

PART II ANAESTHESIA REFRESHER COURSE 2016



DEPARTMENT OF ANAESTHESIA
AND PERIOPERATIVE MEDICINE
UNIVERSITY OF CAPE TOWN



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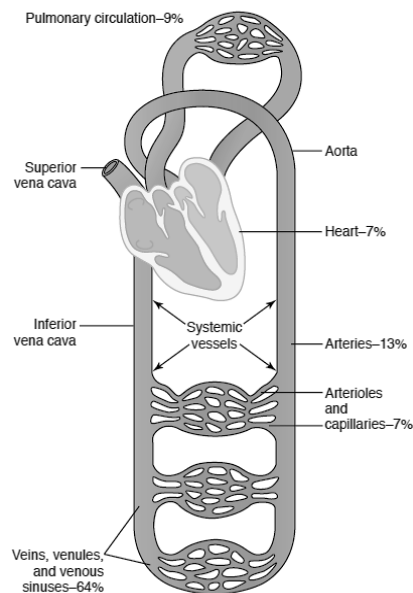
Cardiopulmonary Interaction

Professor Justiaan Swanevelder

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The cardiac and pulmonary systems are operating in series, but also next to each other, and pathology of the one system has a profound effect on the other. Even subtle disruption of this interventricular interaction will affect patient hemodynamics. During the perioperative period there are surgical and anaesthetic influences affecting both cardiac and pulmonary systems. Whenever we intubate and ventilate a patient, the interaction between the two circulations is disrupted. After lung resection there may be an acute increase in right ventricular afterload, which is not appreciated by this thin-walled, low-pressure chamber. This will also affect the left ventricle and compromise cardiac function, especially when the pulmonary system is mismanaged postoperatively. The principles of cardiopulmonary interaction and interventricular interdependence will be discussed.

The factors influencing cardiac output and heart-lung circulation are interdependent. The left and right sides of the heart are connected by the atrial and ventricular septa, and influence each other. The pericardium is a non-compliant sack and contains both the right and the left ventricles. This means that both ventricles are exposed to the same intra-thoracic and intra-alveolar pressure. A change in volume and pressure of one ventricle will directly affect the other. Under normal conditions the left ventricular pressure is more than the right ventricular pressure and the inter-ventricular septum bows into the right ventricle. However, because of the much thinner free wall of the right ventricle it is more sensitive to an increase in pulmonary pressures or right ventricular afterload. Acute pulmonary hypertension will therefore lead to dilatation of the right ventricle, with a consequent trans-septal pressure gradient reversal. The septum can therefore shift to the left and compromise left ventricular filling during diastole. This interaction between the two ventricles during systole and diastole is called ventricular interdependence. The cardiac output on each side of the heart should be virtually equal and changes on the one side will affect the other side. The pulmonary circulation is a low-pressure circuit. Effective functioning of the right ventricle (RV) relies on the pulmonary vascular resistance (PVR) being low. The RV is thin-walled and cannot cope with an acute increase in PVR and will therefore easily fail.



(Guyton Textbook of Medical Physiology, 11th Ed, 2006)

The West Zones are a physiological concept to help understand the interaction between heart and lungs. In Zone 1 there is little flow during the normal cardiac cycle. The alveolar pressure is higher than the capillary and venous pressures. In Zone 2 there may be intermittent flow during the cardiac cycle. The capillary pressure is higher than the alveolar pressure, which is higher than the venous pressure. In West Zone 3 there is continuous flow throughout the cardiac cycle and the capillary pressure, as well as venous pressure, is higher than the alveolar pressure. During normal ventilation, due to gravity, Zone 2 physiology may occur in the top regions of the lung, and Zone 3 physiology in the lower part.

The pulmonary circulation is intrathoracic and is therefore affected by changes to intrathoracic pressure. During normal spontaneous ventilation, the respiratory muscles generate a negative intrathoracic pressure. A deep inspiration will therefore maximize the pressure gradient between the peripheral venous system and the right atrium and improve venous return to the right atrium.

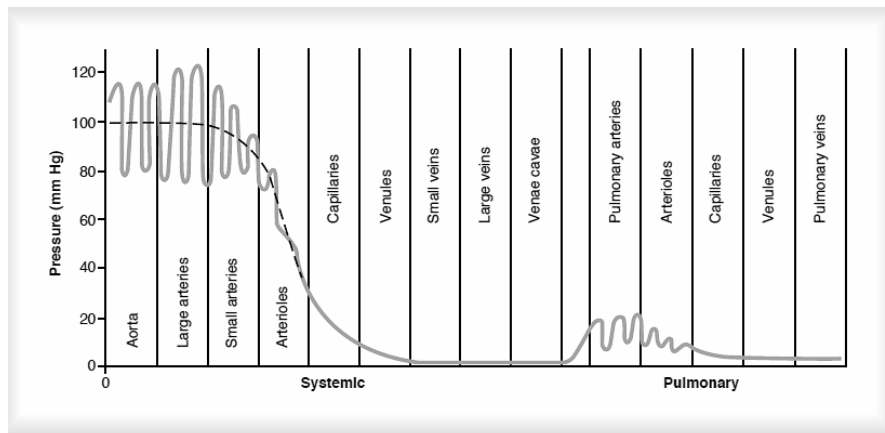


Figure 14-2

Normal blood pressures in the different portions of the circulatory system when a person is lying in the horizontal position.

(Guyton Textbook of Medical Physiology, 11th Ed, 2006)

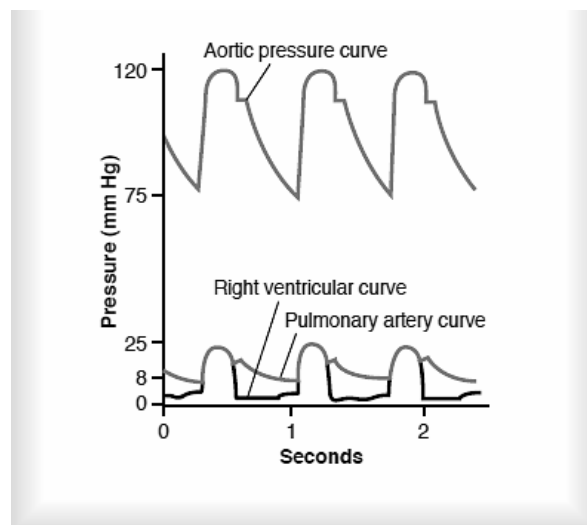
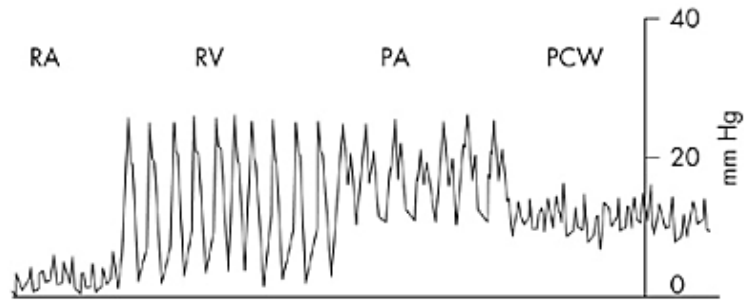


Figure 38-1

Pressure pulse contours in the right ventricle, pulmonary artery, and aorta.

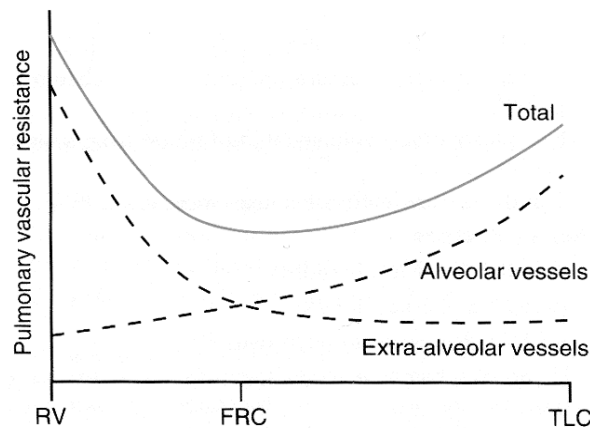
(Guyton Textbook of Medical Physiology, 11th Ed, 2006)



Pulmonary Circulation Pressures in the right heart may be measured with a Pulmonary Artery Catheter (PAC) through the right atrium (RA), through the right ventricle (RV), through the pulmonary artery (PA) and into the distal pulmonary circulation. The catheter is 'wedged' in a distal, small pulmonary artery, to indirectly measure the pulmonary capillary pressure. This is known as the 'pulmonary capillary wedge pressure (PCWP)', which is normally between 7 and 12 mmHg. The pulmonary circulation is according to Ohm's Law:

$$\text{Pulmonary Vascular Resistance (PVR)} = \frac{(\text{Mean Pulmonary Artery Pressure} - \text{Left Atrial Pressure})}{\text{Cardiac Output}} \times 80$$

The normal value is between 100-300 dynes.sec.cm⁻⁵. The PVR is crucial to the performance of the RV.



The above diagram illustrates the relationship between lung volumes and PVR. The optimal lung volume in terms of PVR is the functional residual capacity (FRC). Lung volumes that are either lower or higher, are associated with undesirable elevation to PVR. This is of particular significance during titration of pressures for mechanical ventilation. To the right of the diagram, Zone 1 conditions apply. This will be the case when the airway pressure in the lung is excessive and results in over distention of the alveoli. To the left of the diagram, there is loss of FRC, associated with conditions such as atelectasis or pulmonary oedema. The effect of positive pressure ventilation on the left side of the heart / systemic circulation is explained by the aortic transmural pressure. The thoracic aorta is subjected to changes in pleural pressure, since it is located within the thorax. The transmural pressure of the aorta is the difference between the pressure within the vessel and the pleural pressure.

During normal spontaneous ventilation, the pleural pressure drops, therefore increasing the transmural pressure of the thoracic aorta. This is experienced as an increase in afterload for the left heart. In severe obstructive pulmonary disease such as pulmonary oedema (e.g. when myocardial dysfunction is present), large negative intrathoracic pressure swings may be generated as the patient struggles to breathe. This increase in afterload may be critical. Positive pressure will reduce the afterload of the left ventricle by increasing the pleural pressure and therefore reducing the aortic transmural pressure. Therefore positive pressure ventilation (PPV) at appropriate airway pressure functions to assist treatment when there is significant left ventricular dysfunction. In the context of left ventricular dysfunction and pulmonary oedema, positive alveolar pressure may also increase left atrial return (preload) by pushing fluid out of the alveolus into the pulmonary capillary. This effect is only evident when the left atrial pressure or preload for the left ventricle is already at moderate to high levels. Positive pressure ventilation (PPV) has an important effect on the right side of the heart and pulmonary circulation. West Zone 1 conditions will be created (Alveolar Pressure > Capillary Pressure) and pulmonary blood flow will decrease. That will decrease pulmonary venous return resulting in a drop of cardiac output (CO). The gradient between the peripheral venous bed and the right atrium will be reduced, resulting in a decreased venous return. In the context of LV dysfunction and pulmonary oedema, PPV may also increase LA return (preload) by pushing fluid out of the alveolus into the pulmonary capillary bed. This effect is evident only when the LA pressure and LV preload is already at moderate or high levels. A concern during PPV, particularly where high-end expiratory pressure is required to recruit lung segments, is that the right heart will be compromised. The effect of PPV on the CO will be exaggerated in the presence of situations like hypovolaemia, sepsis, and air trapping in the lungs like in COPD.

The pericardium can limit acute changes in chamber size and limit CO both directly and indirectly.

Shunt and flow calculations through the pulmonary circulation are usually done in the catheterization laboratory. An estimate of the Qp/Qs ratio can be made by using assumed pulmonary venous saturation of 100%. Systemic and pulmonary flow can be calculated using the Fick principle, by measuring haemoglobin concentration, saturations and oxygen consumption. Blood flow is calculated by knowing the amount of oxygen on each side of the vascular bed.

Pulmonary Blood Flow (Qp) = oxygen consumption (VO₂) / (oxygen content in pulmonary vein – oxygen content in pulmonary artery)

Systemic Blood Flow (Qs) = VO₂ / (aortic blood oxygen content - mixed venous oxygen content)

It is assumed that oxygen consumption (VO₂) equals oxygen deliver (DO₂). VO₂ can be calculated using nomograms based on age or surface area. VO₂ can also be measured in the catheterization laboratory in a spontaneously breathing patient. Oxygen content is calculated by the equation above using PO₂ and saturations from the relevant sites. The Qp:Qs ratio is calculated by comparing:

(Pulmonary vein saturation – pulmonary artery saturation)

to

(aortic saturation – mixed venous saturation)

or

$$\frac{Q_p}{Q_s} = \frac{(PV_{sat} - PA_{sat})}{(AO_{sat} - MV_{sat})}$$

The ratio of pulmonary to systemic blood flow is used to assess the significance and direction of intra cardiac shunts, such as ASD and VSD.

Potential Exam Question:

- a. Explain the normal physiological relationship between the right and left cardiac ventricles and their interaction with the pulmonary circulation. (10 marks)
- b. How will the heart-lung interaction be affected in the critically ill patient with special reference to:
 - i. Acute pulmonary hypertension? (20 marks)
 - ii. Ventilation strategies in the critical care unit? (20 marks)

Which of the following is TRUE with respect to cardiopulmonary interactions

- a) West's Zone 1 conditions enhance pulmonary blood flow
- b) During PPV the venous return pressure gradient between peripheral veins and right atrium is increased
- c) During normal respiration West's Zone 1 conditions apply
- d) Mechanical ventilation reduces afterload on the right heart
- e) The optimal pulmonary vascular resistance is achieved at FRC

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Notes

Anaesthesia and Heart Failure

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Introduction

Heart failure (HF) is the clinical syndrome that is the end result of structural or functional impairment of ventricular filling and/or ejection of blood from the heart (diastolic and or systolic impairment). The end result is shortness of breath, fatigue, exercise intolerance, swelling of the peripheries, an increased incidence of ventricular arrhythmias and a shortened life expectancy.

HF is not a diagnosis in itself but is the result of disorders of the pericardium, myocardium, endocardium, heart valves, great vessels or the result of metabolic abnormalities.

The three major risk factors for the development of heart failure are age, hypertension and coronary artery disease.

In the UK up to 4% of deaths are attributable to heart failure and 40% of patients will die within one year of diagnosis. Twenty percent of Americans ≥40 years of age are at risk of HF during their lives.

The incidence of HF increases with age, rising from 20 per 1000 individuals 65 to 69 years of age to >80 per 1000 individuals among those ≥85 years of age. (So it goes)

More than 5 million people in the USA have clinical manifestations of HF.

Perioperatively, heart failure is associated with a substantial increase in morbidity and mortality.

Ejection Fraction

$$EF = \frac{(EDV - ESV)}{EDV} \times \frac{100}{1}$$

Where:

<i>EF</i>	<i>Ejection Fraction</i>
<i>EDV</i>	<i>End Diastolic Volume</i>
<i>ESV</i>	<i>End Systolic Volume</i>

Imaging may reveal preserved or reduced Ejection Fraction (HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction)

ACC/AHA stages of HF

- A** At high risk for HF but without structural heart disease or symptoms of HF
- B** Structural heart disease but without signs or symptoms of HF (NYHA 1)
- C** Structural heart disease with prior or current symptoms of HF (NYHA 1,2,3,4)
- D** Refractory HF requiring specialized interventions (NYHA 4)

NYHA functional classification

- I** No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
- II** Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
- III** Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
- IV** Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.

Classification and definitions of HFrEF and HFpEF

I. Heart failure with reduced ejection fraction (HFrEF) EF ≤ 40 %
Also referred to as systolic HF.

II. Heart failure with preserved ejection fraction (HFpEF) EF ≥ 50 %
Also referred to as diastolic HF.

a. HFpEF, borderline EF 41 to 49 %
These patients fall into a borderline group.

b. HFpEF, improved EF $>40\%$
A subset of patients with HFpEF previously had HFrEF.
May be clinically different from those with preserved or reduced EF.

European Society of Cardiology (ESC) definition of advanced HF

1. Severe symptoms of HF with dyspnea and/or fatigue at rest or with minimal exertion (NYHA class III or IV).
2. Episodes of fluid retention (pulmonary and/or systemic congestion, peripheral edema) and/or reduced cardiac output at rest (peripheral hypoperfusion).
3. Objective evidence of severe cardiac dysfunction shown by at least 1 of the following:
 1. LVEF $<30\%$.
 2. Pseudo-normal or restrictive mitral inflow pattern.
 3. Mean PCWP >16 mm Hg and/or RAP >12 mm Hg by PA catheterization
 4. High BNP or NT-proBNP plasma levels in the absence of noncardiac causes.
 5. Severe impairment of functional capacity shown by one of the following:
 - a. Inability to exercise
 - b. 6-minute walk distance ≤ 300 m
 - c. Peak VO_2 <12 to 14 mL/kg/min.
 6. History of ≥ 1 HF hospitalization in past 6 months.
 7. Presence of all the previous features despite "attempts to optimize" therapy, including diuretics and Guideline directed medical therapy (GDMT), unless these are poorly tolerated or contraindicated, and cardiac resynchronization therapy (CRT) when indicated.

Pathophysiology

The heart chambers become enlarged, with increased wall thickness and stiffness due to fibrosis and hypertrophy of cardiac myocytes.

Diastole is an active process requiring ATP, during which calcium is sequestered back into the sarcoplasmic reticulum. In diastolic heart failure this process breaks down, resulting in a stiff, noncompliant ventricle.

In the healthy heart 75% of ventricular filling (Early, E) occurs passively.

Atrial (A) contraction contributes the rest.

The E/A ratio, therefore, becomes an important marker of diastolic dysfunction.

In HF the atrial component of filling becomes more important and it is easy to understand why atrial fibrillation (AF) is so poorly tolerated.

Pulmonary oedema develops when the increased left sided heart pressures result in increased pulmonary venous and capillary pressures.

Systolic heart failure is the result of the ventricles' inability to generate adequate force to eject the SV.

This reduction in CO, leads to a neuro-endocrine response.

Baroreceptor activity increases sympathetic nervous system (SNS) activity and circulating catecholamines increase which in turn increases O₂ consumption and result in a supply demand mismatch.

The SNS also activates the renin-angiotensin-aldosterone (RAA) system, with consequent sodium and water retention.

However the heart will also release atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) due to volume overload, ventricular dilatation and an increase in ventricular pressure, with resultant diuresis and sodium loss. The other effects of BNP are vascular smooth muscle relaxation, antagonism of the sympathetic nervous system and antagonism of the renin-angiotensin-aldosterone system (RAA).

When this homeostasis and protection of the CVS from the effects of volume overload breaks down and a BNP level of >500 pg/ml is reached, heart failure is highly likely.

This then is a very sensitive blood test for HF.

From the above it is clear then that beta blockers, ACE inhibitors, diuretics and vasodilators will constitute the core of medical management of HF.

Treatment recommendations

Lifestyle changes: weight loss, exercise, smoking cessation and sodium restriction.
Systolic and diastolic blood pressure should be controlled according to clinical practice guidelines.
Diuretics should be used for relief of symptoms due to volume overload.

Fluid restriction: (1.5 to 2 L/day) for stage D patients, with hyponatremia.

Angiotensin-converting enzyme (ACE) inhibitors: (Captopril Enalapril Lisinopril, Perindopril) Recommended for all patients with HFrEF.

Or

Angiotensin-receptor blocker(ARB): (Candesartan, Losartan) Recommended for patients with HFrEF who are ACE inhibitor intolerant .

Beta blockers: (Bisoprolol, Carvedilol, Metoprolol).

Statins: For patients with hypercholesterolemia. (Statins are not beneficial as adjunctive therapy when prescribed solely for HF).

Diuretics: Recommended in patients with HFrEF with fluid retention.

Hydralazine and Isosorbide dinitrate: A combination of Hydralazine and Isosorbide dinitrate can be useful in patients with HFrEF who cannot be given ACE inhibitors or ARBs.

Aldosterone antagonists: (Spironolactone) Recommended for patients with an EF< 35 % and normal renal function.

Digoxin: Can be beneficial in patients with HFrEF, unless contraindicated.

Chronic anticoagulant therapy: (Warfarin or Rivaroxaban) For patients with AF and an additional risk factor for embolic stroke (history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack, or ≥75 years of age)

Omega-3 polyunsaturated fatty acid supplementation. This provides a small beneficial advantage in terms of mortality and admission to hospital for cardiovascular reasons in patients with heart failure.

In addition patients may have:

Permanent pace maker (PPM) or Cardiac Resynchronization Therapy (CRT): Indicated for patients with a LVEF of 35% or less, sinus rhythm, left bundle-branch block (LBBB) with a QRS duration of 150 ms or greater.

Or

Implantable Cardiac Defibrillator (ICD): Patients with cardiomyopathy may well benefit from an ICD.

CPAP: Continuous positive airway pressure can be beneficial to increase LVEF and improve functional status in patients with HF and sleep apnea.

Renal ultrafiltration: May be considered for patients with obvious volume overload to alleviate congestive symptoms if unresponsive to medical treatment.

Surgical management:

Mitral regurgitation due to end stage HF is due to dilatation of the annular ventricular apparatus, changed LV geometry, loss of leaflet coaptation and papillary dysfunction. Surgical MV repair (annuloplasty, with an undersized ring with or without cordal lengthening) can improve EF by 50 %. **(6)**

For patients with Aortic Stenosis: Surgical aortic valve replacement is recommended.

Transcatheter aortic valve replacement (TAVI) for patients who are deemed inoperable. **(7)**

CABG or percutaneous coronary stenting: Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present.

Inotropic support:

Consider the use of intra venous inotropic support for HF patients with acute cardiogenic shock pending definitive therapy or where resolution is expected.

Continuous intravenous inotropic support can also be used for “bridge therapy” in patients with stage D HF refractory to medical treatment who are eligible for and awaiting mechanical circulatory support MCS or cardiac transplantation.

Mechanical circulatory support MCS (LV assist device LVAD/ RV assist device RVAD/ BIVAD / Extracorporeal membrane origination (ECMO):

MCS is beneficial in selected patients with stage D HF in whom definitive management is planned as a “bridge to recovery” or a “bridge to decision” or “bridge to transplant”.

Cardiac transplantation:

Evaluation for cardiac transplantation is indicated for carefully selected patients with stage D HF despite medical treatment, assist device, and surgical management.

Anaesthetic management of patients with heart failure:

Preoperative history and examination:

It is important that patients with HF are identified preoperatively, especially those with evidence of current or recent decompensation, as evidence of decompensation within 6 months of surgery is associated with increased risk of death post-operatively.

A family history of sudden death, along with co-morbidities e.g. ischaemic heart disease, hypertension and diabetes, needs to be clearly elicited.

Does the patient have a history of congenital heart disease, rheumatic heart disease, previous treatment with known cardiotoxic agents (anti-cancer drugs/radiation) or international travel (Chaga's disease, subendocardial fibrosis)?

Alcohol, smoking, drug use?

Previous problems with pregnancy?

Patients unable to sustain 4 ‘metabolic equivalents’ (climbing a flight of stairs) are particularly at risk for perioperative complications.

Examination may reveal peripheral or pulmonary oedema and a third heart sound.

Special Investigations:

Blood tests:

Full blood count (anaemia), urinalysis, serum electrolytes including calcium and magnesium, (especially for patients taking diuretics) blood urea, serum creatinine, glucose, fasting lipid profile, liver function tests, and thyroid-stimulating hormone.

Screening for hemochromatosis.

HIV.

Diagnostic tests for rheumatologic diseases, amyloidosis, or pheochromocytoma.

Biomarkers:

In patients with dyspnea, measurement of B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) is useful for establishing prognosis or disease severity in chronic HF. Cardiac troponin is useful for establishing prognosis or disease severity in acutely decompensated HF.

12-lead ECG

Imaging:

CXR to assess heart size, pleural effusions, pulmonary congestion.

2-dimensional echocardiogram with Doppler should be performed during initial evaluation of patients presenting with HF to assess ventricular function, size, wall thickness, wall motion, and valve function. Ultra sound can also be used to detect interstitial lung oedema (B Lines on Echo)

Radionuclide ventriculography or magnetic resonance imaging can be useful to assess left ventricular ejection fraction (LVEF) and volume when echocardiography is inadequate.

Cardiac catheterisation: May be performed if significant coronary or valvular heart disease is suspected.

Invasive haemodynamic monitoring:

Flotation of a pulmonary artery catheter can be performed to guide therapy in patients who have respiratory distress or clinical evidence of impaired perfusion, where intracardiac filling pressures cannot be determined from clinical assessment e.g. patients who require parenteral vasoactive agents; or in patients who may need mechanical circulatory support (MCS/ventricular assist device /ECMO) or transplantation.

Optimisation of treatment:

Elective surgery should be postponed until medical management has been optimised and risk versus benefit thoroughly assessed.

Stop ACE inhibitors on the day of surgery due to problems with blood pressure lability, but all other anti-failure therapy should be continued in the perioperative period.

There is evidence that perioperative beta- blockade reduces morbidity and mortality in patients at high risk for cardiac complications.

Symptomatic arrhythmias should be treated, and attempts made to control heart rate to around 80 beats per minute.

Intraoperative Management:

Patients undergoing minor peripheral procedures should be offered local or regional anaesthesia where possible.

For more major surgery there is no evidence for the benefits of regional versus general anaesthesia.

Cardiac output = HR × SV

SV is determined by preload, afterload and contractility.

The poorly compliant ventricle must be given the opportunity to fill in diastole. This will require a higher than usual central venous pressure, the avoidance of tachycardia (which reduces the duration of diastole) and in particular the aggressive treatment of arrhythmias.

In the failing ventricle LVEDV is heavily reliant on atrial contraction.

Increases in afterload, especially acutely, can cause a dramatic reduction in cardiac output and should be avoided.

Maintain contractility. Patients with HF are nearly all on beta blockers and have beta receptor down-regulation, therefore agents such as milrinone will be needed to maintain contractility. Counter the vasodilatation with noradrenaline.

Minimise fluid load but prevent hypovolaemia and resultant tachycardia (increased myocardial work and myocardial oxygen demand)

Invasive monitoring and cardiac output measurement need be considered for all major surgery.

Postoperative care:

HF patients do not tolerate artificial ventilation well.

Postoperative pain control is essential to reduce tachycardia.

Supplemental oxygen.

Mobilize as soon as possible.

Careful fluid balance is required.

Avoid NSAIDs to avoid further renal insult.

Reintroduce ACE inhibitors as soon as possible. If omitted for more than 3 days they should be restarted at a lower dose to avoid hypotension.

There should be a low threshold for admission to ICU or HDU.

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Recommended reading:

Oxford handbook of Cardiothoracic Anaesthesia
Kaplan's Cardiac Anesthesia- The Echo Era: 6th edition. Kaplan J. Elsevier
Kurt Vonnegut: Slaughterhouse five

The Poorly-controlled Hypertensive

Professor MFM James

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The presence of hypertension increases the risk of myocardial infarction, heart failure, renal failure and stroke and it is associated with an ageing population, since older people are more likely to be sufferers from systolic hypertension. As this patient group are also more likely to require surgery, the management of hypertension poses considerable challenges to anaesthetic practitioners.

Hypertension is not a disease entity in itself but a diagnosis that incorporates a range of diseases. Most hypertension is referred to as "essential hypertension", implying that the underlying cause of the condition is unknown; this categorisation encompasses approximately 95% of all hypertensive patients, although increasing understanding of the underlying medical conditions will allow better diagnosis of other causative conditions. The remaining 5% of hypertension is "secondary" in which the underlying cause of the high blood pressure is a known medical condition. Secondary hypertension must always be considered in young patients with severe hypertension, any patient with resistant hypertension or in patients with atypical presentations, especially in the perioperative period. In the poorly controlled hypertensive patient, secondary causes should always be considered preoperatively as the consequences of a failure of diagnosis may be catastrophic.

Table 2. Classification of secondary causes of hypertension ¹

Renal	Diabetic nephropathy
	Polycystic kidney disease
	Glomerular disease
	Renovascular hypertension
Endocrine	Cushing's syndrome
	Conn's syndrome
	Hypo and hyperthyroidism
	Hyperparathyroidism
	Phaeochromocytoma
Others	Sleep apnoea
	Coarctation of the aorta
	Pregnancy
	Excessive alcohol intake
	Misuse of drugs (esp cocaine, ecstasy, etc)

The severity of hypertension is categorised into fairly well defined and accepted bands² as illustrated in Table 1. It is most important to appreciate that the classification of hypertension is based on the average of two or more stable readings of arterial pressure taken at two or more visits after initial screening and not on a single isolated recording. However it is increasingly recognised that office or in-hospital pressure recording is the least reliable assessment of blood pressure and validated home blood pressure monitors are better equipped to assess blood pressure control as they avoid the problems of "white coating". The most reliable blood pressure measurement is that obtained in the out-of-hospital setting, and if possible, this should always be sought in a patient who presents with poorly controlled blood pressure in the pre-operative setting ³.

Table 1 **Classification** (all values are in mmHg) :

SBP – systolic arterial blood pressure, DBP – diastolic arterial blood pressure

Note: The South African Hypertension Society only recognises up to stage 3, but the other grades are useful for perioperative decisions.

Category	SBP		DBP
Optimal	<120	AND	<80
Normal	<130	AND	<85
High normal	130–139	OR	85–89
Hypertension			
Stage 1 Mild	140–159	OR	90–99
Stage 2 Moderate	160–179	OR	100–109
Stage 3 Severe	180–209	OR	110–119
Stage 4 Very severe	>210	OR	>120
Isolated SBP hypertension	>140	AND	<90
Pulse pressure hypertension	>80		

Systolic blood pressure rises continuously with age, while diastolic blood pressure reaches a plateau in the fifth or sixth decade and may then decrease⁴. Thus, systolic hypertension is more common in the elderly and consequently an increase in pulse pressure is seen in older patients. Whereas it used to be thought that diastolic blood pressure is the most important determinant of outcome and the prime target for blood pressure control, current thinking is that systolic pressure hypertension, where the pulse pressure exceeds 65 mmHg, is the crucial issue. Consequently systolic hypertension is now regarded as the principal target for blood pressure control in older patients. There is increasing emphasis on the importance of pulse pressure hypertension, which is now being recognised as imposing a significant risk of myocardial infarction and stroke. The incidence of a raised pulse pressure increases with age and is also found more commonly in patients with the metabolic syndrome and in patients with coronary artery disease. The pulsatile stress on the vasculature is increased and this leads to increased risk of plaque rupture, left ventricular hypertrophy and renal failure. This haemodynamic abnormality contributes to endothelial dysfunction as well as an increase in pulsatile load. Hypertension of all types increases the risk of mortality, with severe hypertension (systolic BP greater than 180 mmHg) increasing the relative risk of death sixfold². It is also important to realise that low diastolic pressure may limit myocardial perfusion, which occurs in diastole.

End organ damage, predominantly of the heart, the kidney and brain, is common in hypertension. Even asymptomatic hypertension presents a risk of end organ damage and, as the disease advances, renal injury may progress to end-stage renal failure. The heart will suffer from hypertrophy, coronary artery disease, systolic and diastolic dysfunction, all ultimately increasing the risk of myocardial infarction, cardiac failure and death. The brain is also at substantial risk, with hypertension increasing the incidence of dementia and ischaemic or haemorrhagic cerebral events leading to stroke.

In the heart, a vicious cycle is established by the increased myocardial oxygen demand caused by increased myocardial wall tension which is amplified by left ventricular hypertrophy; both of these changes lead to coronary insufficiency, infarction and heart failure. Concentric hypertrophy leads to increasing ventricular muscle thickness, but a relative reduction in cardiac chamber size and an increase in the ischaemic risk. The ratio of blood vessel cross-sectional area to left ventricular mass becomes progressively less favourable, meaning that cardiac oxygen supply is jeopardised⁷. Sub-endocardial autoregulation is also impaired, leading to diminished tolerance of unstable blood pressure. Diastolic dysfunction is seen increasingly frequently with advancing age, occurring in up to 70% of patients with heart failure. It is associated with severe, long-standing hypertension and is frequently seen in catecholamine excess⁵.

Loss of autoregulation predisposes the kidney to damage from hypotensive events and there is an increasing incidence of glomerular sclerosis and a reduction in glomerular filtration rate with advancing hypertension. Pulse pressure hypertension significantly increases the risk of postoperative renal failure⁶.

The shift of autoregulatory thresholds in the brain in hypertensives is well known and hypertension increases the perioperative risk of both ischaemic and haemorrhagic strokes. Carotid stenosis is more common in hypertensive patients, adding to the ischaemic risk. Pulse pressure hypertension increases the risk of adverse cardiac and cerebral events following coronary artery bypass surgery⁷.

Treatment of hypertension has a marked effect on complications, reducing the incidence of stroke and cardiac failure and substantially improving five-year morbidity and mortality. A variety of drugs have been used to manage hypertension, of which the thiazide diuretics have the longest and best established track record in improving outcome. This is partly due to the fact that these drugs have been the most widely used agents. Five major classes of drugs are recognised for the treatment of essential hypertension (diuretics, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), CCB and beta blockers). The choice of agent depends on conditions that favour, or relatively or absolutely contraindicate the use of individual drugs e.g. beta blockers for patients with IHD but not for patients with asthma. Increasing trial evidence suggests ACE inhibitor plus CCB offer better CVS protection than ACE inhibitor plus diuretic or diuretic plus beta blocker⁸. The range of drugs widely used for chronic treatment of hypertension is shown in Table 2.

Table 2. Long term management drugs

Drug group	Example	Action and effect
Thiazide diuretics	Hydrochlorothiazide, indapamide	Block sodium channels
Beta blockers	Atenolol, bisoprolol, carvedilol, esmolol	Slow heart rate, improve ventricular filling, block renin
ACE inhibitors	Perindopril, enalapril	Block angiotensin converting enzyme
Angiotensin-2 inhibitors	Candesartan, losartan	Block angiotensin-2 receptors
Calcium channel blockers	Long-acting nifedipine, amlodipine	Vasodilatation

The contribution of hypertension to anaesthetic risk has long been controversial. Early studies suggested that hypertension presented a major hazard for anaesthesia, and a number of studies in the 60's and 70's seemed to confirm this. However, both contemporaneous and later studies failed to support the concept that hypertension alone was a major anaesthetic risk factor. A meta-analysis from the Oxford group showed a small but significant increase in the risk of perioperative complications in association with hypertension (OR 1.3, 95%CI 1.17-1.56), but the studies were very heterogeneous, particularly regarding the nature of the perioperative complications recorded and the likelihood of risk. Certainly, the current weight of evidence suggests that hypertension alone carries minimal anaesthetic risk². It is not appropriate to defer surgery on the grounds of hypertension alone in any patient who has a blood pressure <180/110¹.

An important issue, particularly related to the question regarding the postponement of surgery in hypertensive patients, is whether or not treating hypertension alters anaesthetic risk. One study, in particular, had a profound effect on this debate. In this very small study untreated hypertensives showed a markedly higher rate of arrhythmia development during anaesthesia, and of postoperative myocardial ischaemia⁹. The untreated and treated hypertensives both had similar resting arterial pressures, but the untreated group demonstrated greater fluctuations in arterial pressure that possibly accounted for the adverse cardiac events. However a subsequent, much larger study failed to confirm this observation, finding similar risks for perioperative myocardial events in untreated, well treated or poorly treated hypertensive patients¹⁰. More importantly, a major retrospective study by the Oxford group demonstrated that hypertension resistant to treatment ("poorly controlled hypertension") was a major predictor for perioperative silent myocardial ischaemia¹¹. It seems, on balance, that established treatment of hypertension with a good response may reduce the perioperative risks of hypertension and that resistant or poorly controlled hypertension may represent a higher risk group, but data are inadequate at present to make this a definitive conclusion.

Hypertension is associated with increased haemodynamic instability in the perioperative period and this is associated with an increased risk of myocardial injury. Furthermore, hypertension is a major risk factor for coronary artery disease, congestive cardiac failure, renal and cerebral disease, all of which increase the perioperative risk. Hypertension is also associated with dyslipidaemia, diabetes, and obesity, and the side-effects of the drugs required to treat these conditions. Hypertension is therefore associated with an increased likelihood of end organ disease that will certainly increase perioperative risk. However it remains unclear whether uncomplicated hypertension is a perioperative risk factor, and probably on its own is insufficient justification to cancel surgery¹².

Careful preoperative evaluation of the hypertensive patient is important. Such an evaluation should include a review of the quality of blood pressure control and the antihypertensive agents needed to achieve that condition. It is perhaps more important to detect end organ dysfunction that may have resulted from hypertension, as this is much more likely to predict perioperative adverse events than the hypertension alone. Such end organ damage includes cardiac injury, cerebral vascular disease, renal dysfunction and peripheral vascular disease, all of which are independent risk factors for perioperative adverse events. All patients found to have pre-operative hypertension require appropriate investigation. This should include a pre-operative ECG, blood sugar, electrolytes and creatinine (with calculation of GFR) together with a urinary Dipstix for proteinuria. Where the situation is urgent these investigations must be performed even if only post-operatively.

A decision as to when to delay surgery in a patient with poorly controlled hypertension must, therefore, consider the risk-benefit ratio of such a delay. It seems unlikely that significant benefit will be gained in an otherwise uncomplicated hypertensive patient, even with Stage 3 or higher, unless the surgery can be safely delayed for the 2-3 months that will be required to produce significant changes in cardiovascular and arterial morphology. There is evidence in hypertension studies that in high risk patients benefits from CVS protection are seen within 3 months¹³. The decision to delay elective surgery in hypertensives should be based on risk: i.e. BP > 180/110 (always high risk), evidence of target organ damage or subclinical organ dysfunction and/or multiple risk factors diabetes, smoking, and resting ischaemia on ECG. Subclinical organ damage is indicated by proteinuria, estimated GFR <60 mL/minute and ECG evidence of left ventricular hypertrophy. In such patients, surgery should be deferred for at least 4-6 weeks if at all possible and all risk factors (arterial pressure, smoking, elevated cholesterol and diabetes) controlled aggressively. Rapid normalisation of the arterial pressure over a few days immediately prior to surgery cannot be recommended.

Thus all emergency surgery should proceed regardless of the level of blood pressure and urgent surgery should also not be delayed for uncomplicated hypertension, even if relatively poorly controlled. However, there is some evidence that benefit may be gained from treating severe, poorly controlled hypertension, particularly severe pulse pressure hypertension (> 80 mmHg) or severe diastolic hypertension, especially in younger patients for elective surgery. Other patients in whom a delay in elective surgery may be warranted include those with treatable end organ disease risk and those experiencing complications of therapy, particularly related to renal, cardiac or cerebral vascular events. The ACC/AHA guidelines suggest that a systolic arterial pressure greater than 180 mmHg and/or a diastolic arterial pressure greater than 110 mmHg is justification for establishment of control of hypertension prior to surgery. Furthermore, these guidelines state that the use of rapid-acting agents to control blood pressure in the hours prior to surgery may be considered, but advance no evidence for this view¹⁴. This practice may in fact be dangerous in patients that have lost cerebral, renal or cardiac autoregulation. This recommendation may be completely inappropriate when applied to acute beta-blockade in light of the subsequently published POISE study. In this study beta blockade was given acutely 2-4 h prior to surgery to at-risk patients prior to major non-cardiac surgery. Although there was a reduction in the rate of myocardial infarction, all-cause mortality, particularly from stroke, was increased¹⁵. Immediate pre-operative beta-blockade should therefore be used with caution¹⁶. The addition of a statin is probably justified in any patient with a high risk of myocardial injury¹⁷. In high risk patients acute hypotension is more dangerous than modest elevations in BP. Where urgent surgery is required in a patient with Stage 4 poorly controlled hypertension, it may be helpful to attempt to decrease arterial pressure with vasodilator agents by approximately 25% prior to induction of anaesthesia. Short acting agents such as nitroprusside or glyceryl trinitrate may be helpful as they can be discontinued rapidly should hypotension become a problem, but there is no conclusive evidence to support this practice.

The overwhelming evidence at the present time is that patients with mild to moderate hypertension (see Table 1) without subclinical organ dysfunction or additional risk factors should proceed to anaesthesia and surgery without delay. An isolated recording of a very high blood pressure immediately prior to surgery is not necessarily a reason to postpone the case. In such cases, where prior information is available, such as ward blood pressures or information from the patient's family practitioner, suggesting that the resting arterial pressure is well controlled, it may be reasonable to proceed with anaesthesia, but there is no evidence for or against this position. However, such an episode identifies a patient as a potentially unstable hypertensive. There is growing evidence that such patients deserve increased medical surveillance. For poorly controlled, severe hypertension (Stage 3) scheduled for elective surgery, it is probably justified to delay surgery for investigation of target organ injury if such an evaluation is not already available¹⁸. In particular, it would seem indefensible to proceed with anaesthesia in such patients without, at very least, an ECG and some

evaluation of renal function. Clinical history of effort tolerance is important in these patients and may assist in guiding further evaluation. Stage 4 hypertension does appear to present a significant perioperative risk and such patients should be deferred for treatment if at all possible. A suggested algorithm for decision-making is presented in Figure 1.

Figure 1. **Algorithm for the approach to a patient with previously undiagnosed hypertension presenting for anaesthesia and surgery.** All hypertensive patients should be investigated for target organ damage, but this may take place following surgery in asymptomatic patients with Stage 1 or 2 hypertension¹⁹.

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If the decision is made to delay surgery, there remains an obligation on the anaesthetist to advise the surgeon as to how best to manage the patient. If the patient is already on anti-hypertensive medication but is poorly responsive, simply increasing the dosage of currently prescribed drugs would seem to be an inadequate approach. Rather, in consultation with a physician, a change in therapy to beta-blockade, calcium channel antagonists or an ACE inhibitor is probably more appropriate. However, such a change in therapy will require re-evaluation of end organ status. The untreated hypertensive appears to present less of a risk than the poor responder to therapy unless the hypertension is stage 4. There seems little logic to the concept of rapid, overnight reduction in blood pressure as such a strategy will probably increase the risk of intraoperative haemodynamic instability. Again, where surgery can be delayed, a combined approach with the physician is appropriate and consideration should be given in the severe hypertensive to the use of agents such as beta-blockers, calcium antagonists or ACE inhibitors, that can favourably remodel the cardiac and vascular structures, together with statins for those with high cardiac risk. It is important that the anaesthetist emphasises to surgical colleagues the importance of following up the patient properly prior to reassessment for anaesthesia and surgery. In a recent retrospective study, increasing severity of preinduction hypertension was an independent risk factor for postoperative myocardial injury/infarction or in-hospital death. However, only a small percentage of operations for patients presenting with severe hypertension was postponed, and the delay of surgery did not result in interval normalization of blood pressure³⁰, indicating that inadequate follow-up of the postponed cases was conducted.

Once a hypertensive patient is accepted for anaesthesia, consideration must be given to the effects that the prescribed drugs may have on anaesthesia. Withdrawal of anti-hypertensive medication is generally considered inadvisable as many of these drugs may produce severe rebound effects when withdrawn. This applies particularly to alpha-methyl dopa and clonidine where severe hypertension may follow withdrawal. Withdrawal of beta blockers may precipitate angina. In the case of the diuretics, effects on renal function and electrolyte abnormalities must always be considered. The ACE inhibitors/ARB represent a special case and withdrawal of these agents 10 hours prior to surgery appears to be associated with a reduction in the risk of immediate post-induction hypotension³¹. Intraoperatively, haemodynamic stability appears to be more important than absolute values of the blood pressure¹⁵. Controlling the intubation response is important and a variety of agents (including short-acting opiates, glyceryl trinitrate and magnesium sulphate) can be considered for this purpose, but the risks of post-induction hypotension must be borne in mind. Intraoperatively, esmolol, where available, may be very valuable for controlling sudden tachycardia and hypertension, but it must be remembered that beta-blockade is contraindicated if the hypertensive event is due to an excess of catecholamines caused either by administration of adrenaline or cocaine by the surgeon, or endogenous secretion (e.g. pheochromocytoma). In these latter circumstances MgSO₄ as a 4 gm bolus is probably the safest and most effective first line therapy and should be routine initial treatment of any intra-operative hypertensive crisis. Alpha₂-agonists as part of the anaesthetic technique may provide useful blood pressure control together with enhanced analgesia and some protection against myocardial ischaemia³². There is some evidence that the volatile anaesthesia, in particular with sevoflurane, may be beneficial in that it may improve diastolic function³³ and provide some degree of ischaemic preconditioning³⁴. Postoperatively, care must be taken to ensure a hypertensive crisis does not ensue, and good analgesia must be provided and a strategy developed for blood pressure control, including a planned early return to standard preoperative therapy.

In conclusion, the following quotation best describes current status of our understanding of hypertension and the indications for cancelling surgery:

“Modern anaesthesia provided by a well trained, experienced and dedicated anaesthetist offers sufficient perioperative cardiac protection to make cancellation of surgery for the sole purpose of controlling preoperative hypertension is unnecessary under most circumstances.”²¹

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Anaesthesia for Laparoscopic Surgery in Neonates and Children

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Neonates, infants and children have specific anatomical and physiological differences that pose unique challenges with laparoscopic surgery. Apart from paediatric-specific considerations, the anaesthetist must understand the implications of laparoscopic surgery and react appropriately to changes that will occur during these procedures. Pre-operative assessment must identify the effects on each organ system and management strategies must be preempted. Open communication with the surgical team will ensure the success of the operation and limit morbidity.

The benefits of laparoscopic surgery in the paediatric population are the same as in adults and include faster recovery and mobilization, less pain and improved cosmetic result, and shorter hospital stay. Technological advances such as smaller paediatric instruments, harmonic scalpels and laser have made minimally invasive surgery more attractive in the paediatric population. Cost savings from shorter hospital stay and less analgesia are often offset by longer operating times and expensive outlay of equipment. Surgical challenges include loss of tactile proximity, difficult control of bleeding and suturing, and a smaller selection of instruments. Procedures commonly performed via laparoscopy include Nissen fundoplication, cholecystectomy, appendicectomy, first stage orchidopexy, pyloromyotomy, liver biopsy, nephrectomy and anal pullthrough procedures. Removal of malignant tumours is a contra indication to laparoscopic procedures in most centres.

The physics of pneumoperitoneum

Gases

The optimal insufflating gas must be incapable of supporting combustion, have limited systemic absorption, limited systemic effects when absorbed, high solubility in blood and limited physiological effects with intravascular systemic embolism.

CO₂ is the gas of choice as it does not support combustion, is soluble, is easily excreted and relatively well tolerated. It is also cheap and readily available.

Fick's Law of Diffusion

$$V_{\text{gas}} \propto A/t \cdot D(P_1 - P_2)$$

The diffusion of a gas across a membrane is proportional to the area of the membrane in contact with the gas (A), the difference in partial pressure of the gas across the membrane ($P_1 - P_2$), and a diffusion constant (D) where

$$D \propto \alpha^{\text{sol}} / \sqrt{\text{MW}}$$

The diffusion is proportional to the solubility of the gas and inversely proportional to the square root of the molecular weight as well as the thickness of the membrane. Children will absorb a higher proportion of CO₂ as their surface area: body mass ratio is increased and peritoneal thickness is decreased.

Transpulmonary pressure

Transpulmonary pressure (P_{tp}) is the difference between the alveolar (P_{alv}) and intrapleural (P_{pl}) pressure.

$$P_{\text{tp}} = P_{\text{alv}} - P_{\text{pl}}$$

Repetitive increases in transpulmonary pressure are injurious to lung parenchyma and can lead to acute lung injury and acute respiratory distress syndrome (ARDS). Pneumoperitoneum increases the external pressure and thereby intrapleural pressure. Transpulmonary pressure will be decreased, allowing for safe increases in ventilator pressures. Sudden release of pneumoperitoneum without lowering ventilator pressures will cause a sudden increase in transpulmonary pressure with the risk of parenchymal damage.

The physiology of pneumoperitoneum

Pneumoperitoneum exerts effects on organs through direct pressure and CO₂ absorption. The pressure effect is dependent on absolute pressure and the duration of increased pressure. The diffusion of CO₂ across the peritoneum and into the bloodstream is governed by Fick's Law. Physiological effects are exaggerated with decreasing age and size due to decreased muscle bulk, increased surface area to mass ratio, decreased peritoneal thickness and decreased organ reserve.

Respiratory effects

Increased intra-abdominal pressure results in splinting and an upward shift of the diaphragm. This leads to a decrease in functional residual capacity and atelectasis. It also leads to decreased compliance, increased V/Q mismatch and the possibility of bronchial main stem intubation. The Trendelenburg position will aggravate all these effects while the anti-Trendelenburg position will reduce respiratory compromise.

Cardiovascular effects

The main cardiovascular effects are due to a decrease in preload and an increase in afterload. Increased intra-abdominal pressure during insufflation impedes venous return and increase transaortic pressure in the abdomen. Systemic vascular resistance increases in response to these changes. This maintains blood pressure despite an approximate decrease in cardiac output of 30%. A biphasic response is often observed as insufflation pressures with intra-abdominal pressure < 10mmHg increases preload through the displacement of splanchnic blood, whereas further insufflation above 15mmHg will likely impede venous return. Patient position, level of tilt and size of patient will significantly influence these pressure effects at different pressures.

An echocardiographic study of 20 children, by Gentili et al (2000), confirmed an increase in afterload and preload when insufflation pressures were maintained below 10mmHg. Systolic cardiac performance remained unchanged although oxygen consumption increased and cardiac index decreased as the heart had to pump against a higher afterload.

Patients with compromised cardiac contractility may not tolerate these changes in preload and afterload well. Neonate and infants under 3 months of age have a relatively fixed cardiac output due to immature myocardial fibres. They will increase cardiac output through an increase in heart rate.

A review of cardiovascular effects during neonatal laparoscopy, showed an average 20-40 bpm increase in heart rate and a stable blood pressure in 80% of neonates during insufflation. 20% of neonates had a drop in blood pressure exceeding 10mmHg. Volume expansion should be considered for pressures <45mmHg in term neonates.

The direct effect of CO₂ absorption is less dramatic than the pressure effect of pneumoperitoneum. High intravenous PCO₂ increases the incidence of arrhythmias and could cause sympathetic stimulation with tachycardia and increased systemic vascular resistance.

Central nervous system effects

It is generally accepted that increased intra-abdominal pressure will increase intracranial pressure due to an elevated central venous pressure. This will cause decreased drainage from head and neck vessels. CO₂ absorption can also lead to cerebral arterial dilatation which will increase intracranial pressure. Trendelenburg positioning will worsen these effects. It is however generally safe to perform laparoscopic surgery for patients with functional ventriculoperitoneal shunts (VPS) if the intracranial pressure is relatively normal. Newer shunts contain a one way (no-reflow) valve that prevents

backward positive pressure into the intracranial compartment. In theory, increased intra-abdominal pressure will decrease cerebrospinal fluid (CSF) drainage into the abdominal cavity, but as CSF production is only 1-2ml/kg/hr, the pressure increase should be minimal if the procedure is not prolonged and insufflation limited. There have been case reports of surgical emphysema tracking up to the thoracic wall via the shunt tunnel. It is suggested that laparoscopic procedures should not be done for 2 weeks after a new shunt has been inserted as the fresh shunt track might allow air to enter. Laparoscopic procedures have the advantage of lower rates of intra-abdominal sepsis with a lower risk of shunt sepsis. Better postoperative respiratory physiology with better negative intra thoracic pressure, with spontaneous ventilation, will also enhance shunt drainage post operatively.

Renal

Renal output is generally decreased during laparoscopic procedures. This is most likely secondary to a reduced cardiac output. Less invasive surgery should be beneficial for patients with renal dysfunction due to decreased fluid shifts and faster recovery. Platelet function should be assessed in patients with marked uraemia.

Thermoregulation

Temperature control should be better controlled during laparoscopy compared to an open procedure but temperature loss could still be profound in young children and neonates especially if insufflation gas is not warmed.

Neonatal risk factors

Infants under 3 months of age suffer more surgical and anaesthetic complications. Surgical laparoscopic expertise might also be limited. Insufflation longer than 100 minutes, high insufflation pressures, large ETCO₂ variations, low body temperature, a need for vascular expansion and major modification of ventilator settings at start of insufflation are independent neonatal risk factors.

Practical anaesthesia

Preoperative assessment

Identify any acute or chronic co-morbidities that might complicate paediatric anaesthesia as well as laparoscopic surgery per se. Investigations should be tailored to the child's clinical status and history. Children with severe respiratory compromise, sepsis, coagulation disorders, raised intracranial pressure, resistant arrhythmias, cardiac pathology and inotropic support must be properly investigated and the risk of pneumoperitoneum weighed up against the benefit of a less invasive procedure. End organ dysfunction and the potential effects of pneumoperitoneum will be an unsuitable combination for certain patients. A starting haemoglobin and group and screen are advisable in small infants where small volumes of blood loss might be significant in relation to total blood volume.

Patients scheduled for Laparoscopic Nissen fundoplication usually have chronic lung disease due to chronic aspiration. Respiratory pathology will not clear up unless the cause, aspiration, is addressed via surgery. Surgery often has to proceed without respiratory optimisation as postponement might lead to another episode of aspiration. The surgical team must be open to the suggestion of a trial of insufflation. If the patient does not manage with pneumoperitoneum, the abdomen must be deflated and the surgery continued as an open procedure. It is advisable to have an intensive care bed available in case one experiences ventilation problems and want to keep the child intubated and ventilated postoperatively.

Hydration should be maintained during the preoperative starvation period as the effects of pneumoperitoneum are exaggerated when patients are hypovolemic. Patients for Nissen fundoplication will benefit from intravenous hydration as aspiration risk is high and some anaesthetists might prefer a longer NPO period for fluids. Most patients can receive clear fluids up to 2 hours preoperatively.

Premedication can be prescribed according to local practices. Some centres give atropine or glycopyrrolate as part of premedication to blunt the bradycardia associated with peritoneal stretch, but

it might be better to give a small dose of intravenous glycopyrrolate (10ug/kg) intraoperatively in patients that develop bradycardia. The dry mouth associated with routine administration might be uncomfortable for some patients and atropine can cause central excitation in children.

Induction

Induction should be tailored to the patient's unique condition. Care should be taken in kids at risk of aspiration. A slight head up position with gentle gas induction will be suitable for most children requiring Nissen fundoplication. Have suction readily available. Do not instrument the airway until an adequate depth of anaesthesia has been reached and intravenous access has been secured. Patients should be intubated and ventilated. Some texts advocate a cuffed tube to facilitate ventilation at higher ventilation pressures during pneumoperitoneum. Intra-abdominal pressures should ideally never be so high in children that it requires a snug fitting cuffed tube to manage ventilation.

Neuromuscular blockade will decrease pressure with pneumoperitoneum, ease ventilation and improve visualization. It will also decrease the risk of CO₂ embolism. A nasogastric tube placed after intubation will decrease aspiration, deflate the stomach and improve visualization. Urinary catheters should be placed for long procedures.

A slow fluid bolus to optimise intravascular volume prior to insufflation will limit the drop in preload. Consider the patient's cardiovascular reserve when choosing anaesthetic agents considering the drop in cardiac output associated with pneumoperitoneum. Patients with poor contractility might not tolerate the negative inotropic effects of inhalational agents. Remember that small infants are reliant on an increased heart rate to maintain cardiac output and an agent like remifentanyl might decrease the heart rate and cardiac output. Halothane should be avoided, as it is arrhythmogenic, especially with increased levels of absorbed CO₂. Nitrous oxide could cause bowel distension, decrease visualization for the surgical team and increase postoperative nausea and vomiting.

Ventilation

Neonates and smaller children have a far bigger increase in ETCO₂ during insufflation due to the thinner peritoneum and larger surface area to mass ratio. Small children struggle to excrete CO₂ efficiently due to increased instrumental deadspace ventilation. This effect can be minimized by cutting endotracheal tubes shorter and using infant specific HME's with smaller volumes. Minute ventilation must often be increased by up to 25-30% to maintain ETCO₂ at an acceptable level. Listen for equal bilateral air entry after insufflation as endotracheal tubes can easily move into a mainstem bronchus with upwards shift of the diaphragm. If unacceptably high ETCO₂ levels persist, temporary release of pneumoperitoneum can be employed to improve excretion of ETCO₂ until acceptable levels are reached. Care should be taken to decrease peak inspiratory pressures when insufflation is terminated, as an unopposed high alveolar pressure will cause high transpulmonary pressures that will lead to lung parenchymal damage. ($P_{tp} = P_{alv} - P_{pl}$)

The possibility of other causes of respiratory compromise should continuously be excluded such as a pneumothorax, a kinked or blocked tube, aspiration, bronchospasm, machine malfunction, excessive insufflation pressures with splinting of the diaphragm or atelectasis.

The surgical team must be willing to release insufflation if needed to improve the cardiorespiratory condition of the child and to diagnose possible problems. If ventilation difficulty persists, despite optimization of anaesthetic and surgical contributors, the team should consider converting to an open procedure.

Cardiovascular complications

A precipitous drop in blood pressure or ETCO₂ during insufflation could indicate a fluid deficit, too high intra-abdominal pressure, compromised cardiac reserve with poor myocardial function or intravenous air embolism. Ask the surgical team to reduce insufflation pressure while a fluid bolus of 10ml/kg is administered. Consider changing to an anesthetic technique with less myocardial depression such as a Ketamine infusion instead of inhalational agents in small infants with limited myocardial contractility.

If a large intravenous CO₂ embolism is suspected, stop insufflation immediately, ventilate with 100% oxygen and give a fluid bolus. Start inotropes if cardiac output remains compromised after the above measures. Adrenalin would be the agent of choice. CO₂ embolism is rare and resolves quickly. The risk of CO₂ embolism is higher with rapid insufflation with higher pressures. Patient risk factors include hypovolaemia and spontaneous ventilation with negative inspiratory pressures.

Remember that 80% of patients will have a normal blood pressure despite a considerable drop in cardiac index due to increased systemic vascular resistance. A monitor such as near infrared spectroscopy (NIRS) could give a better indication of cardiac output and brain perfusion than blood pressure per se.

Patients with severe cardiovascular compromise could benefit from arterial line placement. A high PCO₂/ETCO₂ gradient could also indicate poor cardiac output. Successful laparoscopic procedures have been performed on children with very poor cardiac function with optimization of fluid status, avoidance of negatively inotropic anaesthetic agents, avoidance of the Trendelenburg position and limiting insufflation pressures to the minimum requirement.

Surgical complications

Constant vigilance and communication should be maintained to respond quickly to any surgical complications. These include venous, arterial or organ puncture with trocar insertion, uncontrolled haemorrhage, bowel perforation due to diathermy or other instruments or failure of the procedure due to limited access. Late complications include failure of the procedure and abdominal herniation into port sites. Conversion to an open procedure should not be considered a complication but a strategy to minimize complication.

Pressure guidelines

There are no consistent, absolute insufflation pressure guidelines for children in the literature. The only recommendation is to keep pressures at the lowest level that will allow adequate visualization. As 10mmHg is often mentioned as the level when preload decreases, one might suggest keeping pressures below 10mmHg if possible. Conversion to an open technique should be considered when pressures are needed that compromise cardiorespiratory stability, despite optimal fluid balance and anaesthetic technique.

Conclusion of surgery and postoperative care

The surgical team must release intra-abdominal gas to reduce postoperative discomfort and ease ventilation although CO₂ should be absorbed fairly quickly. Port sites could be injected with local anaesthetic to aid postoperative analgesia. Adequate analgesia can be achieved with paracetamol, nonsteroidal anti-inflammatory drugs and sublingual tilidine drops. Epidural or caudal analgesia can be used for cases where the likelihood of converting to an open procedure is high. Intravascular volume must be optimized in patients with neuraxial blocks during insufflation. Regional field blocks such as rectus sheath and transversus abdominis plane blocks can be beneficial for patients where port insertion falls within the field block area.

Most patients would be able to return to a normal surgical ward. Infants younger than 60 weeks post gestational age should be observed in a high care ward with apnoea monitoring for at least 12 hours. Patients with severe cardiorespiratory comorbidities should be considered for post-operative intensive care admission until stable.

Notes

How to Read an Article

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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 they are generally invited commentaries, the level of peer review is often lower than that for the investigative articles. They highlight important issues and provide valuable guides to current thinking, particularly in controversial areas where they can provide useful summaries. They are often useful guides to exam candidates as to what is currently considered relevant.

Investigative articles

These are the lifeblood of the journals and form the bulk of the published material. 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 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 sufficient of a literature review 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

In many ways, 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. A reference number from the relevant ethical committee should be stated. In the case of a clinical trial it is now required that the study was lodged with one of the international registries and that the registry number is reported in the paper.

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. 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. The Jadad score is now widely used to evaluate the quality of both randomisation and blinding, together with one point for a careful description of how withdrawals and dropouts were managed.

Randomisation with a clear description of randomisation techniques used	0-2 points
Level of blinding (none, single, double) together with clear blinding methodology	0-2 points
Proper description of withdrawals and dropouts	1 point

Table 1. **Jadad scoring system** (maximum of 5 points). Jadad et al, *Controlled Clinical Trials*, 1996

Probability

The logic underlying the scientific process argues that if a theorem cannot be proven directly, a 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 fixed 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 and this is referred to as the risk of α -error. 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 2.

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.

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, but not with an absolute zero	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 2. **Types of data.**

Types of test (see table 3)

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.

DATA TYPE	Comparisons	Test
Normal distribution	Single comparison, two related groups	Paired t-test
	Single comparison, two unrelated groups	Unpaired t-test
	Multiple sample groups	ANOVA
	Multiple comparisons over time	ANOVA for repeated measures
Non-Normal data		
Ordinal	Single comparison, two related groups	Wilcoxon signed rank test
	Single comparison, two unrelated groups	Mann-Whitney U-test
Nominal	Small numbers, single group comparison	Fisher's Exact test
	Multiple groups, large numbers	Chi-square test

Table 3. **Examples of data types and appropriate statistical tests** (not exhaustive)

Student's t-test has various forms. If the data is obtained from a single subject who is tested twice under different conditions, a *paired* test is used as this minimises the 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 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 data pair are compared, the likelihood of an error increases directly with the number comparisons made. The 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. 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 data that is not normally distributed and data that arise from analysis of categorical information. Scoring systems such as pain scores, APGAR scores, ASA scores etc. are widely used to identify graded responses to various conditions. These are all non-parametric and the use of more powerful parametric tests on such data is wrong. 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 nausea or vomiting) the Fisher's Exact test is very useful for small numbers where a 2 x 2 comparisons are being made. For larger and multiple comparisons, the Chi-square test is used.

An important statistical method that does not rely on probability was introduced by Altman and Bland to test the comparability of two devices that 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 two 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.

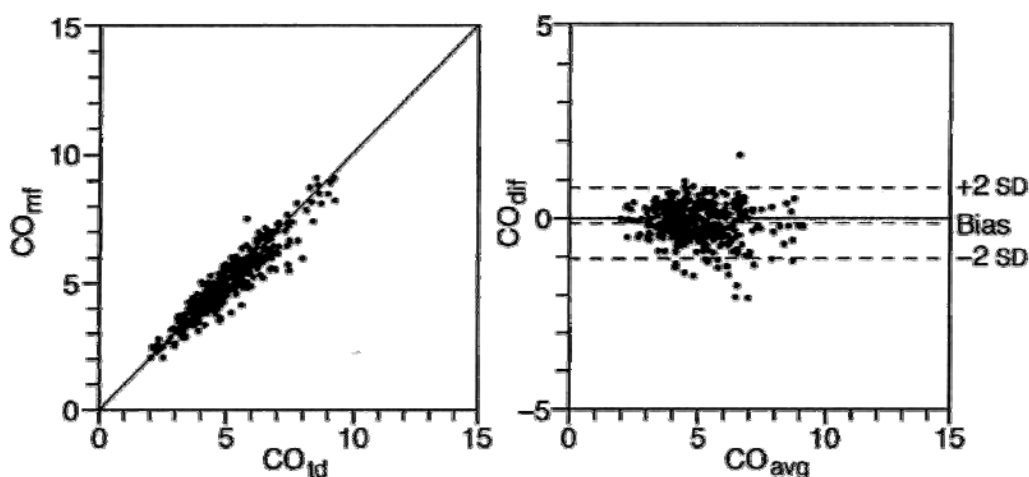


Figure 1. A correlation scatter plot and an Altman and Bland plot of the same data investigating the performance of two different types of cardiac output monitors.

