It is therefore considered to be of good clinical practise to first assess a patient's baseline risk for developing PONV before making a decision to administer prophylactic anti-emetic agents. This objective assessment is done by using a validated risk score that is based on independent predictors for the risk of developing PONV. This enables the clinician to formulate an evidence-based management plan, deciding on the number as well as the specific choice of prophylactic anti-emetics. These anti-emetics can then be be titrated against the specific patient's risk, to prevent a negative clinical outcome. Even though there is strong evidence for these truly independent risk factors to be triggers for the development of PONV, none of those risk factors taken alone as a single predictor is clinically sufficient for a risk assessment or to make decisions for the need for prophylactic antiemetics.

There are at least 8 risk scoring systems of which at least 7 are fully clinically validated by further studies, and these include the following: the Apfel, Simplified Apfel, Eberhart, Koivuranta, Sinclair, van den Baseh, Eberhart simplified Children's system as well as the Palazzo and Evans risk scoring systems. The 2 most commonly used risk scores for inpatients undergoing balanced inhaled anesthesia are the Koivuranta score and the Apfel simplified risk score. These risk scoring systems

are based on 4 predictors: female sex, history of PONV and/or motion sickness, nonsmoking status, and use of postoperative opioids . The incidence of PONV with the presence of 0, 1, 2, 3, and 4 risk factors is about 10%, 20%, 40%, 60%, and 80%, respectively.

It can be considered that patients with 0–1 risk factors belong to the “low” risk category, 2 or 3 risk factors are “medium” risk and more than 3 risk factor are the“high” risk category. Given that several anti-emetics are now generic and inexpensive and newer agents have more favourable side effect profiles, some experts advise to give 1 or 2 anti-emetics to all patients. The problem with this strategy is that it puts the low-risk patients at unnecessary risk for rare but well-described side effects. The NNT to prevent one episode of PONV, will also be unacceptably high to many clinicians, also making this approch not cost effective enough to warrant treatment. Although risk scores are an objective approach for assessing the patient’s risk for PONV or PDNV, they are not completely predictive, with sensitivity and specificity of between 65% and 70%. Many other clinically relevant aspects should therefore also being taken into consideration by the anesthetic clinician when assesing the need for anti-emetic prophylaxis. This will include considering possible complications of an emetic episode, for example in patients with wired jaws, raised intracranial pressure as well as patients who had gastric or esophageal surgery.

Surgical, anaesthetic and patient related factors have been identified as predictors of a patient’s risk for PONV. These risk factors can be applied and individualize for a particular patient to enable risk assessment and stratification. The 2007 Society for Ambulatory Anesthesia (SAMBA) Guidelines for the Management of PONV identifies the most important baseline risk factors which have been validated as independent predictors for PONV.

Of all the predictive models developed for PONV risk-stratification and prediction, a simplified scoring system developed by Apfel and colleagues remains one of the most popular. The Apfel risk scorring system also compares favourably with other more complicated scoring systems. Apfel and colleagues identified the 4 highly predictive risk factors for determining baseline risk. These are; female gender, a history of motion sickness or previous PONV, non-smoker status and the use of peri-operative opioids. The presence of 0, 1, 2, 3, or 4 of these risk factors will correspond to a PONV incidence of 10%, 21%, 39%, 61%, and 79%, respectively. The Apfel score are used to identify the patient’s baseline risk for PONV, identify patients that will need anti-emetic prophylaxis and also to guide anti-emetic strategies in high-risk patient groups. Several studies have shown that risk assessment and prophylaxis based on Apfel scores has led to accurate identification of moderate and high risk patient groups and effective reduction in the incidence of PONV, in these patient populations.

Risk Factors	Points
Female Gender	1
Non-Smoker	1
History of PONV	1
Postoperative Opioids	1
Sum =	0 ... 4

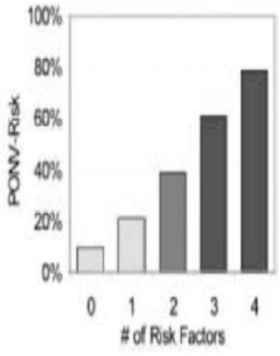


Figure 1. Risk score for PONV in adults. Simplified risk score from Apfel et al.[9] to predict the patient's risk for PONV. When 0, 1, 2, 3, and 4 of the risk factors are present, the corresponding risk for PONV is about 10%, 20%, 40%, 60%, and 80%, respectively. PONV = postoperative nausea and vomiting.

Table 1. Risk Factors for PONV in Adults

Evidence	Risk factors
Positive overall	Female sex (B1)
	History of PONV or motion sickness (B1)
	Nonsmoking (B1)
	Younger age (B1)
	General versus regional anesthesia (A1)
	Use of volatile anesthetics and nitrous oxide (A1)
	Postoperative opioids (A1)
	Duration of anesthesia (B1)
	Type of surgery (cholecystectomy, laparoscopic, gynecological) (B1)
Conflicting	ASA physical status (B1)
	Menstrual cycle (B1)
	Level of anesthetist's experience (B1)
	Muscle relaxant antagonists (A2)
Disproven or of limited clinical relevance	BMI (B1)
	Anxiety (B1)
	Nasogastric tube (A1)
	Supplemental oxygen (A1)
	Perioperative fasting (A2)
	Migraine (B1)

PONV = postoperative nausea and vomiting; BMI = body mass index; MS = motion sickness.

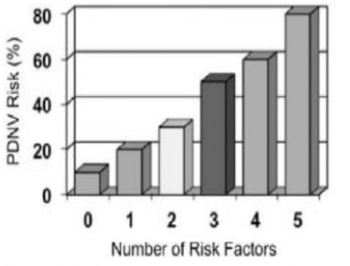
Figure 1: Risk score for PONV in adults. Simplified risk score from Apfel et al., to predict the patients risk for PONV.

The1999 study by Sinclair and colleagues was aimed at the identification and examination of PONV risk factors specifically in ambulatory surgery patients. This study is still one of the most comprehensive studies examining of PONV risk factors and included 17 000 patient's, it was conducted over 3 years and focused specifically on ambulatory surgery patients. In addition to the 4 factors identified by Apfel they also identified the use of general anaesthesia, duration of anaesthesia longer than 30 minutes and certain types of surgeries as independent predictors of PONV. These include plastic, ophthalmologic, and orthopaedic surgeries as high risk procedures for PDNV. However, the study was unable to rule out other independent risk factors associated with the specific surgery as possible contributors to increased rates of PDNV. Other studies, not confined to ambulatory surgery, have also identified the use of volatile anaesthetics and nitrous oxide, and the administration of intra-operative and postoperative opioids as significant risk factors.

White and colleagues also studied these risk factors and suggests that while higher Apfel scores correlates better to a greater incidence of PONV symptoms in the early (0–24 hours) postoperative period, it appears to have little predictive value for emetic symptoms occurring in the late (24–72 hours) postoperative and post-discharge period. Nevertheless, the few studies attempting to identify specific PDNV risk factors have found them to be similar to those typically associated with PONV.

Ambulatory procedures are typically shorter and less invasive than inpatient procedures and are associated with a lower risk of PONV in the PACU. It should be stressed that PDNV presents a significant risk to discharged patients who would no longer have access to fast-onset IV anti-emetics or monitored care. Mattila and colleagues evaluated post-discharge symptoms in over 2700 adult and paediatric ambulatory surgery patients, and also found general anaesthesia, female gender, duration of surgery longer than 30 minutes as major risk factors for PDNV in adults. However, type of surgical procedure had no impact according to this study. In the same study, no specific risk factors for post-discharge vomiting could be identified in a paediatric population, although use of general anaesthesia, age 3 years or older, and duration of surgery 30 minutes or longer correlated with an increased risk of post-discharge nausea. Other studies have suggested that PDNV in children may be correlated to factors such as emetic symptoms prior to discharge, increased age, duration of journey home after discharge, pain at home, and use of postoperative opioids, but these associations need further study.

A more recent study which recruited 2170 ambulatory patients in the United States, reported the incidence of PDNV to be 37% in the first 48 hours after discharge and identified 5 independent predictors of PDNV. These independent risk factors were female sex, age less than 50 years, a history of PONV, use of opioids and nausea in the PACU. Validation of a simplified PDNV risk score based on these risk factors correlated with an incidence of PDNV of 10%, 20%, 30%, 50%, 60%, and 80%, respectively, when 0, 1, 2, 3, 4, or 5 of these risk factors were found to be present.



Risk Factors	Points
Female sex	1
History of PONV	1
Age <50 years	1
Use of opioids in the PACU	1
Nausea in the PACU	1
Sum	0…5

Figure 2. Simplified risk score for PDNV in adults. Simplified risk score from Apfel et al.[19] to predict the risk for PDNV in adults. When 0, 1, 2, 3, 4, and 5 risk factors are present, the corresponding risk for PDNV is approximately 10%, 20%, 30%, 50%, 60%, and 80%, respectively. PDNV = postdischarge nausea and vomiting; PONV = postoperative nausea and vomiting; PACU = postanesthesia care unit.

Risk Factors	Points
Surgery ≥ 30 min.	1
Age ≥ 3 years	1
Strabismus surgery	1
History of POV or PONV in relatives	1
Sum =	0…4

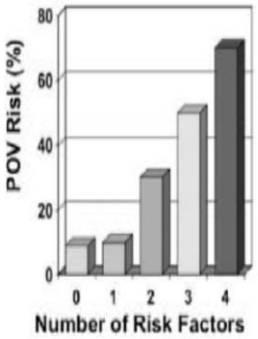


Figure 3. Simplified risk score for POV in Children. Simplified risk score from Eberhart et al.[48] to predict the risk for POV in children. When 0, 1, 2, 3, or 4 of the depicted independent predictors are present, the corresponding risk for PONV is approximately 10%, 10%, 30%, 50%, or 70%, respectively. POV = postoperative vomiting; PONV = postoperative nausea and vomiting.

The use of risk scores in predicting postoperative vomiting has also been extended to paediatric patients. This led to the development of the POstoperative VOmiting in Children score (POVOC score) by Eberhart and colleagues. The incidence of POV in paediatric patients is estimated to be about between 9% and 42% depending on the specific paediatric surgical population group, and can be as high as 80% for specific types of surgeries in high risk groups. It should be noted that studying the incidence of PONV in paediatric patients may be challenging and nausea is often not recorded, as it is often difficult to assess nausea in the younger patient population groups. To develop the POVOC score, Eberhart and colleagues compiled the PONV data from 1257 paediatric surgeries at 4 different institutions to enable them to identify 4 independent risk factors for POV in children. The group identified the following 4 major risk factors: duration of surgery longer than 30 minutes, age 3 years or older, strabismus surgery and a positive history of POV in the child or POV/PONV in a close relative where mother, father or sibling will qualify as a close relative. Similar to the Apfel score, the incidence of POV in a particular patient can then be estimated by calculating the number of risk factors present. The incidence of POV in children can be estimated to be 10%, 30%, 55%, and 70% for where 0, 1, 2, 3, and 4 risk factors is present, respectively. An external validation study has since be done and proposed a modified POVOC score which excluded strabismus surgery as a risk factor and has been shown to accurately predict POV in paediatric patients to the same degree as the Apfel score in adults.

Risk factors for PONV and PDNV

Patient Factors:

1. Female gender
2. History of motion sickness or previous PONV
3. Non-smoking status
4. Use of peri-operative opioids

Paediatric Anaesthetic Risk Factors

1. Age 3 years or older
2. Use of volatile anaesthetic agents or nitrous oxide
3. Family history or individual history of motion sickness or PONV
4. Strabismus surgery

Surgical Factors

1. Duration of surgery
2. Type of surgery: Abdominal, Ear, nose, and throat, Gynaecological, Laparoscopic, Ophthalmologic, Orthopaedic and strabismus surgery.

ANTI-EMETICS IN CLINICAL PRACTICE

Anti-emetic drugs act on one or more of the neurotransmitter receptors found in the central nervous system sites responsible for the emetic response. Prevention and management of PONV and PDNV require familiarity with a broad range of drug classes. A thorough understanding of the underlying physiology, receptor types as well as the neurotransmitters involved, forms the basis of a rational approach in the management of PONV. No single drug is available that has the ability to block all receptor types and therefore no single agent can completely prevent PONV in all cases. It is also important to note that anti-emetic therapy may potentially expose out-patients to various drug related side effects. As discussed previously, the aim of various scoring systems would be to identify patient groups most likely to benefit from prophylactic treatment without exposing patients unnecessary to any possibly drug related side effects. In comparing the various anti-emetics, it is helpful to determine the number needed to treat (NNT) and the number needed to harm (NNH) to determine the possible benefit and risks to the patients of the various treatment options. The number needed to treat is the number of patients that must be exposed to a particular intervention, in this case anti-emetic therapy in order for one patient to benefit from treatment in comparison with those patients receiving placebo or no treatment. The number needed to harm (NNH) is an estimate of the frequency of drug-related adverse effects from the treatment in comparison with patients receiving no treatment. We will discuss the various drug classes that are commonly used in prophylaxis and management of PONV with specific reference to their mechanism of action, receptors involved as well as efficacy.

Serotonin Antagonists

Ondansetron was developed in the early 1990s to treat chemotherapy-induced nausea and vomiting. Since then, serotonin antagonists have become one of the cornerstones of modern anti-emetic prophylaxis and therapy, particularly in the setting of PONV. Serotonin is found in high levels in the enterochromaffin cells of the gastrointestinal tract, as well as in the central nervous system, and may be released to stimulate either the vagal afferent neurons or the CTZ to activate the vomiting centre. Although there are multiple serotonin receptor types, the 5-HT3 subtype appears in its greatest concentration in the NTS, area postrema, and the dorsal motor nucleus of the vagus nerve, which all play a significant role in coordinating the vomiting reflex. The 5-HT3 receptor antagonists (5-HT3 RAs), which include ondansetron, granisetron, dolasetron, ramosetron, tropisetron, and most recently palonosetron, act by inhibiting the action of serotonin in 5-HT3 receptor-rich areas of the brain. Ondansetron (Zofran), granisetron (Kytril), dolasetron (Anzemet), and palonosetron (Aloxi) are all approved for use in PONV by the Food and Drug Administration (FDA) (ramosetron and tropisetron are not available in the United States). Ondansetron, granisetron, and dolasetron are available as intra-venous medications or oral tablets whereas palonosetron is currently only available as an intravenous medication. Furthermore, ondansetron is also available as an orally disintegrating tablet (ODT), which seems to be as effective as the intravenous form.

In general, the serotonin antagonists are safe, effective, and have similar side effect profiles. Side effects are usually short term and of mild to moderate intensity, with the most common being headache, dizziness, constipation, and diarrhoea. However, the differing chemical structures of each drug may explain slight differences in receptor binding affinity, dose response, and duration of action. Seratonin receptor antagonists is not without it's concerns which has prompted the Canadian health authorities to issue a black box warning for the use of Dolasetron, for its potential in causing severe

cardiac dysrythmias. All drugs that can possibly induce torsades du pointes blocks Ikr current and Serotonin antagonists blocks this Ikr current as well as Na channels which leads to a lengthening of both depolarization and re-polarisation. It has since been established that within this drug class, Palonosetron is possibly the only agent not associated with causing QT prolongation.

Most available data suggest that serotonin antagonists are most effective when administered at the end of surgery, but at least one study has suggested that dolasetron may be administered around the time of induction of anaesthesia, with little effect on efficacy. All of the serotonin antagonists are equally effective for the treatment of PONV. Ondansetron as the prototypical serotonin antagonists, has been the most studied. In a quantitative systematic review of placebo-controlled trials of ondansetron, Tramer and colleagues found that ondansetron, 4 mg had an NNT of about 4.6 for the prevention of vomiting, 6.4 for the prevention of nausea, and 4.4 for the prevention of both in the first 48 hours postoperatively. Risk of severe side effects was generally low, with an NNH of 36 for headache, 31 for elevated liver enzymes, and 23 for constipation. This study and others have also suggested that ondansetron is slightly more effective against vomiting than nausea. However, a recent study by Jokela and colleagues found that 4 mg ondansetron reduced the incidence of nausea by 26% over placebo, and vomiting by 33%, a difference that the investigators concluded was not of statistical significance. While not commenting on the anti-nausea versus anti-vomiting properties of ondansetron, a Cochrane systematic review found that ondansetron reduces the relative risk of nausea and vomiting by 32% and 45% over placebo, respectively. The review also evaluated 5 studies of ondansetron and reported no evidence that the risk of PONV differed for groups based on timing of administration. Controversy also exists as to whether ondansetron offers greater benefit for PONV prophylaxis greater than 4 mg, and a study in ferrets has found that the dose-response curve for ondansetron is unique in that it has better anti-emetic efficacy at low (<50 mg/kg) and high (>100 mg/kg) doses, than the mid-range dosages. However, for the purposes of clinical practice the usual recommended dose of ondansetron for PONV is 4 mg intravenously (IV), administered at the end of surgery. Unlike ondansetron, the other 5-HT3 RAs exhibit linear dose-response curves, with increasing doses achieving greater clinical effect until the maximal effective dose is reached. In a multi-centre, dose-ranging study, Taylor and colleagues found that intravenous doses as low as 0.1 mg given at the first symptoms of nausea or vomiting were effective in increasing the percentage of patients experiencing no vomiting in the first 24 hours to 38%, compared to 20% of patients with no vomiting in the placebo arm.

Palonosetron is the newest 5-HT3 RA and has recently been approved in the United States by the FDA for PONV management. Unlike other drugs in its class, which exhibit simple bimolecular binding, palonosetron exhibits positive co-operation in receptor binding. Its molecular structure does not mimic that of the serotonin molecule and it also doesn't only bind at the serotonin binding site of the 5-HT3 receptor. The result is that multiple palonosetron molecules will bind closely to the vicinity of a single receptor and thereby bind more tightly and make it less likely to be displaced by other serotonin molecules. Some molecular data even suggests that palonosetron may promote internalization of the 5-HT3 receptor as an inverse agonist (similar to some G-protein coupled receptor antagonists), decreasing the function of the receptor. This will typically take place after prolonged absence of serotonin agonist exposure. It has been postulated that receptor internalization may be the mechanism responsible for the relatively long duration of action of palonosetro. In a large, randomized, placebo-controlled study by it was found that 43% of patients given 0.075 mg palonosetron before induction exhibited clinical resolution as defined by no emesis and no rescue medication for 24 hours in the first 24 hours postoperatively, compared with the 20% of patients who received placebo. Moreover, patients receiving palonosetron reported less severe nausea and better function due to less interference to normal activities due to the sequelae of PONV. In a separate European study where 0.075mg palonosetron was used as anti-emetic, not only a similar efficacy was found but also a continued benefit over placebo for a prolonged period of 24 to 72 hours where noted. It has been suggested that the long half-life of palonosetron may confer an anti-emetic effect for several days after administration. The drug's long half life may give it an advantage over other anti-

emetic agents due to the prolonged mechanism of action it may prove to be an ideal agent for prophylaxis against PDNV following ambulatory surgery.
Only a few studies have examined the use of serotonin receptor antagonists for the prevention of PDNV. A systematic review by Gupta and colleagues found that ondansetron 4 mg resulted in a relative risk reduction of 23% and 37% for post discharge nausea and vomiting, respectively. In this review it was pointed out that the NNT was 12.9 for nausea and 13.6 for vomiting. Some of the studies suggest that providing patients with the orally disintegrating tablet of Ondansetron before discharge may be particularly helpful in reducing the incidence of PDNV after patients have left the hospital. In one study focussing on paediatric patients, the investigators found that only 14.5% of children who received 5 dosages of ondansetron ODT after discharge experienced post-discharge vomiting, compared with 32% of patients who received the placebo. It is also important to note the pharmacogenomic differences between different patient groups and populations which will aid to our understanding and new research on Serotonin antagonist efficacy. Although pharmacogenomic research is still in its early stages it may provide greater insights into assessing individual patient risk for PONV and explain treatment failure in certain groups where alternative agents may prove to be more effective. The serotonin receptor antagonists are metabolized by cytochrome P450 in the liver, and therefore any differences in the activity or enzyme levels of the CYP2D6 isoform appear to have an effect on the pharmacokinetics and clinical efficacy of the drug in those individuals. In one pharmacogenetic study the investigators have identified patients with more than 2 copies of the CYP2D6 gene or with certain genetic polymorphisms in the CYP2D6 gene as ultra-rapid metabolizers of ondansetron and are therefore more likely to experience treatment failure for POV where Ondansetron have been used. In another study, DNA was analyzed from patients who had suffered from POV and their DNA was matched with that of control patients. The researchers found that variations in the genes of the serotonin receptor subunits, HTR3A and HTR3B, were associated with increased individual risk of developing POV.

Steroids

Dexamethasone has been shown to be useful in the management of PONV. The mechanism of its anti-emetic activity has not been fully agreed upon or established. It have been postulated that corticosteroids act centrally to modulate steroid metabolism. It inhibits prostaglandin synthesis and also influences the release of endorphins. The specific theories how this modulates neurotransmitter metabolism includes central or peripheral inhibition of the production or secretion of 5HT3 or central inhibition of the synthesis of prostaglandins or change in the permeability of the blood brain barrier to serum proteins.

The use of dexamethasone with serotonin antagonists may also have synergistic actions when used in combination with 5-HT3 receptor antagonists, as it may reduce levels of serotonin by the depletion of its precursor tryptophan. By this mechanism the serotonin antagonists further prevent release of serotonin in the gut, and also sensitize the 5-HT3 serotonin receptor to other anti-emetics with anti-serotonergic actions. According to a study by Wang and colleagues, dexamethasone should be administrated with induction for it is most effective for PONV prophylaxis when administered early rather than at the end of surgery. In a systematic review and meta-analysis it was found that dexamethasone reduced the incidence of postoperative nausea by 41%, post-operative vomiting by 59% relative to placebo. The incidences of headache and dizziness were similar between the 2 treatment and placebo groups consistent with the notion that a single dose of steroid treatment is a safe and effective therapy with minimal side-effects. These results are similar to an earlier quantitative systematic review, which reported an NNT of 7.1 for the prevention of early vomiting and 3.8 for the prevention of late vomiting in adults and children.

Karanicolas and colleagues reported that doses of 8 to 16 mg were significantly more effective at reducing PONV than doses of 2 to 5 mg. They concluded that a dose of 8 mg dexamethasone

provided maximal PONV prophylaxis when combined with ondansetron. However, the Society of Ambulatory Anaesthesia guidelines recommend a prophylactic dose of 4 to 5 mg dexamethasone at induction via intra-venous route, which seems to be as effective as 4mg Ondansetron, in preventing PONV.

Dopamine Antagonists

The dopamine receptor antagonists act at the D2 receptors in the Chemoreceptor trigger zone and area postrema to suppress nausea and vomiting. There are three major groups of dopamine antagonists that are commonly been used as anti-emetics, the butyrophenones, the benzamides, and the phenothiazines.

1. Butyrophenones

In addition to their strong D2 receptor antagonism, the butyrophenones are also alpha- blockers, which contribute to their adverse effects of sedation and extra-pyramidal symptoms. Extra-pyramidal side effects can be minimized by the use of the lower dosage ranges recommended for the prevention and treatment of PONV. The two most important anti-emetic agents in this group are haloperidol and Droperidol, of which Droperidol is the agent most commonly in use. The clinical efficacy of Droperidol in a dose range of 0.625 to 1.25 mg IV for adults, before the end of surgery has been well established. Before the FDA issued a “black box” warning on the use of Droperidol, it has been widely used in the prevention and management of PONV as a effective and a cost-efficient anti-emetic. The 2001 FDA ‘‘black box’’ warning for droperidol, highlighted reports of severe cardiac arrhythmias (eg, torsades de pointes) and rare cases of sudden cardiac death. This warning resulted in a caused a precipitous decline in Droperidol use, but despite this decline in its use, many experts and anaesthesia providers still believe that the warning was not justified, and that droperidol remains a safe, effective, and economical feasible anti-emetic. This is because of the fact that these cardiac side-effects was extremely rare, and was limited to high risk patients for example with pre-existing QT- prolongation where Droperidol was used in very high dosages of 2,5 – 5 mg. The only proof that resulted in this highest degree of FDA warning was 10 reported cases over a thirty year period of droperidol use. Droperidol has been found to be a potent blocker of rapid component of the delayed rectifier K current (Ikr) which is the main re-polarizing channel in human myocardial conduction tissue, encoded by human ether a go-go related gene (HERG). Mutations of this gene are involved in congenital long QT syndromes and may also be implicated in anti-emetic induced moycardial dysrythmias.

Using this drug at such large dosages is unnecessary, as it’s anti-emetic efficiency have been well proven in the lower doses. Also, all the other side effects, such as sedation, is also less common in the lower dosage ranges. This FDA warning also recommended that all elective surgery patients who received Droperidol should be placed on continuous electro-cardiographic monitoring for up to 2 to 3 hours following its administration. This recommendation limits its usefulness during short surgical procedures as well as in the ambulatory setting. At the low doses (0,625mg-1,25mg) that Droperidol are recommended for PONV prophylaxis and treatment, evidence of Droperidol-induced cardiac adverse events, in particular torsades de pointes is completely lacking.

The IMPACT trial, a large clinical trial of over 5000 patients, found droperidol equally effective as ondansetron and dexamethasone in the reduction of PONV risk when used as a prophylactic. A meta-analysis on this subject was done by Leslie and colleagues who compared the safety profiles of the 5-HT3 antagonists and dexamethasone with droperidol and found that all three drug classes were well tolerated and had comparable safety profiles, even when used in combination. Accordingly, there has been an increased interest in haloperidol as an anti-emetic. Haloperidol has been used primarily as a potent anti-psychotic agent in the treatment of psychiatric patients. Haloperidol has a faster onset of anti-emetic action but despite its longer half-life compared to Droperidol, its clinical effect does not last equally long. This may be due to its weaker binding affinity to the D2 receptor, making it a less

effective dopamine antagonist, compared to drugs like Droperidol. In a large meta-analysis of clinical trials findings conducted from the early 1960's till the late 1980's, is was found that haloperidol in the dose range of 0.5 to 4 mg in adult patients was an effective anti-emetic for established PONV when compared to the placebo. These studies have shown a NNT of 3.2 to 5.1 patients for the effective treatment of vomiting over the first 24 hours postoperatively. In a smaller study of non-smoking, female patients it was found that Haloperidol 2 mg IV was as effective as Ondansetron 4 mg IV in the prevention of early PONV for the first 24 hours postoperatively. It was also noted that no QTc prolongation was observed in the group that was treated with Haloperidol. Similar studies have also confirmed that no QTc prolongation was observed in the Haloperidol treatment group and it was suggested that haloperidol at a dose of 1mg IV was similar to 4 mg ondansetron via the intra-venous route. It was found that Haloperidol was only effective as an anti-emetic in the but both medications were only effective anti-emetics relative to placebo in the early postoperative phase (0–2 hours). More recent studies by Rossouw and colleagues demonstrated the superior anti-emetic efficacy of haloperidol over placebo as well as the increased efficacy of haloperidol with ondansetron over ondansetron alone. It is recommended that further studies should be done to determine the optimal dosing, timing, and safety profile of Haloperidol before it can be used in regular clinical practice, either as a prophylactic or treatment option.

2. Phenothiazines

The phenothiazines, which include promethazine, chlorpromazine and prochlorperazine, are some of the agents in this class that are commonly used as anti-emetics. It should be noted that although these agents have been used widely in the past, that their use have also fallen out of favour due to the high incidence of adverse effects that are associated with them. Some of the more common side effects may include sedation, restlessness, diarrhoea, agitation, central nervous system depression. They may also potentially cause some rarer and more severe side-effects and this may include extra-pyramidal effects, hypotension, the neuroleptic syndrome as well as supra-ventricular tachycardias. Promethazine 12.5 to 25 mg IV given at the induction of surgery, and prochlorperazine 5 to 10 mg IV given at the end of surgery is some of the drug and dosage selections that have been shown to be effective as anti-emetic agents. These drugs have also shown to be more effective when combined with ondansetron. In a retrospective review it has been suggested also that lower dosage ranges should be used to limit side effects especially where Phenothiazines are used as additive agents along with other anti-emetics. Promethazine at a low dose of 6.25 mg may be more effective than a second dose of ondansetron as rescue treatment for the treatment of PONV in patients who have failed previous ondansetron prophylaxis. Since the development of newer, more receptor specific agents with better side effect profiles, it will be difficult to recommend any of the Phenothiazines as first-line anti-emetic agents.

3. Benzamides

The most commonly used anti-emetic in this group is Metoclopramide. It is a procainimide derivative that blocks D2 receptors both centrally at the Chemoreceptor trigger zone and Area Postrema, as well as peripherally in the gastrointestinal tract. Metoclopramide also increases lower oesophageal sphincter tone and thereby promotes gastric motility and gastric emptying. This pharmacological action of Metoclopramide make it very useful for the prevention of delayed gastric emptying as caused by opioids as well as before a rapid sequence induction. A quantitative systematic review which investigated various regimens of metoclopramide found no significant anti-nausea effect, with weak anti-vomiting properties. It showed a NNT of 9.1 to prevent early vomiting in adults, and an NNT of 10 to prevent late vomiting in the same adult population group. In children, the NNT to prevent early vomiting was 5.8, but with no significant late anti-vomiting effect. A more recent double-blinded study in children undergoing tonsillectomy failed to show any benefit with the use of Metoclopramide, and recommended ondansetron as the superior drug, both in terms of pharmacological effect and side-effect profile, for control of POV. Given the lack of evidence in anti-emetic efficacy, metoclopramide is not currently recommended for the use of PONV, by most authorities and experts.

Anti-Histamines

The anti-emetic properties of antihistamines such as diphenhydramine, dimenhydrinate, cyclizine, doxylamine and promethazine are derived from their blockade of the histamine H1 receptor at multiple sites. The NTS, at the vomiting centre, and vestibular system; are densely populated with H1 receptors and blockage of these receptors exerts a strong anti-emetic action even though they have little direct action at the Chemoreceptor trigger zone (CTZ). These drugs therefore act by blocking acetylcholine receptors in the vestibular apparatus and histamine receptors in the nucleus of the solitary tract, with little effect on any receptors in the chemoreceptor trigger zone.
Their anti-cholinergic activity is responsible for most of their common side effects including sedation, dry mouth, blurred vision, and urinary retention. Although generally inexpensive and readily available, the use of antihistamines in PONV has not been well studied. In a meta-analysis of 18 controlled trials, Kranke and colleagues reported that prophylactic Dimenhydrinate reduces PONV in adults and children up to 48 hours after surgery, with a recommended dose of 1 mg/kg IV. There have been few studies of Dimenhydrinate that specifically compare it with other anti-emetics, and therefore the dosage, timing, and side effect profiles have not been fully established. Doxylamine in combination with Pyridoxine (Diclectin) has been shown to reduce the incidence of POV in women undergoing laparoscopic tubal ligation.

Cholinergic Antagonists

The anti-cholinergic agents are among the oldest anti-emetics agents available and are still widely used in common clinical practise. Both scopolamine (hyoscine) and atropine are potent antagonists of muscarinic and cholinergic receptors in pons as well as the cerebral cortex. These receptors are integral in the emetogenic pathway. Scopolamine blocks impulses from the vestibular nucleus to higher centres in CNS, reticular activating formation and vomiting centre. It also has peripheral effect causing a decrease in salivary and gastric secretions a well as an anti-spasmodic action. Apart from its use as anti-emetic, it is also a very effective treatment of motion sickness, it cause typical anti-cholinergic side effects, and it should be used with caution in the elderly.

It should be noted that atropine has a much weaker anti-emetic effect compared to other anti-cholinergic and should not be used routinely as a anti-emetic in the postoperative period because of its side-effect profile and in particular to its cardio-vascular side effects as well as central anti-cholinergic effects. Scopolamine is the most commonly used anti-cholinergic for the prevention and treatment of PONV, and is also available in a trans-dermal patch, which is non-painful and easy to administer. Most studies investigating scopolamine use for PONV prophylaxis or treatment have made use of the trans-dermal scopolamine (TDS) patch, which releases 1.5 mg of scopolamine over 3 days. In a double-blinded, placebo-controlled study, pre-operative trans-dermal scopolamine (TDS) patch was compared to intravenous ondansetron 4 mg or droperidol 1.25 mg administered before the end of surgery. The investigators found that pre-medication with TDS patch were as effective as ondansetron or droperidol in the prevention of both early and late PONV/PDNV. It should be noted that the group who received the TDS patches had a greater risk of side effects, especially anti-cholinergic side effects such as dry mouth and blurred vision. These findings correlate with earlier systematic reviews where it was found that although the TDS patch is an effective anti-emetic, the high rate of anti-cholinergic side effects associated with its use may limit its usefulness as a single agent or first-line anti-emetic agent. It was found that the NNT for the prevention of POV was 5.6 but the NNH was 5.6 for visual disturbances, 12.5 for dry mouth, and 50 for dizziness.

Scopolamine may therefore be more useful as an adjunct with other anti-emetics agents. In a trial of out-patient plastic surgery patients at high risk for PONV, it was found that the group who have received a pre-operative TDS patch in addition to intra-operative ondansetron had a statistically significant reduction in PON between 8 and 24 hours in comparison with the group who only received

a placebo patch with ondansetron. In another study it was noted that the incidence of adverse effects, including anti-cholinergic effects was not statistically different between the 2 groups, while patient satisfaction in the TDS patch group was significantly higher, suggesting that scopolamine might be a safe and effective adjunct in the management of PONV, especially when used in combination with other drugs for example ondansetron.

Propofol

The exact mechanism how propofol exerts its anti-emetic activity is still unclear. The mechanism may be due to the action of the drug itself, or due to the fact that Volatile anaesthetics, which are a know precipitant of PONV, have been avoided. Some clinicians claim to have success by using small amounts of propofol in the sedative dosage range, in recovery as a rescue treatment in patients with established PONV, but more studies should be done to validate this practise.

It has been observed that patients who receive propofol for induction as well as Propofol TIVA for maintenance tend to have less PONV. This observation has led to many studies and has been supported by several meta-analyses. In one study Gupta and colleagues compared postoperative outcomes under inhaled and intravenous anaesthetic techniques and used NNT to prevent nausea and vomiting in hospitalized and ambulatory patients as end points. They found that maintenance with a propofol infusion resulted in a decreased incidence of PONV and PDNV over inhaled anaesthetics, with NNT of 8.6 and 11.2 for PON and POV for in-patients respectively, and NNT of 12.5 and 10.3 for post-discharge nausea and vomiting, respectively. A clinical trial of over 2000 surgical patients in the Netherlands found that propofol total intravenous anaesthesia (TIVA) resulted in a significant reduction of PONV compared with isoflurane-nitrous oxide anaesthesia; with an NNT of 6.1.

Recent studies have suggested that TIVA alone may not be an optimal approach for PONV prophylaxis, but should rather been used as part of a multi-modal prevention strategy with pharmacological agents especially in high risk patient population groups. In a small randomized trial, White and colleagues found that although there were no significant differences in early PONV outcomes between patients given dolasetron prophylaxis compared with patients who were given propofol-based TIVA for maintenance. Unfortunately they found that PDNV was significantly more common in the group of patients who received Propofol TIVA for maintenance of Anaesthesia. The investigators suggest that although TIVA may be similar in efficacy to dolasetron for early PONV prophylaxis, its effects may be too short-lived to offer any protection against late PONV. Propofol induction and maintenance is therefore not an ideal prophylactic strategy for the prevention of PDNV, since it doesn't offer protection against late (> 24 hours) post-operative nausea and vomiting.