Results

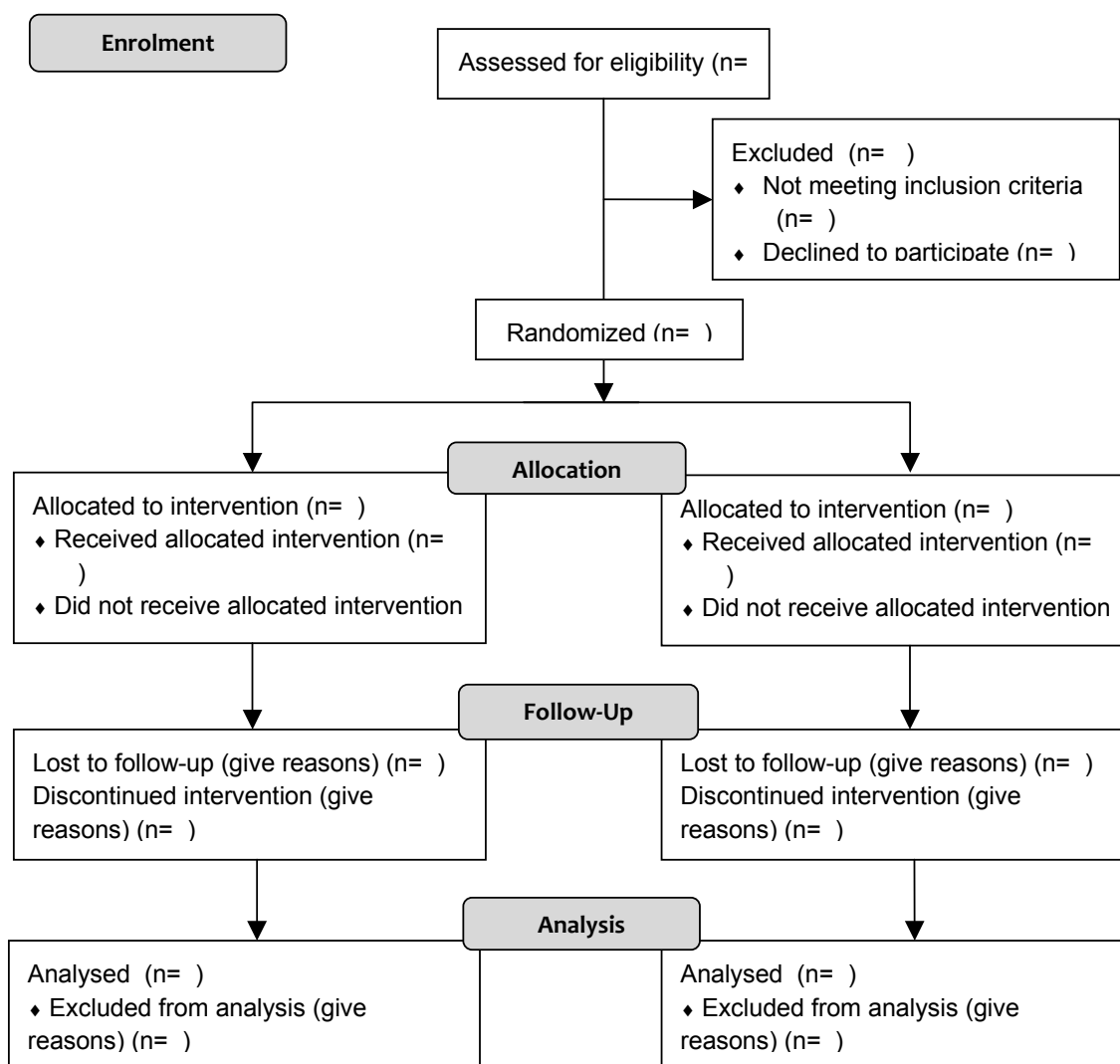
The results of any particular study should be presented in the appropriate statistical format. It is important for the reader to understand the results and thus they must be reported in a clear and intelligible manner. It is all too common for the results to be presented in a confused and unclear fashion. 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 (internal validity). The Boldt fraud was detected 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. Most journals now require what is called a CONSORT diagram. CONSORT stands for Consolidated Standards of Reporting Trials and encompasses various initiatives developed by the CONSORT Group to alleviate the problems arising from inadequate reporting of randomized controlled trials. An example from the CONSORT website is given in Figure 2.

Figure 2. CONSORT DIAGRAM.



CONSORT

TRANSPARENT REPORTING of TRIALS



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. A major challenge has arisen with regard to the CHEST trial as the authors stated that all data was analysed by intention to treat methodology, but a section of the results were reported by the treatment actually received. As the analysis type alters the significance of the reported results, the statistical validity of this approach is currently being debated. 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.

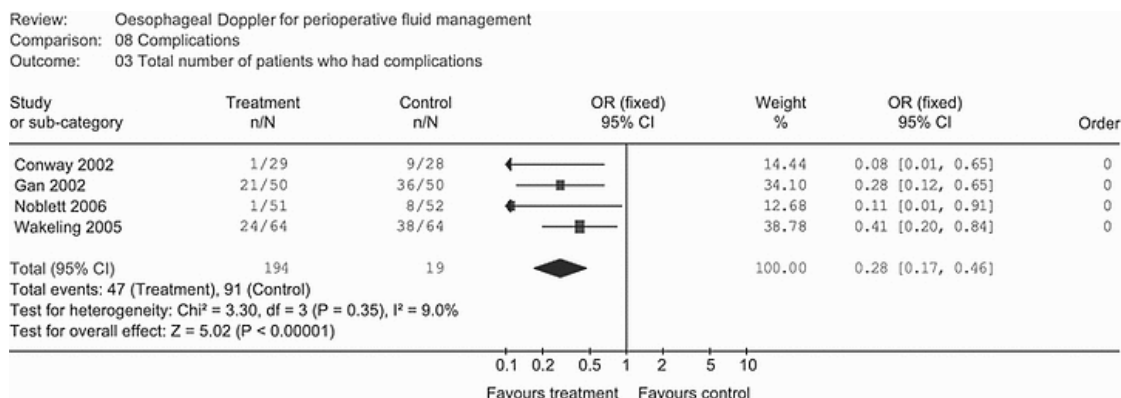
In interpreting the results, a final scan of the statistical method should be performed, particularly looking at the initially stated statistical methods and what was actually performed. All too often, an interesting observation is made that turns out, by chance, to be statistically significant. It is acceptable to report such a finding as an observation requiring future investigation, but it may not be reported as a conclusion. Again this has frequently occurred and led to misleading changes in practice. Where no differences 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 an 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 statistical analysis of 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 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 3).



(Abbas SM, Hill AG. Systematic review of the literature for the use of oesophageal Doppler monitor for fluid replacement in major abdominal surgery. *Anaesthesia*, 2008, 63:44-51).

Figure 3. 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.

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. The test for heterogeneity is important as this gives information regarding the consistency of the information collated into the single plot. If there is significant heterogeneity the validity of the meta-analysis is weakened. 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. Heterogeneity is not significant ($p=0.35$) and thus all the studies included gave reasonably similar results. 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 obtained 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 relevance to students of anaesthesia particularly those preparing for the FCA examinations. 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.

Normally distributed 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 various types of 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 pulling large quantities of data from various studies into a single study 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 the lecture given on the UCT Part II anaesthesia refresher course in Cape Town 2016. It should not be regarded as a definitive source for statistical information.

Further Reading:

1. Dunn OJ, Clark, VA. Basic statistics. John Wiley and Sons, Hoboken, New Jersey, 2009.
2. Pace NL. Experimental design and statistics. In: Barash PG, Cullen BF, Stoelting RK, Cahalan MK, Stock, MC (eds) Clinical Anesthesia (6th Edition) Lippincott Williams and Wilkinson, Philadelphia, 2009, pp192-205.

Approach to Interpretation of a Chest X-Ray (mainly in the ICU)

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This should be approached in a systematic way and there are some questions that need to be answered:

- √ Why (do a CXR)?
 - Medical condition
 - Therapeutic/ monitoring devices
- √ What (to look for)?
 - Systematic approach
 - Patterns
- √ When (to do it)?
 - Routine radiography
 - » Is it justified?
 - Change in condition
 - » Medical
 - » Intervention

The general principles of X-ray interpretation apply to all X-rays - whether taken pre-operatively or in the ICU.

There are a number of technical considerations before any interpretation occurs:

- √ Identification
 - Is it the right patient and date?
- √ Position
 - Side
 - Rotation
 - Angle
- √ Penetration
- √ Depth of inspiration
- √ Associated devices obscuring structures

After this, a systematic review of the X-ray is undertaken, not jumping straight to the obvious abnormalities:

- √ Bones
- √ Soft tissues
- √ Vascular structures
- √ Heart
- √ Pleura
- √ Lung fields

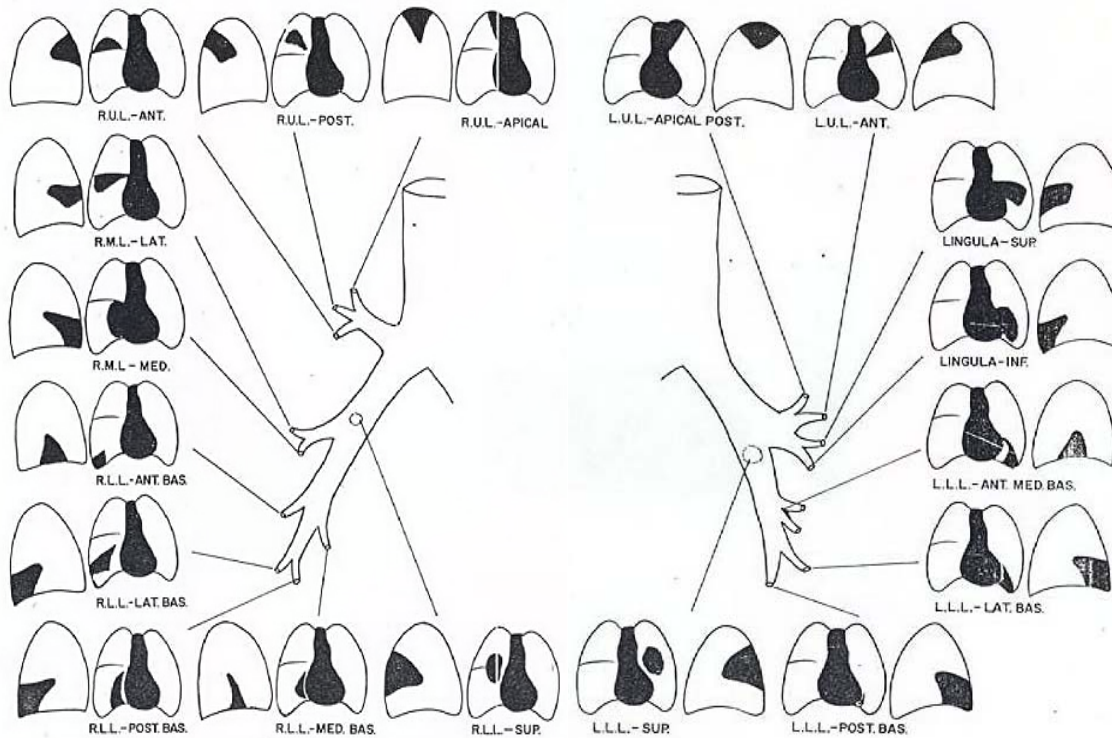
There are some regions that often hide abnormalities and careful looking into the film can reveal surprises so always check:

- √ Airways + oesophagus
- √ Behind heart
- √ Costophrenic angles
- √ Mediastinum
- √ Hilar regions
- √ Apices

Apart from X-rays taken as part of pre-operative evaluation, a clinician's request for an X-ray is usually prompted by one of the following questions:

- ✓ Why sudden onset of distress?
 - Pneumothorax, atelectasis, oedema, embolism
- ✓ Why fall in P_aO_2 ?
 - Fluid, infiltrate, atelectasis, pneumothorax, effusion
- ✓ Change in airway pressures?
 - Barotrauma, collapse, plugging
- ✓ Source of fever?
 - Infiltrate, collapse, atelectasis, effusion
- ✓ Changes caused by intubation
 - Expansion, barotrauma, aspiration, resolution
- ✓ Changes caused by extubation
 - Fluid, aspiration, atelectasis

Lung segments as seen on PA and lateral CXR



X-rays in the ICU are often prompted by invasive procedures and the need to check for position or complications:

Where is the device?

- ✓ ETT
 - 4-5 cm from carina (at level of aortic knuckle)
 - Cuff < width trachea
- ✓ Central venous catheter
 - Within thorax, outside RA
 - No pneumo- or hydrothorax
- ✓ Nasogastric tube
 - In stomach or post-pyloric
- ✓ Chest drain
 - Tip in area to be drained
 - Side holes in pleural cavity

Apart from X-rays taken to answer the questions above, the value of daily routine chest X-rays in ICU patients is controversial:

- v Does routine daily radiography
 - Save or waste money?
 - Detect sufficient clinically inapparent problems to justify expense and radiation exposure?

Routine CXR in medical ICU¹

- v 221 routine CXR reviewed
 - 72 had significant changes
 - » 44 important
 - » 18 prompted management changes
- v Management change
 - Reduced LOS 2.1 days
- v Estimated savings per routine CXR
 - \$98
- v “Policy of obtaining routine CXR is effective and results in net savings”

Efficacy of daily routine CXR in intubated MV patients²

- v Prospective review
 - 74 patients, 538 CXR
 - 354 no change
 - 163 minor findings (40% clinically suspected)
- v 13 patients had CXR with major finding
- v “While a large percentage will not disclose new findings, routine daily studies have a substantial impact on the management of intubated ventilated patients”

Overall – probably depends upon ICU population and ease of obtaining urgent X-rays. Ill patients with ARDS or other major respiratory difficulties merit daily radiography. Routine post-operative patients or long-term ventilated patients in stable condition do not need routine radiography and X-rays should only be requested if specific question as above needs to be addressed.

References

1. Brainsky A, Fletcher RH, Glick HA, et al. Routine portable chest radiographs in the medical intensive care unit: Effects and costs. *Critical Care Medicine* 1997;25(5):801.
2. Hall JB, White SR, Karrison T. Efficacy of daily routine chest radiographs in intubated, mechanically ventilated patients. *Crit Care Med* 1991;19(5):689-93.

Notes

Anaesthesia for the Child with Muscle Disease

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Muscle disorders present a considerable challenge to the anaesthetist as well as to those caring for the child in the post-operative period. While each disorder is uncommon, as a group their common features and the peri-operative implications make them important to consider.

This review will focus on:

- Myotonias
- Muscular dystrophies
- Mitochondrial myopathies

These multisystem disorders have significant implications for anaesthesia.

A further problem which will be considered is the weak or hypotonic child who comes for anaesthesia without a definitive diagnosis.

1. Myotonias

The myotonias are channelopathies in which there is an inherited or spontaneous mutation in the gene coding for sodium, potassium or calcium channels with resulting predisposition to sustained myotonic contractions. In theatre these contractions may be stimulated by pain, cold, stress or diathermy.

Myotonias can be dystrophic (accompanied by progressive muscle wasting and weakness) or nondystrophic. The confusingly named Steinert's Muscular Dystrophy (Type 1 Myotonic Dystrophy) is the commonest myotonia. In its most severe form Steinert's arises in the neonatal period with respiratory insufficiency while milder forms will first become symptomatic in childhood.

While many of the principles can be extrapolated to the other myotonias the following notes are specific to the myotonic dystrophies in which weakness and hypotonia become features of the disease. In addition to muscle weakness and a predisposition to myotonic contraction the following systems are affected:

- Cardiac: conduction defects and dysrhythmias predispose to sudden death (may require implantable cardioverter defibrillator (ICD)); cardiac involvement may be disproportionately severe compared to the muscular effect
- Respiratory: poor cough, predisposed to recurrent aspiration with chronic lung damage, complex sleep disorders (hypersomnia, narcolepsy, respiratory muscle weakness resulting in hypoventilation with hypercapnoea ± hypoxia)
- GIT: delayed gastric emptying with pharyngeal muscular weakness resulting in aspiration risk
- CNS: behavioural and cognitive issues, sleep disorders leading to profound sleep deprivation peri-operatively;

Disease severity and degree of impairment of organ systems should be established pre-operatively and this will guide anaesthetic choices. The individual patient's triggers for myotonic contraction should be identified and serum electrolytes checked and optimised. In the severely affected patient a multidisciplinary team should be involved in peri-operative care with careful planning of post-operative placement.

All triggers should be diligently avoided in the peri-operative period. Suxamethonium is contra-indicated and muscle relaxation can be challenging as chronic meds (such as quinine or procainamide) and the disease process itself may make these patients sensitive to muscle relaxants. Muscle relaxants should be titrated to effect and neostigmine may precipitate a myotonic episode. Monitoring neuromuscular blockade is fraught with difficulty as electrical stimulation may precipitate a myotonic contraction making interpretation of this monitor challenging. Several case reports detailing the uneventful use of sugammadex in these patients exist. Because myotonic contractions are triggered distal to the neuromuscular junction muscle relaxants won't prevent intra-operative contractions.

Complications (particularly cardiac complications) may occur out of proportion to the severity of the disease, occurring in even the mildly affected patient. Close attention should be paid to ECG monitoring and a defibrillator should be close at hand, preferably with external pacing capacity. In a patient with a history of severe arrhythmias and cardiac arrest strong consideration should be given to the placing of adhesive external defibrillating pads.

The volatile anaesthetics may have a direct muscle relaxing effect to counteract myotonic contractions. The anaesthetist should be cognisant of their respiratory depressant effect and ventilation should be supported.

Masseter spasm may cause problems with airway instrumentation and diaphragmatic and intercostal spasm will interfere with ventilation.

Good analgesia will assist in preventing myotonic contractions in the peri-operative period. Opiate-sparing meds and regional techniques are preferred as patients with myotonic dystrophy are exquisitely sensitive to the respiratory depressant effects of drugs. These patients are at significant risk of post-operative pulmonary complications and ventilation may need to be supported for an extended period of time.

The myotonias are not associated with an increased risk of malignant hyperthermia.

2. Muscular Dystrophies

The muscular dystrophies are a group of over 30 genetic disorders characterized by progressive degeneration of skeletal muscle with muscle weakness, dystrophic features on muscle histology and defective muscle proteins identified on molecular genetic testing (See Table 1). Depending on the disorder, inheritance may be X-linked, recessive or dominant and may also result from a spontaneous mutation.

Duchenne's Muscular Dystrophy

The X-linked Duchenne's muscular dystrophy is the commonest form of muscular dystrophy, occurring in 1:3500 live male births. Up to 1/3 of sufferers may have a spontaneous mutation. Most of these boys will be symptomatic by 5 years of age.

They have:

- delayed motor milestones
- progressive muscle weakness with calf pseudo-hypertrophy
- one third are mentally retarded

Once symptoms appear glucocorticoids, which have been shown to slow disease progression to a variable extent, are usually commenced. By 15 years over 50% will have a clinically relevant cardiomyopathy and death is expected in early to mid-adulthood due to a progressive cardiomyopathy or respiratory insufficiency.

Table 1: General classification of the more frequently encountered muscular dystrophies

Inheritance	Disease	Affected protein
X-linked	Duchenne Becker Emery-Dreifuss	Dystrophin Dystrophin Emerin
Autosomal dominant	Limb-girdle-muscular-dystrophy 1A-1G Fascio-scapular humeral Oculopharyngeal Bethlehem	Myotilin (1A), LMNA (1B), Cav-3 (1C) PABP2 GCG rpt COL6A
Autosomal recessive	Limb-girdle-muscular-dystrophy 2A-2J	Calpain, dysfewrlin, sarcoglycans, telethonin, TRIM32, Fukutin-related protein, Titin
Other	Congenital muscular dystrophy (CMD) with CNS involvement: - Fukuyama CMD - Walker-Warburg CMD - Muscle-eye-brain CMD Congenital muscular dystrophy (CMD) without CNS involvement: - Merosin-positive CMD - Merosin-deficient CMD - Integrin-deficient CMD - Ulrich	Fukutin o-mannosyltransferase 1 POMGNT1 ? Laminin- α 2 Integrin α 7 COL6A

Becker's' Muscular Dystrophy is milder with symptoms developing in adolescence. They will also develop a cardiomyopathy which may be disproportionately severe in comparison with the clinically evident muscle involvement and can be expected to die between the fourth and seventh decade.

Female carriers of these mutations may have mild musculoskeletal abnormalities (such as scoliosis) and may develop a cardiomyopathy. It is believed they are also susceptible to the anaesthetic catastrophes that may befall male patients.

The anaesthetic risks related to the dystrophies are substantial and are due to end organ effects of the disease as well as to idiosyncratic reactions to specific anaesthetic drugs.

2.1.1. Respiratory System

Para-spinal weakness leading to kyphoscoliosis contributes to a picture of restrictive lung disease; this is compounded by respiratory (including diaphragmatic) muscle weakness with nocturnal hypoventilation. A poor cough makes recurrent lung infections a problem and the pre-operative visit should focus on the potential for respiratory optimisation prior to surgery as well as planning for post-operative placement.

It would be ideal not to have to ventilate patients with a muscular dystrophy post-operatively but this can be tricky especially after major surgery such as a kyphoscoliosis repair. Non-invasive ventilation, such as BIPAP, is a useful modality to consider in these cases. If they have not been on BIPAP before they should be trained in the pre-operative period.

Pulmonary function testing may be useful in the older child/adolescent with DMD who can comply with the requirements of the investigation. An FVC<50% of predicted has significantly increased risk of post-operative pulmonary complications (POPC), <30% predicted has a very high risk of POPC. VC <680ml correlates well with daytime hypercapnoea.

2.1.2. Cardiac System

All patients with Duchenne's will develop a cardiomyopathy but many won't be symptomatic until late in their disease because they are so sedentary and a resting tachycardia or an arrhythmia maybe the only clinical signs. It is easy to underestimate the severity of the cardiac situation. Kyphoscoliosis makes for a poor acoustic window and so transthoracic ECHO's are hard to do, in addition stress testing is required but is essentially unachievable because, at this stage of the disease, patients have a very limited exercise capacity. Cardiac MRI is the best way to assess cardiac function in these patients and to monitor response to therapies such as steroids, ACE inhibitors, ARB's, beta blockers or digoxin. If they're not already on cardiac medication and pre-operative investigation shows significant cardiac involvement discussion with neurologists and cardiologists may be helpful in establishing the need to postpone non-urgent surgery to optimize the situation medically. In the absence of a cardiac MRI a dobutamine stress ECHO may be useful in identifying impaired function.

A patient identified as having a cardiomyopathy pre-operatively should be invasively monitored with an arterial line and adequate venous access intra-operatively is a priority. Unrecognised hypovolaemia can be a killer in these patients and may precipitate a cardiac arrest, their cardiac system simply cannot respond to ongoing hypovolaemia. Pay absolutely meticulous attention to fluid status, take care with myocardial depressants such as propofol and have your inotropes readily available.

2.1.3. Haematological System

DMD is associated with increased bleeding and this is particularly evident in major surgery such as kyphoscoliosis repair; this tendency is thought to be due to impaired vascular reactivity. Adequate venous access, capable of high flows, is important and, for major surgery, blood products should be available and a cell-saver should be considered. Cyclokapron infusion has been shown to reduce transfusion requirements in muscular dystrophy patients undergoing spinal surgery.

2.1.4. Other

Pseudohypertrophy of the tongue has been described and this may interfere with intubation. This should be sought on pre-operative examination and appropriate preparation made for theatre.

The link between the dystrophies and malignant hyperthermia (MH) has been debated long and hard. Expert opinion is that patients with Becker's' and Duchenne's muscular dystrophy are at no increased risk of MH over the general population BUT instead they are prone to the equally catastrophic Anaesthesia Induced Rhabdomyolysis or AIR, also triggered by the volatile anaesthetics.

Making the distinction is crucial as the treatments are different and early recognition and appropriate intervention may be life-saving.

Like MH AIR seems to be an idiosyncratic reaction. The same child may have had uneventful GA's with volatiles previously and many dystrophic patients will never suffer AIR despite exposure to volatile anaesthetics. The current recommendation for avoiding this catastrophe is to deliver a trigger free anaesthetic from a "clean" machine.

There are three possible clinical presentations for this disaster:

1. Acute hyperkalaemia with cardiac arrest
2. Post-operative rhabdomyolysis without cardiac arrest
3. Gradual increase in temperature and heart rate without signs of hypermetabolism or muscle rigidity

Many cases of hyperkalaemia and cardiac arrest or rhabdomyolysis without arrest have occurred in the recovery room, after the child has started waking up and moving.

If a case of AIR is suspected in theatre or in the recovery room the following actions should be taken (in order):

1. Stop any volatile, change to TIVA and get a "clean" machine
2. Send off blood to check potassium, CK and myoglobin and send urine to check for myoglobin
3. If potassium is $>5.5\text{mmol/l}$ give NaHCO_3 , insulin with 10% dextrose and hyperventilate to shift the potassium intracellularly, kayexelate may also be given via an NGT
4. Insert a urinary catheter and monitor urine output
5. Give fluids and mannitol to keep the urine output over 1ml/kg/hr (to mitigate against tubular obstruction by myoglobin).

If cardiac arrest develops or if it is the presenting event:

6. Give calcium chloride IV to antagonise the cardiac effects of hyperkalaemia
7. Treat the potassium until it is within normal limits and continue to monitor it serially for at least 24 hours
8. Don't give up on resuscitating until the potassium is within normal levels. This may require such extreme measures as renal dialysis and cardiopulmonary bypass.

Dantrolene is of no benefit in this situation.

If you have a patient on your list that you know or suspect to have a muscular dystrophy you should give them a TIVA. Prepare them for this pre-operatively with anxiolysis if needed and ensure that EMLA is applied at least 45 minutes before you cannulation.

3. Mitochondrial Myopathies

These multi-system genetic diseases stem from an inherited or sporadic abnormality in any one of the mitochondrial oxidative complexes. The gene expression may be variable within the same family so that family members with the same mutation may have differing clinical pictures and varying responses to anaesthetic drugs. Patients may present with a variety of symptoms including myopathy, cardiomyopathy, encephalopathy, seizures and gastro-intestinal symptoms.

In situations where ATP levels become inadequate, such as in decreased oxygen delivery or increased oxygen demand, acidosis and cell breakdown occurs. In the peri-operative period this may happen in response to stressors like fasting, fever, shivering and increases in sympathetic tone such as when pain is experienced.

Pre-operative assessment should look for cardiac involvement, assess the severity of the myopathy and its impact on the respiratory function and establish baseline neurological function. Baseline levels of lactate and CK, as well as electrolytes and anion gap should be obtained as a reference.

Anaesthetic recommendations centre on preventing deterioration to lactic acidosis in the peri-operative period:

- Give intravenous glucose ($\leq 5\%$) containing fluids pre-operatively when *nil per os*; unless they are on a ketogenic diet to reduce seizures in which case a protein containing fluid is required.
- Premedicate to avoid anxiety in theatre
- Treat pain adequately
- Maintain haematocrit near normal to preserve adequate tissue oxygen delivery
- Aim for normotension
- Monitor temperature and maintain normothermia
- Check glucose, pH, lactate and electrolytes regularly (in all but the shortest of cases an arterial line is recommended to facilitate regular sampling of blood)
- Avoid lactated fluids

- Avoid respiratory depressants and support ventilation to prevent the development of hypoventilation and a respiratory acidosis
- Avoid tourniquets

The association between mitochondrial myopathies and MH has now been largely dismissed.

The evidence for specific drugs and techniques is scanty and we're forced to rely on expert opinion which is based on case reports, a few case series as well as a theoretical understanding of the disorders and their interactions with anaesthesia. Patients with mitochondrial myopathies are thought to be at risk of a propofol infusion syndrome-like clinical picture which can develop much more rapidly than the classically described syndrome, over just a few hours as opposed to several days. This may be due to the long-chain fatty acids in the lipid emulsion having an adverse effect on fatty acid oxidation and respiratory chain function. As with the dystrophies although incident-free propofol exposure has been shown in several case reports, it is recommended that if you know or suspect someone may have a mitochondrial myopathy propofol be avoided. Sevoflurane, the least respiratory depressant of the volatiles, is probably the best choice for general anaesthesia.

“ There is no theoretically perfect way to anaesthetise all children with mitochondrial disease”
(Niezgoda J & Morgan PG, Anesthetic considerations in patients with mitochondrial defects.
Paediatric Anaesthesia: 2013; 23(9): 785–793).

There has been a case report of rhabdomyolysis following suxamethonium so this drug is best avoided. A variable response to non-depolarizing muscle relaxants requires that these drugs be carefully titrated with neuromuscular monitoring.

4. The Undiagnosed Child

While the child who has a definitive diagnosis of a muscle disorder presents clear challenges to the anaesthetist it is perhaps even more challenging to anaesthetise a child without a clear diagnosis but in whom you suspect a muscle disorder may be present (Table 2).

Table 2: Clinical signs and symptoms possibly associated with a muscle disease

Family history	Muscle disease in the family
Personal history	Hypotonia ('floppiness') in the neonatal period Arthrogryposis Delayed motor development Motor regression Painful cramps Emission of cola-coloured urine following exercise or general anaesthesia
On examination	Weakness Enlarged firm calves Amyotrophy Inexpressive facies ('carp mouth') Waddle-like gait Tachycardia at rest
Investigations	Asymptomatic elevation of CK (creatine kinase) or SGOT (Serum glutamic oxaloacetic transaminase) ECG: atrioventricular conduction defect with no history of previous cardiac surgery

Adapted from: Brandom BW & Veyckeman F, Neuromuscular diseases in children: a practical approach. Pediatric Anesthesia 2013; 23(9): 765–769

For every anaesthetic the questions one would like to have answered before starting, answers that would help in anaesthetic planning would be:

1. Does this child have an increased risk of malignant hyperthermia (MH)?
2. Is this child at risk of anaesthesia induced rhabdomyolysis?
3. Is there an increased risk of a cardiac or respiratory event?

Brandom and Veyckeman suggested “Rules” to help guide management in these difficult cases:

1. **All muscle disorders are multi-organ diseases.** Suspect and prepare for cardiac and respiratory challenges and look for other organ system involvement
2. **Who’s at risk of MH?** Table 3 details diseases with a definite and potential association with MH. MH is seen more frequently in boys and under the age of 18. A family history is helpful but will only detect a minority of cases (<10%).

Table 3: Muscle diseases associated with MH susceptibility

Definite increased risk of MH	The presence of a known MH causative mutation of RYR1 Central core disease Minicore or multicore myopathy Core rod myopathy King–Denborough syndrome Native American myopathy Uniform type I fibres myopathy (CNDMU1) A minority of exertional rhabdomyolysis cases
Weak association (risk probably not increased)	Carnitine palmitoyl deficiency II Hypokalaemic periodic paralysis Brody’s disease

Adapted from: Brandom BW & Veyckeman F, Neuromuscular diseases in children: a practical approach. Pediatric Anesthesia 2013; 23(9): 765–769

3. **Who’s at risk of AIR?** Patients with Duchenne’s or Becker’s Muscular Dystrophy are definitely at risk of AIR. It is not known whether the same risk exists for the muscle diseases involving other proteins of the dystrophin–glycoprotein complex which are far less common (listed in Table 1) but it is suggested that the same approach as for DMD be followed when administering anaesthesia.
4. **Avoid suxamethonium** whenever a muscle disease is known or suspected. Case reports of the use of suggamadex are mounting but, as yet, there is insufficient evidence regarding its use in this heterogeneous group of patients to recommend it.
5. **The challenge of the “floppy infant”:** Causes of weakness are diverse and listed in Table 4. Discussion with the referring paediatrician as to the most probable diagnosis based on clinical examination, CK and lactate levels is a useful start when planning an anaesthetic. If CK is elevated suspect dystrophinopathy and avoid volatiles, if lactate is elevated suspect mitochondrial myopathy and avoid propofol. Consider regional anaesthesia where possible with supplemental ketamine and N₂O. Dexmedetomidine is also emerging as a potential option in this group.

Table 4: Causes of excessive muscle weakness in the neonate and infant

Central nervous system disorders Congenital myopathy: central core disease, myofibrillar myopathies Congenital muscular dystrophy Congenital form of myotonic dystrophy type 1 Spinal muscular atrophy Myasthenic syndromes: neonatal transient myasthenia, congenital myasthenia Metabolic myopathies: mitochondrial myopathies, carnitine deficiency Neuropathies

Adapted from: Brandom BW & Veyckeman F, Neuromuscular diseases in children: a practical approach. Pediatric Anesthesia 2013; 23(9): 765–769

5. Conclusion

Anaesthesia for children known to have muscular disorders is a challenging balance between meeting anaesthetic and analgesic requirements while avoiding excessive suppression of neuromuscular, cardiovascular and respiratory systems.

When looking for an evidence-based approach the literature can be confusing. Case reports are helpful to a point but have potential biases. Each of the diseases discussed is rare and in order to be able to develop an evidence-based approach to the difficult question of the best way to anaesthetise children with known or suspected muscle diseases the anaesthesia community needs to pool its data. It's hoped that, in the future, an international registry may be developed where information from the anaesthetics for children with muscle disorders can be collected and analysed.

It is possible that the greatest challenge lies in managing the undiagnosed patient who may develop a catastrophic reaction to a chosen anaesthetic. Pre-operative vigilance may raise suspicion and intra-operative vigilance lead to early diagnosis and management with possible avoidance of adverse outcome. Post-operative observation is essential.

Recommended reading

Myotonic Dystrophies: Campbell N, Brandom B, Day JW & Moxley R, Practical Suggestions for the Anaesthetic management of a Myotonic Dystrophy Patient. *myotonic.org* 2016 (PDF available for download on the website)

Mitochondrial myopathies: Niezgoda J & Morgan PG, Anesthetic considerations in patients with mitochondrial defects. *Paediatric Anaesthesia*: 2013; 23(9): 785–793

Approach to an undiagnosed child: Brandom BW & Veyckeman F, Neuromuscular diseases in children: a practical approach. *Pediatric Anesthesia* 2013; 23(9): 765–769

Assessing Fluid Responsiveness under Anaesthesia

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Introduction

Fluid therapy has undergone a paradigm shift in terms of the indications (context) and represents a shift towards a more physiological approach to fluid administration. It has been clearly shown that fluid overload causes harm and fluid administration seems to be at best arbitrary in most circumstances. (1)

Fluid responsiveness

The definition of responsiveness came about following seminal work showing that patients are fluid responsive if their stroke volume (SV) increases by 10% following a fluid challenge (usually 500mls of crystalloid). (2) However, fluid administration will only increase SV if two conditions are met, i.e. if the fluid bolus increases the stressed blood volume causing the mean circulating filling pressure to increase greater than the right atrial pressure, thereby increasing the gradient for venous return, and if both ventricles are functioning on the steep part of the Frank-Starling curve. (3, 4) Therefore, it is critical to demonstrate fluid responsiveness before fluid loading and potentially fluid overload patients which leads to tissue oedema and organ dysfunction. (5, 6)

Assessment of fluid responsiveness

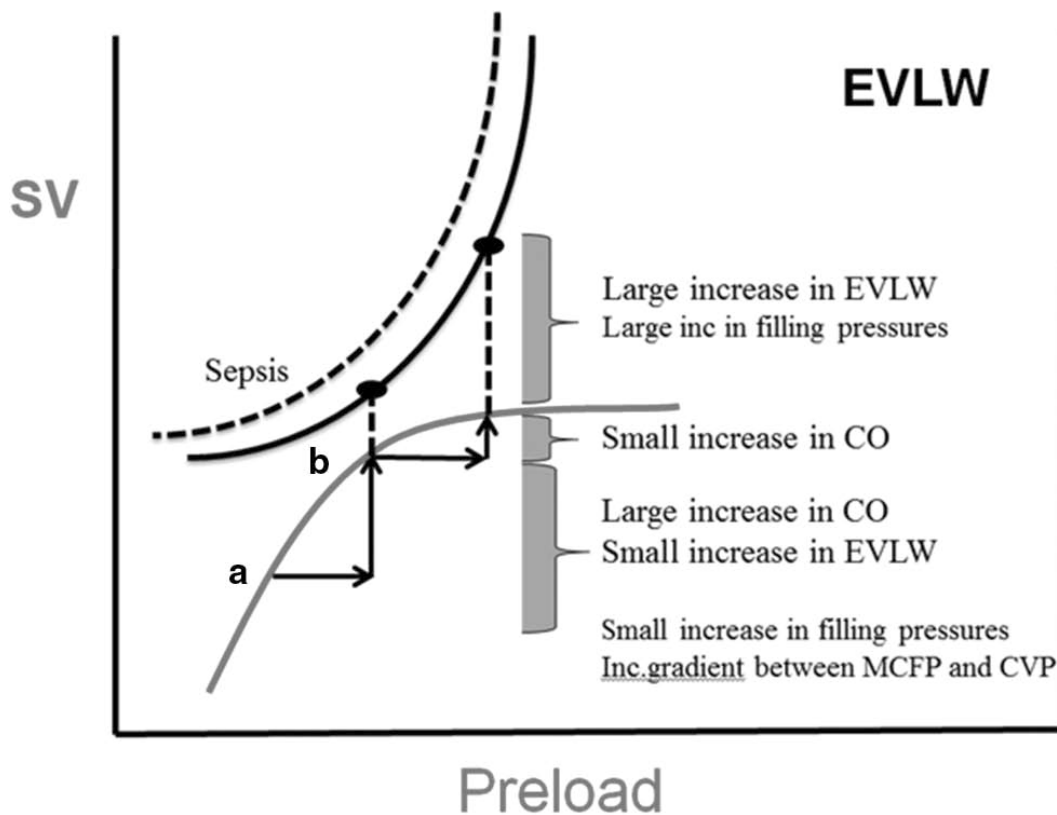


Figure 1. Superimposition of the Frank-Starling and Marik-Phillips curves demonstrating the effects of increasing preload on stroke volume (SV) and lung water in a patient who is preload responsive (a) and nonresponsive (b). With sepsis, the extravascular lung water (EVLW) curve is shifted to the left.
CO = cardiac output, CVP = central venous pressure, MCFP = mean circulating filling pressure.

The most reliable and robust markers of fluid responsiveness are the dynamic markers. These are the following:

- Pulse pressure variation
- Systolic pressure variation
- Stroke volume variation
- Plethysmographic waveform variation
- Passive leg raising

Pulse pressure variation:

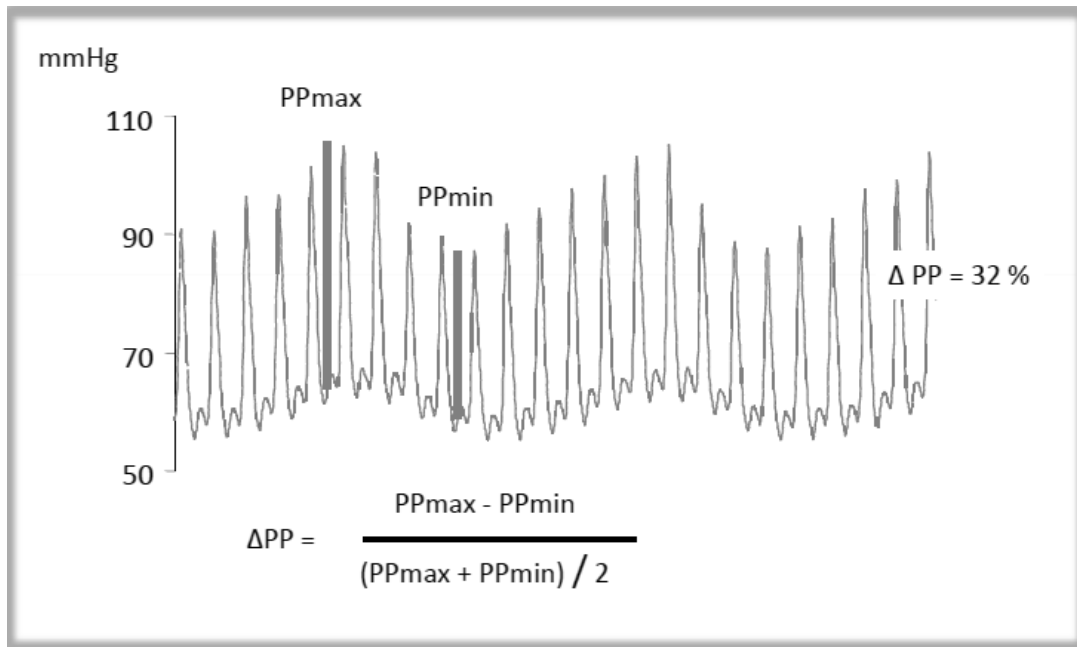


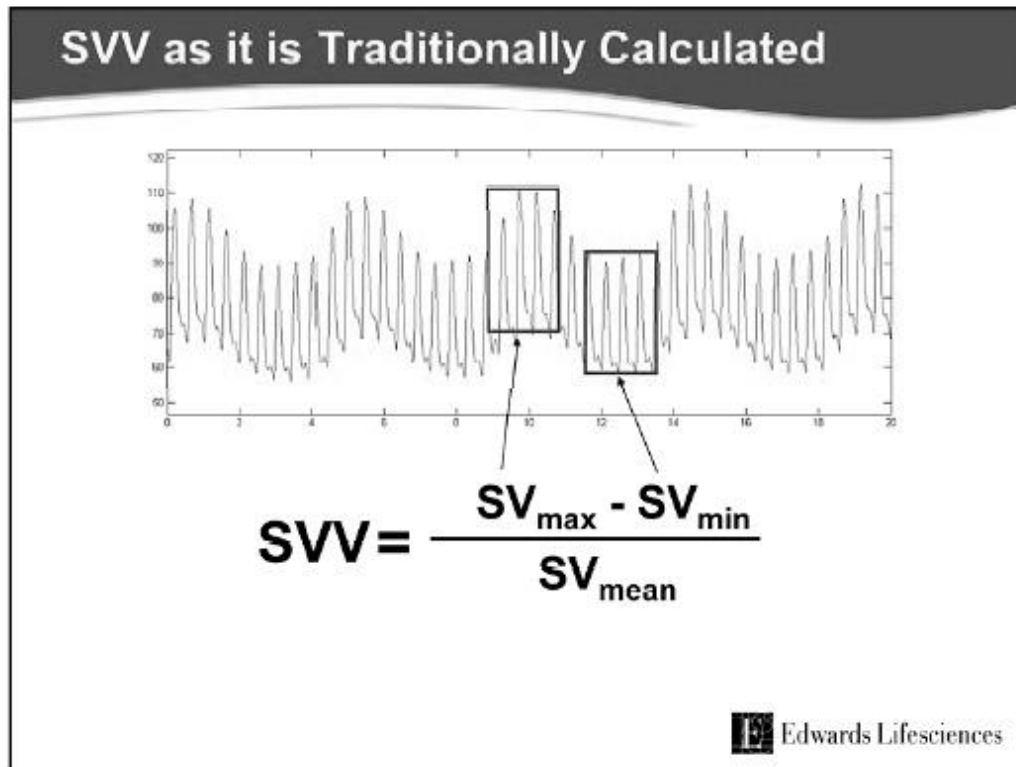
Figure 2: Prof Xavier Monnet – Fluid responsiveness lecture, SASA congress 2012

The respiratory variation in systolic pressure or pulse pressure for that matter relates to changes in intra-thoracic blood volume during controlled positive pressure ventilation. Blood is propelled forward during each inspiration towards the left atrium and therefore provides the left atrium with a preload during each mechanical breath. This concept was originally referred to as preload recruitability of the left ventricle. If this variation is exaggerated during mechanical ventilation and the ΔPP is greater than 10% as calculated by the above formula then the patient will benefit from a fluid bolus.

There are pre-requisites for the interpretation of pulse pressure variation though. The patient must be ventilated with tidal volumes of 8mls/kg or greater during the maneuver and the lung compliance should be normal.(7) Secondly, the patient must be in sinus rhythm since any arrhythmia will result in changes in stroke volume which influences arterial pressure. The last absolute contra-indication will be if the patient is breathing spontaneously, since the tidal volume will vary and result in variation in the arterial waveform, purely related to the changes in tidal volume.

Stroke volume variation

Another dynamic marker to assess fluid responsiveness is to use pulse contour analysis to calculate stroke volume and to look at stroke volume variation (SVV) to measure fluid responsiveness. This remains the most accurate measure of fluid responsiveness since it assesses changes in SV during mechanical ventilation. The changes in SV mirror the changes in pulse pressure (as described above) during controlled mechanical ventilation, based on the following calculation:



A SVV of greater than 10% is associated with fluid responsiveness. Once again this method of assessment of intravascular volume is influenced by the following:

- Spontaneously breathing patients
- Arrhythmias
- Artefact in arterial waveform traces, or devices like intra-aortic balloon pumps which distort the arterial waveform and make interpretation of the area under the systolic part of the waveform inaccurate.

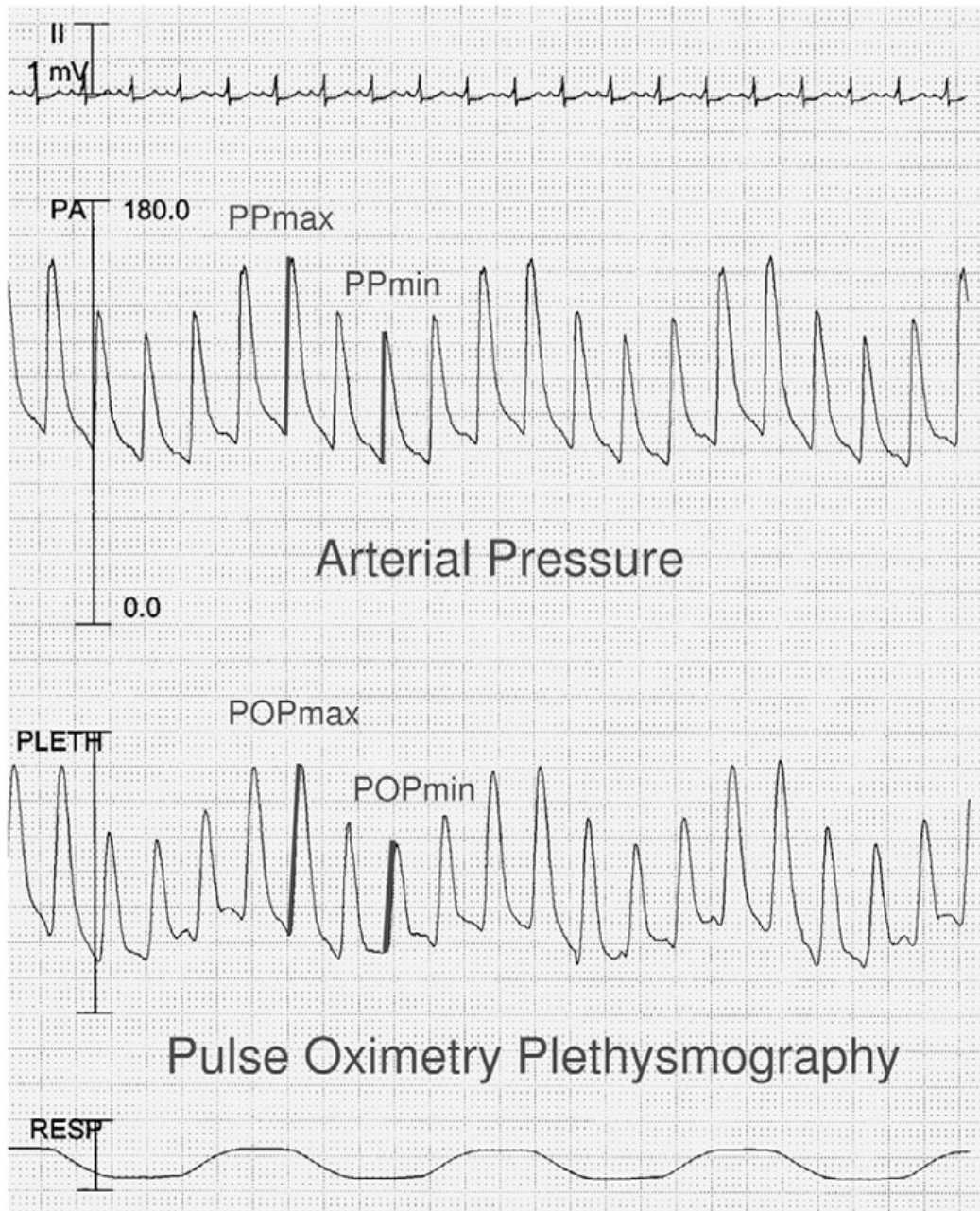
Pulse plethysmography analysis

Pulse oximetry plethysmography (POP) demonstrates a pulsatile waveform similar to the arterial waveform and therefore can be used to infer the same information obtained from the arterial pressure tracing to assess volume responsiveness. In a study of patients mechanically ventilated and sedated the correlation between pulse pressure variation and POP showed excellent correlation ($r^2 = 0.83$) in terms of demonstrating fluid responsiveness however, the monitor has not been validated in the setting of volume expansion. It is not clear what the threshold value should be in terms of a cutoff for predicting fluid responsiveness and whether this will be similar to the thresholds for SVV and PPV. (8) This technique represents an attractive alternative to more invasive techniques which require an intra-arterial catheter; however, further studies are needed to validate this technique. Furthermore, any artefact in the plethysmographic trace will render the information inaccurate and makes the monitor typically one with a low signal to noise ratio.

The calculation to predict fluid responsiveness is similar to the one's described above and is as follows:

$$\Delta POP = [POP_{\max} - POP_{\min}] / [(POP_{\max} + POP_{\min}) / 2] \times 100$$

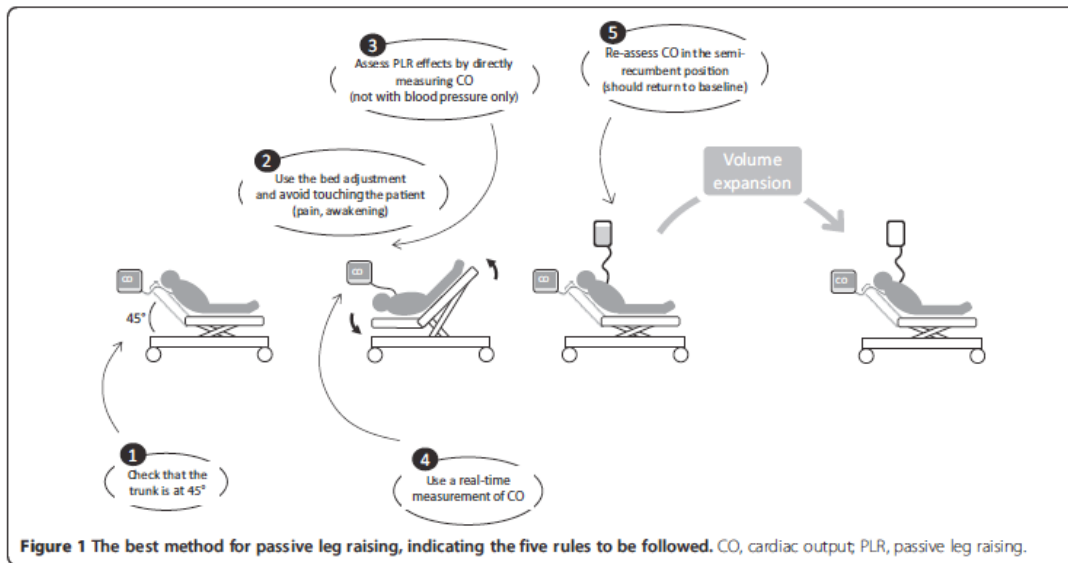
A threshold of 15% has been used to predict fluid responsiveness. See overleaf:



Passive leg raising

Possibly the easiest and least invasive test of assessment of intra-vascular volume is to perform a passive leg raise (PLR). This maneuver requires nothing more than a functioning bed that can be manipulated to raise the legs and ideally a measure of SV to assess response. Mean arterial pressure (MAP) is used in clinical practice as a surrogate of cardiac output but this increases the number of false negative tests reported.(9)

It is important to recognize that the test must be performed in a standardized way to ensure consistent results. The cartoon below demonstrates how the test should be performed.(10)



It is the only test that has been validated in spontaneously breathing patients and is not influenced by cardiac rhythm. This test offers the advantage that no additional fluid is administered to the patient therefore avoiding the risks of fluid overload.

End expiratory occlusion test

This test although not widely used once again relies on the interaction between the cardiac and respiratory system. During inspiration in patients on mechanical ventilation, venous return is impeded and hence cardiac output is decreased. If expiration is paused for approximately 15s, the effects on venous return is inhibited and hence cardiac output increases and hence this phenomenon can be used to assess fluid responsiveness. Therefore, if arterial pressure or stroke volume increases by 5% following an end expiratory occlusion test for at least 15s, the patient would benefit from a bolus of fluid. The advantage of the test is that it remains robust over several cardiac cycles and therefore can be used in patients with cardiac arrhythmias and in patients breathing spontaneously despite being ventilated. (11)

Conclusion

Fluid therapy has evolved and is based on sound physiological principles governing cardio-respiratory interaction. The concept of fluid challenges should be replaced by these more physiological and less harmful tests of fluid responsiveness.

Patients who are volume responsive should only receive fluid if they are likely to benefit from a bolus of fluid and if the benefits of the fluid outweigh the risks associated with fluid overload. Patients should NOT receive fluid until they are no longer fluid responsive. (12)

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Anaesthesia for the Patient with Traumatic Brain Injury

Do we influence patient outcome?

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What is clear is that we cannot influence the primary injury that results in the disruption of neural tissue, pathways, supporting tissue and blood vessels. However it is now clear that the primary injury initiates a set of injurious processes that are not only ongoing, but also render the injured brain susceptible to secondary insults, or “injuries”, that in the uninjured brain would just have been physiological variables that occurred with no consequence.

So surgery and anaesthesia post traumatic brain injury (TBI) takes place in the setting of established injuries, and the brain being in a state with many evolving cascades and pathophysiological processes that render it susceptible to insults that anaesthesia could contribute to. Optimal anaesthetic care does require the anaesthesia provider to understand the milieu that anaesthesia is taking place in. Unfortunately we do not fully understand, or have even identified, all the processes and their implications; but we are beginning to understand the complexity of situation that we find the injured brain in.

Unfortunately, factors that definitely impact the outcome and that we cannot control, are:

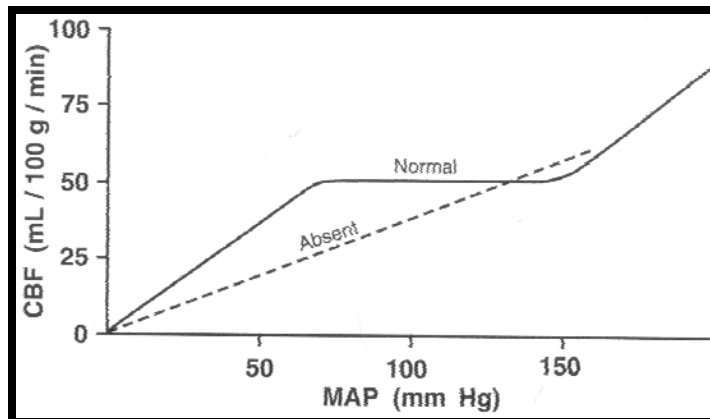
- Age (over 55 years)
- Sex (women do far worse with an equivalent injury than men)
- Genetics (Apo E 4 allele)
- Severity of primary injury

Importantly evidence from the past two decades suggests that the standard of care that patients receive, in the immediate period and through their first few weeks after a traumatic brain injury, can make a significant difference to their final outcome. The difference between centres, even in the developed world, can be as high as a six-fold difference in outcome. So the decisions you make, and the care that you can provide as anaesthetist, probably contribute to both mortality and functional outcomes.

Important components of the pathophysiology of TBI that anaesthesia providers need to be aware of:

- Inflammatory processes
 - o Both the primary injury and secondary insults initiate inflammatory processes including inflammatory cytokines (TNF, interleukin series), prostaglandins, complement and free radical creating peroxidases.
 - o These contribute to increased BBB permeability.
 - o This process has the ability to mop up destroyed or injured tissue as well as surrounding cells, effectively leaving residual “scar” tissue.
- Oedema formation
 - o Two types of oedema occur concurrently after TBI
 - The dominant pathophysiology seems to be **cytotoxic** oedema secondary to swelling of cells (neurons, astrocytes and microglia). Ischaemic conditions result in anaerobic metabolism and a lack of energy substrates for the cells energy-dependent ionic-pumps. This is the putative target of both perfusion pressure (Rosner therapy) and CBF (Lund therapy) TBI treatment- improving perfusion allows the cells to correct their energy deficiency and re-establish ionic pumping, thereby decreasing cell volume and cerebral oedema caused by this mechanism.
 - Vasogenic oedema is the consequence of a damaged blood-brain barrier (especially the endothelial cell component of the barrier) resulting in ions, colloid-like particles and fluid extravasating into the interstitial space of the brain.
Vasogenic oedema is likely the lesser contributor to clinical picture creating a raised ICP, post a TBI, but may be critical with regards the effects of excitatory neurotransmitters, drugs and fluids in this setting.

- Excitotoxicity follows massive release of excitatory neurotransmitters (glutamine, aspartate) leading to activation of NMDA receptors, AMPA receptors and voltage dependent calcium and sodium channels. The calcium and sodium influx initiates catabolic intracellular processes, mainly through enzyme activation that results in membrane degradation and cellular dysfunction, and pre-lethal programmed cell death.
- Raised ICP, reduced CPP
 - o Normal intracranial pressure (ICP) is 10mmHg. There is some debate about the exact value when it is raised, but somewhere between 20mmHg and 25mmHg there is agreement that the rise is sufficient to warrant ICP-reducing therapy. Treatment algorithms typically target attempts to decrease the pressure; failing that then initiating treatment to overcome the perfusion effects of the raised pressure.
 - o There is no evidence that ICP reducing treatment improves outcome, but a raised ICP indicates:
 - Presence of significant pathology
 - A brain at risk of hypoperfusion
 - A risk of herniation
 - Single value of no prognostic value, but high values that are unresponsive to treatment may well be an indication of a poor outcome
 - o Cerebral perfusion is a measure of ensuring the brain is adequately provided with substrates and flow, in the setting of a raised ICP with or without altered or absent autoregulation. So the principal is that due to an inability to accurately determine the degree of autoregulation and perfusion, that one assumes a straight line relationship between perfusion pressure and flow, thereby ensuring an adequate delivery of blood/substrates to the brain. CPP is calculated simply in the Rosner (CPP driven) paradigm by $CPP = MAP - ICP$.



Current evidence and guidelines suggest that CPP targets lie between 60 and 70mmHg, with little benefit above 70mmHg and a trend to worse outcome when CPP drops below 60.

- Cerebral autoregulation
 - o The ability of the brain to respond rapidly to changes in metabolic requirements, and to fluctuations in systemic perfusion parameters, is a product of the highly effective autoregulation system for CBF.
 - o Following traumatic brain injury, autoregulation can be disrupted during the very immediate phase, or it can develop over time (hours to days). Some degree of impairment of autoregulation occurs in every patient after TBI, with some patients experiencing complete disruption of this key flow-metabolism coupling mechanism.
 - o The CO₂ response of the cerebral vasculature seems much better preserved than the pressure response, and even in severe injury changes in CO₂ produce rapid changes in vessel calibre and CBF/ICP. This can be a doubled edged sword as discussed later in parameters under anaesthetic control.

- Cerebral blood flow
 - o Both hypoperfusion and hyperperfusion occur after TBI, and both are detrimental as they indicate a flow-metabolism uncoupling with resultant ischaemia or hyperaemia. The dominant pathophysiology is one of hypoperfusion, and current evidence is the milieu within the neural tissue post TBI, lowers the ischaemic threshold for CBF/100g brain/minute to 15ml, and the threshold appears to be three times higher than the ischaemic threshold in ischaemic stroke (5ml/100g/min), indicating the extreme susceptibility of the brain to “secondary” insults after a traumatic injury, as compared to other serious brain injury states.
 - o Hyperperfusion occurs less often, both in the immediate phase after injury and can follow after any subsequent traumatic ischaemia, and is also associated with a worse outcome as it indicates cerebral vasomotor paralysis (and loss of autoregulation), and also because an increase in CBF, beyond metabolic requirements, will raise ICP and decrease CPP, placing the injured brain at risk of further ischaemia.
- Secondary injuries:
 - o Systolic BP less than 90mmHg in adult patients has been a key cutoff, associated with an almost doubling of mortality if the BP fell below this threshold for periods as short as two minutes at any time during the first few days post injury. Many guidelines, and more recent work, have suggested that this cut-off systolic pressure should be higher,
 - Currently the Emergency Neurological Life Support (ENLS) guidelines, as well as those from the European brain Injury Consortium(EBIC) and the Brain Trauma Foundation(BTF) all contain a systolic arterial pressure(SAP) >90mmHg before an ICP value is available, after which the CPP becomes the management target (CPP 60-70mmHg).
 - The only anaesthetic specific recommendation comes for the AAGBI in the UK where they target a MAP> 80 during the transfer of patients with a TBI.
 - Children BP targets SAP from the BTF are:
 - Over 10 >90 mmHg
 - 1-10 > 70 + (age x 2) mmHg
 - Infant >70mmHg
 - Neonate >60mmHg
 - o Hypoxaemia (PaO₂<8kPa or SPO₂) is the other major secondary insult, carrying a significant mortality effect on its own, and if occurring in the same patient as a hypotensive insult (even if not at the same time) compounds the poor outcome. So whilst the BTF guidelines set 8kPa as the lower limit, EBIC raised this to 10kPa and the AAGBI have this at 13kPa during transfer.
 - o Others:
 - Hyper-/Hypoglycaemia. Hyperglycaemia is correlated with poor outcomes in TBI, but this appears to be more related to the severity of the injury, and there is no work demonstrating that tight control through the use of insulin improves outcome. Indeed, tighter control introduces the possibility of potentially more deleterious hypoglycaemic episodes. So current consensus is that blood glucose should be regularly monitored during the acute stage, and that blood glucose be kept in the 6-10mmol/L range.
 - Hypo/Hypercarbia (Discussed later under factors under anaesthetic control)
 - Seizures are a potential cause of a rise in ICP, and in any patient with an already raised ICP, further rises can result in cerebral tissue herniation. Preventative anticonvulsants should be prescribed in all patients with a suspected raised ICP post TBI, until the ICP is sure to have returned to normal.

So what should the anaesthetic provider be considering during the peri-operative management?

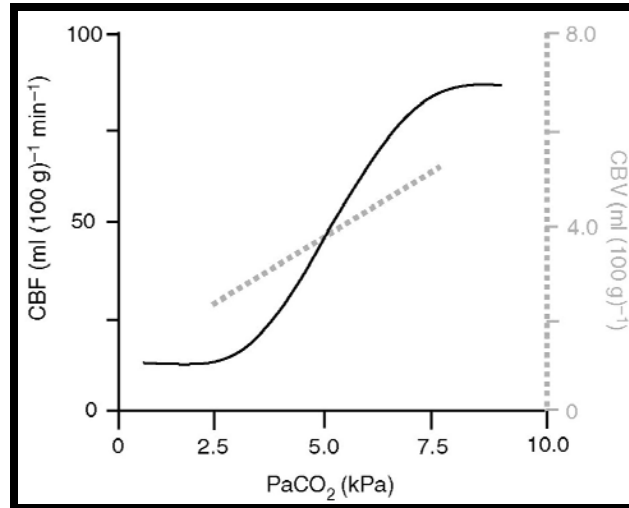
Firstly do no harm- think of other injuries especially cervical-spine, and consider them if unexplained hypotension, dropping haemoglobin, haemodynamic instability or hypoxaemia occurs during anaesthesia.

The anaesthesia provider is in control of several aspects that impact on outcome, namely:

- Timing of intra-cranial surgery
 - In patients with acute space occupying haematomas – both extradural and subdural, time to surgical evacuation in clinically significant haematomas, is a key determinant of outcome. Key indications would be haematomas more than 10mm thick, or with more than 5mm mid-line shift.
 - Subdural haematomas have the best outcome if evacuated within 4 hours of the injury, and delays beyond eight hours are associated with significant worsening of outcome.
 - Extradural haematomas can present with a more lucid period, but the determinant of outcome is time from neurological deterioration, and is measured in minutes rather than the hours for sub-dural haematomas.
- Timing of non-intracranial surgery
 - **Non-neurological extracranial surgery for the TBI patient**
 - Patients fall into 2 categories:
 - With a life-threatening injury, e.g. solid organ (liver, spleen, kidney) rupture and surgery usual proceeds, some authors even suggesting that the neurosurgical (if required) and other lifesaving surgery could be undertaken simultaneously.
 - With a less serious, non-life-threatening condition, e.g. a long-bone fracture.
 - The timing of surgery depends on:
 - Severity of these injuries
 - Effect on the ability to maintain cerebral protection
 - a. A limb-saving vascular procedure may be considered as a matter of urgency in all trauma patients
 - b. Long-bone fractures are more controversial
 - Early (<24 h) fixation of long-bone fractures may:
 - Improve outcome
 - Reduce pulmonary complications and mechanical ventilation time
 - Reduce ICU and hospital stay
 - **Head injury with a non-life-threatening extracranial injury**
 - Factors to consider in patients warranting early long-bone stabilisation:
 - Severity of brain injury
 - Pulmonary dysfunction, coagulopathy and hypothermia
 - Evidence of hypotension
 - Risks of delaying surgery
 - Compound fractures:
 - Can be debrided as part of the resuscitative effort
 - Skeletal traction until definitive fracture fixation
- Airway management: Many severe injuries will be already intubated, but when deciding on best intubation technique one needs to consider the urgency of the situation, the possibility of cervical spine instability, the risk of a full stomach, the possibility of a raised ICP, hypovolaemia or CVS instability and the status of the airway fractures (zygomatic, facial, mandibular), lacerations, bleeding, secretions. In general all patients with a TBI can be assumed to have both a full stomach and the possibility of an unstable c-spine.
 - Consensus that as long as the correct skill-set is available, that general anaesthesia with either RSI or a more elective intubation with a NDMR is preferable, despite concerns about the short-lived affect on ICP during laryngoscopy and intubation.
 - There appears to be no evidence that short-lived ICP rises related to any of the therapeutic manoeuvres, has any effect on outcomes

- Consider the cervical spine during airway management plans
- NICE Guidelines from the UK identify the following as adult patients at risk of C-spine injury and needing urgent CT neck scans:
 - o GCS less than 13 on initial assessment.
 - o The patient has been intubated.
 - o Plain X-rays are technically inadequate
 - o Plain X-rays are suspicious or definitely abnormal.
 - o A definitive diagnosis of cervical spine injury is needed urgently (for example, before surgery).
 - o The patient is alert and stable, there is clinical suspicion of cervical spine injury and any of the following apply:
 - Age 65 years or older
 - Dangerous mechanism of injury (fall from a height of greater than 1 metre or 5 stairs; axial load to the head, for example, diving; high-speed motor vehicle
 - Collision; rollover motor accident; ejection from a motor vehicle; accident involving motorised recreational vehicles; bicycle collision)
 - Focal peripheral neurological deficit e.g. paraesthesia in the upper or lower limbs.
- So whilst there is no evidence that favours any particular technique, a rapid sequence induction with manual in-line stabilisation (MIS) is the currently accepted standard. Once the cervical spine is secured using MIS the front portion of any hard-collar can be released to allow better mask application to the mandible, as well as allowing increased mandibular movement during laryngoscopy.
- The ENLS 2014 Guidelines, are the clearest in terms of a recommendation, and state "Rapid sequence intubation is the preferred method of securing the airway in patients with suspected elevated ICP since it provides protection against the reflex responses to laryngoscopy and rises in ICP. The presence of coma should not be interpreted as an indication to proceed without pharmacological agents, or to administer only a neuromuscular blocking agent without a sedative/induction drug. Although the patient may seem unresponsive, laryngoscopy and intubation will provoke reflexes that elevate ICP unless appropriate pretreatment and induction agents are used."
- Blood pressure
 - o Fluid administration. The first line management of hypotension is IV fluid administration, and whilst much continues to be written about the fluid choice, we do not have any outcome data suggesting any fluid provides better outcomes that are important to the patient; consensus is that hypotonic fluids and fluids containing glucose/dextrose should be avoided. Normal saline and the more isotonic balanced electrolyte solutions are all acceptable and the mainstay of fluid administration.
 - o Colloids also have no proven benefit, the use of albumin may be detrimental but the synthetic colloids are possibly best used for volume resuscitation only, as they offer little other benefit to the injured brain, across the blood-brain-barrier.
 - o Inotropes/Vasopressors
 - No clear benefit of any one over another
 - Consider patient's age and co-morbidity, young healthy patients can tolerate the pure after-load increasing effects of the α -agonists nor-adrenaline and phenylephrine, but elderly patients or patients with long-standing hypertension may not have the myocardial reserve to cope with the increased cardiac work and they may benefit from an agent with some inotropy, such as dopamine or adrenaline.
 - β -blockers are the mainstay of managing any hypertension, which is not an uncommon occurrence, particularly towards the end of a surgical procedure when the anaesthetic agents are terminated and the patient transferred to the critical care environment. All the direct acting vasodilators (nitrates, calcium channel antagonists) inhibit autoregulation and drop MAP, often taking the CPP to much lower levels, whereas the β -blockers preserve cerebral autoregulation, and act almost entirely on decreasing cardiac output.

- Ventilation
 - o CO₂ targets and their effects on CBF and outcomes



- The normal values for arterial CO₂ are on the steep part of CO₂ response curve, such that small changes in CO₂ have significant effects on CBF and on ICP. The injured brain appears to be rendered rapidly ischaemic if the CO₂ falls suddenly, as cerebral vasoconstriction decreases flow to levels that seem to create a secondary injury. This was first demonstrated to make a difference to outcome in 1991 by Muizelaar, and has subsequently been demonstrated to render injured brain ischaemic and change outcome, despite producing a decrease in ICP.
- The CBF/ICP reducing effect of a decrease in CO₂ has a very short (few minutes) response time, but the CSF correct the metabolic change rapidly and within 30 minutes the decreased CO₂ effect is lost and more importantly the vasculature appears to be reset at that value, so an increase back to the previous level is now seen as a rise in CO₂ partial pressure and a rise in CBF/ICP occurs. The reverse occurs for rises in CO₂, so that all clinicians ventilating patients after TBI need to be mindful of the acute and detrimental effects on any change in CO₂ partial pressures. Hence the evolving standard of care is for patients to have end-tidal CO₂ measured from initial intubation at the roadside or in the EC, through the patients whole acute care pathway including intensive care ventilation to prevent potential iatrogenic secondary injury through acute CO₂ changes.
- Current guidelines suggest avoiding hypocapnia (keep greater than 3.3kPa from BTF) and most published opinions and guidelines (AAGBI, ENLS, NICE) target PaCO₂ 4.5-5kPa
- The only role for acute hyperventilation is with imminent brain herniation, when a sudden lowering of the CO₂ can produce a lifesaving drop in ICP, but the anaesthesia provider needs to be aware that this will be successful for a maximum of 30 minutes, so that another management plan must be made to remove the cause of the sudden rise, or to mitigate that rise in another manner.
- o PEEP- has also been considered extensively, but there is no clear role for it, and there is some concern that raising intrathoracic pressure, increases thoracic venous pressures and thereby increases venous drainage pressure from the cranium and is associated with a modest rise in ICP.
 - Whilst there is no evidence that this is detrimental, prophylactic PEEP is not shown to decrease any complications of positive pressure ventilation.
 - So unless PEEP is needed to overcome hypoxaemia, a known cause of secondary to the brain, it may be best avoided in patients with TBI.
 - If PEEP is used, then “modest use” has been described, always less than ICP

- Measures to decrease ICP intraoperatively
 - o Head up 10-20°
 - o Drain off CSF if there is a ventricular drain in place (20-30ml usually enough)
 - o Hyperosmolar therapy
 - Mannitol has been the mainstay of this treatment for decades. Dose 0.25g-1 g per kg body mass. Can be repeated if effective, probably safe for 2-3g/kg total dose over a few days. Early side effects are the diuresis it produces, dropping intravascular volume in the setting of wanting to maintain perfusion pressures. Later side effects are electrolyte abnormalities, and a hyperosmolar renal injury of the plasma osmolality rises above 320mOsm.
 - Hypertonic saline – the last 10 years has seen much published, various concentrations used (2.5, 5 and 7.5% are common) and it would appear that it is a useful alternative to mannitol, but there is little or no evidence that it could be better. Certainly no patient-important outcome (functional outcome improvement or survival) data that supports its use over mannitol. Current literature suggests that mannitol probably still more widely used.
 - o Decrease CMR
 - Analgesia if possibility that pain an issue (ceiling, or more like a “floor” effect once pain is controlled)
 - o Hyperventilation (mentioned in ventilation section)
 - o Removal of mass occupying lesion if not neurosurgical procedure
- Temperature
 - o Hypothermia
 - It has become clear that there is currently no role for the use of induced hypothermia in TBI. Despite an unequivocal effect to decrease ICP, and much experimental work suggesting a role, we now have the 2 large USA studies (NABISH I and II), EURO THERM, a systematic review and a Cochrane review all demonstrating no neurological benefit, and several of the trials have been terminated early because of outcome and safety concerns for the hypothermia groups.
 - o Hyperthermia
 - Avoid hyperthermia, and target temperature in the 36° to 36.5°. Fever can be a manifestation of a severe TBI and the use of paracetamol, and active cooling can be considered although there is currently no evidence for these treatments.
- Haemoglobin management
 - o Physiology of decreasing haemoglobin
 - Demonstrates an increased CBF as Hb drops below 10g/dl, and there have been arguments for this, suggesting improved rheology and flow, and hence improving perfusion and oxygen delivery. However it would appear that this effect is rather as a consequence of the high oxygen extraction requirements, so that when oxygen delivery is decreased by a decreased haemoglobin, that the majority of the available oxygen is extracted early in capillary beds, resulting in low oxygen tension/availability later in the capillary and autoregulation therefore ensures vasodilatation to improve flow, and hence the effect is protective physiology, rather than a supra-normal delivery secondary to viscosity improvements.
 - Brain hypoxia and dysfunction usual appears with acute haemodilution below 6-7g/dl.
 - o Pathophysiology of decreasing haemoglobin in TBI patients
 - The acutely injured brain appears susceptible to reduced oxygenation with hypotension and hypoxaemia being the dominant secondary injuries. In addition retrospective data suggested that patients in large TBI data bases and clinical trials (CRASH and IMPACT) with lower admission haemoglobins, had a worse outcome. The data seemed to suggest a cut-off point around 9g/dl, similar to the cut-off for experimental work demonstrating evidence of cellular distress.
 - However it is not clear whether this is merely a marker of a seriously injured patient, or whether this is an indication where red cell transfusion would

- improve outcome.
- The notion that red cell transfusion will improve cerebral tissue oxygenation is attractive and several studies have demonstrated this effect, but it would appear that in a percentage of patients (between 21-46 %) that cerebral tissue oxygenation actually falls.
- The most recent work (Robertson JAMA 2014) is a prospective trial comparing transfusion triggers of 7 or 10, and also including a arm with erythropoietin, which was previously explored as a neuroprotective agent in TBI following exciting animal work. This work showed no benefit to either a higher transfusion trigger or erythroetin, but the 10g/dl group had a significantly increased incidence of thrombotic complications during the follow-up period.
- o In prospective clinical trials there is no clear data that suggests that transfusing patients to a Hb>11 is better than an Hb>7. So current guidelines and expert opinion recommend only transfusing if anaemia is believed to be symptomatic.
- Coagulopathy
 - o Often reported to be present in up to a third of patients with TBI, and associated with increased morbidity and mortality
 - Our experience is that a coagulopathy caused by the TBI is much less common
 - o What is much more of a problem is patients on anti-coagulants.
 - Warfarin use associated with increased frequency and severity of head injury, together with greater likelihood of death.
 - Estimated that pick-up rate for intracranial lesions may be as high as 1:4 in these patients, and liberal scanning policy may result in 2% increase in scanner workload
 - Whether warfarin should be reversed with FFP or PT Complex is unclear, however a lower threshold to scan/rescan patients is probably warranted.
 - For patients on anti-platelet drugs the evidence is less clear
- Drugs
 - o Drug choice for anaesthesia, has not been shown to make a difference to outcome, but based on first principles there are drug factors that are considered important:
 - Inhalational agents- all the currently used agents (isoflurane, sevoflurane and desflurane) decrease CMRO₂ but may cause vasodilatation especially above 1 MAC. Carbon dioxide reactivity is preserved as is pressure autoregulation at normocapnia. The volatiles may be used in ventilated patients at concentrations up to 1 MAC.
 - Intravenous agent choice needs to consider that thiopentone, propofol and etomidate all decrease CMR and hence in injured brains with enough autoregulation intact, they will decrease ICP. Propofol and thiopentone will result in a larger expected drop in BP than etomidate after an induction dose, but etomidate does have the potential problem of adrenal insufficiency. Ketamine may have the least cardiovascular depression but is still currently contraindicated due to concerns about its effect to increase CBF and ICP.
 - In a rapid sequence induction it is thought that suxemethonium may be the drug of choice, the brief rise in ICP thought to be of no consequence, but the risks of hypercarbia and hypoxia with difficult conditions, or failed airway management with modified rapid-sequence utilizing rocuronium being the alternative.
 - Analgesics
 - Analgesics have no ICP reducing effect unless the patient is experiencing significant pain or agitation, but once the small benefit of analgesia/sedation is achieved there is a 'ceiling' effect resulting no further metabolic sparing or ICP decreasing effect.
 - Opioids have no direct effects on cerebral haemodynamics if ventilation controlled and if administered such that MAP does not change. If administered as a bolus that results in a significant fall in

MAP, then cerebral autoregulation causes vasodilatation to try and maintain flow and CBF and ICP rise

- Paracetamol- analgesic and antipyretic of choice
 - NSAIDS- because of their antiplatelet effect are not first line drugs, and should probably be avoided despite the lack of clear evidence.
- Anaesthetic monitoring choices
 - o Arterial line provides beat-to-beat measurement of arterial pressure, and for arterial blood gas and blood sugar analysis
 - o Central line is useful in polytrauma patients, and should be placed in all patients receiving an ICP monitor to allow the safe infusion of inotropes for CPP driven treatment.
 - o Pupillary size and reactivity is the earliest monitor of tentorial herniation in the sedated and ventilated patient
 - o ICP monitors are valuable in the TBI patient undergoing extensive surgery or surgery at multiple sites. If such surgery is deemed necessary the patient may need to be referred to a unit where ICP monitoring can be instituted
 - Access to neurocritical care
 - o Close to two decades of work has demonstrated the improved outcome in patients with TBI admitted to a critical care unit that is dedicated to the neurological monitoring and management of TBI patients
 - o In addition improved outcomes are demonstrable if the unit is staffed by full-time neurointensivists and then further improvements can be obtained through both the implementation of protocols, but also from protocol adherence projects in units that already have established protocols.
 - o So planning the post-anaesthetic care to be provided by the highest level of neurointensive care available, may be a the final decision that the anaesthesia provider can contribute to, that makes a meaningful difference to the patients outcome following a traumatic brain injury.

SUMMARY

- The injured brain is susceptible to insults that, under physiological conditions, would not cause damage
- Prevention of hypoxia, hypotension, seizures and the rapid evacuation of intracranial haematomas offer the best advantages
- Hypothermia, routine hyperventilation and steroids offer no benefit
- Life-saving surgery may take priority over the TBI
- Non-life-saving surgery should be delayed until the TBI has stabilised, ideally 48--72 hours or more after injury
- If used carefully most anaesthetic techniques and drugs are suitable, with a few exceptions
- Attention to the general principles of care, especially avoiding hypotension, is key to maximising the neurological outcome.

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Cardiopulmonary Exercise Testing

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Abstract

The goal of preoperative risk stratification is to accurately classify patients into low and high-risk groups for perioperative morbidity.¹ Unfortunately, due to the poor performance of clinical risk predictors, some patients will need to go on to further dynamic preoperative testing in order to appropriately risk stratify them. Functional capacity has been associated with both cardiovascular morbidity and mortality following noncardiac surgery. This review will discuss the physiology of exercise, field tests of functional capacity, cardiopulmonary exercise testing (CPET), and the associations between functional capacity and perioperative outcomes in noncardiac, nonthoracic surgery.

Physiology of exercise

Metabolic equivalents (METs) are multiples of the basal metabolic rate (assumed to be 3.5 ml/kg/min). They have been used in the classification of functional capacity.

Maximal oxygen uptake (VO_2max) is the point when oxygen uptake (VO_2) reaches a plateau despite continued increase in the work rate. If fatigue occurs before a plateau is reached, then this point is defined as the peak oxygen uptake ($\text{VO}_{2\text{peak}}$).

The anaerobic threshold is the point where oxygen-independent (or 'anaerobic') metabolism is required in addition to aerobic metabolism to sustain exercise performance. This is usually due to increased flux through the (oxygen-independent) glycolytic pathway, increasing pyruvate generation and lactate production. The anaerobic threshold is usually determined by lactate or ventilator thresholds. Although the aetiology of these thresholds may be different, the term 'anaerobic threshold' (AT) in preoperative evaluation usually refers to the ventilatory threshold. The ventilatory threshold is usually reproducible and safe to measure, even in patients with myocardial ischaemia and heart failure. However, it is not always easy to determine in all patients.²

Differences between oxygen independent metabolism and oxygen dependent metabolism during exercise.

The duration of an exercise test determines the contribution of aerobic and oxygen-independent metabolic pathways to performance. A test duration of at least 10 min is usually recommended when assessing aerobic capacity, which approximates to that of anaerobic threshold testing.³ Metabolism at the onset of exercise is predominantly oxygen-independent. Oxidative phosphorylation only dominates after about 2 minutes of exercise. The time to oxidative phosphorylation is prolonged in heart failure, chronic obstructive pulmonary disease, peripheral vascular disease and diabetes.

The relationship between $\text{VO}_{2\text{peak}}$ and anaerobic threshold is a function of central (cardiorespiratory), peripheral (musculoskeletal) factors, and physical training, and diseases such as ischaemic heart disease and heart failure. The anaerobic threshold may vary from 50% to 100% of $\text{VO}_{2\text{peak}}$.

Performance during exercise is partly dependent on the mechanical efficiency of the individual. Perioperative survival should depend on the cardiorespiratory capacity of the individual, not the musculoskeletal function,³ although recently 'frailty' has been identified as a strong predictor of

perioperative morbidity and mortality. Patients with an acceptable aerobic capacity may be included in a 'poor functional group' due to musculoskeletal factors associated with their 'frailty'. Although these patients are unlikely to die of cardiovascular failure in the perioperative period, they are at increased risk of postoperative complications. It is believed that AT testing minimises the contribution of peripheral factors to poor exercise performance by limiting weight-bearing with cycling.³

Assessment of functional capacity for surgical patients

The basis for the interest in functional capacity for perioperative risk stratification

Major surgery initiates a stress response of up to 72 hours in duration,⁴ associated with an increase in oxygen consumption to approximately $5\text{ml.kg}^{-1}.\text{min}^{-1}$, and occasionally as high as $7\text{ml.kg}^{-1}.\text{min}^{-1}$.⁴⁻⁷ The preoperative assessment of functional capacity is an important determinant of the ability to survive this increase in metabolic demand.⁶ In patients over 60 years of age undergoing major abdominal surgery, an anaerobic threshold (AT) measured during CPET of less than $11\text{ml.kg}^{-1}.\text{min}^{-1}$, was found to be an independent predictor of perioperative cardiovascular mortality.⁵ Myocardial ischaemia in patients with poor functional capacity⁵ significantly increased adverse perioperative cardiac events.

Functional status is now an integral component of the American College of Cardiology / American Heart Association preoperative cardiac evaluation algorithm.^{8,9} The risk stratification is essentially based on whether a patient can complete 4 METS of exercise or not. The risk of myocardial infarction and cardiac arrest increases nearly 3 fold between functionally independent and dependent patients.¹⁰

Clinical assessment of functional capacity

Functional capacity is commonly assessed with stair climbing, the Duke Activity Status Index (DASI),¹¹ the six minute shuttle walk test and cardiopulmonary exercise testing (CPET).

Stair climbing. Classically, the ability to climb two flights of stairs has been used as a prognostic threshold as it requires > 4 METs,¹¹ and it has been associated with perioperative complications.^{12,13} It is important to note that estimation of perioperative aerobic capacity based on stair climbing relates to the VO_2peak and not to anaerobic threshold. Based on the relationship between the AT and the VO_2peak , it is possible despite the ability to climb two flights of stairs that a patient may have an unacceptably low AT.³ Reporting the inability to climb two flights of stairs has been associated with postoperative cardiac events (although this is a composite of arrhythmias, myocardial ischaemia, myocardial infarction and congestive cardiac failure).¹² Stair climbing however, does not predict mortality and has been shown to be a poor predictor of aerobic capacity.³

Duke Activity Status Index and 6 minute shuttle walk test. The distance walked in a 6 minute shuttle work test has been shown to explain about 50 to 60% of the VO_2peak measured by CPET.^{14,15} Increasing distance walked is associated with less postoperative complications.^{14,16} The Duke Activity Status Index (DASI) is a clinical questionnaire which assesses functional capacity. It has a poorer association with the VO_2peak measured on CPET.¹⁵

The result of the inability of the DASI and the 6 minute shuttle walk test to explain the contributors to the VO_2peak in their entirety means that these field tests are associated with a low negative predictive value for aerobic capacity (Table 1). Patients who scored poorly on field tests of aerobic capacity often had clinically acceptable results on objective cardiopulmonary exercise testing as shown in the table.¹⁵ The ability of these field tests to accurately identify patients with poor function is therefore limited.¹⁵

Table 1. Positive predictive value (PPV) and negative predictive value (NPV) for field test results¹⁵

	PPV	NPV
Anaerobic threshold > 11ml/kg/min		
DASI>46	1.0	0.40
Shuttle walk > 360m	1.0	0.46
Anaerobic threshold > 11ml/kg/min and VO2 peak >15 ml/kg/min		
DASI>46	1.0	0.44
Shuttle walk > 360m	1.0	0.49

Despite these limitations, this paper does however provide us with the tools to estimate the VO₂ peak, which may be advantageous at centres where CPET is unavailable;¹⁵

VO₂peak (ml/kg/min) = 13.43 + 0.02 x shuttle walk test distance (m) (R²=0.57)

VO₂peak (ml/kg/min) = 11.82 + 0.23 x Duke Activity Status Index (DASI) R²=0.44)

Functional dependence. Functional dependence is used as a decision point in the ACC/AHA cardiac evaluation model.¹⁷ However, risk stratification based on functional dependence as in the ACC/AHA model is fundamentally flawed¹⁸. Functional dependence is uncommon with only 7% of the NSQIP patients been either partially or totally dependent. Using reclassification statistics,^{19 20} reclassification based on a partially or totally dependent functional status significantly increases the proportion of patients with adverse cardiac events who are incorrectly classified as of a lower risk (NRI -15%, p<0.0001).¹⁰

Cardiopulmonary exercise testing

As field tests have various limitations as discussed above, there remains a need for an objective assessment of exercise capacity. Although there is little consensus on which preoperative investigation is preferable in cardiac risk assessment,^{21 22} CPET is theoretically attractive as it is a test of dynamic cardiovascular function²³ and myocardial ischaemia.^{5 24} Dynamic tests of cardiac function are preferable for cardiovascular risk prediction in the perioperative period.²⁵

Conducting a cardiopulmonary exercise test

To conduct a cardiopulmonary exercise test, the following equipment is required; a calibrated cycle ergometer, online 12 lead ECG with continuous ST segment analysis and a metabolic cart capable of breath-by-breath oxygen and carbon dioxide gas analysis measurement. Calibration of flow and volume sensors and gas analysers (using room air and a factory prepared gas which resembles expired air) is necessary prior to cardiopulmonary exercise testing. Full resuscitation equipment and emergency drugs need to be readily available.

Patient screening through history and examination is important prior to CPET, to ensure there are no contra-indications to CPET. Contra-indications which should be excluded are aortic stenosis, recent myocardial infarction (MI) within the preceding week, and leaking aortic aneurysm.

By convention, CPET is ideally conducted on a cycle ergometer for all patients. The patient was positioned on the bike or seated at a table with the cycle ergometer positioned on the table for arm cranking. A sealed face mask or mouthpiece is needed to ensure accurate respiratory gas analysis. Patients are requested to give a 'best effort' and instructed on the importance of maintaining 60 repetitions per minute during the test.

A common preoperative assessment protocol conducts a ramp test over 10 minutes. The rate of increment in work was predetermined by the formulae shown in Table 2.²⁶ The calculation used for

unloaded oxygen consumption (VO_2) is specific to cycling. As $10\text{ml}\cdot\text{min}^{-1}$ VO_2 is approximately equivalent to an increase in 1 watt of power,²⁷ the expected difference in VO_2 between unloaded and peak VO_2 can be converted into watt increments over the 10 minute period.

Table 2. Calculations for predicted oxygen consumption²⁶

Definition	Calculation
Unloaded VO_2	$\text{VO}_2 \text{ unloaded (ml}\cdot\text{min}^{-1}) = 150 + (6 \times \text{weight (kg)})$
Peak VO_2 female	$\text{Peak VO}_2 \text{ (ml}\cdot\text{min}^{-1}) \text{ Women} = \text{height (cm)} - \text{age (years)} \times 14$
Peak VO_2 male	$\text{Peak VO}_2 \text{ (ml}\cdot\text{min}^{-1}) \text{ Men} = \text{height (cm)} - \text{age (years)} \times 20$
Increment in work rate per minute	$(\text{Watts}\cdot\text{min}^{-1}) = (\text{Peak VO}_2 - \text{Unloaded VO}_2) / 100$

A CPET consists of four stages: rest, unloaded cycling, ramping and recovery. During a rest phase of three minutes, baseline cardiorespiratory data is collected; including resting ECG, ST segment analysis, blood pressure, peripheral oxygen saturation, and respiratory gas analysis. This is then followed by three minutes of unloaded cycling, which allows for oxygen-dependent enzyme induction (VO_2 -on-kinetics) prior to ramping.³ Ramping in wattage is then started according to the predetermined calculations, effected continuously or incrementally every minute until the predicted $\text{VO}_{2\text{peak}}$. Ideally, the patient should continue to exercise until the $\text{VO}_{2\text{peak}}$ is reached, as the $\text{VO}_{2\text{peak}}$ also has prognostic importance.

Monitoring during CPET includes a 12 lead ECG with ST analysis and breath to breath analysis of VO_2 , carbon dioxide production (VCO_2), minute ventilation and the respiratory exchange ratio (RER). The blood pressure should be measure intermittently and peripheral oxygen saturation throughout the test. The recovery period continues until all new ECG rhythm and ST segment changes have returned to pretest levels, and the heart rate was within 10 beats per minute of the pretest heart rate.²⁶

Early termination of a test is indicated if myocardial complications compromise patient safety. These include new S-T segment changes exceeding -2.0 mm (depression) or $+3.0$ mm (elevation) or new significant dysrhythmias.

Interpretation of cardiopulmonary exercise data

The anaerobic threshold (AT) was determined using the modified V-Slope method and was confirmed by changes in other variables such as the respiratory exchange ratio, ventilatory efficiency and end tidal values for oxygen (Table 3). The V-slope method is derived by the knowledge that the slope of a VCO_2 - VO_2 graph cannot exceed 1. However, with increased glycolytic and lactate production, the resultant bicarbonate buffering results in an increase in VCO_2 and the slope of the VCO_2 - VO_2 graph exceeds 1. The point at which this occurs is the AT.²⁷

Table 3. Determination of the Anaerobic Threshold^{26 27}

<i>Using a combination of the following:</i>
Rising ventilatory efficiency for oxygen, despite a plateau for carbon dioxide
Respiratory Exchange Ratio >1
An increase in end tidal oxygen, which precedes a fall in end tidal carbon dioxide
The VCO_2 crossing over the VO_2 when plotted on same axis
Increase in VCO_2 - VO_2 gradient above 1

Although, the AT is theoretically 'easy' to determine as per the table, in reality it is often difficult.² A proposal for an alternatives to the V-slope AT has been made.²

Prognostic capacity of cardiopulmonary exercise testing in noncardiac surgery

There are numerous reports of the association between CPET and short and intermediate term morbidity and mortality following various types of noncardiac surgery. It is suggested that patients with a low AT do not have the capacity to sustain the metabolic energy requirements following major noncardiac surgery. Furthermore, there is also evidence that patients with a low AT have an associated downregulation of monocyte CD+14 expression and lymphopaenia which are associated with morbidity following colorectal surgery.²⁸

A recent systematic review has found that the VO₂peak and AT was associated with 90 day to 3 year survival following hepatic transplant and resection, 90 day survival after AAA repair, morbidity after pancreatic surgery, and mortality and morbidity following intra-abdominal surgery.²⁹ The definitions of prognostic VO₂peak and AT thresholds differed between studies and between surgeries.²⁹ CPET appears to provide prognostically important data in the preoperative period.

What is also evident is that an AT cannot be determined in all patients during preoperative CPET. This is a prognostically poor sign.³⁰

Perioperative management based CPET results

By convention, most perioperative physicians would consider an AT < 10 to 11ml.kg⁻¹.min⁻¹ for a cycling CPET^{5 24 29} as clinically important positive test. Early myocardial ischaemia defined as ST segment depression > 1.0mm within two minutes of unloaded exercise,²⁴ should be considered as a positive result for myocardial ischaemia requiring further coronary investigation.

There is currently no suggested guideline on how to use CPET results to guide the management patients for subsequent major noncardiac surgery. The CPET results allow the physician to understand both cardiovascular function and potential coronary ischaemia. This author suggests the following possible perioperative algorithm (Table 4). Please note that these recommendations are not evidence-based.

Table 4. Perioperative management of high-risk patients according to CPET results

CPET result	Perioperative management for major noncardiac surgery
Early myocardial ischaemia	Preoperative coronary angiography
Adequate AT, without myocardial ischaemia	Perioperative statin therapy
Adequate AT with late inducible myocardial ischaemia	Perioperative statin therapy and beta-blockade
Poor AT without myocardial ischaemia	Perioperative goal directed therapy
Poor AT with late inducible myocardial ischaemia, or unable to reach AT	Consider; i) defer surgery and medically optimise the patient, followed by later re-stratification, or ii) offer lesser procedure with statin and beta-blocker, or iii) offer conservative non-surgical management

CPET cardiopulmonary exercise testing; AT anaerobic threshold

Life-expectancy with and without surgery

The work of John Carlisle has popularised the use of CPET to be used to plot survival curves for preoperative patients. His model follows the following staged approach to predicting survival;³¹ i) determine the background life expectancy using the UK Life Tables (based on the patient's age and sex), then ii) adjust it for co-existing comorbidities (myocardial infarction (MI), angina, stroke, transient ischaemic attack, heart failure, peripheral arterial disease, renal function), and iii) finally adjust the survival curve for physical fitness (using the CPET derived VO₂peak and the VeVO₂).

The impact of surgery on the final calculated survival curve is adjusted for multipliers of surgical mortality in the month following surgery, which can vary up to about 12 times the predicted non-surgical mortality in the following month.³² Open aortic surgery increases mortality by about 10 to 12 times in the postoperative month, and endovascular AAA repair and colorectal surgery in the region of 4 fold.³¹

The strengths associated with this model are the following. Firstly, cardiac risk factors appear to be consistent between populations,¹⁸ so if the model can be internally validated, then it is possible that it could be transferable to other populations. The model does indeed appear to have internal validation in the United Kingdom, with a fairly good fit with the UK Small Aneurysm Trial both for surgery and the surveillance arms of the trial.³² The external validity of the model is questionable, with a rather poorer fit when compared to patients from the US Aneurysm Detection and Management trial.³² It is certainly possible that this model may achieve external validity through; i) substitution of life tables specific to the country in which the model is to be used, and then ii) to adjust the relative importance of the included risk factors (hazard ratios) according to the population in whom the model is to be used. It would obviously have to be validated in the population it is to be adopted for local clinical use.

The utility of adopting John Carlisle's model, is that it would allow for shared decision making between patient and physicians when considering the impact of surgery on the patient's future survival. Importantly it allows one to estimate survival with and without surgery, and the time to survival advantage following a surgical intervention.³²

Ongoing cardiopulmonary exercise testing clinical trials

The biggest problem we currently have is understanding the relationship between CPET, B-type natriuretic peptides and major adverse cardiac events (MACE) and survival following noncardiac surgery. The data is extremely limited in this field.³³ B-type natriuretic peptides have substantial evidence of clinical utility for survival and MACE following noncardiac surgery,^{34 35} and so it is imperative that we understand the relationship between CPET and B-type natriuretic peptides in perioperative prognostication for major noncardiac surgery.

An important prospective observational study hopefully will adequately address this limitation, the Measurement of Exercise Tolerance before Surgery (METS) study.³⁶ This study has finished recruiting, and the one year follow up will be complete at the end of 2016, and so one would hope that the results will be published in 2017. The primary objective of this study is to compare preoperative CPET to subjective assessment for predicting death or non-fatal MI within 30 days after surgery. Secondary objectives include; i) to compare CPET to subjective assessment for predicting 1 year mortality, ii) to compare preoperative DASI, NT pro-BNP, CPET and subjective assessment for predicting death or non-fatal MI within 30 days, and iii) to compare preoperative DASI, NT pro-BNP, CPET and subjective assessment for predicting death 1 year mortality.³⁶ This study will provide

important data to understand the relationship between DASI, BNP and CPET and their associations with mortality and MACE. It is hoped that these data will allow us to i) develop a reasonable risk stratification algorithm for noncardiac surgery, which identifies appropriate indications for further preoperative CPET and/ or B-type risk stratification, and ii) universally agreed upon prognostic markers for perioperative CPET risk stratification.

Conclusion

Functional capacity is an important component of perioperative risk stratification. Field tests have limitations. CPET provides prognostically important data which is associated perioperative morbidity, however there are differing thresholds between different types of surgery. An integrated risk stratification algorithm, which includes CPET and B-type natriuretic peptides is needed. It is hoped the METS study will provide the data necessary to develop such an algorithm.

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Perioperative Pharmacological Protection

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Myocardial injury after non-cardiac surgery (MINS) is a significant problem. In 2008 it was estimated that 200 million adults worldwide undergo surgery every year. Of these, more than 10 million will suffer from a cardiovascular complication within 30 days. In the VISION trial, 8% of patients ≥ 45 years sustained myocardial injury after surgery. 10% of those patients will die within 30 days.

The current approach to preventing MINS involves identifying high risk patients preoperatively. These patients will either undergo further testing and possibly revascularisation or will be managed medically. This lecture will discuss the evidence for the efficacy and safety of drugs used preoperatively and intraoperatively.

Pathophysiology of MINS

The pathophysiology is still not completely understood, but both plaque rupture (type 1 myocardial ischaemia) and supply-demand imbalance (type 2 ischaemia) are likely contributors. Supply-demand imbalance is possibly the dominant feature in the majority of cases, but the evidence is unclear. Factors that precipitate plaque rupture are physiological and emotional stress, the procoagulant response to surgery and episodes of hypertension and tachycardia which increase the shear stress on atheromatous plaque. Factors leading to supply demand mismatch include hypotension, sympathetic stimulation, tachycardia, hypothermia, hypercoagulability, bleeding, prolonged hypoxia and poorly controlled pain. The pharmacological mechanisms of myocardial protection thus involve plaque stabilisation and optimisation of supply-demand factors to improve oxygen supply and reduce demand. Preconditioning and post-conditioning have the potential to decrease the severity of cell death after ischaemia and reperfusion.

Prevention of Plaque Rupture and Thrombosis

The development of acute myocardial infarction and acute coronary syndromes outside the perioperative setting involves 3 pathophysiological mechanisms. The most common (85%) is plaque rupture and subsequent luminal thrombosis. The precursor lesion is known as thin-cap fibroatheroma or vulnerable plaque. The vulnerable plaque is characterised by a soft, lipid-rich necrotic core with a thin overlying fibrous cap which is infiltrated by inflammatory cells. Haemorrhage into the core from the vasa vasorum may precipitate plaque enlargement and rupture. Plaque rupture commonly occurs in areas rich in macrophages. Matrix metalloproteinases (MMP's) are proteolytic enzymes produced by activated macrophages and can weaken the fibrous cap, particularly at the vulnerable shoulder region where the plaque joins the arterial wall.

The medications used to prevent plaque rupture and thrombosis in the short term are statins and aspirin.

The other 2 lesions that can lead to thrombosis are plaque erosion, which occurs on a plaque with a thick cap and a core consisting of smooth muscle and fibroblasts. The least common mechanism is thrombosis on a calcified nodule. Plaque stabilising therapies may not be effective in preventing coronary artery thrombosis from these lesions.

Statins

HMG-CoA reductase inhibitors are commonly referred to as statins. HMG-CoA catalyses the first step in the dedicated cholesterol synthesis pathway and is the rate limiting enzyme. Statins inhibit the formation of mevalonate and isoprenoids. They decrease total cholesterol, LDL cholesterol and triglycerides and increase HDL cholesterol. They also have non-cholesterol or pleiotropic effects. They enhance nitric oxide bioavailability and upregulate eNOS expression. They prevent the formation of superoxide anions by preventing isoprenylation of reduced NADPH oxidase. They have multiple effects improving endothelial function, decreasing oxidative stress and inflammation and inhibiting the

thrombogenic response. They also inhibit vascular smooth muscle proliferation, decrease platelet activation and stabilise vulnerable plaque, predominantly by decreasing macrophage infiltration and lowering MMP secretion in the fibrous cap. Inflammatory markers such as CRP, IL-6 have been shown to be lower postoperatively in patients on statins.

Much of the data regarding the perioperative use of statins comes from observational studies. In the VISION Trial, patients on statins had a lower risk of the primary outcome, a composite of all-cause mortality, MINS and stroke at 30 days after surgery. Subgroup analysis of patients who suffered MINS in the POISE-2 trial also showed a benefit of statin use in mortality reduction. The best evidence from an RCT was published by Durazzo in 2004. 100 patients undergoing vascular surgery were randomised to atorvastatin or placebo for 45 days, with a reduction in cardiac events at 6 months from 26% to 8%. The average time from initiation of therapy to surgery was 30 days. There is unlikely to be another RCT comparing statins to placebo as many high risk patients are on statins before the need for surgery arises, so it will probably be very difficult to randomise patients to placebo currently. There is evidence that statin treatment before coronary artery bypass surgery decreases the incidence of atrial fibrillation, length of ICU stay and hospital stay. There has been no evidence of decrease in risk of acute kidney injury after cardiac surgery and a very recent large randomised clinical trial found no evidence of benefit and an increase in the incidence of acute kidney injury in patients randomised to rosuvastatin versus placebo. Statins have also been associated with a decreased incidence of complications after EVAR and a decreased incidence of stroke after carotid stenting. The Cochrane review on statin use in vascular surgery found the evidence for benefit to be inconclusive, but trials involving only 178 patients were included in the review. There is no evidence of an increased risk of perioperative rhabdomyolysis or other muscle complications in patients taking statins.

The timing of initiation of statins preoperatively is not well defined. The pleiomorphic effects occur quite rapidly, with the lowering of LDL cholesterol taking place over a longer period. It is possible that introduction of statins in high risk patients shortly before surgery may be of benefit, but this has not been demonstrated in a clinical trial.

European guidelines state that patients on a statin should continue perioperatively (Class Ia). Perioperative initiation of statin therapy may be considered in patients undergoing vascular surgery, ideally at least 2 weeks before surgery (IIb). Long acting (e.g. atorvastatin) or extended release formulations (e.g. lovastatin) may be useful perioperatively as there are no parenteral preparations available. Use should be continued for at least 1 month after surgery. All patients with non-coronary atherosclerosis should be on statins for secondary prevention.

ACC/AHA guidelines recommend the same indications for statin use as the Europeans, but add that statin use may be considered in patients with medical indications who are undergoing elevated risk surgery (IIb).

Aspirin

Aspirin (ASA) inhibits platelet function by binding to a serine residue in the platelet COX receptor, preventing the formation of Thromboxane A₂ and subsequent platelet aggregation. Aspirin irreversibly inhibits this process for the lifetime of the platelet (about 7 days). Sufficient platelet function to support thrombosis should return 2-4 days after discontinuation.

It is used, controversially, for primary prevention of stroke, myocardial ischaemia, cancer and death. It is also used for secondary prevention of myocardial ischaemia, stroke and congestive cardiac failure as well as to prevent thrombosis in a cardiac or vascular stent or bypass graft. Aspirin use as secondary prevention in patients with non-ischaemic congestive heart failure is controversial. It has been shown to decrease hospitalisation rates in these patients, but there are no perioperative trials in this setting.

The role of aspirin in primary prevention is not well defined in the general population. Aspirin may be safely discontinued perioperatively in patients using it for primary prevention.

The role of aspirin in secondary prevention after myocardial infarction, coronary revascularisation or stroke is well established, with a significant decrease in mortality. Perioperative withdrawal of aspirin in these patients is estimated to increase the risk of major adverse cardiac events (MACE) by a factor of

3. Abrupt cessation of aspirin in conjunction with perioperative hypercoagulability may contribute to this increase in risk. In patients who continue aspirin perioperatively, the main problem is the risk of bleeding. A meta-analysis of 49 000 patients showed a 50% increase in bleeding events, which did not require extra medical intervention.

POISE-2 randomised 10 010 patients into ASA or placebo groups. Patients were stratified according to whether they were taking ASA (continuation) or not (initiation). There was no difference in myocardial infarction between the two groups (7,0% vs 7,1%), but the risk of major bleeding was increased (4,6% vs 3,8%). There was also an increased risk of kidney failure requiring dialysis in the continuation group. The conclusion reached by the investigators is that aspirin should not be initiated perioperatively, even in high risk groups. There are problems with the POISE-2 data, however. Only 36% of patients in the initiation group met the AHA criteria for aspirin use. In the continuation group it is unknown what the indications were for aspirin use. In the postoperative period about 65% of patients received another antithrombotic agent, which is a significant confounder for the primary outcome. 9,5% of patients in the ASA group received other NSAID's, which can interfere with the antithrombotic effects of aspirin. ASA was also stopped at least 3 (usually 7) days before surgery, which may have increased the risk of thrombotic complications.

Aspirin can safely be stopped 7 days preoperatively in patients using the drug for primary prevention. In patients at high risk for myocardial ischaemic or cerebrovascular events (without a coronary artery stent), the decision to continue ASA may be reasonable, particularly for surgery with low bleeding risk. Management should be discussed between all concerned, including the patient, anaesthetist, surgeon and cardiologist. This approach is supported by European and American guidelines. Aspirin should probably not be interrupted before coronary artery bypass surgery (ACC/AHA guidelines), but the American Thoracic Surgery Society suggest that stopping aspirin before purely elective cardiac surgery in patients without acute coronary syndromes may be reasonable.

Optimisation of myocardial oxygen supply and demand

The agents that have been used include beta adrenergic antagonists (beta blockers) and clonidine, an alpha-2 antagonist.

Beta Blockers

These agents are widely used in patients with hypertension and coronary artery disease. The exact mechanisms by which beta blockers decrease the incidence of perioperative cardiac complications is not entirely clear. A decrease in heart rate is probably the most important mechanism, improving myocardial perfusion. The reduction in myocardial contractility, reducing oxygen demand, is important as well. They also have plaque stabilising and anti-arrhythmic effects. Beta blockers decrease free radical production and matrix metalloproteinase activity. They have immunomodulatory properties by effects on cytokine production. These effects, which would contribute to plaque stabilisation, are only found with long term use. Cardiac apoptosis is mediated by β -1 receptors, so beta blockers may prevent apoptosis and protect against ischaemia-reperfusion injury.

The anaesthetic community has been studying the perioperative use of beta blockers since the mid 1980's. The first large trial using perioperative atenolol was done by Mangano and showed a reduction in mortality for up to two years postoperatively. This was followed by the DECREASE trials, which are all regarded as "insecure" due to scientific misconduct by the lead investigator, Dan Poldermans. The bulk of the patients given perioperative beta blockers came from the POISE trial, which has been criticised for starting high doses of long-acting beta blockers shortly before surgery. However, the beneficial and adverse effects of beta blockers have consistently been found with different drugs and dosing regimes.

The evidence regarding beta blockers can be summarised as follows: In cardiac surgery, the perioperative use of beta blockers has been shown to decrease the incidence of supraventricular and ventricular arrhythmias and decrease length of stay (by 0,5 days). There is no clear evidence of effect on the following outcomes: all-cause mortality, acute myocardial infarction, myocardial ischaemia, cerebrovascular events, hypotension, bradycardia and congestive heart failure.

In non-cardiac surgery, the Cochrane group looked at 36 trials and found the following: there is evidence of increase in the occurrence of the following: hypotension, bradycardia, all-cause mortality and cerebrovascular events. Beta blockers significantly reduced the incidence of acute myocardial infarction, myocardial ischaemia and supraventricular arrhythmias.

Most of the evidence comes from trials which randomised patients shortly before surgery. There are not good trials looking at starting beta blockers more than two days before surgery. The current ACC/AHA guidelines state the following:

- 1) Beta blockers should be continued in patients on chronic therapy (Grade I)
- 2) Guide management of beta blockers after surgery by clinical circumstances (IIa)
- 3) It may be appropriate to start beta blockers in patients with intermediate or high risk pre-operative tests (IIb)
- 4) In patients with ≥ 3 RCRI factors, it may be reasonable to start beta blockers (IIb)
- 5) It may be reasonable to begin perioperative beta blockers long enough in advance to assess safety and tolerability, preferably >1 day before surgery (IIb)
- 6) Beta-blocker therapy should not be started on the day of surgery (III:Harm)

The European guidelines are broadly in agreement, but recommend considering use in patients with ≥ 2 risk factors, ASA status >3 or known ischaemic heart disease. They also recommend the use of atenolol or bisoprolol as first line agents and warn against use without dose titration against a target heart rate. They warn against pre-operative initiation of beta blocker therapy in patients scheduled for low risk surgery.

Clonidine

Clonidine has been used to decrease the risk of MACE for some time, based on the results of small studies. It was an attractive alternative in patients with a contra-indication to beta blockers, especially in light of its other effects, including analgesia and decreased anaesthetic requirements. It is also available in a patch, making it suitable for patients unable to take medication orally.

The evidence for clonidine was equivocal before the POISE-2 trial. In POISE-2, patients in the clonidine group suffered a similar number of cardiac complications as patients in the placebo group. The incidence of clinically significant hypotension and non-fatal cardiac arrest was increased in the clonidine group. There is thus no role for clonidine in preventing adverse cardiac outcomes.

ACE inhibitors and ARB's

There is evidence that ACE inhibitors preserve organ function independent of their blood pressure lowering effects. Unfortunately, they do not have any benefit in terms of cardiovascular outcomes in the perioperative period. There is an increased incidence of hypotension in patients who continue to take the drugs through the perioperative period, but no evidence of harmful outcomes. Conversely, there is no evidence that withholding ACE inhibitors is harmful. ACC/AHA guidelines state that continuation of the drugs is reasonable through the perioperative period. If they are discontinued, they should be restarted as soon as possible. European guidelines suggest omitting the drugs on the day of surgery if used for hypotension, but continuing if used for poor left ventricular function.

Ischaemic preconditioning and post-conditioning

This is a huge and difficult topic deserving its own lecture.

Cell injury occurs during periods of ischaemia as well as during reperfusion. Multiple mechanisms have been proposed to be involved in cellular injury, including the complement system and leucocyte activation, increased free radical concentrations, reduction of oxidative phosphorylation, endothelial dysfunction and the activation of pathways of apoptosis, necrosis and autophagy. The extracellular inflammatory response is also involved in the ischaemia-reperfusion (IR) injury, particularly matrix metalloproteinases. Targeting extracellular proteases as well as intracellular pathways are strategies that have been studied to reduce IR injury.

The intracellular pathways comprise those leading to cell death and those involved in cardioprotection. These biochemical pathways are very complex and the mechanisms have been described in three phases: triggers, mediators and effectors.

The endogenous mediators of the trigger phase are adenosine, opioids, bradykinins and others. These molecules all activate different pathways e.g. JAK-STAT3, JNK MAPKS, ultimately converging on protein kinase C (PKC).

In the mediator phase, adenosine_{2B} receptors and RISK (Reperfusion injury survival kinase) pathways are important in protecting against IR injury. Caveolins are proteins that are thought to be involved in regulating protective signalling.

In the effector phase, mitochondrial potassium channel dependent on ATP (mtK_{ATP}) and PKC are involved. The pivotal event in the reperfusion injury is the opening of the mitochondrial permeability transition pore (mPTP), a large conductance pore in the inner mitochondrial membrane.

Anaesthetic agents involved in preconditioning and post-conditioning:

Volatile agents have been recognised as triggers of preconditioning for some time. The volatile agents signal through adenosine and opioid receptors, modulate G proteins, stimulate PKC and other intracellular kinases, open mtK_{ATP} channels leading to ROS generation and activate RISK to keep mPTP from forming.

Propofol works by a completely different mechanism to the volatile agents. It has free radical scavenging properties and inhibits L-type calcium channels, preventing calcium overload. It also interferes with the preconditioning effect of the volatile agents, as ROS are an important part of the volatile induced preconditioning pathway. There is a theoretical benefit of using propofol instead of a volatile in patients where ischaemic preconditioning already exists, as volatile anaesthetics may not add benefit in this situation.

Opioids have well established preconditioning and post-conditioning effects due to stimulation of opioid receptors. This is predominantly mediated via delta and kappa receptors. It can be initiated centrally as the effect has been shown with 0,1mg of intrathecal morphine. Remifentanyl, fentanyl and intrathecal morphine have been shown to reduce troponin release, length of ICU stay and length of hospital stay in cardiac surgery, but results are conflicting.

Anti-preconditioning agents include sulphonylureas and COX-2 inhibitors.

Despite the large amount of data on the topic, clinical trials have produced confusing and contradictory results. There are probably multiple reasons for this, including the fact that older patients and diabetic patients are relatively insensitive to the preconditioning effects of anaesthetic agents.

There are no firm clinical guidelines regarding the use of volatile based anaesthetics versus TIVA. The ACC/AHA guidelines state that volatile anaesthetics "seem to reduce troponin release, preserve myocardial function, and improve resource utilization (i.e. ICU or hospital lengths of stay) and 1-year outcome", but they do not specifically recommend any anaesthetic regime. The guidelines for non-cardiac surgery state that volatile based or TIVA techniques are acceptable.

In summary, there is no magic bullet for pharmacological myocardial protection in the perioperative setting. There are very limited opportunities for us to add oral agents to a treatment regime and we rely heavily on the primary care providers or surgeons to optimise medical therapy. Careful use of pharmacological agents forms a small but important part of a comprehensive perioperative management strategy in caring for the high risk patient.

Notes

Anaesthesia for Parkinson's disease

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Introduction

Parkinsonism classically refers to a clinical syndrome characterised by tremor at rest, bradykinesia, rigidity, postural instability, masked facies, and micrographia.

Parkinson's disease (PD) is the most common form of Parkinsonism and is a neurodegenerative disease typified by neuronal death, particularly dopaminergic neurones of the pars compacta of the substantia nigra.^{1, 2, 3}

The other forms of Parkinsonism are caused by other neurodegenerative disorders, cerebrovascular disease and drugs.¹ Other conditions implicated include repeated head trauma, tumour, metabolic abnormalities such as Wilson's disease, heavy metal and carbon monoxide poisoning. Drug-induced Parkinsonism results from dopamine receptor block as a result of drugs such as phenothiazines, butyrophenones and metoclopramide.³

Epidemiology

PD occurs worldwide and affects all ethnic groups. Caucasians are reported to have the highest incidence and Asians and African Blacks the lowest. It is primarily a disease of the elderly, increasing exponentially between the ages of 65 and 90, where the incidence is thought to be at least 3%. Some 5-10% of patients have symptoms before the age of 40 years, so-called young-onset PD.³

Aetiology

The aetiology remains uncertain. It is thought that neurodegeneration may be induced by genetic, environmental or infectious factors.³ More recently it is believed to result from a complex interaction between environmental factors and a genetic predisposition in individuals. Indeed the genetic predisposition is now seen as the major contributor to the underlying cause.⁵ The causes of neuronal loss in PD have remained a subject of intensive research. It is believed that mitochondrial dysfunction, oxidative injury, altered protein handling, and inflammatory changes in the brain of these patients lead to cellular dysfunction and death through apoptosis or autophagy.⁴

Although there is certainty over the role of age, not much has been done to understand exactly how age or the ageing process is involved.

A long list of environmental influences has been implicated: industrialisation, rural environment, well water, plant-derived toxins, bacterial and viral infection, organic solvents, carbon monoxide and carbon disulphide.

Pathogenesis

One of the mechanisms at play in the pathogenesis of PD is dysfunctional iron metabolism. Elevated iron levels were first found in neuromelanin-containing neurons of the substantia nigra pars compacta in PD patients suggesting that an iron-melanin interaction contributed to dopaminergic neurodegeneration in PD. The two questions that remain unanswered are why iron levels elevated in only select brain regions and whether this is an early event that causes neurodegeneration or whether it is a consequence of the disease process. It is becoming more evident that elevated iron levels are one of the initial events leading to dopaminergic neurodegeneration in PD. This iron accumulation may be due to a general malfunction in iron metabolism in the CNS which may involve both genetic and environmental factors.⁶

As mentioned earlier it is thought that loss of neurones is a result of mitochondrial dysfunction, oxidative injury, altered protein handling, and inflammatory changes in the brain. Much of this is due to

ageing but it is thought that metabolic diseases including type 2 diabetes mellitus, obesity and cardiovascular disease may accentuate this in causing PD.⁷

Pathophysiology

The basal ganglia refer to the areas of basal forebrain and midbrain known to be involved in the control of movement. They include the striatum, mainly comprising the caudate and putamen, the globus pallidus, the subthalamic nucleus, and the main pigmented component of the substantia nigra known as the pars compacta.³

The classical features of pathology of PD include progressive loss of dopaminergic neurons in substantia nigra pars compacta, significantly reduced levels of dopamine in the striatum and the presence of cytoplasmic proteinaceous inclusions known as Lewy bodies. Degeneration of dopamine containing neurons leads to an imbalance between the striato-pallidal and pallido-thalamic output pathways, which are responsible for the major motor symptoms of the disease⁴. In PD acetylcholine is present in normal amounts in the striatum. However, dopamine deficiency produces an imbalance in the dopamine:acetylcholine ratio, thereby aggravating the symptoms of PD.³

Diagnosis and clinical features

The diagnosis is made mainly on clinical grounds but may be difficult to make in the early stages where signs may be subtle and alternative diagnoses such as arthritis or depression may be entertained until the disease progresses.³

The signs and symptoms of PD can be divided into motor and non-motor categories.⁴

Motor: Bradykinesia, muscular rigidity, resting tremor, and impairment of postural balance leading to disturbances of gait and falling. Other motor features such as freezing of gait, dysphagia, speech disturbances and masked facies may follow.

Non-motor: May precede motor symptoms and may include autonomic disturbances including orthostatic hypotension and urinary dysfunction, sensory alterations, loss of smell, mood disorders especially depression, sleep disturbances, cognitive impairment and dementia.⁴

Treatment

Pharmacotherapy

Levodopa, a pro-drug which is converted into dopamine in the brain, is the mainstay of treatment. It is usually administered together with a peripheral dopa decarboxylase inhibitor (carbidopa - sinamet®, carbilev®) to minimise peripheral dopamine side-effects. It also increases cerebral availability of levodopa. Principal adverse effects of levodopa are nausea, motor complications including "wearing off" phenomenon, dyskinesias and on-off effects, confusion, hallucinations, orthostatic hypotension and sleep disturbances. Levodopa has a short half-life of about 60 minutes which is extended to 90 minutes when combined with carbidopa.⁴

Dopamine receptor agonists include ropinirole (requip®, requip XL®), pramipexole (pexola®, pramipex®), rotigotine, bromocriptine* (parlodel®) and cabergoline. They do not require enzymatic activation, have longer duration of actions and cause fewer side-effects, being more receptor selective.^{3, 4} *Bromocriptine belongs to an older class of dopamine agonists, the ergot alkaloid derivatives. They act non-selectively and stimulate a wide-variety of receptors in the brain.⁸

They are usually used first, particularly in younger patients, as they delay the need for levodopa and are associated with a lower incidence of motor fluctuations and dyskinesias. They may also be added to patients on levodopa who develop motor complications thus allowing a decrease in the levodopa dose.⁴

Occasionally anticholinergic agents may be used in an attempt to restore the balance between cholinergic and dopaminergic inputs in the basal ganglia.⁴ However they are increasingly obsolete owing to limited efficacy and multiple side effects.¹⁰

Catechol-O-methyl transferase (COMT) inhibitors, tolcapone and entacapone (comtan[®]), decreases the degradation of levodopa, increases its bioavailability and extends its half-life while not increasing time-to-peak dose or peak dose concentration. Entacapone is preferred as it has not been associated with hepatotoxicity.^{4, 8}

Monoamineoxidase inhibitors (MAO-I), selegiline and rasagiline (azilect[®]), decrease the breakdown of dopamine in the CNS, thereby benefitting PD patients.^{4, 8}

Apomorphine is a short-acting dopamine agonist with selective activity for D1 and D2 receptors. It is primarily used as a rescue therapy during off-periods of akinesia in patients with fluctuating response to dopaminergic therapy. It may be given subcutaneously by the patient via a "pen" (APO-go[®]). It does cause nausea and domperidone is often given before its administration.^{4, 8}

Amantadine (symmetrel[®]) is an anti-influenza agent which was serendipitously found to be useful in PD. It has modest efficacy and it improves PD symptoms in mildly affected patients with early disease and reduces motor fluctuations in patients with advanced disease. Amantadine modulates the release of dopamine from dopamine terminals in the striatum, possesses anticholinergic properties and blocks glutamate NMDA receptors.⁴

A number of newer agents are in various clinical trials under evaluation. None of them possess disease modifying effects and provide only symptomatic relief for the motor features of the disease. They include:

1. Adenosine A_{2A} receptor antagonists. These have been shown to enhance D2 dependent signalling.
2. Safinamide is an α -amino acid derivative that has dopaminergic and non-dopaminergic mechanisms of action in PD patients. It is a highly selective and reversible inhibitor of MAO-B as well as a blocker of sodium and N-type calcium channels. The former action reduces dopamine breakdown and the latter inhibits the release of glutamate.
3. Newer formulations of levodopa. These include IPX066 which has a combination of an immediate-release and a sustained-release levodopa component.⁴

Non-pharmacotherapy

For patients with PD, exercise therapy may be considered to improve function (Level C). However this improved function subsides rapidly when therapy is terminated. For patients with PD complicated by dysarthria, speech therapy may be considered to improve speech volume (Level C).⁹

Surgical treatment

Ablative procedures for PD such as thalamotomy and pallidotomy, although proven efficacious, have been superseded by deep brain stimulation (DBS). DBS targets the ventralis intermedius nucleus of the thalamus (VIM) and is a specific treatment option for selected patients. The 'ideal' candidate for this is the patient who is severely disabled in the off-drug condition and fully independent in the on-drug situation.

DBS reduces motor fluctuations and dyskinesia in idiopathic PD and lasts for 2-5 years.⁸

Anaesthetic considerations

Preoperative

- Nature and length of surgery intended. Elective or emergency.
- Often elderly. Consider all geriatric issues. Remember elderly patients may have undiagnosed PD.
- With reference to PD consider:

System	Assessment by history and examination	Tests
Head and neck	Pharyngeal muscle dysfunction Dysphagia Sialorrhoea Blepharospasm	
Respiratory	Resp. impairment from rigidity, bradykinesia, uncoordinated involuntary movement of respiratory muscles. Exclude retained secretions, atelectasis, aspiration and respiratory infection.	CXR PFTs ABG
Cardiovascular	Orthostatic hypotension Cardiac arrhythmias Hypertension Hypovolaemia Autonomic dysfunction	ECG
Gastrointestinal	Weight loss Poor nutrition Susceptibility to reflux	Albumin U and E
Urological	Difficulty in micturition	
Endocrine	Abnormal glucose metabolism (selegiline)	
Musculoskeletal	Muscle rigidity	Blood glucose conc.
CNS	Muscle rigidity Akinesia Tremor Confusion Depression Hallucinations Speech impairment	

Adapted from ³ Hall et al BJA 2006

- Continue with usual drug regimen as close to the beginning of anaesthesia as possible. MAO-Is should be discontinued 3 weeks before surgery if condition of patient permits.

Intraoperative

- Regional anaesthesia versus general anaesthesia.
 - o Advantages of RA v GA
 - Allows for communication by patient of subjective feelings accompanying PD attacks.
 - Residual GA or neuromuscular blocker may mask exacerbation of PD
 - Nausea and vomiting associated with GA may prevent effective oral administration of anti-PD medications
 - Attenuation of surgical stress response
 - Possible decrease in chest infections

- o Disadvantages of RA v GA
 - Tremor may disturb surgery
 - Tremor may interfere with anaesthetic monitoring ¹¹
- If GA consider endotracheal intubation for airway protection.
- Possible drug interactions in patients with PD

Drug	Comments
Induction agents • Propofol • Etomidate • Thiopentone • Ketamine	Avoid for stereotactic procedures Probably safe Probably safe Concern about exaggerated sympathetic response. Probably clinically unfounded
Opiates • Fentanyl • Pethidine • Morphine • Alfentanil	Possible muscle rigidity Avoid with MAO-Is Possible muscle rigidity Possible dystonic reactions
Volatile agents • Isoflurane • Sevoflurane • Desflurane • Enflurane • Halothane	Probably safe Probably safe Probably safe Probably safe Possible arrhythmias
Neuromuscular blocking agents • Succinylcholine • Non-depolarising agents	Concern about hyperkalaemia. Literature equivocal. Probably safe

Adapted from ³ Hall et al BJA 2006

- Avoid phenothiazines, butyrophenones and metoclopramide
- Avoid drugs with serotonergic effects. May precipitate serotonergic syndrome.
- Length of surgery
 - o < 3-4 hours. Initiate anti-PD therapy asap after surgery
 - o > 3-4 hours. Consider NG tube and intraoperative levodopa
 - o Dysfunctional bowel. Ideally rotigotine transdermal patches. Consider s/c apomorphine. May need to consult neurologist

Postoperative

- Ward / HCU / ICU dependent on severity of PD / co-morbidities / type of surgery
- Initiate normal anti-PD therapy asap
- Limit opiates as much as possible to avoid ileus
- Physiotherapy and speech therapy as indicated
- VTE prophylaxis

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Obstetric Anaesthesia Update

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Recent developments in the practice of obstetric anaesthesia include a better understanding of the physiology of pregnancy, regional anaesthesia in labour, regional anaesthesia for caesarean section (CS), categorization of the urgency of CS, and clearer definition of fetal indications for CS. The physiological basis for management of spinal hypotension is now well understood. Regional anaesthesia for patients with preeclampsia is well established, and differences in cardiac function in preeclampsia and peripartum cardiomyopathy recognised. In the interests of improved safety in general anaesthesia for CS, the Obstetric Anaesthetists' Association of the UK has introduced improvements and advances in the difficult airway algorithm. A recent UK audit shows that maternal awareness during general anaesthesia for CS remains problematic. Haemorrhage remains a major cause of maternal death, and a structured team approach is necessary to improve outcomes. A multimodal approach is most effective for post-caesarean analgesia. Anaesthesia-related maternal morbidity and mortality in middle and low income countries, including South Africa, remain unacceptably high.

1. New concepts in maternal physiology

Cardiac angiogenesis in pregnancy leads to physiological eccentric cardiac hypertrophy. Neovascularization occurs from pre-existing blood vessels, in response to hypoxia or substrate demands of tissues. The endometrium, decidua and placenta are rich sources of angiogenic growth factors (VEGF, PlGF). Animal studies suggest that anti-angiogenic intermediates may contribute to cardiac dysfunction in peripartum cardiomyopathy (abnormalities in prolactin metabolism, and possibly of transcription), and preeclampsia (soluble tyrosine kinase, sFLT-1). Both conditions may be associated with severe cardiac failure, but typically PPCM is associated with severe systolic-, and preeclampsia with diastolic dysfunction.

2. Regional analgesia for labour

To fully appreciate the relative importance of recent developments in regional anaesthesia in labour, one needs to review the monumental original work of individuals such as Cleland. In the 1930's he showed in anaesthetised dogs that afferent fibres that give rise to the experience of the pain in the first stage of labour enter the spinal cord at T11-T12. This is the basis for the current practice of labour epidural analgesia, pioneered by the Canadian Philip Bromage and others.

As an anaesthetist, it is important to understand the effects of epidural analgesia (EA) on the progress and outcome of labour.¹ A fundamental change in practice during the past 20 years is the recognition that motor block should be avoided during labour, by the use of low concentrations of local anaesthetic. It is now well established that, practiced this way, EA does not prolong the first stage of labour, and that this is independent of cervical dilatation when the block is initiated. The second stage is prolonged by approximately 15 minutes, and there may be an increased incidence of assisted delivery. There is no increase in the caesarean section (CS) rate. The risk of epidural haematoma, sepsis or neurological injury is very low, and EA does not predispose the patient to chronic backache. Fetal blood gases are, if anything, better after EA. There is a gradual increase in maternal temperature. These points should all be made to the mother as part of the consent process.²

Local anaesthetic potency has been well studied. The concept of MLAC, or the minimum local anaesthetic concentration in a 20 mL syringe that produces effective analgesia in labour, allows a comparison of the potency of various local anaesthetics. This has to some extent changed the original theory that ropivacaine is associated with less motor block than bupivacaine, since when equipotent

doses are used, the benefits of ropivacaine are considerably diminished. MLAC does however have limitations; one cannot extrapolate from one population to another, and it only measures one point on the dose-response curve, namely the EC50.

Many sophistications of administration of epidural analgesia have been developed, most of which have limited application in low resource environments. Combined spinal-epidural analgesia (CSE) offers versatility, and allows for walking in labour, as well as rapid initiation of analgesia in patients presenting with severe pain late in labour. A Cochrane review concluded that onset of analgesia is faster, less local anaesthetic is required, but there is more pruritus, and may be more fetal bradycardia using CSE. There is no effect on the progress and outcome of labour. Overall, it was concluded that "there is little basis for offering CSE over conventional epidurals in labour". Patient controlled epidural analgesia has considerable advantages where resources allow for its practice. Intermittent epidural bolus administration is more effective than continuous infusion, requiring less local anaesthetic, and resulting in better epidural spread. Continuous spinal analgesia has only limited applications, since there are technical challenges, and significant risks of post-dural puncture headache and infection. A recent review describes optimal management of regional analgesia in the setting of anticoagulation and anti-platelet drugs.³

New epidural adjuvants such as neostigmine and clonidine have generally been disappointing, displaying a narrow therapeutic range. Non-epidural options for labour analgesia include intravenous remifentanyl. However many experts have cautioned that a high degree of vigilance is required, and severe maternal respiratory depression has been described.

3. Regional anaesthesia for caesarean section

There are now 4 categories of urgency of CS, ranging from "immediate threat to the life of the woman or the fetus", to "at a time to suit the woman and maternity team". The RCOG has also clear guidelines on CTG abnormalities indicating CS. Specific features contribute to a "normal", "suspicious", or "pathological" CTG.

The mechanisms of spinal hypotension are now well described; these are summarised in a review which adopts a physiological approach.⁴ The typical response is a decrease in systemic vascular resistance due to arteriolar dilatation, although there is recent evidence that venodilatation plays a limited role. The net effect is that heart rate and stroke volume are maintained or increase, so that cardiac output, and by implication also venous return, increase. More rarely, reflex bradycardias may occur. Persistent hypotension despite fluid and vasopressor therapy, should alert one to mis-assessment of fluid balance status, or occasionally undiagnosed cardiac disease, for example cardiomyopathy and valvular heart disease. Rarely, high motor block may require cardiac and ventilatory support. A recently published guideline outlines an approach to this problem.

"Low dose" single shot spinal anaesthesia (SA) for CS is no longer recommended. The use of < 8 mg bupivacaine with opiate is associated with an unacceptably high requirement for supplementation of anaesthesia. Considerable literature now also suggests that the dose should not be reduced in obese parturients.

Early administration of vasopressor is now favoured over reliance on a large volume of IV fluid. A vast amount of literature on fluid delivery may be summarised as follows: crystalloid coload is preferable to crystalloid preload; colloid coload is no better than crystalloid coload; colloid preload is more effective than crystalloid preload or colloid coload.

Phenylephrine is established as the vasopressor of choice for managing typical spinal hypotension⁵. The only debate relates to the optimal method of administration. Phenylephrine makes the best sense from the maternal physiological point of view. Ephedrine crosses the placenta readily, and increases

fetal metabolic rate. Large doses of ephedrine may worsen fetal acidosis in a compromised baby, and contribute to an unfavourable oxygen supply/demand ratio.