Over the past several years as experience with TIVA and TCI techniques have increased and costs have decreased, the use of TIVA with propofol has become a more popular anaesthetic option in the ambulatory surgery. One of the greatest limiting factors for increased use of TIVA continues to be cost, especially in health care systems with limited resources where cost plays a major role in determining the anaesthetic options available. Economic analyses by various mathematical models have suggested that routine use of TIVA for PONV prophylaxis is generally not cost-effective when compared with a volatile anaesthetic combined with anti-emetic prophylaxis. Propofol-based TIVA is an important prophylactic option especially in high-risk patients, as part of a multimodal management strategy which includes other known anti-emetics as pharmacological agents.

NOVEL ANTIEMETIC THERAPIES: Neurokinin-1 Antagonists

The neurokinin-1 receptor antagonists (NK1 RAs) are a new class of anti-emetic drugs that competitively inhibit the binding of substance P, a neuro-peptide released from enterochromaffin cells. Substance P plays an important role in emesis as a ligand for neurokinin-1 receptors, which are located in the gastrointestinal tract as well the area postrema. The NK1 RAs are believed to suppress nausea and vomiting by acting centrally on the neurotransmission between the NTS and CPG. In has been postulated that substance P may be the agent involved in triggering the final, common pathway of the emetic response. These agents may also act peripherally to block NK1 receptors in the vagal terminals of the gastro-intestinal tract. The drugs will therefore by this mechanism decrease the magnitude of the emetogenic signals sent to the CPG, to further lessen the emetogenic response.
It was developed due to the pursuit to develop a pharmacological agent that will be able to depress the activity of neurones within the more distal medullary emetic pathway. In the quest to develop a highly effective broad spectrum anti-emetic, pharmocologists shifted their focus away from the well studied serotergenic neurotransmitter systems to the tachykinins. These agents have been identified by immunohistology to be involved in the dorsal vagal complex, an area essential in evoking vomiting. The anti-emetic action of the tachykinin, substance P, within the medullary emetic circuitry was demonstrated in the ferret using resinferatoxin, an ultra-potent capsaicin analogue. Substance P exhibited anti-emetic properties against both centrally and peripherally acting emetic stimuli. It was postulated by Andrews et al., that resinferatoxin exerts its anti-emetic activity by depleting substance P at a central site in the emetic pathway. After this discovery, potent and highly selective non-peptide NK1 receptor antagonists, that cross the blood brain barrier and antagonize the central effects of substance P, were developed as research and therapeutic tools. Since these publications, the physiological role of Substance P in emesis has become well established. Tachykinins are part of the group of neuropeptides with the ability to promote contractile actions in smooth muscles. They share a common C-terminal amino-acid sequence with compounds like Substance P (for pain) and Neurokinin A and B (NKA and NKB). They exert their biological activity through 3 G –protein coupled receptor subtypes, identified as NK1, NK2, and NK3. Since substance P is believed to exert a key role within the central emetic circuitry, selective NK1 receptor antagonists are expected to express potent anti-emetic activity. The nucleus tractus solitary lying ventrally to the area postrema in the subnucleus gelatinosus has been identified as a good candidate for the site of action of NK1 receptor antagonists. Extensive substance P like immunoreactivity has been identified in this region and the tachykinins have been proposed as transmitters in vagal afferents. The NK antagonist's role in the emetic pathway is unique due to its central role in a potential final common pathway. This makes the prospect of a broader spectrum anti-emetic activity, that acts outside of the conventional neurotransmitters pathways, for the first time possible. It should be stressed that the efficacy of NK 1 receptor antagonists in the treatment of nausea and vomiting will be enhanced, when used in combination with other anti-emetics from different classes.

The first NK1 RA to be approved by the FDA was Aprepitant (Emend), and was originally licensed for the treatment of chemotherapy-induced nausea and vomiting. The first clinical trial to study the efficacy of Aprepitant in PONV was a multi-centric, double-blind study conducted by Gan and colleagues. They found that pre-operative Aprepitant, both 40 mg and 125 mg orally were equivalent to preoperative Ondansetron 4 mg IV in terms of nausea control, the use of rescue anti-emetics as well as clinical resolution rates. However, the study also found that Aprepitant was superior to Ondansetron for the prevention of vomiting in the first 24 and 48 hours, with no vomiting in 90% of patients in the Aprepitant 40 mg group and 95% of the Aprepitant 125 mg group. This is in comparison to a success rate of no vomiting for 74% of patients in the Ondansetron group during the first 24 hours. A follow-up study by the same group in an international population confirmed that Aprepitant was superior to Ondansetron for incidences of no vomiting during the first 24 and 48 hours, and also found that peak nausea scores were lower in patients receiving either dose of Aprepitant. A post hoc analysis of the pooled data from both studies found that in the 24 hours after surgery, Aprepitant 40 mg was slightly more effective than Ondansetron in terms of no nausea (39.6% vs 33.1%), no

vomiting (86.7% vs 72.4%), no nausea and no vomiting (38.3% vs 31.4%) as well as no use of rescue anti-emetic drugs (37.9% vs 31.2%). The study group noted that the 125 mg dose was similar to or even slightly less effective than the lower dose. This observation led to the recommendation and approval of a preoperative dose of 40 mg Aprepitant for PONV prophylaxis. NK1 RAs are safe and well tolerated, with the most common side effects being minor problems like dizziness, asthenia, diarrhoea and hiccups. Although further studies are needed to establish its exact role and indications in clinical practice, it is clear that the NK1 RAs will offer many potential benefits for the management of PONV as a highly efficient anti-emetic with a favourable side-effect profile. Some of its clinical applications will be its use as an alternative prophylactic or rescue treatment for patients who have failed prophylaxis or treatment with the conventional anti-emetics in other classes. Aprepitant may be particularly useful in the ambulatory setting, it is available in both the oral form as well as a recently approved intravenous form (fosaprepitant) that are useful as rescue treatments for established PONV. Although clinical trials with the intravenous formulation have not been conducted in the PONV setting, its availability will promote the use of Aprepitant in the peri-operative setting.

Opioid Antagonists

Peri-operative opioid use has long been known to increase the risk of PONV by decreasing gastric motility and delaying gastric emptying via the inhibition of central mu-opioid receptors. The use of central-acting opioid receptor antagonists, such as naloxone, have been suggested to possibly exert an anti-emetic effect. Preliminary studies have found that low-dose naloxone (0.25mg/kg/h) is effective in reducing the incidence of PONV compared with placebo in both adults and children. A recent small scale study of patients undergoing knee replacement surgery found that epidural sufentanil containing low-dose naloxone was more effective in reducing the incidences of PONV when compared with sufentanil without naloxone. It should be noted that this therapeutic option have not been thoroughly investigated, and clinical trails should be conducted before use can be recommended.

NON-PHARMACOLOGIC TECHNIQUES

Since no single pharmacologic therapy is completely effective for PONV prophylaxis, non-pharmacologic techniques have recently been explored as reasonable adjuncts to anti-emetic drugs. Of all the non-pharmacologic techniques, dry needling is one of the most recognised, studied and accepted forms of treatment of PONV. The mechanism of action in the prevention of nausea and vomiting is not entirely clear, but it have been postulated that may stimulate and activate A-b and A-d fibres to modulate neurotransmission in the dorsal horn in the spinal cord. Alternatively, influencing the release of endogenous opioids and inhibit gastric acid secretion. Most data about dry needling in PONV have examined the use of a point located 4cm proximal from the wrist crease between the flexor carpi radialis muscles and the palmaris longus tendon. A recently revised Cochrane database review of 40 randomized controlled trials in the use of dry needling found it to be effective in the prevention of PONV, with NNT of 5 and 11 for both nausea and vomiting, depending on the baseline risk for nausea and vomiting for the specific patient group (30% vs 70% baseline risk). There are several variations on the traditional technique for example the use of trans-cutaneous electrical stimulation. These treatment options may also be of particular benefit in the ambulatory setting, as it is easy to use, could be applied rapidly, could be performed by physiotherapists and do not require special training. Another benefit is its favourable side effect profile compared with pharmacologic techniques, making it a reasonable adjunct to anti-emetic drugs. In a large prospective survey it was found that there were no serious adverse events due to the use of dry needling and the risk of adverse events was 14 per 10,000 treatments, with the most common being mild side effects such as fainting or treatment failure with exacerbation of symptoms.

THERAPIES LACKING SUFFICIENT EVIDENCE

Several pharmacological and supplementary therapies that have previously been used was recently found to lack sufficient evidence to be recommended for routine management of PONV and PDNV. Although the use of supplemental oxygen in the reduction of the incidence of PONV was previously thought to be an effective treatment option, these findings have not been confirmed by subsequent studies. A systematic review of 10 trials where supplementary oxygen was used as an adjunct therapy, reported that the relative risk of overall PONV in patients receiving 80% FiO_2 was 0.91, and it was therefore concluded that supplemental oxygen did not reduce the incidence of PONV. In one randomized trial of women receiving ambulatory laparoscopy gynaecological surgery, no significant differences in PONV or anti-emetic rescue use was found between women receiving 80% supplemental oxygen and those patients who received 30% oxygen in the control group.
The use of cannabinoids, like nabilone and dronabinol in PONV management has also not been confirmed in clinical studies as an effective therapy and are lacking evidence. In one systematic review of 30 trials evaluating cannabinoids in the setting of chemotherapy-induced nausea and vomiting, it was found that dronabinol had superior anti-emetic activity when compared with phenothiazines. However, the analysis failed to demonstrate any statistically significant improvement in anti-emetic efficacy between dronabinol and placebo, and therefore further studies have been recommended. The commonly reported unpleasant side effects of most cannabinoids, for example dysphoria, depression, and hallucinations, make this therapy an unlikely option for regular use in clinical practice.

Despite the longstanding, traditional use of ginger (Zingiber officinale) as an anti-emetic therapy, its use in the setting PONV management could not have been validated as an effective treatment option. This was confirmed by a systematic review of 6 randomized controlled trials where no benefit in the use of ginger was concluded. This was also confirmed in a relatively large placebo-controlled trial of laparoscopic gynaecological surgery where it was found that ginger failed to reduce the incidence of PONV.

MANAGEMENT STRATEGY

As no single intervention can completely prevent or treat PONV, it is important to formulate multimodal approaches to minimizing the risks of PONV to the individual patient as well as to maximize the clinical efficacy of the interventions chosen. There is no clear, universally excepted protocol or formula for the prevention and management of PONV, and its management should be individualized for every patient. Any effective management strategy should consider the following points:

(1) Assessment of risk for developing PONV and baseline risk reduction.
(2) Prophylactic agents and options available and possible drug side-effects
(3) Cost-effectiveness of prophylactic or treatment option,
(4) Whether combination therapy is indicated and best drugs available
(5) Rescue treatment in the event of failed prophylaxis or established PONV.
(6) Management of difficult and high risk patients.

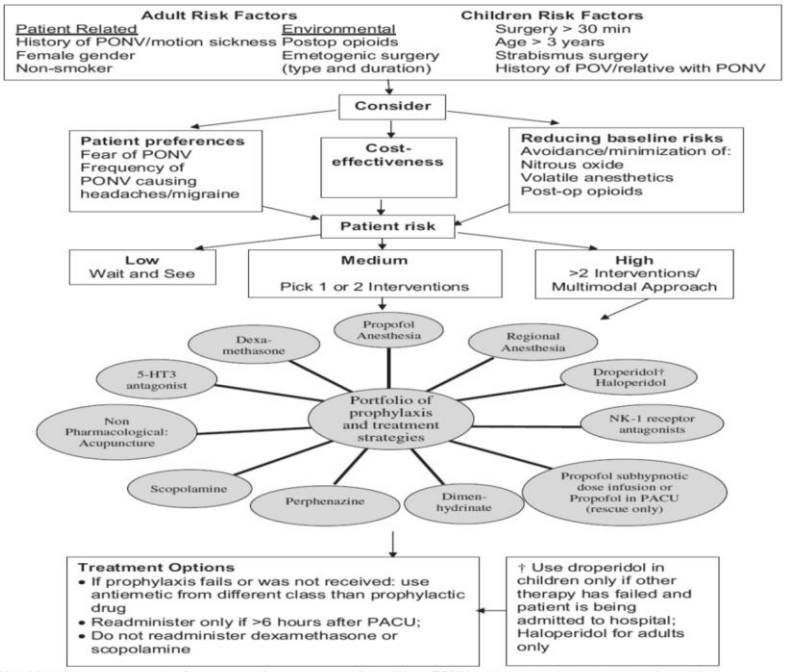


Figure 4. Algorithm for management of postoperative nausea and vomiting. PONV = postoperative nausea and vomiting.

1. Assessment of Risk and Baseline Risk Reduction

Most guidelines on PONV agree that not all patients should receive PONV prophylaxis. In general, patients who are at a small risk for PONV are unlikely to benefit from prophylactic therapy and would be put at unnecessary risk from the potential side effects of these drugs. Thus, prophylaxis should be reserved for those patients at moderate to high risk for PONV. In should be noted when using these guidelines, that the sensitivity and specificity of the various risk scoring systems are not 100%, but only approximately 70%, and therefore always have a degree of uncertainty. Clinicians using these guidelines to determine the level of risk for their patients should decide when prophylaxis would be appropriate, depending on their own patient population as well as institutional norms. A 20% incidence of PONV may constitute an acceptable small risk in some institutions, whereas it may be considered a moderate risk in an ambulatory surgery setting warranting prophylactic intervention. The decision to give anti-emetic prophylaxis should always involve discussion with the patient explaining best available evidence as well as therapies available.

As discussed earlier, the Apfel score may be a useful clinical tool in assessing individual patient risk. After taking these patient factors as well as the surgical risk factors into consideration, the patient's overall risk for PONV can be determined. Our anaesthesia technique should be tailored to minimize the patient's baseline risk. This will involve all aspects of the anaesthetic for example our choice of induction and maintenance agents, the use of anti-emetics, and reversal of NMBA where all possible emetogenic precipitants should be avoided. One example where anaesthetic technique plays a big role would be the appropriate use of a regional anaesthetic or neuro-axial block over a general anaesthesia which can significantly reduce a patient's risk of PONV. In high-risk patients, avoidance of volatile anaesthetics and nitrous oxide through the use of TIVA with propofol may be appropriate. Two meta-analyses have found that avoidance of nitrous oxide reduces the risk of PONV, with an NNT of 13 to prevent early and late vomiting. It should be noted that in studies on patient groups with a high baseline risks for the development of PONV, the investigators found that the NNT was about 5 - 13, whereas in studies in which baseline risk was below this level or average, omitting nitrous oxide had no effect on outcome. These studies and observation emphasizes the importance of assessing a patient's risk factors and individual baseline risk for PONV as well as suitability for anti-emetic prophylaxis before formulating an appropriate approach for the management of PONV.

A separate systematic review by Tramer and colleagues found that high-dose neostigmine (>2.5 mg) was associated with increased risk of PONV. They concluded that reduction of the use or dose of neostigmine would be another strategy to decrease PONV risk and neuro-muscular blockage and reversal could possibly be avoided in certain high risk patients. Baseline risk reduction may also be achieved by minimizing the use of intra-operative and postoperative opioids with non-opioid adjuncts, such as simple analgesics, non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, and local anaesthetics. Regional anaesthetic blocks, local anaesthetic wound infusion catheter devices as well as PCA opioid administration may also reduce the total post-operative opioid use by patient in the recovery period following major surgery. Minimization of neostigmine dosage has since been removed from the list of strategies to reduce baseline risk as new evidence did not find this to be helpful. However, more recent data disputed the clinical importance of neostigmine's effects on PONV. Following the analysis of systematic reviews of randomized control trails on minimization of neostigmine dosage the recommendation has been removed from the 2014 guidelines lists of strategies to reduce the baseline risk. Systematic reviews show that supplemental oxygen had no effect on nausea or overall vomiting, although it may perhaps reduce the risk of early vomiting. As a result, supplemental oxygen has also been removed from the list of recommendations to reduce baseline risk. In children, subhypnotic doses of propofol infusion in combination with an antiemetic significantly reduce incidence of PONV.

To summarise, strategies recommended to reduce baseline risk as recommended by the 2014 guidelines include the following:

1. The avoidance of general anesthesia by the use of regional anesthesia;
2. Preferential use of propofol infusions;
3. Avoidance of nitrous oxide;
4. Avoidance of volatile anesthetics;
5. Minimization of peri- operative opioids;
6. Adequate hydration.

Table 2. Strategies to Reduce Baseline Risk

Avoidance of general anesthesia by the use of regional anesthesia[11,52] (A1)
Use of propofol for induction and maintenance of anesthesia[47] (A1)
Avoidance of nitrous oxide[43,54,55] (A1)
Avoidance of volatile anesthetics[47,2121,47] (A2)
Minimization of intraoperative (A2) and postoperative opioids[9,21,25,54,56–58] (A1)
Adequate hydration[261,325](A1)

GA = general anesthesia.

g.

Prophylactic agents and options available and possible drug side-effects

According to the 2003 and 2007 guidelines, 3 classes of drugs have been proven clinically effective as prophylactic agents. This includes the serotonin antagonists, the butyrophenones like Droperidol and the steroids, as it was validated by randomized controlled trials, which are considered to be the strongest level of evidence. Clinically approved drugs that are new or have recently being approved after further studies since the last guidelines includes newer serotonin receptor antagonists, for example Palonosetron, as well as the Neurokinin receptor antagonist, for example aprepitant. Most prophylactic guidelines recommend the administration of PONV prophylaxis using 1 to 2 interventions in adults at moderate risk for PONV.

The full list of clinically approved drugs for prophylactic use include the following:

1. Serotonin receptor antagonists: Ramosetron and Palonosetron;
2. NK-1 receptor antagonist: Aprepitant, Casopitant, and Rolapitant;
3. Corticosteroid: methylprednisolone;
4. Butyrophenone: Haloperidol
5. Antihistamine: Meclizine.

Concerns have been raised regarding the effects of the first generation 5HT3 receptor antagonists on the QTc interval. Dolasetron is no longer marketed in the United States because of its risk of QTc prolongation and torsade de pointes. However, the use of Droperidol in combination with a 5HT3 receptor antagonist, such as Ondansetron, did not increase the risk of QT prolongation. Recent studies raised concerns about the effect of dexamethasone on postoperative infection and blood glucose levels 6 to 12 hours postoperatively.
The recommended pharmacologic anti-emetics for PONV prophylaxis in adults include the 5-hydroxytryptamine (5-HT3) receptor antagonists (Ondansetron, Dolasetron, Granisetron, Tropisetron, Ramosetron, and Palonosetron), neurokinin-1 (NK-1) receptor antagonists (Aprepitant, Casopitant, and Rolapitant), corticosteroids (dexamethasone and methylprednisolone), and butyrophenones (Droperidol and Haloperidol), antihistamines (Dimenhydrinate and Meclizine), and anticholinergic (transdermal scopolamine). While PONV prevention is recommended in a subset of patients, current evidence does not support giving prophylactic anti-emetics to all patients who undergo surgical procedures. However, with safer drugs and more inexpensive generics becoming available, properly conducted cost-effectiveness studies need to be done and may possibly support the universal use of prophylactic anti-emetics despite the potential side-effects. Ondansetron 4 mg, Droperidol 1.25 mg, and dexamethasone 4 mg were equally effective, and each independently reduced PONV risk by approximately 25%.

Cost-effectiveness of prophylactic or treatment option,
The cost-effectiveness of PONV prophylaxis is an important consideration in formulating a management strategy, and the availability of anti-emetics may differ in various health care settings. It is also very difficult to determine and compare the cost-effectiveness of various anti-emetic therapies. The models that analyse cost-effectiveness vary widely in terms of the costs they take into account, as well as the criteria they use in drawing conclusions. It is also important to bring into consideration other costs apart from the cost of the anaesthetic drugs and anti-emetics used. Inadequate prevention and management of PONV will increase the time period that these patients will stay in the recovery unit. Recovery units are densely staffed with highly skilled nursing personal, expensive monitors and sometimes additional anaesthetic assistance is required and these factors all contribute hugely to healthcare costs. The inability to discharge ambulatory patients from hospital as well as re-admission of these patients also plays a huge role in resource cost management.

A cost-effectiveness study by Hill and colleagues compared Ondansetron 4 mg, Droperidol 0.625 mg, Droperidol 1.25 mg, and placebo, and determined that the use of any of the 3 anti-emetic prophylactic options was more cost-effective and achieved higher patient satisfaction rates when compared with placebo in high-risk patients. The use of decision-analysis models in high risk patient groups have shown that prophylactic anti-emetic therapy was more cost-effective than no prophylaxis followed by subsequent rescue therapy. In one such study Dolasetron or Droperidol was used as prophylactic agents. Other studies have suggested that treatment of PONV may be more cost-effective than prophylaxis for patients at both low (30%) baseline risk, due to the high efficacy of Ondansetron for the treatment of established PONV. Despite conflicting data, it seems that studies comparing anti-emetic therapy with placebo tend to find that using an anti-emetic is more effective than placebo and preferable to no prophylaxis. It remains unclear which anti-emetic therapies are most cost-effective and what doses of medication are most cost-effective. Low cost anti-emetic medication with proven efficiency used as prophylactic and treatment option will enable cost saving. It seems that PONV prophylaxis may not be cost-effective for all patient risk groups. This also stresses the importance of doing risk assessments to enable the identification of high risk patients who would benefit from prophylactic medication. Future studies have been encouraged to enable the development of cost effective management guidelines in hospitals. This will enable reporting of cost-effectiveness as a ratio of resources available to enable comparison of interventions in terms health consequences. It should be stressed that the importance of patient satisfaction should always be key and may also influence financial consequences.

Combination Therapies and Multimodal Prevention

Because there are no single anti-emetic agent that are completely effective in preventing or treating PONV, the concept of combination therapy using multiple agents has become particularly appealing. A good multimodal management approach will include the following components:

1. Pre-operative anxiolysis
2. Use of regional anaesthesia
3. Use of Propofol for induction and maintenance (TIVA) of anaesthesia
4. Avoidance of volatile anaesthesia
5. Avoidance of Nitrous oxide
6. Minimization of intra- and postoperative opioid use
7. Use of Opioid sparing analgesics
8. Minimization of high dose neostigmine reversal
9. Prophylactic anti-emetics (Mono- or combination therapy)
10. Non-pharmacological methods such as dry needling.

As noted earlier, the IMPACT trial found that Ondansetron 4 mg IV, Dexamethasone 4 mg IV, and Droperidol 1.25 mg IV are equally effective as single agents for the prevention of PONV. Due to their established efficacy and widespread use, these 3 agents are the most commonly studied anti-emetics used in combination therapy. The IMPACT trial examined the effect of various combinations of the 3 therapies, and determined that each of the 3 anti-emetics acted independently, such that combinations of any 2 or 3 of them would reduce the risk of PONV in an additive manner. The IMPACT trial was developed to determine the most efficient multimodal prophylactic regimen and has shown that given prophylactic combinations of anti-emetics and anaesthetic techniques, each therapeutic option of Ondansetron, dexamethasone, droperidol and TIVA reduced the risk of PONV by a quarter. Moreover, it demonstrated that all interventions acted independently of each other and that the action of the drugs was independent of the patients risk in reducing the incidences of PONV.

These findings are similar to other meta-analyses and systematic reviews, which have reported that combinations of 5-HT3 RAs and either Droperidol or Dexamethasone are equally safe and effective in reducing PONV. A cost-effectiveness analysis by Pueyo and colleagues compared each of the possible 2-drug combinations of Ondansetron, Droperidol, and Dexamethasone. The investigators found the Ondansetron and Droperidol combination to be less expensive than, but as effective as the Ondansetron and Dexamethasone combination. They also found the Ondansetron and Droperidol combination to be more effective than Droperidol and Dexamethasone, but at a slightly increased in cost. The evidence would suggest that combination therapy using any of these 3 drugs would be a reasonable strategy for decreasing PONV risk in moderate and high risk patient groups. In general, combination therapy can be used as a single intervention for patients at moderate risk for PONV. For patients at high risk of PONV, combination anti-emetic therapy should be used in conjunction with other anaesthetic, pharmacologic and non-pharmacological techniques to further reduce the risk of PONV. This approach is often labelled ‘‘multimodal management’’ or ‘‘balanced anti-emesis,’’ as it combines multiple therapeutic options to minimize baseline risk and maximize anti-emetic efficacy. An example of one of these multimodal approaches is the technique used by Scuderi and colleagues, who used preoperative anxiolysis, aggressive hydration, supplemental oxygen, droperidol and dexamethasone at induction, ondansetron at the end of surgery, TIVA with propofol and remifentanil, and ketorolac, with no use of nitrous oxide or neuromuscular blockade. This multimodal approach achieved a clinical resolution rate of 98% compared with 76% achieved with anti-emetic monotherapy using ondansetron 4 mg, and a 59% CR rate on placebo. The researchers did note patient satisfaction scores were much higher in the patient groups that received anti-emetic prophylaxis than those receiving placebo and rescue anti-emetic therapy. Habib and colleagues have compared 3 regimens: a multimodal management strategy, which included TIVA with propofol, ondansetron, and droperidol; a combina- tion therapy with ondansetron and droperidol, and receiving isoflurane and nitrous oxide (no TIVA); and TIVA with propofol only. The CR rates at 24 hours were 80% for the multimodal approach, 63% for the combination therapy group, and 43% for the TIVA-only group. In slight contrast to the study by Scuderi and colleagues, patient satisfaction scores were found to be highest for the multimodal approach, over both combination therapy with inhaled anaesthetics or TIVA only.

Rescue Treatment and Management of PDNV

Despite our best efforts including baseline risk reduction and anti-emetic prophylaxis, some high risk patients' peri-operative course will still be complicated by PONV or PDNV. Before initiating rescue anti-emetic drugs, patients must be fully assessed and other factors that may possibly contribute to PONV should be considered and managed. This may include unaddressed pain, excessive opioids or mechanical reasons, for example blood in the throat or stomach, abdominal obstruction or gastric inflation. In general, patients who have not previously received anti-emetic prophylaxis should be given a serotonin antagonist, while patients who have already received prophylaxis should be given a rescue anti-emetic from a different treatment class than the prophylactic drug. One should also consult the anaesthetic document and treatment charts to establish whether anti-emetic prophylaxis was given and if so, what agents and dosages were given.
Unlike PONV prophylaxis, there are relatively few trials that have studied treatment options for established PONV. In one systematic review, different anti-emetic regimens were evaluated and where Serotonin antagonists were used as rescue treatment for established PONV it was found that the NNT was about 4 to 5, enablting resolution of symptoms. Treatment doses of serotonin antagonists for established PONV are generally smaller than those needed for prophylaxis: Ondansetron 1 mg or Granisetron 0.1 mg have proved to be very efficient. Even though, as an anti-emetic rescue, the dose of 1 mg Ondansetron has been shown to be as effective as a 4 mg dose, , most clinicians still tend to use the 4 mg dose in clinical practice. It should also be noted that those patients who received a serotonin antagonist for prophylaxis, will not receive further benefit when given a repeat doses within 6 hours after the initial prophylactic dose. Alternatives to serotonin antagonists should be used and agents recommended include dexamethasone 2 to 4 mg, droperidol 0.625 mg, or promethazine 6.25 to 12.5 mg. Dexamethasone and transdermal scopolamine are not commonly recommended as rescue treatment for emetic episodes that occur more than 6 hours postoperatively, because of their longer duration of action.

CONCLUSION

Several guidelines available in the literature can be used as comprehensive, evidence based reference tools for the management of patients at risk for PONV. These guidelines are based on high quality clinical trails as well as consensus among authorities in the field of PONV. It should be noted that not all surgical patients might benefit from anti-emetic prophylaxis, thus, identification of patients who are at increased risk of PONV is imperative.

Although anti-emetic prophylaxis cannot eliminate the risk for PONV entirely, it can significantly reduce the incidence. When developing a management strategy for each individual patient, the drug choice should be based on patient preference, possible side effects and contra-indications as well as the patient's level of PONV risk.

Among the interventions considered, a reduction in baseline risk factors and use of non-pharmacologic therapy are least likely to cause adverse events. PONV prophylaxis should be considered for patients at moderate to high risk for PONV. Depending on the level of risk, prophylaxis should be initiated with mono-therapy or combination therapy using interventions that reduce baseline risk including non-pharmacologic approaches, and anti-emetics with known efficiency. Anti-emetic combinations are recommended for patients at moderate and high risk for PONV. Because the effects of interventions from different drug classes are additive, combining interventions has an additive effect in risk reduction. When rescue therapy is required, the anti-emetic should be chosen from a different therapeutic class than the drugs used for prophylaxis. One may also consider a treatment anti-emetic from a different therapeutic class that will act on a different receptor than the drugs used for prophylaxis, as well as a different mode of administration. For any institution there are significant challenges in implementing a widely accepted and practiced comprehensive PONV prevention

protocol that are based on a detailed patient risk-assessment,. A practical risk assessment, using a more liberal preventive strategy may be a better alternative in a busy clinical environment. Managing PONV risk should become an integral part of our anesthetic assessment and management without causing delays.

The first important step in reducing PONV risk is to reduce baseline risk factors among patients at risk. PONV prophylaxis drug choice in adults should be considered for use as mono-therapy or in combination for patients at moderate risk for PONV. There is increasing evidence that the combination of several potentially beneficial factors (multimodal approach) may lead to an improved outcome. Double and triple anti-emetic combinations are recommended for patients at high risk for PONV. All prophylaxis in children at moderate or high risk for POV should be with combination therapy using a serotonin antagonist and a second drug with a known safety profile, for example dexamethasone. Anti-emetic rescue therapy should be administered to patients who have an emetic episode after surgery. If PONV occurs within 6h after surgery, patients should not receive a repeat dose of the prophylactic anti-emetic. An emetic episode more than 6h after surgery can be treated with any of the drugs used for prophylaxis except dexamethasone, aprepitant, palonosetron and transdermal scopolamine.

SUMMARY

Although awareness has greatly increased over the past several decades and the number of available treatment options has increased likewise, PONV and PDNV remain a common problem in both major and ambulatory surgery. Appropriate management of PONV begins with an assessment of risk and baseline risk reduction, followed by consideration of anti-emetic prophylaxis and appropriate drug selection. Patients who suffer from PONV should be examined and thoroughly assessed, and rescue treatment should be given, generally in a different drug class as what was used for prophylaxis. In patients who are at increased risk, combination therapy or multimodal approaches are recommended in preventing PONV and PDNV. Due to the brief time period that ambulatory surgery patients are under direct medical care, it is of particular importance to recognize and prevent these problems. The value of appropriate administration of longer-acting anti-emetics for example oral Palonosetron or trans-dermal Scopolamine patch, cannot be overstressed. This plays an important role in; the prevention of possible minor and serious complications, maximizing patient satisfaction and ensuring a speedy return to normal activity, all the while aiming to keep health care costs at a minumum. To summarize this, one should always apply the following 3 management steps:\

1. Identify the patients of developing PONV
2. Keep the baseline risk as low as possible by using a balanced anaesthetic approach possibly with propofol TIVA and opioid sparing analgesia and with propofol and when indicated
3. Use a rational anti-emetic prophylactic regime, with possible combination therapy, if needed.

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42

Perioperative Concerns and Considerations for Bariatric Surgery

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South Africans do not have a problem with obesity…doctors in South Africa have a problem with obesity.

The World Health Organisation has declared that the level of obesity internationally is of epidemic proportions, and has initiated the 2025 global vision plan. This aims to curb the increased incidence of obesity internationally. Thus far NO country has shown any reduction in obesity incidence over the past 30 years…this goal is thought to be optimistic. In a large, international study published in Lancet (2014), it was shown that the incidence of obesity internationally had risen by 27.5 % in adults over the preceding 33 years. This differs to the other global pandemics (with intervention): tobacco use and childhood malnutrition for example are both on a clear decline of incidence. There is an associated reduction of life-span of 8 – 10 years (morbid obesity). 3.4 million annual global deaths are as a direct result of obesity (with an even higher attributable rate of obesity-related pathology). Two thirds of the world's obese population live in developing countries! (where the rate of obesity is still on a steady increase).

	Obese women	**Obese men**
United States	32.6 %	30.6 %
South Africa	42 %	13.5 %

South African women are almost 70% overweight! (This too, surpasses the incidence in American women). An obese patient should be viewed and managed with similar concern (physiologically) to a patient with a critical illness.

Weight loss of even ***5 – 10 %*** in the obese patient will: improve impaired glucose tolerance, reduce the effect of type 2 Diabetes Mellitus, improve hypertension, and reduce hyperlipidaemia. The conventional means of weight loss (diet, physical exercise, drug therapy) has been shown to have some effect; this is, however, usually of limited and non-sustained measure. This talk highlights the impact of bariatric surgery as a means of managing the scourge of obesity (including the multitude of co-morbid medical conditions found in increasing incidence in the obese population). Bariatric surgery is one of the burgeoning areas of medical specialization: there has been an exponential increase in the number of bariatric procedures performed. In the United States in 1992 there were 16200 surgeries performed; this had increased to 220 000 by 2008! South African numbers have lagged behind, but this field is booming in (especially) the private health care sector.

Management of patients for bariatric surgery is an arduous process, requiring a full multidisciplinary approach to "theatre readiness". This includes the patient's primary physician, endocrinologist, surgeon, anaesthetist, psychiatrist, psychologist, dietician, specialist nurses, therapists (occupational, physio-). Preparation includes an aggressive weight-loss programme (which includes dietary and exercise)

Scientific validation of the interventions surrounding bariatric surgery/ peri-operative impact has been slow, with few large-scale/ high-impact randomized control trials in the literature currently. There is thus much deliberation regarding best practice in certain components of this. The research base is increasing.

Candidate Selection

The selection of candidates is a stringent process. The WHO has criteria, but does also stipulate that local centers should develop their own adjustments depending on experience and facility availability (e.g. critical care services). The choice of cutting or not is always a balance of risk, although many benefits of surgery are noted.

Concomitant metabolic disease has superseded an absolute BMI value for surgery. This is evident in that a BMI of > 30 kg/m2 (on its own) is not an independent predictor of cardiovascular disease.

The current value is increasingly seen as improving glucose tolerance, reduction of microvascular complications of diabetes mellitus, and the induction of remission in diabetic patients (this is regardless of the BMI).

NICE/ American NIH

- BMI > 40 kg/m^2 (regardless of co-morbidities)
- BMI 35 – 40 kg/m^2 (if obesity-related disorders – DM or OSA)

The international Diabetes Federation adds:

- BMI 30 – 35 kg/m^2, in severely poorly-controlled Type 2 DM.

Surgery is **NOT** recommended for patients < 30 kg/$m^{2.}$
Thus if criteria are met patients will be referred to the multidisciplinary team for assessment and review suitability for surgery.

Absolute contraindications to performing bariatric surgery are rare. If the multidisciplinary team deems the psychological impact of the procedure to be too much for the patient, this would be the strongest decision against the procedure. The main other determinant of offering surgery would be the team's experience, and local facilities available. There is a very steep learning curve for proficiency with the procedure: it is generally accepted that approximately 100 cases are required for this.

- Anaesthesia-related: e.g. severe cardiovascular disease (i.e. risk posed by peri-/ post-operative period weighed up against long-term benefits of the procedure).
- Medical-related (relative) contraindications:
    - Oesophageal varices
    - Chronic pancreatitis
    - Portal hypertension
    - Inflammatory bowel disease
    - Liver cirrhosis

The question thus stands: who requires surgery most urgently:

- Super-morbidly-obese patient?
- Lower obesity BMI, but with co-morbidities?

Owing to the steep learning curve, it may be reasonable practise to choose the "healthiest"/ least complicated case early on (whilst establishing a bariatric surgery programme).

Anaesthetic Considerations for Bariatric Surgery

1. Patient considerations
    a. Obesity pathophysiology (refer to physiology texts)
    b. Pathological conditions
2. Laparoscopic surgery (not discussed in this lecture)
    a. Type of surgery
3. Technical aspects
4. Airway
5. Ventilation
6. Pharmacology
7. Post-operative
    a. Placement
    b. DVT Prophylaxis

Pathological Consequences of Obesity

System	Association/ Disease Manifestation
C.N.S.	
⇨ Psychological	Depression Social stigma ↓ Self-esteem
⇨ Neurological	↑ CVA (because of marked increase in many risk factors) Carpal tunnel syndrome
C.V.S.	**↑ Risk of sudden cardiac death**
⇨ Heart	Hypertension, with subsequent LVH Dysrhythmias (fatty infiltration of conducting pathways; obese patients ↑ 49 % risk of atrial fibrillation vs. general population) Congestive cardiac failure; Cor pulmonale (??OSA)
⇨ Vascular	Ischaemic heart disease/ Myocardial infarction Peripheral vascular disease Varicose veins Deep venous thrombosis
Respiratory	Obstructive Sleep Apnoea vs. Obesity Hypoventilation Syndrome Restrictive lung disease Asthma Pulmonary Hypertension
G.I.T.	↑ GORD Hiatus hernia Non-Alcoholic-Steato-Hepatitis (NASH): reversible, but can lead to *cirrhosis* (if no weight loss) ↑ Cholecystitis
G.U.T.	End-stage renal disease Renal calculi Urinary incontinence
⇨ Female	↑ Menorrhagia Endometriosis PCOS Infertility risk increased
⇨ Male	Alteration of testosterone levels (?implication unsure)
⇨ Pregnancy-related	↑ Pre-eclampsia + Eclampsia Macrosomia
Endocrine	Diabetes Mellitus (insulin-resistant) Hyperinsulinaemia Dyslipidaemia Hypothyroidism **Metabolic Syndrome** (Syndrome X) Cushing's Syndrome
Haematological	Hypercoagulable Polycythaemia (relative drop in PaO_2 stimulates renal production of erythropoietin)
Musculoskeletal	Osteoarthritis of weight-bearing joints Back pain Gout Acanthosis nigrans
Malignancy	Breast Colorectal Prostate Cervical Endometrial

This is a summary of disorders associated more commonly with obesity. A more complete explanation of the pathophysiology surrounding these is beyond the scope of this talk.

1. Obstructive Sleep Apnoea

Untreated obstructive sleep apnoea (OSA) of prolonged duration is associated with an increased all-cause mortality peri-operatively. As many as 70 % of the patients undergoing bariatric surgery will be diagnosed with OSA. Half of these patients are, however, undiagnosed! OSA is associated with a multitude of pathophysiological changes, but of main (ongoing concern) includes: difficult bag-mask ventilation, possible difficult intubation, complications of hypertension (systemic and pulmonary), and dysfunctional respiratory drive. The anaesthetic agents further exacerbate the abnormal control of the respiratory system (particularly opioids). OSA is an independent risk factor for adverse post-operative events in patients undergoing bariatric surgery.

In a well-performed American study, it was shown that the severity of OSA (as evidenced by a higher Apnoea-hypopnoea index) was not directly correlated to the incidence of perioperative complications in patients undergoing bariatric surgery.

Parameter	**OSA**	**OHS**
Gender	M>F	M=F
Obesity present	Possibly (increased in obese)	Yes
Ventilation Pattern	Normal (except when apnoiec)	Hypoventilation
$PaCO_2$	Normal (↑ in apnoea)	↑
PaO_2	Normal (↓ in apnoea)	↓ (Worse in REM sleep); increasing reliance on hypoxic drive for ventilation
SaO_2	Normal (↓ in apnoea)	↓
Nocturnal airway obstruction	Yes	No (except with concomitant OSA)
Sleep awakening	Yes	No
Pulmonary Hypertension	Uncommon	More common, more severe
Nocturnal monitoring	AHI: ≥ 5 obstructive breathing events per hour of sleep.	↑ $PaCO_2$ > 1.3 kPa from baseline (awake); ↓ SaO_2 unexplained by apnoea.

The pathophysiological/ pathological effects of OSA can be reduced or reversed following application of CPAP (continuous positive airway pressure) or BiPAP (bi-level positive airway pressure). This is for a duration determined by the disorder targeted pre-operatively (i.e. individualized).

Duration of CPAP	**Reversed**
2 weeks	Correct abnormal ventilatory drive (hypercapnoeic patients)
3 weeks	↑ Left ventricular ejection fraction (patients with CCF)
4 weeks	↓ Blood pressure ↓ Heart rate ↑ Ejection fraction by 35 %
4 – 6 weeks	↓ Tongue volume ↑ Pharyngeal space
8 weeks	↓ Hypertension (morning) ↓ Cardiovascular risk (IF used for > 4 hours per night)
3 – 6 months	↓ Pulmonary hypertension

2. Cardiovascular Evaluation

Patients should undergo early preoperative workup. This is to ensure that the benefits of bariatric surgery outweigh the potential risks/ side-effects. Those patients at increased risk of complications include:

- Male > Female
- 50 years old
- Congestive cardiac failure present
- Peripheral vascular disease
- Renal dysfunction

There is an increased incidence of cardiovascular disease secondary to pathophysiology and pathological co-morbidities. Many of these could be diagnosed pre-operatively.
The most important would include: arrhythmias (fatty deposition in the conducting system), dilated cardiomyopathy, pulmonary hypertension.

Evaluation using cardiopulmonary exercise testing has shown promise in assessing these patients.

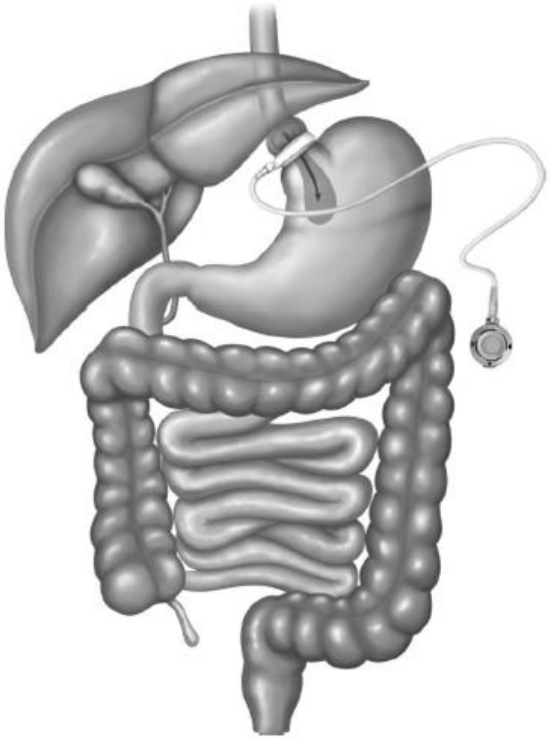
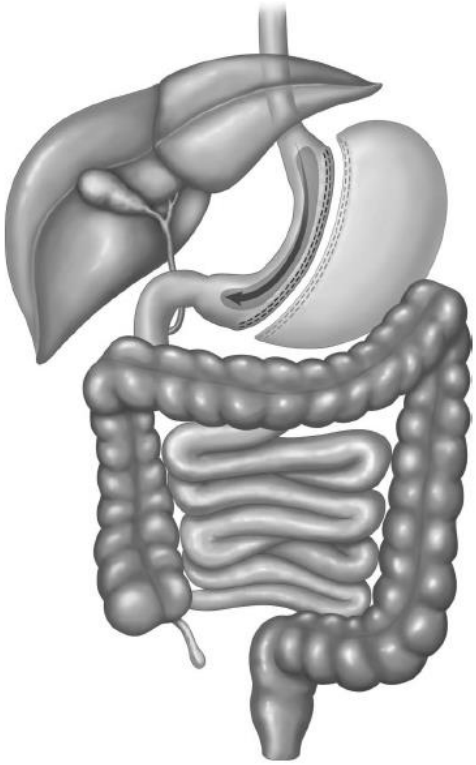
Principles of the Surgical Process

The principle guiding bariatric surgery is a reduction in the volume of the gastric cavity with an earlier onset of satiety, with the consumption of smaller meals (the patient rapidly loses hunger while eating as a result of the anatomical stomach changes, OR as a result of the early passage of food from the stomach)

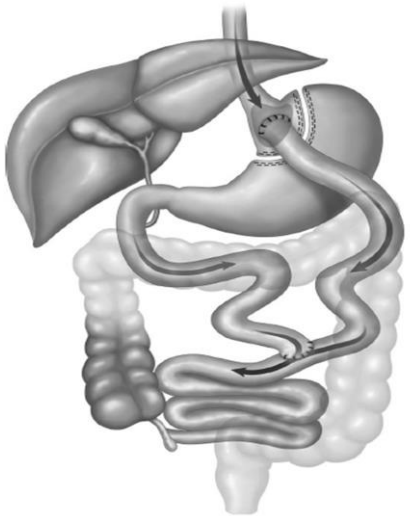
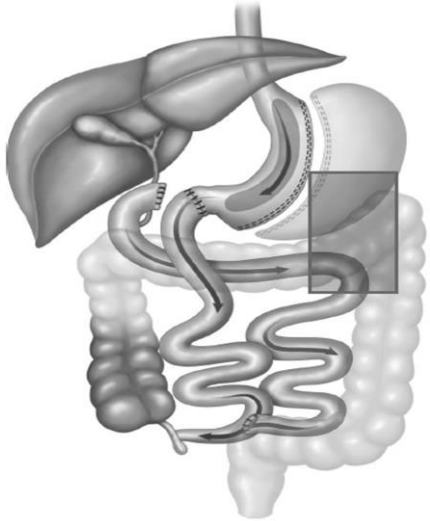
All surgical options can be performed as open or laparoscopic procedures; laparoscopy has dramatically improved outcomes following these surgeries (with a marked drop in both morbidity and mortality). This is beneficial in the obese patient, fraught with physiological derangement and (often) multiple medical co-morbidities. Laparoscopic approach to surgery is associated with a decline in incisional hernias and a dramatic decline in the incidence of wound infections.

The main approaches include:

↓ stomach size	↓ size of gastric outlet	Malabsorptive procedures
Mechanical gastric banding Thus food enters the small, upper gastric pouch and passes to the intestine. This results in earlier filling: patient feels fuller earlier. Difficult to eat large volumes quickly.	A full stomach remains full for longer, as gastric transit of food is prolonged.	Intestinal bypass surgery Thus early satiety due to: ⇒ ↑ Satiety hormone (YY_{3-36}) ⇒ Blunting of Hunger hormone (Ghrelin) Early satiety much more rapidly than other types of surgery. There is also associated change in other gut hormones, including a changed responsiveness to insulin resistance. This mechanism plays a role in the resolution of T2DM..

1. Reduction in stomach size	
Adjustable Gastric Band (AGB): good option in sicker patients 	**Sleeve Gastrectomy (SG)** 
Laparoscopic surgery to form a band (silastic band just below gastro-oesophageal junction): • Upper pouch = 25 ml volume • Lower pouch = larger segment There is a saline reservoir port (subcutaneously) used to inject to tighten the band over subsequent weeks. This allows a balance to be reached between early satiety vs. unpleasant side-effects (i.e. slowly). NB Requires patient compliance and vigilance.	Laparoscopic surgery used increasingly in the last 8 years, with good success. Stomach volume ↓ with **NO** outflow tract obstruction. The stomach is transected vertically: • High-pressure gastric tube • Large pouch remnant (up to 200 ml) Result is early fullness. Metabolic changes similar to RYGB (see below)
PROBLEMS: Band displacement OR over-eating (↑ size of small upper pouch)	**PROBLEMS:** Metabolic side-effects (although unusual) can be similar to jejuno-ileal bypass (but NOT as severe)

2. Reduced size of gastric outlet
These procedures are uncommonly performed, but essentially increase the duration of gastric transit of food. Thus once the stomach is full, full for longer

3. Malabsorptive procedures		
Jejuno-ileal bypass	**Roux-en-Y Gastric Bypass (RYGB):** common (upper end of obese range)	**Duodenal bypass:** extremely obese patients
This is an old technique (initially performed from the mid-1960's), heralding a breakthrough in management of weight loss. It is an extreme procedure; it is NOT commonly performed		
The proximal jejunum is anastomosed to the distal ileum, approximately 10 cm from the caecum.	Staple line across upper stomach, reducing the volume to 25 – 45 ml. There is a Roux-loop reconstruction resulting in a partial malabsorption (this can be long or short) A restrictive anastomosis between the pouch (neo-stomach) and Roux-loop: restriction. This is attached to the jejunum.	This involves bilio-pancreatico diversion (with possible duodenal switch). Procedure: • Partial gastrectomy (with 400 ml pouch) • Intestinal bypass carries food to distal small intestine • Bile & pancreatic juices carried in 2nd limb • Then join at common limb for digestion & absorption
There are MARKED, severe complications associated with this procedure (including acute, severe liver failure: prevalence of 7%, which can result in hepatic fibrosis)	Life-long follow-up; Requires long-term dietary supplementation;	More complications vs. RYGB

4. Other (investigational) interventions

e.g. endoscopic sleeves, electrical neurostimulation, gastric plication surgery. These are newer mechanisms of bariatric intervention, unvalidated.

Risks & Complications of Surgery (N.B. See Addendum B at end of notes for a comparison of M&M)

30-day **mortality** overall ± 0.1 – 0.3 %

Patient Factors	**Procedural**
• Age ↑ • BMI • OSA • Hypertension	• Surgeon experience • Surgery Complexity • Open > laparoscopic procedure

Morbidity
Surgical

• Staple line leak: 3 %	• Post-operative pulmonary complications : 2.2 %
• Wound infection: 2.3 %	• Haemorrhage: 1.7 %

- Staple line leaks 3 %
- Wound infection 2.3 %
- Post-operative pulmonary complications 2.2 %
- Haemorrhage 1.7 %

Long-term

- Malabsorption (one needs to look at what is bypassed, and how much is bypassed)Vitamin/mineral deficiencies
- Vitamin D deficiency (prominent with low [Ca^{2+}]) is now lined with cardiovascular disease
- Low [Ca^{2+}] is associated with increased osteoporosis; Low Fe^{2+}
- Vit B12 (Common in modern, and older surgical approaches)
- Vit B group vitamins (especially Thiamine)
- Hypoalbuminaemia
- "Dumping" syndrome: excessively-rapid passage of food into the small intestine.
- reactive hypoglycaemia worse by high glucose consumption (thus regular, low g.i. meals; ± octreotide)
- Related to type of surgery (i.e. jejuno-ileal bypass & Biliopancreatic diversion **highest**)

Approximately **one third of patients require reversal of the surgery** (2/3 of these patients die before surgical reversal). The reversal is associated with 13 % mortality at surgery, 23 % post-reversal mortality, and 11 – 12 % more than 30 days post-surgical mortality.

Dumping Syndrome
Excessively rapid passage of food into the s.i.
Initially: pallor, sweating, dizziness, pending doom
(lasts for approximately 30 min's)
Then diarrhoea.
If persistent: electrolyte changes.
Can occur for months following surgery.
Management: dietary changes, with small (regular) low g.i. meals
± Somatostatin analogues

Benefits of Bariatric Surgery

There has been extensive work done to determine the sustained, and perceived, benefits of bariatric surgery. We know that there is associated weight loss (especially with types 1 and 3 mentioned above). The benefits to treat obesity-related disorders are well-documented; and current literature suggests a reduction in mortality in obese patients by 30 %!! (especially cancer- & T2DM-related mortality).

Questions surrounding the cost-benefit of bariatric surgery have been addressed. Obesity is expensive to maintain: food consumed, medications, extra health-care services sought out, building alterations. In treating obesity, one largely addresses the diseases associated (highlighted in the table below).

The secondary benefits would include a reduction of analgesic requirement, respiratory disorder dysfunction, and ongoing psychiatric problems. Obese patients are less productive at work, and take an increased amount of time off (as sick days). Thus by improving that: patients have less need for healthcare facilities, medication, and days off work. The return of investment from the procedure will balance out within four years (this would be a massive saving long-term). Medications dramatically decrease within two weeks following surgery. The balance of this is potentially some of the side-effects of surgery (GORD; nutritional supplements required).

System	**Benefit of Bariatric Surgery**
Weight-loss	Most patients have sustained weight-loss (months). Recommendations: MAX 0.5 – 1 kg/week post-surgery. This is good for fat loss; otherwise will ↓ muscle bulk, and worsen cardiac function. The patient's weight will drop until ± 10 – 20 % of IBW. At this point energy intake equates to expenditure. VERY few patients overshoot (only really in malabsorption disorder, found with bigger procedures: remedied by repeat surgery). If BMI 47 kg/m^2 • 56 – 61.2 % loss for all patients • 47.5 % AGB • 61.6 % RYBG • 68.2 % gastroplasty • 70.1 % BPD ± DS RYGB > ABG (but almost comparable at 36/12 with good post-op surveillance and follow-up) BPD > RYGB, but associated with major complications. **Lowest weight:** 12 – 18/12, with some regain **not** unusual. 20 years (Swedish study): 25 % reduction mean following RYGB; 15 % AGB (i.e. weight reduction from initial per-surgical weight)
C.N.S. ⇨ Psychological	Psychological resolution marked! There is an improvement of body image dysphoria. There is a marked, quantifiable improvement in quality of life (QOL) scores. Obese patients are at increased risk of psychiatric disorders (e.g. anxiety d/o, depression, eating d/o). These QOL scores improve within 1 year post-surgery, and persist for > 10 years. Food urges need to be controlled (and can be difficult to manage) *Weight regain is associated with worsening of ALL of the above.*
C.V.S. ⇨ Heart	50 % ↓ in morbidity This reduction in mortality is essentially due the ***reduction*** of the triad: • Hypertension resolved in 61.7 % • Dyslipidaemia (70 % improvement/ resolved) • Hyperinsulinaemia These remain reduced from baseline at 10 years post-surgery. There is a remodeling reversal of the cardiac pathophysiological changes (with normal left volume function within 3 years post-procedure).

	Thus cardiomyopathy associated with LVH, and diastolic dysfunction, will start to improve.
⇨ Vascular	There is a reduction in blood pressure; this is delayed, and often not permanent (unfortunately).
Respiratory	**Airway:** early reduction in fat deposition (peripharyngeal). This is then associated with a marked decline in OSA/ OHS (85.7 % reduction in incidence). The severity of OSA is improved (but the patient may still be moderate-severe severity). **Asthma:** there is generally early resolution thereof. The postulated mechanism is due to subcutaneous tissue, and a reduction in the restrictive chest wall mechanics.
G.I.T.	**GORD:** improves with RYGB (vs. fundoplication)! BUT there may be worse GORD in SB & AGB. GORD may be ± contra-indication for procedure decreasing the stomach size. **NASH:** bariatric surgery has been shown to be effective in reversing the histological changes (in even established liver disease). Data is conflicting, however, as the hepatic fibrosis ensuing may worsen.
G.U.T.	Difficult assessing the effect of bariatric surgery on renal function (there is a loss of muscle mass, with no individual parameters improving.
There are no RCT's relating to reproductive function following bariatric surgery. These are purely observational assessments. Recommendations based on these are difficult to validate.	
⇨ Female	Regulate ovulation ↓ hyperandrogenism
⇨ Male	↑ Sperm number, but ↓ quality
⇨ Pregnancy-related	↓ Materno-foetal risk
Endocrine **see Addendum C	**Diabetes Mellitus (insulin-resistant)** MUCH literature has evaluated the effect of bariatric surgery on the reduction in blood [glucose]. It is clear that there is rapid resolution which precedes even the weight-loss following surgery. The presence of T2DM slackens the indication for surgery (vs., presence only of ↑ BMI only). This ensures remission from the scourge of the disease, but also a concomitant (dramatic) improvement in CVS outcomes. Only 10% of patients on adequate medical therapy will be able to achieve the adequate cardiovascular goals (Hgt, BP, [LDL]). Bariatric surgery may be the solution. There are concerns, however, regarding long-term efficacy/ sustainability.
Musculoskeletal	**Osteoarthritis of weight-bearing joints, back pai**n MARKED improvement in functional status, and regain of autonomy in the obese patient. "Can you tie your shoelaces?" is a better assessment of improvement of independence and QOL than a reduction in body weight.

Most patients will be satisfied with the changes and improvements in health and co-morbidities. There are noticeable (and helpful) cosmetic, lifestyle and body image improvements.

Technical aspects

Equipment: electronic, big operating tables with increased weight-bearing capacity are required. The possibility exists for the use of two operating tables strapped together (but this has not been validated for use).
Positioning of patient: it is advisable for the patient to position themselves on the operating table prior to induction. This ensures comfortable position, reduces injury to the patient (pressure or traction), and limits injury in health-care workers. DOCUMENT the patient position, including padding, etc.

Patient position is also critical intra- and post-operative to prevent physiological consequences of incorrect position. Patients are positioned head up (anti-trendelenberg or at least head up 30°).
This takes weight of chest wall and abdomen off the diaghragm, and aids ventilation, weaning or extubation success. Supine position is also associated with cardiovascular collapse.
Trendelenberg worse: mass of fat, + Auto-transfusion
Thus flood the pulmonary circulation, with a further reduction in FRC, and subsequent atelectasis: these all dramatically decrease the PaO_2.
Patients are put into modified Lloyd-Davis for surgery. Padding is important to alleviate nerve pressure, compartment syndrome (and thus possibly rhabdomyolysis) and bedsores.

There is often difficult intravenous access: opt for early ultrasound-guided placement of peripheral/ central intravenous access.
Monitoring: non-invasive blood pressure measurements may become extremely challenging; this is high-risk surgery, with haemodynamic changes (laparoscopy, fluids, etc) and so an arterial is mandatory.
All standard ASA monitoring should be in place.

Airway

These patients are reported to have difficult intubation (and do fulfill several criteria on the ASA assessment thereof). Thus preparation is key, including multiple airway adjuncts. The definition of the **difficult airway** varies, but is generally accepted as ≥ 3 attempts at laryngoscopy with failure of intubation of the trachea for more than 10 minutes. These may be associated with complications. (the complications are noted to be more frequent and more severe in the morbidly obese).
BMI does not independently predict the risk of a difficult intubation.
Brodsky, et al proposed the following, with relative success at predicting difficult intubation:

Neck circumference > 40 cm	5 % difficulty
Neck circumference > 60 cm	35 % difficulty

The patient correctly positioned for intubation is the most important factor at increasing success.



Thus the head, upper body and shoulder are significantly elevated above the patient's chest. One should draw an imaginary line (horizontal) connecting the sternal notch and the external auditory meatus.
(**H**ead **E**levated **L**aryngoscopy **P**osition – **HELP**)

This has been shown to afford a 97 – 99 % success rate of tracheal intubation. Only 33 % of the patients in the study had a Grade I C&L view; 15 % required a gum-elastic bougie. The one failed direct laryngoscopy allowed easy bag-mask ventilation, but the patient was easily-intubated with a fibre-optic scope.
There is much discrepancy regarding the appropriate means of securing the airway in a patient with suspected difficulty. Intubating-LMA's have shown great success (with 96 % first time intubation success). Video-laryngoscopy (C-MAC, Airtraq, Glidescope) has revolutionized my practise of securely intubating the obese patient's trachea.

Two-thirds of problems occur at **extubation**, due to the loss of reflex control in the transitional state. This is associated with hypoxia concomitantly. The aim is thus for rapid emergence and airway control.

The risk of hypoxia is minimized if there is minimal airway instrumentation at extubation, or if CPAP is applied immediately post-extubation. This can be via a well-fitting mask, or via a laryngeal mask. Various recommendations are made, e.g. Pressure-support ventilation (12 cm H_2O/ 4 cm H_2O

PEEP) gives better spirometry, better saturations and better lung function for two days following surgery (vs. conventional extubation with supplemental oxygen).

Pharmacology can aid this process. Desflurane reportedly results in a more rapid emergence, improved psychometric and motor function. This significance might be borderline when compared to Sevoflurane, or Propofol.

What would a good option be? We can use more soluble agents (sevo vs. Iso), with titratable intravenous agents (Dexmedetomidine or Remifentanyl). Application of a BIS monitor (or other processed EEG) will allow for one to titrate the anaesthetic agents down towards the end of the case.

Residual Anaesthesia (of 0.1 MAC) does have an effect on respiratory drive (central): Desflurane and Sevoflurane preserve the respiratory response; Isoflurane, Halothane and Enflurane do suppress the respiratory drive.

Rapid Sequence Intubation (RSI) or not?
Two thirds of aspiration occurs at induction and extubation. Obese patients do have an increased risk of GORD, thus prophylaxis is recommended even if there are no symptoms.

Drug	**Dose**
PPI	20 mg Omeprazole
H_2-Receptor Antagonist	50 mg Ranitidine
Prokinetic	10 mg Metoclopramide
Antacid	30 ml Sodium citrate

It was thought that the gastro-oesophageal sphincter was incompetent, and moved in the obese patient…this does not appear to be the case. The neck anatomy of these patients is distorted (so cricoid pressure does not reliably prevent/ minimize the risk of aspiration). Thus, there is enough evidence pointing to the fact that if the patient is a conventional risk of aspiration (not related to obesity) then a RSI would be prudent.

Otherwise these patients follow the same fasting guidelines as the general population.

Extubation must be PLANNED! Post-extubation stridor is common. Thus the patient must be awake, with high inspired oxygen preceding this. The patient should be in the ramped position (makes re-intubation easier, and also reduces hypoxia).

In these patients the risk: benefit ratio favours a controlled airway manipulation and induction over rapid muscle relaxation.

Ventilation

This includes bag-mask ventilation, as well as ventilation of the lungs via endotracheal tubes. Bag-mask ventilation is difficult due to reduced chest wall compliance, as well as upper airway obstruction. Their lung mechanics differs; the lung itself does not grow in the obese patient, and thus the tidal volume should be determined on I**BW** (vs. actual body weight which is associated with lung trauma)
58.6 % of the patients recruited to the ARDS-NET trial were obese. Despite the absence of large-scale trails focusing on this, lung-protective ventilation is still the strategy of choice in the obese. There is NO clear evidence regarding the best mode of ventilating these patients. There are very few studies looking at this; but these are often in healthy patients, with non-restrictive lungs.

Volume-controlled: CO_2 decreases
Oxygenation problems improve with **Pressure-controlled** (CMV) and cardiovascular support. (This may result in better V:Q).
The Ohio study performed in adolescents showed no difference with regards to oxygenation, ventilation (CO_2), haemodynamics, or anaesthetic requirements when comparing volume-control, pressure-control and pressure-control-volume-guaranteed ventilation. Thus, the recommendation

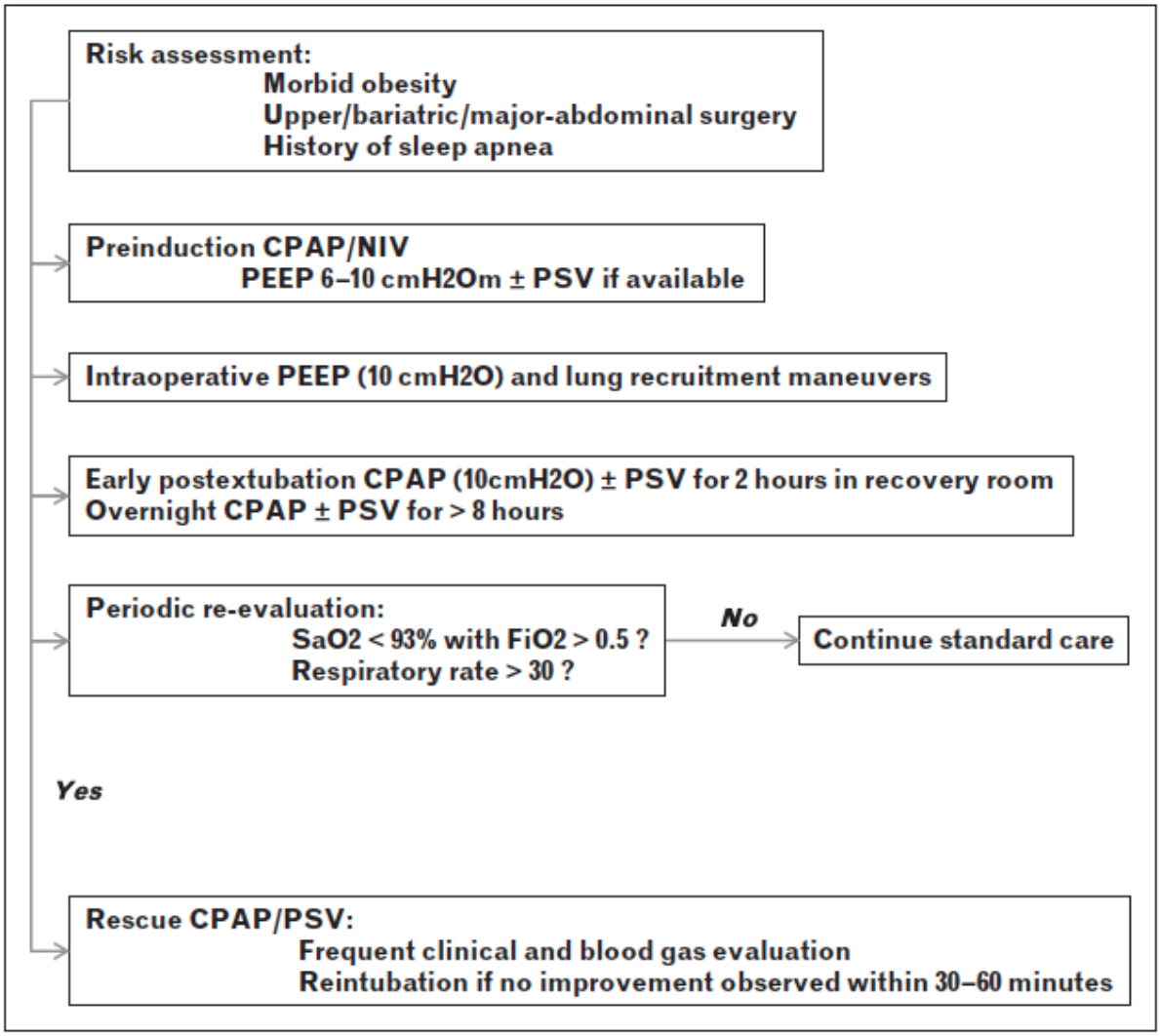
now us to test both modes of ventilation and determine which gives the best PEEP with the least amount of haemodynamic effects (which improved oxygenation).

PEEP & Recruitment

The risk of atelectasis is high and thus manouevres are required t prevent this, and keep alveoli open. Atelectasis occurs commonly (as much as 15 %), early on (within the first 5 minutes of surgery). This worsens with laparoscopic surgery.

The current effective recommendations include PEEP applied from the start of the case (10 cm H_2O is better than 5 in several studies), with regular vital capacity recruitment manouevres (40 cm H_2O for 15 seconds), repeated every 10 minutes.

Pplat does not seem to be as much of a problem as in the non-obese patients. Eloquently designed rat studies demonstrated that chest wall weight might prevent the alveolar over-distension. This needs to be properly borne out in a human RCT (observational and case studies currently).



Approach to morbidly-obese patients at risk of developing atelectasis, following high-risk surgeries

Post-operative Concerns

Emergence from anaesthesia, as well as the post-operative period carries great risk to the patient following bariatric surgery.

1. Patient placement: ICU vs. High-Care vs. Day-case

If no adequate post-operative facility exists: elective surgery for the bariatric surgical patient (and obese patient) should **NOT** proceed. The establishment of a good service takes planning and facilities. These patients may be critically ill as a baseline (adipose tissue has been show to secrete IL-6 and TNF-α).
The **Modified-Montefiore Obesity Surgery Score (M-MOSS)** is used to decide regarding placement of patients in the post-operative period. This applies to patients having undergone a RYGB procedure.

- Age > 50 years
- Male
- BMI $\geq$ 50 kg/m^2
- Confirmed OSA
- Significant medical/ surgical history
- Previous surgery

IF the patient has $\geq$ 4/7: deemed to be moderate – high risk, and ICU placement is advisable.
As experience is gained so there is a decreased need for super-intensive care.

2. Basics

- Nurse at 45 degrees head up
- Routine monitoring (including invasive blood pressure)
- Supplemental oxygen; incentive spirometry ± CPAP (as outlined previously)

(This can be given immediately post-operatively)

3. Analgesia

This can be difficult to manage in the obese. The purpose is to reduce post-operative pulmonary complication, reduce the incidence of post-operative chest infections, and naturally control the patient's pain.
Multi-modal analgesia is practiced. This includes local anaesthetic (wound infiltration in laparoscopic surgery; a thoracic epidural for open bariatric surgery). Epidural placement is technically difficult, and has a high failure rate in this population group. Regional anaesthesia (rectus sheath catheters) is also a mainstay of analgesic
Patient-controlled analgesia is effective (I would recommend the use of an opiate combined with ketamine). Other intravenous opiates are avoided.

Paracetemol, i.v.	Dose is approximately the same as in non-obese population (large V_D), but more regular dosing. Thus: 1g every 4 – 5 hours.
NSAID's	If there is no contra-indication
Tramadol	Regular use is effective
Ketamine	Effective in analgesic doses to decrease opioid need
α-2-agonists	Intra-operative Dexmedetomidine; post-operative oral Clonidine is an excellent analgesic adjunct.

Psychology literature suggests that this patient group have decreased analgesic needs compared to the general surgical population. This is postulated to be as a result of increased patient motivation, or central opioid receptor changes.
It is important to note that the risks associated with OSA/OHS persist for days post-surgery, due to the increasing REM sleep. Thus the risk of post-operative MI is at 2 – 3 days post-surgery, usually at night. Pain needs to be controlled well to minimize this effect.

4. Antibiotics

These will be administered as required. These patients are at increased risk of surgical site infection (co-morbidities, e.g. DM, duration of surgery, tissue hypoxia, inadequate dosing of antibiotics). This risk is reduced with laparoscopic surgical approach.

5. Fluid Management

The total body water is changed due to the obesity. Loss should not be large if laparoscopic surgery; there are massive changes, however, associated with open surgery. The presence of T2DM requires a change in fluid maintenance (i.e. glucose-containing maintenance as a background).
Pulmonary hypertension and cor pulmonale must be excluded in order to optimize fluid status.

6. VTE (Venous Thromboembolism) Prophylaxis

Morbid obesity is associated with a doubling of risk of sudden death secondary to pulmonary embolism (PE). There is a reported 2.4 – 4.5 % increased incidence of PE following bariatric surgery. Thus bariatric surgery independently will place the obese patient in a moderate- to high-risk category. Most of these occur following hospital discharge (usually 1st 30 days).

Additional risk factors include: RYGB > AGB surgery
Open > laparoscopic surgery

Higher risk groups:

• Morbid obesity	• OSA or OHS
• Elderly	• Previous DVT/ PE
• Male	• Co-morbid medical disease
• Immobility	• Prolonged surgery

There is no class I evidence regarding the use of any specific prophylactic measure in the bariatric surgery patient. There are, however, three main options available in the armamentarium of management (with no method being effective in complete eradication, but markedly reduced incidence of DVT).

a) Mechanical

b) Early mobilization (within 2 hours post-return to the ward): recommended for all patients.

c) Sequential compression devices

The studies show conflicting data regarding the independent usefulness of these. There is reduction in patients, but should be used in combination with pharmacological in high-risk patients. Use for **ALL** patients post-bariatric surgery

d) Pharmacological

There has been much controversy regarding a dosing regime, as well as what type of drug to use. Various studies have examined these. Current evidence (scanty) suggests that Low-molecular weight heparin (LMWH) is more effective than unfractionated heparin, without increasing the risk of bleeding.