4. Preeclampsia

Preeclampsia remains one of the major challenges for anaesthetists worldwide⁶. The main theory of the development of the disease is abnormal placentation, in particular failure of normal invasion of the spiral arteries by the cytotrophoblast, which leads to a failure of vascular remodelling. Anti-angiogenic intermediates and markers of oxidative stress may contribute to endothelial dysfunction and the systemic inflammatory response, resulting in the clinical signs of preeclampsia. Whether a unified hypothesis for the aetiology of preeclampsia is possible remains controversial, as outlined in an insightful recent editorial.

The last ACOG recommendations for the use of the pulmonary artery catheter (PAC) in preeclampsia were in 2002. PAC monitoring is now rarely employed and only has a limited role if there is multiple organ failure, in combination with echocardiography. Currently, haemodynamic monitoring starts with noninvasive blood pressure measurement, with a low threshold for arterial line placement in complicated cases with poorly controlled blood pressure, pulmonary oedema, or eclampsia. Passive leg raising in combination with transthoracic echocardiography when available, has been employed in the assessment of fluid balance. Minimally invasive cardiac output monitoring has been employed mainly as a research tool.

Pioneering work by AT Dennis using transthoracic echocardiography (TTE), has provided detailed evidence of cardiac dysfunction in preeclampsia. There is usually increased left ventricular mass and normal to increased inotropy - the "invasoconstrictor state". Diastolic dysfunction is common, but there may rarely be severe systolic heart failure. There may be a degree of overlap between heart failure in preeclampsia and in peripartum cardiomyopathy, but the latter is characterised by severe systolic dysfunction. The haemodynamics of both conditions have been well summarised in recent reviews.⁶

SA has become accepted as the method of choice for caesarean section if there is no epidural catheter in place. In most cases there is only modest afterload reduction. Caution is required in cases with pulmonary oedema, and ideally TTE should be performed to assess left ventricular function. In cases with severe heart failure, carefully titrated general anaesthesia is preferable.

The obtundation of the haemodynamic response to tracheal intubation in severe preeclampsia remains a challenge. A recent review summarises the limited literature on magnesium sulphate, opioids, beta blockers, hydralazine and nitrates when used for this purpose. All have their advantages and disadvantages, and correspondence in response to the review makes a strong argument for the continued use of bolus IV magnesium sulphate after the induction agent in this situation.⁷

Anaesthetists should be aware that preeclampsia is associated with an increased risk of adverse long term cardiovascular outcomes, such as chronic hypertension, stroke, ischaemic heart disease, and chronic renal failure.

5. General anaesthesia

The recent NAP5 audit in the UK showed that the incidence of awareness during CS is still high, at 1:670 compared with 1:19600 for all operations. The Obstetric Anaesthetists' Association and Difficult Airway Society have developed the first UK national obstetric guidelines for the management of difficult intubation during general anaesthesia.⁸ Planning and multidisciplinary communication are emphasised, as well as the use of nasal oxygenation and mask ventilation immediately after induction, limiting intubation attempts to two, and early release of cricoid pressure if difficulties are encountered. Early insertion of a supraglottic airway is recommended, and a detailed approach to "can't intubate, can't ventilate" is outlined.

6. Obstetric Haemorrhage

Haemorrhage remains a major cause of maternal death worldwide. Important aspects in prevention and treatment are as follows:⁹

1. Timely referral to a centre with obstetrics and anaesthesia expertise.
2. Accurate estimation of blood loss.
3. Early establishment of peripheral lines and arterial line.
4. Rapid and effective administration of oxytocic drugs.
5. Access to blood products.
6. The ratio is controversial: 6 Packed cells: 4 FFP: 6 Platelets is reasonable.
7. Recognition of the importance of fibrinogen levels; early administration of tranexamic acid, cryoprecipitate, or fibrinogen concentrate if available. Evidence from randomised trials in this regard is awaited. Recombinant factor VIIa is of limited value.
8. Rapid referral to the operating theatre.
9. Availability of senior obstetrician in theatre, particularly for placenta praevia, or any major haemorrhage.
10. Close observation of the surgery by the anaesthetist.
11. Point of care monitoring of coagulation status by viscoelastic devices may be useful if available.
12. Low threshold for postoperative ventilation; accompany the patient during transport.

7. Post caesarean analgesia

Postoperative analgesia depends upon the anaesthesia technique employed for CS. Multimodal analgesia is employed in many units worldwide post SA. Respiratory depression is uncommon using small doses of spinal morphine.¹⁰ Combinations of paracetamol, NSAID and 75 -100 µg intrathecal morphine are highly effective, with minimal side effects, and provide superior analgesia to TAP blocks.

8. Maternal mortality

A recent systematic review in the Lancet¹¹ including over 600,000 deliveries, showed a risk of death in women undergoing obstetric procedures, of 1.2 per 1000 women. Anaesthesia accounted for 2.8% of deaths, and 13.8% of deaths after CS. Exposure to general anaesthesia increased the odds of maternal death (odds ratio 3.3), compared with regional anaesthesia. The CEMD in South Africa for the past 2 triennia has however revealed a high number of avoidable fatalities associated with SA.

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Anaesthesia for the Obstetric Patient with Cardiac Disease

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These notes serve to give an approach to anaesthesia for the pregnant patient with cardiac disease. I have tried to achieve reasonable coverage of the commoner and/or riskier cardiac pathologies that an obstetric anaesthetist may encounter, and have highlighted the impact of physiological alterations in pregnancy, as well as the haemodynamic goals for managing each lesion. I have not covered the following: management of arrhythmias in pregnancy, cardiopulmonary bypass in pregnancy, the parturient with a transplanted heart, and the rarer congenital heart lesions.

1. Cardiac disease as a cause of maternal death

In South Africa's 2011-2013 Saving Mothers Report, there were 169 notified deaths due to cardiac disease. These comprised 34% of all deaths due to "underlying medical & surgical disease", and were by far the largest contributor to that category. There has been a steady increase in the institutional maternal mortality rate (iMMR) for cardiac disease in SA over the past 3 triennia. The iMMR rose to 5.78 per 100,000 live births in 2011-2013. Cardiac disease is, after non-pregnancy related infections (largely HIV/AIDS), the second most common indirect (non-obstetric) cause of maternal death. The bulk of these deaths in SA are due to **peripartum cardiomyopathy**, complications of **rheumatic heart disease** and **dilated cardiomyopathy**.

In the developed world, where cardiac disease is now the leading cause of maternal mortality, most deaths are due to acquired disease: **aortic dissection**, **cardiomyopathy** and **myocardial infarction**. These conditions still predominate over the growing number of maternal deaths due to congenital heart disease.

2. Normal cardiovascular adaptation to pregnancy, labour & delivery

Pregnancy is sometimes called "nature's stress test", because previously asymptomatic cardiac disease may be unmasked as the pregnant woman fails to adapt to normal physiological changes.

By understanding these physiological changes, the anaesthetist can predict whether a patient with a known cardiac condition will likely decompensate in pregnancy, and can plan the most appropriate anaesthetic monitoring and techniques.

Pregnancy: In summary, the main changes during pregnancy are an increased cardiac output, blood volume and red cell mass, together with a decrease in peripheral and systemic vascular resistance.

At around 32/40, the total blood volume plateaus at almost double its pre-pregnancy value. In addition to plasma volume expansion, there is an increase in red blood cell production of up to 40% via erythropoiesis. Plasma volume increases proportionally more than the red blood cell mass, resulting in a "physiological anaemia" from haemodilution, with haemoglobin levels as low as 11 g/dL considered physiological.

The sharpest rise in cardiac output occurs by the beginning of the first trimester, and there is a continued increase into the second trimester. After the second trimester, there is debate as to whether cardiac output increases, decreases, or plateaus. By 24 weeks, the increase in cardiac output can be up to 45% in a normal, singleton pregnancy; this is due to a bigger stroke volume in the 1st trimester, and additionally due to increased heart rate later on.

Development of the high-flow low-resistance materno-placental circulation contributes to a reduction in blood pressure and widening of the pulse pressure. Systolic, diastolic, and mean arterial pressures decline during pregnancy; DBP & MAP do so more than SBP. Arterial pressures decrease to a nadir during the second trimester (dropping 5–10 mm Hg below baseline), but most of the decrease is seen to occur in early pregnancy (6-8/40), when compared with preconception values. Arterial pressures begin to increase during the third trimester and return close to preconception levels postpartum.

Heart rate increases during normal gestation. Unlike many of the prior parameters that reach their maximum change during the second trimester, heart rate increases progressively throughout the pregnancy by 10 to 20 bpm, reaching a maximum heart rate in the third trimester. The overall change

in heart rate represents a 20% to 25% increase over baseline.

Diastolic function is unchanged in normal pregnancy, whilst systolic function increases in the second trimester. The LVEF increases. Temporary cardiac remodelling occurs with an increase in left ventricular wall thickness and left ventricular wall mass of 28% and 52% above pre-pregnancy values, respectively, throughout pregnancy. LV hypertrophy is eccentric.

Typical transthoracic echocardiographic findings in a normal pregnancy include mild 4-chamber dilatation (changes in the right atrium and ventricle are typically greater than in the left atrium and ventricle) with transient, trivial mitral regurgitation and physiological tricuspid and pulmonary regurgitation. Aortic regurgitation is not seen in a normal pregnancy.

Aortocaval compression in the supine position occurs from as early as 13 to 16 weeks' gestation. At term, there is nearly complete obstruction of the IVC. Venous return from the lower extremities occurs through the intraosseous vertebral veins, paravertebral veins, and the epidural veins, but is less than usual IVC return, resulting in a decrease in right atrial pressure. Up to 15% of women at term experience bradycardia and a substantial drop in blood pressure when supine, the so-called *supine hypotension syndrome*.

Labour: The maximum cardiac output associated with pregnancy occurs during labour and immediately after delivery, with increases of 60% to 80% above levels seen before the onset of labour. During labour (but between uterine contractions), CO increases from pre-labour measurements by approximately 10% in the early first stage, by 25% in the late first stage, and by 40% in the second stage. This is related to many factors, including increasing heart rate and preload associated with the pain of uterine contractions, increases in circulating catecholamines, and the autotransfusion of 300 to 500 mL blood from the uterus into the systemic circulation immediately after each contraction. Other factors, including positional changes (supine versus left lateral recumbent position) and blood loss, influence haemodynamic changes in individual patients. During uterine contractions, 300 to 500 mL of blood is displaced from the intervillous space into the central circulation (i.e., autotransfusion) via the relatively unimpeded ovarian venous outflow system.

Postpartum: In the immediate postpartum period, cardiac output may be as much as 75% above pre-delivery measurements. This surge results from relief of vena caval compression, diminished lower extremity venous pressure, a reduction of maternal vascular capacitance & alterations in sympathetic activity. After vaginal delivery, increases in CO and SV persist for at least one hour, while HR decreases and blood pressure remains unchanged. These factors, in combination, typically result in unchanged mean arterial pressure in the early postpartum period. However, patients with heart failure are at increased risk of developing pulmonary oedema.

After caesarean delivery, mean arterial pressure remains stable, but CO increases by approximately 30 to 50 percent, compared to pre-delivery values. This is an acute change that occurs within 2 minutes of delivery of the fetus and persists for about 10 minutes.

In patients with cardiovascular disease, other factors that affect haemodynamic status during and immediately after delivery include the underlying cardiac pathology, gestational age, anaesthetic agents, intravascular fluid status, positioning of the patient, and the route, dose, and choice of uterotonic agents.

Cardiac output falls to just below pre-labour measurements at 24 hours postpartum. It returns to pre-pregnancy levels between 12 and 24 weeks postpartum. Heart rate falls rapidly after delivery, reaches the pre-pregnancy rate by 2 weeks postpartum, and is slightly below the pre-pregnancy rate for the next several months. Other anatomic and functional changes of the heart are also fully reversible.

3. Symptoms and signs of normal pregnancy and heart disease

Many normal women show subtle signs suggestive of cardiac failure during uncomplicated pregnancy and delivery. Shortness of breath, fatigue & a reduction in exercise capacity are common. Many pregnant patients have peripheral oedema, distended central veins, audible flow murmurs or a third heart sound indicative of volume overload.

The anaesthetist must know when to suspect cardiac disease in pregnancy and labour if appropriate management decisions are to be made. The following signs are always abnormal in pregnancy and indicate potential underlying cardiac disease:

- A loud fourth heart sound
- Any diastolic murmur

- A grade 3/6 or more systolic murmur
- Fixed splitting of the second heart sound
- An opening snap

The presence of one or more of these signs indicates the need for echocardiographic evaluation.

4. The antenatal anaesthetic consult

Ideally every woman with known cardiac disease should be assessed by a multidisciplinary team (obstetrician, cardiologist and anaesthetist) prior to conception, early in pregnancy, & regularly thereafter, so that an individualised management plan can be developed, based on her specific cardiac anatomy and pathophysiology and likely risk.

This should include plans for:

- management of the cardiac condition through pregnancy
- management of possible cardiopulmonary decompensation during labour & delivery
- the timing, location and mode of delivery
- monitoring, IV access and anaesthetic techniques applicable to the delivery plan
- contingency plans for obstetric complications, e.g. need for emergency CS, or PPH
- resuscitation in case of cardiopulmonary arrest, in terminal cases- “living will” issues

Specifically, the anaesthetist should review:

- all cardiology consultation notes
- all cardiac surgical notes detailing palliative or reparative procedures
- relevant recent cardiac testing, including echocardiograms, ECG, catheterisation reports
- details of any pacemaker, biventricular pacemaker, and/or implantable cardioverter defibrillator (ICD) that has been inserted

These will elucidate whether the patient has intracardiac shunting, cyanosis, left and/or right ventricular dysfunction, pulmonary hypertension, a history of previous heart failure, left ventricular obstruction, previous dysrhythmias, pacemaker or AICD, significant endocarditis risk, anticoagulation considerations.

Risk stratification is important, and here the AHA, ACC and ESC provide guidance on *lesions known to carry high maternal or fetal risk* (mortality 5-50%):

Congenital heart disease:

- Prior Fontan procedure
- Severe pulmonary arterial hypertension
- Cyanotic congenital heart disease
- Complex congenital heart disease with residua such as heart failure, valve disease, or the need for anticoagulation
- Congenital heart disease with malignant arrhythmias

Valvular heart disease

- Severe aortic stenosis (valve area $<1.0 \text{ cm}^2$, mean transvalvular gradient $>40 \text{ mmHg}$, or peak aortic valve velocity $>4 \text{ m/sec}$), with or without symptoms.
- Mitral stenosis with NYHA class II to IV symptoms
- Aortic or mitral regurgitation with NYHA class III to IV symptoms
- Aortic and/or mitral valve disease with severe left ventricular dysfunction (defined as a left ventricular ejection fraction less than 40 percent) or severe pulmonary hypertension (defined as pulmonary artery pressure >75 percent of systemic pressure)
- Marfan syndrome
- Mechanical prosthetic valve

Risk factors for maternal cardiac events are:

1. New York Heart Association functional class III or IV or the presence of cyanosis. In general, maternal outcomes correlate with the NYHA functional class. Patients with NYHA class I or II disease have a maternal mortality rate less than 1%, whereas those with class III or IV disease have a mortality rate between 5% and 15%.
2. Prior cardiac events (CCF, TIA or stroke)
3. Left heart obstruction (aortic valve area of less than 1.5 cm^2 or mitral valve area of less than 2

- cm². Left ventricular outflow tract pressure gradient of more than 30mmHg)
4. Systemic ventricular dysfunction (LVEF <40%, or a restrictive or hypertrophic cardiomyopathy)
 5. Previous dysrhythmias requiring treatment

Patients identified as “high-risk” should be delivered where there are maximal resources available.

5. Obstetric considerations

High risk patients will often undergo scheduled induction of labour, to ensure appropriate medical professionals are definitely available, to optimally manage anticoagulation, or because of deteriorating maternal cardiac function. Placement of IV access, patient monitors, and preparations for analgesia & anaesthesia (including epidural catheter insertion) should occur before painful contractions begin. These patients usually labour in semi-Fowler’s position with a left lateral tilt. There should be regular monitoring for any signs or symptoms of cardiac decompensation.

Generally, the plan is for these patients to deliver vaginally, unless there is an obstetric indication for CS. Most high-risk parturients require neuraxial anaesthesia to minimise the haemodynamic instability related to pain & stress in labour, so a contraindication to neuraxial techniques may render vaginal delivery inadvisable. Maternal cardiac indications for caesarean delivery are very few, but may include: aortopathy (where there is a risk of aortic dissection in labour), severe pulmonary hypertension and Eisenmenger’s syndrome (where there is the risk of RV failure with cardiogenic shock). Caesarean delivery may be offered where there has been fetal exposure to warfarin within two weeks of delivery, as vaginal birth carries greater risk of fetal intracranial haemorrhage.

A vaginal “cardiac delivery” usually necessitates epidural analgesia, so that the mother does not feel the urge to bear down whilst the fetal head descends during second stage. Once the fetus has descended fully, an operative vaginal delivery is performed (outlet forceps or vacuum extraction). This aims to reduce or avoid the cardiac risks of the mother performing the Valsalva manoeuvre whilst pushing, i.e. increased intrathoracic pressure causing reduced venous return, reduced preload and reduced cardiac output. A “trial of pushing”, where the pulse oximetry waveform is examined during maternal expulsive efforts, is sometimes useful to assess the parturient’s haemodynamic tolerance of pushing, especially in those with intracardiac shunts where raised intrathoracic pressure may increase the chance of right-to-left shunting.

Current American Heart Association (AHA) recommendations, published in 2008 & endorsed by the American College of Obstetricians and Gynecologists (ACOG), do not recommend infective endocarditis prophylaxis for vaginal or caesarean delivery in the absence of infection. In patients with the highest risk lesions with established infection that could cause bacteraemia (such as chorioamnionitis or pyelonephritis), the underlying infection should be treated in the usual fashion. The ACC/AHA adult congenital heart disease guidelines of 2008 comment that it is reasonable to consider antibiotic prophylaxis against infective endocarditis before vaginal delivery at the time of membrane rupture in select patients with the highest risk of adverse outcomes. This includes patients with prosthetic cardiac valves or prosthetic material used for cardiac valve repair and patients with unrepaired or palliated cyanotic heart disease, including surgically constructed palliative shunts and conduits. There is no strong evidence for this suggestion.

6. Pharmacological considerations

There are implications for women with high-risk cardiovascular disease related to various drugs commonly used during the peripartum period.

Oxytocin: decreases mean arterial pressure and systemic vascular resistance, often with compensatory tachycardia; may slightly increase pulmonary artery pressure. In patients with significant cardiac disease (esp. pulmonary hypertension or tight AS), it has been recommended that ultra-low doses of oxytocin (0.05-0.5 IU) be administered extremely slowly, or that it be omitted.

Misoprostol: does not affect maternal cardiac function, even at high doses

Prostin F2α® (dinoprost tromethamine): Side effects include bronchospasm and alterations in the ventilation/perfusion ratio, resulting in increased intrapulmonary shunt fraction and hypoxaemia. It can induce hypertension at high doses. Avoid in patients with an intracardiac shunt. Avoid in patients with single ventricle physiology as it may significantly decrease cardiac output.

Ergometrine: contraindicated in patients with cardiovascular disease, especially those with systemic, pulmonary, or pregnancy-induced hypertension, because of the following side effects:

- Vasoconstriction (potentially causing sudden systemic hypertension and resultant stroke, seizure, or myocardial ischemia in patients with hypertension, especially preeclampsia)
- Coronary vasospasm (can induce MI in patients with IHD)
- Increased pulmonary artery pressure (potentially causing shunt reversal and cyanosis in patients with intracardiac shunts)

Magnesium sulphate: Cardiac dysfunction is associated with very high magnesium levels and appears to be secondary to respiratory arrest and hypoxia.

β agonists (for tocolysis): 1-10% of patients will experience tachycardia, hypertension, and palpitations. In <1 percent, side effects include arrhythmia, cardiac arrest, chest pain, hypotension, myocardial infarction, myocardial ischemia, pulmonary oedema, and paradoxical bronchospasm. β agonists should be used cautiously in women with cardiac lesions sensitive to these effects and generally should be avoided in women with heart failure. Patients with hypertrophic obstructive cardiomyopathy (HOCM) are especially at risk for left ventricular outflow obstruction and decompensation with β agonist administration.

Antihypertensive drugs: Labetalol, dihydralazine and nifedipine are the commonest antihypertensives used in the labour ward. The safety of these drugs depends on the patient's underlying cardiovascular physiology, e.g. patients with MS may tolerate the reflex tachycardia that occurs with dihydralazine administration poorly. Nifedipine should be avoided in women with aortic stenosis or HOCM because decreasing SVR decreases coronary perfusion in aortic stenosis and can worsen outflow obstruction in HOCM. Beta blockade, however, is helpful in HOCM because it helps prevent infundibular spasm. In general, antihypertensive agents should be used cautiously (low dose and gradual titration) in women with cardiac lesions sensitive to hypotension.

7. Anaesthetic management: General principles

7.1. Monitoring during labour, delivery and caesarean section

In addition to standard labour monitors, i.e. NIBP and CTG, additional continuous maternal monitoring is advisable in high-risk cardiac patients to detect development of complications such as myocardial ischemia, arterial desaturation, or pulmonary oedema. Included are:

- Electrocardiogram (ECG), ideally a 5-lead ECG with computerized ST-segment trending and multiple-lead monitoring
- Pulse oximetry, with both audible and visible waveform display. This is particularly important for patients with cyanotic congenital heart disease or right-to-left shunting.
- Intra-arterial catheter, to detect hypotension, & to allow beat-by-beat analysis of the effects of uterine contractions and maternal expulsive efforts on overall haemodynamics. In high-risk or unstable patients undergoing caesarean delivery, the intra-arterial catheter should be inserted prior to induction of either regional or general anaesthesia. This also facilitates management of vasoactive drug administration and measurement of arterial blood gases.
- Central venous catheter, for vasoactive drug administration in unstable patients (e.g. hypotension, pulmonary oedema, or peripartum haemorrhage) with high-risk cardiovascular disease
- Pulmonary artery catheter (PAC) - rarely indicated in parturients with high-risk cardiac disease. The risk of complications (eg, arrhythmias, incorrect interpretation of data, pulmonary artery rupture) during catheter placement and management is high in this population because of conduction and anatomic abnormalities. However, a PAC may be helpful in certain situations, e.g. severe pulmonary hypertension requiring titration of pulmonary vasodilatory agents such as nitric oxide.
- Echocardiography — Perioperative transoesophageal echocardiography (TOE) or transthoracic echocardiography (TTE) is indicated to determine the cause of any unexplained persistent or life-threatening circulatory instability. During general anaesthesia, TOE is the best method to assess volume status (eg, hypovolemia), as well as regional and global cardiac function.

7.2. Other equipment

- External defibrillator pads, if history of poorly-tolerated tachyarrhythmias
- Intravenous catheter filters- for prevention of paradoxical air embolism in patients with intracardiac or extracardiac shunts.
- Syringe drivers for immediate IV infusion of vasopressor & inotropic drugs that may be required for the specific cardiac lesion. Bolus doses of both phenylephrine and ephedrine must be

prepared in advance.

7.3. Neuraxial labour analgesia

There are a number of good reasons why, in general, neuraxial analgesia is desirable in high-risk cardiac patients in labour:

- The excellent analgesia it affords minimises pain- and anxiety-induced catecholamine release, thereby attenuating cardiac output surges in labour. Epidural placement in early labour is ideal.
- Titration of the epidural infusion can meet the increasing analgesic needs as labour advances.
- A passive second stage of labour is possible because the urge to push is diminished.
- If caesarean delivery becomes necessary, a denser surgical block can be established.

Either an epidural or a low-dose combined spinal-epidural (CSE) epidural can be safely performed in most cases. However, close monitoring of arterial blood pressure is necessary.

For patients in active labour with severe pain, CSE using intrathecal opioid without local anaesthetic in the intrathecal space may be preferable to an epidural technique alone, because of faster onset of analgesia, with minimal haemodynamic effects. For patients in early labour who are relatively comfortable, this difference is less important.

Labour epidural considerations specific to cardiac patients:

- In a patient with an intra- or extracardiac shunt, the loss of resistance technique should employ saline (rather than air) to avoid paradoxical air embolism. This can occur if the epidural needle is unintentionally placed into an epidural vein & air injected.
- An individualised risk-benefit assessment must be made regarding administration of an adrenaline-containing test dose via the epidural catheter. Even a small IV dose of adrenaline in obstetric patients with certain cardiac conditions (e.g. aortic aneurysm or dissection, HOCM, or severe mitral or aortic stenosis) may result in disastrous decompensation due to tachyarrhythmia or hypertension. If adrenaline must be avoided, the alternatives are to use a test dose containing only a local anaesthetic +/- an opioid, or to treat the first dose of the labour epidural solution as the "test dose." The risks of inadvertent intrathecal and intravascular injection, namely local anaesthetic systemic toxicity and high spinal, respectively, are likely to be catastrophic in patients with limited cardiac reserve. Therefore, it is reasonable to consider each and every dose of epidural local anaesthetic solution to be a "test dose."

7.4. Parenteral labour analgesia

Patient-controlled analgesia (PCA) via intravascular opioid infusion with remifentanyl or fentanyl is not a good alternative in a high-risk cardiac patient because pain control is often suboptimal and catecholamine release is not adequately mitigated. Furthermore, achieving even moderately effective analgesia may require an opioid dose that suppresses ventilation. The resultant carbon dioxide retention can cause respiratory acidosis, as well as further catecholamine release. Both catecholamine release and respiratory acidosis can lead to exacerbation of pulmonary hypertension, arrhythmias, ischaemia, or decompensated heart failure in patients at risk.

7.5. Neuraxial anaesthesia for caesarean delivery

Most high-risk cardiac patients are reasonable candidates for either a low-dose combined spinal-epidural (CSE) or a very slowly titrated epidural anaesthetic, if they must undergo caesarean section (CS). It is crucial that an intra-arterial catheter is inserted for continuous arterial blood pressure monitoring prior to establishing the neuraxial block.

There is growing experience with a low-dose CSE technique, which combines the benefits of (1) a slower-onset of the neuraxial block, allowing the anaesthetist to adequately maintain preload and afterload, and (2) the reliability of a subarachnoid block for surgical anaesthesia. A suggested dosing regimen for safe, effective CSE is a low intrathecal dose of bupivacaine 4 to 5 mg plus fentanyl 20 to 25 mcg followed by slow loading of the epidural catheter with local anaesthetic (e.g. 3 to 5 ml of 2% lignocaine without adrenaline, given every 5 minutes) to achieve a T6 surgical level.

A one-shot spinal anaesthetic cannot be advocated for most high-risk cardiac parturients- the rapidly-evolving sympathectomy induced by a spinal dose appropriate for abdominal surgery may result in profound hypotension. Worst affected would be those with cardiac lesions where maintenance of preload or afterload is crucial (e.g., aortic stenosis, aortic coarctation, HOCM, mitral stenosis, or

congenital heart disease with right-to-left shunting).

Traditionally, any neuraxial technique has been considered absolutely contra-indicated in patients with left ventricular outflow tract obstruction. However, careful and well-monitored epidural anaesthesia for CS has been reported to be well tolerated, even in severe aortic stenosis or HOCM.

7.6. Epidural considerations for CS in cardiac patients

Slow dosing of epidural anaesthesia (e.g. 3 to 5 mL of LA without adrenaline every 5 minutes up to a T6 level) and vigilant attention to continuous monitoring, are necessary to avoid severe cardiovascular instability. An intra-arterial catheter must be placed prior to administration of epidural anaesthesia in all high-risk patients. Additional 3 to 5 mL epidural doses of 2% lignocaine will likely be necessary if surgery continues beyond an hour.

- Phenylephrine, for bolus use or as an infusion, must be immediately available to treat hypotension. Other vasopressors (e.g. ephedrine) should be readily available. Choice of vasopressor depends on the heart rate and the underlying cardiac lesion.
- Left uterine displacement must be employed immediately after placement of the epidural.
- Fentanyl 50 to 100 mcg via the epidural catheter is a useful adjunct to reduce intraoperative discomfort, either after delivery of the baby, or before that in the absence of fetal compromise.
- For lasting post-op analgesia, preservative-free morphine 2 to 3 mg, or hydromorphone 1 mg, can be administered via the epidural catheter after delivery. Patients receiving neuraxial opioids must be watched for adequacy of ventilation, oxygenation, and level of sedation.
- Fluid must be administered cautiously. Slow co-loading with reduced volumes of crystalloid (e.g. 250 mL increments, with monitoring of the patient's haemodynamic and clinical response to each increment), reduces the chance of iatrogenic fluid overload and pulmonary oedema.

Low-dose sequential combined spinal-epidural CSE techniques for women with high-risk cardiovascular disease undergoing caesarean delivery are also used. It is important when using such a technique to start a phenylephrine infusion immediately before performing the intrathecal injection (e.g. 3 mg plain bupivacaine + 15 mcg fentanyl + 0.15 mg preservative-free morphine). A reasonable starting dose for phenylephrine is 0.5 mcg/kg per minute, which is then titrated to maintain the patient's BP as close to baseline as possible (the usual range is 0.1 to 2 mcg/kg per minute). Alternative vasopressors must be readily available.

7.7. General anaesthesia for CS in cardiac patients

Here, the choice of drugs is based on the haemodynamic goals relevant to anaesthetising the specific cardiac lesion. Although established obstetric anaesthetic practise dictates a true rapid sequence induction, in high-risk cardiac patients, the maintenance of haemodynamic stability takes precedence over worries about aspiration. The patient should still be well pre-oxygenated and cricoid pressure applied, but the induction should proceed slowly. Also, opiates should not be withheld at induction out of concern for neonatal respiratory depression. If they are indicated to obtund the sympathetic response to intubation, they should be used in appropriate doses, and the paediatrician informed beforehand of this. Nitrous oxide should be avoided if the patient has pulmonary hypertension or an intracardiac shunt.

7.8. Postpartum care

The intensity of postpartum monitoring is determined by the patient's underlying cardiovascular disease and any obstetric or cardiac events that occurred during labour and delivery. Most high-risk patients should be closely monitored for at least the first 72 hours. Women with lesions such as pulmonary hypertension related to Eisenmenger syndrome, peripartum cardiomyopathy, or a dilated aorta due to Marfan syndrome are at particularly high risk for morbidity and mortality during the postpartum period. Most fatalities occur in the first week after delivery, but others occur as late as three to four weeks postpartum. Fluid balance must be carefully monitored and anticoagulation re-established if necessary. Good postoperative analgesia (e.g. epidural analgesia) is useful in reducing the cardiovascular stress response following CS. It has been suggested that neuraxial analgesia may reduce the DVT risk by promoting microvascular flow.

8. Specific cardiac conditions

8.1. Stenotic valvular lesions

8.1.1. Mitral stenosis

- Commonest valvular pathology encountered in pregnancy; always rheumatic
- Pressure gradient between LV and LA may progress to pulmonary oedema, pulmonary hypertension & RV failure
- Echocardiographically severe once valve area $<1 \text{ cm}^2$; dyspnoea at rest is an important clinical marker of severity
- Women with severe mitral stenosis often do not tolerate the cardiovascular demands of pregnancy because (1) the expanded blood volume of pregnancy increases the risk of pulmonary congestion and oedema and (2) the physiologic tachycardia of pregnancy shortens the left ventricular filling time, thereby increasing left atrial and pulmonary arterial pressures.
- If pulmonary hypertension is already present, the patient may be offered termination of pregnancy
- With very tight MS in pregnancy, percutaneous balloon valvotomy should be considered.
- Atrial fibrillation is associated with a higher risk of maternal morbidity in women with mitral stenosis. Tachycardias & dysrhythmias compromise CO by reducing time for diastolic filling. Rate control is essential, e.g. β -blockers and digoxin for fast AF. Patients with chronic AF due to large left atria may be anticoagulated
- Avoid aggressive fluid administration, as this may result in pulmonary congestion in patients with severe MS, particularly in those who also have preeclampsia. Patients are at highest risk for pulmonary oedema immediately after delivery. Bear in mind that adequate preload is needed to maintain LV filling
- Negatively inotropic drugs pose a problem not just for LV contractility: depression of right ventricular function is particularly deleterious in patients with MS and significant pulmonary hypertension.
- Hypoxaemia & hypercarbia worsen pre-existing pulmonary hypertension by increasing PVR. Administer supplemental oxygen and avoid over-sedation.
- Vaginal delivery with carefully titrated epidural and invasive arterial BP monitoring is preferable in patients with symptoms or tight stenosis
- *Neuraxial techniques for CS:* Avoid spinal anaesthesia in patients with severe MS. The rapid onset of a sympathectomy and consequent venodilation and decrease in preload may cause life-threatening hypotension. A very slowly titrated epidural anaesthetic or a low-dose sequential combined spinal-epidural is reasonable after an intra-arterial catheter has been inserted for continuous monitoring of BP.
- *General anaesthesia for CS:* If a GA is needed for CS, an intra-arterial catheter should be placed prior to induction. Use of beta blockers to avoid tachycardia during induction, laryngoscopy, and intubation is reasonable. Avoid induction agents that cause tachycardia (e.g. ketamine) or decrease SVR (e.g. high doses of propofol). Remifentanyl can be used as a supplemental agent during and after induction to provide maternal haemodynamic stability without risk of inducing prolonged neonatal depression. Avoid situations likely to increase PVR, e.g. hypoxaemia, hypercarbia, nitrous oxide, prostaglandin F₂
- *Pulmonary oedema risk in the post-partum period:* Patients with severe MS are at risk for “flash” pulmonary oedema after delivery. Theoretically, the increased venous capacitance caused by a labour epidural should help in this regard. Flash pulmonary oedema in an awake patient may present as acute hypoxaemia and coughing. If the signs and symptoms of pulmonary congestion are mild, treatment may include steep head-up positioning, administration of 100 percent oxygen via mask ventilation with as much positive end expiratory pressure as the patient can tolerate, and IV furosemide administration. If more severe symptoms persist, the anaesthetist must be prepared to induce general anaesthesia, intubate, and apply positive pressure mechanical ventilation. Nitroglycerin infusion is avoided in the immediate postpartum period as it can significantly increase PPH due to uterine atony.

8.1.2. Aortic stenosis

- If asymptomatic before conception, then pregnancy usually well-tolerated
- In severe stenosis (valve area $<0.5 \text{ cm}^2$ or gradient $> 60 \text{ mm Hg}$), mortality is up to 5%
- Acute aortic valve replacement may be required in cases of severe symptomatic stenosis.
- A fall in SVR is poorly tolerated in tight AS, due to fixed CO

- Tachycardia, bradycardia, hypovolaemia and aortocaval compression are poorly tolerated
- Hypotension can lead to acute LV failure secondary to ischaemia. Drops in BP should be managed aggressively with alpha-adrenergic agonists (phenylephrine, noradrenaline) and appropriate fluid to replace losses. Avoid ephedrine due to the risk of tachycardia.
- Epidural anaesthesia is useful in labour.
- *Caesarean delivery*: General anaesthesia is indicated in severe aortic stenosis; however, there are many case reports of successful, carefully-titrated neuraxial anaesthesia with a vasopressor infusion and continuous BP monitoring. Described techniques include slowly-established epidural block, CSE with a low spinal dose & careful epidural top-up, and even cautious spinal block with a spinal catheter. Avoid single-shot spinal anaesthesia in patients with AS.
- *General anaesthetic technique*: An intra-arterial catheter is placed before induction. Induction agents and doses are selected to reduce the likelihood of severe hypotension, while establishing an anaesthetic depth adequate to minimize the sympathetic response to intubation. Hypotension is treated urgently by infusion of phenylephrine, which should be prepared and immediately available. Noradrenaline is a suitable second-line agent. Fluid is administered to optimize intravascular volume. If tachycardia occurs, it should be treated promptly by deepening general anaesthesia and/or administering a β -blocker to control heart rate. Remifentanyl may be used as a supplemental agent during and after induction to provide maternal haemodynamic stability.

8.1.3. Pulmonary stenosis

Isolated pulmonary stenosis constitutes 10% of congenital heart disease (CHD). It is a component of tetralogy of Fallot, and may persist after its repair. Isolated PS is often asymptomatic, but the increased work required of the RV may lead to RV failure. Percutaneous balloon valvuloplasty can be offered to women with deteriorating RV function. Goals during labour and delivery are to maintain RV preload and contractility, and to maintain LV afterload for coronary perfusion. Vaginal delivery with epidural analgesia is preferred, as caesarean section is associated with increased maternal mortality.

Haemodynamic goals include maintenance of right ventricular preload, left ventricular afterload and right ventricular contractility. Aortocaval compression may result in profound hypotension as a result of acute reductions in right ventricular preload. Excess fluid may precipitate acute right heart failure or atrial fibrillation. Spinal anaesthesia may be associated with an uncontrolled reduction in right ventricular preload and should therefore be avoided in severe cases.

8.2. Regurgitant valvular lesions

8.2.1. Mitral and aortic regurgitation

- Patients with moderate degrees of MR or AR usually tolerate pregnancy well because reduced SVR during pregnancy improves CO. However, patients with chronic severe MR or AR have left ventricular dilation and decreased myocardial contractility, as well as increased pulmonary artery pressure and symptomatic congestive heart failure.
- In patients with severe MR or AR, haemodynamic goals include maintaining a relatively low SVR and a relatively fast heart rate (HR) to decrease regurgitation and increase forward flow.
- The following anaesthetic considerations apply to patients with severe or symptomatic MR or AR:
- *Neuraxial analgesia for labour*: An epidural for labour and delivery is very beneficial, and should be commenced early in labour. In patients with symptomatic heart failure, an intra-arterial catheter should be inserted for continuous blood pressure monitoring prior to neuraxial intervention.
- *Neuraxial anaesthesia for caesarean delivery*: Patients with MR or AR usually tolerate both spinal and epidural anaesthesia well, because the decrease in afterload lessens the regurgitant volume. Ephedrine may be used to maintain systemic BP, as well as maintain the HR above 70 to 80 beats per minute. Particularly when spinal anaesthesia is chosen, vasopressors must be immediately available to treat the potential rapid development of hypotension; doses should be judicious to avoid overtreatment.
- *General anaesthesia for caesarean delivery*: If general anaesthesia is needed for CS, an intra-arterial catheter should be inserted prior to induction in patients with heart failure due to severe MR or AR. Careful titration of propofol is preferred for induction, because of its ability to reduce SVR. Also, adequate doses of induction and maintenance anaesthetic agents are necessary to avoid increased BP due to sympathetic stimulation during tracheal intubation,

surgical incision, and the subsequent surgical procedure. For patients with heart failure, transoesophageal echocardiography is the best method to assess volume status during general anaesthesia and has the added benefit of direct qualitative monitoring of MR or AR severity.

- *Acute mitral or aortic regurgitation:* Patients with acute onset of severe MR (e.g. due to rupture of a papillary muscle associated with acute myocardial infarction) or AR (e.g. due to aortic dissection) are unstable, and may require tracheal intubation, controlled ventilation, and inotropic and/or vasodilator support, whilst preparations are made for emergency caesarean delivery. Furthermore, unstable patients may require concomitant emergency cardiac surgery at the time of delivery. Phosphodiesterase inhibitor inodilator agents (e.g. milrinone) are used to maintain stroke volume through a combination of peripheral dilation and increased contractility.

8.3. Mixed valvular lesions

As a general rule, therapy should be directed to the management of the dominant, most severe valvular lesion. Often a compromise is reached for the maintenance of haemodynamic objectives in mixed lesions. Importantly, avoid rapid HR and treat dysrhythmias aggressively. Maintain preload, minimize sudden increases in central blood volume and avoid sudden decreases in SVR. Use cardiovascular monitoring appropriate for the severity of the underlying lesion and the patient's clinical condition.

8.4. Valvulotomy and prosthetic valves

Generally, women who have undergone valvular surgery and are asymptomatic before pregnancy are able to tolerate pregnancy and delivery. Symptomatic patients with underlying LV dysfunction and/or pulmonary hypertension may decompensate in pregnancy. Pregnant patients with previous valvulotomy have fewer complications and less fetal morbidity than those with prosthetic valves. Women with prosthetic valves are at higher risk of complications including valve infection, thromboembolism, and bleeding due to anticoagulant therapy. Women with aortic valve replacement have a lower incidence of complications than those with mitral valve prostheses, possibly due to better ventricular function and less stringent anticoagulation compared to mitral valve lesions.

Because mechanical heart valves are associated with an increased incidence of thromboembolic events during pregnancy, therapeutic anticoagulation throughout pregnancy is essential. There is as yet no consensus on optimal management of anticoagulation in pregnant women with prosthetic valves, because of a dearth of prospective randomised trials. The 2014 AHA/ACC guidelines on VHD management continue to recommend warfarin over unfractionated heparin and the low molecular weight heparins as the most effective anticoagulant in pregnant patients with mechanical prostheses in their 2nd and 3rd trimesters. They recommend discontinuation of warfarin, with initiation of a continuous unfractionated heparin infusion (targeting aPTT >2 times control), at around 36/40 or in good time before planned vaginal or caesarean delivery. The unfractionated heparin is stopped four to six hours before delivery (in practice, once the woman is in active labour) or surgery. No neuraxial analgesia/ anaesthesia should be administered until the aPTT value is near normal or the blood heparin concentration is near zero; until then, IV opiate analgesia offered. For patients who have recently received long-term warfarin therapy, the presence of a normal (or near-normal) prothrombin time (PT) and International Normalized Ratio (INR) should be confirmed before administration of a neuraxial technique.

If *therapeutic* anticoagulation with high-dose LMWH [an alternative to warfarin, provided that peak anti-factor Xa can be measured] has not been stopped before labour, then no neuraxial technique should be performed for 24 hours from the time of the last dose. Standard UFH can be substituted for LMWH by 38 weeks' gestation to allow (1) faster resolution of anticoagulant activity and (2) the ability to monitor anticoagulation activity through measurement of the aPTT. Protamine reversal of LMWH heparin therapy to allow administration of neuraxial analgesia/ anaesthesia is not recommended. Protamine neutralizes approximately 60% of the anti-factor Xa activity caused by heparin; however, this effect is unpredictable.

If caesarean delivery is required in a patient with abnormal coagulation, general anaesthesia is administered.

The re-institution of anticoagulation after delivery should be discussed with the obstetrician and cardiologist. When an epidural catheter has been used, ASRA guidelines should be used to guide timing of catheter removal relative to anticoagulant dosing.

Bioprosthetic valves typically do not require anticoagulation (unless there are other thromboembolic risk factors). Patients with mechanical valves and bioprostheses should receive daily low-dose aspirin in the 2nd and 3rd trimesters.

8.5. Mitral valve prolapse

Mitral valve prolapse (MVP) is fairly common in women of childbearing age. Primary MVP is characterized by a redundant valve that prolapses into the atrium during systole. MVP can be secondary, and associated with an atrial septal defect, endocarditis, or mitral stenosis. Other associations include von Willebrand's disease, Ehlers-Danlos syndrome, kyphoscoliosis, pectus excavatum, osteogenesis imperfecta, myotonic dystrophy, and, most notably, Marfan's syndrome. Progressive mitral regurgitation occurs in about 15% of patients with MVP.

Generally, pregnancy is very well tolerated.

Anaesthetic management: The severity of coexisting disease often dictates whether invasive haemodynamic monitoring is required. Neuraxial analgesia or anaesthesia is an excellent choice for labour and vaginal or caesarean delivery. The sympathectomy and decreased concentrations of catecholamines achieved with this technique are beneficial. The differential diagnosis of hypotension or neurologic events that occur following neuraxial anaesthesia should include cardiac arrhythmias, which occur with greater frequency in patients with MVP. When general anaesthesia is required, sympathomimetic agents (e.g. ketamine, pancuronium) should be avoided because of the high incidence of arrhythmias with their use. It also seems prudent to avoid agents that sensitise the myocardium to catecholamines. Ephedrine may precipitate or exacerbate tachyarrhythmias. Hypotension can be treated with small doses of phenylephrine. Management of the rare patient with MVP and evidence of ventricular dysfunction is similar to that for the patient with severe mitral regurgitation.

8.6. Cardiomyopathy in pregnancy

8.6.1. Peripartum cardiomyopathy

The European Society of Cardiology has defined peripartum cardiomyopathy (PPCMO) as follows: "Peripartum cardiomyopathy is an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found. It is a diagnosis of exclusion. The left ventricle may not be dilated but the ejection fraction is nearly always reduced below 45%." Echocardiography demonstrates features of dilated cardiomyopathy with impaired ejection fraction, global dilatation and sometimes thinned-out walls. The symptoms and signs are similar to those in patients with idiopathic dilated cardiomyopathy.

In South Africa, the incidence is estimated at 1 in 1000 live births. The aetiology of PPCMO is unknown; risk factors might include preeclampsia, twin pregnancies, advanced maternal age and African ethnicity. A possible pathophysiological mechanism for PPCMO is the production of a 16 kDa fragment of prolactin as a consequence of oxidative stress. The 16 kDa form of prolactin mainly affects the endothelium and might, together with additional antiangiogenic factors such as soluble fms-like tyrosine kinase 1 (sFLT-1; also known as vascular endothelial growth factor receptor 1), disturb the angiogenic balance in the peripartum period, thereby promoting metabolic shortage in the heart, with potential negative effects on cardiac function.

Patients present with acute or sub-acute episodes of left ventricular failure. Diagnosis of PPCMO may be delayed if their symptoms are wrongly ascribed to the normal physiological changes of pregnancy. Tachyarrhythmias can occur in PPCMO, including SV, AF, and rarely, VT. There is an increased risk of thromboembolism due to the potential development of mural thrombus.

Prognosis is poor. The degree of dysfunction at presentation, judged either by NYHA functional class or echocardiography, is of prognostic value. The mortality rate is between 15 and 50%. 30-50% will improve and recover a left ventricular ejection fraction of 50% or more.

Medical management is the same as for other forms of heart failure, although certain drugs are contra-indicated for use in pregnant & lactating women (ACE-inhibitors, spironolactone). Anticoagulation is indicated, given that peripartum cardiomyopathy increases the risk of thromboembolic events

Obstetric management involves expedient delivery of the fetus by caesarean or instrumental vaginal delivery, with the mode based on obstetric indications. In most cases, induction of labour can be attempted if the mother's condition can be stabilised. Vaginal delivery carries less risk of PPH,

haemodynamic instability, postoperative infection and pulmonary complications than CS. However, if the patient's condition worsens, then a CS may be less stressful than a long labour.

Anaesthetic management for vaginal or caesarean delivery in women with PPCMO is guided by the same principles as for any patient with severe cardiomyopathy. General anaesthesia, CSE anaesthesia, continuous spinal anaesthesia, and epidural anaesthesia have been described. Single-shot spinal anaesthesia is not recommended. Monitoring should include invasive arterial blood pressure. Cardiac output monitoring and/or echocardiography may be used to aid perioperative management. Use of intraoperative TOE is indicated to determine the cause of any unexplained persistent or life-threatening hemodynamic instability. TOE monitoring is useful to guide fluid management and vasoactive therapy during major surgical procedures, because it allows evaluation of LV and RV size, global and regional systolic and diastolic ventricular function, valvular regurgitation, and estimation of pulmonary artery pressure.

The use of neuraxial analgesia or anaesthesia for either vaginal or caesarean delivery is often determined by the anticoagulation regimen. If GA is necessary, a slow "cardiac" induction technique with a cardio-stable induction agent (e.g. etomidate) and high doses of opioid should be used. Inotropes, such as dobutamine or phosphodiesterase inhibitors (e.g. milrinone) may be necessary to offset the myocardial depression of intravenous and volatile anaesthetic agents. Vasopressors may also be required to counteract vasodilation and maintain coronary perfusion. Preload should be maintained.

Uterotonic drugs should be used cautiously due to their associated side effects. Following delivery the patient should be recovered in a critical care environment with ongoing invasive haemodynamic monitoring, careful fluid management and adequate analgesia.

8.6.2. Hypertrophic cardiomyopathy

The majority of pregnant patients with HOCM tolerate pregnancy well if they were asymptomatic with good effort tolerance prior to conception. Their expanded blood volume helps to keep the LV well-filled. However, those with poorer functional class may deteriorate to the point of overt cardiac failure, as the pregnancy-induced increases in heart rate and myocardial contractility and decrease in SVR may together worsen their dynamic left ventricular outflow tract obstruction. Aortocaval compression is also poorly tolerated, as it decreases LV filling. β -blocker therapy is continued throughout pregnancy, and some of these women may have permanent pacemakers or AICDs if they have a history of ventricular dysrhythmias.

Caesarean delivery is usually only for obstetric indications, as these patients typically tolerate the second stage of labour well, given that the increased SVR helps maintain ventricular function. Oxytocin boluses after delivery are potentially very dangerous, as the systemic vasodilation they cause may increase outflow tract obstruction. Ergometrine is an acceptable alternative uterotonic agent.

The goals of anaesthetic management are (1) maintenance of intravascular volume and venous return, (2) avoidance of aortocaval compression, (3) maintenance of adequate SVR, (4) maintenance of a slow heart rate in sinus rhythm, (5) aggressive treatment of acute tachyarrhythmias which may reduce LV diastolic filling, and (6) prevention of increases in myocardial contractility. Beta-blocker therapy should be maintained during labour and delivery. Neuraxial analgesia techniques, including combined spinal-epidural analgesia using an intrathecal opioid, have been used safely during labour, despite concerns about preload & afterload reduction. Epidural analgesia attenuates increases in HR and contractility from endogenous catecholamines (pain and anxiety) during labour. Phenylephrine is the preferred vasopressor should hypotension ensue. Ephedrine should be avoided as it may increase the dynamic obstruction.

An elective CS may be performed safely with epidural anaesthesia. HOCM represents a relative contraindication to the use of single-shot spinal anaesthesia for caesarean delivery because of the rapid onset of the sympathetic blockade. .

Patients with HOCM tolerate general anaesthesia well. Volatiles should be carefully titrated to realise the beneficial effects of some myocardial depression without an excessive decline in SVR. Invasive haemodynamic monitoring is recommended to ensure adequate volume loading and prompt replacement of any blood loss. Dilute oxytocin infusion is preferable to bolus administration.

Postoperatively, these patients are at risk of worsening outflow obstruction from the diuresis that occurs in the first 48-72 hours postpartum and need close monitoring.

8.7. Peripartum ischaemic heart disease (IHD)

Acute myocardial infarction (AMI) is fortunately uncommon in pregnancy, with a quoted incidence of 1:10,000 pregnancies, but may be expected to occur more commonly as women delay childbearing into the fifth decade and beyond. AMI in pregnancy carries a very high maternal and fetal mortality- if it occurs in the two weeks before delivery, then maternal mortality may be up to 45%. Less than half of cases have angiographically abnormal coronaries, and in those without atherosclerosis, arteritides, coronary spasm & in situ thrombosis are implicated. Often there is no history of preceding angina. The cardiac demand imposed by pregnancy, labour & delivery can provoke ischaemia in those with IHD. As there is overlap between the presenting signs, symptoms and even ECG changes with those encountered in healthy pregnancy, the diagnosis of AMI must be confirmed with a cardiac-specific troponinT level >0.15ng/mL.

Management of AMI is directed at improving the O₂ supply-demand ratio, and includes O₂ therapy, left lateral positioning, aspirin, β -blockers, nitroglycerine & calcium channel blockers. Statins and ACE-inhibitors are contraindicated in pregnancy. Percutaneous coronary angioplasty with stenting is becoming established as the treatment of choice in pregnant woman with AMI; as thrombolysis carries a high bleeding risk for mother & fetus, and CABG in pregnancy is associated with a high fetal mortality.

Ideally, delivery of the fetus should be delayed for a minimum of 2 weeks after AMI if at all feasible. A short labour and assisted vaginal delivery with epidural analgesia is ideal. Some of these patients will have received a heparin infusion or be on anti-platelet therapy, e.g. clopidogrel & aspirin, so ASRA guidelines regarding the timing of epidural catheter placement and removal must be considered.

For caesarean delivery, a slowly-titrated epidural is recommended. A spinal anaesthetic is relatively contraindicated. Anxiety during line and epidural placement should be prevented with a judicious dose of sedative (e.g. midazolam 0.5-1 mg). Every effort must be made to prevent heat loss in theatre, and shivering should be treated aggressively (pethidine 12.5-25 mg). Phenylephrine is the agent of choice for the treatment of hypotension.

If general anaesthesia is indicated, then induction drugs should include high-dose opiates or remifentanyl to reduce the sympathetic response to laryngoscopy & intubation. Beta blockers are a reasonable choice, in addition. Induction agents that provoke tachycardia (e.g. ketamine) or markedly decrease SVR (e.g. high-dose propofol) should be avoided. Tachycardia should be promptly treated by deepening anaesthesia or administering beta blockers (e.g. esmolol or labetalol). Phenylephrine is the preferred vasopressor. During emergence and tracheal extubation, tachycardia and hypertension may lead to myocardial ischaemia and may need to be managed, by ensuring adequate analgesia, and administering intravenous beta blockers and/or vasodilators.

8.8. Congenital heart disease in the pregnant patient

8.8.1. General considerations

Here there is a wide spectrum of pathology, of varying severity. Questions to be asked include:

1. What is the exact cardiac anatomy?
2. What is its functional significance? Is there shunting, and if so, in what direction?
3. What surgical interventions have been performed, and when? Is the pathology unrepaired, palliated, incompletely repaired or fully repaired?
4. What is the impact of pregnancy physiology on the particular pathology?

The following risks and predictors for maternal or fetal complications in women with congenital heart disease during pregnancy have been identified:

- Pulmonary hypertension (pulmonary vascular disease)
- Maternal cyanosis
- Poor maternal functional class
- History of arrhythmia
- Maternal anticoagulants

An elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) level (>128 pg/mL) at 20 weeks of gestation may be an independent risk factor for cardiovascular events during pregnancy in women with congenital heart disease.

Acyanotic Shunt Lesions: Small Left To Right Shunts

Lesions such as a *small* atrial septal defect, ventricular septal defect, or patent ductus arteriosus may produce a modest degree of left-to-right intracardiac shunting, which is often well tolerated during pregnancy. For patients with a left-to-right shunt, haemodynamic goals are to maintain or decrease SVR while avoiding significant decreases in PVR that may increase pulmonary overcirculation. Left-to-right shunts can eventually lead to pulmonary hypertension and reversal of the shunt flow, with resulting cyanosis. Severe obstetric haemorrhage that leads to acute systemic hypotension can also lead to transient reversal of the shunt flow.

Atrial septal defect

In the presence of a normal PVR an unrepaired ASD should be well tolerated. 20-30% will have coexisting mitral valve prolapse (see before). The pre-existing tendency to atrial arrhythmia may increase with the raised cardiac output. The potential to shunt right to left together with hypercoagulability in pregnancy increases the risk of paradoxical embolism, especially with increases in intrathoracic pressure during labour. These patients should be considered for DVT prophylaxis in the presence of immobility or additional risk factors for venous thrombosis. Surgical or device closure of the ASD, ideally carried out before pregnancy, removes this risk. There is no need for antibiotic prophylaxis in ASD other than for the first year after a device closure.

Ventricular septal defect or patent ductus arteriosus

A small defect with normal right sided pressures confers no added risk in pregnancy. Because of the large pressure gradient across the defect paradoxical embolism cannot occur. Membranous VSDs are the most common and may be associated with aortic regurgitation. Large defects causing pulmonary vascular disease are discussed later under pulmonary hypertension.

Anaesthetic management

Anaesthetic management of patients with these defects should include avoidance of intravenous infusion of air bubbles and use of loss-of-resistance to saline (rather than air) to identify the epidural space. Early administration of epidural labour analgesia minimizes pain-associated increases in maternal plasma catecholamine concentrations and SVR. These changes can worsen the severity of left-to-right shunting. Slow titration of neuraxial anaesthetic drugs should result in a more gradual onset of sympathetic blockade, which helps avoid the rapid decrease in SVR that can cause an asymptomatic left-to-right shunt to become a right-to-left shunt with maternal hypoxaemia. The drop in SVR should be managed with appropriate volume replacement and the judicious use of vasoconstrictors. For maintenance of labour analgesia, a continuous infusion of the lowest possible concentration of local anaesthetic is preferable, avoiding, if possible, large intermittent bolus administration. Neuraxial opioids have minimal haemodynamic effects & allow the use of lower concentrations of local anaesthetic with less potential for vasodilation and hypotension. Assisted vaginal delivery to minimize the cardiovascular stress associated with delivery is useful. General anaesthesia is reserved for parturients who require C/S but have contraindications to neuraxial techniques. General anaesthesia with mechanical ventilation tends to decrease SVR but may also decrease PVR, so the net effect is difficult to predict. Generally, hyperventilation and hyperoxia should be avoided since these conditions lower PaCO₂ and may lower PVR. Systemic hypotension may best be treated with phenylephrine because it will increase both SVR and PVR.

Cyanotic Shunt Lesions

Congenital heart disease with right-to-left shunt is associated with recirculation of desaturated blood. Peripheral cyanosis occurs when >5 g/dl of unsaturated haemoglobin is present. Importantly, an anaemic parturient with low SpO₂ may not manifest cyanosis, whereas with polycythaemia, cyanosis appears at higher SpO₂. Cyanotic lesions are more likely associated with congestive heart failure, worsening of functional status, fetal loss, preterm labour, and IUGR. Fetal, not maternal factors are usually responsible for intolerance of the pregnancy and labour.

The physiologic response to hypoxaemia in women with cyanotic lesions is polycythaemia, which is a useful compensation up to a haematocrit of 60%. An increase in blood viscosity beyond this level offsets any advantages that an increase in haematocrit brings in terms of oxygen delivery. Polycythaemia contributes to tissue ischaemia in low flow states because of the increase in blood viscosity and can lead to thrombosis in situ. Maternal haematocrit >60%, SaO₂ <80%, RV hypertension, and syncopal episodes are all poor prognostic signs in pregnant women with CHD. Cyanotic CHD may be associated with multiple coagulation factor deficiencies increasing the risk of peripartum haemorrhage.

Tetralogy of Fallot

Tetralogy of Fallot (TOF) is the commonest cyanotic CHD lesion. Tetralogy of Fallot consists of (1) nonrestrictive VSD; (2) over-riding aorta; (3) dynamic subpulmonic right ventricular outflow tract (RVOT) obstruction; and (4) RV hypertrophy. The worse the RVOT obstruction, the greater the right-to-left shunt of blood through the VSD. Other possible secondary pathologies include RV systolic and diastolic dysfunction, and end-organ visceral damage from chronic hypoxemia, polycythaemic microvascular sludging and reduced CO.

Most pregnant women with tetralogy of Fallot have had corrective surgery. The surgical treatment, typically performed in childhood, involves closure of the ventricular septal defect and widening of the pulmonary outflow tract. This operation is generally successful. If these corrected patients have good functional capacity pregnancy is not associated with any increased risk, even in the presence of the significant pulmonary regurgitation. Severe PR may arise secondary to transpulmonic valve annular patching at initial corrective surgery, and may cause RV dilatation, RV systolic failure & elevated RA pressures. In some cases, a small ventricular septal defect may recur, or progressive hypertrophy of the pulmonary outflow tract may occur slowly over the first few decades of life. The cardiovascular changes of pregnancy (e.g., increases in blood volume and cardiac output, reduced SVR) may unmask these previously asymptomatic residua of corrected tetralogy of Fallot. The severity of symptoms depends on the size of the ventricular septal defect, the magnitude of the pulmonic stenosis, and the contractile performance of the right ventricle. Thus, patients with corrected tetralogy of Fallot should undergo echocardiography before and during early pregnancy, even if they have been asymptomatic for many years.

Tetralogy of Fallot is also the most common uncorrected cyanotic congenital heart lesion seen in pregnant women. In this situation, pregnancy is discouraged because the decreased SVR of pregnancy increases the volume of the right-to-left shunt and increases cyanosis.

Anaesthetic management for patients with successful correction of tetralogy of Fallot often does not differ from that for women without this lesion. However, patients with corrected tetralogy of Fallot may demonstrate various atrial and ventricular arrhythmias, owing to surgical injury to the cardiac conduction pathways. A baseline 12-lead ECG and continuous ECG monitoring in labour is advocated.

The parturient with uncorrected TOF or corrected TOF with residua is at much higher risk.

Management principles: If the parturient with TOF is post transpulmonic valve annular patch repair with residual severe pulmonic insufficiency, then it is important to:

1. Maintain RV preload to compensate for the RV dilatation. Augment preload with IV fluids and avoid sudden decreases in preload following neuraxial or GA.
2. Maintain RV inotropy if RV systolic dysfunction is present with appropriate inotropes (e.g. adrenaline, dopamine, milrinone, dobutamine).
3. Maintain RV chronotropy to decrease the diastolic run-off of pulmonary artery blood into the RV through the incompetent or absent pulmonic valve. Heart rates can be maintained with inotropes or anticholinergics as indicated.
4. Decrease PVR to reduce regurgitant pulmonary artery blood flow back into the lower resistant RV during diastole

Haemodynamic goals for uncorrected TOF include:

1. Maintain normal sinus rhythm to augment RV diastolic filling.
2. Maintain adequate RV preload to relieve the dynamic RVOT obstruction.
3. Reduce chronotropy to minimize RVOT muscular infundibular spasm.
4. Avoid increases in inotropy (e.g. catecholamine surges during labour), which may worsen the dynamic RVOT obstruction.
5. Maintain SVR to keep the VSD shunt going left-to-right and to augment right coronary artery perfusion to the hypertrophied RV.

Various anaesthetic and analgesic techniques have been used in patients with TOF for vaginal birth and CS. The choice between various neuraxial techniques for labour, and between regional versus GA for CS, should be based on the patient's condition and the desired haemodynamic goals.

Administration of neuraxial analgesia during early labour is advisable to limit increases in pulmonary vascular resistance and consequent right-to-left shunting. For caesarean delivery, neuraxial anaesthesia should be administered slowly; single-shot spinal anaesthesia is a poor choice because the abrupt reduction in SVR with this technique may cause reversal of shunt flow and hypoxaemia.

8.9. Coarctation of the aorta

Aortic coarctation comprises approximately 6 – 8% of CHD and consists of a discrete narrowing of the descending aorta, most commonly distal to the left subclavian artery, with proximal hypertension and distal hypoperfusion. Patients with an uncorrected coarctation who reach adulthood generally develop collateral blood flow to allow for adequate distal aortic perfusion. LV hypertrophy and LV diastolic dysfunction are consequences of the chronic increase in afterload. Pregnancy-related changes (decreased SVR, increased blood volume, and increased CO) are poorly tolerated by patients with a coarctation, and they are at high risk of fetal loss due to uterine hypoperfusion. They are also at increased risk of ascending aortic arch complications (dilatation, aneurysm, and rupture) and premature coronary artery disease. Coexisting congenitally malformed bicuspid aortic valves may predispose these patients to accelerated aortic stenosis. Wide fluctuations in blood pressure during labour may increase the risk for intracranial aneurysm rupture or aortic dissection, which has led some obstetricians to recommend performance of an elective caesarean delivery, particularly if there is gross widening of the ascending aorta.

Management principles

Management of parturients with coarctation of the aorta is similar to that of fixed supraaortic stenosis.

Proximal BP (brain, heart) must be measured in the right upper arm while distal BP (uteroplacental, mesenteric) should be measured in the leg. This helps to differentiate the underlying pathology from any superimposed preeclampsia that might develop. Preeclampsia in a parturient with a coarctation requires aggressive treatment of the proximal hypertension to reduce the risk of aortic dissection. The treatment of upper-limb BP may lead to excessive hypotension below the aorta, causing uteroplacental insufficiency and fetal distress.

Anaesthetic options

Anaesthetic choices and considerations are similar to those for patients with aortic stenosis. Epidural, CSE, and spinal block for labour analgesia and CS have been used successfully in parturients with coarctation of the aorta. Single-shot spinal anaesthesia is a poor choice due to the potential for precipitous cardiovascular changes. If GA is undertaken, BP increases during endotracheal intubation and surgical stimulation should be minimized.

Surgically Corrected Congenital Heart Disease

Fontan procedure for univentricular circulation (cavopulmonary palliation)

The various forms of Fontan operation create two separate circulations in series in the presence of a functionally univentricular heart. An anastomosis or conduit is created between the vena cavae and the pulmonary artery which increases pulmonary blood flow as palliation for patients with underlying tricuspid atresia, hypoplastic left heart syndrome, double inlet ventricle and pulmonary atresia. These patients are therefore not cyanosed, but experience a long term low output state as they have a single ventricle responsible for supporting systemic CO. They are at risk of ventricular failure when exposed to the increased demands of pregnancy, particularly if the systemic ventricle is morphologically a right ventricle, as it is not designed to pump against SVR chronically and eventually decompensates. Embolic material entering the pulmonary arterial tree could significantly impede pulmonary blood flow since there is no ventricular pump to force blood past the obstruction, so these patients are generally anticoagulated for life.

Pregnancy post-Fontan operation is usually well tolerated although there is a 2% risk of death. Maternal outcome depends on functional capacity and ventricular function, which is more likely to be adequate if the single ventricle is morphologically left.

The hallmarks of anaesthetic management post-Fontan repair are the maintenance of univentricular systolic function, maintenance of preload, and avoidance of pulmonary arterial pressure elevation. Since pulmonary CO is passively driven by the gradient between the CVP and PAP, it is necessary to keep PVR as low as possible. Factors that contribute to PAP elevation warrant close attention. A review of the limited case reports in the anaesthesia literature shows that epidural analgesia is well tolerated and indeed recommended for the first stage of labour. Effective analgesia will help to smooth out large fluctuations in pulmonary blood flow secondary to the tachypnoea associated with contractions. Although the decreases in pulmonary blood flow caused by bearing down and pushing in the second stage of labour might decrease cardiac output, perioperative complications are low and

peripartum cardiac decompensation is rare.