Intervention	**Dose**
Low-molecular weight heparin (e.g. Enoxaparin)	30 – 40 mg subcutaneous, 12-hourly This should commence pre-surgery
Unfractionated Heparin	5000 i.u. subcutaneous, 8-hourly

Although the dosing has been a topic of controversy (ideal vs. total body weight), a few studies suggest that conventional adult dosing is as effective as higher/ adjusted doses in the post-bariatric surgery patient. The duration of continuation of this has not clarified (and this should be individualized according to local practice, and patient risk profile).

e) Prophylactic Inferior Vena Cava (IVC) Filter

These have been recommended for use in patients with previous DVT/ PE. Their use is, however, associated with much controversy: independently the risk of IVC filter placement may surpass the risk of VTE. If used it must be in conjunction with the other interventions.

Although there are no clear guidelines, the American Society of Bariatric and Metabolic Surgery Committee's recommendation is to establish local practises, and follow them well. Identify at risk patients, and manage as appropriately.

7. Rhabdomyolysis

This disorder is not seen commonly post-operatively, with a wide range of incidence reported (0.4 – 75 %). It is, however, increasing in incidence following bariatric surgery (as case studies highlight). Rhabdomyolysis occurs as a result of compression by the excess weight, injury and subsequent necrosis of skeletal muscle. It manifests post-operatively usually at 24 hours, but can be as early as 3 hours post-operative.
The clinical manifestation ranges from erythema, vesicles overlying the affected muscle and severe muscle pain to subsequent acute renal failure (ARF, due to tubular necrosis), compartment syndrome, and death.
ARF has an incidence of 20 – 50 % of patients developing rhabdomyolysis secondary to bariatric surgery; if developed, there is an associated 20 % mortality reported.
At-risk patients:

- Prolonged surgery
- Excessive positioning
- A.S.A. III – IV
- Co-morbid medical disease (diabetes mellitus, hypertension)

These patients at risk require early monitoring of creatinine and creatinine phosphokinase (CK) levels, possibly as a routine. Rapid increase is very suggestive of the diagnosis (together with clinical features).
Prevention of the risk factors (shorter surgery, positioning, adequate padding intraoperatively) has not been shown to be highly effective.
Early, and rapid, identification and supportive management is the mainstay of preventing major morbidity and mortality.

Childhood Obesity

Childhood obesity has become a new health scourge to be dealt with in the 21st century. The age range assessed generally includes 5 years to adolescence. The performance of bariatric surgery has remarkably increased in prevalence over the last 5 years in order to curb the problems associated with childhood obesity. This field is fraught with ethical dilemnas: who is to blame, what is the best intervention, who consents for the procedure, is this failure of medical therapy, when to operate? This adds another major dimension to management of obesity: parental guilt, and potential misgiving. This would need to be managed appropriately, and sensitively.
Childhood overnourishment is complex and features social, psychological, economic, and cultural factors. This coupled with an increase is sedentary behaviour has led to this now (nearly) global epidemic. South Africa has been cited to be the fattest sub-Saharan country, and this extends to childhood. 13.5 % of South African children aged 6 – 14 years old are obese. The global prevalence is approximately 10 %; the USA has an incidence of 18 %. This rose by 47.1% between 1980 and 2013! Energy-dense foods fuel the average South African (and following a "Banting"-type dietary regime is largely outside the realm of the average South African). This along with a sedentary lifestyle has been attributed the largest driving force of pre-pubescent obesity.

BMI is used to interpret this, but its usefulness varies according to patient age and gender. BMI is a difficult predicting tool during puberty and in times of rapid growth. BMI-for-age curves are used, separately for boys and girls (differing body fat composition-for-age).

BMI-for-age > 85%:	Overweight
BMI-for-age > 95%:	Obese

Obese children are more likely to become obese adults, and thus increase duration of time to pathological disorders found with increasing incidence in obesity. Overweight children are more likely to develop more severe obesity as adults.

Problems with childhood obesity

- Social and psychological (depression, reduced self-esteem)
- ↑ Blood pressure, and subsequent hypertension
  - ↑ [cholesterol], and Hypercholesterolaemia
- Breathing problems: OSA, asthma
- Abnormal glucose tolerance test, earlier onset T2DM
- Fatty liver
- Gallstones
- Joint disorders

Conclusion

Bariatric surgery is a life-saving measure. It is a costly initial outlay, but large-body evidence suggests that this money shows return within 4 years (reduction in health care bills, reduction in medications, reduction in other life-aids). The problem noted in South Africa (and much of the developing world) this is not a procedure that is available to the lower-middle class. South African medical aids have been slow on the uptake to fund this. It is surgery offered to a very small subset of the South African population (essentially private health care currently). And (rightfully so) offered in only specialized units.

An experienced multi-disciplinary team is required to assess and select the best/ most appropriate candidates. The goal for the patient will determine surgical choice (weight-loss vs. management of co-morbid medical disease)

The aim is to ensure a low morbidity and mortality, with sustained long-term weight-loss. These are “patients-for-life”, and thus a patient’s motivation needs to be assessed (ensuring good rapport with the team).

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Addendum A

Definitions

1. BMI: Body Mass Index

This is the basis of our means of assessment of degree/ severity of obesity. It allows an analysis of weight relative to height.

Problems:

- No indication of age or body composition (i.e. lean muscle mass). Thus a better assessment of this would be triceps (skin fold) thickness, hydrodensity, bioelectric impedance, or complete assessments with CT/MRI scan measurements. It thus does not differentiate fat and muscle mass.
- Central adiposity vs., total body fat %. It is the central adiposity that carries a markedly increased risk of cardiovascular disease. It is assessed by waste circumference, hip circumference, and waist:hip.

$$\text{BMI} = \frac{\text{mass}}{\text{height}} \left[\frac{kg}{m^2}\right]$$

BMI (kg/m^2)	Modern Classification	WHO (2004)	Risk of co-morbidities
< 18.5	Underweight	Underweight	
18.5 – 25	Normal	Normal	
25 – 29.9	Overweight	Overweight/ pre-obesity	↑
30 – 35	Obese	Obesity Class I (moderate)	Moderate
35 – 40		Obesity Class II (severe)	Severe
40 – 50	Morbid Obesity	Obesity Class III (very severe)	Very severe
50 – 60	Super obese		
≥ 60	Super-super obese		

- Total Body Weight (TBW)

Actual body weight of the patient.
In the obese population lean body weight (see below) and adipose tissue do NOT ↑ proportionally.
Initially used to define obesity (TBW approximately 20% ↑ of ideal body weight)

- Ideal Body Weight (IBW)

This relates to height and body frame. It is an indicator of maximum life expectancy.
This is not helpful, as patients of same sex and height (regardless of body weight) would receive the same drug dosages; it also does NOT factor in obesity changes.

IBW = 45.4kg + [0.89 x (height – 152.4cm)] female
IBW = 49.9kg + [0.89 x (height – 152.4cm0] male

OR: **IBW = height (cm) – x** ***x = 100, male; 105, female***

- Body Surface Area (BSA)

This relates the patient's weight and height. It disregards gender of the patient, and fails to distinguish between fat vs. muscle mass.
This is a helpful measure with dosing of certain medications.

$\text{BSA} = \sqrt{\frac{W \cdot H}{3600}}$ W: weight in kg; H: height in cm.

- Lean Body Weight (LBW)

This is a description of size of patient devoid of almost all body fat. Its usefulness is for assessing the degree of metabolic disorders, as well as prescribing some drugs.

≈TBW – (body fat weight)
(1.07 x TBW) – (0.0148 x BMI x TBW) female
(1.10 x TBW) – (0.0183 x BMI x TBW) male

- Predicted Normal Body Weight (PNW)

This equation is utilized to predict the expected normal weight of the overweight/ obese individual. Its primary use is for the determination of pharmacokinetic parameters.

Addendum B

Complications associated with each type of bariatric surgery

	AGB	**SG**	**RYGB**	**BPD ± DS**
Mortality	0.3 % (good option in sicker patients)	Safe & wide use (less data: only used < 10 years)	0.4 % mortality (in centres of excellence)	Higher (>1 %)
g.i.t. s/e's	Vomiting common (MUST exclude obstruction by band migration: 1.4 % of all cases)		Vomiting is common (BUT exclude pathology) •Anastomotic breakdown •Rapid eating •Over-eating •Diarrhoea (40%0 may progress to foecal incontinence Cholelithiasis: 2 % in 1st year; diagnose with ultrasound.	
Blood/ CVS		Haemorrhage risk	4 % haemorrhage (early) Pulmonary embolism, DVT (early): < 0.5 %	Haemorrhage Risk of PE & DVT (patient subset problematic)
Anastomosis	NO anastomosis, BUT gastro-oesophageal perforation. Leads to intra-abdominal sepsis (0.5 %) Infection at the adjustment port (years later!); MUST exclude perforation/ erosion/ intra-abdominal sepsis.	Anastomotic leaks Anastomotic stenosis (similar incidence to RYGB)	Anastomotic leak at any of the sites •Severe peritonitis •Sepsis •Multi-organ failure •Bowel perforation •Male age •Re-surgery •Less surgical experience **LATE** Intestinal obstruction Anastomotic stricture	Anastomotic leak Anastomotic stenosis There is an increased incidence of early complications. This is usually associated with ↑ BMI & ↑ co-morbidities (vs. RYGB) Incisional hernias: 38%

	AGB	**SG**	**RYGB**	**BPD ± DS**
Nutritional	Few/ limited (no intestinal bypass) BUT can be issues related to patient's rate of weight-loss, & patient compliance.	Vit B12-deficiency Fe^{2+} deficiency Dumping syndrome	Vitamin and mineral deficiency ↓ Ca^{2+} SUPPLEMENT for ongoing nutritional support Dumping syndrome Hyperinsulinaemic hypoglycaemia	Definite vitamin and mineral deficiency Dumping syndrome
Weight-loss				Dramatic, rapid. This can further exacerbate the nutritional dysfunction (65 % of patients)
Other	Limited post-operative alopecia (4.5 % of patients)	↓ Operative time ↓ post-op. duration of admission. ↑ Risk of eating d/o		

Notes for Case Scenario (discussed in the lecture)

Nitrous Oxide

Should a modern anaesthetist be using such an old fashioned drug?

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Introduction

Nitrous oxide has been in widespread use in the operating theatre, dental rooms and labour ward since 1867. If you do the maths, this translates to 148 years. We have found new agents to replace other earlier anaesthetic drugs such as ether and thiopentone. But nitrous oxide remains in widespread use. Are we using it out of habit, because the alternatives (eg Xenon) are expensive and difficult to obtain, or because it holds advantages to a modern day anaesthetic with an impressive safety profile?

Every day we make the choice whether to turn the nitrous oxide dial on or off, often subconsciously. Usually this choice is based on habit. For Part 2 this is not good enough, and we need to be making informed decisions based on a risk/benefit analysis. Let us review what we know.

Physics

Nitrous oxide has a boiling point of -88,5^{0}C and a critical temperature of 36,5^{0}C. This means it is a gas at room temperature and pressure, but a liquid under pressure. It is non explosive and non-flammable but supports combustion.

It is insoluble with a blood/gas partitions coefficient of 1:1. This gives it a rapid onset and offset, and titratability. Almost all of the inhaled nitrous is eliminated through exhalation with less than 0,01% undergoing biotransformation by bacteria in the GIT.

Nitrous has a MAC of 104%. This means it cannot be used as a sole anaesthetic agent. Instead we use the concentrating effect and augmented inflow effect to increase the uptake of volatile agents during the induction period. The supplementary anaesthetic effects of nitrous oxide also mean a lower concentration of volatile is required to attain 1 MAC.

This is useful not only during the maintenance of anaesthesia, but trials have also supported the use of nitrous oxide during induction. Although commonly used during paediatric induction, studies have also supported its use during gas induction for adults:

- Muzi et al showed decreased time to intubation, less breath holding and expiratory stridor during induction with the addition of nitrous to sevoflurane.
- Hall et al demonstrated shorted induction time as well as a smoother induction with less adverse events and a higher success rate for first LMA insertion when adding nitrous oxide to sevoflurane during a vital capacity induction technique.
- Ng et al also demonstrated a shorter induction time when introducing nitrous oxide prior to intravenous propofol administration.

The rapid elimination of nitrous oxide also holds benefits during the emergence period:

- Jakobsen et al demonstrated a decreased time to orientation when adding nitrous oxide to sevoflurane.
- Einarson et al demonstrated decreased time to spontaneous respiration and extubation when adding nitrous oxide to isoflurane.
- Servin et al and Sukhani et al demonstrated a decreased time to orientation when adding nitrous to a propofol TIVA technique.

Nitrous oxide is however more soluble than nitrogen, which has raised concerns about absorption atelectasis. However Peyton et al demonstrated that in fact nitrous oxide can improve oxygenation due to its persisting concentrating and second gas effects. This is only important with significant ventilation/perfusion mismatch, which is found in anaesthesia. The effect on the PaO_2 is significant and greater than the effect of the absorption atelectasis.

Since it is more soluble than nitrogen, it can fill air filled spaces more rapidly than nitrogen can diffuse out. Hence it is contraindicated in patients with pneumothorax, pulmonary bullae, pneumocephalus, 70 days after injection of an intraocular gas bubble, during middle ear procedures and in patients at risk of venous air embolism (CPB, seated craniotomy). It is due to this that we have also been taught to avoid nitrous in abdominal procedures and laparoscopic procedures. However some will debate this teaching. Orhan-Sungar et al did a meta-analysis where they found that although nitrous oxide caused time dependent bowel distention, this did not affect surgical conditions, time to bowel movement or length of hospital stay. Taylor et al demonstrated that when nitrous oxide was added to laparoscopic cholecystectomies, the operative conditions were identical to where it had been omitted.

Please note that nitrous oxide can diffuse into endotracheal and LMA cuffs, so cuff pressure should be monitored more regularly with a manometer.

A note about nitrous oxide and altitude. James et al demonstrated that the analgesic effectiveness of 50% nitrous could raise pain thresholds by 71.5%. At 1460m the pain threshold was only raised by 40% and at 3300m was only 19%. This is directly related to the decreasing partial pressure (despite the same % of nitrous) at increasing altitude. Similarly nitrous oxide has decreasing anaesthetic efficiency at increasing altitude.

Physiology

Originally hypoxia was thought to be important to the mechanism of action of nitrous oxide, and initially its use was frequently associated with cyanosis and clonic limb movements. I am happy to report that it's mechanism of action does not involve hypoxia.

Nitrous is a weak hypnotic, weak immobiliser, potent analgesic and causes no EEG slowing. It is grouped with ketamine and xenon.

Analgesic actions of nitrous oxide are via a supraspinal mechanism. Corticotrophin-releasing factor (CRF) causes activation of the descending noradrenergic pathways, which synapse in the dorsal horn of the spinal cord. This noradrenalin release causes release of GABA which in turn inhibits the second order neurons, thereby decreasing the ascending transmission of pain impulses to the brain.
Nitrous oxide's sedative/immobilising/amnestic effects occur via different mechanisms. The NMDA subtype of the glutamate receptor is noncompetitively inhibited by nitrous, thereby inhibiting glutamate medicated excitatory neurotransmission. The two pore domain potassium channel, especially TREK-1 also decreases neuronal excitability when activated. Neuronal nicotinic acetylcholine receptor inhibition is thought to be contributory to the amnesia.

Please note that nitrous oxide does not act by enhancing $GABA_A$ receptors unlike the volatiles and intravenous induction agents. This gives rise to some controversies. When we add a GABA agent such as isoflurane or propofol to our anaesthetic technique, do we significantly attenuate the effect of nitrous oxide on the descending noradrenergic inhibitory interneurons, thereby decreasing it's analgesic effect? Although animal studies seem to support this there is poor clinical evidence to back this up. But it is possible that when used as a part of a modern balanced anaesthetic effect nitrous' analgesic effect may be minimal. However the ENIGMA II trial subset analysis did seem to indicate less chronic pain postoperatively. Further study is required.

It is well known that fentanyl will decrease MAC of a volatile agent. If enough fentanyl is given, nitrous does not seem to decrease MAC any further. However if remifentanyl is used nitrous oxide continues to be MAC sparing. This is thought to be due to remifentanyl's NMDA receptor potentiation, which fentanyl does not do. Can nitrous oxide therefore block remifentanyl induced hyperalgesia?

Pathophysiology

Nitrous oxide causes methionine synthase inhibition. This occurs via the irreversible oxidation of the of the cobalt ion in cobalamin (vitamin B12). The cobalamin is now biologically inactive and it can no longer act as a cofactor for methionine synthase. The resultant inactivation of the pathway means a decrease in the amount of methionine produced and an increase in its precursor homocysteine. The methionine acts as a methyl donor for over 100 metabolic steps such as the synthesis of DNA, cellular proteins, catecholamines, neurotransmitters and myelin. This is thought to possibly place the patient at

risk for immune suppression, decreased wound healing, neurotoxidity and teratogenicity. The interference in the folate / vitamin B 12 cycle could place the patient at risk for megaloblastic anaemia. The increase in homocysteine levels might place the patient at risk for endothelial dysfunction, hypercoagulability, the development of atherosclerosis, neurodegenerative diseases (eg dementia) and potentiation of excitotoxicity.

This inhibition of methionine synthase is related to several factors.

1) The amount of nitrous administered
   70% nitrous will decrease enzyme activity by up to 50% within 46 min and result in negligible enzyme activity beyond 200min. Enzyme recovery takes 3-4 days.
2) Duration of nitrous administration
   It is well known that a common side effect of long term ICU sedation with nitrous is subacute combined spinal cord degeneration. This is also seen in nitrous abusers. We do not know whether any of the other potential side effects of nitrous oxide are time dependent.
   Although chronically elevated homocysteine levels have been linked with cardiac disease, we do not known if an acute increase in homocysteine carries any clinical risk. In addition a number of trials have reported varying levels and duration of this postop increase. Perhaps there is another mechanism than methionine synthase inhibition at play?
3) Susceptible patients
   Most of our patients will have adequate stores of S-adenosyl methionine (a precursor of methionine synthase) to recover from nitrous related enzyme inhibition. Some of our patients will not have these stores and it is important to be aware of the susceptible population.

- Inadequate intake (elderly, alcoholics, malnourished, vegans)
- Increased requirements (pregnancy, infancy, malignancy)
- Malabsorption (pernicious anaemia, gastrectomy, ileal resection, Crohn's disease, chronic antacid use, intestinal parasites)
- Multifactorial (critically ill)

Clearly the above population regularly requires surgery. Moreover this is frequently the population that benefits from nitrous oxide's MAC sparing ability. Pre-operative supplementation with folate, B6 and B12 a week before orthopaedic surgery was shown by Badner et al to prevent the postoperative increase in homocysteine when nitrous oxide was used. Rao and colleagues could not show an effect with a single IV dose in the pre-anaesthetic holding area.

4) Rare genetic disorders involving the mutation of the MTHFR (5,10 methylene-THF reductase) gene such as type 3 homocysteinuria, have been associated with adverse outcomes following anaesthesia involving nitrous oxide. Genetic polymorphisms in this gene may also be at important.

Systemic effects and clinical controversies

Cardiovascular

We were all taught for the DA that although nitrous oxide causes in vivo cardiac depression, it is offset by the accompanying sympathetic nervous system activation. Some anaesthetists have been concerned that in patients with severe LV dysfunction or shock (significant pre-existing sympathetic activation) that if one uses nitrous in addition to opioids, the in vivo myocardial depression can be unmasked. However volatiles can cause more myocardial depression than nitrous can, especially at values above 1 MAC. This being the reason many of us find it useful to add nitrous to our anaesthetic technique, i.e. to bring down our level of volatile while still attaining adequate depth of anaesthesia. This can be particularly useful in the elderly or patients with poor cardiac reserve and patients on cardiaovascular depressant drugs. McKinney et al demonstrated less cardiovascular depression with 50% nitrous oxide and isoflurane than with 1 MAC of isoflurane alone. Note that this sympathetic activation may raise pulmonary vascular resistance and nitrous oxide is relatively contraindicated in patients with pulmonary hypertension.

As previously mentioned the nitrous induced methionine synthase inhibition can cause raised homocysteine levels one week postoperatively. The concern is that this may contribute to perioperative myocardial ischaemia. A study by Badner et al in 90 patients undergoing carotid endarterectomy demonstrated that the nitrous group had a higher incidence of postoperative myocardial ischaemia. However the depth of anaesthesia was not equivalent in the groups which may have significantly affected the outcome, as this has been shown to be an independent predictor of

postoperative mortality (Monk et al). Subgroup analysis of the GALA trial (GA vs LA for carotid surgery) could not find an association between nitrous oxide and death, stroke or myocardial infarction. In addition a post hoc subanalysis of the POISE trial could also not link nitrous use to cardiac complications.

THE ENIGMA TRIALS
ENIGMA I was published in 2007 and allocated 2050 patients to nitrous or control groups. The primary endpoint was the duration of hospital stay. There was no difference between the two groups. There were a number of secondary end points, including PONV, wound infections, and myocardial infarction in which nitrous oxide did compare unfavourably. There are a number of problems with these conclusions though. Firstly the control group received 80% oxygen/20% air, which is not applicable to our current clinical practice and may account for some of the differences in results. There was also a difference in anaesthetic depth in the two groups (0,87 MAC in the control vs 1,31 MAC in the nitrous group) which as mentioned previously can also confound results. For the secondary endpoints they undertook multiple comparisons, which increase the chance of a type 1 error. The study was also not blinded and the authors have been accused of bias by highlighting the adverse secondary outcomes rather than the neutral primary outcome.

This gave rise to the next trial, ENIGMA II. 7112 patients undergoing major non-cardiac surgery were enrolled and assigned to nitrous (70%) and non-nitrous (70% air) groups. These were all patients with either suspected or confirmed coronary artery disease. They demonstrated that nitrous did not increase the risk of death and cardiovascular complications (non-fatal myocardial infarction, stroke, pulmonary embolism or cardiac arrest).Neither did it increase the risk of surgical site infections. Nitrous did increase the risk of PONV but this could be prevented by the administration of prophylactic antiemetic drugs. Interestingly it demonstrated that nitrous may reduce the risk of persistent pain postoperatively, but this is a subject that requires further study.

Central Nervous System
The CNS will be discussed under the following headings:

- Intracranial dynamics
- Postoperative Cognitive Dysfunction
- Neurodevelopment
- Awareness
- Neurotoxicity vs neuroprotection
- Myelinopathies

<u>Intracranial dynamics</u>
The typical teaching has been that nitrous oxide will increase cerebral blood flow (CBF) and therefore cerebral blood volume will also increase. This may raise the intracranial pressure. Nitrous oxide also increases cerebral metabolic rate and blunts autoregulation. As a result some anaesthetists are reluctant to use it in neuroanaesthesia.
However the studies are confusing. For example one study shows blunted autoregulation with the use of nitrous and 1 MAC Sevo but shows intact autoregulation when used with 1,5 MAC Sevo. Different effects on CBF have been demonstrated with different volatiles. However the biggest problem with these studies is that they do not test how we use nitrous oxide in common clinical practice. We typically use the addition of nitrous oxide to decrease the volatile required to maintain a MAC of approximately 1. We do not add nitrous oxide on top of a volatile already at 1 MAC or above.
The problem with that is it adds confounding factors. Firstly an increase in depth of anaesthesia has independently been associated with an increase in postoperative mortality (Monk et al). Secondly at these relatively high levels of volatile agent, the adverse effects of the volatile itself on the intracranial dynamics will predominate.
What we do know is that nitrous oxide is more haemodynamically stable than most other anaesthetic agents. And hypotension is associated with a worse neurological outcome. Nitrous oxide is also easily titratable and has a rapid offset, which is advantageous in neuroanaesthesia. In addition the vascular reactivity to carbon dioxide is preserved when using it in combination with propofol and volatiles.

<u>Postoperative cognitive dysfunction (POCD)</u>
Clinical trials do not support a link between the use of nitrous oxide and POCD. POCD seems to have its roots in a neuroinflammatory response to surgery, environmental factors and sleep disturbances, and the choice of anaesthetic plays little role in its development.

Neurodevelopment
There has been concern with the role of nitrous oxide after a study in rats showed that a combination of midazolam, isoflurane and nitrous oxide caused widespread apoptosis and learning impairment. The problem with this is firstly that it is an animal study, and the direct extrapolation of data of animal studies to humans in the perinatal period is problematic for many reasons. Secondly most anaesthetic agents can be linked to neurodegenerative changes in some animal model. There is no current human evidence to suggest adverse neurodevelopmental effects with the use of nitrous oxide in routine clinical practice.

Myelinopathies
Due to the inhibition of methionine synthase nitrous oxide has been linked to subacute combined spinal cord degeneration in long term nitrous use (eg ICU) or abuse. It may also lead to other abnormalities such as an altered mental state, seizures and spasticity. However this responds to vitamin B12 and folate supplementation. A patient at risk (eg untreated B12 deficiency) should either be treated preoperatively or nitrous should be avoided.

Neurotoxicity vs Neurodevelopment
The available data is confusing. Selective NMDA receptor antagonists worsen neuronal injury and it has been shown in rats that when hyperbaric nitrous oxide is given, morphological changes consistent with neurotoxicity can be demonstrated. The problem is once again that in common clinical practice we do not use hyperbaric nitrous, and we commonly co-administer a GABA agent (propofol, volatile) which prevent these changes. On the other hand, glutamate induced stimulation of NMDA receptors (which nitrous blocks) will increase neuronal calcium levels which leads to neuronal injury or death. Therefore NMDA receptor antagonists may be neuroprotective (as demonstrated in rats).

The only human data we have in this regard is a post-hoc analysis of a data subset from the IHAST trial (Pasternak et al). The subset analysed were the patients who had temporary cerebral artery clipping, i.e. the patients probably at the greatest risk of ischaemic cerebral injury. In this subset nitrous had no long term adverse effects on gross neurological or neuropsychiatric function. When analysing the full cohort it was found that nitrous had no adverse effects on the outcomes either. There was actually a trend to an improved 3 month outcome and more patients discharged home vs long term care centre.

Awareness
Although some studies and a meta-analysis by Tramer et al showed it in a favourable light, others did not. There were 2 patients with awareness in the ENIGMA trial, both in the nitrous group. Hence this remains controversial, although the pharmacokinetics and pharmacodynamics support the use of nitrous to prevent awareness.

BIS and Entropy are reported to be insensitive however to nitrous oxide. This may result in an inappropriately deep anaesthetic, which may contribute to perioperative mortality.

Respiratory
Nitrous oxide use is regarded by some as being a risk factor for postoperative hypoxia due to several factors. Let us examine these factors:

1) Diffusion Hypoxia
   This has been overemphasised in the past and is easily preventable by correct anaesthetic technique. Patients in recovery only require supplemental oxygen if significant accompanying cardiorespiratory disease.
2) Blunted hypoxic drive
   Not only nitrous oxide does this, most anaesthetic agents do. Nitrous also has a rapid elimination and hence this is unlikely to be clinically significant postop.
3) Absorption atelectasis
   As mentioned earlier the persisting concentration and second gas effects of nitrous actually improve oxygenation in a patient with V/Q mismatch (anaesthesia). This effect outweighs the absorption atelectasis (Peyton et al).

Einarson et al demonstrated that the addition of nitrous to sevoflurane actually improved time to spontaneous respiration and extubation. This is thought to be due to the fact that nitrous causes less respiratory depression than volatiles. Hence an equipotent nitrous/volatile mix will do this.

PONV
Nitrous is a risk factor for PONV. This is dose dependent. However this risk is easily prevented with prophylactic antiemetic administration. And it should be noted that the use of volatiles and opioids carry greater risk.

Haematological
Nitrous inhibits methionine synthase which may cause megaloblastic anaemia and bone marrow suppression with its various sequelae. In a healthy patient it is thought to occur after 12-24 hours of exposure. In susceptible patients though, the time period may be much shorter. Although changes in the bone marrow have been demonstrated, it is uncertain whether they have clinical significance in terms of adverse outcomes. Symptoms respond to folate and vitamin B12 supplementation.

Immune suppression and wound infection
Once again this is thought to be a possible consequence of methionine synthase inhibition. The resultant decrease in protein synthesis may negatively influence wound healing. Other mechanisms such as decreased neutrophil chemotaxis and alveolar macrophage activity have also been demonstrated.
However surgery and anaesthesia on its own impair immune function irrespective of anaesthetic agents.
The ENIGMA I trial demonstrated decreased wound healing as a secondary outcome. The major criticism to this finding though is that the control group received 80% oxygen. This in its own may affect wound healing. The ENIGMA II trial however demonstrated no increase in wound infection in the nitrous vs control groups. Fleishman et al studied the effect of nitrous on wound healing in colonic surgery and could find no significant difference in the 2 groups.

Other
Nitrous oxide may have other benefits such as anaesthetic sparing effects (volatile, opioid and propofol and even rocuronium) which can result in a cost saving in anaesthesia. This has to be weighed up against other factors such as the cost of the nitrous itself, the need for scavenging and the cost of antiemetics.

Conclusion

Nitrous oxide has been in widespread use for 150 years in anaesthetic theatres, dental rooms and labour wards. It has proven itself useful and is still in use today. In recent years concerns have been raised regarding its side effect profile and pathophysiology. Some trials initially supported this. However a large volume of these trials were either on animals and/or conducted in ways that did not mimic the use of nitrous oxide in current safe clinical practice. The ENIGMA II trial has laid many of these concerns to rest and there is room for further study in its role in persistent postoperative pain prevention.

Questions to ponder

1) You have been asked to assist the planning with new theatres for a regional hospital. Would you recommend that nitrous oxide pipelines be laid for use?
2) You have a regular list with a vascular surgeon. He heard a rumour from his colleague that his patients may benefit from pre-operative supplementation with folate and vitamin B12. He would like to know why. Would you recommend that this be instituted routinely?
3) Where do you find nitrous oxide useful in your clinical practice? Do you think this may change after this refresher?

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Anaesthesia for Thoracic Surgical Emergencies

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Thoracic emergencies require quick and thorough assessment, with rapid diagnosis, and *appropriate management* in order *to ensure survival*. The *immediate* cardiorespiratory and/or volume compromise provide an explanation for the *high morbidity* and *mortality* of these cases.

Anaesthesia for thoracic emergencies defies dogmatic prescription or structured enrollment in a rigid framework. As a result, what follows is an outline of the more common, yet life-threatening emergencies that may be encountered in daily anaesthetic practice.

MASSIVE HAEMOPTYSIS

Haemoptysis, defined as expectoration of blood from the lower respiratory tract, is a frequently encountered symptom in clinical practice. Haemoptysis must be differentiated from *epistaxis* (bleeding from the nose) or from *haematemesis* (bleeding from the upper gastrointestinal tract).

As the incidence of tuberculosis (TB), multi-drug-resistant tuberculosis (MDR-TB), human immune deficiency virus (HIV) and fungal lung infections in immune suppressed patients increases, the number of cases with haemoptysis is likely going to increase.

The amount of blood lost during haemoptysis varies widely, from streaking of the sputum, to rapidly fatal massive haemoptysis. *Massive haemoptysis*, or rather, life-threatening haemoptysis, represents, fortunately, only 5% of the total number of cases of haemoptysis. There is no clear consensus as to what represents massive haemoptysis: more than 100 ml in 24 hours, or more than 1000 ml in 24 hours, or more than 25 ml/hour or more than 300 ml during one expectoration. Lack of consensus regarding the cutoff volume, the unreliable estimation of both expectorated volume and the rate of bleeding have led to the use of a *"magnitude of effect"* definition of massive haemoptysis, i.e. compromise of the cardiorespiratory status.
Massive haemoptysis has thus been defined as haemoptysis that leads to *abnormal gas exchange*, *airway obstruction* and/or *haemodynamic instability*.

The most common causes of massive haemoptysis are:

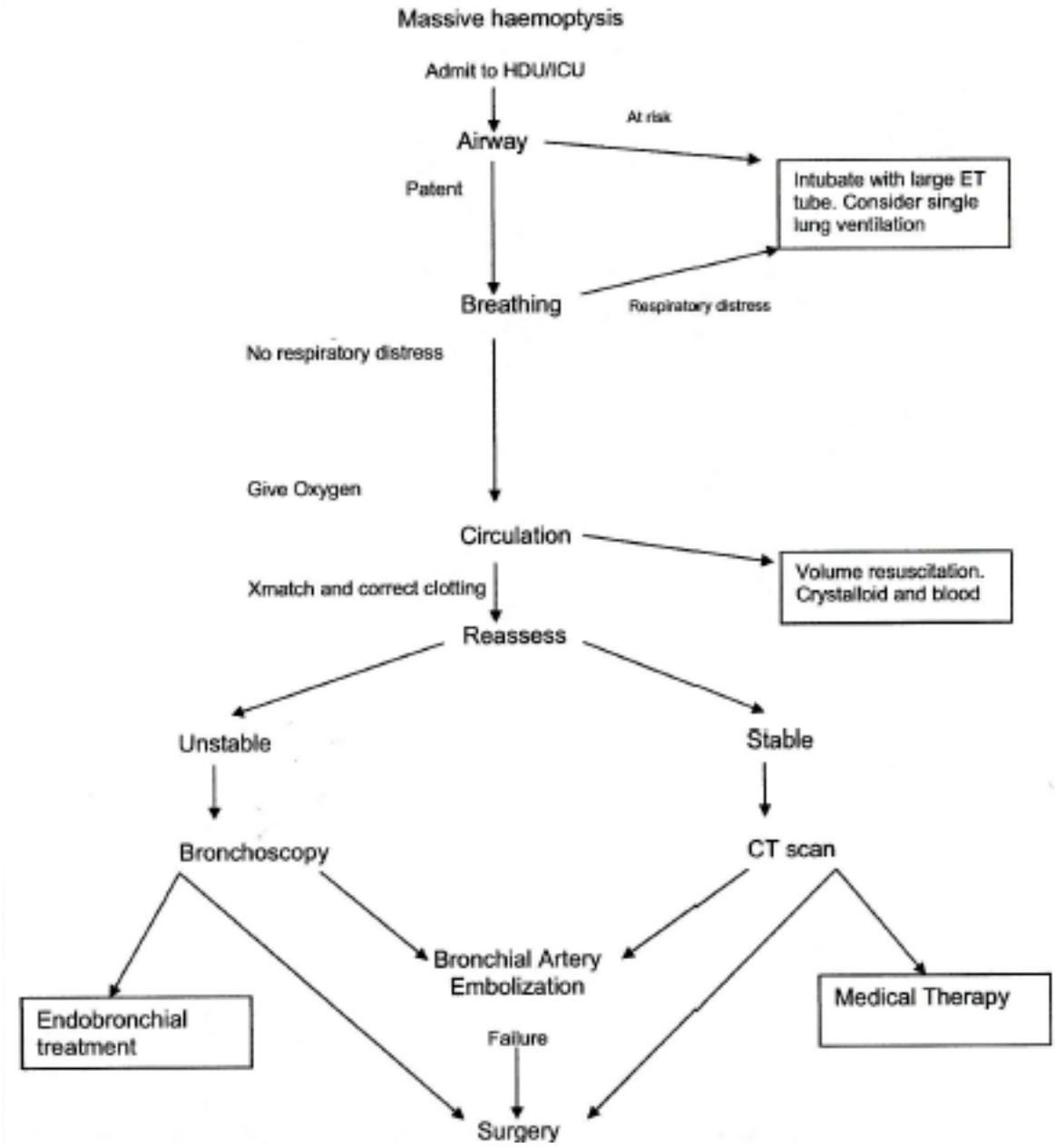
- infections: (TB, fungal – mycetoma);
- bacterial/necrotizing pneumonia and lung abscess;
- bronchogenic carcinoma;
- Kaposi's sarcoma
- pulmonary infarct;
- mitral stenosis;
- arteriovenous malformation;
- coagulopathy.

The lungs have dual artery supply: *pulmonary* and *bronchial* arterial systems.
The *pulmonary circulation* accounts for 99% of the arterial supply and is responsible for the gas exchange. It is a high volume, low-pressure system – the maximal pressures normally do not exceed 40 mmHg. The most common pattern (40% of patients) is a single right bronchial artery with 2 left bronchial arteries arising at T5 - T6 level.
The *bronchial circulation* makes up the remaining 1% and it carries a much smaller volume of blood, but it does so at higher, systemic pressures. There are numerous anastomoses between these two systems.

Bleeding in massive haemoptysis originates in 90% of cases from the high-pressure *bronchial circulation*, leaving other 5% for the pulmonary circulation and other 5% from non-bronchial systemic circulation (aorta, intercostals, coronaries, phrenic arteries).

Mechanisms of bleeding are multifactorial. In the presence of chronic inflammation and infection bronchial arteries hypertrophy and proliferate. There is increased blood flow and neovascularization. The resultant thin walled vessels are at risk of rupturing into the airway causing haemoptysis.

Treatment for massive haemoptysis can follow the algorithm bellow:



The initial approach for management of massive haemoptysis involves:

- protection of the airway (might require some type of lung isolation);
- maintenance of gas exchange – high flow oxygen administration;
- suctioning/expectoration/removal of blood and clots (suppression of cough should be avoided);
- prevention of soiling of the unaffected lung by appropriate positioning of the patient (if the side of bleeding is known);
- volume resuscitation by means of wide-bore venous access;
- admission to a highly monitored environment (high/intensive care unit);
- intubation and ventilation for those patients unable to maintain airway and/or oxygenation.

Rigid bronchoscopy under general anaesthesia may be required for direct visualization of the large airways in an attempt to identify the source of bleeding as well as for the initial temporization of bleeding: cold saline lavage, application of topical vasoconstrictive agents, or application of Fogarty balloon catheter for endobronchial tamponade. Other bronchoscopic/endobronchial measures of management include: laser photocoagulation, electrocautery and criotherapy.

In the management of massive haemoptysis early *multidisciplinary consultation* with interventional radiologists, thoracic surgeons, physicians and pulmonologists is essential to ensure prompt successful intervention in the face of a serious condition that has a high mortality (30-85%).

Definitive management in the treatment of massive haemoptysis consists of selective *bronchial artery embolization* by means of interventional radiology. It provides control of bleeding in more than 85% (75% to 90%) of cases. During the procedure the patient undergoes a descending thoracic aortogram to identify bronchial artery anatomy and bleeding site. The most commonly used embolic material is polyvinyl alcohol. Recurrence is relatively common, occurring in 10-50% of cases and outcome is dependent on underlying disease.

Surgery is the treatment of choice for arteriovenous malformations, trauma (including pulmonary artery rupture), and treatment of resistant mycetoma. Otherwise is only indicated following failure of bronchial artery embolization, due to high mortality rates, particularly in the context of significant co-morbidities.

Medical therapy should be instituted and early and concerns antibiotic therapy, antituberculous drugs, antifungals or underlying condition-specific medical therapy (blood products for bleeding abnormalities or immunosuppression and plasma exchange for autoimmune disorders).

Following massive haemoptysis, treated either by endoscopy, fadiological intervention or surgery, it is important to perform a bronchoscopy to clean the trachea-bronchial tree to remove any blood or clots in the distal airway.

TRAUMA

Trauma is the leading cause of death worldwide, across all age groups. *Thoracic injuries* account for 25-50% of these deaths.

Thoracic trauma encompasses the sequelae secondary to trauma of all of the thoracic organs: heart, great vessels, lungs, airways, oesophagus, diaphragm, and chest wall.

Thoracic injuries are *dynamic*. The semi-rigid thorax protects the heart, the lungs, major airways and vessels. It translates in that a great deal of force is necessary to damage these organs and very often, insults to the chest are associated with *multisystem injuries*.

Thoracic trauma is a *morbid business*. Mortality from chest injuries is around 10%. In fact, only two thirds of the patients will actually reach the hospital alive. Of those that do, the immediate identification and treatment of the *six most lethal injuries* is paramount.

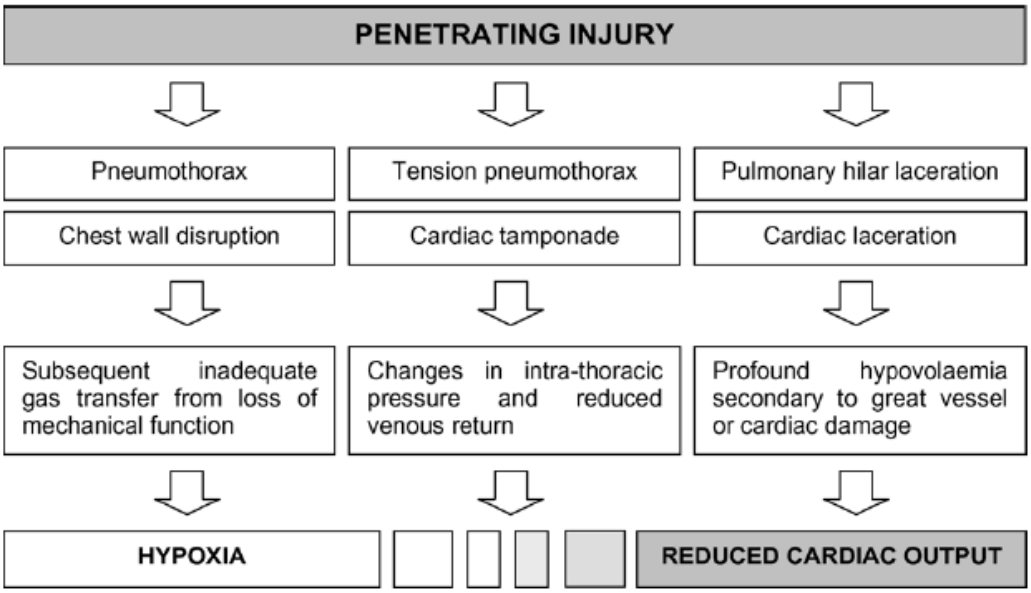
The six most immediate lethal injuries to the chest that should be sought and dealt with include:

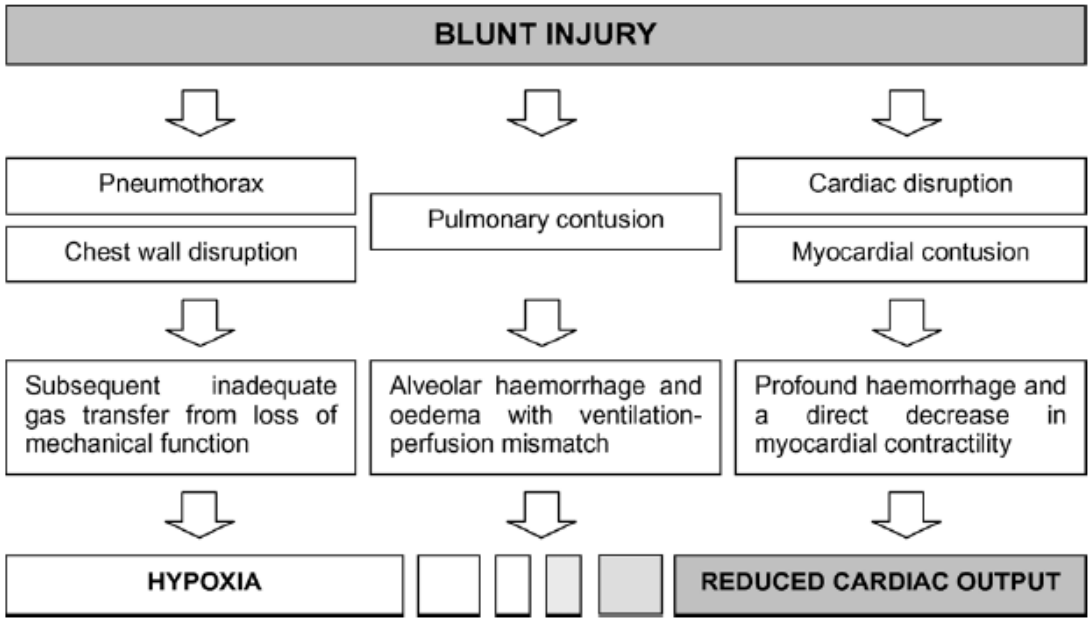
- airway obstruction;
- tension pneumothorax;
- cardiac tamponade;
- open pneumothorax;
- massive haemothorax; and
- flail chest.

It is crucial that *continuous reassessment* of the patient be undertaken so manifestations of evolving injuries may be detected and appropriate management initiated. The assessment of the thoracic

trauma patient should follow the well-known *ATLS protocols* with primary and secondary surveys done in the recommended fashion.

Pathophysiologic consequences of trauma, penetrating or blunt, can be illustrated as follows:





The main consequences of chest trauma occur as a direct result of its combined effects on respiratory and haemodynamic functions. *Death* following thoracic injury is often secondary to impairment of oxygen delivery and/or transport.

Several compensatory mechanisms exist in response to the physiological changes resulting from thoracic trauma, although they can be rapidly exhausted. The therapeutic goal is to augment, or supplement these compensatory mechanisms during acute resuscitation, the major two interventions being *ventilatory support* and the *arrest of haemorrhage*. Impairment of oxygen transport mechanisms and the resultant hypoxia can also contribute to mortality (secondarily, though) following the brain injury pathway.

Despite being potentially life-threatening, thoracic trauma can be managed conservatively/non-operatively in the majority of patients. Only 10% of these patients will require *emergency thoracotomy* as a component of initial resuscitation. Emergency or urgent surgical intervention will often be required for coexisting injuries.

EMERGENCY THORACOTOMY

There are numerous different terms for emergency thoracotomy. These depend on:

- the circumstances in which the procedure is performed,
- the status of the patient, and
- the location of the procedure itself.
-

Emergency thoracotomy can be undertaken at any stage of the resuscitative process, and so, can be defined in terms of the urgency of the procedure in relation to the patient's physiological status. Thereby, *emergency thoracotomy* may be defined as that occurring either immediately at the site of injury, in the emergency department, or in the operating room, as an integral part of the initial resuscitation.
An *urgent thoracotomy* is one that takes place under more controlled circumstances and in the context of appropriate physiological stability and hitherto successful resuscitation.
Lastly (for the sake of completion) an *elective* (formal) *thoracotomy* is one that is performed during the course of elective surgical access to the thorax.

Emergency resuscitative thoracotomy is a temporizing measure of most benefit to victims of trauma who arrive with at least some signs of life such as agonal ventilation, pupillary reactivity or cardiac electrical activity.
The overall survival after emergency resuscitative thoracotomy is about 7%. The outcome in blunt trauma is dismal, whereas in penetrating trauma (like isolated cardiac injury) survival may be as good as 20-30%.

Despite different patterns of injury with blunt and penetrating trauma,

- hypoxia,
- haemodynamic instability,
- acidosis,
- hypothermia,
- coagulopathy

are commonly established on presentation. Operations with good technical results but bad patient outcomes secondary to irreversible metabolic distress prompted surgeons to begin truncating initial procedures on severely injured patients after achieving haemostasis and controlling spill from the alimentary tract. These temporized patients would undergo aggressive correction of their acidosis, coagulopathy and hypothermia in ICU with plans for a return trip to OT for definitive management of their injuries – if they survived resuscitation. This technique of *quickly* and *solely* controlling haemorrhage and contamination in order to establish a survivable physiology is known as *"damage-control"*.

The use of *"damage-control" thoracotomy* led to better than expected survival rates in these critically injured patients.

Since its introduction in clinical practice, the recommended indications for emergency thoracotomy have become increasingly selective.

The primary indication for thoracotomy is generally accepted to be a penetrating injury of the thorax in patients on the point of arresting, or who have just arrested, or in those who are in profound shock. Several studies have shown that there is *no value* in performing emergency thoracotomy in moribund patients with blunt trauma.

"Damage-control" thoracotomy emphasizes temporization of injuries by performing rapid and relatively simple maneouvres:

- left anterior thoracotomy for evacuation of pericardial tamponade – improves cardiac output and controls the cardiac haemorrhage;

- direct control of haemorrhage form the heart, lung, or great vessels, thus, facilitating fluid resuscitation – "turning off the tap";
- open cardiac massage – improved resuscitative cardiac output and coronary perfusion;
- cross-clamping of the aorta to arrest massive blood loss from below the level of the diaphragm – redistributes the limited blood volume to myocardium and brain;
- left hilar clamping for massive systemic air embolism and bronchopleural fistula.

Thoracic damage control differs from that of the abdomen in its greater emphasis on simple and rapid definitive techniques: vascular shunting, wide drainage of oesophageal injuries and chest-wall packing. Precise execution and awareness of the little room for error affords the patient good chances of survival for a second trip for definitive management.

The general principles of *trauma anaesthesia* such as oxygenation, restoration of circulating volume, correction of hypothermia and coagulopathy will dully apply when dealing with patients with thoracic injuries.

Pre-oxygenation with 100% oxygen for 3-4 minutes might not always be possible in the agitated trauma patient.
The standard approach for securing a definitive airway is direct laryngoscopy and rapid sequence intubation with cricoid pressure and manual in-line stabilization of the cervical spine. Unanticipated difficult intubation should be managed in accordance with the *ASA Difficult Airway Algorithm – Trauma Version.*

The choice of drug for induction is less important than using a dose appropriate for the cardiovascular status of the patient.
Hypotension postinduction should be promptly treated with sympathomimetics and ongoing volume resuscitation.
Worsening hypotension and difficulty with ventilation should prompt a diagnosis of *tension pneumothorax* until proven otherwise.

Maintenance using a low-dose volatile agent with fentanyl and a non-depolarizing muscle relaxant is usually sufficient to achieve good anaesthesia.
Nitrous oxide would be best avoided – increase in the volume of gas-containing lesions (pneumothorax, air embolism).

Monitoring should include invasive arterial and central venous pressures (mostly for inotropes administration). TOE might be considered. Temperature monitoring is important. An awareness monitor like bispectral index should be useful, particularly in the setting of trauma to help avoid both over- and under-dosing of anaesthetic drugs.

One of the more challenging aspects of the management of patients with thoracic injuries is *lung isolation*. Techniques for lung isolation include: double lumen tubes (right or left), right main stem intubation, Univent tubes, bronchial blockers.
Right main stem intubation (apart from the fact that is easily achieved – not always intentionally!!) will result, most often, in ventilating only the middle and lower right lobes and as such, result in the highest shunt fraction and highest incidence of hypoxia.
All the other devices will require some expertise (definitely more than 2 thoracic cases per month!!).

Double lumen tubes are often difficult to insert during rapid sequence intubation. Add to this the *potential difficult airway* - if an airway injury already exists – and the potential *hypotension*, *hypoxia*, *associated injuries* in polytrauma patients, and superimpose all, on *limited experience* in thoracic anaesthesia. Failure to successfully place lung isolation devices – given these circumstances - is definitely going to be more than the usually quoted rate of 39%!!

Many anaesthetists do not undertake lung isolation techniques for emergency trauma thoracotomy.

If the patient is to remain intubated the double lumen endobronchial tube should be changed to a conventional endotracheal tube.

FLAIL CHEST & LUNG CONTUSION

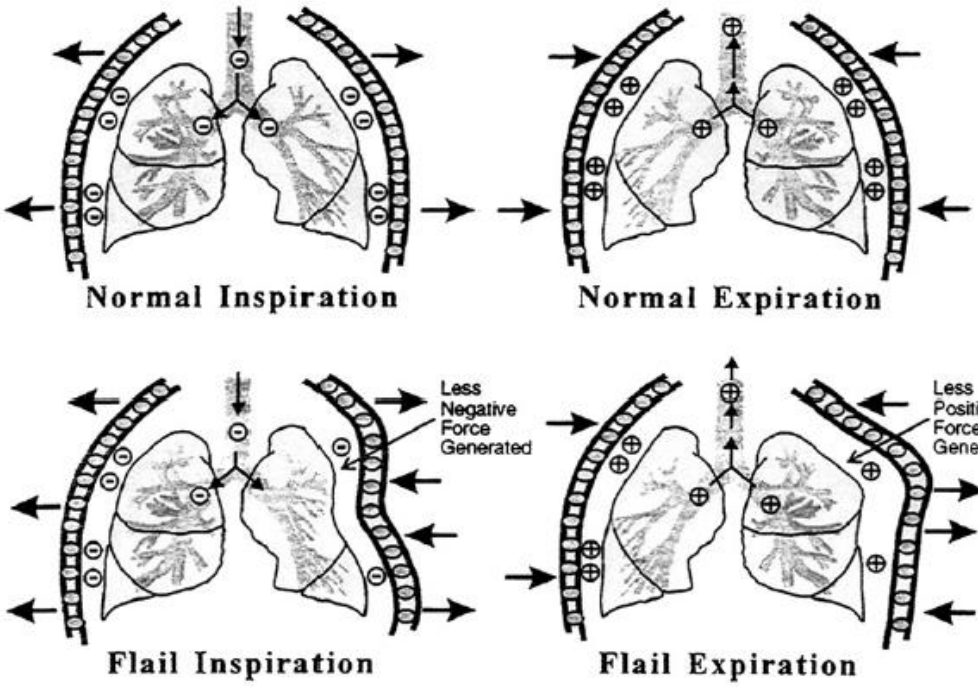
Rib fractures are common, yet they often appear trivial in the setting of *major multisystem injury*. Up to 50% of rib fractures may be missed on the initial chest X-rays. Rib fractures themselves, without associated injuries cause significant morbidity due to *pain* and the subsequent *atelectasis*, as well as the underlying *pulmonary contusion*.

The presence of *rib fractures* in the context of trauma indicates an overall:

- increased injury severity,
- increased requirement for ICU care,
- increased likelihood of abdominal injury, and an
- increased overall mortality rate.

The impact of *the presence of rib fractures* is amplified at *the extremes of age*.

In children, the ribs and the chest wall are much more pliable and as a result, fractures of the ribs are not commonly encountered, and when they are, they are just an indication of the significant energy transfer. Given this pliability, *pulmonary contusion* is more common. Also important, paediatric patients with rib fractures have an increased mortality rate, particularly when combined with *closed head injury*. The elderly are also at increased risk of morbidity and mortality from rib fractures. Patients older than 65 years with 3 or more rib fractures have a 5-fold increased mortality rate (20%) and a 4-fold increased incidence of pneumonia (30%) compared with younger patients. For each additional rib fracture the risk of pneumonia increased by 15% and the mortality risk increased by 20%.



Flail chest has been defined as a fracture of more than 3 consecutive ribs in 2 or more places. A better definition may be ‘an incompetent segment of chest wall large enough to impair the patient’s respiration”.

Flail chest is characterized by paradoxical motion of the affected chest wall segment during respiration such that the flail segment collapses during inspiration and expands during expiration.

During inspiration, the flail segment decreases the negative intrathoracic forces required for adequate ipsilateral lung expansion. The lateral motion of the flail segment lessens the positive intrathoracic pressure needed during expiration.

Pulmonary contusion is the associated injury to the underlying lung tissue. It is the most common injury identified in the setting of thoracic trauma.

The important feature of the flail segment of the chest wall is the underlying *pulmonary contusion* that invariably accompanies this injury (to various degrees), coupled with r*espiratory failure* and *pain*.

Respiratory failure associated with flail chest is due to the underlying *pulmonary contusion*.

The contused lung has been shown to be primarily responsible for the acute morbidity, whereas the chest wall injury is responsible for the need for long-term mechanical ventilation and chronic disability.

Pulmonary contusion is the result of transgression of blood and plasma from the vascular space into the interstitial and alveolar spaces decreasing compliance and ventilation per unit volume, increasing the shunt fraction. Pulmonary vascular resistance increases (as a compensatory mechanism to minimize shunt fraction) in proportion to the contused volume decreasing blood flow to the injured area. The uninjured lung, both ipsilateral and contralateral, also demonstrates changes consisting of thickened septa and oedema with implications for diffusion. Evidence from animal studies shows that pulmonary contusion is not merely a localized process, but probably has global pulmonary and systemic effects relating to cytokine expression and immunosuppression when occurring in a sufficient portion of the lung.

Despite the prevalence and recognized association of *pulmonary contusion* and *flail chest* as a combined, complex injury pattern with interrelated pathophysiology and despite advances in imaging modalities and therapeutic measures, the *high mortality* and *morbidity* continue to be a challenge in improving the outcome of these patients.

The unchanging morbidity and mortality of flail chest/pulmonary contusion and the existence of a wide range of management philosophies, particularly with respect to fluid management and ventilator support, lead to the publishing in 2012 of an updated EAST (Eastern Association for the Surgery of Trauma) practice management guideline.

The recommendations are evidence-based on the available literature and address specific areas of concern, like:

- appropriate fluid replacement;
- management of ventilation perfusion mismatch;
- pain management;
- maintaining adequate pulmonary toilet, and
- management of the unstable chest wall.

Here they (the recommendations) are! Patients with flail chest and pulmonary contusion:

- should undergo standard trauma evaluation/resuscitation;
- should not be excessively *fluid restricted* but rather should be resuscitated as necessary with isotonic crystalloid or colloid solution to maintain signs of adequate tissue perfusion. Once adequately resuscitated, fluid administration should be meticulously avoided. *Diuretics* may only be used in the setting of fluid overload/congestive heart failure;
- should not be *mechanically ventilated* in the absence of respiratory failure. Mechanical ventilation should be done according to the institutional/physician preferences and terminated when not needed anymore. PEEP and CPAP should be included in the ventilator regimen;
- should be provided with *appropriate analgesia*. Epidural catheter is the preferred mode of analgesia. There is no evidence for the effectiveness of paravertebral analgesia;
- should receive *aggressive chest physiotherap*y;
- should not receive steroid for the treatment of pulmonary contusion;
- should be considered for surgical fixation in cases of severe flail chest failing to wean from the ventilator or when thoracotomy is required for other reasons.

While these recommendations might look quite impressive, the body of knowledge regarding management of the flail chest/pulmonary contusion has significant quantitative and qualitative gaps (there is not even a single level I evidence-based recommendation in these guidelines!!).

There are also numerous other areas for further investigation and in search of credible evidence, like:

- hypertonic saline for resuscitation of pulmonary contusion patients;
- new modalities of analgesia;
- techniques of surgical fixation of the unstable chest wall.

TRACHEO-BRONCHIAL TREE DISRUPTION

Tracheobronchial tree injuries are uncommon, but *life-threatening*. *Death* is the immediate consequence, whereas inappropriate management leads to disabling *airway stricture*.

The incidence of tracheobronchial injuries is around 0.5-2%. Most of these injuries are the result of blunt or penetrating trauma, although *iatrogenic injuries* (intubation) and less common causes, such as strangulation, burns or caustic injury are also encountered.
Tracheobronchial injuries are not isolated. They occur in association with other injuries and these are the major determinant in the patient outcome. Head, facial, and cervical spine injuries are frequent and important predictors of morbidity and mortality. Equally frequent are: intra-abdominal, other intra-thoracic and skeletal trauma.

Airway injuries become the first priority in trauma, and because of their acuity and critical importance in stabilizing the patient, assessment, diagnosis and management proceed simultaneously.

Symptoms and signs that may indicate the diagnosis are:

- dyspnea (particularly unexplained/isolated) and respiratory distress;
- hoarseness/dysphonia;
- subcutaneous emphysema;
- haemoptysis;
- pneumothorax (especially with a large air leak or with failure to expand the lung after chest drain).

Tracheobronchial injury requires a *precise preoperative diagnosis* and a *well thought out plan* of surgical management, which may be *unique* for every single patient, in order to restore the continuity of the tracheobronchial tree.
Most penetrating injuries occur in the cervical area – easy access. Most blunt injuries occur in the distal trachea - seem to be located within 2 cm of the carina, with a predilection for the right side – maybe as a result of a heavier right lung with a shorter right main stem bronchus, with relatively more mobile lungs within the pleura against a fixed carina.

What needs to be recognized is the fact that, whatever the mechanism, *securing the airway* in order to maintain oxygenation, in patients with tracheobronchial injuries can be a daunting task.

Knowledge of *the location of the injury* is paramount in providing the best airway.
The critical tool for both assessing the injury and securing the airway is *fiberoptic bronchoscopy*. It allows determination of the site and extent of injury and it allows accurate placement under direct vision of an endotracheal tube. The goal in most cases (particularly for injuries in the upper and middle third of the trachea) is to place the cuff of the endotracheal tube beyond the injury, or at least to protect the injury from positive pressure ventilation. Some authors went so far as to recommend, in situations where this is feasible, conservative management (by bridging the defect by means of a stent/artificial airway) provided that air leak stops and normal healing occurs as documented by regular trachea-bronchoscopy. Lower (distal third) and carinal injuries are more difficult to manage and heroic measures like thoracotomy, jet ventilation via transbronchial catheters and ECMO have been described.

One cannot overemphasize the importance of *maintaining spontaneous ventilation* in these patients.
Once the airway is secured, management depends on the surgical decision related to the location and extent of tracheal injury as well as the associated systemic injuries.
Close cooperation between the anaesthetist and the surgeon is critical to the successful management of a tracheobronchial injury. Depending on the location and extent of the injury, anaesthetic airway management can rely on: single-lumen tube, or
jet ventilation through a small catheter, or, simply,
sterile endotracheal tube inserted through the operative field into the transected airway.

Most of the tracheal injuries should be able to allow primary resection and anastomosis. Extensive injuries of the carina are more problematic and should be repaired rather than resected. A number of

release maneouvres combined with neck flexion ("guardian suture") that will have to be maintained in the postoperative period, can also be utilized.

In the postoperative period, management of associated injuries and their complications may dominate the care of these patients. Careful airway observation, liberal use of bronchoscopy to help clearing the secretions and avoidance of pressure/traction on suture lines is important.

The complications of tracheobronchial repair consist of *anastomotic leak with fistula formation* (can be life-threatening) and late (1 to 4 weeks post injury) *stenosis*. The incidence of these complications is about 5-6%.

AIR LEAKS

Patients sustaining thoracic trauma may develop *air leaks* from the airways or lung into the pleural space from a variety of causes. Such leaks have also been loosely referred to as *bronchopleural fistulas*.

Air leaks can be defined as any extrusion of air from normal gas-filled cavities, including the upper airways, sinuses, tracheobronchial tree, and gastrointestinal tract.

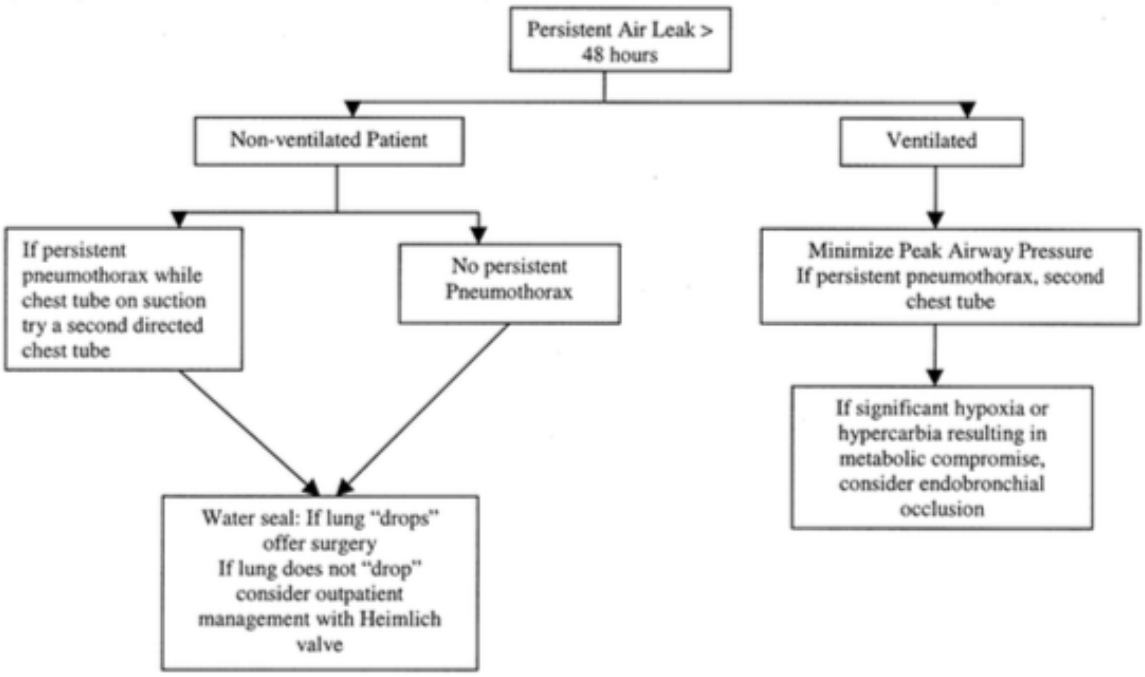
Direct communication between the pleural cavity and the lobar or segmental bronchi are *central air leaks* – "true" *bronchopleural fistula*. Air leaks originating from the lung parenchyma and located peripherally are called *parenchymal-pleural fistula* or *alveolar-pleural fistula* and are *peripheral air leaks*.

The overall approach to patients with central or peripheral air leaks is different. While the central air leaks will require repair of the injury, the peripheral air leaks will need conservative, supportive therapy.

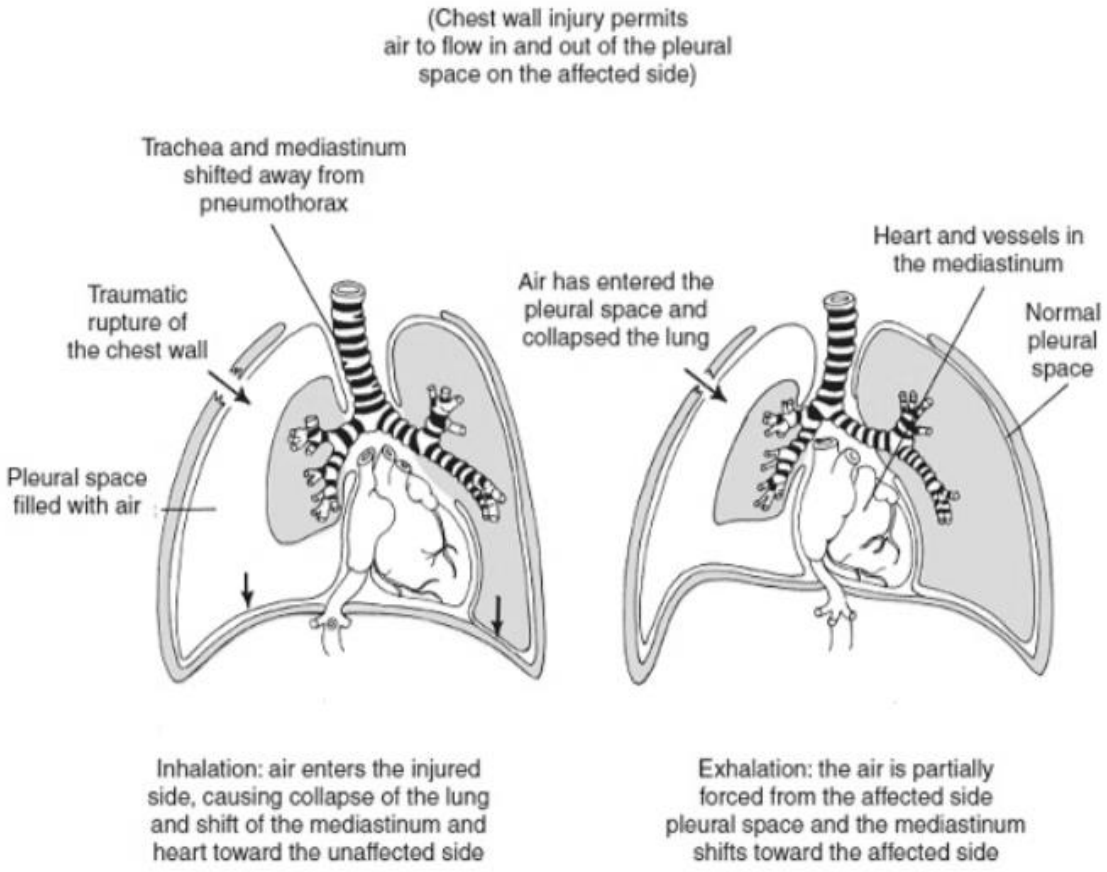
Conditions relevant to thoracic trauma, include:
- pneumothorax;
- pneumomediastinum;
- pneumopericardium;
- subcutaneous emphysema.

The timing and the decision-making regarding operative interventions are determined by whether or not - the patient is ventilated,
- there is pre-existing lung disease, and/or
- the degree of respiratory embarrassment caused by the leak.

Many institutions have an algorithmic approach to dealing with these situations, as outlined below:



Pneumothorax is the presence of air in the pleural cavity with associated lung collapse.
Traumatic pneumothorax occurs as a result of thoracic injury from trauma, surgery, or other iatrogenic interventions.



A *tension pneumothorax* occurs when air enters the pleural cavity during inspiration, but owing to a ball-valve action, cannot escape during exhalation. A tension pneumothorax can produce *circulatory compromise* due to decreased venous return and mediastinal shift and can produce *respiratory compromise* due to compression of the ipsilateral lung by direct tension and compression of the contralateral lung by mediastinal shift.

An *open pneumothorax* communicates with the environment and has been referred to as a "sucking" chest wall wound. The "sucking" refers to the air being drawn into the hemithorax during a spontaneous inspiration, similar to the paradoxical respiration of flail chest.

Pneumothoraces less than 20% might not be even detectable clinically.
Even small pneumothoraces (< 10%) require drainage in ventilated patients, or patients who will require air transport or general anaesthesia, since they can acutely enlarge and tension.

Subcutaneous emphysema is characterized by painless swelling of the tissues due to air tracking along tissue planes. Air may track deeper into the mediastinum, retroperitoneum, scrotum, and into the limbs. If very tense and causing distress, it can be drained by skin incision.

Pneumomediastinum is characterized by the presence of air in the mediastinum as a result of perforation of the pharynx or other gastrointestinal organs (duodenum, oesophagus and air tracking along tissue planes.

The Macklin effect is a pathophysiological process that develops along the following steps:
- alveolar rupture;
- air dissection along bronchovascular sheaths, and
- spreading of this pulmonary interstitial emphysema into the mediastinum leading to pneumomediastinum.

Pneumopericardiaum is characterized by the presence of air in the pericardial sac. It is an uncommon condition, mainly associated with penetrating trauma, and occasionally life-threatening.

CARDIAC INJURIES

Varying from the most dramatic and obvious following penetrating trauma, to the subtle and only suspected, mostly in blunt trauma, cardiac injuries have a wide spectrum of manifestations and require an equally wide variety of management measures.

Cardiac injuries occur in up to 30% in blunt trauma patients. *Blunt trauma to the heart* can result in:
- pericardial rupture;
- cardiac chamber rupture;
- valvular disruption;
- sudden cardiac death (commotio cordis), and
- myocardial contusion.

Myocardial contusion is the most common blunt cardiac injury, occurring in 15% of fatal blunt trauma. It is frequently overlooked, when other more obvious and urgent injuries are present.
Many cases of myocardial contusion are limited and uncomplicated, but a few lead to life-threatening sequelae: arrhythmias;
low cardiac output,
ventricular rupture, and
atrio-ventricular regurgitation due to papillary muscle necrosis.

Evaluation and management parallels that of myocardial infarction: serial ECGs, serial troponin levels, continuous cardiac/cardiac output monitoring.