The caesarean section rate seems to be higher than the general population. Neuraxial anaesthesia for caesarean section, in addition to its usual benefits, preserves spontaneous ventilation, which is desirable in Fontan patients. The gradual onset of epidural anaesthesia is preferable to the rapid fall in preload from spinal anaesthesia. No increased risk from general anaesthesia has been identified provided the haemodynamic goals are achieved. Oxytocin will decrease systemic vascular resistance and increase heart rate and pulmonary vascular resistance, and ergometrine will increase systemic vascular resistance, making the immediate postpartum period a risky one. Prevention of uterine atony is very important because postpartum haemorrhage is poorly tolerated. The maintenance of intravascular volume is crucial to managing postpartum haemorrhage.

Considerations for Labour in Pulmonary Hypertension and Eisenmenger's Syndrome:

Pulmonary hypertension is defined as a mean PAP >25mmHg at rest (>30mmHg during exercise and pregnancy). Pulmonary hypertension secondary to cardiac disease may result from longstanding high pulmonary blood flow due to systemic-to-pulmonary shunts, venous hypertension from cardiac or valvular dysfunction, or chronic thromboembolic disease. The syndrome of primary pulmonary hypertension is characterized by markedly elevated pulmonary artery pressures in the absence of an intracardiac or aortopulmonary shunt. Patients with primary pulmonary hypertension, unlike those with Eisenmenger's syndrome, often have reactive pulmonary vasculature that can respond to vasodilator therapy.

Eisenmenger's syndrome (ES) represents the most common cyanotic cardiac defect in adults. Chronic left to right shunting and high pulmonary blood flow in longstanding CHD lesions (e.g. large ASD, VSD, PDA, or large surgical systemic-pulmonary anastomoses following palliation or definitive repairs of CHD) result in right ventricular hypertrophy, elevated PVR and significant ventricular and arterial remodelling on the right side. ES carries a maternal mortality ranging from 30 – 70% along with high incidence of fetal demise, so patients are usually counselled against pregnancy. Sudden death is common and may be due to stroke, arrhythmia, abscess, or heart failure. 25 year survival after diagnosis of ES is reported to be 42% in the absence of pregnancy. A significant number of complications occurs 2-6 weeks post-partum.

Mortality and morbidity is also high in PPH and many authors consider pregnancy to be contraindicated. The risk for maternal mortality is nearly 30% for primary pulmonary hypertension.

1. Pathophysiology: ES is defined by a PVR greater than 800 dyn·s/cm⁵ along with right-to-left or bidirectional shunt flow. Correction of the shunt may resolve the pulmonary hypertension, but once pulmonary arteriolar remodelling (i.e., medial hypertrophy) develops the elevated PVR is irreversible, differentiating ES from primary pulmonary hypertension.
 - i. Symptoms: Fatigue, dyspnoea, cyanosis, oedema, clubbing, and polycythaemia.
 - ii. The underlying right-to-left shunt, hyperviscosity from polycythaemia, and the development of heart failure promote thrombus formation and may elevate stroke risk.
2. Peripartum Considerations: Patients with ES are often unable to accommodate the increased oxygen demands of pregnancy.
 - i. Reduced SVR from pregnancy coupled with the irreversible elevated PVR of Eisenmenger's increases right-to-left shunting and cyanosis.
 - ii. Reduction in functional residual capacity adds to the hypoxaemia, further reducing oxygen delivery to the fetus and increasing fetal demise.
 - iii. Management of patients who desire to remain pregnant should be carried out utilizing a multidisciplinary approach among obstetricians, cardiologists and anaesthetists trained in high risk deliveries.
3. Anaesthetic Management for Labour: Historically, regional anaesthesia was thought to be contraindicated and general anaesthesia was the standard. A recent review of cases of non-cardiac surgery including labour and caesarean section in Eisenmenger's syndrome indicates that regional anaesthesia is indeed safe for these patients. Anaesthetic delivery requires utmost vigilance to maintain the above haemodynamic goals with any type of anaesthesia. Vaginal deliveries will often require an assisted second stage to reduce cardiac stress.

Anaesthetic and Haemodynamic goals for Eisenmenger's syndrome:

Avoid elevations in PVR: Prevent hypoxaemia, acidosis, hypercarbia and pain. Provide supplemental oxygen at all times.

Maintain SVR: Reductions in SVR will increase right to left shunting.

Avoid myocardial depressants and maintain myocardial contractility.

Maintain preload: Avoid aortocaval compression.

Maintain sinus rhythm.

4. Labour: Early and effective analgesia is critical to maintain the balance of SVR and PVR by avoiding catecholamine surges from pain. Intrathecal opioid administration (CSE) in first stage of labour is ideal, however if anticoagulation is a concern then a low-dose remifentanyl infusion or patient controlled analgesia are possible options.

- i. Slow titration of local anaesthetic with aggressive treatment for any reduction in SVR (i.e., systemic hypotension) using phenylephrine will provide good results for second stage of labour as well as instrumental delivery.
- ii. Maintenance of intravascular volume status using careful fluid boluses along with use of phenylephrine for decreased SVR should be used to prevent onset or exacerbation of cyanosis.
- iii. Pudendal blockade may also be employed to avoid the risk of extending the epidural blockade (and decreasing SVR) to cover stage 2 of labour and for delivery.
- iv. Oxytocin, ergometrine and prostaglandin F_{2α} should be used with extreme caution because of systemic and pulmonary vascular side effects.

5. Anaesthesia for caesarean section: Either epidural or general anaesthesia is acceptable.

- i. Single shot spinal anaesthesia is contraindicated.
- ii. Slow titrated doses of local anaesthetic to obtain a surgical block can be safely used.
- iii. Tight haemodynamic monitoring and control is of utmost importance. Avoidance of elevations in PVR is critical.

6. For general anaesthesia, slow titration of induction agents is preferred as rapid sequence inductions carry high risk of SVR alterations and subsequent haemodynamic collapse. This places the patient at increased risk of aspiration, so strict NPO guidelines, use of pharmacologic prophylaxis against aspiration (sodium citrate, H₂ blockade, etc.), and mask ventilation using cricoid pressure are recommended. Propofol and thiopentone should be avoided or used with extreme caution due to marked reductions in SVR, whereas ketamine and etomidate seem appropriate. Inhalational agents should be used with caution because of their propensity to decrease SVR. Nitrous oxide should be avoided because of its propensity to increase PVR. Maintenance of anaesthesia may be accomplished using careful titration of intravenous agents such as nondepolarizing neuromuscular blockers, opioids, and sedative-hypnotic agents such as midazolam or ketamine. Potent inhalational agents are typically used at concentrations of less than 0.5 MAC.

7. Monitors

- i. Pulse oximetry may be the most important monitor as changes in saturation directly correlate with alterations in shunt flow.
- ii. Intra-arterial monitoring is generally employed to closely follow blood pressure.
- iii. Central venous catheters are controversial. CVP catheter placement carries a risk of air embolism, thrombus and pneumothorax which can be devastating in these patients.
- iv. Pulmonary artery catheters are contraindicated in obstetric patients with ES for a number of reasons. The anatomic abnormality causing ES typically renders "flow-directed" flotation of PA catheters difficult or impossible, and the risk of arrhythmia, pulmonary artery rupture and thromboembolism are elevated. Cardiac output measurements will be inaccurate due to the large shunt.
- v. PAC is generally employed for those patients with PH but not ES.
- vi. If general anaesthesia is employed, TOE may provide the best real time monitor of cardiac preload and of the status of right-to-left shunting.

8. Anaesthetic Management specifics for primary pulmonary hypertension: Refer to the hemodynamic goals for ES, with one caveat: reduction in SVR will not alter the shunt fraction for primary pulmonary hypertensive patients as there is no shunt, but will cause a marked drop in cardiac output due to relatively fixed right-sided pressures. As a result of small numbers of

cases, there is no consensus about ideal anaesthetic management for labour and delivery.

- i. Vaginal delivery is preferred using epidural anaesthesia (or CSE), with assisted second stage labour (i.e. forceps delivery) to minimize stress on the right ventricle.
 - ii. Oxytocin has been used successfully both for induction of labour and to increase uterine tone postpartum. Careful titration is required as it can decrease SVR and elevate PVR to decrease both coronary perfusion pressure and forward flow. Avoid prostaglandin F2 α and ergometrine because of pulmonary side effects and vasoconstrictive effects, respectively.
 - iii. Caesarean section has been associated with increased mortality; however patients with severe disease causing right heart failure may require operative delivery. The anaesthetic should be tailored to each patient's underlying cardiac function, as epidural and general anaesthesia have similar outcomes. If there is pre-existing right ventricular failure, any big drop in SVR caused by epidural anaesthesia may lead to a drop in CO. Any hypotension may also cause right ventricular ischaemia, leading to a further deterioration in right ventricular function. The adverse effects of general anaesthesia include increased pulmonary arterial pressure during laryngoscopy and intubation, the adverse effects of positive-pressure ventilation on venous return and the negative inotropic effects of certain anaesthetic agents. An opiate-based technique for induction and maintenance is probably best.
9. Postoperative concerns: Cardiac output and systemic vascular resistance increase immediately after delivery, so this is a critical period for patients with pulmonary hypertension. All patients should remain in an ICU for a number of days postpartum, so that changes in systemic and pulmonary vascular resistance can be treated with inhaled nitric oxide and prostacyclin as necessary. Many sudden deaths occur in the first week after delivery.

Marfan's syndrome

Life-threatening aortic complications of Marfan's syndrome are caused by cystic medial necrosis, resulting in dilatation, dissection and even rupture, usually of the ascending aorta, as well as valvular regurgitation. Mitral valve prolapse (most frequently of the posterior leaflet), and myxomatous degeneration of the mitral valve occur frequently in MFS. Dilatation of the main pulmonary artery is not uncommon. Accelerated coronary artery disease accounts for the high incidence of ischaemia-related dysrhythmias & conduction disorders.

Half of all aortic dissections in women of childbearing age occur during pregnancy. Haemodynamic stress and perhaps hormonal effects (oestrogen causes collagen to 'soften') contribute to an increased risk for aortic dissection during pregnancy

The risk of a desired pregnancy must be assessed before conception by an echocardiogram and MRI. If the aortic root is <40mm in diameter, there are seldom serious cardiovascular complications during pregnancy. If the aortic root diameter is >40mm, pregnancy is inadvisable, irrespective of NYHA functional class. All pregnant women with MFS are considered high risk, and require on-going evaluation, including echocardiograms every six weeks during their pregnancies.

Vaginal delivery is acceptable for the asymptomatic patient. Anaesthetic management focuses on minimizing aortic root shear forces and wall stress through invasive monitoring, pharmacologic intervention, and analgesia. Epidural labour analgesia should be initiated early in order to prevent pain-induced catecholamine release, elevated BP, and increased CO. Significant hypotension should be treated with phenylephrine to avoid the beta-agonist effect of ephedrine.

In low-risk women with MFS, CS is indicated only for obstetric reasons. Either regional or general anaesthesia can be used for CS, although regional anaesthesia is preferred. The same caveats should be applied to epidural anaesthesia for CS as for labour and vaginal delivery. For general anaesthesia, pharmacological strategies should be used to prevent a hypertensive intubation response. Volatile agents are useful because they decrease myocardial contractility. Positive pressure ventilation must be used carefully to avoid inducing pneumothorax, which may occur to the presence of bullous emphysema.

In women with MFS who are high risk on the basis of cardiac symptoms, an aortic root size >40mm, significant aortic valve disease, or the presence of aortic dissection, it is even more important to use invasive monitors and vasoactive infusions to minimise abrupt swings in BP. Perioperative use of beta-blockers is important to control heart rate and BP. The use of beta-agonists, vagolytics, and

ergometrine should be avoided because they may cause a rapid rise in CO and increase the risk of dissection. Atropine should be used carefully to treat bradycardia-induced hypotension. Vasodilators, e.g. nitroglycerine, should not be used as sole agents as the increased in left ventricular ejection velocity that they induce leads to stress on the aortic root. The concurrent use of labetalol and nitrate infusions is preferable when treating hypertension.

Other anaesthetic considerations in women with MFS include potential airway management problems secondary to high arched palate and the potential for cervical spine instability. Another concern is the potential for dural ectasia, which is the expansion of the dural sac surrounding the spinal cord and which may be symptomatic. Dural ectasia has been associated with failure of subarachnoid block for caesarean delivery in a number of case reports.

9. Cardiopulmonary resuscitation (CPR) during pregnancy

The commonest causes of maternal cardiac arrest are haemorrhage, cardiovascular diseases (including myocardial infarction, aortic dissection, and myocarditis), amniotic fluid embolism, sepsis, aspiration pneumonia, PE, and eclampsia. Important iatrogenic causes of maternal cardiac arrest include hypermagnesaemia from magnesium sulphate administration and anaesthetic complications.

The evidence regarding advanced treatment strategies for cardiac arrest in pregnancy is largely observational. The November 2015 ILCOR guidelines on advanced life support for adult cardiac arrest are applicable, with a few modifications in pregnant women.

The pregnant woman should be intubated promptly after the initiation of CPR, not only to facilitate oxygenation and ventilation but also to protect the airway from the aspiration of gastric contents. Bag-mask ventilation with 100% oxygen using good technique to prevent gastric insufflation is very important before intubation. Currently, ILCOR guidelines do not advocate the application of cricoid pressure before securing the maternal airway, as this technique is difficult to teach to lay rescuers and may result in difficulties with intubation.

Chest compressions should be performed slightly above the centre of the sternum to adjust for the elevation of the diaphragm.

Defibrillation should be applied at the recommended adult doses.

Patient position has emerged as an important strategy to improve the quality of CPR and resultant compression force and cardiac output. Aortocaval compression may significantly reduce venous return in the supine position and can occur for singleton pregnancies at approximately 20 weeks of gestation. Chest compressions in the left lateral tilt position result in less forceful compressions than are possible in the supine position. Manual left lateral uterine displacement (LUD) effectively relieves aortocaval pressure in patients with hypotension, and it is reasonable to try this technique first. If it fails, the use of a Cardiff wedge is advised. No cardiac arrest outcome studies have yet been published examining the effect of LUD or other strategies to relieve aortocaval compression during resuscitation.

Evacuation of the gravid uterus relieves aortocaval compression and may improve resuscitative efforts. In the latter half of pregnancy, perimortem caesarean delivery may be considered part of maternal resuscitation, regardless of fetal viability. Perimortem caesarean delivery should be considered at 4 minutes after onset of maternal cardiac arrest or resuscitative efforts (for the unwitnessed arrest) if there is no return of spontaneous circulation.

Recommended reading list

1. Chestnut D, Wong C, Tsen L, Ngan Kee W, Mhyre J, Beilin Y, Nathan N ed. Chestnut's Obstetric Anesthesia: Principles and Practice 5th edition. Elsevier 2014
2. Gambling, Douglas and McKay ed. Obstetric Anesthesia and Uncommon Disorders 2nd edition. Cambridge University Press 2011
3. Arendt K. Anesthesia for labor and delivery in high-risk heart disease: General Considerations UpToDate. Literature review current to April 2016
4. Wilson et al. Prevention of Infective Endocarditis: Guideline from the AHA. *Circulation*. 2007;116:1736-1754.
5. Nishimura et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease. *J Am Coll Cardiol*. 2014;63(22):2438-2488
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The Paediatric Patient with an Inhaled Foreign Body

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Foreign body (FB) aspiration is one of the leading causes of death in young children. During the 19th century, the treatment of FB aspiration by means of purges, bleeding, and emetics were largely ineffective. Mortality rates were estimated at 23%. This rate, however, plummeted with the development of bronchoscopic techniques. In 1897 Gustav Killian, a German ENT, performed the first bronchoscopy, using a rigid oesophagoscope to successfully remove a pig bone from a farmer's right main bronchus.

Despite an overall improvement in mortality with the discovery of new management techniques, FB retrievals are still high risk procedures. Most deaths occur at the time of aspiration due to complete upper airway obstruction. Of those children who reach hospital, the mortality is low; in fact, in many large case series in the 1990s, the in-hospital mortality has been reported as zero.² Despite this, significant perioperative morbidity and mortality can still occur and may potentially be reduced, prevented or anticipated with appropriate management and precautions.

Demographic profile

Age

1-3 years. Children of this age are prone to foreign body aspiration because they put objects in their mouths (particularly while running) and have less ability to chew food in the absence of molar teeth¹ □

Gender

Boys (60%) > Girls

Type of foreign body

Organic (80 %) usually food

- Nuts, especially peanuts are frequent offenders. Not only do they obstruct, peanut oil is an irritant, causing local mucosal oedema as well as reactive airways and a chemical pneumonitis.
- Seeds, other food particles³⁻⁶

Inorganic (20%)

- Corrosive: batteries that decompose to release battery acid, destroying surrounding tissues
- Non corrosive: metal, plastic knobs, bits of toys, stationary

Exceptions occur in Italy, with FB most frequently aspirated by boys found to be their own teeth; and Turkey, where adolescent girls represent the larger presenting population, aspirating headscarf pins!⁶

Where is it most likely to lodge?

- The majority of FB's get stuck in the main bronchial tree, accounting for 88% of cases. The right main bronchus is favoured as a result of its less acute anatomical angle.
- A less significant proportion of FB's become lodged in other parts of the airway.
- Laryngeal/ tracheal foreign bodies albeit rare (11%), have the highest mortality risk (45%) and many don't make it to hospital.
- Only 1% of foreign bodies become lodged in the lower distal airways.
- A small percentage of objects fragment (often organic) and lodge in multiple distal airways.

Patient presentation

The presentation of a child with an inhaled foreign body may vary from complete obstruction of the upper airway with hypoxia and cardiac arrest, to partial obstruction, presenting with coughing, wheezing, stridor and dyspnoea, or alternatively, the patient may be completely asymptomatic. Presentation and diagnosis within 24 hours of aspiration occurs in approximately 50 to 75% of cases. For simplification, presenting children may be divided into broad categories:

- **Longstanding FB (>24hrs):** FB is usually in bronchus or more distal airway. These patients are often mismanaged as asthma or pneumonia. They often develop secondary consequences of a longstanding inhaled foreign body, such as a chronic cough, wheeze, consolidation and infection distal to the obstruction. Child is usually un-distressed but may present as a LRTI.

- **Acute presentation (<24hrs):**
 - o **Un-distressed** child. Here parents usually suspect diagnosis, especially when a cough develops after a witnessed near choke. The child, while saturating well, may present with a wheeze and/or hyperinflation or collapse over the suspect area. Some present with normal chest examination despite a persistent cough. There is always the risk of FB dislodgement and these children may become distressed at some point, though there is usually time to optimise and investigate within reason. It is safe practice to admit to hospital for observation and optimization.
 - o **Acutely distressed** child with a partial obstruction. These children present in respiratory distress; wheezing, with stridor and tachypnoea, experiencing some degree of subcostal/intercostal recession, or tracheal tug. They may have consolidation, or hyperinflation with air trapping. This child needs definitive management as an emergency measure. These patients have insufficient time for optimal pre operative preparation.
- **Airway emergency:** Patient presents as acutely choking, often due to complete obstruction of trachea/larynx. Asphyxia is imminent, and immediate airway management is critical. Cricothyroidotomy may be lifesaving as a temporary measure. (Follow Guidelines: The Choking Child, BLS, APLS)

History and Examination

Presentation and diagnosis within 24 hours of aspiration occurs in approximately 50 -75% of cases. Up to 30% present more than a week later, as they are initially asymptomatic.

As this affliction often involves a patient group that is pre-verbal, the diagnosis is based on suspicion as a result of presenting features or parental concern. Aspiration witnessed by caregivers is more sensitive than specific and correlated data suggests good positive predictive values as opposes to negative.⁶ It may also provide clues as to the nature and location of the FB, and alert one to the probability of complications.

The presenting symptoms of foreign body aspiration may vary depending on its location, size, and chronicity. The child may be comfortable and in no apparent distress or may present in extremis with impending airway failure. Coughing, wheezing, shortness of breath, fever, and recurrent pneumonia may each be the presenting symptom.

Fidkowski, et al correlated data comparing the sensitivity and specificity of symptoms cough, dyspnea, wheeze, cyanosis and stridor. As a symptom, coughing is sensitive, but has a lower specificity, so may result in many false positive diagnosis, hence unneeded risk of bronchoscopy. Stridor, and cyanosis, while specific, has poor sensitivity, hence more false negative diagnosis, with dire consequences as result of missed FB aspirations. So one is unable to make a definitive diagnosis on symptomatology alone.⁶

At most, only one third of children with an aspirated FB have the *classic triad of cough, wheeze and decreased breath sounds*.

The longer the FB has been in place, the more likely this triad will be present and the more prominent the symptoms. Children with FB aspirations regularly present to hospital without symptoms, and have normal physical examinations.⁷

Signs such as cyanosis, stridor, severe intercostal/sternal recession or evidence of reduced conscious level are consistent with upper airway obstruction requiring emergency management.

A history of voice change or barking cough may indicate laryngeal oedema or upper airway foreign body obstruction.² A late presentation may well include signs of pneumonia, such as fever, cough, tachycardia, tachypnoea and focal chest signs.

Suggestive diagnostic features include but are not limited to:

Normal examinaion, mild subtle symptoms Parental suspicion Cough	Persistent cough, wheeze Hoarseness or voice changes Fever Aphonia Asphyxia, Cardiopulmonary arrest
Persistent cough, wheeze Hoarseness or voice changes Fever Aphonia, voice changes,	Haemoptysis, Wheezing Decreased breath sounds on the affected side Signs of air trapping Signs of atelectasis or consolidation, (pneumonia misdiagnosis)

What else could it be?

As mentioned, a persistent cough has been shown to have a sensitivity of 78% and specificity of 37%. Similarly, abnormal findings on auscultation had a sensitivity of 78% and specificity of 50%.⁸

No symptoms or clinical findings are 100% specific. Differential diagnoses must be considered such as

asthma, pneumothorax, croup or RTI's

When assessing the patient, ask four W questions as they determine management plans.
When, where, what, (w)variety?

When?

How long has it been between the aspiration and presentation? This may provide information regarding clinical features that one may expect to find.

Where is it likely to be located?

The position of a FB determines its potential for complete obstruction. A tracheal FB has a high risk of complete obstruction, a life threatening emergency as opposed to a FB lodged in the distal airway.

What?

What has the baby aspirated? Most events are unnoticed, though sometimes caregivers have suspicion. It's important to establish the nature of the FB, as this would determine possible complications e.g. corrosive batteries or irritant inducing peanuts.

Rotting organic matter compared to a smooth plastic object as opposed to a sharp pin create different concerns with regards to potential complications, surgical management and hence anaesthetic planning.

Identifying the object, provides clues whether the FB is radio opaque and would reveal itself on CXR

What (W)variety/ type of obstruction is present?

There are four main categories::

- o **Check valve:** FB allows air to be inhaled distally, but not to pass during exhalation, resulting in hyperinflation of the distal lobe, emphysema or worse, tension pneumothorax
- o **Ball valve:** Air can be exhaled but not inhaled, resulting in collapse of the broncho pulmonary segment beyond the FB
- o **Bypass Valve:** FB partially obstructs inspiration and exhalation. This may initially result in an expiratory wheeze, then inspiratory and expiratory, as local oedema develops. (Exhalation impeded at first with intra thoracic obstruction as the intra thoracic airway narrows during exhalation in spontaneous ventilation.)
- o **Stop valve:** Complete obstruction, with resultant collapse and consolidation of distal lobe.

Special investigations

Chest X-Ray

Most FB's are radiolucent. Opaque FB's occur only in 10-25% of cases.

Within 24 hours of aspiration, CXR's are often normal, as opposed to CXR>24 hours after aspiration, where 33% of films are reported as abnormal as a consequence of secondary changes occurring in the lung.

Secondary changes presenting as radiological findings include:

Midline shift Atelectasis Lobar collapse Consolidation	Air trapping Pneumothorax/tension (rare) Emphysematous changes

X-rays must include views of the *entire neck*. *AP and lateral views* essential for FB location

AP alignment of flat objects suggests oesophageal FB, as opposed to sagittal alignments, more common to tracheal FB. FB's that transgress the borders of normal airway anatomy shadows are most likely not in the airway.

Lateral views are useful to indicate soft tissue swelling of neck

Inspiratory and expiratory views are useful to indicate air trapping when suspecting a check valve effect.

Lateral decubitus views may be an alternative to inspiratory and expiratory views, if the child is unable to co-operate.

Fluoroscopy

Offers a dynamic, real-time view of respiratory system. Findings suggestive of a FB include intra-luminal narrowing as well as midline shift if air trapping is present. Currently fluoroscopy is not sensitive or specific enough for routine use in establishing a diagnosis.

CT and virtual Bronchoscopy

CT and virtual bronchoscopy are more sensitive diagnostic modalities for FB aspiration as compared to chest radiography.

In prospective studies, all cases of FB aspiration were correctly identified by CT. Due to the accuracy and no false negative findings on CT, authors suggested that a negative CT did not warrant a follow up rigid bronchoscopy examination.¹²

The presence of secretions or airway tumours may, however, provide false positive findings.

Limitations of CT such as expense and radiation exposure need to be weighed against the gains of being able to assess the nature and exact location of the FB, as well as airway changes such as oedema, and bronchiectasis, thereby facilitating adequate surgical planning.

Flexible bronchoscopy

Results are comparable to CT for diagnosis of FB.

Prospective trials have been conducted with the use of flexi scope as a diagnostic tool in cases where there is no clear aspiration history and negative clinical findings. Authors suggested children only receive a rigid bronchoscopy if they have acute asphyxiation, a radio opaque foreign body, unilateral pulmonary signs or obstructive emphysema. All other children received a flexible scope examination.

When this algorithm was applied, it was found to reduce the rate of negative findings on rigid bronchoscopy, thereby reducing the exposure of patients to the unneeded risk of rigid bronchoscopy.^{11,13} Kadmon et al¹⁴ proposed a computer model based on history, physical examination, and radiographic findings to calculate a score predicting the likelihood of FB aspiration in children. They further suggested an algorithm to observe a child, perform diagnostic flexible bronchoscopy, or perform therapeutic rigid bronchoscopy on the basis of the calculated score. A prospective study is still required to determine the usefulness of this model.

In addition to aiding in the diagnosis of aspirated FB's, flexible bronchoscopy is becoming more popular for the removal of FB's.

Flexible bronchoscopy does still require sedation/general anaesthesia in the paediatric population. (unlike adults). It is better suited for the removal of tiny FB located distally or in upper lobes, hence providing access where the rigid scope does not. Surgeons are also less likely to favour flexi scopes over rigid bronchoscopes, as grasping tools are less available for flexi scopes, and surgeons feel they have less control with the flexible scope, finding it clumsy to handle, making it more likely to drop the FB.

Rigid Bronchoscopy

The gold standard for both diagnosis and management, it continues to be the favoured diagnostic and therapeutic modality to retrieve aspirated FB's. Most surgeons are familiar with its use and extraction instruments are widely available. It provides good visualization, a means to control the airway, and allows for both spontaneous and assisted ventilation. But it's not without its share of complications. It requires a deeply anaesthetised immobile patient, as coughing and movement may result in severe injuries, including tracheal rupture.

Pre-operative management

Should the case be done in the middle of the night or wait for the next morning?

Timing depends on the patient's airway patency. In the case of an distressed or imminently obstructing child, one should not delay urgent bronchoscopy. If the child is already apnoeic, emergency resuscitative efforts are employed immediately.

In stable patients, retrospective reviews conclude no increase in poor outcome when delayed to the next morning, ensuring optimal conditions and experienced surgical and anaesthetic teams. Medical personnel experience and familiarity has been linked to outcome.²⁴

To date, no clear guideline exists for stable patients. This decision best made based on departmental practice, bearing in mind that operator experience does influence successful outcome.

Last meal

Establishing the timing of the last meal is important to minimise aspiration risk. No reports of gastric aspiration were noted in literature.

In acutely urgent cases, the danger of delayed removal FB outweighs the aspiration risk in a well-conducted anaesthetic. Literature suggests gastric content is drained via NGT, post induction, but before bronchoscopy, to minimize aspiration. In delayed presentations, or the stable unobstructed child, one may delay for the patient to be NPO as appropriate, with admission to hospital for close observation.

Premedication

Routine sedative premedication is generally avoided, due to the potential risks of over-sedation and airway loss, as well as a paradoxical response to sedation, resulting in an agitated child with resultant respiratory compromise.

Anticholinergic

Initially routinely used as a means to decrease secretions, as well as decrease the severity of the vagally mediated bradycardia induced by bronchoscopy. While utilized by our predecessors in the times of halothane, it is less popular as routine administration at present with the advent of sevoflurane.

IV access established preoperatively or post induction?

Where possible, EMLA and IV establishment pre operatively, if well tolerated, would be ideal. The benefit of preoperative IV access must be weighted against the risk of patient distress and so, compromising the airway. Many prefer to establish IV access post induction.⁶

Intra operative considerations for rigid bronchoscopy

Since FB retrievals involve a shared airway, it is essential that there is good, clear communication, and that the anaesthetic and surgical plan is thoroughly discussed and agreed on ahead of time. In addition to an ENT surgeon, one may consider consultation with a cardiothoracic (FB below T4 level) or general surgeon depending on location of the FB and the severity of the obstruction.⁶

Main anaesthetic considerations for bronchoscopy:

- An immobile, anaesthetised patient despite intense airway stimulation,
- Adequate oxygenation and ventilation of patient,
- Optimal surgical exposure despite a shared airway.

Current debates in anaesthetic practice relate predominantly as to whether to:

- Administer an IV or gas induction
- Electively establish controlled IPPV or allow spontaneous respiration
- Maintain anaesthesia with volatiles or administer TIVA

Gas vs. IV induction

This remains a controversial debate. While both are successful, no randomized trials have been conducted comparing their rates of complication and safety. The choice is essentially governed by the *concern of causing deterioration of a partial proximal obstruction to a complete tracheal or a complicated distal one, where the FB is difficult to retrieve*. When there is a progression from SV to PPV, the likelihood of dislodgement increases. Since IV induction is associated with greater chance loss of SV and the need for PPV, there is a greater theoretical risk of FB dislodgement. The likelihood of this occurrence in practice is rare, and cautious IV induction while maintaining SV is possible, but quite challenging for most anaesthetists.

Advantages of gas induction:

- o Not needing to establish IV access in an awake child
- o Less likelihood of loss of spontaneous ventilation
- o Better haemodynamic stability and ability to titrate to effect with easier reversibility
- o Compensation for leak around bronchoscope in trachea

Disadvantage

- o Induction takes longer and is less predictable.
- o Anaesthetic depth less predictable

Recommendations

- Current practice recommendations suggest inhalational induction, maintaining SV
- Avoid nitrous oxide, as a precaution in case of air trapping
- Liberal administration of lignocaine spray to topicalize the airway, vocal cords and trachea to reduce reflex responses and cardiovascular stimulation of bronchoscopy.

Spontaneous vs. Positive Pressure Ventilation

There is currently NO evidence to suggest one technique is superior to the other. Both have been used with success, with no significant impact on outcomes. As mentioned above, PPV is associated with concerns relating to *FB dislodgement*. Other reasons for maintaining SV include the concern of *air trapping* in the case of a check valve type obstruction, as well as *not being able to ventilate adequately* if there is a *leak around the scope*, as occurs with *proximal foreign bodies in the trachea*. In practice, most use PPV intermittently to assist the patient manually when required.

Some degree of manual PPV is required in order to achieve the depth of anaesthesia required for safe bronchoscopy. Inadequate anaesthesia increases the chance of patient movement, coughing and straining, and so increases the risk for tracheal injury. Despite this, intentional, pre-planned IPPV has yet to be addressed in clinical trials with regards to its outcomes.

Spontaneous ventilation	Positive pressure ventilation
<u>Advantages</u> - Continued oxygenation/ventilation despite interruptions with the breathing circuit. - In theory less likely to push FB deeper into airway, less likely to trap air distal to FB if check valve obstruction present.	<u>Advantages</u> - Rapid achievement of anaesthetic depth required for RFB, esp. with TIVA or IV induction. - The reported rate at which practitioners converted from SV to IPPV implied that it's more reliable to achieve.
<u>Disadvantages</u> - Increased airway resistance and work of breathing through bronchoscope. - Difficulty achieving deep plane anaesthesia- hence more coughing, movement. - Often there is an air leak around bronchoscope, challenging the capacity for controlled PPV, with proximal FB. SV compensates for this.	<u>Disadvantages</u> - Difficult to ventilate adequately patient with proximal FB due to leaks around bronchoscope. - Concerns relating to dislodgement of FB, either resulting in more distal migration, complicating retrieval; or worse, resulting in a partial obstruction becoming a total proximal occlusion. - These occurrences however are rare and over stated, most FBs are firmly lodged and hence unlikely to change position.

Intra-operative management

Muscle Relaxation

Few anaesthetists are prepared to commit to the routine administration of muscle relaxation, (and so PPV) despite this being the best predictor of patient immobility.

Instead, most admit to administering an "as required" dose of muscle relaxant, most commonly Suxamethonium, as a last resort when all other measures are inadequate.

Spontaneous ventilation during proximal FB retrievals is favoured as PPV in a paralysed patient may be ineffective due to air leaking around scope with resultant inadequate ventilation.

Closing the mouth and nose may assist in creating a seal for PPV, but as this manoeuvre disrupts surgical access, it's mainly used as a rescue strategy.

Steroids

Dexamethasone is administered by most (doses 0.15mg/kg to 0.25mg/kg), in effort to reduce postoperative laryngeal oedema following instrumentation. It also has benefits as an adjunct in prevention of PONV. Additional PONV prophylaxis advised.

Antibiotic prophylaxis

No routine administration, but decided upon on a case-by case-basis upon discussion with surgeon.

Physiotherapy

Albeit used in the past, it is strongly advised against as it may dislodge FB.

Manual jet ventilation

Useful when patient is rendered apnoeic and one is unable to ventilate adequately via bronchoscope side port.

Manual jet ventilation may occur via bronchoscope side port or by use of a separate tracheal catheter. Despite trial findings of less hypoxia with MJV as compared to T-Piece ventilation via side port, most consider this a rescue measure, warning *against its routine use in paediatrics, due to the risks of barotrauma*.

Lignocaine Spray

Once an adequate anaesthetic depth is achieved, (using eye signs, respiration pattern and abdominal wall tone), the cords and upper trachea are sprayed under direct laryngoscopy with 3mg/kg lignocaine.

Dense airway topicalization decreases the irritant effects of bronchoscopy. Some authors suggest coating the rigid scope with remicaine gel, though this has yet to be validated.

Volatile vs. TIVA as maintenance of anaesthesia

Debates regarding best anaesthetic maintenance technique, whether volatile or TIVA or some combination of the two, as well as which agents are preferred, are inexhaustible. Decisions are closely related to the pathology present, the patient baseline, as well as the experience and expertise of the practitioner and facilities available.

Volatiles

Most practitioners sensibly prefer to use volatiles suitable for induction, for maintenance as well. Given the fluctuating nature of anaesthesia for bronchoscopy, one is unable to guarantee sufficient depth of anaesthesia such that the patient will not cough and spasm when exposed to irritant agents like Isoflurane.

Historically, *Halothane* was considered the agent of choice, enabling a deep plane of anaesthesia while maintaining SV. The downfall, was its propensity for arrhythmias, more so in the face of hypercapnoea, (common with bronchoscopy given the inadequacy of ventilation that may occur), as well as bradycardias, worsened by vagal stimulation by bronchoscopic examination.

Sevoflurane was shown to be as effective an agent in providing anaesthetic depth with maintenance of SV, sans the arrhythmogenic, and bradycardic potential. Due to its insolubility it also resulted in a rapid induction, but also wake up, both at the end and during (unfortunately) the procedure; a result of interruptions in ventilation common to rigid bronchoscopy. (fluctuations in depth of anaesthesia). Sevoflurane also increases the incidence of emergence delirium when used as a sole agent. Despite this, it is currently the preferred volatile.

TIVA

TIVA offers the advantage of having adequate control over anaesthetic depth regardless of the mode of ventilation. There is less pollution of the theatre environment It MAY also offer better haemodynamic stability during scope insertion, and ensure an immobile patient even with interruptions in ventilation. Chen et al showed that a TIVA technique with spontaneous ventilation had a higher incidence of body movement, breath-holding, and laryngospasm in comparison with an inhaled technique. However the doses used in their trial were much less than other studies showing preference for TIVA .

Success is dependant of finding the correct drug dose for a particular patient and an anaesthetist who is comfortable with TIVA/TCI practice in paediatrics, as well as familiar with his choice of drug/ drug combination. Most trials administered TIVA with Propofol (200 to 400µg/kg/min) and Remifentanil (0.05 to 0.2µg/kg/min) infusions in combination with vocal cord topicalization. They managed to maintain SV, sometimes requiring intermittent manual positive pressure assistance.

A multitude of drug combinations, in a variety of suitable dose suggestions have been successfully described, with no one technique superior to the other. A combination of volatile and IV drugs as titrated boluses as well as continuous infusions have also offered successful endpoints.

Some common practices include:

- Traditional TIVA, consisting of a Remifentanil and Propofol combination
- Some advocate Sevoflurane with low dose Remifentanil infusions in the range of 0.05-0.15µg/kg/min with or without Propofol titrations/bolus to augment deeper anaesthesia.
- Newer combinations deserving a mention include Dexmedetomidine.

Dexmedetomidine

Ultra selective α_2 agonist, offering excellent sedation, and analgesia and no respiratory depression. Despite its wide spread use in adults, its only recently found a niche in paediatrics, currently gaining popularity for paediatric procedural sedation (MRI), also an adjunct, decreasing doses of opiates and traditional agents required for anaesthesia and sedation, as well as in prevention and management of emergence delirium. Given its preservation of respiratory integrity, it may be useful as an adjunct in the child with a compromised airway- when used appropriately, with caution!

Most practitioners have had concerns about the risk of haemodynamic instability i.e. bradycardia and hypotension. (Careful titration as well as suitable patient selection minimize the frequency of this side effect.) The exciting advancements of the uses and caveats of Dexmedetomidine in paediatric practice are beyond the scope of this note. Of more relevance, its use in paediatric endoscopic procedures is still in its infancy, and so further trials are still necessary.

Small trials found the low dose combination of Dexmedetomidine and Propofol (not for foreign body retrieval exclusively) offered advantages over Propofol-Remifentanil, such as:

- Maintenance of spontaneous breathing while providing adequate surgical plane
- Maintenance of airway dynamics. (Both a key component of airway surgeries)
- Minimal desaturation due to airway mishaps
- Minimal unwanted movements causing interruption of surgery
- Stable hemodynamics, opposed to Remifentanyl or Propofol
- Opioid sparing effect

Chen K, et al also published a small case report consisting of three children and two elderly patients, using a Dexmedetomidine-Propofol combination for FB retrieval. They found adjunct use of Dexmedetomidine provided good levels of anaesthesia, without respiratory depression. While the drug was well tolerated haemodynamically in paediatrics, elderly patients experienced instability.

The same group also compared the use of Dexmedetomidine-Propofol (DP) to Remifentanyl-Propofol (RP) TIVA with a spontaneous breathing technique, for FB removal in 77 children. They concluded that *DP TIVA provided more stable respiratory and haemodynamic parameters, but required a longer recovery time.* RP TIVA was associated with a lower respiratory rate as well as a marginally higher end tidal CO₂ at the end of the procedure. Perioperative haemodynamics being more stable in the DP group. The rate of breath holding between the two groups was comparable, while the incidence of coughing in PACU higher in the DP group. More trials were indicated.

Suma Mary Thampi et al describe a small group of case reports, in which they used a combination of Dexmedetomidine and Propofol for tubeless endoscopic surgical procedures (not only FB retrieval), and also describe similar outcomes. The only drawback listed is that as a sole agent, the doses of Dexmedetomidine required for good operating conditions resulted in significantly longer wake up times as compared to drugs traditionally used for TIVA.

Additional Considerations

When the FB is within the surgeons grasp, particularly as it is retrieved through the vocal cords, it is critical to maintain anaesthetic depth. Ideally one would prefer to momentarily arrest vocal cord movement at this moment. This may be achieved by administration of a small bolus of Propofol. After the extraction of the FB and the removal of the rigid bronchoscope, one may consider decompression of the stomach, via NGT. Gaseous gastric distention may occur intraoperatively, may impede efficient diaphragmatic excursion, impairing breathing, and increases possibility of PONV. The choice of ventilation during emergence is influenced by pulmonary gas exchange and the degree of airway oedema. For uncomplicated cases, spontaneous ventilation assisted by mask ventilation as needed may suffice. Intubation post-procedure may be indicated for a compromised airway, pulmonary complications or residual neuromuscular blockade if administered.

Perioperative Complications

Acute

- Relating to patient injury as result of bronchoscope insertion
- Inability to oxygenate or ventilate
- Aspiration

Longer term

- Airway compromise as result of subsequent tissue oedema
- Missed injury
- Infection
- Complications due to nature of foreign body (battery corrosion) or as a consequence of longstanding history (bronchiectasis).

Dropping the foreign body during retrieval is a potentially life-threatening complication. The FB may become snagged and dislodged at the cords/larynx, causing severe or complete airway obstruction. Due to bronchial oedema of the affected side, the object may fall into the 'good' lung, so compromising gas exchange. If the object becomes lodged in the trachea, the FB needs to be retrieved rapidly. If this is not possible and severe desaturation occurs, the FB may need to be pushed down one bronchus to allow some gas exchange. In attempt to lessen the incidence of dropping the FB, try to ensure vocal cord relaxation prior to retrieval by increasing anaesthetic depth, supplemental topicalization, or paralysis as previously mentioned.

The risk of adverse events (desaturation, haemorrhage, laryngospasm, pneumothorax) following surgery was 9.5% in a recent study, but if the patients were symptomatic preoperatively the rate was nearly four times higher (36.5%).

Potential complications to consider include:

Airway

Laryngeal Oedema (2° to FB or instrumentation), laryngospasm. Complete airway obstruction (2° to dislodged FB during coughing or removal). Failure to remove object, dropping the FB, tracheal/bronchial laceration, rupture. Injury of oral cavity, teeth, mucosa with the bronchoscope.

Breathing

Hypoxia/bronchospasm/hypercarbia. Coughing, regurgitation and aspiration of gastric contents
Pneumothorax

Pneumonia, soiling of the healthy lung, bleeding

Circulation

Cardiac dysrhythmias, bradycardias. Cardiac arrest

Neurological

Convulsions (due to hypoxia/hypercarbia)

Other

Cardiorespiratory arrest and death

Early discharge after uncomplicated bronchoscopy is desirable. In one study, 65% of children were discharged home within four hours after rigid bronchoscopy. In another study, 60.7% children had a hospital stay less than one day.

Prolonged pulmonary recovery may prevent early discharge.

Factors Predicting Prolonged Recovery

- Evidence of inflammation on preoperative radiographs,
- Aggravation of pulmonary lesions on postoperative films, and
- Prolonged duration of bronchoscopy. Ciftci et al found bronchoscopy time to be prolonged in children with postoperative complications in comparison with those without
- Chen et al found that postoperative hypoxemia was associated with prolonged emergence from anaesthesia and with foreign bodies that were plant seeds.

Postoperative placement should hence be evaluated on a case-by-case basis, taking the patient's pre operative state, intra operative complications, surgeon's preferences, as well as hospitals capacity to offer adequate monitoring post operatively.

Summary

- Inhaled FB cause significant morbidity and mortality. Expertise of personnel, clear clinical plans and familiarity with equipment is essential for optimal outcome. Communicate.
- A high index of clinical suspicion is required in those without obvious diagnosis.
- Ask about the four W's
- Clinical symptoms and physical examination are insufficient to exclude the diagnosis.
- A normal CXR does not exclude FB.
- Do not delay lifesaving bronchoscopy in the distressed child, regardless of NPO status or investigations.
- No sedative premed. Don't agitate the child unnecessarily. Aim for calm and smooth induction
- Gas inductions are still induction of choice. Avoid N₂O.
- Maintaining spontaneous ventilation as far as possible, especially with proximal FB's.
- Keep the child deeply anaesthetised, but ensure adequate oxygenation and ventilation.
- The best means to ensure this varies between practitioners and institutions.
- A spontaneous breathing technique with intravenous opioid infusions (Remifentanyl) and anesthetic agent supplementation (Propofol) is currently favoured by many. As is TIVA - if knowledgeable. Dexmedetomidine is rapidly gaining popularity.
- SV patients often require intermittent assisted ventilation to manage atelectasis, hypoventilation.
- DO topicalize the airway liberally with lignocaine.
- DO administer dexamethasone
- DO decompress the stomach at the end if needed
- Extraction of the FB is a dangerous part of the procedure, and can precipitate complete obstruction. DO ensure vocal cords are adequately relaxed at this time.
- Assess for, and consider complications.

Useful Reading

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Managing the complications of neuraxial anaesthesia:

The “big short” of it all

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“An ounce of prevention is worth a pound of cure.”

Benjamin Franklin

Prevention is better than cure...but sometimes cause may be unavoidable. This lecture attempts to emphasize our role in the reduction of complications associated with neuraxial anaesthesia and analgesia, who to be aware of (patient profile), as well as how to manage some of the rare (and more common) complications of regional anaesthesia.

Almost all operations below the neck **could** be performed under neuraxial anaesthesia. This is, however, not practical...nor safe...in some circumstances. Neuraxial blockade has been shown to be a safe means of anaesthesia – when managed well! There is little agreement in the literature regarding the management of these myriad of disorders, and much decision-making is left up to opinion (this is especially true of the “catastrophic”, rare complications). These need to be identified early, and can thus reduce the potentially life-changing complications. This is an attempt to find some consensus, and provide at least a guide from the literature – and current, “routine” practice.

Healthcare practitioners need to develop good and safe techniques, as well as expertise, in placing and managing neuraxial regional anaesthesia. This attempts to reduce the risk of complications – dural puncture, infections, direct spinal cord damage.

Concerns regarding consent for all procedures has occupied thoughts of several parties – patients, medical practitioners, lawyers, academics, health councils. We are often unaware of the relative incidence of the well-known complications, and struggle to put this into terms that the patient can grasp. There is controversy with regards to the more common complications. In academic practice we generally disclose the common, more benign risks¹⁴...and possibly brush over the ones that are exceedingly rare (and could cause permanent damage).

Most of anaesthetic practice revolves around risk:benefit assessments. I propose that we should

$\frac{\text{Complication}}{\text{Number of blocks}} : \text{Benefit} : \text{Block Success Rate}$

evaluate every patient for a regional, neuraxial block as follows:

We need to know what the risk is associated with the procedure being performed (although these numbers are still unclear for some of the – thankfully – rarer complications), and convey what the benefit of the block would be to that *particular* patient. Finally, we need to not shy away from the potential for block failure (remember that the inherent risk of the procedure is not necessarily diminished with a failed block, and now the patient has not gained the known benefit).⁹

Due to the most obvious, immediate complications possible with the placement of neuraxial anaesthesia, these blocks should only be performed in a patient with routine ASA monitoring in-situ by a healthcare professional versed in handling airway and cardiovascular collapse (cardiopulmonary resuscitation). These complications do not **only** take place with more junior anaesthetists: NONE are immune to these potential disasters.

Definitions

Neuraxial anaesthesia:

This is a form of central regional anaesthesia inducing numbness in the distribution of injection (extensive). It is predominantly in the region around the abdomen, and can extend down to the toes. It may occur in the epidural (nerve roots) or subdural (peri-spinal) spaces.

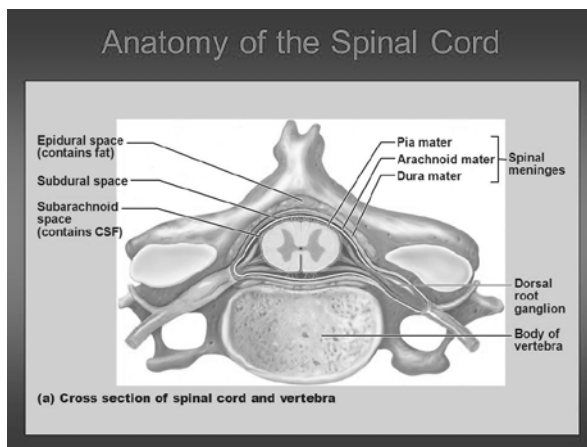
The injection is performed under local anaesthesia and sometimes with intravenous sedation. Patients experience little or no discomfort with this technique.

Epidural:

Either performed as a sole procedure (for analgesia, or anaesthesia); or it is used in combination with spinal or general anaesthesia. There is a wider application than the “one-hit” spinal anaesthetic. The epidural space runs from the foramen magnum (cephalad) to the sacrococcygeal membrane (caudad). The ligamentum flavum heralds the commencement of the epidural space. It is the fatty tissue in this region with nerves, blood vessels, lymphatics tracing through the course of it.

The epidural space was first used for anaesthesia and analgesia in 1885 (described by Dr. James Leonard Corning), and a catheter inserted into the epidural space in 1947 by the Cuban Dr. Manual Curbelo. Epidural anaesthesia can be secured throughout the length of the vertebral column, and can be accessed by any of midline, paravertebral or trans-foraminal approaches.

Epidural injections (with or without catheter placement) are used for a myriad of surgical and pain (acute and chronic) interventions. It has even been promoted for the use in sympathetically-mediated disorders.



*THE CENTRAL NERVOUS SYSTEM Human
Anatomy Sonya Schuh-Huerta, Ph.D.*

Subdural space:

This is a potential space, which may be opened by the separation of the arachnoid mater from the Dura mater. Its presence was discovered on cadaveric examinations.

Vertebral/ spinal canal:

This is the space in the vertebrae, through which the spinal cord traverses. The canal is enclosed within the vertebral foramen of the vertebrae.

Intrathecal Injection

Drugs are administered via the spinal canal, or into the subarachnoid space, so that they rapidly (immediately) reach the cerebrospinal fluid (CSF). It is indicated in neuraxial anaesthesia, chemotherapy and pain management. Drugs are administered in this way to avoid the blood-brain-barrier, and thus have direct action.

Haematoma:

A localized swelling filled with blood, usually the result of a damaged vessel wall. This can be induced by trauma (including iatrogenic), or spontaneous.

Spinal subdural or epidural hematoma occurs in the subdural or epidural space, resulting in mechanical compression of the spinal cord.

Abscess:

An abscess is a localized collection of pus in the tissues of the body. It is most likely the result of bacterial infection. Source control and drainage is the definitive means of management.

Meningitis:

This is an inflammatory process involving the meninges, caused by a multitude of antimicrobials and

inflammatory processes. The patients classically present with severe headache, fever, photophobia and muscles rigidity. It can dramatically progress to seizures, confusion, delirium and death of the patient.

Hypotension:

Hypotension is generally defined as a systolic blood pressure of < 90 mm Hg, and a diastolic blood pressure of < 60 mm Hg. Hypotension is usually only deemed to be a problem if symptom exist (i.e. if features of diminished organ perfusion are prevalent). Under anaesthesia this is usually decided at 10 – 20 % reduction from the baseline blood pressure. The flow to vital organs varies between patients, with auto-regulation normally having a key role in perfusion to the brain, heart and kidneys. Tissue perfusion is not directly correlated with blood pressure, except in severe disease states; this is often associated with a concomitant reduction in the cardiac output.

Informed Consent⁶:

This is an ethical and legal process whereby we (healthcare providers) obtain patients' permission for medical procedures/ interventions. It involves key constituents whereby an assessment of the patient's competence for understanding and decision-making (as well as voluntary nature) is evaluated. Information regarding risks and benefits is then conveyed, including your plan for intervention. The patient is then given the opportunity to address and concerns, or seek clarity; at this point the decision and authorization for the process is granted.

In the lecture we will evaluate the current state of consent for neuraxial anaesthesia and analgesia (the role we do, and SHOULD play), as well as how to formulate your own consent document.

Complications – Overview

Epidural placement in the thoracic spine is perceived to be more hazardous than lumbar epidural. The incidence of complications, however, is still seen to be exceedingly rare. There is difficulty performing large randomized, control, prospective trials in these situations – especially when looking for such infrequent complications. It is further worth noting that although it is tempting to analyze and compare subgroups, different approaches to the neuraxial region (spinal, epidural, caudal) convey differing risks and the patient population risks could also be major contributing factors.⁴

We readily disclose the complications which occur commonly (and are more benign/ easier to manage) – hypotension, perhaps a “patchy block”, nausea, pruritis. There seems to be a lack of information regarding the rare, more catastrophic complications. This is probably multi-factorial: registrar wants to gain necessary experience, they happen so infrequently, we are unsure of the relative risk...so we do not garner the information, the complications sound terrible so it is better to not “frighten” patients, possible language/ cultural/ communication breakdowns.

The overall incidence of complications (major and minor) is approximately 3 %¹⁰.

- A. Inappropriate drug responses
- B. Dural disruption
- C. Nerve injury
- D. Infection
- E. Bleeding

A. Inappropriate Drug Responses

1) “High Spinal”: Complete Spinal Blockade

Definition: This is essentially total anaesthesia of the spinal cord to levels higher than what would be expected from conventional neuraxial anaesthesia (on a spectrum from high to total spinal cord blockade up to the level of the brainstem).

Aetiology/ risks:

Risk	Explanation
Obesity and pregnancy	Favours cephalad spread of local anaesthetic
Fluid in epidural space (infusion)	Compresses subarachnoid space – meant for epidural
Nature of local anaesthetic	Dose, volume, baricity

Incidence: Unknown, but this has been referred to as the most concerning complication for spinal anaesthesia. (15 causes of maternal death or hypoxia in 2009 ASA closed claims procedures were as a result of high spinal! This is CONCERNING)²

Clinical presentation²:

Signs and symptoms usually manifest soon after injection of the local anaesthetic.

- Massive sympathectomy that results in a severe hypotension;
- Block of the cardiac accelerator fibers (T1 to T4), inhibiting compensatory tachycardia;
- Brainstem hypo-perfusion: respiratory depression, and nausea;
- Loss of control of respiratory accessory muscles (intercostal, abdominal);
- Complete diaphragmatic paralysis if the C3 to C5 roots are blocked;
- Aspiration of gastric contents due to loss of consciousness and compromise of airway reflexes

Diagnosis: It is critical to note that this is a clinical diagnosis, requiring immediate attention and supportive intervention.

Differential Diagnosis of Complete Spinal Block²		
Drug overdose	Respiratory depression	Hypotension
Anxiety/ panic attack	Pulmonary embolus	Vascular injection of local
Seizures	Pulmonary oedema	anaesthesia
	Amniotic fluid embolism	Hypoglycaemia

Management: Supportive, and full ACLS guidelines (as required).

Early recognition may stave off the full development to cardiac and respiratory arrest.

- Place the patient in the reverse Trendelenberg position (thus promoting caudad spread)
- Manage hypotension aggressively: fluids and vasopressors as appropriate
- Initiation of necessary ventilator support

2) Unintentional Subdural Injection

Definition: The spinal subdural space is a potential space, or a region of iatrogenic dissection of the dural membranes. It is most likely as a result of a malpositioned catheter (epidural)

Aetiology: Subdural injection may occur with spinal anaesthetic (i.e. incorrect deposition of the anaesthesia into the subdural space...and not the intrathecal space). This is less likely to cause any major problems, except "block failure".

Epidural catheter may be causative of unintentional subdural injection. It is most likely attributed to technical difficulty:

- multiple attempts at catheter placement
- needle twisting before catheter insertion (sheering of Dural layers)

This is hence associated with catheter placement into the **subdural**, and not epidural space. This can have catastrophic consequences.

Clinical presentation^{2,5}:

- Excessive sensory blockade – usually slow onset
- Potentially unilateral blockade
- Sympatholysis not in keeping with local anaesthetic dose delivered
- Variable motor blockade
- Respiratory distress
- Cardiac arrest

Diagnosis: High index of suspicion. The most important feature is often a bizarre cluster of signs and symptoms.

e.g. slow onset, very narrow block distribution in the presence of a life-threatening hypotension. This coupled with motor sparing may be very indicative of subdural catheter placement.

Radiological investigation:

- Plain films – antero-posterior, and lateral
- Fluoroscopy
- CT epidurography

Management: Supportive, and full ACLS guidelines (as required).

There are no reports in the literature of associated mortality associated with this...but this is most likely due to meticulous, and rapid assessment and intervention.

3) **Hypotension**

Four questions need to be asked of every patient receiving neuraxial anaesthesia:

- Will I pre-/ co-load the patient?
- Which fluid will I administer?
- What volume of fluid will I administer?
- What will my vasopressor strategy be?

Incidence: The incidence ranges from 25 – 75 % (higher in caesarean section), with a 20% reduction in blood pressure as a result.

Pathophysiology: Hypotension is most likely due to pharmacological sympathectomy. This results in peripheral vasodilatation and venous blood pooling; the result is a reduced venous return (to right side of heart), and thus a resultant reduction in cardiac output.

Pregnancy (caesarean sections) may have higher susceptibility to these changes: T4 level of block required for surgery, physiological changes of pregnancy, increased endothelium-derived vasodilators.

A summary table of fluids administered to rectify a re-distribution of intravascular volume following neuraxial anaesthesia: ¹⁰

	Preload	Co-load
Crystalloid	X	✓
Colloid	✓	⚡

This is a controversy that still rages. Literature suggests that a colloid preload, or crystalloid co-load (of 20ml/kg in divided doses) is recommended to best overcome the sympathectomy of the spinal anaesthesia.

Pre-load is defined as: 10 – 20 ml/kg fluid administration within the 20 minutes preceding the administration of neuraxial anaesthesia.

Co-load is defined by: rapid administration of intravenous fluids immediately following spinal injection (i.e. fluid bolus completed within 5 minutes of neuraxial anaesthesia).

Management of the hypotension is with fluid and vasopressor therapy administered timeously. There is no proven prophylactic intervention that fully reduces the need for vasopressors in many cases.²⁴ Significant amounts of time should not be spent on delivering a preload prior to an emergency neuraxial anaesthetic technique, as preload has not been shown to be superior to co-load of fluid.

B. Dural Disruption

1) Post-Dural Puncture Headache (PDPH)

This is merely a summary of this disorder for rapid-fire review.
(A very complete and excellent resource is from Dr. F. Roodt²²)

Definition:

It is a leak of CSF through a Dural hole, causing traction on the meninges and meningeal vessels.
This is associated with a resultant intracranial hypotension.

Diagnostic criteria (International Headache Society):

A. Headache that worsens within 15 minutes after sitting or standing and improves within 15 minutes after lying, with at least one of the following and fulfilling criteria C and D:

Neck stiffness	Photophobia
Tinnitus	Nausea
Hypocausia (impaired hearing)	

B Dural puncture has been performed

C Headache develops **within 5 days** after Dural puncture

D Headache resolves either:

- spontaneously within 1 week
- within 48 hours after effective treatment of the spinal fluid leak (usually by epidural blood patch)

Note:

In 95% of cases relief is rapid. When headache persists, causation is in doubt.

Aetiology/ Incidence:

Spinal anaesthesia: 1.5 – 11.2 %

Epidural: 1 % will have Dural puncture, BUT 45 – 80 % risk of PDPH!
associated with a resultant intracranial hypotension.

Risk Factors

Technical	Patient
➤ Bigger needle size	➤ < 45 years old
➤ Type of spinal needle (Quinke > pencil-point needle)	➤ Pregnant (↑↑ risk)

Signs and Symptoms

Patients report frontal/ occipital headaches as well as neck stiffness in a large percentage of patients. Symptoms are often worse on sitting or standing (vs. supine). 1/5 of patients will express ocular or auditory symptoms.

Management Overview

Conservative: Rest (recumbent), analgesics (basic up to Sumatriptan if severe, migraine-like)

Invasive: Epidural blood patch, with sterile autologous blood transfusion ± 15 – 20 ml blood performed 1 – 2 spaces below original epidural site (can be repeated up to 3 times, recommended > 24 hours apart)

2) Pneumocephalus

Definition: VERY rare complication resulting in air entering the intracranial cavity, secondary to placement of neuraxial block.

Aetiology: loss-of-resistance to air may cause tracking into the intra-parenchymal, subarachnoid, intraventricular, subdural, or epidural spaces resulting in a space-occupying lesion.

This may also occur secondary to spinal/ subarachnoid anaesthesia.

Clinical presentation²:

Patients will exhibit features of a neurological space-occupying lesion.

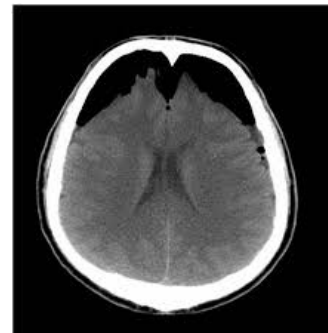
Most commonly this will present with a sudden-onset, severe headache following neuraxial anaesthesia. Less commonly patients will complain of tinnitus, blurred vision, dizziness, seizures and an altered level of consciousness.

Diagnosis: Plain X-Ray, or CT brain.

One will observe air-filled cavities throughout areas of the brain.

“Mount Fuji” sign: significant air volume over frontal cortices, which implies tension pneumocephalus (seen on the adjacent CT Scan).

Differential Diagnosis:



Post-Dural puncture headache	Meningitis
Intracranial haemorrhage	Chemical arachnoiditis

Management: Spontaneous reabsorption occurs within 1 – 7 days, with most patients recovering with no neurological complications. Conservative/ supportive management is the mainstay during this time, and includes analgesia, bed rest, and reassurance. A high FiO₂ has shown promising results, but this could also have a counter effect – leading to an increase in the pneumocephalus.

Surgical intervention may be required if the symptoms do not resolve, or the patient's neurological status persists.

C. Nerve Injury

In the presence of neuraxial anaesthesia aetiology of permanent spinal cord/ or nerve root dysfunction is not clear.

Chronic pain management and systemic anticoagulation were amongst the most attributable factors for spinal cord injury. Epidurals (and spinal anaesthetics) for obstetric reasons were more likely to be associated with low-severity and temporary injuries.

Incidence was found to be 0.04% in a closed claims report published in 2007. There is, however, more recent evidence indicating that the overall incidence of serious neurological complications may be increasing.

Moen et al. reported that the overall frequency of severe neurological complications after spinal anaesthesia was approximately 0.4: 10,000. Various risk factors can predispose to this (see table below), but the incidence of radiculopathy is dramatically increased if there is pain on injection or paresthesia on needle insertion.

Technique	Cardiac Arrest	Death	Seizure	Neurological Injury
Spinal (N = 40640)	26 (1:1563)	6 (1:6773)	0	24 (1:1693)
Epidural (N - 30413)	3 (1:10137)	0	4 (1:7603)	6 (1:5068)
Peripheral Blocks (N = 21278)	3 (1:7092)	1 (1:21278)	16 (1:1329)	4 (1:5320)

Complications related to regional anaesthesia

Cardiac arrest following neuraxial anaesthesia remains the major cause of death (30%). This is however still half of the incidence observed in patients undergoing general anaesthesia.

Cauda equina syndrome may occur as a result of local anaesthesia-induced neurotoxicity in the distribution of the sciatic nerve. This is more likely to occur following epidural block (vs. spinal anaesthesia), and in patients with (often undiagnosed) spinal stenosis. This may include burning pain in one (or both) leg(s), sensory disturbances, as well as the potential for bladder/bowel dysfunction. These patients should be assessed (CT or MRI) if these symptoms persist for more than 24 – 48 hours.

These patients need to be in a monitored area so that any changes in neurological status can be detected rapidly, and neurological/ neurosurgery intervention sought.

Magnetic Resonance Imaging (MRI) has become the diagnostic imaging modality of choice in spinal cord, spinal epidural space, ligament and soft tissue damage. Early and accurate diagnosis is vital to reduce morbidity and permanent disability.

We are not sure of the total incidence of such rare events...as much of the incidence detection relies on self-reporting more than randomized, controlled, prospective trials.²⁰ This does not mean that all events are reported. A more reliable and valid method to capture the true incidence of rare neurological complications would be an international, multicenter, prospective, standardized trial, the logistics of which can be highly impractical.

Risk Factors for Post-operative Neurological Deficits³		
<u>Anaesthesia-related</u>	<u>Surgery-related</u>	<u>Patient-related</u>
Epidural space issues, haematoma, abscess	Surgical stress/ compression (e.g. clamps)	Congenital abnormalities
Needle trauma, neuropathy	Surgical haematoma (rare, but more common than needle trauma)	Pre-existing neuropathies
Local anaesthetic toxicity, cauda equina	Positioning injury	Pre-existing tumour/ lesion

<u>"Difficult" Neuraxial Anaesthesia</u>	
Failed block - Unsatisfactory - Segmental/ incomplete - Block Failure	Unplanned "dural tap"
Difficulty with identifying epidural space	Difficulty with return of CSF
Difficulty advancing catheter	Paresthesia on needle/ catheter insertion
Traumatic block placement (blood present)	Total/ high spinal

Management of a “failed” spinal¹

Aspirate cerebrospinal fluid (CSF) – before and after anaesthesia delivery

Evaluate sacral dermatomes

1. Aspiration of CSF after injection implies intrathecal injection

Administer appropriate total dose (clinician decision). There will usually be some local anaesthetic in the CSF.

Change the distribution:

Alter the patient position

Alter the drug properties (e.g. baricity)

2. NO CSF after injection:

Do NOT repeat dose, unless

NO sensory fallout with full examination

D. Infection

Differentiation:

1. Abscess – epidural, spinal, subdural, paravertebral, paraspinous, psoas
2. Meningitis
3. Encephalitis
4. Sepsis – bacteraemia, viraemia, fungaemia
5. Osteomyelitis
6. Discitis

Pathophysiology:

- Haematogenous spread
- Contiguous from adjacent structures
- Direct inoculation – surgery, trauma, needle puncture
- Cryptogenic

Aetiology:

Staphylococcus	Brucellosis	<i>Mycobacterium tuberculosis</i>
Streptococcus (i.e. from health care workers oro-/nasopharynx)	Toxoplasma	Viral
Histoplasma	Listeria	Fungal Including cysticercosis

It is important to note that the presence of catheter colonization is not necessarily going to result in the development of infection.

1) Epidural abscess

(There are other abscesses which can occur following neuraxial anaesthesia, but the incidence of these appears to be even lower than the spinal epidural abscess)

This is an absolute medical emergency. We readily learn/ react to a cold, threatened limb: the same should apply to compression of the spinal cord.

Incidence: RARE (incidence difficult to clearly elucidate)

1:65000 – 1:500000 following neuraxial anaesthesia.

Male = female patients in incidence. Age > 80 years old is an independent risk factor.

Aetiology: trauma, following neurosurgical procedures, following neuraxial anaesthesia, intravenous drug abuse.

It is NOT increased in incidence in patients who are immune suppressed.

The mean duration/ delay of presentation is 5 days, but can be weeks after the event.

67 % of cases will have *Staphylococcus aureus*, or *Staphylococcus epidermidis* as the causative agents.

Pathophysiology: It occurs more commonly in the thoracic region which is fat-rich, thus ensuring increased spread of the offending organism into the vessel-rich posterior region (larger space). Spread can be *direct* (catheter inoculation, or vertebral osteomyelitis). This is more likely in the adult population.

An epidural abscess can also develop by *spread/ seeding* from a peripheral site (this is more prominent in children). This may occur secondary to infective endocarditis, indwelling catheters, urinary tract infections, peritoneal/ retroperitoneal infections, and other sites.

Investigations: remove the catheter tip, and send for MC&S.
A blood culture would be prudent
MRI or CT Scans
Neurosurgical review and intervention

Management: Early antibiotics (appropriate therapy)
Source control (laminectomy, decompression)
CT-guided percutaneous drains

There is some thought that antibiotics alone (if early enough intervention) would be sufficient. This is difficult to confirm without surgery at times.

Prognosis: This is related to the stage of presentation. The neurological deficit is much more likely to be temporary (vs. haematoma). Most patients will have full neurological recovery if intervention in the stage of persistent back pain/ nerve root radiculopathy.

Prevention:

- Closed system as far as possible
- Micropore bacterial filter at ALL times
- Remove catheter within 3 – 5 days (or change set/ catheter/ fluid)

NO intervention is proven to reduce this.

The minimum interventional sterility recommended by the British and American societies of Anaesthesia: gown, mask, gloves, cap, hand washing, sterile packs.

2) Meningitis

Incidence: 1:39000, and this develops usually within hours – days.

Aetiology: Bacterial (oro-pharyngeal!! From health care workers) – *Streptococcus*,
Pseudomonas
Viral
Fungal

Diagnosis: history and examination (including usual well-known signs of meningitis)
Cerebrospinal fluid MC&S (see table below)

	Acute Bacterial	Aseptic	Viral	Chronic
Neutrophils	↑↑↑	↑	↑	↑
Lymphocytes	↑	↑↑	↑↑	↑↑
Glucose	↓↓	→	→/↓	↓
Protein	↑↑	→	→/↑	↑↑

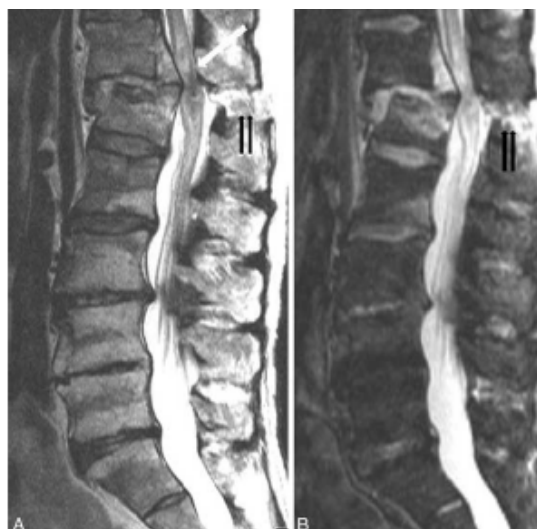
Changes in CSF per Aetiology of Meningitis

Treatment: Empiric, and then directed antibiotic therapy

E. Bleeding (Epidural Haematoma)^{1, 12, 18}

Definition & Aetiology: the accumulation of blood in the potential space between the dura and the brain. This can technically be intracranial or spinal, although the focus of this discussion will be spinal. Even a small amount of blood can cause catastrophic complications (due to the spinal column being a confined, non-expansile space).

Incidence: it is quoted as **1:150000** (although up to 1:18000 with epidural anaesthesia, and 1:158000 with intrathecal/ “spinal” anaesthesia), in most literature. The incidence does, however, depend on patient factors: obstetric epidurals have a suspected incidence of 1:200000, whereas the incidence in an elderly female for a knee arthroscopy with an epidural in-situ is quoted at **1:3600!!**



In a large Swedish study reviewed from 1990 – 1999 ¹¹ it was revealed that there were 33 haematomas present following 1.26 million spinal, and 450000 epidural anaesthetics performed.

Risk Factors: The most significant risk is a patient receiving more than one medication which will affect haemostasis. $\frac{3}{4}$ of patients who develop a spinal haematoma have a pre-existing coagulopathy (primary/ inherent, or secondary due to anti-coagulant administration)

<u>Patient</u> ¹⁴	<u>Anaesthetic</u>	<u>LMWH dosing</u>
Female	Difficult needle placement	UFH/ LMWH admin: ➤ Immediate pre-op ➤ Intraoperative ➤ Early post-operative
↑ age	Traumatic catheter placement	
Ankylosing spondylitis/ spinal stenosis	Epidural > spinal	
Renal insufficiency	Indwelling epidural catheter with LMWH admin	Anti-clotting med's
		Twice-/thrice-daily LMWH admin

Thus there is usually more than one pre-disposing factor in the development of this exceedingly rare complication.

Clinical presentation²: early detection is critical, but this is often compounded by the difficulty in detecting changing neurological features.

- 83 % of patients will have worsened motor blockade (out of keeping with injected local anaesthetic concentration)
- 25 % complain of severe back pain (this is not similar/ related to transient neurological symptoms)

The diagnosis is regularly delayed because:

- Post-operative numbness/ weakness

Is the key feature of presentation; this is often mistaken to be a normal effect of the local anaesthetic (instead of the sinister spinal cord ischaemia which ensues).

Later:

- Features of increased intra-cranial pressure (headache; convulsions; hemiplegia, disorientation, convulsions)

Diagnosis¹³: the clinical picture along with radiological investigations are the benchmark of diagnosis. A neurosurgeon should be consulted urgently. Diagnosis will be confirmed with either a CT Scan or MRI (95 % diagnosed on T2-weighted imaging).

MRI, however, is the only method that can differentiate haemorrhage from oedema. This is of relevance to long-term outcome (prognosis).

Management: Rapid surgical intervention is the mainstay of treatment. This means surgery within 6 hours from the apparent onset of symptoms!

Prognosis: 89 % of patients developing an epidural haematoma will have a permanent neurological fallout! 50 % of patients who had surgery performed within 8 hours of symptomatology regained full neurological function. Spinal cord ischaemia is $\pm$ reversible if patients underwent a laminectomy within 6 – 8 hours of **onset** of neurological dysfunction!

Anticoagulation and neuraxial anaesthesia^{1, 14}		
	Before insertion	After insertion/ Post-surgery
Warfarin	Discontinue 4 – 5 days pre-surgery.	Remove catheter when INR < 1.5.
<u>Unfractionated Heparin</u>		
Subcutaneous	No contra-indication if total daily dose < 10000 i.u. (if more, see i.v.)	Recommence prophylactic dose; Remove ± 1 hour prior to the next dose.
Intravenous	Neuraxial only 2 – 4 hours after last dose	Can heparinise with a catheter in-situ, but increased complications potentially: MONITOR neuro!
<u>Low Molecular Weight Heparin (LMWH)</u>		
Prophylactic	12 hours delay from dose to neuraxial block.	Wait 6 – 8 hours (from neuraxial blockade) before giving first prophylactic dose of LMWH; Prophylactic dose can be administered 2 hours post-removal of epidural catheter.
Treatment	24 hours interval from dose to neuraxial blockade.	Delay 24 hours before recommencing high-dose LMWH (or change to UFH).
<u>Antiplatelet Medications</u>		
NSAID's/ Aspirin	No impact on neuraxial anaesthesia, i.e. proceed. CAUTION: if on non-specific NSAID's, AND other anti-coagulant prophylaxis (avoid neuraxial) Consider: COX-II-i if patients requiring anti-inflammatory therapy, and anticoagulation.	Can commence as is deemed necessary on a patient-to-patient basis.
Thienopyridine derivatives (Clopidogrel, ticlopidine)	These should be stopped 7 days (Clopidogrel) and 14 days (Ticlopidine) prior to surgery.	Avoid in the period whilst the epidural catheter is still in-situ. Anticoagulation should be with short-acting agents.
GP IIb/IIIa inhibitors (abciximab, tirofiban)	6 – 8 hours prior to the neuraxial intervention (Tirofiban): allows return of platelet function. 24 – 48 hours prior to Abciximad	Avoid in the period whilst the epidural catheter is still in-situ.
Thrombolytics/ fibrinolytics	The original recommendation was the avoidance of these drugs in any patient who had undergone any procedure, vascular puncture, intervention in the preceding 10 days. Clear evidence with regards to neuraxial anaesthesia is unclear, but it is wise to avoid definably if possible.	Follow [fibrinogen], and monitor spinal cord compression. **Fibrinogen is last component of clotting cascade to recover.

NOTES on above:

Guidelines recommend that if the patient is on treatment doses of low molecular weight heparin that this is not recommended immediately post-surgery, and is avoided whilst the epidural catheter remains in-situ. If the patient required anticoagulation in order to treat a deep vein thrombosis (or pulmonary embolus) then a Heparin infusion should be commenced, and this dosed as per the aPTT.

High-dose anticoagulants (“treatment” dose):

- Enoxaparin 1 mg/kg, 12-hourly
- Enoxaparin 1.5 mg/kg, daily
- Dalteparin 120 i.e./kg, 12-hourly
- Dalteparin 200 i.U./kg, daily
- Tinzaparin 175 i.U./kg, daily

A delay of at least 24 hours is recommended before needle insertion, following administration. This should allow normalisation of haemostasis.

Pre-existing Neurological Conditions

Patients with neurological disorders may be difficult to assess post-operatively (largely due to the difficulty in assessing their pre-operative neurological status). They are, however, at an increased risk of post-operative neurological dysfunction (1.1%), and block failure; this relates to difficulty with patient positioning, surgical difficulty, protracted labour, and the choice of anaesthetic technique. It may also be exacerbated by previous spinal surgery.¹⁵

Some disease states (e.g. Multiple Sclerosis) may worsen independently of any surgical or anaesthetic intervention peri-operatively. Thus each patient with a pre-existing disorder should be assessed individually to make the appropriate decision regarding regional/ neuraxial anaesthesia. These are, however, often patients who would benefit from regional anaesthetic intervention. It highlights that one cannot make “blanket decisions” regarding patient management.

Patients with chronic neural deficits are at an increased risk of further – or worsening long-term sequelae. This is most likely due to a “double crush” insult (all-population risk of local anaesthetic effects, as well as dysfunctional patient and surgical factors). The majority of patients (>80 %) with previous spinal surgery will have spines amenable to future neuraxial block placement (including catheters in-situ) within 2 vertebral levels of the spinal surgery.¹⁵ Spinal surgery does not appear to worsen technical problems associated with epidural placement in patients with underlying neurological disorders.

Worsening neurologic deficits include:

- Motor/ sensory deficits
- Bladder/ bowel dysfunction
- Painful paresthesia

Approach Overview in patients with pre-existing neurological disorders¹

Determine if Regional/ neuraxial anaesthesia is essential. If so, then modify regional technique in an attempt to reduce the “double crush” insult.

- Anaesthetic agent with a ↓ potency
- ↓ in volume of the local anaesthetic, or concentration, or dose
- Avoid vasoconstrictors

There is, however, little evidence of benefit in human studies.

1. Pre-existing peripheral neuropathy

- e.g. Diabetes Mellitus
Severe peripheral vascular disease
Multiple sclerosis
Chemotherapy (cisplatin/ vincristine)

In a recent review, 2/567 patients with diabetes mellitus had worsening sensorimotor fallout following an uneventful neuraxial anaesthetic (single-dose spinal); this is most likely attributed to the neuraxial blockade.

One needs to evaluate the risk:benefit for each patient, with a potential alternative for anaesthesia and analgesia.

There is, however, little evidence that this will clinically impact outcome.

2. Pre-existing CNS Disorders

- e.g. Multiple sclerosis
Post-Polio syndrome

There is, however, little evidence that this will clinically impact outcome in a detrimental fashion

It is still advisable to evaluate the risk:benefit of the chosen intervention, and seek an alternative wherever appropriate.

3. Reduced spinal canal (stenosis/ masses)

- If there is a known lesion: determine risk:benefit.
- e.g. epidural (associated with ↑ local anaesthetic volume administration) results in an increased MASS effect (vs. a one-shot spinal)
- Patient with chronic pain: image (CT/ MRI) to determine most appropriate site of injection (largest effective space)

Take caution with patient positioning, and reduce pressure on vulnerable sites – in, especially, these patients at risk of further injury.

Conclusion

Neuraxial anaesthesia is often regarded in a nonchalant manner by junior anaesthetists and surgeons as a much safer option to a general anaesthetic. The above review should remind us all of the important, albeit occasionally rare, complications of neuraxial blockade. There is compelling evidence that there may be a reduction in mortality in patients undergoing spinal anaesthetic alone vs. general anaesthetic (Odds ratio = 0.44) in a subset analysis of the POISE II trial.⁸ This is not a randomized prospective trial, and there are flaws and bias in this. It also varies markedly from POISE I trial (2013 analysis), which concluded in a subset analysis that neuraxial anaesthesia was associated with worsening outcome (cardiovascular morbidity and mortality).

The general assessment is that large, multi-centre randomised control trials will occur; these will possibly be in specific areas of concern assessing the relative benefit of one technique and intervention over another. POISE II analysis does highlight some important benefits, as well as advantages and disadvantages of research...and anaesthesia.

Little conformity exists amongst trials: it is difficult to randomize participants, events being sought are often exceedingly rare (i.e. large trials required), the practise of the technique is difficult to standardize (various healthcare providers all providing their “best” service).

The data is reassuring. In the 3rd National Audit Project of the Royal College of Anaesthetists published in 2009 the conclusion drawn was that although complications do occur with central neuraxial blockade – rarely – these will usually resolve within 6 months of insult. This data (and other studies of the like) aid in ensuring that we can adequately counsel our patients, and perform safe anaesthesia. We need to ensure (as per the recommendations laid out by Dr. Buggy)⁴ that we improve reporting of these by confidential closed loop investigations. This should start to reflect the more

accurate incidence of these rare events. The most important consideration is to be cognizant of the fact that we should never “just do a spinal”, but be aware of risks associated with any procedure.

We find ourselves in an ever-increasing litigious society, with technology-savvy patients. I implore you to discuss the presence (or absence) of specific consent forms for neuraxial anaesthesia with your department. Part of the lecture will be focused on establishing a safer epidural service, and ensuring patient understanding and “buy-in” of this process. We need to document, and keep written proof of consent with our patients. Consent ensures that the appropriate risk: benefit is agreed upon between the healthcare provider and the patient²³. As described in the Durban study, more than 50 % of patients feel that there should be a specific anaesthetic consent form (this is despite 36 % of patients not wishing to be alerted to any possible complications)/

The complications of neuraxial anaesthesia – whether minor or major – require rapid detection and intervention to prevent sequelae.¹⁰

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Performing Safe Peripheral Nerve Blocks

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The purpose of this note is to highlight certain important safety aspects related to peripheral nerve blocks, which if considered may lead to fewer misadventures.

Key concepts covered

1. Consent
2. Awake or asleep
3. Ultrasound and nerve stimulation
4. Avoiding complications
 - a. Local Anaesthetic Systemic Toxicity (LAST)
 - b. Nerve injuries
 - c. Infection
 - d. Bleeding
5. Managing complications
 - a. LAST
 - b. Nerve injuries
6. Practical aspects
 - a. Block room
 - b. Protocol

Consent

The first step in performing a safe peripheral nerve block is to understand what surgery is planned, the extent of the incision, possible deviations from routine and the likely severity and distribution of pain. This information should be obtained from the primary surgeon timeously in order to plan for the *correct block*.

The critical aspects of the consent process should address the following

- *Description of the procedure*
- *Reason for doing it*
- *Potential complications and their management*
- *Alternative strategies and their implications*

If doing a block adds risks to the patient, why perform it? The decision to perform it has to be context sensitive i.e. performing the right block for the right patient at the right time. What has to be considered is the risk associated with an alternative analgesic strategy. Opioid related risks are not insignificant; respiratory depression, PONV as well as delayed mobilization, feeding and discharge. Avoiding these through the use of peripheral nerve blocks may confer an overall benefit to the patient. Patient preference must be considered and should be discussed as part of the consent process.

Awake or asleep

Paresthesia or pain on injection inconsistently heralds contact with neural tissue but in some cases it does and hence ASRA's recommendation is that blocks should rarely be performed under GA or deep sedation. Where patient co-operation is unpredictable or by patient preference it is acceptable to perform the block asleep. In children there is no greater incidence of injury above baseline risk (awake adults) and hence it is acceptable to perform blocks in asleep, non-moving patients where benefit likely outweighs risk.

Ultrasound and nerve stimulation

There is no doubt that a significant learning curve exists with the use of ultrasound guided regional anaesthesia but with a growing acceptance of this modality it will become the norm. Ultrasound has been shown to have a number of benefits over nerve stimulation

- Faster to perform
- Faster onset
- Longer duration

- More often successful
- Lower incidence of vascular injury

There is however no difference in neurological injuries when comparing US guided to nerve stimulation techniques.

Using both modalities may offer added safety

- Detect and prevent intrafascicular injection
- Identification of nerves with motor or sensory response

Avoiding Complications

1. Local anaesthetic toxicity

The incidence of seizure is about 7.5/10000 (1:800 – 1:1500) and cardiac arrest 1.4/10000
Incidence depends on vascularity of the block region.

Consider:

- Awake patient
- Regular interaction (re-assessment)
- ECG monitoring
- Aspirate on injection
- Incremental injections
- Use test dose when placing a catheter
 - adrenalin 5µg/ml or 15µg total dose (an increase in HR by 20 or SBP by 15mmHg is positive for an intravascular injection)
- Single shot: absorption dependent on site with highly vascular areas reaching peak effect sooner. Plasma levels tend to peak within 40min, hence monitored care for 30-40 minutes post block
- Infusion: Consider dose adjustment in
 - Older, frailer patients with impaired cardiac function who may be more susceptible to cardiac effects of LA and may have impaired perfusion of organs of clearance.
 - Patients with liver impairment (Amide LA are metabolized by the liver)
 - Patients with renal impairment (10-15% unchanged bupivacaine excreted in urine)

2. Peripheral nerve injuries

Long-term sequelae are quoted as 2-4/10 000.

Post-operative neurological symptoms (PONS) are common but rarely permanent. (0-2.2% by 3 months and 0-0.2% by 1 year).

Attributed risk includes *patient*, *surgical* and *anaesthesia* factors with the first two being the most significant contributors. Interestingly it is general anaesthesia and not peripheral blocks that is an independent risk factor for peripheral nerve injuries.

Patient related factors increasing the risk of neurological injuries

- pre-operative neurological deficit
- peripheral vascular disease
- smoking
- vasculitis
- hypertension
- anatomically ulnar and common fibular are more superficial hence more likely to be injured

Surgical related factors increasing the risk of neurological injuries

- Physical insult
- Tourniquet
 - Time and pressure dependent
- Inflammation (Post Surgical Inflammatory Neuropathy)
 - Often delayed (within 30 days of surgery)
 - Usually followed by normal recovery
 - Often beyond block/surgical distribution
 - Neuropathic pain followed by weakness
 - Immune mediated idiopathic response to physiological stress
- Procedure specific
 - Each surgical procedure has a footprint associated with it
 - Orthopaedic surgery singled out as high risk

- o It is often difficult to tease out patient versus surgery as specific risk contributors because specific population may present for specific procedures and hence bring their risk profiles to the surgery
 - Shoulder
 - Arthroscopy (<0.1%- 10%)
 - Open rotator cuff (<2%)
 - Total shoulder replacement (TSR) (transient brachial plexus injury in up to 17%)
 - Reverse TSR (0.6 - 3.6% permanent which is 11 times higher than anatomic TSR)
 - Elbow
 - Arthroscopy – (up to 4.2%)
 - Replacement – ulnar neuropathy persists in up to 10%
 - Hip
 - Arthroscopy (0.4-13.3%)
 - THR (1%) (dislocation, manipulation, leg lengthening)
 - Revision THR (3x higher risk)
 - Knee
 - Arthroscopy (up to 25% sensory deficit in anterior knee)
 - Anterior cruciate ligament repair (parasthesia up to 75%)
 - TKR (0.3-9.5%, especially common fibular nerve)
 - Ankle
 - TAR – (incidence of 1.3%, fibular nerve and cutaneous sensory branches)

Many patient and surgery related risks for post-operative neurological injury are inherent and cannot be modified but being aware of the risks allows for appropriate upfront discussion and planning. Consider some or all of the following as steps to limit neurological injury.

Appreciate normal anatomy (and its variation)

Avoid adjuncts to LA

- o Minimizes drug substitution errors
- o Minimizes vasoconstriction of intraneural blood vessels

Equipment

- Ultrasound
 - o Practice in simulated environment
 - o Know its limitation and how to interpret images
- Nerve stimulation
 - o Use in conjunction with US to minimize risk of intrafascicular injection (avoid injecting if twitch present at <0.2mA)
- Needles
 - o Bevel
 - Short with 20-30° (i.e. less sharp than the 12-15° needles) to decrease risk if intrafascicular penetration
 - o Appropriate length
 - Block dependent (long enough to reach but excessive length leads to bending in tissue and is more difficult control)

Technique

- Approach the nerve tangentially
- Do not purposefully seek needle to nerve contact
- Avoid intentional intra-neural injection
- Avoid excessive pressure on injection
 - o injection pressures greater than 20psi are associated with intraneural intrafascicular injections). It is recognized that manual assessment of pressure is poor. Pressure monitoring is valuable as a negative predictor of peripheral nerve injury i.e. low pressure correlates with no nerve injury. High pressure however does not predict nerve injury consistently. *Currently no consistent data to recommend these devices for routine practice.*

Chlorhexidine and arachnoiditis – is there an association?

- Circumstantial evidence at best
- Recommendation: antiseptic of choice
- Physical and temporal separation of disinfectant from block tray and instruments
- Allow the skin to completely dry on skin before needle placement (2-3 minutes)
- Avoid needle/catheter contamination

Performing blocks in patients with pre-existing neuropathy

- Diabetics, previous exposure to chemotherapeutic agents
 - Nerves are more sensitive to LA. Consent the patient. If benefits likely to be greater than risks then consider modifying your practice:
 - Decreased dose of LA by
 - Decreasing concentration
 - Decreasing volume
 - Avoid or decrease use of vasoconstrictors
 - Use US
 - To facilitate perineural needle/LA placement
 - Decrease total LA dose
- Patients with inflammatory neuropathy (Guillain-Barre syndrome, post surgical inflammatory neuropathy)
 - These patients are at an increased risk regardless of anaesthetic
 - Exercise great caution
 - Perform a block only if risks and benefits clearly discussed
- Patients with CNS disorder (multiple sclerosis, post-polio syndrome, amyotrophic lateral sclerosis)
 - these patients will experience a worsening of neurological symptoms regardless of anaesthetic. Anecdotal evidence that regional anaesthesia may be reasonable in stable disease but careful discussion of risks and benefits needed

3. Infection

In as far as possible appropriate infection control measures need to be adhered to.

Be aware of immunocompromised patients

- Diabetics
- HIV
- Patients on steroids

Cleaning

- Chlorhexidine (2%) with isopropyl alcohol (70%)
 - better than 5% povidone iodine with 69% isopropyl alcohol
 - (0.28 vs. 1.77 /1000 catheter days CLEAN Trial, Lancet Nov 2015)

Single shot peripheral nerve block

- Full barrier precautions are not necessary
- Sterile gloves, a no touch technique
- Face mask – conflicting data but reasonable to wear
- Appropriate probe cover

Catheters for peripheral nerve blocks

- Full barrier protection
 - Gown, sterile gloves, mask, cap, drapes
- Use a bacterial filter
- Tunneling may decrease risk of infection
- Limit the number of disconnection when topping up infusion pumps
- Limit the duration (on average 3 days but can be extended significantly with meticulous care)

4. Bleeding

Performing peripheral nerve blocks in anticoagulated patients

- Performing superficial blocks where compression following vascular puncture is possible is permitted in patients on anticoagulants once risks and benefits have been reviewed. For deeper blocks or where external compression is more difficult (lumbar plexus, infraclavicular) follow guidelines related to neuraxial anaesthesia in patients on anticoagulants.

Using US limits inadvertent vascular puncture

Key strategy to decrease complications: Follow up blocks more than once a day

This will timeously alert you to

- o developing neurological complications (including compartment syndrome)
- o identify patients with inadequate analgesia
- o infection

Managing complications

1. Local anaesthetic toxicity

Supportive

Stop administering LA

If signs and symptoms of neurotoxicity develop administer midazolam 0.05 – 0.1mg/kg. If not available administer propofol 0.5-1mg/kg

CPR with effective ventilation to avoid respiratory acidosis and hence decrease of LA sodium channel binding

Adrenalin – initial resuscitation dose of adrenalin should probably be lower (probably 1-5 mcg/kg)

Consider cardiopulmonary bypass

Specific

Lipid emulsion (20%) (Intralip ®)

Bolus (1.5ml/kg)

Infusion (0.25ml/kg/min)

May need additional bolus and increase infusion rate to 0.5ml/kg/min

2. Peripheral nerve injuries

If deficit limited to

common site of compression (ulnar/common fibular)

– Observe (OT/Physio/Manage pain)

block distribution

- mild sensory symptoms – Observe (OT/Physio/Manage pain)
- more severe symptoms – neurologist

If deficit not limited to block distribution

Consider:

Cause	Intervention
surgical	explore
coagulopathy	correct
ongoing compression	image and correct
compartment syndrome	check pressure

- Nerve conduction studies and EMG should be done after 3 weeks following injury for diagnosis and prognosis.
- If no resolution of symptoms within 3-5 months obtain peripheral nerve surgeon referral
- In the setting where progressive recovery following surgery is followed by the development of new neurology/unexplained pain consider post-surgical inflammatory neuropathy (PSIN) and refer to a neurologist.

Practical points to improve safety

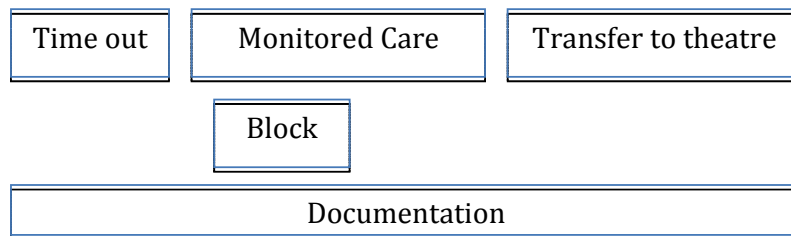
- Avoid performing blocks under time pressure.
This is a sure way to compromise on safety, settle for suboptimal LA deposition and not leaving enough time for the establishment of an adequately working block or a rescue plan.
- Have a dedicated block room away from the surgical area.

Block room

The following should be considered:

- Privacy
- Enough space to accommodate
 - o Patient on a bed
 - o Monitoring equipment
 - o Tray with adjuncts
 - o Ultrasound machine
 - o Resuscitation Trolley
- Plug points (Sufficient number and easily accessible)
- Minimum monitoring equipment
 - o ECG, pulse oximeter, NIBP
 - o Capnography if deep sedation is necessary

Protocol



1. Time out

- Introduction
 - o Patient
 - o Doctor performing the block
 - o Assistant
- Surgical Consent
- Anaesthesia consent
- Site marked
- Any contraindications
- Starvation period
- Allergies
- Monitoring on

2. Perform the block

3. Monitored care

Patients should be monitored for 2 reasons

1. Block assessment – is it adequate for surgery?
 - Do we need to supplement?
 - provide rescue blocks
 - plan for alternative anaesthetic strategies
2. Observe for signs and symptoms of local anaesthetic toxicity

Patient should probably stay in a monitored environment for at least 30 to 40 minutes after the last administered dose of LA. This will allow enough time in most blocks to ascertain efficacy as well as the development of peak plasma LA concentration.

Useful References:

1. The Second ASRA Practice Advisory on Neurologic Complications Associated With Regional Anesthesia and Pain Medicine: Executive Summary 2015. *Reg Anesth Pain Med* 2015;40: 401–430
2. South African Society of Regional Anaesthesia - guidelines in print
3. NYSORA.com
4. MB Welch et al. Perioperative Peripheral Nerve Injuries - A Retrospective Study of 380,680 Cases during a 10-year Period at a Single Institution. *Anesthesiology* 2009; 111:490–7.

Paediatric Premedication

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The original anaesthetic agent, di-ethyl ether, was pungent, depressed the myocardium, increased tracheobronchial secretions and caused significant nausea and vomiting. Soon after its discovery, the concept of premedication to alleviate or modify these inevitable side effects became established.

Pre-operative anticholinergic agents (scopolamine / hyoscine, atropine) as well as sedative analgesics (omnopon / papaveretum, morphine) became common practice. This had the advantage of addressing the more severe side effects of ether anaesthesia and rendering the patient more accepting of the rather unpleasant inhalational induction, but required a painful intramuscular injection!

Despite the introduction of intravenous induction with a barbiturate (thiopentone) and more pleasant volatile agents with less side effects (halothane); routine premedication persisted for decades in the belief that it was essential for safe anaesthesia.

In paediatric practice, the intramuscular injection was undesirable, and a variety of oral agents were utilised (as they became available) to achieve the same effect.

No universal agreement on the ideal paediatric premedication regime existed and institutions adopted individual preferences, often formulating a so-called "standard oral premed (SOP)" that was routinely prescribed to most paediatric (and adult) patients.

Thus, traditionally, the primary goals of premedication were:

- Anxiolysis
- Amnesia
- Analgesia
- Anti-emesis
- Antisialagogue

Secondary goals were more situation specific:

- Pulmonary aspiration prophylaxis
- Bronchodilation
- Modifying autonomic responses
- Maintain, stabilise or modify comorbid disease therapy

With the modern anaesthesia agents available to us, the requirement of a premedicant has changed. Pre-operative anxiety has become the prime focus of attention in modern premedication in both adults and paediatrics. It should be tailored to the individual, taking into account the patient's underlying medical condition, psyche and surgical requirements.

Pre-operative anxiety may be a significant and challenging problem in a child. It may lead to severe distress to the child, the parents and operating theatre staff; if not managed with sympathy and in a structured fashion. In children, there is a link between pre-operative anxiety and an increased incidence of adverse postoperative complications, such as increased analgesic requirements, emergence delirium and negative behavioural changes (e.g. sleep disturbance, altered appetite, bed-wetting or separation anxiety).¹⁻³ These behavioural changes may persist for months.

Kain et al., based at the New Haven Children's Hospital, Yale University, USA; designed and validated a clinical assessment tool for a standardised evaluation of peri-operative behaviour in children.⁴

This is the modified Yale Pre-operative Anxiety Scale (mYPAS) as demonstrated in Table 1.

The mYPAS is an observational state anxiety measure for children comprising 22 items in 5 categories, and has demonstrated high reliability and validity for measuring children's anxiety in the pre-operative holding area, on entering the operating theatre and during induction of anaesthesia.

A majority of children experience significant stress and anxiety before surgery.¹ Pre-operative anxiety is particularly prevalent in the 2 to 6 year age group, but is present in most older children and adults to some degree. Below the age of one year it is less of a problem and children below 6 - 8 months do not usually reveal any anxiety when separated from their parents.

Parental anxiety is an equally important factor. The anxious parent aggravates any anxiety in the child and calm parents diminish it.

Activities 1. The child looks around, is curious, plays with toys, reads (or other behavior appropriate for the age Group); moves around the preanesthetic/treatment room to get toys or seeking family members; might move towards the equipment in the surgery room; 2. The child does not explore or play, may look down, plays with own hands or sucks its thumb (blanket); may sit close to family members while it is playing, or may show a manic quality while playing; 3. The child moves without concentration from the toy to family members, movements are not connected to the activity; movements or play is frantic/agitated; twisting, moving on the table; may push the mask or grab family members; 4. Tries to escape, pushes with feet and arms, may move its entire body; in the waiting-room, runs around without purpose, does not look at the toys, does not want to be apart from family members, clings on desperately. Vocalization 1. Reads (vocalization not adequate for the activity), asks questions, makes comments, stutters, laughs, answers questions promptly, but is usually quiet; child is too young to speak in social situations or too absorbed in the play to answer; 2. Answers to adults but whispers, "baby talk", only shakes its head; 3. Quiet, no sound or does not answer to adults; 4. Weeping, moaning, grunting, silent cry; 5. Child is crying, or might yell "no"; 6. Crying, high pitched and sustained cry. Expressing emotions 1. Happy, smiling, or concentrated on the play; 2. Neutral, no discernible face expression; 3. From worried (sad) to frightened, sad, worried, or teary eyes; 4. Distressed, crying, uncontrolled, eyes might be wide opened. State of arousal 1. Alert, looks around occasionally, notices or follows anesthesiologist's actions (might be relaxed); 2. Withdrawn, calm and silent, might suck its thumb, or its face might be like an adult's face; 3. Attentive, looks around quickly, might be startled by noises, eyes wide opened, body is tense; 4. Whines in panic, might cry or shun others, turns body around. Interaction with family members 1. It is concentrated while playing, is sitting down inactive or shows behavior appropriate to age and does not need family members, might interact with family members if they initiate the interaction; 2. Seeks interaction with family members (gets close to them and talks to family members that were silent until then), seeks and accepts support, might lean against family members; 3. Looks silently to family members, apparently observes their actions, does not seek contact or consolation but accepts it if it is offered, clings on to family members; 4. Keeps family members at a distance or might leave the area when parents are present, might push family members away or cling desperately to them, not letting them go away.

Table 1. The modified Yale Pre-operative Anxiety Scale

To improve the peri-operative course of children, preparatory techniques for anaesthesia are primarily focused on relieving the pre-operative anxiety of the child, as well those of the parents. It is thus essential that measures be taken to relieve their anxiety and this may be achieved with:

- Behavioural intervention
- Parental presence at induction of anaesthesia
- Sedative premedication

Behavioural intervention

In the more affluent health systems, behavioural intervention is gaining popularity as a method of alleviating pre-operative anxiety in children. Intervention may be targeted at the child, parent, or both. Methods include interactive computer packages, video games, clini-clowns, hypnosis and acupuncture (for the parents). Although there are benefits with these techniques, they do not provide superior anxiolysis if compared with pharmaceutical premedication.^{6,7}

Specialised play therapists or child life specialists (USA) are beneficial for both children and parents in the preparation of children scheduled for surgery, and reportedly decrease pre-operative anxiety.

Kain et al. demonstrated that a comprehensive, family-centred pre-operative behavioural preparation programme significantly benefited children in terms of reduced anxiety, increased compliance, reduced emergence delirium, and reduced analgesic requirements.⁸ Similarly, the UK-based Positive Outcome and Experience Management Strategies (POEMS) programme has been formulated to teach anxiety-relieving strategies to caregivers and health personnel.

Such interventions are restricted by their time-consuming nature and are costly; limiting their acceptance and implementation in resource-poor environments.

Child psychologists advocate a cognitive-behavioural approach, incorporating distraction techniques, a child-friendly environment and developmentally appropriate toys; to minimise the negative impact that distressing procedures like surgery can have on hospitalised children. Evidence-based guidelines to improve psychological outcomes have been published by the British Psychological Society; endorsing the presence of the parent / carer, provided the parent / carer does not display a high level of distress themselves.⁹

Parents present at the induction of anaesthesia

This is a controversial strategy in reducing pre-operative anxiety. Initial reports suggested that parental presence at induction resulted in decreased anxiety and increased co-operation in children; but subsequent prospective studies appear to refute this.

Several randomised controlled trials compared parental presence, midazolam and control groups; with these studies consistently demonstrating that children benefited from sedative premedication, but that parental presence provided no additional advantage. Parents, however, tended to be more satisfied with the overall anaesthetic induction when they were present.^{5, 10-12}

This has been confirmed by other investigators and a Cochrane review.¹³⁻¹⁴ However, some children did benefit from parental presence, as shown by a post hoc subgroup analysis of previous studies and a prospective study by Kain et al.^{10, 13, 15} It appears that calm parents may confer an advantage, while highly anxious parents do not.

Despite this lack of evidence to support parental presence, it is controversial, and anaesthetists remain divided as to its role. A limitation of several of the studies examining parental presence was the exclusion of children with a chronic illness or previous surgery – these might well be the group of children who could benefit the most from this strategy. Most of the studies were single-centre studies, and this reduces the external validity of the findings.

Sedative premedication

Sedative premedication is well established as a pre-induction technique to relieve anxiety in paediatric anaesthesia

BENZODIAZEPINES

Midazolam (Dormicum®)

Currently, midazolam is the most widely used agent, with a long history of safety and efficacy. As a premedicant, it has several benefits; including a rapid and reliable onset, minimal respiratory depression, anterograde amnesia and reduced emergence delirium.

Usually administered orally at a dose of 0,5 mg kg⁻¹ (maximum of 15 mg) producing sedation and anxiolysis within 20 min.

May be administered via the intranasal (0,25 mg kg⁻¹), sublingual (0,25 mg kg⁻¹), rectal (0,5 mg kg⁻¹) or intravenous (0,05 mg kg⁻¹) routes.

The intravenous formulation of midazolam is bitter and not well tolerated orally or sublingually. It is also irritant if given nasally, but may be alleviated by pretreating with lignocaine and can be administered with an atomiser.

Midazolam has been extensively studied, and is established as the 'gold standard' for managing pre-operative anxiolysis against which other pre-induction strategies are compared.

There are detractors to midazolam; including the potential for a prolonged effect and for paradoxical reactions.¹⁶ It is not universally accepted as the optimal premedicant.

Paradoxical reactions are uncommon (0,1 % patients), but can result in a restless and agitated child. It is more common after intravenous administration or with higher doses. The mechanism is unclear – most are idiosyncratic, but there may be a genetic link. Midazolam should be avoided if a child has a history of such a reaction.

Other benzodiazepines

Temazepam, **lorazepam** and **diazepam** are used as adult premedicants, but while occasionally used (and studied) in paediatrics, offer no advantage over midazolam and are thus not widely used.

α₂ ADRENORECEPTOR AGONISTS

Clonidine (Catapress®)

Clonidine has resurfaced as a sedative premedicant in paediatric anaesthesia and its use is increasing. It is primarily a central-acting α₂ adrenergic agonist (with some α₁ and imidazoline₁ receptor agonist activity) with sedative and analgesic properties.¹⁷

Administered orally (2 µg kg⁻¹) or intranasally (2 µg kg⁻¹). It is well tolerated with predictable effect, making it an excellent alternative to midazolam.

The onset time of approximately 45 min is longer than that for midazolam, but its analgesia- and anaesthesia-sparing properties is a distinct advantage. Where postoperative pain may be a particular concern, e.g. a patient with chronic pain, then the analgesic effect of clonidine may be specially beneficial.

Peri-operative hypotension and bradycardia may occur, but does not usually pose a clinical problem.

Dexmedetomidine (Precedex®)

Dexmedetomidine is a much more highly selective α_2 receptor agonist with a shorter duration of action than clonidine. Similar to clonidine, it decreases the requirements for volatiles (i.e. it lowers MAC) and opiates, provides analgesia without respiratory depression and reduces catecholamine release.

No oral preparation is currently available, but may be administered parentally in the pre-operative setting. It was shown to be as effective as Midazolam at inducing pre-operative sedation and anxiolysis at an intravenous dose of $1 \mu\text{g kg}^{-1}$, but has been administered intramuscularly ($2,5 \mu\text{g kg}^{-1}$). However, parenteral administration is painful and not generally acceptable in paediatric patients.

Yuen and associates found that intranasal administration ($2 - 4 \mu\text{g kg}^{-1}$) is effective with a smooth and predictable onset and with high patient acceptability. Compared to intravenous dosing, the onset was delayed, but it avoided the initial hypertensive response and is relatively easy to administer.¹⁸

NMDA RECEPTOR ANTAGONISTS

Ketamine (Ketalar®)

Ketamine has a long history of use as a sedative premedicant. Its analgesic effect and the ability to sedate without significant respiratory depression makes it an attractive agent for premedication, but it is associated with some disturbing side effects, e.g. increased secretions, nausea and vomiting, prolonged recovery and emergence delirium.

It is administered orally (5 mg kg^{-1}), intranasally ($2,5 \text{ mg kg}^{-1}$) intramuscularly (5 mg kg^{-1}) or intravenously (1 mg kg^{-1}). Owing to the availability of agents like midazolam or clonidine, which have fewer side effects, its role is often reserved for the older developmentally delayed, autistic or exceptionally unco-operative or combative child. In these patients, intramuscular ketamine may be effective, particularly if the procedure cannot be delayed or rescheduled. Ketamine has abuse potential and is restricted in many countries, despite it appearing on the WHO essential drug list.

ANTI-HISTAMINES

Trimeprazine (Vallergan®)

The use of anti-histamines for premedication has declined with the availability of more suitable agents such as midazolam and clonidine. It does have the advantage of having anti-pruritic and anti-emetic properties. It has a long duration of action, which may be an advantage in situations where the timing of surgery is unpredictable. It is hypnotic and thus contra-indicated in children with compromised airway (as are most premedicants) and there may be some respiratory depression.

Dose is $1 - 3 \text{ mg kg}^{-1}$.

Hydroxyzine (Aterax®)

Advantages are its anti-pruritic, anti-emetic and bronchodilator properties.

Dose is $0,5 - 1 \text{ mg kg}^{-1}$.

Promethazine (Phenergan®)

Usually administered intramuscularly with an opiate, e.g. morphine, to counteract the nausea, as it is an effective sedative anti- nausea agent. Rarely used in modern paediatric practice.

Dose is $0,5 \text{ mg kg}^{-1}$.

ANTICHOLINERGICS

Anticholinergics were prescribed to reduce bradycardias during induction, prevent bronchial or salivary secretions, prevent bronchoconstriction and to prevent neonatal hypotension. *Routine* use of an anticholinergic drug for premedication in paediatrics is no longer advocated, but some anaesthetists still prescribe it as a premedicant for certain procedures (e.g. bronchoscopy, strabismus surgery) or if planning to use certain drugs (e.g. suxamethonium or ketamine).

Atropine

It is effective as an antisialogogue by reducing the volume of secretions, but it also makes them more tenacious and difficult to suction. Unpopular with patients as a premedicant as it causes photophobia (pupil dilation), dry mouth, palpitations (tachycardia) and pyrexia as it interferes with heat regulation. It has central effects and may cause the central anticholinergic syndrome.

Dose $20 \mu\text{g kg}^{-1}$ orally

Glycopyrrolate (Robinul®)

A more potent antisialogogue with less tachycardia and inhibition of gastric acid production. It does not cross the blood-brain barrier and is devoid of central effects.

Dose $10 \mu\text{g kg}^{-1}$ orally

Scopolamine

Not used much nowadays, but more sedative than atropine with anti-emetic properties, thus better suited as a premedicant.

Dose $10 \mu\text{g kg}^{-1}$ parenterally

ANALGESIC AGENTS

Opioids

Opioids are not ideal agents for relieving anxiety or amnesia, but there is a sedative effect. They may be of benefit to patients who have pre-operative pain. The main disadvantage of the opioids are a high incidence of nausea and vomiting and potentially dangerous respiratory depression (especially if there is no pre-operative pain). The concept of pre-emptive analgesia (reduced analgesia requirements postoperatively if given analgesia prior to surgery) has not been supported by clinical studies.

Morphine ($0,1 \text{ mg kg}^{-1}$) is the most commonly used opiate, usually given intramuscularly with a sedative anti-emetic agent, e.g. promethazine. The intramuscular route makes it unpopular as a paediatric premedicant.

Fentanyl ($5 - 15 \mu\text{g kg}^{-1}$) via the oral transmucosal route (lollipop), is approved in some countries as a premedicant for paediatric patients, with a typical onset of sedation in 15 - 20 min. The associated respiratory depression and the potential to induce nausea and vomiting, limits its popularity.

Paracetamol (Panado®)

It is logical to supply an oral analgesic as a premedicant for predictably painful surgery. This enables the oral analgesic to be absorbed and active when the patient emerges from anaesthesia, resulting in an opiate-sparing effect and consequent less postoperative nausea. It has no anxiolytic, sedative or amnesic effects.

It is often used as the carrier / diluent for other premedicants, e.g. midazolam (bitter on its own).

Dose is 20 mg kg^{-1} for the first dose.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Ibuprofen (Brufen®) is similarly prescribed pre-operatively for its analgesic effect. Like all NSAIDs, it has numerous contra-indications, e.g. bleeding risk (platelet effect), risk of renal failure, peptic ulcer disease, asthma, etc.

Dose 5 mg kg^{-1} orally

BUTYROPHENONES

Droperidol

Fallen out of favour as it was labelled with a "black box" warning by the FDA (USA) for QT prolongation on the ECG with a risk of sudden death. This is very rare and only associated with high doses.

It should not be used as a sole premedicant as it induces a neuroleptic state and some patients describe an "outer calm, inner turmoil" state. It is an excellent anti-emetic.

Often combined with trimeprazine.

Dose $0,1 - 0,2 \text{ mg kg}^{-1}$ (maximum of 5 mg)

OTHER AGENTS

Chloral hydrate

Has a very long history, but is not licensed for human use by most authorities, including our own MCC, and has thus been withdrawn from the local market. It has a narrow therapeutic index.

Dose 50 mg kg^{-1} (maximum dose is 1 g for infants and 2 g for children).

Melatonin

Primarily used to treat sleep onset insomnia and delayed sleep phase syndrome in children as well as non-painful procedural sedation. It has been used as a sedative premedicant with some success and is currently the alternative for Chloral hydrate.

Dose $0,25 \text{ mg kg}^{-1}$ orally

Paediatric premedicants for specific purposes

Caffeine

Used as a respiratory stimulant to prevent apnoeas in premature or ex-premature infants up to 60 weeks post-gestational age. It is a CNS and metabolic stimulant with multiple effects on membrane

receptors and ion channels. Oral caffeine is completely absorbed within 45 minutes of ingestion. Dose is 10 mg kg⁻¹ orally or intravenously (available in some countries) 2 hours pre-operatively.

Conclusion

The principal objective of pre-anaesthetic preparation of a child is to manage the common and difficult to treat problem of anxiety. Anxiety in children has been associated with significant negative clinical outcomes. Strategies to reduce anxiety include the use of various behavioural preparation techniques, parental presence at the induction of anaesthesia and a variety of sedative premedicants. Sedative premedication has a long history and is firmly established, while behavioural techniques are gaining wider acceptance. Parental presence remains the most controversial with little evidence to suggest that it confers a benefit to the child; but is widely accepted and practised. Parents on the other hand report it to be beneficial; and many centres employ it routinely with great success, drastically reducing the need for sedative premedicants. What is clear is that parental anxiety is a significant factor in the intensity of the child's anxiety.

Furthermore, pre-induction strategies must be tailored to the patient, taking in to account the available resources, the anticipated surgery and anaesthesia techniques to be utilised.

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Anaesthetic Management of the Patient with an Acute Ischaemic Stroke

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This talk will focus on the following 3 categories:

- A. Advances in acute ischaemic stroke management
- B. Anaesthetic management of the patient with an acute ischaemic stroke
- C. Perioperative stroke following noncardiac and nonvascular surgery

A. Advances in acute ischaemic stroke management

As defined by the World Health Organisation (WHO), stroke is a 'clinical syndrome consisting of rapidly developing clinical signs of focal (or global in the case of coma) disturbance of cerebral function lasting more than 24 hours, or leading to death, with no apparent cause other than a vascular origin'.¹ Stroke is a devastating disease. The WHO places stroke as the second leading cause of death in patients over 60 years of age, and the 5th leading cause in patients aged 15 to 59. Stroke is the leading cause of long-term disability globally.

There are two broad categories of stroke, haemorrhage and ischaemia, which are very different conditions. A comprehensive discussion on the management of acute ischaemic stroke (AIS) is beyond the scope of this talk. For further reading I refer you to the 2013 AHA/ASA guidelines on the management of AIS.² Some key aspects of management of AIS are highlighted here, as well important revisions made to the guidelines in 2015 with specific reference to endovascular treatment.³

Time is brain

Patients presenting with AIS require timely evaluation and diagnosis to allow for treatment/s to begin as soon as possible within narrow therapeutic windows to offer maximum benefit. Organised protocols and stroke teams speed clinical assessment, performance of necessary diagnostic tests, and decision for early management.

With regard to neurological assessment, standardized stroke rating scales, preferably the National Institutes of Health Stroke Scale (NIHSS: see Appendix A) amongst others, provide important information about stroke severity and prognostic information, and influence decisions about acute management.

Emergency imaging of the brain is recommended before initiating any specific therapy to treat AIS. Most of the time CT is adequate, but some cases require further imaging.

Intravenous recombinant tissue-type plasminogen activator (r-tPA)

tPA is a widely accepted therapy for IAS and still remains the mainstay of early treatment.^{2,3} r-tPA was approved by the US FDA in 1996 based mainly on the findings of the NINDS r-tPA Stroke Trial.⁴ It is associated with improved outcomes if given at a dose of 0.9mg/kg intravenously within 3 hours of stroke onset. Select patients may still benefit from r-tPA up to 4,5 hours following stroke onset, but earlier treatment is more likely to result in a favorable outcome. The biggest risk associated with its administration is intracranial haemorrhage (ICH), which may be fatal. Patients eligible for intravenous r-tPA should receive it without undue delay even if endovascular treatment is being considered. See tables 1 and 2 for the inclusion and exclusion criteria for r-tPA following IAS.

Table 1 (below):

Inclusion and exclusion characteristics of patients with AIS who could be treated with r-tPA within 3 hours from symptom onset

Inclusion criteria
Diagnosis of ischemic stroke causing measurable neurological deficit
Onset of symptoms <3 hours before beginning treatment
Aged ≥18 years
Exclusion criteria
Significant head trauma or prior stroke in previous 3 months
Symptoms suggest subarachnoid hemorrhage
Arterial puncture at noncompressible site in previous 7 days
History of previous intracranial hemorrhage
Intracranial neoplasm, arteriovenous malformation, or aneurysm
Recent intracranial or intraspinal surgery
Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg)
Active internal bleeding
Acute bleeding diathesis, including but not limited to
Platelet count <100 000/mm ³
Heparin received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal
Current use of anticoagulant with INR >1.7 or PT >15 seconds
Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)
Blood glucose concentration <50 mg/dL (2.7 mmol/L)
CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)
Relative exclusion criteria
Recent experience suggests that under some circumstances—with careful consideration and weighting of risk to benefit—patients may receive fibrinolytic therapy despite 1 or more relative contraindications. Consider risk to benefit of IV r-tPA administration carefully if any of these relative contraindications are present:
Only minor or rapidly improving stroke symptoms (clearing spontaneously)
Pregnancy
Seizure at onset with postictal residual neurological impairments
Major surgery or serious trauma within previous 14 days
Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
Recent acute myocardial infarction (within previous 3 months)

Inclusion criteria

Diagnosis of ischemic stroke causing measurable neurological deficit
Onset of symptoms within 3 to 4.5 hours before beginning treatment

Relative exclusion criteria

Aged >80 years
Severe stroke (NIHSS>25)
Taking an oral anticoagulant regardless of INR
History of both diabetes and prior ischemic stroke

Table 2 (above):

Additional inclusion and exclusion characteristics of patients with AIS who could be treated with r-tPA within 3 to 4,5 hours from symptom onset

What's new in endovascular stroke treatment?^{3,5}

Endovascular therapy is the most important development in the management of AIS since tPA. Endovascular stroke therapy includes mechanical clot retrieval and intra-arterial thrombolysis. These have been performed since the late 1990's, but with an air of uncertainty surrounding efficacy and patient selection mainly because there was no strong evidence that it was any better or safer than intravenous tPA. In 2013, three clinical trials were published (Interventional Management of stroke (IMS) III, Mechanical retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), and Local versus Systemic Thrombolysis for AIS (SYNTHESIS Expansion)) which suggested that endovascular therapy was no more effective than tPA alone.

- **The rise of stent retriever therapy^{3,5}**

5 new randomized trials on endovascular stroke treatment resulted in updated AHA/ASA recommendations being published in 2015. These trials (Multicenter Randomized Clinical Trial of Endovascular Treatment for AIS in the Netherlands (MR CLEAN)⁶, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial,⁷ the Extending the Time for Thrombolysis in Emergency Deficits — Intra-Arterial (EXTEND-IA) trial,⁸ the Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to an Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT),⁹ and the Solitaire with the Intention for Thrombectomy as Primary Endo-vascular Treatment (SWIFT PRIME) trial),¹⁰ showed that endovascular therapy is highly beneficial as compared with intravenous tPA alone in stroke caused by large artery occlusions in the anterior circulation, and that there was no significant increase in the rate of symptomatic brain haemorrhage. The NNT for one additional person to achieve functional independence in these trials ranged from 3 to 7.5! Improved outcomes may be attributed to improved technology resulting in faster and more complete recanalization than with earlier devices, or with r-tPA alone. Mechanical thrombectomy requires patients to be at an experienced stroke centre with rapid access to cerebral angiography and qualified neurointensivists. Few centres have sufficient

resources and expertise. And although not every patient will be eligible for endovascular therapy (only about 10%), the near future may see the reorganization of systems of stroke care to facilitate timeous intervention.

As it stands, the new recommendation is that stent retriever therapy be offered to patients meeting *all* the following criteria:

- Prestroke mRS score 0 to 1 (see Appendix A)
- AIS receiving r-tPA within 4,5 hours of onset
- Causative occlusion of the internal carotid artery or proximal MCA
- 18 years and older
- NIHSS score of 6 or higher
- ASPECTS of 6 and higher, and
- Treatment can be initiated within 6 hours of symptom onset

- Intra-arterial fibrinolysis

Initial treatment with this strategy is beneficial for carefully selected patients with major ischaemic strokes (MCA occlusions). At present, a clinically beneficial dose of intra-arterial r-tPA is not established, nor does it have FDA approval for this route of administration. As such, stent retriever therapy is recommended over intra-arterial fibrinolysis as first-line therapy. Intra-arterial fibrinolysis may, however, be initiated within 6 hours in carefully selected patients who have contraindications to intravenous r-tPA. The consequences of this are currently unknown.

B. Anaesthetic management of the patient with an acute ischaemic stroke

As endovascular treatment of AIS has emerged over the years, so too has the need for peri-procedural anaesthetic management. The Society for Neuroscience in Anesthesiology and Critical Care (SNACC) published a consensus statement on the anaesthetic management of endovascular treatment for AIS in 2014.¹¹ They identified the need for recommendations on the topic because most anaesthetic management in the past had been dependent on individual or institutional preferences. Evidence and expert opinion on the topic were considered, some of which are discussed and expanded upon below.

1. Expediting pre-procedure assessment

Endovascular treatment of AIS is urgent and needs to happen timeously. The target of therapy in AIS is to reperfuse the ischaemic penumbra, which is the threatened but salvageable tissue surrounding the infarct core. Time is of the essence because if reperfusion occurs too late and the vulnerable tissue has already progressed to irreversible infarction, then apart from reperfusion being futile, it may also precipitate haemorrhage in the area. As illustrated by a survey of members of the Society for Vascular and Interventional Neurology (SVIN), surgeons felt that general anaesthesia (GA) was associated with a significant time delay, this being the reason they often preferred procedural sedation over GA unless contraindicated. The urgent scenario of intervention for AIS leaves little time for a thorough anaesthetic assessment, especially where patients have decreased level of consciousness and/or no collateral history available. However, certain key information should have been obtained during patient workup and is usually readily available for the anaesthetist before the procedure. This patient information includes the following (apart from the last 6 bullet points in italics which may or may not always be available):

- Time the patient was last seen normal
- Neurological status including National Institute of Health Stroke Scale (NIHSS) score
- Blood pressure & heart rate
- Blood results
 - o Serum glucose
 - o Full Blood Count
 - o Platelet count
 - o INR, PT, PTT
 - o Serum electrolytes and renal function
- CXR & ECG
- CT/MRI imaging, particularly arterial territory involved

- Administration of IV tPA
- Age
- Weight
- Allergies to drugs including iodinated contrast medium
- Contraindications to MRI
- History of comorbidities including diabetes and hypertension
- Medications including oral anticoagulant use

2. Anaesthetic Technique:

i. General anaesthesia versus sedation and local anaesthesia^{11,12,13}

The question of the best anaesthetic technique for the management of endovascular treatment for IAS has been difficult to answer because there are no good data from which to draw definite conclusions. The imbalance between stroke severity at baseline is most important to consider as the patients who are sicker with more severe strokes (and higher NIHSS scores) usually ended up in the GA group. Furthermore, the choice between sedation and GA is often driven by institutional and neurointerventionalist preferences, and there is also huge variability in the level of sedation achieved or drugs used for GA.

Overall, retrospective studies suggest that GA compared with sedation may be associated with worse clinical outcome for reasons such as increased time to intervention, instability during induction and emergence, more blood pressure shifts (particularly hypotension) impacting on cerebral perfusion, and GA not allowing for neurological assessments during and immediately after the procedure. Prolonged intubation was associated with a higher risk of pneumonia and/or sepsis in some studies. This being said, both GA and sedation have pros and cons as outlined in table 3 below.

<u>General anaesthesia</u>	<u>Local anaesthesia</u>
Pros: • Immobility • Pain control • Airway protection	Pros: • Smoother haemodynamics • Neurological examination during procedure
Cons: • Haemodynamic changes • Additional workforce • Potential time delay	Cons: • Lack of airway protection • Potential for movement • Uncontrolled pain and agitation • Prolonged procedure time

Table 3: Comparison of general versus local anaesthesia for endovascular therapy in AIS

Recommendations regarding anaesthetic technique published by SNACC in 2014 are as follows:

- GA is recommended for patients who are already intubated for medical reasons, for uncooperative patients, and most patients with posterior circulation strokes (class IIa, Level B evidence)
- Local anaesthesia (LA) with sedation and GA are feasible options for cooperative patients who can protect their airway (class IIa, Level B). Anaesthesia should be carried out as quickly as possible to prevent delay.
- Preparation should be made to rapidly convert LA sedation cases to GA if necessary (class IIa, Level C)
- Anaesthetic technique and pharmacological agents should be individualized based on clinical characteristics of each patient, in close communication with the neurointerventionalist

After SNACC, a retrospective cohort study was conducted from MR CLEAN. From this study population, they analysed patients with AIS of the anterior cerebral circulation who received intra-arterial treatment between 2002 and 2013 in 16 Dutch hospital, looking at the difference in primary outcome between GA and non-GA in 348 patients. Those patients receiving therapy without GA had a higher probability of good clinical outcome (as assessed by functional outcome on the modified Rankin Scale (mRS: Appendix A) at discharge) compared with those who underwent GA. This study was still fraught with many of the same limitations as the earlier trials.

Following MR CLEAN, the 2015 AHA/ASA updated guidelines for the early management of AIS regarding endovascular treatment suggested that it might be reasonable to favour conscious sedation over GA, however the ultimate selection should be individually 'based on patient risk factors, tolerance of the procedure, and other characteristics'.

Look out for the ANSTROKE trial: Sedation versus General Anaesthesia for Endovascular Therapy in Acute Stroke – Impact on Neurological Outcome. This is a prospective randomized trial which will look at neurological impairment at 3 months following endovascular intervention. Hopefully this will provide some of the answers we need.

ii. Neuroprotection and anaesthetic agents:

Unfortunately, many agents that have shown neuroprotective promise in animal models of stroke have failed to show protection in human trials. Thiopentone, isoflurane, sevoflurane and xenon have all been investigated and there is no human evidence that they have significant neuroprotective effects in focal ischaemia.

Magnesium sulphate has also been looked at as a neuroprotective agent in acute stroke. The FAST-MAG trial was a multicentre, randomized, double blind, placebo-controlled clinical trial in which magnesium sulphate was administered pre-hospital to stroke patients. 1700 patients were randomized to receive either 4g of magnesium sulphate or saline within 2 hours of stroke onset, followed by 16g of magnesium sulphate or saline as an infusion over 24 hours in hospital. There was no difference between the 2 groups as assessed by the mRS at 90 days. This is postulated to be because magnesium may cross the blood-brain barrier too slowly to have adequate local effect with insufficient suppression of the molecular ischaemic cascade, especially as a single agent. Also, overall improved stroke care may have made any beneficial effect more difficult to detect. What the FAST-MAG trial did succeed in demonstrating was that 75% of patients received treatment within the first 'golden hour' of stroke onset which is exciting news for future in-field therapeutic drug administration.

3. Oxygenation and ventilation

There is no convincing evidence to support hyperoxia following stroke. Hyperoxia may be neuroprotective for acutely ischaemic brain tissue, but prolonged supplemental oxygen for 24 to 72 hours yields conflicting reports. What we *must* avoid is hypoxia.

Hypoxia following stroke may occur as the result of altered central regulation of respiration, airway obstruction, weak respiratory muscles and/or aspiration. These problems may be exacerbated by sedation without ventilatory support. It is recommended that patients do not need intubation if they can maintain adequate oxygenation (saturation >94%) and ventilation with or without supplemental oxygen. All moderate to deeply sedated patients should receive supplemental oxygen. Indications for intubation are decreased level of consciousness or signs of brainstem dysfunction with compromised protective airway reflexes, those with active nausea/vomiting before the procedure, those who are hypoxic or hypercarbic, and those who develop airway obstruction under sedation. Continuous pulse oximetry and capnography should be applied for all cases.

What about carbon dioxide? Apart from inducing hypocapnia temporarily for the acute management of raised intracranial pressure, normocapnoea should be maintained throughout the peri-procedural period.

4. Haemodynamic management

Hypertension at presentation of IAS occurs in more than 60% of cases. Apart from many of the patients having chronic hypertension, elevations in blood pressure are frequently seen in response to cerebral ischaemia and higher pressures are associated with worse outcomes. Blood pressure usually settles by 25% within 24 hours of stroke onset. An interesting finding from the International Stroke Trial is that both high and low blood pressure at presentation increase the chance of poor outcome. Optimal management of hypertension in this setting is tricky. Although lowering the blood pressure may reduce cerebral oedema and decrease the risk of haemorrhagic transformation, this is at the risk of decreasing collateral flow in the ischaemic penumbra. A Cochrane review through to 2008 as well as a multitude of studies including three large, prospective trials (COSSACS, SCAST, CATIS) show no conclusive evidence that reducing the blood pressure improves outcome following stroke. The ENCHANTED trial is currently underway since 2012 (completion should be December 2016). The study has 2 arms, the first comparing doses of tPA, and the second comparing strict BP control (systolic to 140-150mmHg) with standard control (target systolic 180mmHg). Hopefully this, too, will provide answers we need.

The SNACC consensus statement recommends that blood pressure should be monitored to maintain systolic pressures above 140mmHg with fluids and vasopressors if necessary, but less than 180mmHg. Do not rapidly lower systemic pressures. Diastolic pressure should be kept below 105mmHg. Vasopressor choice should be based on individual patient characteristics. Following

successful recanalization of occluded vessels, the anaesthetist and interventionalist should communicate about optimal blood pressure.

5. Fluid management

Extrapolating from acute stroke patient data, euvolaemia should be maintained. Intravascular volume depletion is common, especially in older patients, and may worsen cerebral blood flow. For most patients, isotonic saline without dextrose is adequate, but may be individualized on the basis of cardiovascular status and electrolyte disturbances.

6. Temperature control

Although hypothermia is beneficial in patients with cardiac arrest and selected infants with hypoxic-ischaemic encephalopathy, available data does not support routine use of hypothermia in IAS. We know from the IHAIST trial which investigated mild hypothermia in the setting of potential focal ischaemia, that mild hypothermia during surgery for ruptured intracranial aneurysm did not improve outcome. So without conclusive evidence, the question of whether patients with IAS should be cooled still remains. There are 2 clinical trials that may shed some light on the matter. The first is the Intravascular Cooling in the Treatment of Stroke (ICTuS) 2/3 study, the purpose of which is to determine whether the combination of thrombolysis *and* hypothermia is superior to thrombolysis alone in IAS. The ICTuS 2 has been halted and the trial is due to continue as ICTuS 3. Results are unavailable. The second is the EuroHYP-1 trial which will randomize patients with IAS within 6 hours to best medical treatment *and* hypothermia, or best medical treatment alone. This trial has been recruiting since 2013. Interim analysis is due to be carried out in June 2016, so watch this space.

Approximately one third of patients with IAS are febrile and this is associated with poor neurological outcome due to increased metabolic demands, enhanced release of neurotransmitters, inflammatory response, and increased free radical production. It is recommended in the SNACC Consensus Statement that antipyretic medications and cooling devices be used to target temperatures between 35 and 37 °C. Shivering should be treated with pethidine.

7. Management of anticoagulation

Heparin is administered during interventional treatment of AIS either as repeat boluses or as an infusion to reduce catheter-related embolic and thrombotic events. It is usually stopped after the procedure and is not routinely reversed with protamine. If the procedure is complicated by intracranial haemorrhage (ICH) or iatrogenic subarachnoid haemorrhage, protamine should be administered immediately based on the dose given and the subsequent ACT values.

Warfarin: in earlier studies, patients on therapeutic warfarin with an INR >1,7 were arbitrarily excluded from receiving recombinant prothrombinase, and endovascular treatment was offered to selected patients. Studies have shown conflicting data in terms of both increased risk and no increased risk for development of symptomatic ICH in anticoagulated patients.