Treatment should be supportive and addressing the presenting abnormalities (arrhythmias, hypotension).

Penetrating injuries to the heart are the most dramatic of all trauma cases. The presentation of these patients depends on whether the clinical features of *haemorrhage* or *pericardial tamponade* predominate.
Tamponade, when present, is a favourable sign portending a better chance of survival. Leakage of blood into the pericardial sac impair venous filling and restricts cardiac activity. It is characterized clinically by: *Beck's triad* – distended neck veins, muffled cardiac sounds and hypotension;
pulsus paradoxus – decrease in systolic pressure with inspiration;
Kussmaul's sign – increase in venous pressure with inspiration.
Pericardiocentesis in these circumstances can be a temporary therapeutic measure before definitive therapy is instituted.

The type of injury, the time spent resuscitating these patients, we all have our stories, and it boils down to understanding the mechanism of injury, high index of suspicion, early diagnosis, a good deal of hypothermia with good resuscitation and availability of blood and blood products, while relying on swift surgical technique in opening the chest, arresting the blood loss and repairing the damage.

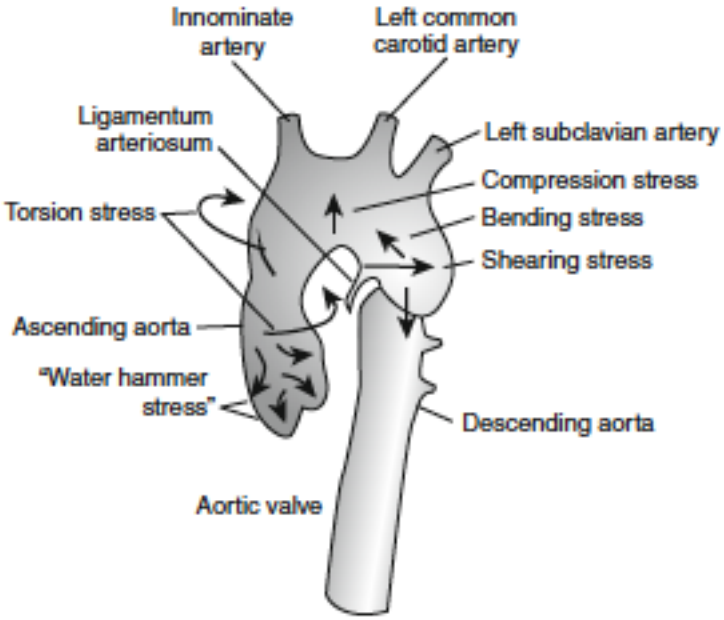
GREAT VESSEL INJURIES

Injuries to the great vessels of the thorax (aorta and brachiocephalic branches), due either to blunt or penetrating trauma, have 80% mortality prior to arrival at the hospital. From those that reach the hospital, 30-50% will die within the first 24 hours.

More than 90% of injuries to the great vessels of the thorax are caused by penetrating trauma. The innominate artery, pulmonary veins, vena cavae, and most frequently the thoracic aorta are especially susceptible to blunt injuries.

Aortic blunt injury usually involves the proximal descending aorta at the isthmus, but other segments, such as the ascending aorta or the transverse arch, mid-distal descending aorta, or even multiple sites have been reported.

There are several different mechanical forces that act in the pathogenesis of blunt aortic injury: shear, torsion, stretching, combined with hydrostatic forces ("water hammer stress": high-pressure reflected wave greatest at the aortic arch is further intensified).



Pathologically, blunt injuries to the aorta can be classified as:

- intimal haemorrhage with or without laceration,
- medial laceration,
- complete laceration,
- false aneurysm formation, and
- periaortic haemorrhage.

Once the patient arrives in the emergency department, evaluation and resuscitation following the principles of ATLS are done. Teamwork and multidisciplinary approach are essential.

The degree of external trauma may not fully predict the severity of injury.

Understanding the mechanism of injury, thorough assessment through the primary and secondary survey and a high index of suspicion will direct the investigations while resuscitation continues as needed. The interventions preceding diagnostic studies may include:

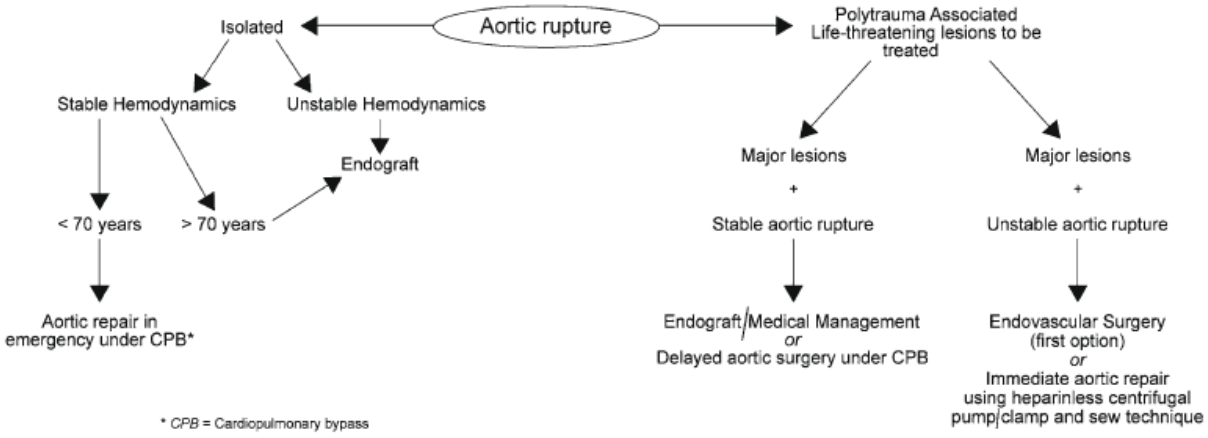
- definitive airway control,
- cardiorespiratory resuscitation,
- blood transfusion,
- chest drain, and in some cases
- craniotomy, thoracotomy, laparotomy, and pelvic fixation.

Suggestive radiological signs (more valuable by their absence, since they are not specific!) on the chest X-ray are:

- widened mediastinum > 8 cm;
- mediastinum:chest ratio >0.25;
- opacification of aorto-pulmonary window;
- irregular aortic knob;
- blurred aortic contour;
- deviation of nasogastric tube;
- tracheal deviation to patient's right;
- depressed left main bronchus;
- pulmonary contusion;
- widened left paraspinal stripe;
- left apical cap;
- fractures (ribs, thoracic spine, clavicle, scapula.

CT imaging is essential in determining the site, type, and the extent of injury, and is crucial in determining the suitability of an endovascular repair and for procedural planning.
Aortography and transoesophageal echocardiography can also provide important information.

Management of aortic injuries depends on the presence of associated/life-threatening injuries, haemodynamic stability and the type of lesion as outlined below:



The treatment of aortic injury, once the diagnosis has been made is almost always prompt.

There is a small group of patients that can be treated expectantly with tight blood pressure and heart rate control either because of their severe comorbidities or because of minimal aortic disruption.

A period of non-operative management may be indicated for patients who are unstable from associated injuries, those with traumatic brain injury, severe pulmonary contusion unable to tolerate one lung ventilation.

Open surgical repair, in spite of all the advances in surgical and anaesthetic techniques, perfusion management, neuromonitoring and postoperative management, still has a mortality rate of 30%. Open surgical repair has the potential to induce major haemodynamic, respiratory, and physiologic stresses in patients who might have other complex injuries. Considerations include:

- potential for massive blood loss;
- haemodynamic alterations induced by aortic cross-clamping;
- requirement for one lung ventilation;
- spinal cord and visceral ischaemia during cross-clamp;
- hypothermia;
- coagulopathy.

Spinal cord ischaemia remains unpredictable and a major cause of morbidity after open repair. Risk factors for developing paraplegia after aortic surgery include:

- duration of aortic cross-clamping – limiting the aortic cross-clamp time to under 30 minutes is crucial in determining the frequency of postoperative spinal cord injury;
- intraoperative hypotension, and
- surgical technique.

The incidence of paraplegia, even with the use of some form of distal perfusion remains 15%. The use of spinal cord protection by means of intrathecal catheters in order to manipulate cerebrospinal fluid pressures still awaits evidence.

Other complications after open aortic repair include: respiratory failure,
pneumonia,
renal failure,
stroke,
coagulopathy,
worsening of pre-existing co-morbidities.

In recent years, *delayed aortic surgery* has represented one of the advances in the treatment of severely traumatized patients. Delaying surgery is not without risk: studies quote a 5% risk of rupture!

Endovascular treatment of thoracic aortic injuries is another therapeutic option, either as definitive repair or as a bridge until the patient is stable enough to undergo open repair.
Endovascular stenting has good results and acceptable mortality and morbidity rates.
Potential benefits:

- can be done under local/regional;
- does not require thoracotomy, one lung ventilation;
- there is no blood loss;
- requirements for anticoagulation are minimal;
- the incidence of paraplegia following stent/graft repair approaches zero: 1.6%.

Limitations of endovascular repair include:

- rigorous anatomic criteria as to the suitability of endograft procedure;
- development of an endoleak;
- lack of long-term data.

Anatomic criteria for endovascular graft include:

- proximal neck of the lesion should be more than 10 mm in length;
- distance of more than 5 mm from the left subclavian artery;
- absence of thrombus, calcification, and haemorrhage on the aortic wall on the neck site.

In spite of the low morbidity and mortality rates, endovascular repair of traumatic aortic injuries presents the practitioner with a certain number of concerns, particularly related to device issues: early endoleak, left subclavian artery compromise, left carotid artery occlusion, behaviour/performance in the long-term as the young trauma patient ages.

OESOPHAGEAL DISRUPTION

The incidence of blunt and/or penetrating trauma that leads to *oesophageal injury* is rare. There are a number of reasons for this. Oesophagus is a relatively protected organ within the confines of the thoracic cage and as such, it requires an impressive force in order to produce damage – and that is why oesophageal trauma is associated with injuries of other organs that might end up being lethal or taking precedence in requiring urgent attention.

In addition to *oesophageal injuries* resulting from blunt or penetrating trauma, more commonly encountered are the iatrogenic oesophageal injuries (perforation as a result of endoscopic procedures) as well as the corrosive oesophageal injuries (foreign bodies or caustic agents ingestion).

Presentation will vary (from completely asymptomatic or vague discomfort, to severe pain, hypersalivation and upper gastrointestinal haemorrhage) depending on the mechanism of trauma and associated injuries and will dictate the management course: investigations and therapeutic measures.

Unlike diaphragmatic disruptions, *missed* oesophageal injuries have a high mortality, while delayed diagnosis of this type of lesions leads to a 30% increase in mortality rates.

Anaesthesia for surgical repair of oesophageal disruption involves respiratory, haemodynamic, and gastrointestinal considerations and requires careful consideration taking into account the type and the anatomical level and extent of the injury. Very often this type of surgery is delayed until haemodynamic circumstances have stabilized and the more serious injuries have been taken care of.

The aim of the operative intervention for traumatic oesophageal injury consists of removal of infected material, debridement of the oesophagus, assessment of the extent of injury, decortication of the soiled areas, closure of the oesophageal defect (if possible) with re-establishment of the patency of the digestive tract free of pathological lesions.

High rate of complications post-oesophageal surgery, mainly related to the anastomotic leak, and dependence on many other parameters like age of patient, nutritional status, type of injury and time to diagnosis, make for a rocky recovery road to complete re-establishment of a functional digestive tract.

DIAPHRAGMATIC DISRUPTION

The reported incidence of *traumatic diaphragmatic injury* has been reported as anything between 1% up to 7% in blunt injuries and up to 15% in patients with penetrating injuries. But they are often missed and notoriously underreported.

Traumatic diaphragmatic hernias are classified both with regard to aetiology and with regard to the time of presentation.

The aetiology includes traumatic diaphragmatic hernias from blunt trauma, penetrating trauma and iatrogenic injury (during abdominal or thoracic procedures – when they can be difficult to identify because of a low index of suspicion).
More commonly (50-80%) they occur on the left side - maybe because of the cushioning effect of the liver on the right side. Left-sided defects may present with herniation of the stomach, large bowel, small bowel, spleen, whereas right-sided perforations are limited to liver, large bowel or omentum into the thoracic cavity. In 1 to 2% of cases diaphragmatic hernias can be bilateral.

A high index of clinical suspicion is the clinician’s best tool when seeking to make the diagnosis.

Diaphragmatic injury rarely occurs in isolation. Diaphragmatic rupture most commonly presents (is recognized) late, as it is possible for the diaphragmatic injury to occur without immediate herniation of intra-abdominal organs into the chest (unless it is picked up early by a chest radiograph done to image the extent of other associated injuries).

Identification of any diaphragmatic defect is, in itself, an indication for surgical repair due to the risk of intestinal obstruction and/or visceral strangulation.

In cases of acute herniation secondary to trauma, the abdominal approach is the best for repair of the diaphragm – most likely the associated injuries will "steal the show". For patients in whom a delayed rupture is identified, thoracic approach is often preferred. Minimally invasive surgery has taken over the management of chronic diaphragmatic hernia as well and either a laparoscopic or thoracoscopic approach has been described.

Mortality for diaphragmatic hernia repairs is dictated by the severity of associated injuries, being almost similar for both blunt and penetrating trauma (10-30%).

DISRUPTIVE TECHNOLOGY

Disruptive technology can be defined as a *new technology* that unexpectedly displaces an established technology. Introduction of the printing press, the television, the widespread availability of cellular phones, are all examples of disruptive technology. Not only did they change the world in which we live, but they also displaced previously successful technological methods.

The term disruptive technology has not been widely used in surgery and medicine. However, this term seems particularly applicable to express/explain *the impact of new technology on the treatment of surgical patients.*

In the treatment of *thoracic trauma* there are a couple of advances that significantly affected the way we manage these patients. These are:

- *eFAST* (extended Focused Assessment with Sonography for Trauma) examination;
- the use of *thoracoscopy;*
- delayed and *endovascular repair* of traumatic aortic disruption;
- *operative fixation of rib fractures*;
- *pulmonary tractotomy* as a lung-sparing technique;
- new models of miniaturized/simplified *ECMO*.

eFAST examination
The use of ultrasound has been embraced in the evaluation of injured patients for a while, now. Used initially for the detection of fluid in the peritoneal cavity where it replaced the diagnostic peritoneal lavage, it moved on to diagnose the presence of cardiac tamponade replacing pericardiocentesis and diagnostic pericardial window. The eFAST examination uses the ultrasound to provide the early diagnosis of pneumothorax. Loss of the "lung-sliding" and the absence of comet-tail artefacts has a high sensitivity, high accuracy and high negative predictive value for the diagnosis of pneumothorax.

Thoracoscopy
Minimally invasive technique for the diagnosis and treatment of traumatic injuries of the chest, thoracoscopy has proved useful in determining the cause of persistent pneumothorax, in diagnosing injuries to the diaphragm, great vessels, heart, lung, oesophagus, removal of foreign bodies. And it does all these things with less postoperative pain, a shorter recovery period, and a greater chance of returning to the pre-injury levels of activity.

Delayed and endovascular repair of thoracic aortic injury
One of the most devastating injuries – blunt injury of thoracic aorta – with a high mortality and morbidity, has undergone a paradigm shift with respect to treatment. From early open repair, patients with acute traumatic aortic injury now undergo, in 65-70% of cases, delayed endovascular treatment. While TEVAR can be done without significant heparinization, without requiring lung isolation or changes in position for patients in traction for long bones and pelvic fractures, it stil raises concerns

over progressive aortic dilatation with aging, adequacy of stent graft characteristics and durability and the need for surveillance radiography.

Operative fixation of rib fractures
The indications for surgical stabilization of rib fractures are changing and seem to include, apart from patients with chronic pain, those in the acute setting of trauma with respiratory failure and those with flail chest. The only injured patients that can escape operative fixation with plates, Kirschner wires and various bridging devices, are those that are haemodynamically unstable. Operative fixation of the ribs contributes to - fewer days of mechanical ventilation,
decreased rates of VAP,
shorter ICU length of stay,
lower mortality rate,
decreased incidence of sepsis,
fewer tracheostomies, and
decreased chest wall deformities.

Pulmonary tractotomy
Penetrating lung injuries are associated with a high morbidity and mortality. Therefore, techniques that achieve haemostasis while preserving the maximal amount of pulmonary parenchyma are desirable.A major advance in the treating of these injuries was the introduction of pulmonary tractotomy whereby the tract of the lung injury is opened and damaged bronchi and vessels are ligated instead of performing a lobectomy or a pneumonectomy. It is a fast and effective technique that allows preservation of lung parenchyma while reducing the mortality rates.

ECMO
As an extracorporeal device that provides cardiac and respiratory support, ECMO is the buzz word of the ultimate in state of the art technology meant to be saving the world. It definitely seems to be providing support for complex thoracic procedures in patients with severely compromised pulmonary function, who otherwise would not tolerate a conventional surgical and anaesthetic approach. Advances in technology with respect to miniaturization and simplification have provided true portable support ability.

EMPYEMA/LUNG ABSCESS

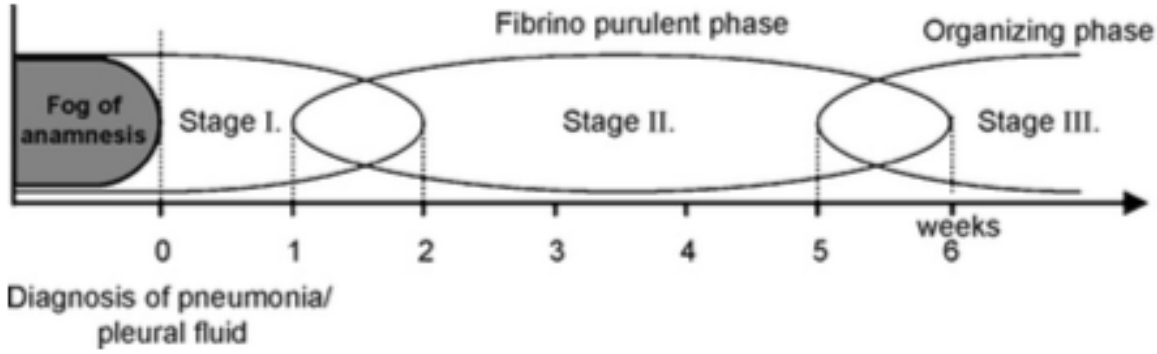
An *empyema* is a collection of pus within the naturally existing anatomical cavity. It must be differentiated from an *abscess,* which is a collection of pus within a newly formed cavity.

Empyema thoracics is a dynamic process defined as a pleural space infection, localized or involving the entire pleural cavity.
The incidence of empyema is increasing worldwide and has a mortality rate of 10-20%. In the elderly and chronic debilitated patients, mortality rates can reach 25-75%.

Empyema can occur either as:
- *primary empyema* – a complication of a disease of the pleura or the lung (parapneumonic effusions, tuberculous, malignant effusions); or
- *secondary thoracic empyema* – resulting from a previous intervention to the chest (invasive procedures – lung resections, trauma – blunt or penetrating).

The complete, unintervened process of development of thoracic empyema takes about 5-6 weeks and it evolves in three stages. In stage I (exudative phase the visceral pleura remains elastic and the dimensions of the thoracic cavity are maintained.
In stage II (fibrinopurulent phase) the pleural fluid becomes thick and purulent. The fibrin deposits construct bridges which septate the effusions creating multiple loculations.
In stage III (organizing phase) a sheet of inflammatory tissue gradually compresses the underlying tissue causing contraction of the affected hemithorax. The mediastinum is shifted ipsilaterally, the diaphragm is elevated and the spaces between the ribs are narrowed.

Something must be said about bacteriology (however boring that might be!). Pleural fluid culture remains negative in about 40% of aspirates. Streptococcal species account for 50% of positive cultures with the other 50% comprising Staphylococcus species, anaerobes and Gram-negative organisms. In the hospital-acquired infections, methicillin-resistant Staphylococcus aureus (MRSA) may account for 60% of cases, whereas Gram-negative organisms such as Escherichia, Enterobacter and Pseudomonas species account for the majority of the remainder.



The primary therapeutic aim: “ubi pus evacua” – if you find pus, remove it – has not changed since the age of Celsus!

The basic principles for treatment of thoracic empyema are:
- systemic treatment of the underlying cause of infection;
- removal of infected fluid and debridement of the pleural space;
- full re-expansion of the lung;
- supportive measures to improve patient’s condition and prevent complications including physiotherapy, nutritional support and thromboembolic prophylaxis.

Surgery is indicated when chest drainage and antibiotic treatment have failed to achieve resolution. “Trapped lung” is a common result of inadequately treated parapneumonic effusions and is characterized by the inability of the lung to expand fully and by an impairment of perfusion, leading to a “restrictive” respiratory syndrome.

Anaesthetic management of these patients requires careful consideration as they may have significant co-morbidities, be acutely unwell and have underlying severe chronic lung disease. In these circumstances, surgery is potentially life-saving and any delay can only lead to a worsening of the patients’ condition.

The major consideration in a patient with empyema is the presence of a *potential communication* of the septic pleural cavity with the trachea-bronchial tree i.e. bronchopleural fistula and *the possibility of soiling* of the unaffected lung. To this end, *lung isolation* before positive pressure ventilation is an absolute indication and the use of a double lumen tube (rather than a bronchial blocker) is going to facilitate suctioning/removal of pus.

One must remember that surgical access might not necessarily be improved by single lung ventilation due to the presence of adhesions and pleural thickening.

Lung abscess is a localized area of lung suppuration.
It carries a high morbidity and mortality (10%).
Surgical treatment is indicated in large abscesses (> 6 cm), those resistant to medical therapy and those that complicate (rupture, haemorrhage).
From an anaesthetic point of view, the same considerations as outlined above, apply.

TRACHEOBRONCHIAL TREE OBSTRUCTION

Tracheobronchial tree obstruction is a relatively common condition encountered in both adult and pediatric population.

There are two different groups of pathologies that lead to the same result (obstruction): *foreign bodies* and *central airway obstruction*. Both these groups can present either dramatically in acute respiratory distress or can evolve silently only requiring intervention later, when “in extremis”.

FOREIGN BODIES

The majority of *foreign bodies* are inhaled by children younger than 3 years. Adults (peak incidence in the sixth decade of life) can also inhale foreign bodies intentionally (dementia, psychiatric conditions) or unintentionally (altered sensorium).

Aspiration of a foreign body is a potentially lethal event. Many deaths occur before arrival at the hospital. Nevertheless, anaesthesia and bronchoscopy for removal of foreign bodies have increased morbidity and mortality.

The clinical progression of foreign body aspiration occurs in three stages:
- the initial stage is characterized by a choking episode followed by coughing, gagging, and even obstruction of the airway;
- the second stage is usually asymptomatic – the initial symptoms resolve;
- the third stage indicates a complicated foreign body aspiration, which can be associated with pneumonia, haemoptysis, fever.

Rigid bronchoscopy is the gold standard for both diagnosis and treatment.

Full pre-operative assessment is important and will also attempt to obtain the answer to the following questions that might modify the anaesthetic technique:
- where is the foreign body located ?
- what was aspirated ?
- when did it happen ?

Location of the foreign body determines the potential for complete obstruction: the more centrally located (trachea), the greater the potential for complete obstruction. The location of the foreign body differs between adults (right side of the trachea-bronchial tree) and pediatric patients (central airway) Hypoxia, stridor, voice changes, drooling, are ominous signs.

The type, nature of aspirated foreign bodies raises issues of similar concerns. Organic materials have an ability to absorb water and swell, aggravating the obstruction. They can also fragment easier leading to problems of removal. They can also produce inflammation and irritation locally with the risk of bronchospasm.

Time to presentation of foreign bodies raises concerns related to infection, granulation formation with more difficult retrieval.

Radiographic evaluation includes anteroposterior and lateral views of the extended neck and chest. Both inspiratory and expiratory views should be obtained to evaluate for unilateral air trapping.

There are four main types of obstruction at the bronchial orifice:
- bypass valve obstruction – the obstruction is incomplete and will result in a normal radiographic evaluation;
- check valve obstruction – the foreign body permits airflow into the lung segment but blocks the airflow out of the lung segment;. This results in a mediastinal shift away from the obstruction on an expiratory film;
- stop valve obstruction – particularly when the foreign body has been there for a while! It is characterized by no airflow into the lung segment with its collapse;

- ball valve obstruction – permits airflow out of the lung segment but not into it. It results in atelectasis and a mediastinal shift toward the obstructed segment on an expiratory film.

The management of aspirated foreign bodies depends on the clinical picture.

Clear communication and good cooperation between the anaesthetist and the bronchoscopist is essential: *sharing of an obstructed airway*.

Also, it is vitally important that appropriately sized equipment (and a size smaller) is available and in good working order.

Anaesthetic considerations revolve around: methods of induction;
ventilation during bronchoscopy, and
maintenance of anaesthesia.

Administration of an antisialogogue can prove beneficial in reducing the secretions and avoiding frequent suctioning.

The choice of induction is determined by the consideration of converting a proximal partial obstruction into a complete obstruction by theoretically dislodging an unstable foreign body.
Maintaining spontaneous ventilation during induction has the benefit of avoiding positive pressure ventilation and dislodging the foreign body.

After induction of general anaesthesia the rigid bronchoscope is inserted through the glottis and the anaesthetic breathing circuit is connected to the side-port of the bronchoscope allowing for assisted ventilation as needed.

Liberal use (within the limits of the maximum toxic dose) of local anaesthetic can prove helpful in achieving good anaesthesia and analgesia during the procedure and maintaining oxygenation of the patient.

Maintenance of anaesthesia during the procedure can be achieved either with volatiles or with intravenous drugs.
Optimal head position, open cords, reinflation of atelectatic zones and slow prolonged breaths with adequate pressure can provide ventilation past a partial obstruction.

In extreme situations of cardiopulmonary failure due to foreign body obstruction, ECMO may facilitate foreign body removal and cardiopulmonary recovery.

CENTRAL AIRWAY OBSTRUCTION

Central airway obstruction (CAO) is an interesting, relatively new concept that concerns all the medical and surgical specialties caring for patients with diseases of the chest.

CAO refers to obstruction of *the trachea* and *main stem bronchi*. It can result from a variety of disease processes and is the cause of *significant morbidity* and *mortality*. If left untreated, *death from suffocation* is a frequent outcome.

Management of these patients is difficult, but the new therapeutic modalities made available allow for expeditious relief of almost all airway obstruction.

CAO can be caused by a variety of malignant and non-malignant processes:

- malignant: bronchogenic carcinoma;
  metastatic carcinoma (breast, colon, renal, melanoma)
  laryngeal carcinoma;
  mediastinal tumours.
- non-malignant: lymphadenopathy;
  vascular rings;
  tracheomalacia;

goitre;
foreign bodies.

A particular patient's presentation will depend not only on the underlying disease, but on the *location* of the lesion as well as on the *rate of progression* of airway obstruction. Patients may develop symptoms suddenly, as can happen with foreign body aspiration, or more gradually, as is often the case with slowly growing malignant obstructions.

Signs and symptoms develop when the CAO impairs airflow to the point of increasing the work of breathing or altering the cardiopulmonary interactions. The air hunger of patients with CAO is not related to hypoxia or hypercapnia, but rather to "the increased effort required to obtain the normal velocity of air delivered to and from the lungs".

It is important to note that the trachea is typically significantly narrowed to less than 8 mm before exertional dyspnoea is present. Once the lumen is less than 5 mm, symptoms present at rest.

Pre-operative evaluation of the patient with CAO is crucial in order to ensure survival of these extremely sick patients.

Conventional chest X-ray may not be very informative.
CT and *MRI* studies can provide important information: whether or not an ETT can be used, the size of the ETT, and how far it can be safely advanced down the trachea.
Dynamic flow-volume loops can differentiate between the level (intra- or extra-thoracic) and the nature (fixed or variable) of the obstruction.

The effects of CAO on ventilation depend on:
- the size of the airway at the level of obstruction;
- the location of the obstruction;
- the nature of the lesion; and
- the phase of ventilation.

Bronchoscopy (either rigid or flexible) is always necessary in assessing airway obstructions. A variety of bronchoscopic interventions can relieve the CAO, like surgical resection, core-out, laser ablation, balloon dilatation, cryotherapy and airway stenting.

Bronchoscopy poses special problems for the anaesthetist because the airway must be shared ! These problems are magnified in the situation of an obstructed airway.

An anticholinergic drying agent may be helpful, especially in the presence of excessive secretions – suctioning may interfere with gas exchange.

Achieving airway control depends on the nature of the patient's airway disease. An inhalation anaesthetic induction can avoid the need for a muscle relaxant and is indicated in patients with a variable intrathoracic obstruction. For fixed obstructions, an intravenous anaesthetic induction with muscle paralysis is more appropriate.
Once the trachea is intubated there is the possibility that the airway distal to the ETT can collapse or remain obstructed.

A rigid bronchoscope should always be available to re-establish the patency of the airway:
- an obstructive lesion can be "cored out";
- a stenosis can be dilated;
- an airway stent can be deployed.

Ventilation can be achieved either via a closed system or via jet ventilation.

Dynamic hyperinflation is a real possibility. This may result from central airway resistance that is more pronounced during exhalation.

*A sten*t is a hollow cylindrical prosthesis that maintains luminal patency and provides support.

A stent can exert a barrier effect (preventing further endoluminal growth);
splinting effect (preventing collapse of the lumen); or
both.

Airway stents provide durable palliation and symptom relief in the great majority of malignant central airway obstruction.

A variety of stents are available for application in the tracheobronchial tree: tube stents,
metallic stents, and
hybrid stents.
They have different characteristic based on the materials they are made of and have special indications for use.

Providing anaesthesia for airway stent insertion is a field of high stakes.
The *balance between risks and benefits* is a knife-edge. If there is potential to change the ASA classification status of a patient from IV to II, than, maybe, the risks are worth taking. One must always remember that it can also become an *unjustified ordeal for the very sick*!

Anaesthetic considerations for airway stenting include:
- sitting up may be required in certain circumstances;
- administer supplementary humidified oxygen;
- small dose of glycopyrrolate can be beneficial in dealing with secretions;
- consider steroids;
- techniques can vary from inhalational to TIVA/TCI;
- can intubate, can't ventilate is a likely scenario;
- the rigid bronchoscope is the solution to a securely ventilated and oxygenated patient.

Waking up following stent insertion is more difficult than induction. Stent insertion might not produce the relief expected, and the whole process might downgrade the above-mentioned ASA classification!

BRONCHOPLEURAL FISTULA

Bronchopleural fistula (BPF) can be defined as a persistent abnormal communication between the bronchial tree and the pleural space. Occasionally, there is an additional communication to the surface of the chest: cutaneous BPF.

The incidence of BPF varies between 4% and 20% (following pneumonectomy) and it carries an extremely high mortality risk (20 – 70%).

BPFs can occur from a variety of causes:
- breakdown following surgery;
- rupture of cavity, cyst, abscess, bleb, bulla;
- erosion of bronchial wall by infection (empyema, pneumonia, TB) or neoplasm;
- penetrating trauma;
- iatrogenic: intubation, use of an ETT exchanger,
  mechanical ventilation,
  biopsy,
  thoracentesis.

Approximately two thirds of BPFs are related to surgery, while the remaining are related to tuberculosis, pneumonia, empyema and lung abscess.

Surgical procedures associated with the development of a BPF include pneumonectomy, segmentectomy and wedge resection of the lung.

The BPFs related to surgery could be classified as:

- central – because of the breakdown of pneumonectomy/lobectomy stumps, or
- peripheral – because of breakdown of distal staple lines.

Predisposing factors include:

- right-sided resection;
- long avascular bronchial stump;
- poor surgical technique;
- induction chemo-/radiotherapy;
- residual cancer;
- pre-existing infection;
- nutritional status (hypoalbuminaemia);
- coexistent medical problems (diabetes, steroid administration)
- the need of postoperative mechanical ventilation.

A distinction is appropriate between BPFs that present *early* (during the first several days following surgery) and *delayed* (weeks to years later). Whereas the former results from the stump dehiscence and calls for early closure, the latter is accompanied by an *empyema* and requires clearance of the infection prior to definitive closure.

Acute dehiscences present as sudden, large increases in air leak evident in the thoracostomy drainage system with varying degrees of respiratory distress.

Depending on the size of the leak, respiratory support required varies from just supplemental oxygen to intubation of the contralateral bronchus and single lung positive pressure ventilation.

Bronchoscopy confirms the diagnosis and helps evaluate the location and the size of the fistula as well as the amount of stump - if that is the case – available to proceed with repair.

The vast majority of small, peripheral BPFs heal with appropriate drainage and conservative management (adequate clearance of secretions, nutrition, appropriate antibiotic therapy).

The larger BPFs deserve respect both for their capacity to “steal” tidal volume and cross-contaminate the contralateral lung and the ability to become a useful tool, in experienced hands, for tormenting unsuitably prepared exam candidates.

Anaesthetic management considerations for BPF revolve around:

- careful assessment of the ability to ventilate the patient;
- minimization of airflow across the fistula;
- maintenance of adequate gas exchange in the unaffected lung;
- avoidance of tension pneumothorax;
- prevention of contamination of the remaining lung.

A lot can be said about “assessment of the ability to ventilate the patient” and also about the fact that “experience is the name that most people give to their mistakes”.

Understanding of the pathophysiology of BPF and the determinants of gas flow through the fistula can give one a rational approach in dealing with chest drains and leaks while attempting to maintain oxygenation.

Gas flow takes the path of least resistance. The relative flow of air/gas through a fistula versus normal pathways depends on the transpulmonary pressures and the relative resistance to flow along each pathway. High transpulmonary pressures increase the diameter of fistula and reduce the resistance, thereby increasing the flow through the fistula. Whereas *maintaining spontaneous ventilation* (if possible) is not going to increase the flow through the BPF. In patients with BPF that are already ventilated there are strategies that one can employ in an attempt to minimize the flow through the fistula, like:

- minimize inspiratory pressures;
- decrease inspiration (alter I:E ratio);
- minimize PEEP;
- use differential ventilation via a DLT with reasonable volumes through the unaffected lung (conventional positive pressure ventilation) and CPAP with oxygen below the

critical opening pressure of the BPF on the affected side. Alternatively, the affected lung can also be ventilated with high frequency ventilation.

High frequency ventilation is a term that encompasses a spectrum of alternative techniques collectively characterized by respiratory rates in excess of 60/minute, like

- high frequency positive pressure ventilation HFPPV;
- high frequency jet ventilation HFJV;
- high frequency oscillation ventilation HFOV.

This type of ventilatory support is complex, labour intensive, and requires close monitoring.
Most surgeons will want to begin with a *bronchoscopy* in order to evaluate the size, the position, and the local conditions of the fistula.

If a chest tube is not already in place, one should be established and placed on underwater seal. An appropriate drainage system will ensure against a tension pneumothorax while initiating positive pressure ventilation.
During positive pressure ventilation large BPFs will "steal" tidal volume through the low resistance pathway on offer.
Several anaesthetic options exist: from the *awake bronchoscopy* with topical airway anaesthesia, to the *standard intravenous induction* following thorough preoxygenation and swift bronchoscopy (before significant desaturation occurs) with DLT insertion facilitated by a paediatric bronchoscope. Another option is an *inhalation induction* while maintaining spontaneous ventilation in the sitting up position with the "fistula-side down" – in an attempt to achieve lung isolation at the same time with prevention of contamination of the unaffected side.

Meticulous pre-oxygenation prior to induction is important.
Use of plenty of topical anaesthesia to the airway can help.
Use of short-acting agents allows return to spontaneous ventilation if undue difficulty is encountered.

Once intubation is achieved, the options include conventional two-lung ventilation or differential lung ventilation as outlined above.