As there are no answers here, be aware as the anaesthetist that patients with therapeutic INR may present for intervention, and you may be asked to reverse the warfarin.

Aspirin and clopidogrel will be administered peri-procedurally if an endovascular stent is used. Aspirin will be withheld for 24 hours after the procedure if thrombolytic therapy was performed.

8. Glycaemic control

All patients coming for endovascular treatment of AIS should have had their blood sugar measured pre-procedure. The majority of data published on stroke and blood glucose levels show an association of worse outcomes with glucose levels greater than 140mg/dL (7.7mmol/L). We all know that tight glucose control carries the very real risk of hypoglycaemia and poor clinical outcomes.

As blood sugar may fluctuate widely under the added stress of anaesthesia, measurement should be at least every hour. Glucose below 60mg/dL (3.3 mmol/L) should be treated with intravenous dextrose to achieve levels of at least 70mg/dL (3.9 mmol/L). The AHA/ASA guidelines for AIS recommend serum glucose concentrations in the range of 140-180 mg/dL (7.8-10 mmol/L) using protocol driven insulin infusions (not subcutaneous insulin).

9. Complications of endovascular treatment

- i. Intracranial haemorrhage (ICH) is an important complication that may occur in 6% of intravenous and 10% of intra-arterial thrombolysis cases, and between 1,5 and 15% of cases with newer endovascular devices. The cause of ICH is usually either haemorrhagic transformation of an infarct, or due to direct vessel trauma by the neurointerventionalist. The ICH may not always be clinically evident, but symptomatic cases often need urgent intracranial pressure management. Any heparin given during the procedure will need to be reversed. If the patient has had tPA, they may need FFP, cryoprecipitate, and platelets. Following ICH, systolic blood pressure should be maintained >140mmHg but below 180mmHg.
Prepare for conversion from sedation to GA where indicated.
- ii. Other complications include
 - At the site of injection: Catheter-induced blood vessel dissection and vasospasm, haematoma, limb ischaemia, thromboembolism, retroperitoneal haematoma.
 - Related to the endovascular treatment: arterial reocclusion, distal embolization, vasospasm and vessel dissection.
 - Sedation related issues include movement, aspiration, inadequate ventilation. These often require conversion to GA at which point the anaesthetist should be particularly vigilant about blood pressure fluctuations.

10. Peri-procedural monitoring

Standard continuous monitoring for all cases (GA and sedation) should include ECG, non-invasive oxygen saturation, temperature, end tidal CO₂ and respiratory rate. Blood pressure should be invasively monitored, but the procedure should not be delayed because of difficulty placing an arterial line. Where the a-line is difficult to place, non-invasive blood pressure should be measured at 3 minute intervals until the the interventionist cannulates an artery, at which point continuous arterial blood pressure monitoring should commence.

Neuromuscular blockade should be monitored under GA.

11. Post-procedural care

It is recommended that patients be cared for in a stroke unit or an ICU specializing in neurovascular care following neurovascular intervention. Therapeutic goals hinge on avoidance of secondary brain injury. Level of monitoring and care will be dictated on an individual basis by patient severity.

C. Perioperative stroke following noncardiac and nonvascular surgery

In non-cardiac surgery, the incidence of stroke ranges from 0.1%-0.6% within 30 days of surgery.^{14,15} Perioperative stroke is associated with a 3- to 8- fold increase in mortality, and for those who survive the event, often significant morbidity. A devastating complication for all involved. 15% of perioperative strokes present on day 0 or day 1, but the majority (up to 48%) present on days 2 to 8 following surgery. The significant majority of perioperative strokes are ischaemic rather than haemorrhagic.¹⁵ The Society for Neuroscience in Anaesthesiology and Critical Care (SNACC) published a consensus statement in 2014¹⁶ which provides evidence-based recommendations on issues surrounding the perioperative care of patients at high risk for stroke during or after non-cardiac, non-carotid, non-neurologic surgery. For the purpose this consensus statement, 'perioperative stroke' was defined as 'a brain infarction of ischaemic or haemorrhagic etiology that occurs during surgery or within 30 days after surgery'. This Consensus Statement provides a rational approach to the management of perioperative stroke, and I highly recommend taking a look at the article. I would like to briefly highlight the importance of identifying patients at high risk of perioperative stroke, and address the issues of time to surgery following stroke and perioperative stroke detection.

- Identifying patients at high risk of stroke preoperatively

Prospective data identifying risk factors for stroke in the non-cardiac population are lacking, and as such, risk factors have been identified from analysis of various databases. The three most consistent risk factors are advanced age, renal failure and a history of stroke or transient ischaemic attack.^{15,16,17} Other major risk factors include atrial fibrillation, valvular heart disease, cardiac failure and female sex. It is imperative that patients at high risk of perioperative stroke (most notably those with a history of any previous cerebrovascular event) presenting for surgery are well informed of the risks. Mashour et

al showed that non-cardiac, non-major-vascular surgery in patients with 3 or 4 of the above risk factors have a 0.7% incidence of perioperative stroke. More than 5 risk factors increase the incidence to 1.9%.¹⁸

- Timing of surgery following stroke

The SNACC Consensus Statement suggests that the decision to proceed with surgery should consider the risks of perioperative stroke versus the risks of delaying surgery, bearing in mind the impaired cerebral autoregulation and chemoregulation following the insult. Since the SNACC recommendation to wait at least one month (with little supporting data), new data have been published by Jorgensen and colleagues in 2014.¹⁹ Their Danish nationwide cohort study included 481,183 patients aged 20 and older undergoing elective non-cardiac surgery from 2005 to 2011. Their outcome measures were risk of major cardiovascular events (MACE; including ischaemic stroke, myocardial infarction, and cardiovascular mortality) and all-cause mortality up to 30 days after surgery. What they showed was more association with bad outcomes if surgery was carried out less than 9 months after the cerebral event. 'After 9 months, the associated risk appeared stable yet still increased compared with patients with no stroke'.

- Screening for perioperative stroke in general surgery

Recognition of stroke following surgery is a challenging problem because signs may be obscured by the residual effects of anaesthesia. Where warning signs are missed, potential treatment could be delayed and impact on neurological outcome. An ideal stroke assessment scale in the perioperative setting should be easy to administer, quick, detect neurologic deficits after surgery, distinguish distracting factors (such as residual anaesthetic and analgesic effects) from signs and symptoms of perioperative stroke, be simple to use, and have good inter-rater reliability.

A review was published in January this year looking at diagnostic tools for screening of perioperative stroke in general surgery.²⁰ Of the 21 stroke assessment scales they identified in the literature, many were technically demanding and time consuming. Only 2 stroke assessment scales have been applied in the perioperative setting: the the Western Perioperative Neurologic Scale (which was designed for use following cardiac surgery) and the NIHSS which has been extensively used in clinical trials including cardiac, neurological and carotid surgery. No scale has been tested in non-cardiac, non-neurologic surgery to date.

Any patient who develops new neurological deficits that cannot otherwise be explained should be seen by an acute stroke team as soon as possible. Prevention of secondary insult is paramount by avoiding hypoxia, hypotension, arrhythmias, hyperpyrexia, and hyper/hypoglycaemia. Because intravenous thrombolysis is generally contraindicated within the first 14 days following surgery, endovascular treatment may be an option.

APPENDIX A

The National Institutes of Health Stroke Scale (NIHSS) is a systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit. The NIHSS was originally designed as a research tool to measure baseline data on patients in acute stroke clinical trials. Now, the scale is also widely used as a clinical assessment tool to evaluate acuity of stroke patients, determine appropriate treatment, and predict patient outcome. The scale is designed to be a simple, valid, and reliable tool that can be administered at the bedside consistently by physicians, nurses or therapists. The NIHSS is composed of 11 items and is used to evaluate the effect of acute cerebral infarction on the levels of consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss. A trained observer rates the patient's ability to answer questions and perform activities. Ratings for each item are scored with 3 to 5 grades with 0 as normal, and there is an allowance for untestable items. The single patient assessment requires less than 10 minutes to complete.

For a comprehensive copy of the NIHSS go to ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf

Score ^[3]	Stroke Severity
0	No Stroke Symptoms
1 – 4	Minor Stroke
5 – 15	Moderate Stroke
16 – 20	Moderate to Severe Stroke
21 – 42	Severe Stroke

The Modified Rankin Scale (mRS) is used for measuring the degree of disability or dependence following stroke.

The scale runs from 0-6, running from perfect health without symptoms to [death](#).

- 0 – No symptoms.
- 1 – No significant disability. Able to carry out all usual activities, despite some symptoms.
- 2 – Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
- 3 – Moderate disability. Requires some help, but able to walk unassisted.
- 4 – Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
- 5 – Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
- 6 – Dead.

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Anaesthesia for TURP

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Overview

Transurethral Resection of the Prostate (TURP) is a very common urological procedure performed in both developed and developing countries with ageing populations. The advantages, disadvantages, risks and possible complications of this procedure are well known. The anaesthetic options should be considered for every patient on an individual basis, to ensure a successful peri-operative outcome.

Spinal anaesthesia is considered the technique of choice for transurethral resection of prostate surgery. TURP Syndrome is a rare but potentially life-threatening complication of a TURP procedure. It occurs as a consequence of the absorption of the fluid, which is used to irrigate the bladder, into the prostatic venous sinuses and into the systemic circulation. Symptoms and signs are caused by fluid overload, electrolyte disturbances as well as hyponatraemia and hypo-osmolality. In TURP syndrome, hypo-osmolality is more important than hyponatraemia in causing central nervous system disturbances. The clinical spectrum is broad and presentation may vary and be unpredictable. It lacks a stereotypical presentation and therefore it may be difficult to diagnose if not suspected or actively investigated for. TURP syndrome therefore comprises the effects produced by rapid changes in osmolality and circulating volume. The specific type of irrigation fluid used may further contribute to specific side-effects and complications that in turn expose the patient to additional risks, such as visual impairment with the use of 1.5% glycine. Clinical suspicion and pre-operative prevention strategies are extremely important to increase early diagnosis and treatment.

Treatment is largely supportive and relies on the management of the underlying causes. This can be achieved by the discontinuation of irrigation fluid, organ support as well as correction of electrolyte abnormalities. TURP syndrome treatment can therefore be divided into the management of volume changes as well as the management of solute changes (hyponatraemia, hypo-osmolality) and the treatment of the direct toxicity of the irrigation fluid.

Between 1% and 8% of TURP procedures are complicated by TURP syndrome and if not diagnosed and treated correctly, lead to significant patient mortality and morbidity. Newer techniques of TURP surgery as well as the choice of irrigation fluid, promise to reduce the incidence as well as risk of TURP syndrome.

Introduction

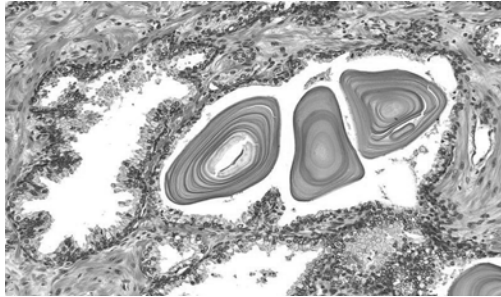
Approximately 40 000 transurethral resections of the prostate (TURP) procedures are performed annually in the UK whereas the number for South Africa is unknown. TURP remains the surgical gold standard for the treatment of benign prostatic hyperplasia (BPH). It is performed by means of endoscopic surgery and often with spinal anaesthesia. The perioperative morbidity from this procedure is high and ranges between 18% and 26%. Complications such as TURP syndrome, bladder rupture, hypothermia as well as general surgical complications such as myocardial ischaemia and infarction are well described. The incidence of TURP syndrome during TURP surgery varies between 1 and 8%, depending on a range of factors such as the size of the prostate, duration of the procedure as well as the surgical technique performed and experience of the surgeon. TURP syndrome is a major contributor to the high mortality rate of complicated TURP surgery.

TURP is usually performed in patients in whom the prostate weighs <60g. Open prostatectomy is the procedure of choice for malignant disease and if the prostate is very large (>100g). Open prostatectomy is a much larger procedure with a lengthy recovery period, but is not complicated further by TURP syndrome. The size of the prostatic size can be assessed by bimanual examination, trans-rectal ultrasound scanning as well as endoscopic inspection.

Functional anatomy and physiology of the prostate

The word prostate comes from the Greek word *prostates*, which literally means "protector" or "guardian". It is a compound tubulo-alveolar exocrine gland of the male reproductive system. The function of the prostate is to secrete a slightly alkaline fluid (milky or white in appearance) that usually constitutes roughly 30% of the volume of the semen, along with the seminal vesicle fluid and

spermatozoa. The alkalinity of semen helps neutralize the acidity of the vaginal tract, prolonging the lifespan of sperm. The prostatic fluid is expelled in the first ejaculate fractions, together with most of the spermatozoa. Spermatozoa expelled in prostatic fluid have better motility, longer survival and provide preservation of genetic material. Skene's gland, also known as the female para-urethral gland, is homologous to the male prostate gland. The female prostate, like the male prostate, secretes prostatic specific antigen (PSA) and levels of this antigen increases greatly with carcinoma of the gland, making this a useful cancer marker. The prostate also contains some smooth muscles that help expel semen during ejaculation.



Micrograph of benign prostatic glands with corpora amylacea. (H&E stain.)

The normal weight of the prostate in adult males ranges from between 7 and 16 grams, with a mean weight of about 11 grams. The size of the prostate among patients with negative biopsy results is related to their weight and BMI, so it is important to control their weight. The prostate surrounds the urethra caudal to the urinary bladder and it can be palpated during a rectal exam.

The secretory epithelium of the prostate is mainly pseudo-stratified, comprising of tall columnar cells and basal cells, which are supported by a fibro-elastic stroma. The fibro-elastic stroma also contains randomly oriented smooth muscle bundles, which are continuous with the bladder. The epithelium is highly variable and also contains areas of low cuboidal, squamous epithelium as well as transitional epithelium in the distal regions of the longer ducts. The urethra originates from the bladder, within the prostate where it is referred to as the prostatic urethra and then also merges with the two ejaculatory ducts. The prostate is not encapsulated but is surrounded by an integral fibro-muscular band sheathed within the pelvic floor muscles, which enables contraction during the ejaculatory process.

The prostate was first described by dividing into lobes and later classified into zones. The "zone" classification is more commonly used in pathology, was first described by McNeal in 1968. He found that the relatively homogeneous cut surface of an adult prostate did not resemble "lobes" generally described anatomically and thus devised a description based on "zones". The prostate gland has four distinct glandular regions, two of which arise from different segments of the prostatic urethra:

Zone	Fraction of gland	Characteristics
Peripheral zone (PZ)	Up to 70% in young men	The sub-capsular portion of the posterior aspect of the prostate gland that surrounds the distal urethra. It is from this portion of the gland that 70–80% of prostatic cancers originate.
Central zone (CZ)	Approximately 25%	This zone surrounds the ejaculatory ducts. The central zone accounts for roughly 2.5% of prostate cancers although these cancers tend to be more aggressive and more likely to invade the seminal vesicles.
Transition zone (TZ)	5% at puberty	10–20% of prostate cancers originate in this zone. The transition zone surrounds the proximal urethra. This is the region of the prostate gland that grows throughout life and is responsible for the disease of benign prostatic enlargement.
Anterior fibro-muscular zone	Approximately 5%	This zone is usually devoid of glandular components, and composed only, as its name suggests, of muscle and fibrous tissue.

Table 1: The "zone" classification as used in pathology:

Lobe	Characteristics
Anterior lobe (or isthmus)	roughly corresponds to part of transitional zone
Posterior lobe	roughly corresponds to peripheral zone
Lateral lobes	spans all zones
Median lobe (or middle lobe)	roughly corresponds to part of central zone

Table 2: The "lobe" classification as used in anatomy:

Embryonic Development

The prostatic part of the urethra develops from the middle, *pelvic* part of the urogenital sinus and is of endodermal origin. Endodermal outgrowths arise from the prostatic part of the urethra, which then grows into the surrounding mesenchyme. The glandular epithelium of the prostate differentiates from these endodermal cells, and the associated mesenchyme differentiates into the dense stroma and the smooth muscle of the prostate. The prostate glands represent the modified wall of the proximal portion of the male urethra. It arises by the 9th week of embryonic life along with other developments of the reproductive system. Condensation of mesenchyme, urethra and Wolffian ducts gives rise to the adult prostate gland. The prostate is a complex organ as it is made up of several elements of glandular and non-glandular components tightly fused together. The most important histological cell types are the glandular cells, the myo-epithelial cells as well as the sub-epithelial interstitial cells

Secretions

Prostatic secretions are generally composed of simple sugars and are often slightly alkaline. The protein content is less than 1% and includes proteolytic enzymes, prostatic acid phosphatase, beta-microseminoprotein, PSA as well as zinc.

Regulation

To function adequately, the prostate needs male androgens as well as dihydrotestosterone to effectively regulate prostatic function.

Anatomy

The prostate gland encircles the urethra as it emerges from the base of the bladder. It consists out of glandular (secretory acini) and non-glandular (smooth muscle and fibrous tissue) components enclosed by a fibro-muscular band or capsule. It has a rich blood supply and its venous drainage is via the large, thin-walled sinuses adjacent to this capsule.

We have described the four histological zones (the McNeal zones) as the central, peripheral, anterior (fibro-muscular) and transitional (peri-urethral) zones. The transitional zone forms the two pear-shaped lobes which surrounds the proximal urethra on either side. This area only comprises 5% of the total normal prostatic volume but is the most common site where benign prostatic hypertrophy occurs. It is also in this area where up to 10% of prostatic carcinomas has their origin.

Twenty per cent of men at the age of 40 years have hyperplasia of the transition zone, but this number increases to 50% at 50 years and 70% at 60 years. This hyperplastic tissue increases in size till it eventually encroaches on the proximal urethra, causing urinary obstruction. The normal prostatic tissue becomes compressed against the capsule, and this is then often referred to as the 'surgical capsule'.

The nerve supply to the prostate arises from the prostatic plexus, which originates from the inferior hypogastric plexus. This plexus carries both sympathetic fibers, which originates from T11 to L2 as well as parasympathetic fibers from S2 to S4. Pain fibers from the prostate, prostatic urethra, and bladder mucosa originate primarily from the sacral nerves S2 to S4. Pain signals from bladder distension travel with sympathetic fibers and have their origin in T11–L2. The sensation of bladder stretch is perceived by proprioception and is carried by the parasympathetic fibers of S2–S4.

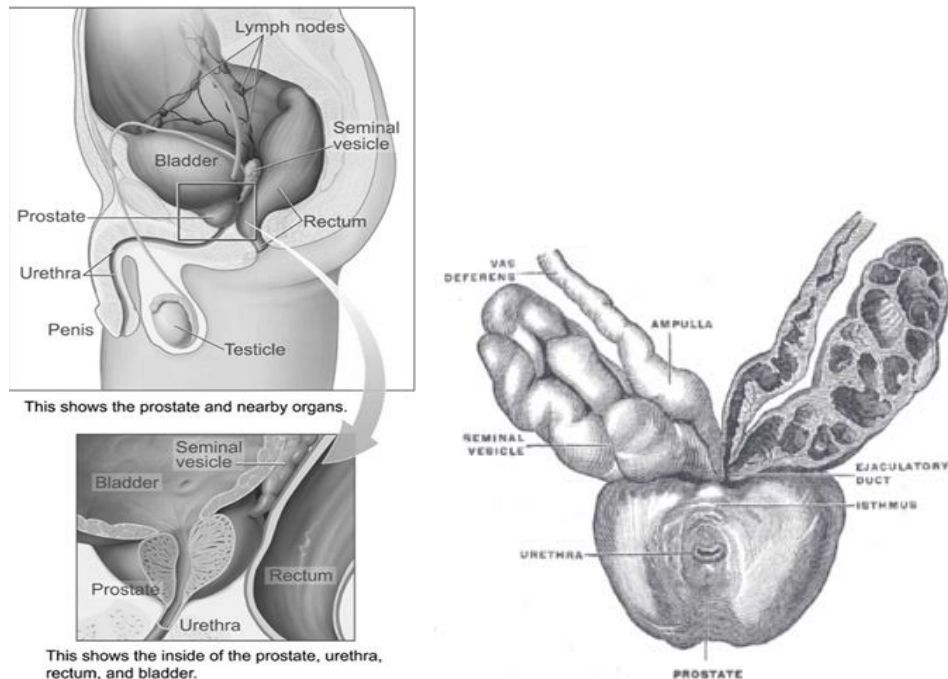


Figure 2: Prostate with seminal vesicles and seminal ducts, viewed from in front and above.

Anatomy	Description
Precursor	Endodermic evaginations of the urethra
Artery	Internal pudendal artery, inferior vesical artery, and middle rectal artery
Vein	Prostatic venous plexus, pudendal plexus, vesical plexus, internal iliac vein
Nerve	Inferior hypogastric plexus
Lymph	External iliac lymph nodes, internal iliac lymph nodes, sacral lymph nodes

Table 3: Details of prostate anatomy.

Surgical technique:

The operation is performed using a resectoscope, through which a diathermy loop is passed. The aim of the procedure is to resect the hyperplastic tissue while sparing the surgical capsule. The difficulty is that the hyperplastic tissue does not form a well-defined plane with the normal prostate tissue or surgical capsule. The prostatic tissue is resected in small strips under direct vision using the diathermy loop. This loop could be used to either cut or coagulate tissue. The bladder is continuously irrigated with fluid to allow direct vision, this is important to wash away blood clots as well as debris to ensure continuous visualization. At the end of the procedure, a three-lumen catheter is inserted and irrigation is continued for up to 24 hours after the operation. The procedure usually takes 30 to 90 minutes, depending on the size of the prostate and the level of experience of the surgeon. The procedure is performed in the lithotomy position, often with head-down (Trendelenberg) tilt.

Irrigation fluid

The ideal irrigation fluid is transparent to ensure good visibility, electrically non-conductive to prevent dispersion of the diathermy current, isotonic, non-toxic, and non-haemolytic when absorbed, easy to sterilize, and inexpensive. Historically, the most commonly used irrigation fluid in the UK used to be 1.5% glycine, which has an osmolality of $220 \text{ mosmol kg}^{-1}$. This trend has changed over recent years due to the realization of the morbidity associated with its use as well as the availability of safer irrigation fluids and techniques. Glycine is therefore hypotonic when compared to plasma ($280\text{--}300 \text{ mosmol kg}^{-1}$). Other solutions available include mannitol 5%, sorbitol 3.5%, water as well as 0.9% saline with bipolar diathermy.

Patient population and general considerations

Patients are usually elderly, and may have coexisting diseases involving several systems. In one large case series, the average age of patients presenting for the TURP procedure was 69 years and only 23% of these patients did not have a co-existing significant medical condition. In this study, the most commonly associated medical conditions involved the cardiac (25%) as well as the pulmonary (14.5%) systems. Patients also suffered significant co-morbid conditions that influenced their peri-

operative course, which may include previous myocardial infarction (12.5%), cardiac arrhythmias (12.4%), renal insufficiency (9.8%), and diabetes (9.8%).

Preoperative assessment should include a full medical history and clinical examination to evaluate the physiological baseline function of the patient as well as to exclude any co-morbidities. Blood tests and special investigations such as a full blood count, electrolyte screen, ECG and CXR are usually indicated because of the patient's age and medical conditions. Special attention should also be paid to the cardiovascular system. Patients at risk of cardiovascular illnesses may need further risk assessment and medical optimization prior to surgery. Conditions such as myocardial ischaemia and cardiac failure should especially be identified preoperatively due to their higher risk of peri-operative complications. Cardiac failure should be treated with anti-failure medication, as irrigation fluid absorption during the procedure results in an extremely high risk of morbidity and mortality. Chronic prostatic hypertrophy may cause obstructive renal insufficiency and urinalysis is mandatory to exclude a urinary tract infection. If an UTI is undiagnosed and left untreated, it will increase the risk of postoperative sepsis due to a bacteraemia. Patients with osteoarthritis or prosthetic joints often render positioning difficult and these conditions increase the risk of musculoskeletal injury, pressure sores and even possible hip dislocation.

Benign prostatic hyperplasia:

Benign prostatic hyperplasia (BPH) occurs in older men where the prostate often enlarges to the point where urination becomes difficult. Symptoms include frequency or the need to urinate often as well as hesitancy or taking a while to initiate urination. With progression of this condition, the prostate grows even larger and it may constrict the urethra and further impede the flow of urine, making urination difficult, painful and in extreme cases even completely impossible.

BPH can be treated medically, or with minimally invasive procedures or by means of surgical reduction of the prostatic size. Minimally invasive procedures include transurethral needle ablation of the prostate (TUNA) and transurethral microwave thermotherapy (TUMT). These are outpatient procedures and may be followed by the insertion of a temporary prostatic stent, to allow normal voluntary urination, without exacerbating obstructive symptoms.

TURP involves the removal of mostly transitional zone tissue in a patient with BPH. Older men often have amyloid deposits, which forms dense accumulations of calcified proteinaceous material (*corpora amylacea*) resides in the ducts of their prostates. The corpora amylacea may obstruct the lumens of the prostatic ducts, and contributes to the pathophysiology and symptoms of BPH.

Prostate cancer

Prostate cancer is one of the most common cancers affecting older men in developed countries and therefore a significant cause of death for elderly men. Recently various controversies and contradictions have been published regarding the efficiency of markers for prostate cancer. Traditionally prostate cancer may be suspected and diagnosed by means of a physical rectal exam, measurement of prostate specific antigen (PSA) level in the blood as well as checking for the presence of the protein engrailed-2 (EN2) marker in the urine. Several large studies in the UK and in the US is underway to evaluate the sensitive and specificity of these markers.

Vasectomy and risk of prostate cancer

In 1983, the Journal of the American Medical Association reported a connection between vasectomy and an increased risk of prostate cancer. Reported studies of 48,000 and 29,000 men who had vasectomies showed 66% and 56% higher rates of prostate cancer, respectively. The risk increased with age and the number of years since the vasectomy was performed. These results have been questioned in later years, due to the very high incidences of prostatic cancer in elderly men, any reason for presenting to an urologist can potentially act as a confounding factor.

Anaesthetic technique

General Anaesthesia
Useful in patients who are unable to lie supine for any length of time
Useful in those who have a persistent cough
Incidence of myocardial ischaemia is the same for spinal and GA
Lithotomy, head down reduces Vt and FRC.
Position also increases the risk of aspiration - tracheal intubation + IPPV can counteract these problems.
Under light planes of GA, penile erection can interfere with surgery- this can be managed by deepening anaesthesia
Post op analgesia will be needed

Table 4: General Anaesthesia

Regional Anaesthesia
Useful for those with significant respiratory disease
Good post-op analgesia
Allows anaesthetist to monitor level of consciousness and detect any early signs of TURP syndrome
Earlier recognition of capsular tears and bladder perforation, if patient complains of peri- umbilical or shoulder pain (provided the spinal level is not above T10)
Spinal anaesthesia does not prevent penile erection, which can interfere with surgery

Table 5: Regional Anaesthesia

Spinal anaesthesia

Spinal anaesthesia is regarded as the technique of choice for TURP surgery, although there is little evidence to demonstrate significant difference in outcomes between general and spinal anaesthesia.

Spinal anaesthesia may offer several advantages over general anaesthesia. It is particularly useful for patients with significant respiratory disease it confers good postoperative analgesia and may reduce the stress response to surgery. More importantly, spinal anaesthesia allows the anaesthetist to monitor the patient's level of consciousness, which makes it easier to detect the early signs of TURP syndrome. Early recognition of capsular tears and bladder perforation is also possible when spinal level is limited to T10, as the patient will complain of peri-umbilical or shoulder pain. Spinal anaesthesia has traditionally been avoided in patients with ischaemic heart disease; however, the incidence of myocardial ischaemia is the same for spinal and general anaesthesia. The aim is to establish a spinal block up to the level of T10, which enables the elimination the pain and discomfort caused by bladder distension. The T10 block can be obtained in most patients with a standard dose of 2.5–3.0 ml of 0.5% plain or hyperbaric bupivacaine. Pencil-point spinal needles are associated with a very low rate of dural puncture headache.

Severe hypotension is uncommon with this low dose T10 block technique. The lithotomy position may compensate for the sympathetic block by improving pre-load as well as venous return. It must be kept in mind that when the legs are lowered at the end of the operation, hypotension may be unmasked in certain hypovolemic patients. Treatment of hypotension with vasoconstrictors rather than rapid fluid administration is encouraged to reduce the risk of fluid overload. Careful monitoring of vitals such as heart rate and arterial pressure is essential throughout the operation as well as afterwards. If required, sedation may be provided with the benzodiazepines or via propofol or dexmedetomidine infusion. It must be kept in mind that sedation may cause confusion, disinhibition, restlessness and deep sedation may mask the cerebral symptoms of TURP syndrome. Deep sedation is therefore counterproductive as it negates the benefit of early TURP syndrome detection, one of the main reasons why spinals are such a popular anaesthetic technique for TURP surgery.

General anaesthesia

Circumstances where general anaesthesia are the preferred technique may include patients with a contra-indication to spinal anaesthesia, those unable to lie supine for a prolonged period of time, or patients with a persistent cough which make surgery difficult. Other general contra-indications may include valvular heart disease (aortic stenosis) as well as clotting and haemostatic abnormalities. The choice of airway intervention will mostly depend on patient factors as the patients BMI and reflux risk will play an important role. The lithotomy position in combination with a head-down tilt reduces tidal volume and functional residual capacity, and increases the likelihood of gastric regurgitation. Tracheal intubation and positive pressure ventilation will counteract these problems and will provide more

secure airway protection. However, the use of a laryngeal mask airway with spontaneous ventilation in selected patients is also a very popular alternative. Postoperative analgesia may be provided by a single-shot caudal or epidural injection, with 20–25 ml of plain 0.25 - 0.375% bupivacaine with or without an opioid. Under light planes of general anaesthesia, penile erection may interfere with surgery. This problem can usually be managed by deepening of the anaesthesia.

Local anaesthesia

Limited TURP procedures in high-risk patients have been performed by local infiltration of the perineum and the prostatic fossa. However, the quality of intra as well as post-operative analgesia is inferior to other anaesthetic techniques and can only be done when the prostate gland size is quite small (<40 g).

A single, slow i.v. bolus of gentamicin (2–4 mg kg⁻¹) or other comparable alternative antibiotic should always be given to prevent bacteraemia during instrumentation of the urinary tract.

Potential intra-operative problems

Excessive intra-operative absorption of irrigation fluid may lead to the TURP syndrome. Blood loss is inevitable and may be substantial with long surgery and patients with haemostatic problems.

Myocardial ischaemia may occur in up to 25% of patients during TURP surgery, with myocardial infarction occurring in 1–3%. Elderly patients are prone to hypothermia, particularly if the irrigating solution is used at room temperature. Warmed irrigation fluids have not been shown to cause any increase in blood loss by local vasodilation and should be used in conjunction with active patient warming devices.

Occasionally, perforation by resectoscope of either the prostatic capsule (up to 10% of cases); urethra or bladder (up to 1.1% of cases) may occur. Small perforations do not require further surgical intervention but antibiotic therapy is recommended to prevent septicaemia. Prostatic capsular perforation may be associated with excessive bleeding, and may require placement of a retroperitoneal drain. Intra-peritoneal perforation may present as shoulder-tip pain in patients with spinal anaesthesia.

Potential post-operative problems

Postoperative pain is not usually severe after either spinal or general anaesthesia with a multi-modal pain management strategy. Discomfort from bladder spasm or from the urinary catheter may occur commonly. It is unusual for patients to require opioids after the operation. Catheter pain may be treated with lidocaine or remicaine gel.

Bladder spasm may be treated with muscarinic receptor antagonists (e.g. hyoscine butylbromide or oxybutynin). It should be kept in mind that muscarinic antagonist can potentially precipitating delirium in elderly patients. Other therapeutic options are benzodiazepines or small sub-hypnotic dosages of ketamine. Clot retention may occur post-operatively especially where irrigation was inadequate or discontinued for a period of time. Clot retention leads to bladder over distension, which can be extremely painful and may precipitate severe bradycardia due to the vagal overstimulation. Mechanical measures such as flushing the bladder or milking the catheter may be successful with smaller bladder clots. In some patients the only option to resolve this problem would be to take them back to theatre for a formal evacuation of the bladder haematoma. It should be kept in mind that these patients may be significantly hypovolaemic. A pre-operative, haemoglobin is essential and a general anaesthetic should be considered. This patient group is at particular risk for developing deep venous thrombosis. Low-molecular-weight heparin should be considered in patients at higher risk (dehydration, hypovolaemia, poor mobility, malignancy, intercurrent illness, and obesity). Postoperative cognitive dysfunction (POCD) is also very common due to various factors such as the elderly patient population and risk of sepsis.

Implications of patient position and complications related to positioning

Trendelenburg. Pulmonary and cardiovascular changes in this position are more extreme than those associated with the supine position. Diaphragmatic movements are limited severely by the weight of the abdominal viscera; which further reduces the functional residual capacity and increases atelectasis. Ventilation-perfusion mismatch, raised intracranial pressure, raised intraocular pressure and passive regurgitation are all potential complications. The severity and likelihood of these potential complications increases with the amount of Trendelenburg tilt.

Lithotomy Position. It is important to remember that the leg elevation redistributes pooled lower limb blood centrally and may lead to volume overload in susceptible individuals. There

is usually some unintended distal movement of the endotracheal tube upon assuming the lithotomy from the supine position. Unanticipated stimulation of the carina may lead to bronchospasm or unintentional endo-bronchial intubation may occur. Resting the arms by the side of the patient can lead to crushed or even amputation of digits when the leg section of the table is replaced or elevated at the end of the procedure. It is therefore of utmost importance that attention should be given with positioning in terms of awareness of possible complications as well as pressure point care. It is also important to assess any limitation of joint movement before induction of anaesthesia as this may impose important constraints on possible positioning. It may also lead to nerve injuries where abnormal posture and positioning cause strain or pressure on peripheral nerves. Extreme flexion of the hip joints can cause neural damage by stretch, for example the sciatic or obturator nerves. Direct pressure compression may cause compression of the femoral nerve where it passes under the inguinal ligament and this may cause pressure necrosis. The common peroneal nerve and saphenous nerve are particularly at risk of compression injury as they extend distally around the neck of the fibula and medial tibial condyle, respectively.

In the lithotomy position, calf compression is always essential as it is inevitable that this position predisposes the patient to venous thromboembolism and compartment syndrome. The etiology of compartment syndrome in the calves is multi-factorial and due to the decrease in perfusion pressure caused by a combination of the weight of extremities against the supportive devices, reduction in the compartment capacity and elevation of the lower limb above the heart. Limb elevation also results in venous stasis, which predispose to venous thrombosis. The most important and consistent factor for the development of compartment syndromes is the duration of the procedure in lithotomy position. Patients requiring the lithotomy position for a period of >5 h are at extremely high risk and should be considered for continuous invasive compartment pressure measurement.

Haemorrhage

Blood loss during TURP is inevitable and is typically in the region of 500 ml. It is difficult to quantify due to the large volume of irrigating solution used. Patients lose between 2.5 and 4.5 ml of blood per minute of resection irrespective of the anaesthetic technique used. In theory, blood loss can be estimated by assaying the haemoglobin concentration of the discarded irrigation fluid, by measuring the electrical conductivity of the discarded irrigation fluid. In a laboratory setting, blood loss can also be assessed by radioactive albumin or red-cell labeling techniques. Visual assessment of the color of the discarded irrigation fluid is unreliable. In clinical practice, frequent measurement of the patients haemoglobin is the most useful investigation.

Factors associated with excessive bleeding include a large prostate gland, extensive resections (>40 to 60g of prostate chippings), prolonged surgical time (>1 h), coexisting infection as well as the presence of a pre-operative urinary catheter. The histological feature of the gland is not associated with any differences in bleeding tendency.

Urokinase released from prostate tissue may provoke systemic fibrinolysis and may worsen postoperative haemorrhage. Where blood loss is extensive, a bolus of tranexamic acid, e.g. 15 to 25mg kg⁻¹, may reduce the volume of haemorrhage. It will be prudent to give a prophylactic dose of tranexamic acid pre-surgery to patients with risk factors for excessive bleeding. Blood products should also be on standby for patients at risk of massive haemorrhage as well as for patients with cardiac risk factors where hypovolaemia may result in morbidity due to myocardial ischaemia. For patients with normal preoperative haemoglobin, who undergo a small resection (<30g), it is very unusual to require a blood transfusion during or after the operation.

TURP syndrome

TURP syndrome is essentially a clinical diagnosis based upon a collection of signs, symptoms and laboratory investigations such as electrolyte abnormalities and osmolality, caused by the excessive absorption of irrigating fluid into the circulation. It is characterized by acute changes in the intravascular volume, plasma solute concentrations, osmolality as well as some specific features depending on the type of irrigation fluid used. 1.5% Glycine, despite all its risks and potential complications (for example blindness), has till recent been used as an irrigation fluid in the UK. The effects are proportional to the volume of irrigating solution absorbed. The presentation is not always uniform, and milder cases may end up unrecognized. Other types of endoscopic surgery that also require the use of irrigation solution, e.g. hysteroscopy, may also give a clinical picture similar to that seen with TURP syndrome.

Presentation of TURP syndrome:

CVS	CNS
Bradycardia	Apprehension
Hypertension/ hypotension	Disorientation
Elevated CVP	Nausea
Angina	Visual disturbance
ECG changes (e.g. wide QRS, elevated ST, VT/ VF with severe hyponatraemia)	Confusion
CVS collapse	Coma or Seizures

Table 6: Signs and symptoms of TURP.

Mild-to-moderate forms of the TURP syndrome may occur in 1–8% of patients. The overall mortality is 0.2–0.8% and may present as early as 15 min after the onset of resection or as late as 24 h after the operation. It is therefore important to continue the monitoring of patients with risk factors for TURP syndrome post-operatively for at least 24 hours preferably in a high care environment. Severe TURP syndrome is rare due to more awareness and better prevention and monitoring; but it still carries an extremely high mortality of up to 25%.

Commonly with the use of 1.5% glycine as irrigation fluid, early features of this syndrome include restlessness, headache, tachypnoea or a burning sensation in the face and hands. Visual disturbance such as transient blindness have also been reported. Features of increasing severity include respiratory distress commonly due to pulmonary oedema, hypoxia, nausea and vomiting indicative of cerebral oedema, confusion, convulsions and coma. General anaesthesia will mask the early symptoms, resulting in a late presentation of the syndrome with advanced cardiovascular instability.

Irrigation fluid is absorbed at a rate of between 10 and 30 ml min⁻¹ of operating time. Up to 20% of patients will absorb larger volumes of irrigation fluid of over a liter of volume during an average TURP procedure. 1% Ethanol can be added to the irrigation solution and the patient's breath is then tested for ethanol every few minutes. A positive breath ethanol test indicates that a significant quantity of irrigation fluid has been absorbed. This method is well evaluated and is practically easier to implement than other methods used to identify early development of TURP syndrome. Some of the more complex methods include the gravimetric weighing method where the patient is placed on a bed scale and any increase in body weight equates to fluid absorption. The other uses a volumetric fluid balance method where the clinician calculates the difference between the amount of irrigating fluid used and the volume recovered from the cystoscope during irrigation.

The rate of absorption is influenced by the following factors:

1. The pressure of the irrigation fluid. The height of the bag should be kept as low as possible to achieve adequate flow of fluid, 70cm is usually satisfactory. However, the surgeon will frequently stop and drain the bladder to remove chippings, this is beneficial as the hydrostatic pressure within the bladder will drop significantly.
2. Low venous pressure. If the patient is hypovolaemic or hypotensive, a pressure gradient is formed and irrigation fluid will be absorbed into the intra vascular space.
3. Prolonged surgery, especially longer than an hour. The longer duration of surgery allows more time for absorption of irrigation fluid.
4. Large blood loss. A larger number of open venous plexuses or possible hypovolaemia, will increase the amount of irrigation fluid absorption.
5. Capsular or bladder perforation. Perforation allows a large volume of irrigation fluid into the peritoneal cavity, from where it is rapidly absorbed into the systemic circulation.

Solute changes in the plasma or extra-cellular compartment may alter neurologic function independent of volume-related effects. The effects of altered solute concentration may be different, depending on the type of irrigation fluid used. Acute hyponatremia can be caused by the rapid absorption of a large volume of sodium-free irrigation fluid. This will result in a form of acute water intoxication, which may result in severe central nervous system complications, such as acute cerebral oedema.

Spinal anesthesia associated with hypotension may also contribute to nausea and vomiting. CNS symptoms such as confusion may be caused by a range of different aetiological factors such as derangements of sodium, osmolality, ammonia, glycine, spinal hypotension as well as sedative drugs such as benzodiazepines, propofol or narcotics. A high index of suspicion for the development of TURP syndrome should always be maintained and it should be investigated for with any deterioration in the patient's neurological condition.

Volume changes

Acute volume changes predominantly affect the cardiovascular system. The rapid absorption of a large volume of irrigation fluid can cause severe hypertension with a reflex bradycardia. This may precipitate acute cardiac failure and pulmonary oedema, especially in patients with a poor baseline, those with a reduced cardiovascular functional reserve or congestive cardiac failure. The severity of the hypertension patients develops is not always related to the volume of fluid absorbed. It is influenced by a large interplay of physiological factors such as the patient's baseline cardio-vascular status and ability to compensate for large fluid boluses.

Rapid equilibration of hypotonic fluid with the intra-cellular fluid compartment may also precipitate intra-vascular hypovolaemia and sudden hypotension. Hypotension and hypovolaemia may be exaggerated by the sympathetic block of spinal anaesthesia, which will result in the impairment of autonomic nervous system function and regulation of vascular tone.

Solute changes

Acute changes in plasma sodium concentration and osmolality predominantly affect the central nervous system. Acute hyponatraemia is produced initially by the dilutional effect of a large volume of absorbed hypotonic, irrigation fluid. Renal water haemostasis as well as stimulation of baroreceptors will then result in a natriuresis, which will actually worsen the hyponatraemia. As previously mentioned, the neurological presentation of TURP syndrome may include the development of headaches, altered level of consciousness, nausea, vomiting, seizures, coma, and death. However, hypo-osmolality is more important than hyponatraemia in CNS pathophysiology, symptomatology as well as CNS fluid and solute haemostasis.

The Nernst equation predicts that a moderate decrease in extracellular sodium concentration only minimally alters membrane excitability. Patients who are hyponatraemic but have a normal osmolality are likely to be asymptomatic. Rapid reduction in plasma osmolality overwhelms neuronal compensatory mechanisms. Free water is absorbed into the brain parenchyma, causing water intoxication, cerebral oedema and raised intracranial pressure.

Serum sodium concentration should be measured in conjunction with serum osmolality. The correct management of hyponatraemia during TURP syndrome should depend on the serum osmolality. If the osmolality is normal or nearly so, no intervention is recommended to correct serum sodium, in an asymptomatic patient as rapid correction of hyponatraemia may lead to central pontine myelinolysis (CPM), a very serious potentially fatal complication.

The presence and severity of hyponatraemia and hypo-osmolality symptoms has been described as the most important factor determining the need for treatment as well as for morbidity and mortality. An acute decrease to $<120 \text{ mmol litre}^{-1}$ is invariably symptomatic and should be treated with hypertonic saline. Dilutional hyponatraemia may prolong the action of non-depolarizing neuromuscular blocking agents and can also results in conduction abnormalities as it may cause broadening of the QRS complex or T-wave inversion, independent of myocardial ischaemia.

Hyponatremia

Profound hyponatremia has been implicated as the cause of visual disturbances, encephalopathy, seizure, pulmonary edema and even cardiovascular collapse as well as death. The incidence of serum sodium concentration $<125 \text{ mmol/L}$ after TURP surgery may even be as high as 15% but it should be noted that the mortality of symptomatic (headache, nausea, vomiting) hyponatremia may be as high as 40%.

Dilution hyponatremia may be aggravated by renal natriuresis as well as electrolyte dilution due to the intravenous infusion of hypotonic crystalloids. Great care should be exercised when deciding on choice and volume of intravenous fluids for infusion during TURP procedures, bearing in mind that absorption of irrigation fluid is inevitable.

Hyponatremia is common, and serum sodium concentration decreases occurs in 7% to 26% of patients and may be extreme, resulting in up to a 50 mmol/L decrease in the serum sodium concentration. Decreases from a normal preoperative sodium level, to levels as low as 105 mmol/L , have been reported with the use of hypotonic irrigation fluids and may occur rapidly within only 15 minutes of resection time.

Even with marked hyponatremia, some patients may show no signs of water intoxication, and can remain asymptomatic. The reason for this is that measured and calculated osmolality does not always

correspond to the presence of osmotic active particles which cannot be measured by conventional techniques.

Severe hyponatremia has also been associated with hemolysis, renal failure, cardiovascular complications, electrocardiogram changes and conduction abnormalities, respiratory compromise, seizures, coma and death. Despite all these complications, one need to bear in mind that hyponatremia may not be the sole or even the primary cause of the neurological manifestations of TURP syndrome.

Hypo-osmolality

As mentioned before, the crucial physiological derangement responsible for CNS dysfunction is not hyponatremia per se, but acute hypo-osmolality. Basics of the blood-brain barrier neurophysiology should be considered with its effective pore size of 8 Angstrom. The tight junctions and small pore size of the blood-brain barrier, results in a barrier that is essentially impermeable to sodium but freely permeable to water. Water will then cross freely across the blood-brain barrier with any osmotic changes across the membrane or barrier. Signs of water intoxication induced by administration of vasopressin and 2.5% glucose solution can be reversed by administration of any osmotically active agents such as urea and mannitol without correcting the serum sodium concentration. The presence of osmotically active agents that are not accounted for or measured with an arterial blood gas sample, but still counts towards the plasma osmolality should always be considered.

The Nernst Equation predicts that decreases in extracellular sodium concentration accompanied by hypo-osmolality seen with TURP, only minimally alters the neuronal excitability. When decreasing the normal serum sodium of 140 mmol/L to 100 mmol/L, the calculated trans-membrane resting potential increases from -60 mV only by 9 mV, according to the Nernst Equation. Thus, theoretically, serum sodium concentration should not substantially contribute to neuronal excitability independent of serum osmolality, even when these changes are of the magnitude typically associated with severe TURP syndrome.

The brain reacts to a sustained hypo-osmotic stress within seconds to minutes, with intracellular decreases in Na^+ , K^+ , Cl^- as well as the so-called "idiogenic osmoles", which are the other osmotically active particles that are not measured. Reduction of intracellular osmotic active agents will result in a decrease in intracellular osmolality and this will prevent any further swelling or development of cerebral oedema. This is accomplished by various energy (ATP) dependent membrane ion pumps, which can actively pump out various ions to defend the cells against various osmotic stressors. However, with severe and acute osmotic change (within minutes), such haemostatic mechanisms may not compensate fast enough, resulting in the movement of free water into the brain. Cerebral edema caused by acute hypo-osmolality then increases the intracranial pressure, which will result in bradycardia and hypertension, the so-called Cushing reflex. Therefore, cerebral edema is not actually caused by decreased serum colloid oncotic pressure, but by decreased serum osmolality.

Only a few studies correlates patient outcome after TURP surgery with both serum sodium concentration and osmolality. In a series of 72 patients undergoing TURP, serum sodium concentrations decreased by 10 to 54 mmol/L in 26% of the patients, while osmolality only changed in two patients (3% of the study population). These two patients had both hyponatremia and hypo-osmolality and both developed pulmonary edema and cerebral encephalopathy, symptoms of severe TURP syndrome. It was found that their serum sodium concentration decreased by 27 and 30 mmol/L and serum osmolality to 260 and 256 mmol/L respectively. It is interesting to note that the five patients in this series with the largest decreases in serum sodium concentration (by up to 54 mmol/L) had no changes in serum osmolality and no signs of TURP syndrome. One can hypothesize that the decreases in sodium occurred slow enough to allow for patient compensatory mechanisms to maintain a balanced osmolality. Mortality and morbidity should not be predicted by solely looking at serum sodium concentration, and serum and urinary osmolality should also be considered as it probably plays a more important role.

Treatment of Hyponatremia and Hypo-osmolality

Precautions should always be taken to avoid severe hyponatremia and hypo-osmolality, by early diagnosis of the development of TURP syndrome. Diuretics have also been implicated in the rapid onset of hyponatremia. Diuretics have traditionally been used to treat hypervolemia after TURP procedures. One should note that this is not ideal and perhaps a dangerous practice because their use may worsen hyponatremia and hypo-osmolality and therefore lead to the development of TURP syndrome. Furosemide act within minutes on the ascending loop of Henle where they inhibit chloride uptake, which causes urinary sodium loss and promote salt-wasting and therefore further worsens

hypo-osmolality. Mannitol also causes sodium losses during the first 12 hours of treatment after TURP surgery but does not lower serum sodium levels during the first three to five hours postoperatively. One can argue that furosemide should not be used in the treatment of TURP syndrome in isolation, but perhaps only in conjunction with the use of hypertonic saline.

A patient's serum sodium concentration and osmolality may continue to decrease for some time after the TURP procedure. This may be due to the further slow absorption of irrigation fluid from the perivesicular and retroperitoneal spaces into the circulation.

The TURP syndrome can start as late as 4 to 24 hours after surgery and this late presentation may be with coma, blindness, generalized seizures or hemiplegia. These problems may be prevented by the use of a loop (salt-wasting) diuretics with a concomitant infusion of saline or hypertonic saline. This technique could even be used in the presence of near normal serum sodium concentration during the first 12 hours postoperative. It will be protective against osmotic imbalances caused by bladder irrigation, which may precipitate TURP syndrome and some investigators have even recommended this regime as a prophylactic measure.

These clinicians have suggested an approach advocating the pre-treatment with hypertonic saline before TURP procedures or before the development of TURP syndrome. The idea is that pre-treatment with hypertonic saline should decrease the degree of dilutional hyponatremia and therefore should also protect patients against the development of TURP syndrome. This approach may be successful in decreasing the incidence of hypo-osmolality caused by the TURP syndrome. The problem is that this treatment will most likely exacerbate the incidence and severity of the TURP syndrome's hypervolemic manifestations. We have already established the fact that the serum sodium concentration will not always reflect serum osmolality. Serum sodium concentration should therefore always be reported with the serum osmolality when irrigation solutions have been used which contains osmotically active solutes such as glycine, mannitol or sorbitol. If osmolality is near normal, no intervention to correct sodium is recommended for asymptomatic patients, even in the face of reduced serum sodium concentration.

This recommendation is also important to prevent the feared complication of central pontine myelinolysis (CPM), which may occur, with unnecessary and too rapid correcting of hyponatremia. Demyelination can occur in the extra-pontine areas, the process is also referred to as "osmotic demyelination syndrome". This complication is most often seen in women, probably due to the sex differences in cellular ion pump capacity, but it has been reported after rapid serum sodium concentration correction in male TURP patients also.

The management of severe hyponatremia in severe TURP syndrome is challenging especially due to possible iatrogenic complications resulting from treatment. It has also shown that were the treatment of symptomatic hyponatremia accompanied with hypo-osmolality have been instituted too slowly, the patient outcome has been associated with a higher morbidity and mortality than when compared with rapid correction.

Many reports suggesting that a 1.5 to 2.0 mmol/h⁻¹ correction rate is safe, have failed to consider the changes in plasma osmolality. Several investigators have suggested that osmotic stress is probably greater when correcting chronic- compared with acute-hyponatremia. It has also been suggested that the rate at which hyponatremia and hypo-osmolality has developed should be brought into consideration when its treatment is planned. Where hyponatremia and hypo-osmolality have developed over a shorter time period, the clinician should be more aggressive with its correction and treatment in returning the plasma osmolality and solute balances back to normality.

It is known that extracellular changes in plasma osmolality equilibrate within minutes across the blood-brain barrier and brain cell membranes. Hypo-osmotic stress within the plasma (extra-cellular compartment) therefore affects intracellular ion and amino acid concentrations acutely. There is up-regulation of ion pumps for the export of organic osmolytes from the cellular compartment back into the plasma as well as a down-regulation of the synthesis of intra-cellular amino acids. These haemostatic compensatory mechanisms are highly effective responses to protect the intra-cerebral compartment against hypo-osmotic stressors. Once the down-regulation of intra-cellular amino acid synthesis have been induced by hypo-osmolality, it is not known how fast this compensatory mechanism can be reversed again, after osmolality has been restored. Due to the slow reversal process for the synthesis of amino acids, any rapid correction of acute asymptomatic hyponatremia or hypo-osmolality may result in central pontine myelinolysis (CPM).

As mentioned before, the presence of symptoms has been described as the single most important factor determining morbidity and mortality from hyponatremia in severe TURP syndrome. The most

important consideration whether to institute treatment of hyponatremia would be the presence and severity of its symptoms. Instituting therapy in the absence of symptoms risks too rapid a correction because the correction rate is difficult to control and monitor. Therefore, osmolality should be monitored and corrected aggressively only until symptoms have substantially resolved. After the resolution of symptoms, it is recommended that the Na^+ correction should be continued slowly at an average correction rate of no more than $1.5 \text{ mmol L}^{-1}/\text{hr}^{-1}$.

Hyperammonemia

The portal bed and kidneys can metabolize glycine once it has entered the systemic circulation. The primary metabolic pathway used by the liver and kidneys, to metabolize glycine, is oxidative deamination. The deamination of glycine leads to the formation of two potentially toxic metabolites: glyoxylic acid and ammonia. The central nervous system can also metabolize glycine, as it contains a glycine cleavage enzyme system that splits glycine into carbon dioxide and ammonia.

It seems logical that an increase of serum ammonia during TURP surgery is the result of glycine absorption from the glycine irrigation fluid used. Patients undergoing TURP surgery without the use of glycine as an irrigation fluid do not develop hyperammonemia. Although acute alteration in CNS function can be caused by hyperammonemia, the exact role of hyperammonemia in terms of its contribution to the severity of the symptoms and complications still remains controversial and unclear. Ammonia is considered to be a cerebral depressant, and may contribute to the development of coma, in patients with severe TURP syndrome.

Hyperammonemia can be effectively treated with metabolic active substances such as L-arginine. L-arginine is therefore the methods of choice for limiting the increase of plasma ammonia concentration when glycine irrigants are used. It acts on the liver to prevent the hepatic release of ammonia and also accelerates the conversion of ammonia to urea. The time necessary to deplete endogenous arginine stores may be as little as 12 hours. Prophylactic administration of IV L-arginine markedly reduces the increase in blood ammonia concentration when fasted patients have received intravenous glycine. When L-arginine have been infusion towards the conclusion of glycine administration it effectively prevent further increases in the blood ammonia concentration and also accelerated its metabolism to normal serum levels. Doses of 4g (20 mmol) infused over three minutes and 38g (180 mmol) infused over 120 minutes have been recommended. No toxicity was noted with either of these regimens.

Glycine and its metabolites

Glycine is a major inhibitory neurotransmitter in the CNS and retina. Glycine toxicity may cause nausea, headache, malaise, and weakness as well as visual disturbances. Although sodium can also lead to the development of visual disturbances and transient blindness on the basis of cerebral oedema, glycine is the most common culprit. Glycine can even exert a direct depressant effect on the myocardium, which may be tolerated poorly in patients with poor baseline myocardial function.

N-methyl D-aspartate (NMDA), the major inhibitory neurotransmitter, acts on the NMDA receptor and the activity of this receptor is potentiated by glycine. Glycine may also have a central stimulation action and may lead to encephalopathy and seizure via the same N-methyl-D-aspartate (NMDA) receptor. NMDA receptor activity is markedly potentiated by glycine and, along with its role as an inhibitory transmitter, may facilitate excitatory transmission in the brain through allosteric activation of the NMDA receptor. Glycine therefore has a paradoxically excitatory effect on the CNS, which may precipitate encephalopathy and seizures. Magnesium, who has a protective role, exerts a negative control on the NMDA receptor, also having a membrane-stabilizing effect. Magnesium plasma levels may also be reduced through dilution by the absorption of hypotonic irrigation fluids, and this may contribute to the increased susceptibility to seizure activity. Magnesium should be considered as part of the prophylaxis and treatment therapy for seizures in patients with severe TURP syndrome.

The liver and kidneys metabolize glycine by oxidative deamination to glyoxylic acid and ammonia. The redistribution half-life of glycine is 6 min. The terminal half-life of glycine is dose-dependent and varies from 40 min to several hours as seen during glycine toxicity, depending on the duration of the glycine infusion. Glycine, the major inhibitory neurotransmitter along with gamma-aminobutyric acid (GABA) is known to act on both the spinal cord and midbrain levels and also have a significant role in higher cortical neurotransmission. Its role in post-TURP encephalopathy and seizure activity is well known, suggested by the significant serum hyperglycinemia seen in patients with encephalopathy and seizures after TURP procedures. A large concentration of glycine may be harmless if it is limited to the plasma but can be fatal in the brain. Signs of glycine toxicity include nausea, vomiting, headache, malaise and weakness. These symptoms will present with a 1.5% Glycine infusion rate of $3.5 \text{ mg/kg}^{-1} \text{ min}^{-1}$, which equate to an infusion rate of 54 mL/min in the averaged size adult male patient.

Visual disturbances in TURP syndrome vary in severity from blurred vision to complete blindness. Several investigators have remarked on the unusual calmness of their patients experiencing what would seem to be an extremely frightening complication. Some patients present with either a sluggish or a fixed and dilated pupils with total loss of light/dark discrimination. Hyponatremia and cerebral edema may also contribute to the visual disturbances seen with glycine toxicity. Patients with cortical blindness, on the other hand, lose all visual sensation (light perception and the blink reflex) but retain the pupillary responses to light and accommodation. Although it is difficult to separate the effects of serum sodium concentration from those of other retinal neurotransmitters, sodium appears to play only a minor role in the visual disturbances.

It is now recognized that glycine is the most likely cause of visual disturbances in patients with TURP syndrome. A large series of symptomatic patients, with visual changes, had their serum glycine levels measured to be able to compare it to the symptomatology. The findings from these studies concluded a serum glycine concentration threshold of > 4000 micro mol/L for symptomatic visual impairment and > 14000 micro mol/L for blindness. Glycine is the major inhibitory neurotransmitter in the retina. Glycine is found in the inner plexiform layer as well as in the bipolar cells of the human retina, where it causes hyperpolarization of ganglion cells. The changes in the visual evoked potentials, caused by glycine in the absence of large osmolality changes have also been well documented. From these observation it can be concluded that glycine will cause retinal pathology independent of cerebral edema caused by hypo-osmolality.

Glycine may also exert toxic effects on the kidneys. A study in rats found histologic evidence of glycine toxicity in their kidneys six hours after either intravenous or intra peritoneal administration when large doses of 1.5% glycine solution was given. This study did not investigate whether the kidney would eventually recover from the apparent toxic insult. Hyperoxaluria from the metabolism of glycine into oxalate and glycolate has also been proposed as a route whereby glycine could cause renal failure in susceptible patients.

Seizures after TURP procedures associated with hyponatremia and hypo-osmolality are likely to be resistant to benzodiazepine and anticonvulsant therapy. Benzodiazepines may result in apnea, which will worsen the patient's condition. An NMDA-receptor antagonist or glycine antagonist will therefore be a more rational therapeutic choice.

Magnesium is a commonly available drug, safe to use and effective antagonist at the NMDA receptor. Magnesium levels may be dramatically lowered after TURP surgery due to dilution or in patients who have been treated with a loop diuretic. Therefore, a trial of magnesium therapy for seizures in patients in whom glycine irrigation fluid was used should always be considered.

Vision returns to normal within 24 hours as glycine approaches normal levels because the half-life of glycine is approximately 85 minutes. Reassurance should be given to the patient that vision is expected to return to normal within this time period.

In a study where three hundred and sixty patients with symptomatic BPH were randomized into a prospective, controlled trial, three types of irrigation modalities were compared. One hundred and twenty patients were irrigated with glycine 1.5% solution (glycine group), 120 patients used glucose 5% solution (glucose group) and 120 patients used normal saline 0.9% solution (saline group). Patient demographics, operation time, hospital stay, postoperative amino acid glycine assay, troponin levels as well as perioperative complications were studied. No difference was found in the postoperative haemoglobin and haematocrit levels between the groups. A high glycine level was associated with the TURP syndrome. Of the seventeen patients who developed TURP syndrome; all were in the glycine group and they had the highest postoperative amino acid glycine levels. Slight increases in serum sodium levels were detected in the saline group. Transient hyperglycemia and hypokalemia occurred in the immediate postoperative period in the glucose group. Endoscopic TURP surgery performed with either 5% glucose or 0.9% saline irrigating solution was associated with a lower incidence of TURP syndrome, lower catheterization period, shorter hospital stay and no cardiac toxicity in comparison with the use of .5% glycine solution.

Treatment

If TURP syndrome is suspected, surgery must be abandoned as soon as possible and intra-venous fluids should be stopped. Treatment should involve supporting respiration (if necessary, with intubation and ventilation) as well as circulatory support. Bradycardia and hypotension should be treated with atropine and adrenergic drugs. IV anticonvulsants (e.g. diazepam or lorazepam) should be used to control seizures. IV magnesium therapy should be considered, if seizures are difficult to control. Blood should be obtained for sodium, osmolality and haemoglobin.

Treatment of Severe TURP syndrome

1.	2.	3.	4.
Suspect or diagnose TURP syndrome	Stop surgery Give 100% oxygen	ABG	If $[Na] < 120 \text{ mmol l}^{-1}$ Treat with 3% NaCl
Clinical diagnosis	Airway: consider Intubation	Check Hb, sodium and osmolality	Aim to correct $[Na]$ by 1 mmol/l-1/hour
ABG	Breathing: IPPV	If hypervolaemic and pulmonary oedema: Treat with furosemide and 20% mannitol or hypertonic saline IV.	Admit to ICU/ HCU
Serum osmolality	Circulation: Inotrope/ vasopressors	Consider A-line and CVP	Hourly monitoring of Hb, Sodium and osmolality

Table 7: Management of severe TURP syndrome.

Management of severe TURP syndrome.

Diuretic therapy, such as IV furosemide, is only recommended to treat acute pulmonary oedema caused by transient hypervolaemia. Furosemide worsens hyponatraemia, but is a very effective therapy for the renal elimination of free water. Mannitol treatment (e.g. 100 ml of 20%) causes less sodium loss than loop diuretics.

Use of hypertonic saline

Hypertonic saline (3%) is indicated to correct severe hyponatraemia. This treatment is recommended if serum sodium is less than $120 \text{ mmol litre}^{-1}$ or if severe symptomatology develops (transient blindness, persistent nausea and vomiting, severe headaches, and pronounced hypotension). The rate of correction should be tightly regulated not should never exceed $2 \text{ mmol litre}^{-1} \text{ h}^{-1}$ in the first 24 h. Too rapid correction may lead to hypervolaemia, cerebral oedema and CPM. Once the symptoms of TURP syndrome have resolution, a slower average correction rate of less than $1.5 \text{ mmol L}^{-1}/\text{hr}^{-1}$ should be targeted. Correction to normal serum sodium concentration is not indicated, the aim should be clinical improvement of symptomatology. Hypertonic saline should be given into a large vein.

Invasive monitoring of arterial and central venous pressures is very helpful in managing patients with large fluid shifts. Transferring the patient to a high-care or intensive care environment after operation is advised. TURP syndrome may worsen as irrigation continues after the operation as well as continues absorption of irrigation fluid takes place from the retroperitoneal space. Visual disturbances caused by glycine typically resolve fully within 24 hours and it requires no further treatment. Patient reassurance is vital to allay anxiety.

Newer techniques of prostatic resection

Newer techniques of prostatic resection use different types of energy (heat, laser, ultrasound, or microwave) to vaporize prostatic tissue and coagulate surrounding blood vessels. These techniques are reported to cause less haemorrhage than conventional TURP surgery. Unfortunately, specimens for histology cannot be obtained. Since monopolar diathermy is also not used here, normal saline may be used as the irrigating solution, minimizing the risk of the TURP syndrome. The use of saline irrigation with bipolar TURP cautery causes a smaller reduction in serum sodium and hemoglobin levels and less fluid overload than monopolar TURP surgery with conventional irrigation fluids.

Authors concluded that bipolar saline irrigation during TURP surgery is a safer technique as it virtually eliminates the risk of TURP syndrome in high-risk patients with large prostates that require lengthy resections. With bipolar saline irrigation, patients absorb a much more physiological fluid, which result in less dilutional hyponatremia, when compared with patients in which hypotonic irrigation fluids was used. Normal saline is therefore closest to the ideal irrigation fluid currently available for TURP surgery. Its electrical conducting properties prohibit its use with conventional monopolar TURP resection systems, but bipolar cautery makes its use possible. This change in practice has revolutionized TURP procedures in terms of patient safety and prevention of complications such as the TURP syndrome.

Conclusion

Our understanding of the pathophysiology leading to the TURP syndrome has improved in recent

years. Complex changes in intravascular volume, plasma electrolyte concentrations, osmolality as well as neurophysiologic function are all involved in the pathophysiology contributing to the TURP syndrome. The prevention, diagnosis, and treatment of TURP syndrome are challenging. Abnormalities in serum solute concentrations as well as intra-vascular volume status can occur simultaneously and may suggest opposing diagnoses and treatments.

Although the monitoring of serum sodium concentration during TURP surgery is common practice and is effective for assessing intravascular absorption, it may be more important to monitor serum osmolality. Hypo-osmolality seems to be the major contributor to neurological and hypovolemic changes. Supportive care remains the mainstay of management for renal, pulmonary, and cardiovascular complications of TURP syndrome. Formulating a management plan may include the management of complications such as hyperammonemia, hyperglycinemia, hyponatremia, hypo-osmolality, encephalopathy and seizures.