Conventional two-lung ventilation can utilize a number of *strategies* in order to reduce mean airway pressures and *minimize fistula airflow*, like:

- small tidal volumes,
- rapid respiratory rates,
- reduced inspiratory times,
- elimination of PEEP (fistula would release the pressure).

There are also *non-operative* therapeutic measures that can be applied to those patients with BPFs who are poor operative candidates like: continued chest tube suction;
various drainage systems
Heimlich valves;
bronchoscopic approaches (application of sealants, stents, one-way endobronchial valves).

References

Available on request

Notes:

45



New Tools and Trends: Airway Rescue



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Introduction

Mastery of airway assessment and management remains a key area of knowledge and core skill for anaesthetists at all levels. The specialist anaesthesiologist is expected to have a commanding grasp of the majority of airway devices and techniques, and should be intimately familiar with dealing with airway emergencies. It is essential to become adept with the use of airway rescue devices and techniques in the non-emergency situation, before such skill is required in anger.

Airway equipment continues to develop along several themes, with new devices appearing with a regularity only matched by the paucity of good quality evidence about their clinical efficacy. Adequate comparative data frequently takes years to emerge. Anaesthesiologists, particularly those involved in equipment procurement, should familiarise themselves with the medical (not marketing) literature, and the suggested guidelines for device assessment.[1]

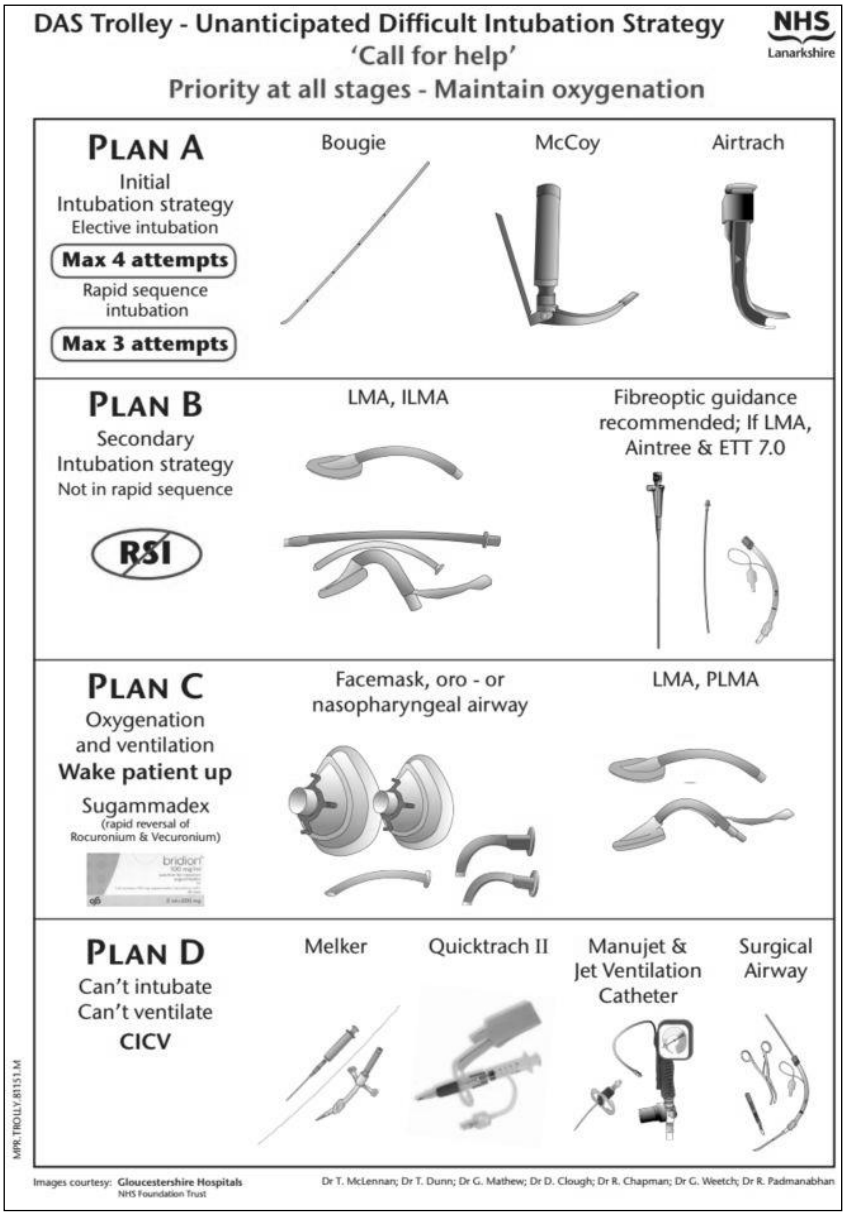
By the time you attend the Refresher Course, these notes will likely be out of date; by the time the exams arrive, the lecture will already be stale. Keeping in touch with the latest developments is a worthy challenge – but keep in mind your examiners have the same battle. OpenAirway.Org (www.openairway.org) is a free, open-access "meducation" (FOAM) resource dedicated to airway management, where you may find the latest information.

New trends

Algorithms for airway rescue and the management of anticipated difficulty continue to be developed and renewed. The major national and professional anaesthesia societies release updated algorithms in a roughly 5 year cycle, which are usually to be found on their respective webpages. The Difficult Airway Society (DAS)[2] and Vortex[3] (see below) guidelines are useful for study and reference in theatre. The 2015 DAS guideline update is anticipated in November 2015. SASA's most recent version was published 2014 and distributed in March 2015.[4] It includes lists of recommended equipment for all levels of care. Significantly trends in the various guidelines include:

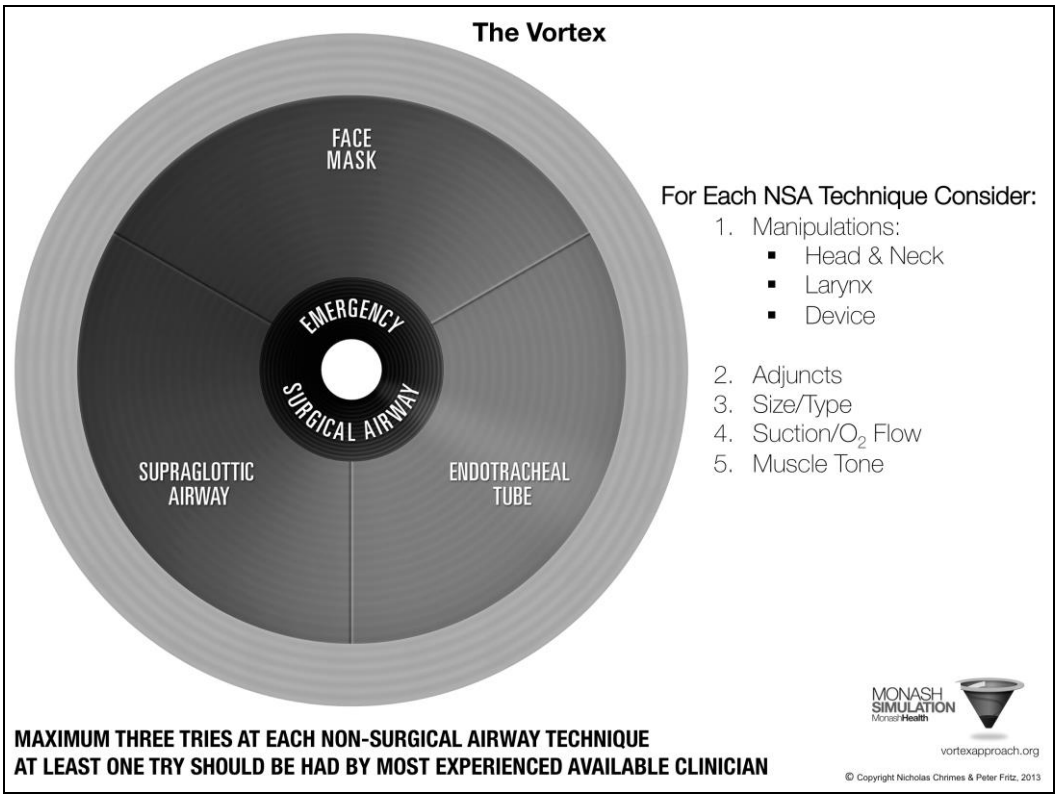
- Early use of video laryngoscopes where suitable skill exists
- Including the use of VL as an initial plan in anticipated difficulty
- Emphasis on supraglottic airways (SGAs) as rescue devices in failed intubation
- SGAs for cardiac resuscitation to minimise interruptions of chest compressions
- A move from referring to CICV (can't intubate, can't ventilate) to the more focused CICO (can't intubate, can't oxygenate) nomenclature
- Planning of multiple strategies (Plan A, B, C etc.) before commencing airway management.

An updated collection of airway algorithms from various sources (ASA, DAS, Vortex, SASA, etc.) can be found at www.openairway.org/algorithms



1. Example of cognitive aid to sequential plan for management of a difficult airway. http://scottishairwaygroup.co.uk/wp-content/uploads/2013/11/ART_NHS_Lanarkshire.pdf

Increasingly, **cognitive aids** for airway emergencies are being developed in recognition of the frequency of human factor errors in airway emergencies. One popular (and useful) example is the Vortex Approach, which encourages the practitioner to move through the three main non-surgical options (mask, supraglottic and endotracheal tube) in any sequence, with optimisation techniques at each stage. This helps to avoid the task-fixation that can occur with failed intubation.



2. Vortex Approach. Open access from http://www.vortexapproach.com/Vortex_Approach/Vortex.html

Recent studies of **paediatric airway** anatomy have shown that our traditional understanding of the round, 'funnel-shaped' airway based on cadaveric research was mistaken.[5] *In vivo* investigation using measurements from video bronchoscopy and MRIs in sedated children demonstrate the glottis to be the narrowest section. Furthermore, the cricoid is elliptical, not circular. This has increased the motivation for cuffed endotracheal tubes in children, provided they are of the high volume, low pressure (HVLP) design. As the cricoid cartilage ring cannot expand, it is still the most common site of post-intubation tissue ischaemia and fibrosis. Cuffed tubes should be chosen ½ size smaller than the traditional uncuffed ETT (age/4 + 3.5), and a leak with the application of no greater than 20 cmH_20 pressure should be elicited with the cuff deflated. Ideally, a cuff pressure manometer should be used with all cuffed ETTs to limit the cuff pressure to <20cm H_20; a similar recommendation is made for cuffed supraglottic airways in children.

Simulation training in airway management is becoming more and more common. The fidelity of training models and especially immersive simulation systems and environments is continuously increasing. Participants find simulation very enjoyable after initial misgivings. A recent systematic review found simulation training at least as good as other forms of instruction, with greater participant enjoyment and satisfaction, and effects on process behaviour.[6] Data is not yet conclusive that this leads to enhanced patient safety, however.

Pre-oxygenation and oxygen delivery: NODESAT, ApOx, DSI and THRIVE

Recent attention in the anaesthesia and emergency medicine literature has focused on effective pre-oxygenation in critically ill patients, and the prevention of desaturation during airway interventions (particularly emergency intubation). These patients are at much greater risk than those undergoing elective surgery die to the presence of lung pathologies, decreased level of consciousness, reduce innate airway protection, increased metabolic demands, reduced oxygen carrying capacity and often decreased respiratory drive as they near the point of decompensation. Strategies to increase effective pre-oxygenation and decrease the likelihood and rate of desaturation (the so-called 'NODESAT' philosophy[7])in this patient cohort include:

- Pre-oxygenation with CPAP or assisted ventilation to increase mean airway pressure – this can be achieved with the use of a bag-valve-mask-reservoir (eg. Ambu® Bag) with a PEEP valve, by manually assisting ventilation on a circle system, or by using non-invasive ventilation (NIV) by face mask (many ICU and anaesthesia ventilators can do this in pressure support mode).[8] Nasal cannula oxygen, especially using high-flow systems, also provides a degree of CPAP.[9]
- Apnoeic oxygenation ('ApOx') during intubation attempts[10] – ideally, this is achieved by the use of specifically designed high-flow nasal cannula (eg. using the THRIVE system - Transnasal Humidified Rapid-Insufflation Ventilatory Exchange[11]), but normal nasal cannulae at flow rates of 10-15 L/min for short periods are effective and well tolerated.[12, 13] This has also been described in paediatric patients at risk of desaturation.[14] A laryngoscope modified to deliver oxygen is also a proposed option.[15]
- Delayed Sequence Intubation (DSI) – A strategy for the patient who is delirious or combative due to the effects of the presenting medical condition and/or hypoxia, and is therefore challenging to pre-oxygenate. A dissociative dose of ketamine is used to optimise compliance without causing apnoea, and therefore improve pre-oxygenation; it can be thought of procedural sedation, where the procedure in question is adequate pre-oxygenation. While the utility is obvious to any anaesthetist familiar with the use of ketamine in critically ill patients, the evidence is still limited to one prospective but observational trial which showed improved oxygenation without complication.[16]

Laryngoscopes

Without doubt, the greatest area of development of new airway rescue tools over the last decade has been in the field of indirect laryngoscopy. Although several novel and effective optical laryngoscopic devices exist (eg. the AirTraq and Bonfils), the rapid improvement and decrease in cost of miniature video camera chips and LED light sources (fuelled by the smartphone industry) has led to an explosion of video laryngoscopes (VLs). At least 13 manufacturers exist at the time of writing:

- Glidescope – various iterations (original, GVL, AVL, Ranger, Cobalt, Titanium)
- Storz C-MAC – numerous blades available (MAC 2-4, MIL 0-2, D-blade)
- McGrath – Series 5, McGrath MAC with multiple blades
- King Vision – disposable ducted and plain blades
- AirTraq – Optical laryngoscope now offering a video attachment
- TrueView – Optical laryngoscope which has a camera attachment
- Pentax AWS – ducted VL with disposable blades
- Intubrite VLS – VL with LEDs designed to cause fluorescence of the vocal cords
- VividTrac VL – 'Plug&Play' disposable USB VL, not yet supported in SA
- CoPilot VL – Not yet supported in SA
- AP Advance VL – Not yet supported in SA
- Coopdech VLP – Not yet supported in SA
- Anatech Disposable VL – Not yet supported in SA
- Numerous other rather dubious copies and untested devices are available online…

The most recent devices in the South African market are the King Vision, McGrath MAC and Intubrite VL. The Glidescope Titanium series blades may be available before the end of 2015.

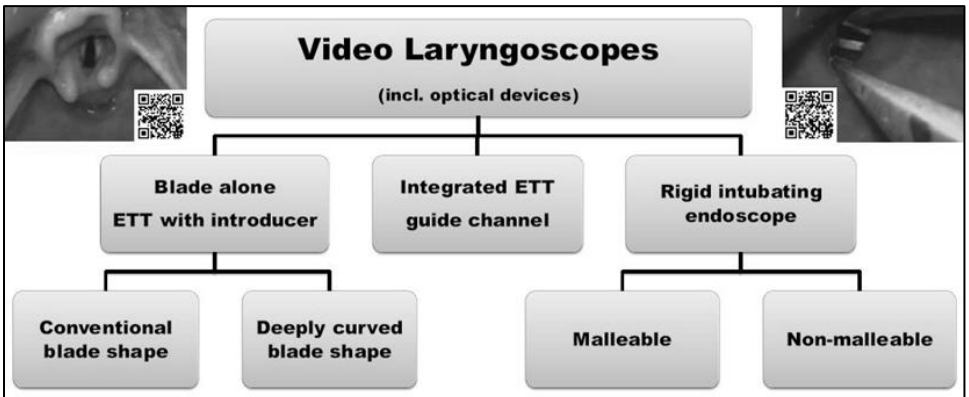
It is beyond the scope of these notes to try and compare the features and evidence behind all these devices. The Glidescope, C-MAC and AirTraq have the best breadth and depth of literature describing their use. However, it is helpful for the practitioner to understand the fundamental principles and function of the major classes of VL. If the optical/video stylets are omitted, there are 3 basic blade shapes, which determine the strengths, weaknesses and appropriate technique for each VL. Blades can either be traditional deeply curved/hyper-angulated or feature a tube guide channel/duct and close to 90° bend. The following table describes the important considerations.

Blade shape	Traditional	Hyper-angulated	Channelled/Ducted
Examples	Storz C-MAC Glidescope Direct TrueView Intubrite VL	Glidescope AVL Glidecope Titanium C-MAC D blade	Pentax AWS AirTraq King Vision
Insertion technique	Right side of mouth with subsequent tongue sweep (traditional technique)	Mostly in midline Devices with flange (C-MAC D) allow tongue sweep	Midline
Ideal uses	Routine VL use Anticipated difficulty without abnormal anatomy (eg. obesity) Teaching intubation	Anticipated difficulty Anatomical abnormalities Airways masses Failed DL	C-spine injury Airway swelling Novice VL users
Strengths	Short learning curve DL often possible May nor require an introducer	Excellent visualisation in many airways that would otherwise require flexible fibreoptic intubation	Easiest to co-ordinate aim of tube (aim with device) Minimal mouth opening required
Weaknesses	Least advantage from video system	Require greatest skill Always require introducer	Can be awkward to insert due to length of device Tendency to insert too deeply
Ideal introducer	Any bougie with coude tip Malleable stylet in “hockey stick” shape	GlideRite stylet Malleable stylet in “hockey stick” shape Steerable introducers	Gum elastic bougie through endotracheal in channel
Ideal forceps	Magill	Boedeker[17] or Suzy[18] forceps	Not applicable

It is important to realise that any intubation performed by indirect laryngoscopy should be expected to require a device to guide the tube around the increase curvature of the airway. This may be an introducer, bougie or forceps. The ideal introducers/bougies for the various types of VL are detailed above. When using a hyperangulated VL blade, it may be necessary to use specially curved forceps.[17, 18]



3. Shaped forceps (eg. Suzy or Boedeker) for use with video laryngoscopes, and standard Magill forceps.[18]



Understanding VLs – Making Sense of the Species

Feature	Class and example of type (**Bold** text indicates pictured example)		
Fundamental structure	Laryngoscope **Glidescope**, C-MAC, King Vision	Video/optical intubating endoscope* **Clarus**, Bonfils, **Shikani**, Levitan	
Optics	Video camera **C-MAC**, Intubrite, King Vision, Glidescope	Fibreoptic* **Bonfils**, Shikani, Levitan	Optical (lens/prisms)* **ViewMax**, AirTraq, TruView
Blade design	Conventional C-MAC, **Glidescope Direct**	Deep curve **Glidescope**, C-MAC dBlade	ETT guide channel King Vision, Pentax AWS, **Airtraq**
Insertion technique	Conventional **C-MAC**, Glidescope Direct	Midline AirTraq, Glidescope, **King Vision**	Retromolar **Bonfils**, Shikani, Levitan
Display location	Separate screen Glidescope, C-MAC, **IntuBrite**, CoPilot, Airtraq Video Adaptor	Handle-mounted **McGrath**, C-MAC PM, King Vision, Pentax AWS, Clarus, AP Advance	Eyepiece* AirTraq, Bonfils, Shikani, Levitan, TruView
Light source	Built-in Glidescope, C-MAC, **AP Advance**	External (cable or pod) **Bonfils**	Laryngoscope handle **TruView**, Viewmax, Levitan
Disposal	Sterilization Glidescope, C-MAC, Bonfils, Levitan, Shikani	Disposable blades Glidescope Cobalt, King Vision, Pentax AWS, AP Advance	Disposable unit AirTraq
Power source	Rechargeable battery	Conventional batteries	

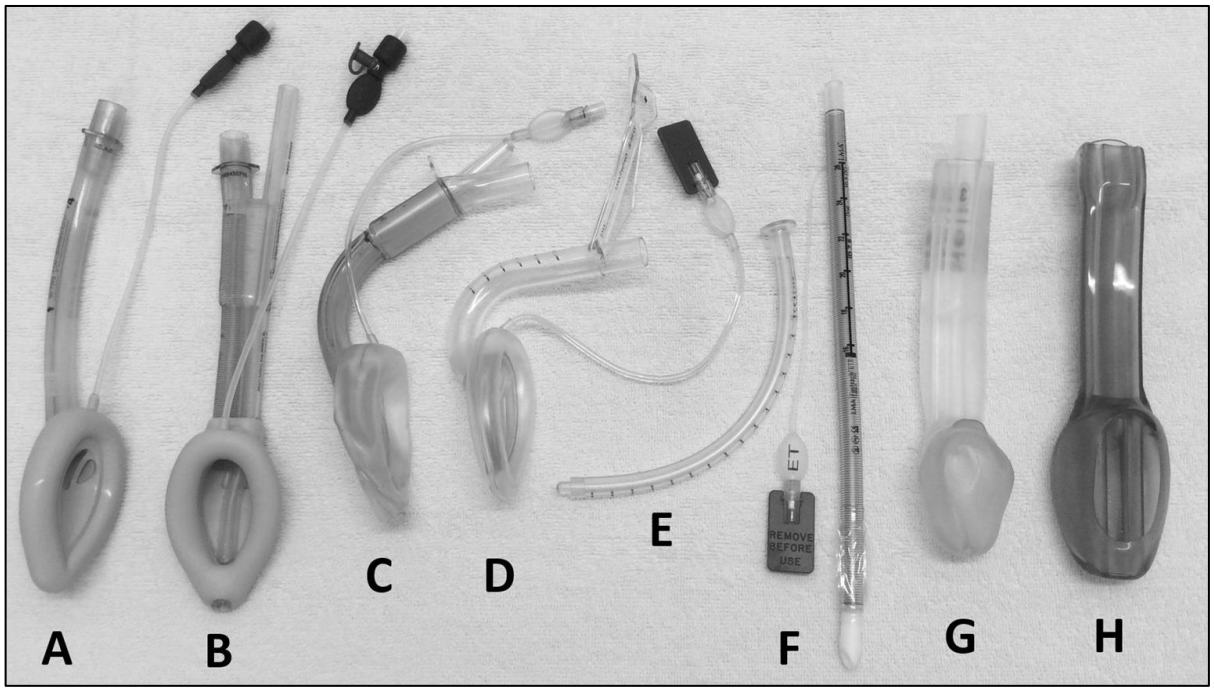
*NB: Not video laryngoscopes in the true sense of the term, but included here for comparison. Examples of types are not exhaustive.

4. Proposed classification of characteristics of indirect laryngoscopes.[19]

Supraglottic airways

There has been a noticeable trend in the airway management algorithms to strengthen the role of supraglottic airways (SGAs) in the management of both anticipated and unanticipated difficult airways.[2, 20, 21] (For the purposes of these notes, the term SGA will be presumed to include the various forms of supraglottic and extraglottic airway devices).[22] Since Brain's original release of the LMA-Classic in the late 1980's, SGAs have become thoroughly entrenched in our practice. Recent audits demonstrate that, in many settings, their use exceeds that of endotracheal intubation.[23, 24] There are now more than 40 commercially available SGAs on the market. Understandably, the weight of evidence for efficacy rests with the older devices.[25]

The efficacy of SGAs as rescue airways is undisputed. With over 2500 studies, the LMA-Classic is undoubtedly the most well documented device,[25, 26] and has been shown to provide effective ventilation in CICO events in 94% of cases.[27] Although there is not the same level of evidence, this performance may be extrapolated to many of the newer devices.[28-35] Increasingly, the use of 2nd generation SGAs (which provide a mechanism for gastric drainage) is being recommended for airway rescue.[29, 36-39] The LMA-ProSeal remains the gold standard in this regard, but several newer devices such as the i-Gel, 3gLM and Air-Q Intubating Laryngeal Airway (ILA) may offer additional benefits.[30, 34, 40-63]

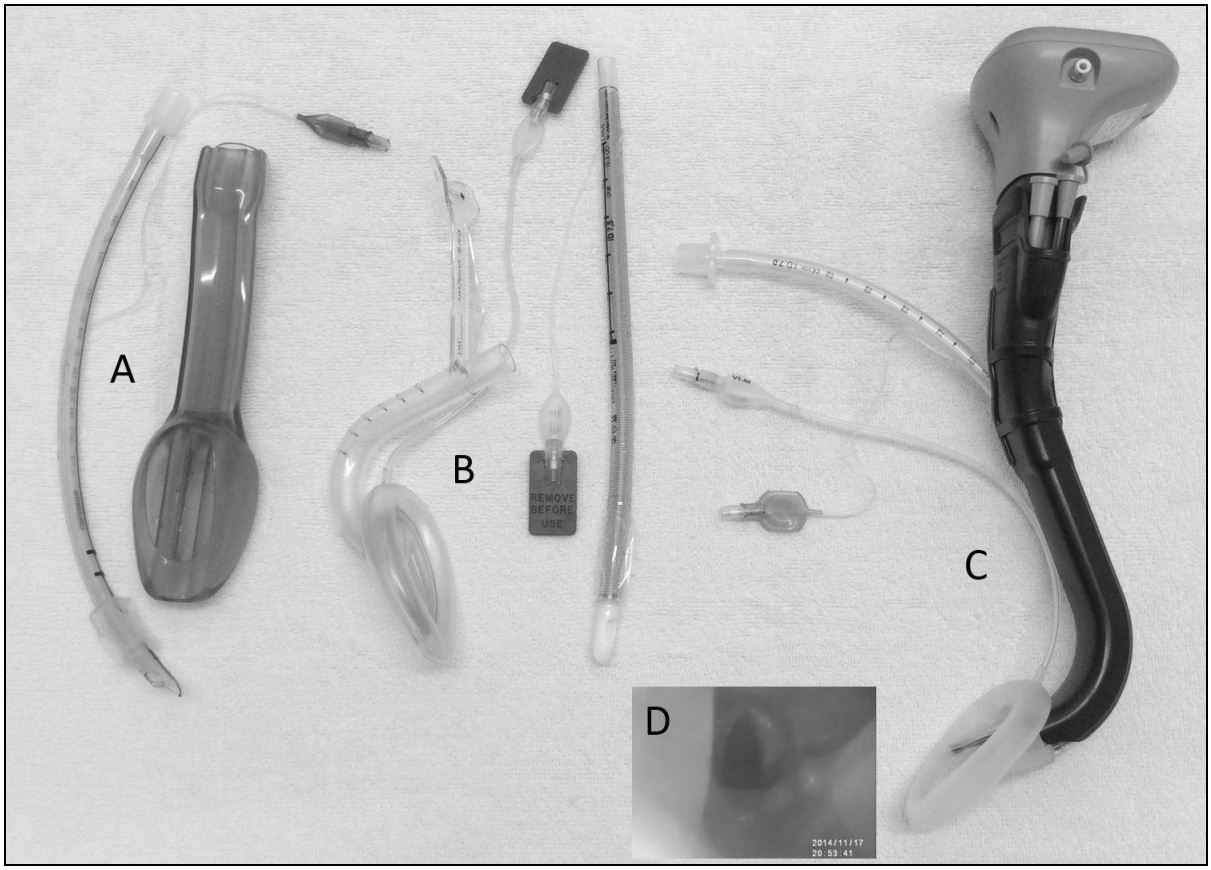


5. A variety of SGAs. A: LMA-Classic B: LMA-Proseal C: LMA-Supreme D: LMA-Fastrach (disposable version) E: LMA-Fastrach push-rod F: LMA-Fastrach ETT G: i-Gel H: 3gLM

The 'Holy Grail' of airway management is a device which can be inserted with minimal training, provides good protection against aspiration, serves as an effective conduit for the placement of an endotracheal tube, is cheap and disposable, and is effective in all patients. This device does not yet exist (or has not yet been proven in the literature). SGAs meet the first criterion (easy insertion), and provide effective ventilation and oxygenation in the majority of patients. The LMA-Fastrach (Intubating Laryngeal Mask Airway, ILMA) has been demonstrated in many studies to provide reliable intubation in patients with difficult airways and is the current gold standard for blind intubation through an SGA, but does not provide any strategies to prevent aspiration.[61, 64-71] However, its performance as a rescue airway remains unsurpassed, and all practitioners should be intimately familiar with its use and the manoeuvres to optimise success.[43, 62, 67, 70, 72-74] Whilst the proprietary silicone wire-reinforced Fastrach ETT is the most effective for intubation through the ILMA, other options do exist.[75-77]

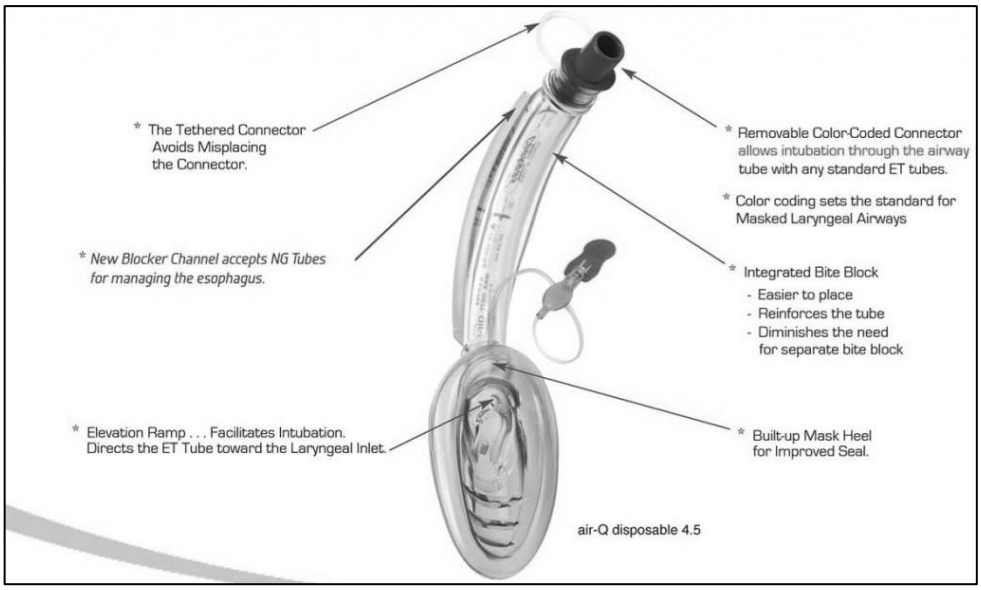
Although fibreoptic-guided intubation through many SGAs proposed for airway rescue can be achieved, it is advisable to use the more modern and cheaper devices such as the i-gel, Air-Q and 3gLM which allow adequate diameter ETTs to be inserted through the device.[30, 34, 35, 40-44, 46-55, 57-59, 63, 72, 73, 78-84] More studies are required to elucidate whether these devices are on par with the ILMA. Use of other SGAs (including the i-gel, ProSeal, etc.) may require an intermediate step, such as the use of an Aintree catheter.[28-32, 34, 35, 39, 50, 54, 85-92]

Intubating laryngeal masks have also been equipped with video capabilities to allow intubation though the SGA under indirect video laryngoscopy. The first device with this ability was the LMA-CTrach, a modification of the LMA-Fastrach which included a fibreoptic bundle and video display. Despite promising results, this device was withdrawn from the market.[59, 74, 93-105] Recently, the TotalTrack VLM has been introduced. This device feature a disposable intubating laryngeal mask coupled with a reusable video camera and display. Three clinical trials have been completed and are in press. The results of the first clinical trial by a South African group show success rates and efficacy rivalling that of the ILMA and CTrach, but further study is required.[106]

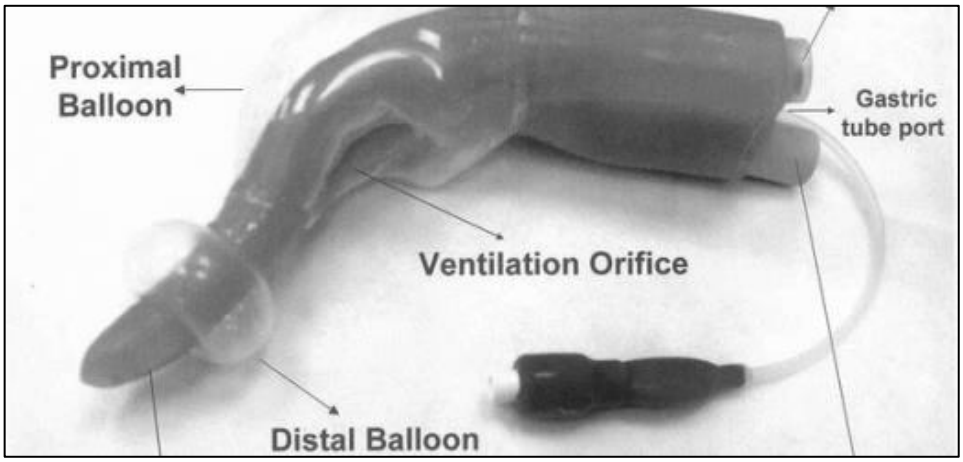


6. Intubating supraglottic airways. A: 3gLM and Parker Flex-Tip ETT B: LMA-Fastrach and proprietary silicne wire-reinforced ETT C: TotalTrack VLM D: Video image through TotalTrack VLM

Three SGAs falling into the proposed 3rd generation have been announced but are not yet in regular clinical use: the Elisha, Baska, and 3gLM.[22, 107, 108] All are designed to facilitate blind intubation through the device, allow gastric drainage, and have 'self-energising' seal, where the act of delivery of positive pressure ventilation causes a dynamic increase in sealing pressure. The 3gLM is also designed with multiple mechanisms to prevent aspiration.[83] The Elisha are described in one preliminary trial each,[108, 109] and while two publications on the 3gLM are in press (***author's data***), results released in conference presentations elucidate SGA function approaching that of the LMA-Proseal, with a good success rates for blind intubation as described.



7. Air-Q Intubating Laryngeal Mask. Image from http://cookgas.com/index.php/products-newer-older-air-q-blocker/



8. Elisha Airway Device. Source: http://anestesiar.org/WP/uploads/2014/02/Elisha-520x245.gif



9. Baska Airway. Source: http://www.device.com.au/wp-content/themes/custom/js/timthumb.php?src=http://www.device.com.au/wp-content/uploads/2013/03/baska_mask.jpg&w=460&h=345

Surgical airways



The NAP4 audit yielded thought-provoking data regarding surgical airways. The majority of surgical access to the airway performed by anaesthetists was by cricothyroidotomy, but this failed in 65% of attempts.[24] Interestingly, the majority of failed attempts were needle cricothyroidotomy. Where surgical cricothyroidotomy was perfomed, the success rate was much higher. Admittedly, a large portion of the surgical cricothyroidotomies were performed by surgeons already in the operating theatre, but the data lends to the hypothesis that an open surgical technique is more successful in any hands than a needle technique.

Certainly, the current paradigm is that surgical airway access should be performed with a bimanual, tactile, "scalpel, finger, bougie" technique, whereby access to the trachea is confirmed by palpation with the little finger before a bougie and thereafter an endotracheal tube is inserted.

Resources

Links to most of the above content, a large collection of open-access airway material and the latest version of these notes can be found at www.openairway.org

The references (listed below) are available on request from ross@wildmedix.com

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46

Endovascular Aortic Surgery

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Abdominal aortic aneurysms

Epidemiology and Pathogenesis

An aneurysm is defined as a segmental, full thickness dilatation of the arterial wall exceeding the normal diameter by 50%. The normal anteroposterior diameter of the infrarenal aorta is generally accepted as 2cm, therefore 3cm is the threshold for diagnosing an infrarenal abdominal aortic aneurysm (AAA). They are characterised by progressive expansion as explained by Laplace's law. The average growth rate is 2-3 mm/year for aneurysms <5,5 cm in diameter and 3-4 mm/year in larger aneurysms, but this varies considerably between individuals. Most aneurysms are asymptomatic until they rupture. Rupture has a very high mortality of 85-90%. Less than half of victims reach a hospital, and of those 30-50% will die. The goal, therefore, is to identify and treat aneurysms before they rupture. Abdominal aortic aneurysms are relatively common, occurring in up to 12% of older males. They are thought to be responsible for 13 000 deaths a year in the USA, but this may be an underestimate as they probably cause other unexplained sudden deaths which are not included in this number.

Abdominal aortic aneurysms are located between the diaphragm and the aortic bifurcation. An aneurysm is classified as infrarenal if it begins below the renal arteries, pararenal if it involves the origin of the renal arteries and suprarenal if it involves the origin of one or more visceral arteries. The term juxtarenal aneurysm is used for those that extend close to the origins of the renal arteries, but are anticipated to require suprarenal cross-clamping (if an open repair is performed). About 85% are infrarenal and often involve the iliac arteries. The more cephalad the aneurysm, the more complex is the repair.

The pathogenesis of aneurysms is distinct from atherosclerosis and involves a degenerative process of all layers of the vessel wall. The pathophysiology is characterised by four events: infiltration of the vessel wall by lymphocytes and macrophages, destruction of elastin and collagen in the media and adventitia by proteases, including matrix metalloproteinases, loss of smooth muscle cells with thinning of the media and neovascularisation. Dissection is a separate disease process usually involving the thoracic or thoracoabdominal aorta. Dissection may cause aneurysmal dilatation, but is rarely the cause of isolated infrarenal aneurysms.

Non-modifiable risk factors include older age, male sex, greater height and a family history of the disorder. Smoking is the strongest modifiable risk factor, others being hypertension, an elevated cholesterol level, obesity and atherosclerotic occlusive disease. AAA's can occur in patients with Marfan's or Ehlers-Danlos syndrome type IV, but these diseases more typically affect the thoraco-abdominal aorta. Up to 85% of patients with a femoral artery aneurysm and up to 62% of those with a popliteal artery aneurysm have an abdominal aortic aneurysm. The prevalence is increased among whites compared to blacks, Asians and Hispanics. Lifestyle factors associated with reduced risk include regular exercise and a favourable diet (including vegetables, nuts, fruit and moderate alcohol intake). Diabetes mellitus is associated with a decreased risk. The prevalence in the rich world seems to be declining, probably as a result of declining smoking rates.

The risk of aneurysm rupture is increased with large aneurysm diameter (>5,5 cm), current smoking, low FEV_1, elevated blood pressure, female gender, greater aortic expansion rate (>0,5 cm/year) and the presence of symptoms.

	Annual Risk of Rupture
Aneurysm Size	1 year incidence of rupture (%)
<5.5 cm	≤1.0
5.5 – 5.9 cm	9.4
6.0 – 6.9 cm	10.2
≥7.0 cm	32.5

Diagnosis

Asymptomatic aneurysms may be discovered by abdominal palpation, screening or during investigation for another condition. They can also present with symptoms or the first presentation may be with rupture. The most common symptom due to the aneurysm is pain, which may be in the abdomen, back or flank and be confused with other disease processes. More proximal aneurysms usually present with back pain while more distal aneurysms tend to present with lower abdominal pain or radiculopathy. Ischaemic symptoms due to thrombosis or thromboembolism are unusual. Systemic manifestations may occur due to infection or inflammatory aneurysms. Inflammatory aneurysms are associated with systemic symptoms, weight loss and elevated inflammatory markers (e.g. CRP). They are associated with a higher perioperative risk and EVAR is the treatment of choice if possible.

Rupture of the aneurysm usually presents with sudden onset severe pain and other symptoms related to the site of the rupture (e.g aorto-iliac or aorto-caval fistula). The classical triad is acute, severe abdominal pain, hypotension and a pulsatile abdominal mass, but these may not all be evident. Abdominal palpation has fortunately not been associated with rupture of an aneurysm. Large or extensive aneurysms may be associated with disseminated intravascular coagulation (DIC) in up to 4% of cases. Uncommon presentations include myocardial infarction due to acute blood loss, heart failure due to arteriovenous fistula, groin pain or sudden appearance of a groin hernia and upper GIT bleeding due to aorto-duodenal fistula (usually after repair, but may be primary).

US recommendations support one time screening in men 65 to 75 years of age who have ever smoked and selective screening in men 65 to 75 years of age who have never smoked. UK guidelines advocate one time screening of all men aged 65. The optimal cohort of people who will benefit from screening, however, remains controversial. Physical examination has low accuracy for screening, with an unacceptably low sensitivity for smaller aneurysms. Ultrasonography is the method of choice, with 95% sensitivity and 100% specificity. CT and MRI scanning have risks and are reserved for preinterventional planning or for diagnosis in symptomatic patients. Use of a screening strategy has shown a substantial reduction in death from abdominal aortic aneurysm and the need for emergency surgery, with an associated increase in elective intervention.

Management

Small abdominal aortic aneurysms (3.0 to 5.4 cm in diameter) should be monitored for expansion. Current guidelines for the frequency of monitoring are: aneurysms with a diameter 3.0 to 3.4 cm, every three years; 3.5 to 4.4 cm, yearly; 4.5 to 5.4 cm, every six months. Medical therapy involves risk factor modification such as smoking cessation, dietary modification and treatment of hypertension and hypercholesterolaemia and other co-existing conditions. No drugs (beta-blockers, antibiotics, anti-inflammatory agents (e.g. mast cell stabilisers), ACE-inhibitors, ARB's, statins and antiplatelet agents) have shown any benefit in decreasing the rate of aneurysmal growth, but randomised trials are ongoing. Most patients should be on a statin to decrease cardiovascular risk.

Two large randomised trials compared elective open surgery with surveillance in asymptomatic aneurysms 4.0 to 5.4 cm in diameter with no survival benefit. The risk of rupture increases significantly for aneurysms above 5.4 cm and is the threshold for repair (open or endovascular). The risk of surgery generally outweighs the risk of rupture below this threshold. Repair of small aneurysms should be undertaken if they are symptomatic (signifying impending rupture) or expand by more than 0,5 cm in diameter over a period of six months. Other factors that may prompt repair at a threshold of less than 5,5 cm include young age with good health, female gender, presence of a saccular aneurysm (most are fusiform) and a family history of abdominal aortic aneurysm. The patient's operative risk and life expectancy must be taken into account when deciding to pursue elective repair.

Methods of repair

Open surgical repair (OSR) was first performed in the 1950's and the first endovascular repair was performed in 1987. Endovascular repair avoids the need for surgical exposure of the aorta and the physiological insult of aortic crossclamping. Endovascular repair may be performed by vascular surgeons, cardiologists or interventional radiologists. Endovascular repair is currently performed in about 75% of patients undergoing abdominal aortic aneurysm repair. It is not presently an option in treating suprarenal aneurysms, but this is likely to change with advances in endograft technology.

Four large trials (EVAR 1, DREAM, OVER and ACE) compared open with endovascular repair, each with a follow-up period of 7-10 years. Endovascular repair confers an initial survival benefit, with 30 day or in-hospital mortality of 1,4% vs 4,2% for OSR. This early benefit disappears over a period of 1 to 3 years. Endovascular and open repair are associated with similar overall mortality over the long term (8-10 years), as well as similar aneurysm-related mortality. Among patients who underwent endovascular repair, 20 – 30% required a secondary intervention, usually related to the development of endoleaks. The majority of reinterventions are percutaneous or require a groin incision, but 2 – 4% of patients required conversion to open repair. Long-term surveillance after endovascular repair involves CT scanning 1 and 12 months after the procedure and yearly thereafter. This is expensive and involves exposure to high doses of radiation, especially in young patients over a long follow-up period, and repeated exposure to contrast media with potential adverse renal effects. It is estimated that the excess risk of cancer from a CT scan is 1:2000. Ultrasound, including contrast enhanced ultrasound (using microbubbles) is an alternative in centres with expertise. MRA may also be an acceptable modality for post-procedure surveillance.

About 20% of patients undergoing open repair require a second operation, usually for complications such as hernia or adhesions. CT scanning at 5 year intervals is recommended for detecting new or recurrent aneurysmal disease after open surgical repair. The choice between OSR and EVAR can be difficult. OSR is preferred if aneurysm anatomy is unfavourable and may be the treatment of choice in young patients (<60 years) with life expectancy >10 years, even with anatomy favourable for endovascular repair.

One large trial (EVAR-2) has compared EVAR with no intervention in patients deemed unfit for open repair, with no long term all-cause mortality benefit. There are problems with this trial, however, and the NICE guidelines state that this trial is “not definitive”.

EVAR is used in the management of asymptomatic as well as ruptured aneurysms. Balloon occlusion eof the aorta may be used in the resuscitation of a shocked patient until the ruptured aneurysm sac is excluded from the circulation by the endograft.

Endovascular repair

Preprocedure aortoiliac imaging:
CT angiography with 3D reconstruction is the technique of choice for preoperative imaging. It is used to assess the extent and orientation of the aneurysm as well as anatomical factors that may change the surgical approach e.g. horseshoe kidney, accessory renal arteries, retrocaval left renal vein or occlusive disease of the mesenteric arteries. In the emergency situation (AAA rupture), CT scanning is performed in stable patients. If the patient is unstable, on-table angiography and intravascular ultrasound (IVUS) are possible alternatives. MRA is not usually used as it does not demonstrate wall calcification well.

Measurement definitions:
Aortic neck diameter – The aortic diameter at the lowest renal artery
Aortic neck length – The distance from the lowest renal artery to the origin of the aneurysm
Aortic neck angulation – The angle formed between points connecting the lowest renal artery, the origin of the aneurysm and the aortic bifurcation
Conical/reverse tapered aortic neck – Occurs when the diameter of the aorta 15 mm below the lowest renal artery is ≥10 percent larger than the diameter of the aorta at the lowest renal artery.
Infrarenal aortic length – The distance from the lowest renal artery to the aortic bifurcation.

Anatomical suitability:
The endograft must exclude blood from the aneurysmal sac. In order to do this, the graft must provide a seal at the aneurysmal neck and distally in the iliac arteries (proximal and distal landing zones). The security of the graft depends on the radial force generated at the landing zones.

An aortic neck diameter of <32 mm is required for adequate fixation. The endograft diameter is determined by adding 15-20% onto the aortic neck diameter. Under-sizing a graft will lead to an inadequate seal. Over-sizing may lead to kinking of the graft with subsequent thrombus or endoleak or

infolding of the graft with endoleak. It may also lead to immediate or delayed neck expansion. A conical neck increases the risk of endoleak or endograft migration.

Aortic neck length should be at least 10-15 mm to allow infrarenal fixation. This segment of aorta should ideally be relatively normal, as calcification or thrombus may interfere with fixation and lead to migration or endoleak.

Aortic neck angulation should ideally be <60°, to prevent kinking, endoleak or migration. This is not an absolute contraindication and depends on device conformability.

Iliac artery and access vessel morphology must be suitable, without significant stenosis, aneurysmal dilatation, calcification or tortuosity. Inferior mesenteric artery, unilateral or bilateral internal iliac artery embolization may be needed before EVAR to decrease the risk of type 2 endoleak.

Preoperative assessment and optimisation

Cardiac risk assessment and optimisation should be performed according to published guidelines (ACC/AHA or ESC). Most patients should be on a statin, other drugs may be used according to guidelines. Most drugs should be continued on the day of surgery, ACE-inhibitors being a notable exception.

Respiratory assessment and optimisation is important as many of these patients are current or former cigarette smokers.

There is a significant risk (up to 2%) of severe perioperative renal dysfunction due to comorbidities, use of intravenous contrast media and potential dislodgement of atheroma near the renal arteries as well as impingement on the renal arteries by the endograft. If renal function has been affected by preoperative contrast use, sufficient time should be allowed to lapse (typically 2 weeks) for the creatinine to return to baseline before surgery is performed, if possible. The role of preoperative acetylcysteine is not well defined in preventing contrast induced nephropathy.

Conduct of the procedure

Aortic stent grafts:
These typically consist of a delivery system, the main body and other modular components such as iliac extensions or cuffs. The device is usually delivered through the femoral artery, either percutaneously or by cutdown. If the femoral artery is too small, an abdominal incision is required to create an iliac conduit. The main body consists of a self-expanding nickel-titanium (nitinol) or stainless steel stent attached to a graft, either made of polyester (e.g. Dacron) or PTFE. Most devices are bifurcated, with access to the contralateral iliac artery required to pull down and deploy the iliac component. Some available grafts are aorto-uniiliac with a separate contralateral iliac limb. Older stent grafts comprised three separate components (aortic with two iliac extensions). Other modular components that may be needed are iliac extenders and aortic cuffs. The support structure may be entirely internal to the graft or external, consisting of hooks, wires or anchors.

Advanced devices and techniques are used to avoid ischaemic complications. Fenestrated grafts are custom-made and have holes allowing blood flow into visceral arteries e.g. renal arteries allowing suprarenal fixation in aneurysms with short necks. Branched grafts have a separate small graft sutured to the basic endovascular graft for deployment into a vessel to preserve flow into it. Branched grafts have been designed to accommodate the internal iliac and renal arteries. The chimney (or snorkel) endografting technique is used to preserve perfusion to branch vessels when an endograft needs to be placed in a suprarenal position to gain additional neck length. Peripheral stents are placed into the branch vessel(s) before the aortic endograft is completely deployed. The branch vessel stent is deployed alongside the endograft (parallel position between the inside of the aortic wall and outside the endograft). Although this technique maintains flow into the visceral vessels, complications related to device insertion and type I endoleak continue to be a problem.

Endovascular aneurysm repair is accomplished through an orderly sequence that includes gaining vascular access, placement of arterial guidewires and sheaths, imaging to confirm aortoiliac anatomy, main body deployment, gate cannulation (bifurcated graft), iliac limb deployment, graft ballooning, and completion imaging.

Heparin 80-100 U/kg is given before stent deployment, aiming for an ACT>200s. Repeated doses may be necessary, so the ACT should be monitored every 30-45 minutes. Protamine may or may not be given to reverse heparin at the end of surgery.

Antibiotic prophylaxis is used according to local guidelines. We use cephazolin, which should not be continued for longer than 24 hours after surgery.

Complications

- Vascular injury: bleeding, dissection, thromboembolism, aneurysm rupture.
- Late – angulation, kinking, thrombosis, endoleak (see below).
- Conversion to open - unusual during primary EVAR, but 2% over the long term.
- Colonic ischaemia. This is uncommon, but when it occurs it has a 50% mortality.
- Spinal cord ischaemia – the incidence is 0,21%, probably due to atheromatous embolization.
- Abdominal compartment syndrome may occur after endovascular treatment of a ruptured aneurysm due to the large volume of blood in the abdomen.
- Post-implantation syndrome – this is an inflammatory response unrelated to infection that occurs in the first few days after surgery. It may be severe, leading to ICU admission. Treatment is supportive.
- Endoleak is a term that describes the presence of persistent flow of blood into the aneurysm sac after device placement, indicating failure to completely exclude the aneurysm from the aortic circulation. Type I and type III endoleak identified at the time of endograft placement are repaired and generally respond to additional ballooning or the placement of additional endograft components. Open conversion is almost never required. Type II and type IV do not require any specific intervention when identified at the time of endograft placement.

Five types of endoleaks are described

Type I endoleak is due to an incompetent seal at the proximal (Ia) or distal (Ib) attachment sites. Aetiologies include under-sizing of the diameter of the endograft or ineffective attachment of the endograft to a vessel wall that is heavily calcified or surrounded by thick thrombus. Type I endoleak is associated with significant pressure elevation in the aneurysm sac and has been linked to an ongoing risk of rupture. All type I endoleaks should be corrected promptly, as spontaneous resolution, though possible, is not typical, and treatment can usually be accomplished by endovascular means. The initial treatment of procedural type I endoleak typically involves re-ballooning of the distal attachment sites, but placement of additional aortic cuffs, iliac limb extensions, or balloon expandable stent is sometimes required. Open conversion is almost never required at the time of EVAR, but is sometimes needed for delayed type I endoleak.

Type II endoleaks are caused by flow into and out of the aneurysm sac from patent branch vessels (e.g. lumbar arteries, inferior mesenteric artery). The incidence of type II leak has been correlated with the number of patent aortic branches prior to endograft placement. Type II endoleaks are the most frequent type, occurring in 10 to 25 percent of endovascular aortic aneurysm repairs.

Type III endoleaks represent flow into the aneurysm sac due to separation of the components of the modular graft system (IIIA), or tears in the endograft fabric (IIIB). Type III endoleaks are as serious as type I endoleaks because they pressurize the aneurysm sac. As with type I endoleaks, the treatment usually involves deployment of additional stent graft components to seal the fabric defect or bridge disjoined modular components.

Type IV endoleak is due to egress of blood through the pores of the fabric and typically resolves in 24 hours. It has not been associated with any long-term adverse events and does not require any treatment. It can, however, be quite disconcerting to see at completion aortography, because it often obscures the more serious type I or III leaks.

Type V endoleak (endotension) occurs in the postoperative period as continued aneurysm sac expansion without a demonstrable leak on any imaging modality. These are not apparent at the time of initial graft placement.

Anaesthetic Requirements

The patient must be able to lie still for 1-4 hours.

Adequate hydration must be maintained to reduce the risk of contrast nephropathy. Many experts would also recommend using sodium bicarbonate (3 ml/kg over one hour followed by 1 ml/kg/hr until 6 hours post-op).

Management of anticoagulation as described.

Monitor serial haematocrits and prepare for massive transfusion (rare). At least a group and screen should be done before surgery. A rapid infusion device and cell salvage should be available in case of haemorrhage. Central venous cannulation is usually unnecessary during EVAR, but at least two large bore peripheral venous cannulae are essential.

Control of blood pressure. Blood pressure should be kept near normal without significant fluctuations to maintain organ perfusion and minimise the risk of ischaemic complications. A mean arterial pressure in the 60's (mm Hg) is needed at the time of deployment to prevent premature deployment and distal migration. If necessary, propofol, esmolol or increased concentrations of the volatile agent may be used to lower blood pressure at this stage of the procedure.

Control of temperature. Active warming with a forced air warmer may be necessary. Warm all intravenous fluids.

Radiation safety is important. Personal protective equipment should be used by all staff in the operating theatre. The surgeon may request episodes of apnoea during screening or at the time of device deployment.

The procedure may be performed in a remote site (radiology suite or catheterisation laboratory) with all the attendant issues.

Anaesthetic choice

General anaesthesia, neuraxial or local anaesthesia with or without sedation are all options. Observational data suggests lower mortality and shorter ICU and hospital stays with avoidance of general anaesthesia, but there are no randomised controlled trials comparing different techniques. Potential advantages of neuraxial or local anaesthesia include avoidance of general anaesthetics with myocardial depressant effects, less alteration of pulmonary mechanics, avoidance of sympathetic stimulation of laryngoscopy and extubation, early detection of anaphylaxis, early detection of aneurysm rupture, decreased blood loss. Potential advantages of general anaesthesia include less concerns about anxiety or patient movement, decreased bowel peristalsis with better imaging and the ability to reliably provide periods of apnoea.

Local anaesthesia is provided by infiltration, which may be supplemented by ilio-inguinal and iliohypogastric nerve blocks or TAP blocks. Sedation and analgesia is provided as necessary. Ischaemic limb pain can be challenging to manage.
Single shot spinal, continuous spinal and epidural techniques have all been used. The goal is to provide analgesia covering T6-L3 dermatomes for a period of up to four hours. Hypotension must be aggressively treated to maintain cerebral and cardiac perfusion.

General anaesthesia usually involves endotracheal intubation and controlled ventilation. Control of haemodynamics is important to avoid aneurysm rupture and to maintain organ perfusion. Analgesic requirements are minimal as incisions are typically small.

Monitoring

Electrocardiography – Five lead ECG with automated ST segment monitoring is required. Ensure the ECG electrodes will not interfere with image acquisition during X-ray screening.

Arterial cannulation is necessary to monitor blood pressure and to allow blood sampling. The cannula should be sited in the limb with the higher blood pressure if there is a discrepancy between the two upper limbs. You may need to attach tubing from the surgeon to measure distal limb pressure after stent deployment. Ensure a male-to-male connector is at hand.

Postoperative Care

The patient will usually be nursed in a high care ward or ICU.
Early enteral feeding should be possible.
Analgesia is given as required
Adequate intravenous fluids are given to prevent contrast nephropathy
Monitor peripheral pulses to detect thromboembolic complications.
Monitor for bleeding.
Antithrombotic therapy – resume preoperative therapy if applicable (e.g. aspirin). Venous thromboembolism prophylaxis should be prescribed.

TEVAR

Endovascular repair of the thoracic aorta was initially used as an alternative in patients considered unfit for open surgery but is now considered an acceptable alternative to open surgery for many patients. It is primarily used as therapy for aortic aneurysm, but is also used to treat other pathologies such as aortic dissection, blunt thoracic aorta injury, aortic intramural haematoma, penetrating aortic ulcers, aorto-oesophageal fistula and others. Benefits include avoidance of sternotomy and thoracotomy, no need for crossclamping of the aorta, less respiratory complications, lower incidence of end-organ ischaemia, less blood loss and quicker recovery.

Pre-operative assessment involves CT angiography. Due to the higher intraluminal pressures, 2 cm seal zones are required in the thoracic aorta. Important vessels that may be covered by the graft include the branches of the aortic arch and visceral arteries. Hybrid procedures (open and endovascular) may be necessary to debranch the aorta by creating a surgical bypass (e.g. carotid-subclavian, ascending aortic-carotid). The endograft is generally placed above the coeliac axis to preserve mesenteric perfusion. If the graft extends below the mesenteric or renal vessels, the options are a chimney or snorkel stent, fenestrated or side-branched grafts or open surgical bypass. Open visceral or subclavian debranching is usually performed before the endovascular procedure, either as a staged procedure or at the same sitting.

Spinal cord protection by means of CSF drainage will be necessary if there will be extensive coverage of the thoracic aorta (>20 cm), if there is a history of previous aortic aneurysm repair or if there is internal iliac artery occlusion. Spinal cord monitoring (somatosensory and motor evoked potentials) may also be necessary and require appropriate anaesthetic management. CSF drainage may be necessary after surgery in cases of delayed neurological injury.

Aortography, intravascular ultrasound or transoesophageal echocardiography are used to position and deploy the endograft at the target locations.

Other management principles and complications are similar to those for EVAR. Noteworthy principles the left radial artery should be avoided if there is a possibility the stent will cover the left subclavian artery.

Notes

47
Anaesthesia for minimally invasive cardiac surgery

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Patients undergoing minimally invasive procedures have smaller incisions, less surgical trauma, and less pain. These patients are often ideal candidates for early extubation and accelerated recovery following surgery, however achieving these goals requires a collaborative effort from cardiac surgical and anaesthesia teams, and ICU staff. The anaesthetic provided should be tailored to facilitate rapid recovery, and may include regional anaesthesic techniques to help provide analgesia with less systemic opioids. As approaches to cardiac surgery become less and less invasive, the expectation for quick extubation after the procedure has increased as well. A reasonable approach is to tailor the anaesthetic to permit emergence and extubation at the end of the procedure, if all the other considerations allow this.

Off-pump coronary artery bypass (OPCAB) surgery is performed on a beating heart without the use of cardiopulmonary bypass. Several similar terms have come in and out of fashion over the past 20 years. In the late 1990s, Calafiore introduced minimally invasive direct coronary artery surgery through left anterior small thoracotomy incision or mini-sternotomy (LAST procedure). This led to a new interest in off-pump and minimally invasive cardiac surgery. The terms minimally invasive direct coronary artery bypass (MIDCAB) and totally endoscopic coronary artery bypass (TECAB/"robotic surgery") are also often heard. Most of these techniques involve the use of a mechanical stabilizer designed to stabilize the target area of the heart where the coronary artery anastomosis is performed, plus/minus an endoscope. The main limitation of these techniques is that access is limited to the left anterior descending and proximal right coronary arteries. Access to the other coronary vasculature and the heart valves is more difficult. The potential benefit of minimally invasive coronary artery surgery is that the side-effects of cardiopulmonary bypass can be avoided. This also resulted in an increase in popularity of OPCAB through median sternotomy, allowing access to more coronary arteries, and the avoidance of one-lung ventilation, which is required for coronary artery surgery through left anterior small thoracotomy. The median sternotomy also allowed rapid initiation of cardiopulmonary bypass in failed off-pump procedures, when a patient becomes hemodynamically unstable.

In the late 1990s a port-access heart surgery system (HeartPort Surgical System Inc) was developed which allowed initiation of CPB, including aortic occlusion, administration of cardioplegia, and cardiac venting entirely with percutaneously inserted catheters, and small incisions to access the surgical site. This technique was however cumbersome and expensive, but was the start of modern-day minimally invasive cardiac surgery.

Recently a video-assisted port access, minimally invasive technique (right mini-thoracotomy) has been developed to repair or replace the mitral and tricuspid valves, as well as repair of uncomplicated congenital heart pathologies such as secundum ASD. This has become very popular. The videoscope allows the surgeon to operate by looking on a video screen, while the rest of the theatre team can also follow the operation. Special surgical instruments are needed to perform this surgery. In addition there are surgeons who have develop a mini-sternotomy technique to replace the aortic valve, as part of their minimally invasive spectrum of procedures. All these minimally invasive techniques present new challenges to the surgeon and anaesthetist.

OPCAB/MIDCAB/LAST

Complete revascularization of the heart by accessing all coronary territories requires adequate exposure and stabilization of target coronary arteries. This may be challenging with limited access. The left anterior descending and proximal right coronary arteries are easily exposed with minimal cardiac displacement and haemodynamic compromise. The circumflex, diagonal, posterior descending, and distal right coronary arteries are more difficult to expose. The application of slings, pericardial sutures and the placement of surgical packs help to displace and elevate the heart anteriorly, providing adequate exposure. A slight Trendelenburg position with rotation of the operating table to the right reduces haemodynamic compromise due to compression of the heart, while performing an anastomosis on the posterior or lateral walls. Exposure of the posterior descending

artery may require a steeper Trendelenburg tilt, such that the apex of the heart is almost pointing towards the ceiling. In order to prevent bleeding from the open coronary artery during anastomosis, the target vessel is usually occluded with slings or microvascular clamps. A humidified carbon dioxide mister-blower is often used to prevent blood obscuring the surgical site. Intracoronary shunts may be used to maintain perfusion, display the suture line and reduce back-bleeding.

The introduction of mechanical stabilizers greatly improves the feasibility of beating heart surgery, allowing good quality anastomoses. The most commonly used stabilizer is the Octopus System (Medtronic), which offer stable access to all coronary arteries. The use of a stabilizer may produce echo artefacts.

Anaesthesia

The conduct of stable anaesthesia is critical to the success of minimally invasive cardiac surgery and/or beating heart surgery, which is performed without cardiopulmonary bypass. Continuous positive communication with the surgeon is critical. Proper patient selection is an important determinant of success. The most important anaesthetic considerations are the prevention of haemodynamic instability and ischaemia. Preoperative assessment should include a review of the angiogram and discussion with the surgeon about the order of grafting. Adequate premedication is required and tachycardia should be avoided. The anaesthetic technique should lend itself to the maintenance of normothermia, and early extubation and ambulation. The operating room should be kept warm to avoid radiant heat loss. The patient’s head could be covered with drapes. A warming mattress and fluid warmer may be used. A forced-air warming blanket is used over the lower half of the body unless the saphenous vein is harvested. The cardiopulmonary bypass machine and perfusionist should be on standby, but is usually not necessary. Conversion to CPB may become necessary during surgery, if the patient becomes unstable. Timing is important when making a decision to convert the operation. Facilities for defibrillation, cardiac pacing and intra-aortic balloon pump counterpulsation should be available. For multiple vessel OPCAB the use of a cell saver reduces the need for blood transfusion.

Standard cardiac monitoring is necessary. Transoesophageal echocardiography (TOE) is helpful in high-risk patients with severe valvular and left ventricular dysfunction, and in the detection of regional wall motion abnormalities, which represents early ischaemic changes. During surgery on the circumflex or posterior descending coronary arteries, the heart is displaced and standard TOE views are not visualized. The ECG pattern may change during cardiac displacement and following the ST segment trend is necessary. The surgeon must communicate to the anaesthetist when the heart is being displaced, when a coronary artery is occluded, and when a shunt has been inserted or removed. Likewise, the anaesthetist must keep the surgeon informed about the use of inotropic and vasoactive medications, ST segment or rhythm changes, hypovolemia and/or new regional wall abnormalities demonstrated on TOE. A comprehensive TOE examination following the completion of anastomoses allows regional wall motion abnormalities to be excluded. The use of pulmonary artery catheters has fallen out of fashion after TOE has become almost routine practice during cardiac procedures. However continuous monitoring of mixed venous oxygenation may usefully detect changes in cardiac output and oxygen delivery.

Induction and maintenance of anaesthesia are depending on local extubation practice. The use of shortacting anaesthetic agents for induction and maintenance allows for earlier emergence and the possibility of early extubation. A balanced anaesthetic technique using propofol, short acting opioids, and volatile agents is popular. Lung isolation techniques (double lumen ETT or bronchial blocker) may be needed to provide one-lung ventilation during thoracotomy or "mini-thoracotomy". This is to assist the surgeon with an improved operating field. A tachycardia during surgery may be avoided by using short-acting beta-blockers. Magnesium sulphate may be used to prevent and treat atrial and ventricular arrhythmias during OPCAB surgery.

Thoracic epidural anaesthesia (TEA) is commonly employed to supplement postoperative analgesia for numerous surgical procedures. Although its use has fallen out of fashion for cardiac surgery, it attenuates the stress response, reduces anaesthetic requirements and promotes early extubation by providing postoperative analgesia. While improvement in outcomes remains debatable, the potential benefits of TEA in both non-cardiac and cardiac surgery are well described. Specifically in patients undergoing CABG, benefits include improved analgesia and pulmonary function, earlier extubation and reduced arrhythmias. Concern regarding epidural hematoma following epidural catheter

placement prior to systemic heparinization for CPB, have prevented widespread use of TEA for patients undergoing cardiac surgery. Thoracic paravertebral blockade may be used to provide unilateral analgesia.

In off-pump cardiac surgery only partial heparinization (100U/kg) is required during the surgical anastomoses, to maintain an activated clotting time of 250–300 s. This is usually reversed with a matching dose of protamine. Minimally invasive on-pump surgery will of course require full heparinization (300U/kg).

The main cause of haemodynamic instability during OPCAB surgery is the decrease of venous return due to chamber compression and abnormal patient positioning. Ischaemia due to occlusion of the coronary arteries during surgical anastomosis may also cause haemodynamic instability. Displacement of the heart increases the risk of intraoperative arrhythmia. Usually the surgeon will revascularize vessels on the anterior aspect of the heart first, before any lifting or rotation is performed. Changes in arterial pressure and cardiac output may occur rapidly during surgical manipulation of the heart, and an efficient anaesthetist will pre-empt this. Optimizing preload, and the use of vasoconstrictors and inotropes may improve cardiac output. The use of pacing wires may be necessary before arterial occlusion. If adequate haemodynamic parameters cannot be maintained it may be necessary to convert to cardiopulmonary bypass. Continuous good communication with the surgeon is of the utmost importance.

The advantage of off-pump surgery is to avoid the complexity and some complications of cardiopulmonary bypass. This includes interference with the coagulation system, and possible multiple-organ dysfunction occurring through a combination of the systemic inflammatory response syndrome, flow abnormalities and embolization. Although the possible reduction of subtle neurological deficit and cognitive dysfunction was initially proposed, several studies have now shown no specific benefit when CPB was avoided. Although the potential for emboli originating from the aorta and the bypass circuit is reduced, the need for aortic manipulation is not eliminated. The renal impairment and respiratory dysfunction that may occur following CPB, have also not been universally demonstrated to be reduced with an off-pump technique.

OPCAB surgery demands a high level of vigilance from the anaesthetist and is technically demanding for the surgeon. The ability to respond quickly to haemodynamic changes is essential, including conversion to CPB. Patients with severe left ventricular dysfunction requiring multiple grafts may be unsuitable for an off-pump technique.

Cannulation

Minimally invasive cardiac procedures often use smaller venous cannulas that have higher resistance. This means that venous drainage by gravity only is insufficient for adequate CPB flow. For this reason augmentation of venous drainage is often required in order to achieve adequate CPB flow. Augmentation of venous flow can be achieved by utilizing either vacuum assisted venous drainage (VAVD) or centrifugal assisted venous drainage (CAVD).

The surgical procedure and strategy will dictate the arterial cannulation technique required. The options for cannulation site include ascending aorta, femoral artery, and axillary artery. The ascending aorta is commonly used for procedures that include an upper or lower hemi-sternotomy, e.g. aortic or mitral valve procedures. The femoral artery is often used for procedures that utilize a right thoracotomy incision, e.g. mitral valve, atrial septal defect (ASD), or tricuspid valve repair (TVR) procedures. The axillary artery has been used for minimal access ascending and aortic arch surgery through an upper hemi-sternotomy.

Surgical procedure and strategy will also dictate the venous cannulation technique used. If an upper or lower hemi-sternotomy is performed then direct right atrial (RA), superior vena cava (SVC), or inferior vena cava (IVC) cannulation with can be utilized. If a right thoracotomy is performed then the right femoral vein is commonly cannulated and placement is guided via TOE. The femoral venous cannula can be advanced through the RA and into the SVC for bi-caval single cannula drainage or can be placed at the junction of the IVC and RA for bi-caval dual cannula drainage. SVC cannulation can also be performed percutaneously using a modified Seldinger technique through the internal jugular (IJ) vein with a large-bore cannula.

Minimally invasive procedures of the right heart (e.g. ASD or TVR) require SVC drainage and the internal jugular vein can be cannulated. An EndoClamp catheter can be utilized to facilitate endovascular aortic cross clamping, antegrade cardioplegia delivery, aortic root venting, and aortic root pressure monitoring during mitral valve or right heart procedures. The most common strategy for cardioplegia delivery in minimally invasive procedures is via direct cannulation of the aorta with a small (14Fr or 16Fr) cardioplegia needle. The needle also allows aortic root venting to be performed. Retrograde cardioplegia catheters can also be directly inserted.

Percutaneous transcatheter procedures

- Aortic Valve
- Tricuspid Valve
- Pulmonary Valve
- Mitral Valve

Transvascular procedures on the heart have become very popular over the past 10 years, and with rapid technological improvements driven by the trade, morbidity and mortality outcomes are now almost comparable to that of traditional open surgical procedures.

Percutaneous techniques to treat mitral valve regurgitation in a minimally invasive transvascular fashion have been under development over recent years. The Mitraclip and Edwards Mobius techniques are just some of the new advances to fix the anterior to the posterior leaflet, to achieve mitral valve competency. In addition, reduction of the mitral valve annulus (e.g. Edward Monarch coronary sinus annuloplasty device) and ventricle dilatation (e.g. Myocor Coapsys ventricular chamber remodeling device) with percutaneous techniques adds to a spectrum of procedures, which can address many aspects of mitral regurgitation and dilated cardiomyopathies.

A full discussion of the exciting new range of transcutaneous aortic valve implantation techniques is outside the scope of this presentation, however, the basic principles will be addressed. Over the past 15 years the TAVI (American-TAVR!) procedure has developed from a novel new ambitious idea to an almost routine event in developing countries. In Germany more aortic valves are replaced today via the percutaneous route than by openheart surgery. This practice is very much driven by public demand for a minimally invasive approach, as well as a very active industry continuously developing new technology. The most commonly used prostheses are the Edward Sapien and Medtronic CoreValve.

Minimally invasive cardiac surgery and transcutaneous catheter laboratory procedures are here to stay. The anaesthetist being involved in perioperative patient management is integral to the success of these patient outcomes. The development of all this new technology could also not have happened without successful and refined anaesthetic techniques.

References

Can be provided on request