These pathophysiological processes and therapeutic interventions can also be applied to similar syndromes occurring during gynaecological endoscopic surgery (eg. endometrial ablation), where saline, glycine or sorbitol irrigation solutions have been used.

It is clear from the decreasing incidence of TURP syndrome over the past 40 years that progress has been made in its prevention and treatment. Consensus regarding the exact definitions of what constitutes acute and chronic hyponatraemia and hypo-osmolality still needs to be agreed upon. The etiology and pathophysiology of the encephalopathy associated with TURP syndrome are multifactorial. Additional studies should be done to establish what the best therapeutic options and management strategies might be. The management of hyponatraemia and hypo-osmolality has been described and great care should be taken to avoid CPM when correcting these abnormalities. The introduction of new therapies for the medical and surgical management of prostatic hypertrophy will minimize the risks associated with TURP syndrome.

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Difficult Airway Society 2015 Guidelines

An overview for FCA Part 2 Candidates

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Introduction

The original Difficult Airway Society (DAS, www.das.uk.org) Guidelines for Unanticipated Difficult Intubation were published in 2004.¹ Widely accepted and referenced, these guidelines were a success for the society, and undoubtedly improved patient safety, but had become quite out of date. However, it was decided to wait for the completion of the United Kingdom's Fourth National Audit Project (NAP4)^{2,3} in 2011 before beginning to update the intubation guidelines, in order to incorporate these findings. Over 23 000 abstracts and nearly a thousand full text articles were reviewed in the process. The new DAS intubation guidelines were officially published and simultaneously presented at the 1st World Airway Management Meeting (WAMM) in Dublin, Ireland, in November 2015.^{4,5} It is important to note that while these guidelines (like their 2004 predecessors) are evidenced-based, they are comprised of consensus expert opinion. Input from the DAS membership was included at the annual scientific meeting in November 2014, and online from members worldwide (including South Africa).

Available guidelines

DAS has produced a series of guidelines, which are updated at irregular intervals by the appropriate working groups. These include the general difficult airway guidelines⁴ (2015), obstetric⁶ (2015, in conjunction with the OAA), paediatric⁷ (in conjunction with the APA) extubation⁸ (2013), and fiberoptic intubation via supraglottic airway guidelines. These are reproduced at the end of these notes for your reference and convenience, but only the latest intubation guidelines are discussed.⁵

DAS have continued the theme of having a 'Plan A/B/C/D' approach to unexpected difficulty. This ensures that the practitioner does not become fixated on one technique (for instance, intubation) and allow the patient to become dangerously hypoxic when changing approach (for instance, mask ventilation or placement of a supraglottic airway device (SAD/SGA)) would allow oxygenation. Implicit in this strategy, however, is the presumption that patients are carefully assessed preoperatively, and an alternative airway approach (for instance, awake fiberoptic intubation) is performed if the standard approaches are not feasible. Thus, these guidelines should not be relied upon in *anticipated* problems, but rather for *unanticipated difficulty*.

All DAS current guidelines are freely available for download from the DAS website at www.das.uk.com/guidelines. A larger collection of algorithms including guidelines from other organisations and societies (ASA, Vortex, Canadian, SA Resuscitation Council, etc.) can be found at www.openairway.org/algorithms/.

It should be noted that algorithms along *do not* constitute the full extent of the guidelines. Reading or using the algorithms alone, without the accompanying article,⁵ will inadequately prepare the practitioner to make evidenced-based decisions at a specialist level. These notes highlight the most salient points, new changes, and some controversies.

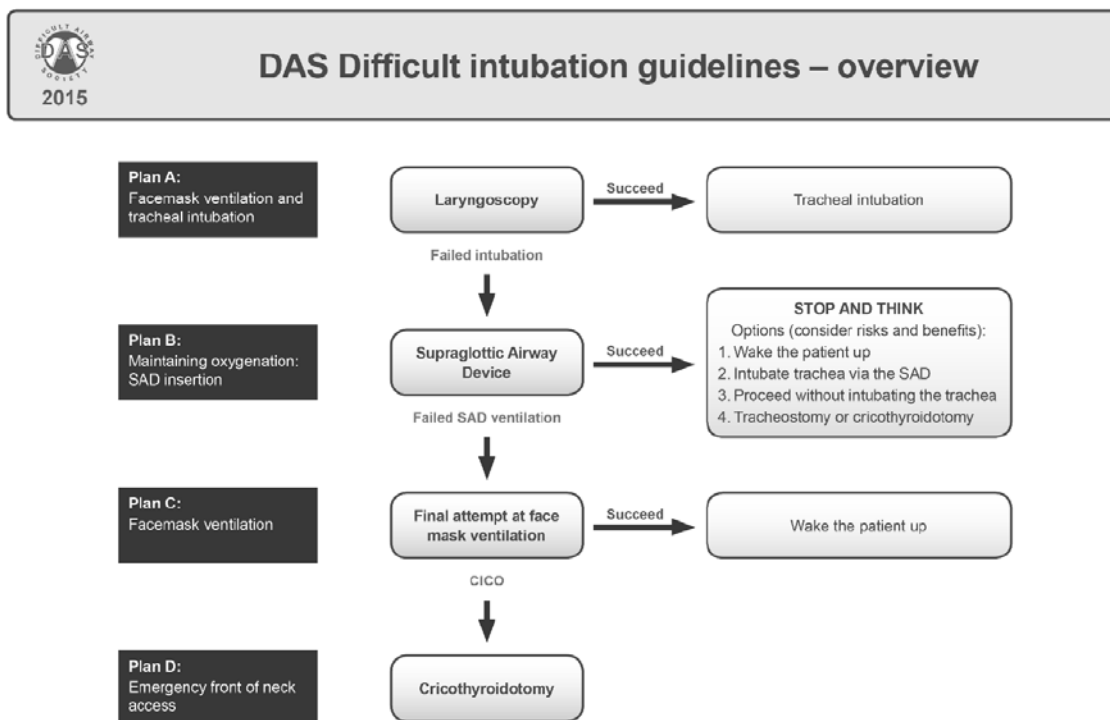
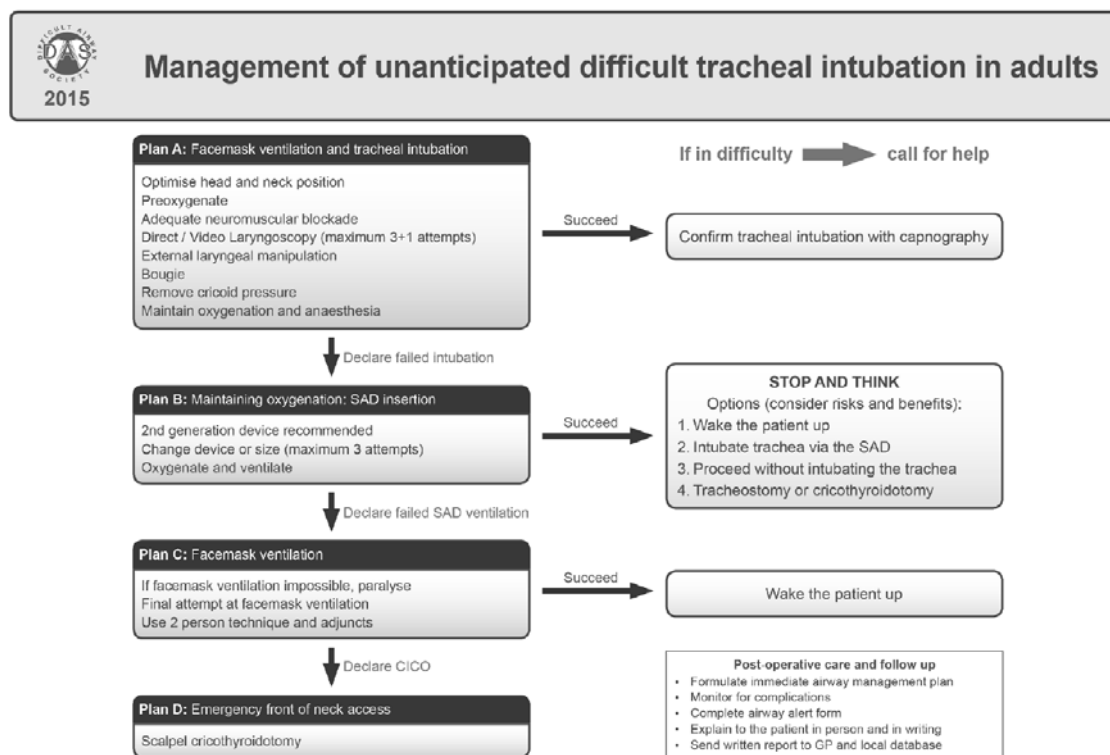


Figure 1. DAS 2015 Difficult intubation guidelines - overview. See note under references for usage permissions.



This flowchart forms part of the DAS Guidelines for unanticipated difficult intubation in adults 2015 and should be used in conjunction with the text.

Figure 2. DAS 2015 guideline on 'Management of unanticipated difficult tracheal intubation in adults.'

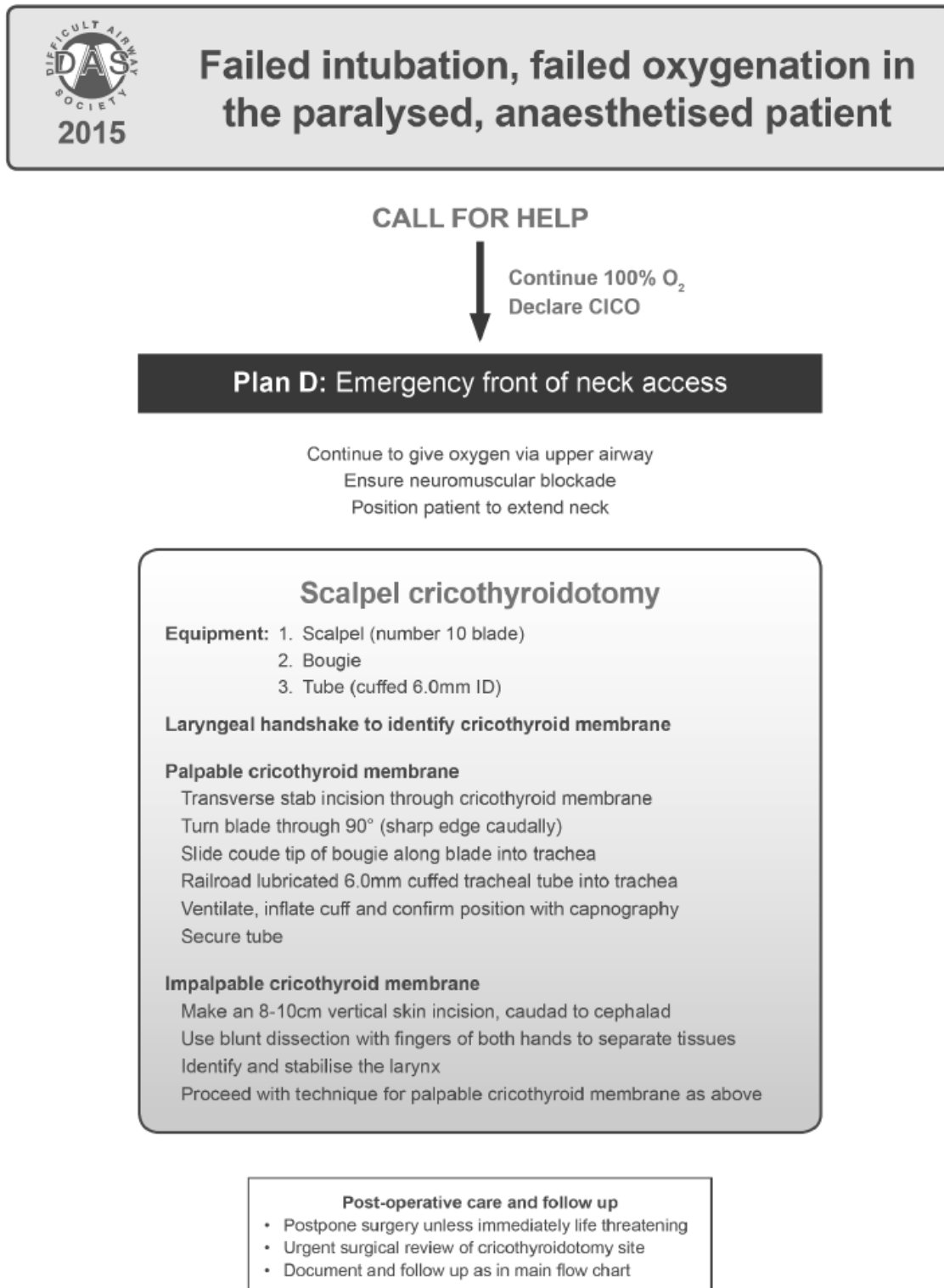


Figure 3. DAS 2015 guideline for emergency front-of-neck surgical airway access in the failed intubation, failed oxygenation situation in the anaesthetized patient.

Significant changes in the 2015 guidelines

Simplification of the difficult intubation guidelines

Previously, the DAS guidelines were different for situations of unexpected difficulty in elective (routine induction) compared to emergency (rapid sequence induction) patients. It was recognised that this created unnecessary complication and reduced performance in critical situations. Furthermore, fear of aspiration is believed to cause practitioners to delay in taking essential steps to ensure oxygenation in patients where difficulty was encountered in RSI. The new algorithms do not distinguish between these situations, and stress ensuring oxygenation over other concerns in an emergency.⁵

The observer will note that two versions of the 2015 algorithm have been created. A simplified 'Overview' algorithm states only the critical steps, and is intended to be rapidly accessible in an emergency situation. A more detailed version has the identical layout and steps, but includes prompts for optimisation of each step. This is ideal for study purposes, or even to serve as a checklist for a second practitioner in an emergency.

Facemask ventilation and intubation

Emphasis in the new guidelines is placed upon optimizing the conditions for facemask ventilation and subsequent intubation as the routine 'Plan A' in daily airway management. This includes making and stating a plan for failure, adequate pre-oxygenation, and good positioning. The value of ramping the patient to achieve the optimal 'sniffing' position is well recognized. Stress is placed on obtaining a position where the external auditory meatus and sternal notch are in the same horizontal plane with the patient's face is parallel to the ceiling – the so-called 'ear-to-sternal-notch' (E2SN) position – which straightens the curvatures of the airway and provides an visual axis for intubation.^{9 10}

The 2015 guidelines include the concept of early use of videolaryngoscopy (VL), either as a standard approach, or when difficulty is encountered. This is based on increasing evidence that VL improves glottis view in difficult airways, and increases intubation success rates in appropriately skilled hands. It should be noted, however, that this presumes the practitioner is well trained with the device in question. All anaesthetists should make efforts to ensure they are skilled with VL. Furthermore, a shaped stlyet or bogie should always be used conjunction with VL.

It is well established that neuromuscular blockade (NMB) improved intubation conditions, and does not cause deterioration in ability to provide facemask ventilation. The guidelines stress considering administration of further paralytics when in difficulty, and advocate for the use of NMB monitoring, especially when airway management attempts are prolonged.

Maintenance of oxygenation

The guidelines emphasize the early recognition of difficulty or failure to intubate, and encourage that the situation is immediately declared. Rapid placement of an SAD in this situation (even when facemask ventilation is possible) affords the anaesthetist the opportunity to remain calm and consider options carefully. For the first time, the guidelines suggest using a 2nd generation SAD in all such situations. (See discussion of this below). However, failure to obtain adequate oxygenation within two attempts with an SAD (allowing a third attempt with a second type/size of SAD after the first two failures) should prompt immediate progression to front-of-neck access. It is important to note that repetitive insertion attempts cause worsening airway trauma, and more than 3 attempts seldom results in an improved success rate. Bougie-guided insertion of Proseal LMA (Brimacombe maneuver) has been shown to improve first-insertion success and should be considered if the anaesthetist is practiced in this technique.

"Stop and Think"

If the placement of an SAD is successful in establishing oxygenation and ventilation, the practitioner is prompted to consider four options: waking the patient up with the SAD in place; performing a fiberoptic-guided intubation through the SAD; proceeding without intubation; or performing a formal tracheostomy or cricothyroidotomy. In settings with access to a flexible endoscope, blind intubation through the SAD is considered redundant.

Inclusion of this phase is aimed at eliminating the fixation on need to intubate the patient, and giving the practitioner a chance to carefully consider the options. This emphasis on avoiding 'human factors' errors in airway management is a strong theme in the new guidelines, as these errors were implicated in 40% of cases of harm in NAP4.³ Further work into the use of cognitive aids for crises in airway management is ongoing.

Front-of-neck access

Previously known as 'surgical airway' techniques, the terminology 'front-of-neck access' has become more popular to help emphasise that this is a set of approaches which are not limited to surgeons. All airway practitioners (especially anaesthetists) should be experts in obtaining a surgical airway, even if the skill is never required in anger.

Predominantly on the basis of the findings of NAP4, the guidelines have now been simplified to remove needle/cannula cricothyroidotomy and proceed directly to a surgical cricothyroidotomy (or cricothyrotomy, if you prefer the American nomenclature). The reasons behind this are two-fold: Firstly, needle 'cric' was associated with a very poor success rate in NAP4. Secondly, recent work has shown that practitioners in an emergency crisis often vacillate between needle and scalpel when offered the choice. By simplifying the algorithm and providing one didactic technique, the cognitive loading and delay is diminished. However, the guidelines do suggest that anaesthetists receive frequent training and simulation on CICO situations.

The 2015 guidelines clearly describe the advised technique for cricothyroidotomy. The required equipment is a scalpel with number 10 blade, a coudé-tipped introducer/bougie, and a 6.0 cuffed endotracheal tube. The non-dominant hand is used to perform a 'laryngeal handshake' (gripping and moving the larynx from side to side to clearly identify its position). The index finger is then moved in the midline to palpate the thyroid and cricoid cartilages, and the cricothyroid membrane between them. If these can be palpated, a single horizontal stab incision is made, the blade rotated into a vertical orientation, and pulled sideways to allow insertion of a bougie (preferably a Frova introducer, to allow immediate oxygen insufflation). If the cartilaginous structures are impalpable, an 8-10 cm vertical incision is made in the midline of the neck, followed by blunt dissection with the fingers until the cartilages are palpable, and then a stab incision and insertion of bougie, as above. Finally, a 6.0 cuffed ETT is inserted to allow ventilation.

Debates & controversies

The use of cricoid pressure during rapid sequence intubation remains extremely controversial, with vociferously divided opinions in the literature and online media. While it is not discussed further here, anaesthetists should have an understanding of the evidence for, and criticisms against, its use. In recognition that *injudiciously* applied cricoid pressure (CP) can worsen laryngoscopic view, a gradual release of CP during difficult intubation, and complete release during insertion of a supraglottic airway, is advocated in the new guidelines. It is important to realize that by the time a rescue SGA is required, ensuring oxygenation takes precedence over prevention of aspiration, and maintaining CP while inserting an SGA can hinder the distal tip of the SGA from becoming adequately seated in the cricopharyngeus muscle ring. This will prevent adequate sealing, may worsen risk of aspiration, and in the worst-case scenario can cause the tip of the device to enter the trachea, causing complete airway obstruction (this is infrequently seen with devices such as the laryngeal tube airway).

The routine use of 2nd generation supraglottic airways has been promoted by these guidelines, and echoed in the literature. Largely, this is based on numerous studies which show improved protection against aspiration in various non-emergency models.¹¹⁻¹⁵ While outcomes data is very limited, it is worth noting that in the NAP4 study, only one case of aspiration with an SAD occurred with a 2nd generation device, although absolute numbers were not sufficient to draw a strong conclusion. While it makes inherent sense to use devices offering aspiration protection, it must be remembered that the most critical function of placing an SAD in a failed intubation is to provide oxygenation. Some of these devices require more operator skill, most are more costly than the 1st generation equivalent, and they may not be immediately at hand.

Videolaryngoscopy has undoubtedly had an enormous influence on the practice of difficult airway management over the last decade, but is not a panacea. Importantly, while VL often facilitates an improved view of the larynx, it can still be exceptionally difficult to insert the ETT. Anaesthetists must understand the limitations of VL, and the appropriate techniques and introducers/bougies/stylets to use with each type of blade. Finally, in our context, VL remains unavailable in a great many settings. Making certain we maintain excellent direct laryngoscopy (DL) skills is therefore essential.

The removal of cannula cricothyroidotomy from the guidelines has been met with significant resistance. Anaesthetists, as a group, are generally more comfortable with percutaneous techniques which involve a needle rather than a blade. Other detractors argue that equipment for surgical cric is not always immediately at hand, whereas a large bore IV cannula is always close by. Furthermore, the argument that success rates of surgical cric in NAP4 were much better than needle cric is tainted by the fact that all surgical cricothyroidotomies in the audit were performed by surgeons who were

present in theatre or arrived on scene. Work from Australia has shown that cannula cricothyroidotomy and oxygen insufflation can be readily and reliably achieved in an animal simulation model by practitioners who are well (and frequently) trained in the technique (*Dr Andy Heard, pending publication*). However, this in itself is not necessarily an achievable outcome in many settings.

The technique of surgical airway access is also hotly debated. The DAS guidelines advise a standardized “scalpel-bougie-tube” technique, where other experts promote scalpel-finger-bougie, needle-guidewire-dilator-tube, scalpel-hook-tube, scalpel-hemostat-tube, etc. While we are unlikely to see RCTs of these techniques in clinical practice, numerous studies on laboratory and animal models are underway. Most importantly, the savvy anaesthetist should know the potential pitfalls of any technique, and be confident and practiced in performing the one method they have selected.

Additional Guidelines

Provided below for your reference. High-quality versions of all guidelines are available from the DAS web site and may be freely used for educational purposes with attribution. (See the comment under ‘References’ with regards to permissions for reproduction).

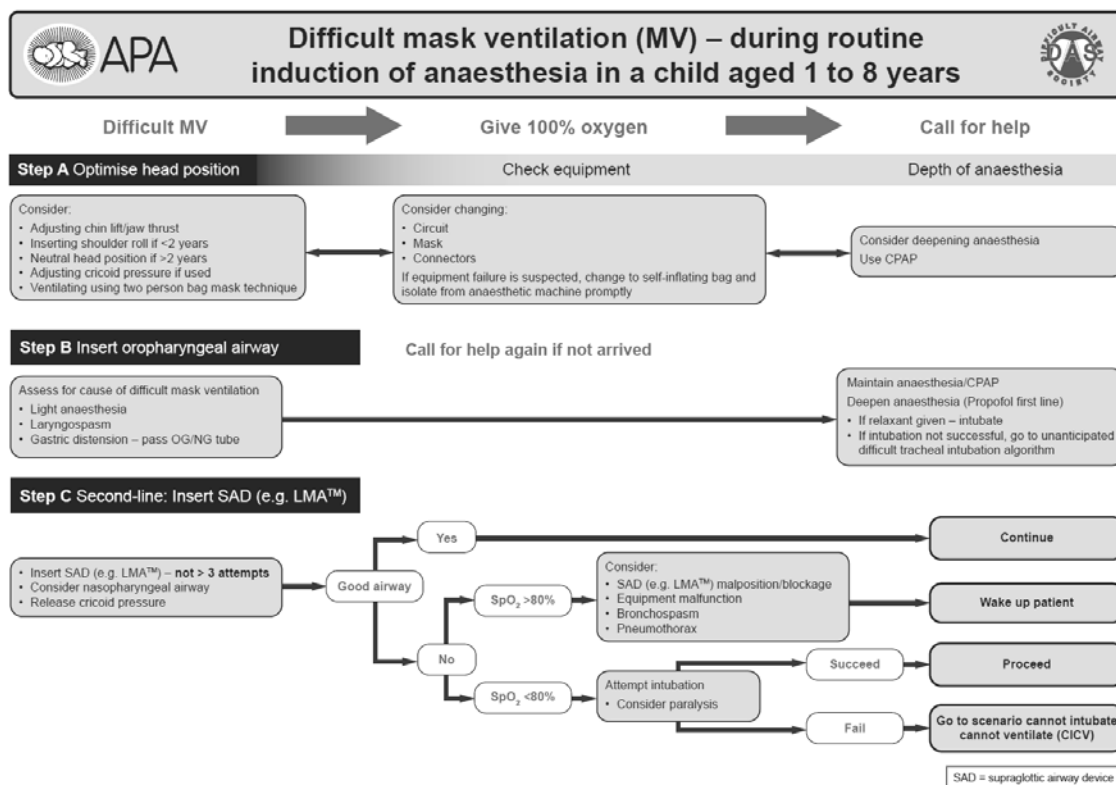


Figure 4. DAS/APA algorithm for difficult mask ventilation in children.

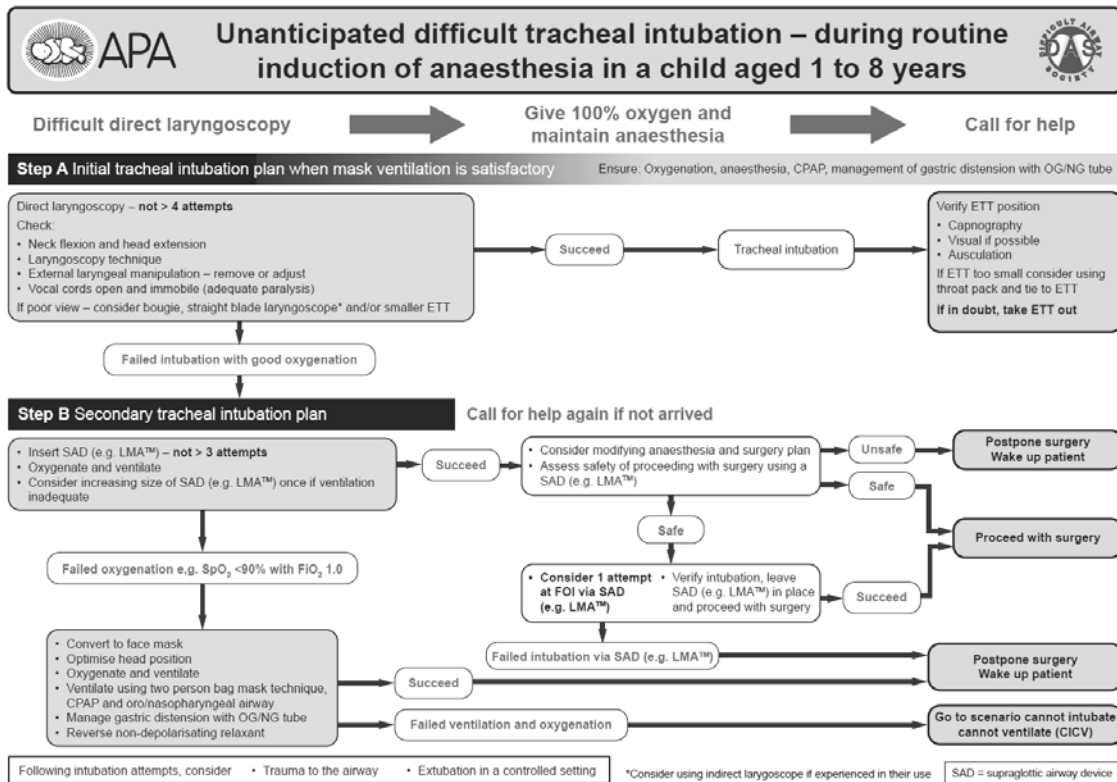


Figure 5. DAS/APA algorithm for unexpected difficult tracheal intubation in children.

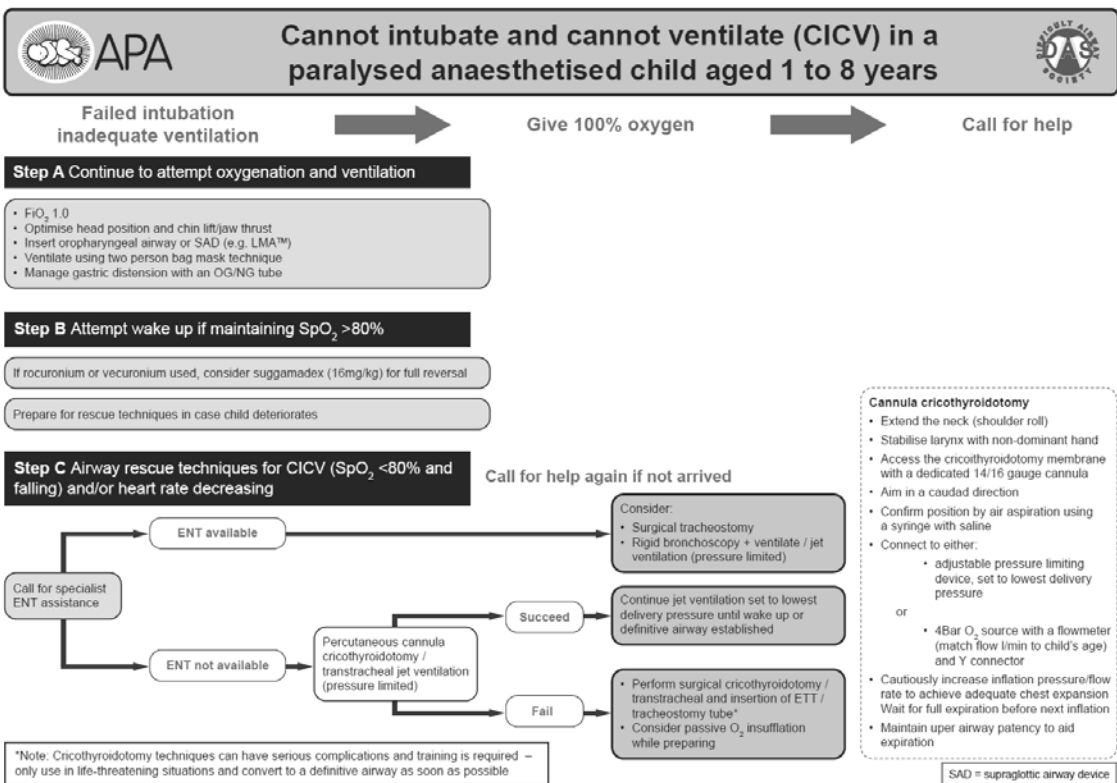
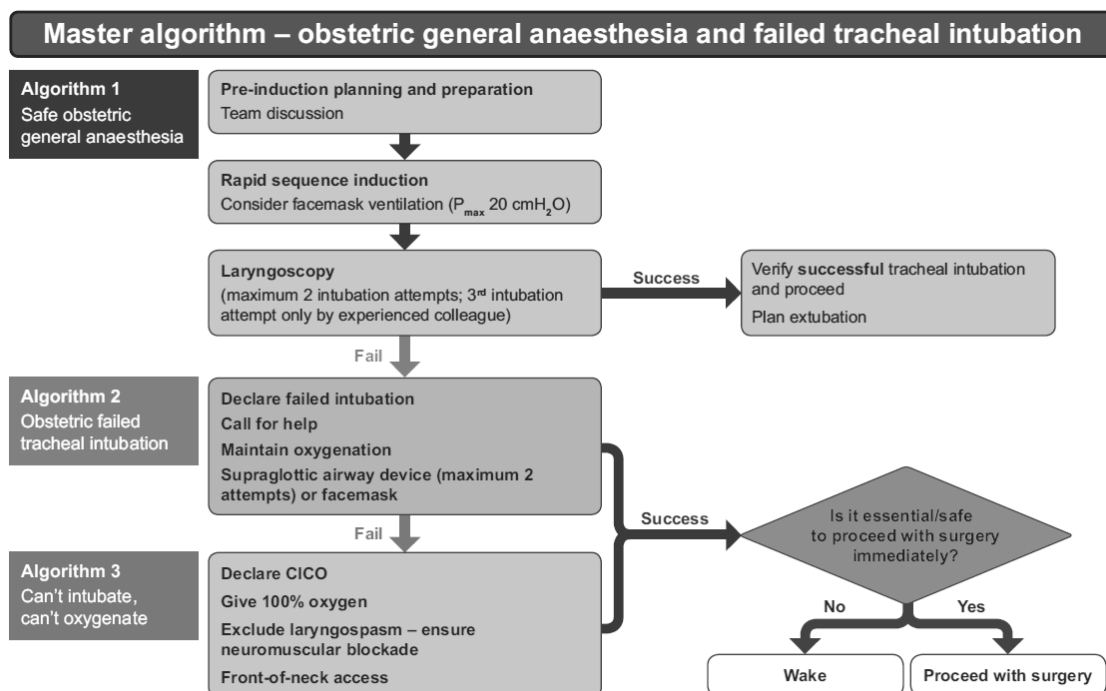


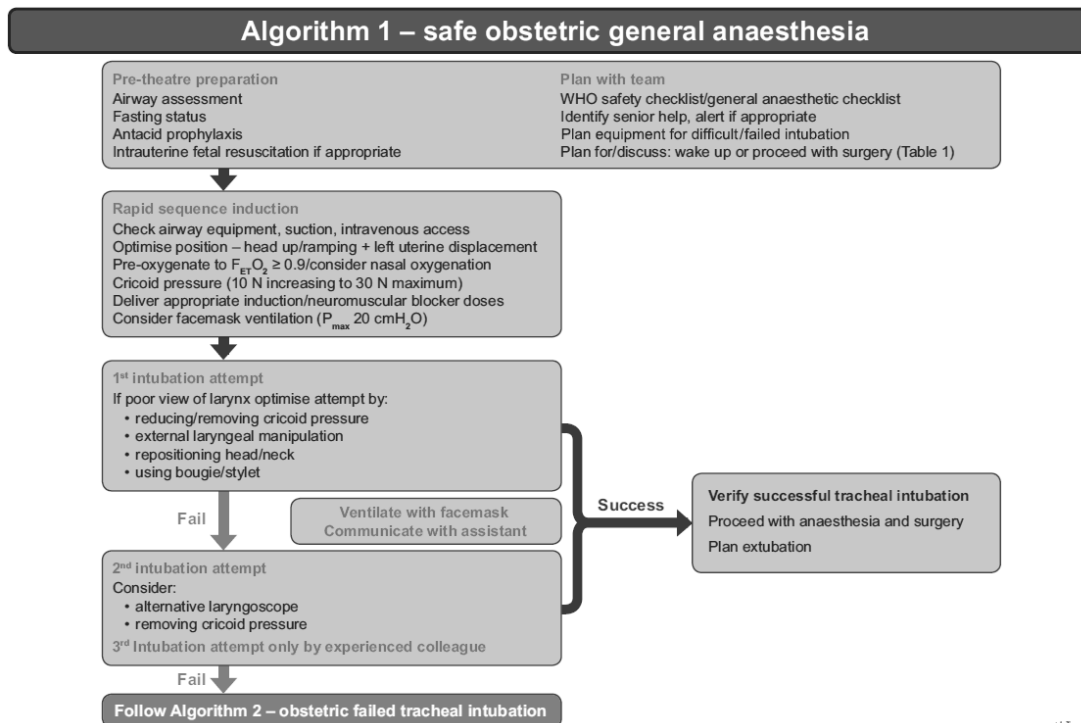
Figure 6. DAS/APA algorithm for CICO in children.



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Figure 7. DAS/OAA master algorithm for failed intubation in obstetric general anaesthesia.



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Figure 8. DAS/OAA Algorithm for safe obstetric GA.

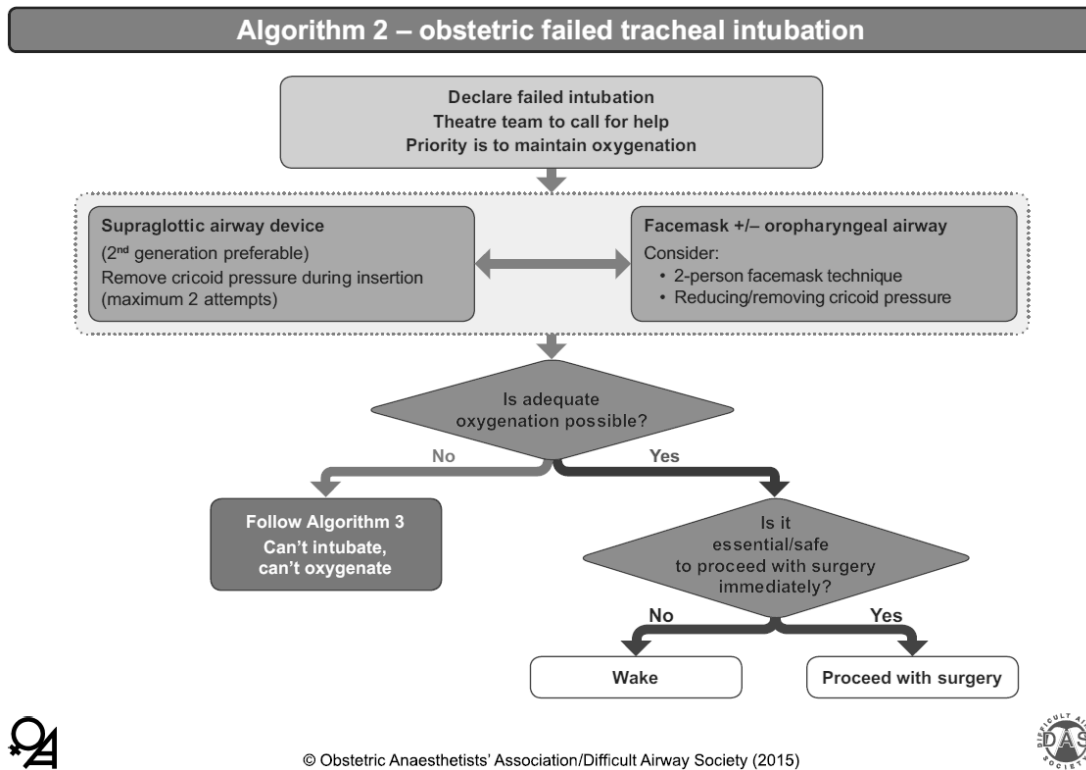


Figure 9. DAS/OAA algorithm for failed intubation in obstetric GA.

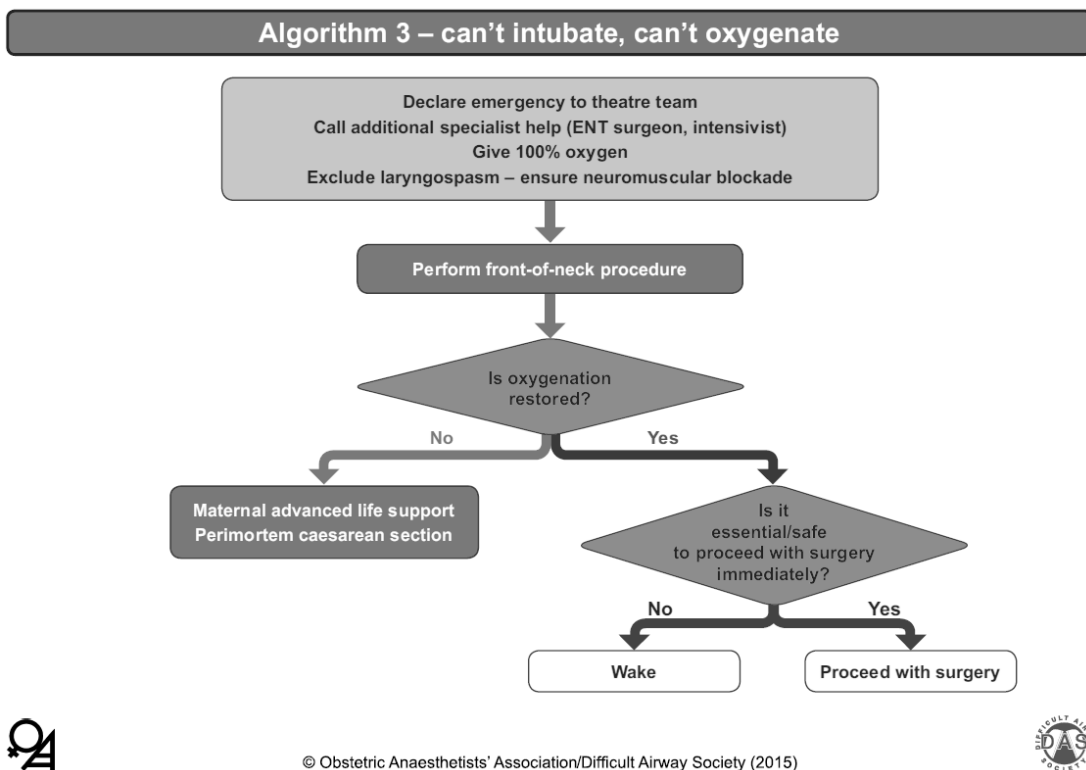


Figure 10. DAS/OAA algorithm for CICO in obstetric GA.

Table 1 – proceed with surgery?				
Factors to consider		WAKE ←————→ PROCEED		
Before induction	Maternal condition	• No compromise	• Mild acute compromise	• Haemorrhage responsive to resuscitation
	Fetal condition	• No compromise	• Compromise corrected with intrauterine resuscitation, pH < 7.2 but > 7.15	• Continuing fetal heart rate abnormality despite intrauterine resuscitation, pH < 7.15
	Anaesthetist	• Novice	• Junior trainee	• Senior trainee
	Obesity	• Supermorbid	• Morbid	• Obese
	Surgical factors	• Complex surgery or major haemorrhage anticipated	• Multiple uterine scars • Some surgical difficulties expected	• Single uterine scar
	Aspiration risk	• Recent food	• No recent food • In labour • Opioids given • Antacids not given	• No recent food • In labour • Opioids not given • Antacids given
	Alternative anaesthesia • regional • securing airway awake	• No anticipated difficulty	• Predicted difficulty	• Relatively contraindicated
After failed intubation	Airway device/ventilation	• Difficult facemask ventilation • Front-of-neck	• Adequate facemask ventilation	• First generation supraglottic airway device
	Airway hazards	• Laryngeal oedema • Stridor	• Bleeding • Trauma	• Secretions



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Figure 11. DAS/OAA table of factors to consider after an airway emergency during caesarean section.

Table 2 – management after failed tracheal intubation	
Wake	Proceed with surgery
• Maintain oxygenation • Maintain cricoid pressure if not impeding ventilation • Either maintain head-up position or turn left lateral recumbent • If rocuronium used, reverse with sugammadex • Assess neuromuscular blockade and manage awareness if paralysis is prolonged • Anticipate laryngospasm/can't intubate, can't oxygenate	• Maintain anaesthesia • Maintain ventilation - consider merits of: □ controlled or spontaneous ventilation □ paralysis with rocuronium if sugammadex available • Anticipate laryngospasm/can't intubate, can't oxygenate • Minimise aspiration risk: □ maintain cricoid pressure until delivery (if not impeding ventilation) □ after delivery maintain vigilance and reapply cricoid pressure if signs of regurgitation □ empty stomach with gastric drain tube if using second-generation supraglottic airway device □ minimise fundal pressure □ administer H₂ receptor blocker i.v. if not already given • Senior obstetrician to operate • Inform neonatal team about failed intubation • Consider total intravenous anaesthesia
After waking	
• Review urgency of surgery with obstetric team • Intrauterine fetal resuscitation as appropriate • For repeat anaesthesia, manage with two anaesthetists • Anaesthetic options: □ Regional anaesthesia preferably inserted in lateral position □ Secure airway awake before repeat general anaesthesia	



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Figure 12. DAS/OAA table for management of failed obstetric intubation.

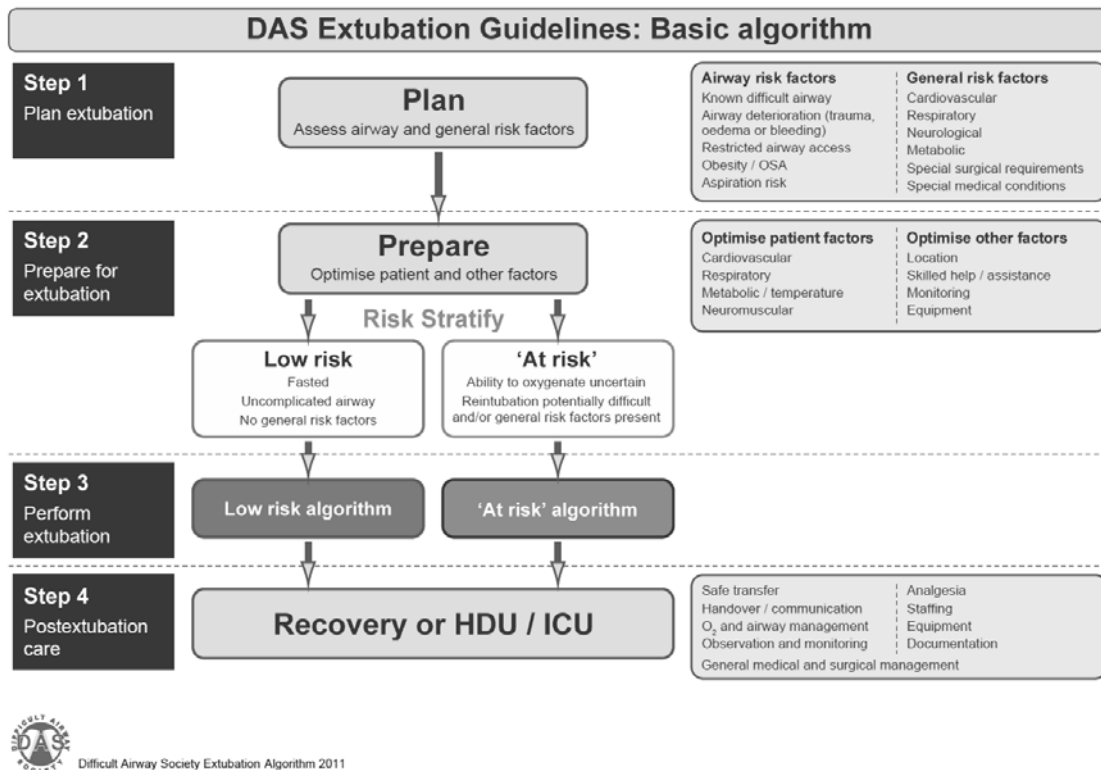


Figure 13. DAS extubation guidelines - basic algorithm.

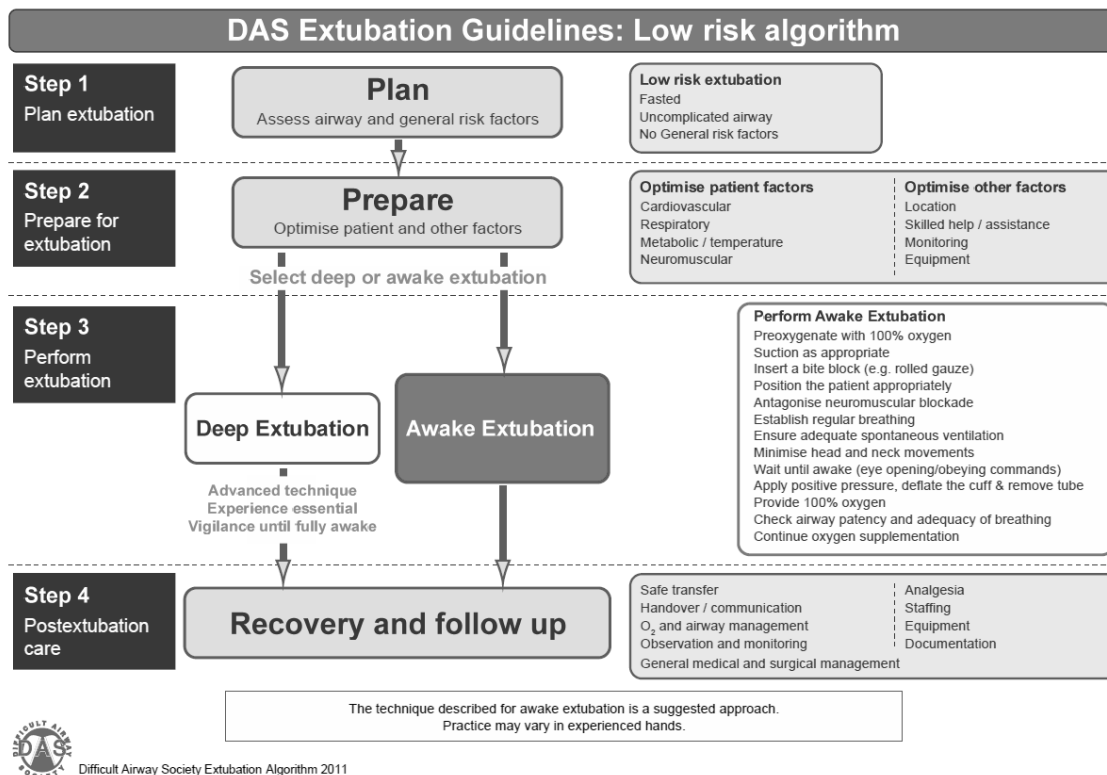
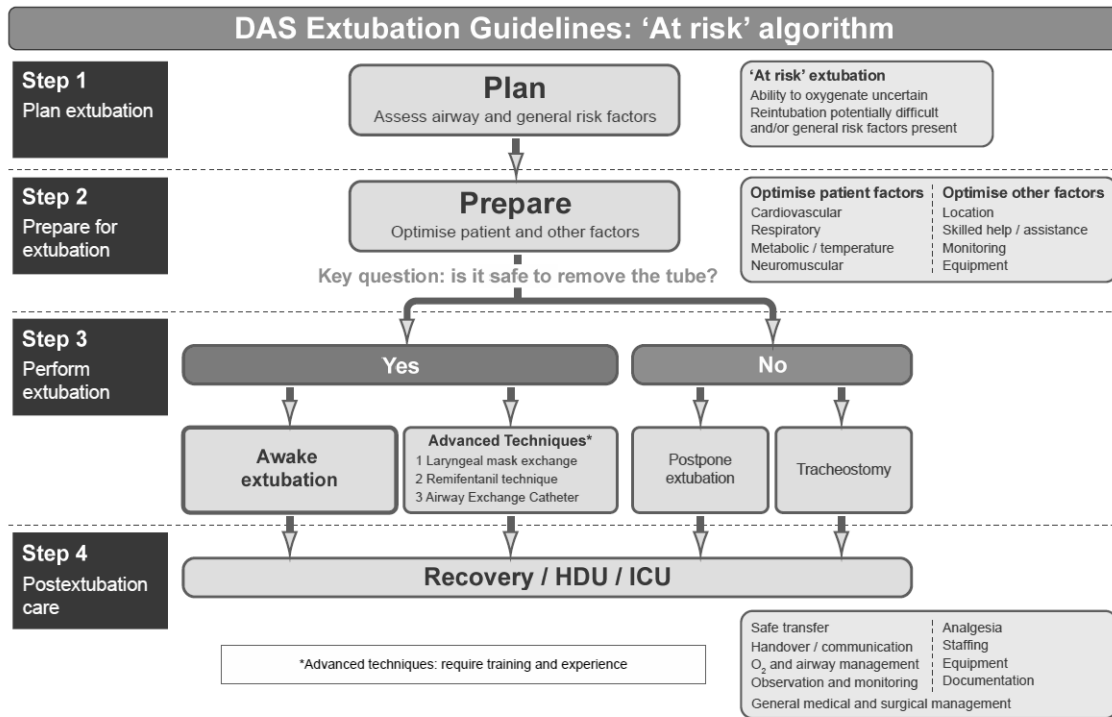


Figure 14. DAS low risk extubation algorithm.



Difficult Airway Society Extubation Algorithm 2011

Figure 15. DAS 'At Risk' extubation algorithm



FIBROPTIC GUIDED TRACHEAL INTUBATION THROUGH SUPRAGLOTTIC AIRWAY DEVICE (SAD) USING AINTREE INTUBATION CATHETER

Please ensure the SAD is in place; give 100% oxygen;
confirm adequate sedation/anaesthesia, ventilation & paralysis



Aintree catheter

- ◆ 56cm long hollow catheter
- ◆ 6.5mm outer diameter; 4.7mm inner diameter
- ◆ Easily preloaded onto an appropriately sized intubating fibrescope (maximum insertion cord diameter - 4.2mm)
- ◆ Flexible enough for loading over fibrescope
- ◆ Stiff enough to facilitate railroading of tracheal tube
- ◆ Comes with 2 rapifit adaptors (please refer to manufacturer's guidelines)
- ◆ Used for SAD assisted orotracheal fibreoptic intubation

4



Note depth of AIC. With assistant immobilising SAD and the operator maintaining the position of AIC, the FS alone is withdrawn after removal of securing tape.

5



Briefly disconnect SAD (along with swivel connector) from anaesthetic circuit, deflate cuff (if present) and start withdrawing SAD (along with swivel connector), applying counter pressure on AIC to prevent movement. Once the SAD cuff becomes visible, grasp AIC in the mouth and fully remove SAD with the swivel connector. The process should be done with care. Again note the depth of AIC at the lips, ensuring that it never exceeds 26cm.

6



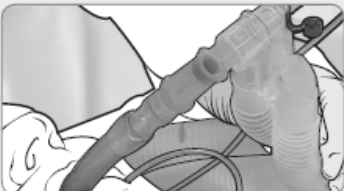
Using a laryngoscope, railroad the tracheal tube (ETT) over AIC ensuring a 'tip anterior' orientation. Use a conventional ETT - minimum size is 7.0 and pre cut to appropriate length.

7



Reconnect circuit and re-establish anaesthesia and ventilation. Confirm end-tidal CO₂. Consider FS confirmation of ETT position.

1



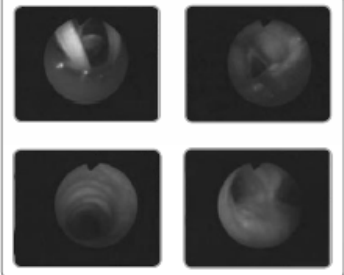
Having prepared the fibrescope (FS) and camera system, lubricate the outer surfaces of both the Aintree Intubation Catheter (AIC) and FS. Preload AIC onto FS and secure with tape. Attach a 15mm bronchoscopic swivel connector (with port) to SAD and attach the anaesthetic circuit to the swivel connector. Confirm adequate anaesthesia, muscle relaxation and assisted ventilation.

2



The SAD should be immobilised by an assistant. Introduce FS with loaded AIC through top port of swivel connector into the SAD lumen.

3



Sequentially visualise SAD aperture bars (if present), glottis, tracheal rings and finally carina as the FS passes caudally. **Never advance beyond carina.**

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 Authors: Dr. Rajmohan Padmanabhan, Consultant Anaesthetist, NHS Lanarkshire
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 Illustrations produced by Andy Morris, Medical Illustration Department, NHS Lanarkshire. 26/07/2011

The AIC was invented in Liverpool, UK;
 Reference: Anaesthesia, 1996, volume 51, pages 1123-1126.

◆ This is not an airway rescue technique
 ◆ It should be performed in a controlled stepwise process
 ◆ The process is designed to provide continued ventilation/oxygenation via the SAD and swivel connector until the SAD is removed and tracheal tube is railroaded in place
 ◆ Oxygen can be delivered via the AIC in situations where railroad of tracheal tube is prolonged; assisting ventilation via this route is often suboptimal (narrow diameter/lack of cuff) - Refer to manufacturer's guidelines for methods of oxygen delivery.

Recommendations
 1. Consider a second anaesthetist in addition to a trained assistant.
 2. Use a camera system for fibrescope.

Caution
 The aintree catheter is not recommended with the LMA Supreme.

Figure 16. DAS guideline on fibreoptic guided tracheal intubation through a supraglottic airway device using the Aintree Intubation Catheter.

References

All current DAS guidelines can be downloaded freely from the DAS website, www.das.uk.com/guidelines. A larger collection of algorithms including guidelines from other organisations and societies (ASA, Vortex, Canadian, SA Resuscitation Council, etc.) can be found at www.openairway.org/algorithms/.

Note on permissions: The DAS 2015 guidelines are open access for non-commercial use and may be reproduced provided the correct source is cited: **Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults**. C. Frerk, V. S. Mitchell, A. F. McNarry, C. Mendonca, R. Bhagrath, A. Patel, E. P. O'Sullivan, N. M. Woodall and I. Ahmad, Difficult Airway Society intubation guidelines working group. *British Journal of Anaesthesia*, 115 (6): 827–848 (2015) doi:10.1093/bja/aev371. Similarly, the obstetric guidelines are reproduced from Mushambi MC, Kinsella SM, Popat M, Swales H, Ramaswamy KK, Winton AL, Quinn AC. **Obstetric Anaesthetists' Association and Difficult Airway Society guidelines for the management of difficult and failed tracheal intubation in obstetrics**. *Anaesthesia* 2015; 70: 1286 – 1306, with permission from Obstetric Anaesthetists' Association / Difficult Airway Society'. Extubation guidelines are reproduced from Popat M, Mitchell V, Dravid R, Patel A, Swampillai C, Higgs A. **Difficult Airway Society Guidelines for the management of tracheal extubation**. *Anaesthesia* 2012; 67: 318–340, with permission from the Association of Anaesthetists of Great Britain & Ireland/Blackwell Publishing Ltd.

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Neuromuscular Blocking Agents An Update

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Is there still a need for suxamethonium?

Suxamethonium is the oldest muscle relaxant in clinical use. It has been in clinical practice for almost seventy years and has survived a slew of attempts to have it replaced. However if it were a new drug vying for registration today it would probably not even make it to clinical trials due to its side effect profile. Interestingly suxamethonium's history began with a side effect. It was first tested as a cardiovascular agent in 1906 by Hunt and Taveau they observed that suxamethonium slowed the heart and increased the blood pressure. Initial trials were performed on animals already paralysed with curare and the neuromuscular effects of suxamethonium were not noticed until 1949 by Bovet almost half a century later.

Suxamethonium was introduced into clinical practice in 1951. Suxamethonium's use was initially very different to how it is used today. It was initially used in relatively low doses so as to maintain spontaneous ventilation and yet facilitate surgery by inducing some degree of muscle relaxation. Suxamethonium rapidly gained great popularity reaching its heyday in the early 1980's when it was often used as an infusion to maintain paralysis. The rapid onset and rapid recovery remains the gold standard against which all other muscle relaxants are judged.

Mechanism of action

Suxamethonium is structurally two acetylcholine molecules joined end-on-end on the acetyl side to make a succinyl di-ester of choline, i.e. succinylcholine. Its therapeutic actions and side effects are attributed to its acetylcholine moieties.

Suxamethonium used to be considered a bis-quaternary neuromuscular blocking agent, and historically it was thought that two quaternary -onium heads are required for any compound to be a potent neuromuscular blocker. However, the notion that monoquaternary compounds will not make potent neuromuscular blockers was overturned by the realisation that vecuronium is monoquaternary.

Contrary to popular belief suxamethonium does not have bisquaternary mechanism of action. It takes two molecules of suxamethonium, like acetylcholine, to open one nicotinic channel. In other words, each half-molecule of suxamethonium acts like one molecule of acetylcholine, and each molecule of suxamethonium uses only one of its two half-molecules at a time.

Side effect profile

With increased use came increased awareness and incidence of side effects. In fact suxamethonium has so many side effects that even classification of the side effects can prove controversial. Lee classified these side effects according to mechanism of action as:

- Depolarisation of the endplate and muscle
- Agonistic actions at other nicotinic sites
- Muscarinic effects
- Abnormal breakdown
- Idiosyncratic actions
- Drug interactions
- Changing nature of block after prolonged use.

Metabolism of suxamethonium and suxamethonium resistance

Suxamethonium is hydrolysed by plasma cholinesterase. Plasma cholinesterase has several variants. The atypical enzymes can be identified by their resistance to fluoride, dibucaine and other laboratory reagents. Hyperactive plasma cholinesterase variants also exist, although they are rarer. Increased plasma cholinesterase activity decreases the amount of suxamethonium reaching the neuromuscular endplate presenting clinically as no or a decreased effect of the injected suxamethonium. Some apparent genotypically normal patients have a mild to moderate increase in enzyme activity and increased activity has been described in patients with hyperlipidaemia, nodular goiter, obesity, diabetes mellitus, psoriasis, essential hypertension, thyrotoxicosis, nephrosis, bronchial asthma, alcoholism, anxiety states and schizophrenia.

Current uses of suxamethonium

Suxamethonium's side effect profile has certainly resulted in changes to the way it is used today. Repeat doses and infusions are rarely used nowadays and its clinical indications have shrunk. Most recognised modern indications revolve around two of suxamethonium's almost indisputable characteristics - firstly that suxamethonium produces superior intubating conditions faster than any other NMBA and secondly that suxamethonium has a shorter duration of action and is therefore inherently safer. Typically the indications of the use of suxamethonium today would be:

- Rapid sequence tracheal intubation (Speed of onset)
- Difficult airway management (Brief profound paralysis and rapid return to spontaneous ventilation)
- Very brief dense block or brief procedures (Electroconvulsive therapy, Oesophageal dilatation, etc.)

Speed of onset of suxamethonium

Since rapid sequence intubation is typically used in situations where the patient is at high risk of aspiration, the underlying goal is to secure the airway in the minimal amount of time possible. Thus, the time required for the NMB to provide adequate intubating conditions is of great importance, with a shorter time translating into better patient outcomes, assuming all other factors are equal. Suxamethonium has long been regarded as the 'gold-standard' in this regard, yet recent evidence suggests that the poor reputation of rocuronium in regards to the time required is primarily due to inadequate dosing. Recommended doses for suxamethonium tend to be reliably stated as 1.0-1.5mg/kg, whereas rocuronium dosages have often been quoted as 0.6mg/kg, which, as will be established below, is inadequate for use in RSI.

Speed of onset of a muscle relaxant is dependent on several factors. Speed of onset of a neuromuscular blocker is directly proportional to the number of molecules present at the neuromuscular junction. In this respect suxamethonium has a distinct advantage over the other muscle relaxants due to its low molecular weight (290 vs 637 for Vecuronium and 530 for Rocuronium). A 1mg/kg dose of suxamethonium will contain about twice the number of molecules as a non-depolarising muscle relaxant given at the same dose. If given in big enough doses all neuromuscular blocking agents will have a rapid onset of action. Pancuronium forms part of the lethal injection used for executions in the USA. Massive doses of pancuronium are given as part of the lethal execution cocktail (approximately 100mg during an execution) and the onset time to flaccid paralysis has been reported to be around 30 seconds.

Speed of onset of suxamethonium is also a function of dose. In one study the incidence of 'excellent' intubating conditions was significantly more frequent, in patients receiving succinylcholine 1.5 mg/kg compared to a lower dosage of 1mg/kg.

Suxamethonium has a predictable rapid onset of action. A dose of 1.5mg/kg will produce good paralysis and intubating conditions within 45 to 60 seconds of administration. Rocuronium has long been considered to have a slower onset of action than suxamethonium, this is however just a dosing issue. Numerous well documented studies show that the higher the dose of muscle relaxant, the more rapid the onset of paralysis. A recent Cochrane review reported that intubating conditions were equivalent when rocuronium was dosed at a more appropriate dose of 1.2mg/kg.

Apart from increasing the total dose there are other methods of speeding up the onset of muscle relaxation.

Priming technique – Since the introduction of rocuronium the use of the priming technique has dramatically decreased. This was a popular method for performing a modified rapid sequence intubation in the days before rocuronium. In essence a small dose of non-depolarising muscle relaxant (approximately 20% of the usual ED 95 dose or 10 % of the usual intubating dose) was given 2 to 4 minutes before administering a second large dose for tracheal intubation. This technique accelerated the onset of block with a non-depolariser by between 30 and 60 seconds allowing intubation to be performed approximately 90 seconds after the second dose. There were of course drawbacks - intubating conditions were frequently suboptimal and this technique increased the risk of aspiration, visual disturbances and patient discomfort. A relatively recent study showed that rocuronium can also be primed (0.06mg/kg followed by 0.54mg/kg 3 minutes later) resulting in a significant decrease in the time of disappearance of T1 measured by TOF stimuli (50.67 ± 7.39 s in the priming group and 94.00 ± 11.62 s in the control group). No patient discomfort or ptosis was reported in this study and intubating condition were described as excellent.

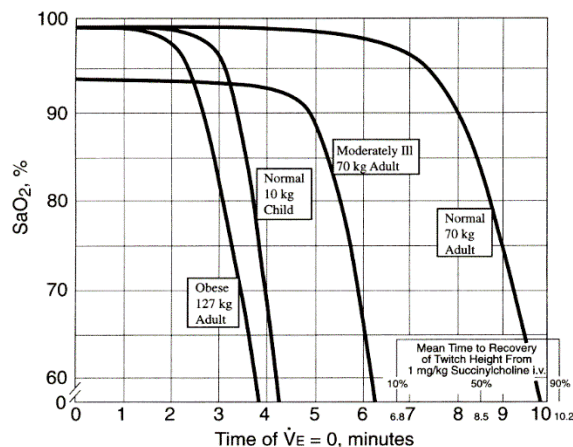
The onset time of the neuromuscular blocking drug is also influenced by haemodynamic factors, including muscle blood flow and cardiac output. Cardiac output is particularly important in this regard and any agent enhancing or retarding cardiac output would influence speed of onset of paralysis. Induction agents such as etomidate and ketamine, which maintain CO and blood pressure, have been shown to accelerate the onset of the block and to improve intubating conditions when used in association with rocuronium. An elegant study looked at changes in onset time of rocuronium (0.6mg/kg) in patients pretreated with ephedrine and esmolol - showed that pretreatment with ephedrine resulted in a decrease in onset time of paralysis (52.2 ± 16.5 s) and increase after pretreatment with esmolol (114 ± 11.1 s) compared with control (87.4 ± 7.3 s). These changes were ascribed to the changes in cardiac output brought about by ephedrine and esmolol.

Duration of action

A distinct difference between suxamethonium and the non-depolarising muscle relaxants is the duration of action. The paralysis induced by suxamethonium lasts for five to ten minutes, whereas the non-depolarisers have a duration of action of 30-90 minutes, depending on the drug and dose used. The significantly shorter duration of action of suxamethonium is often mistakenly thought to be of benefit in the decision to utilise this drug, in the belief that suxamethonium will 'wear off' in time for the patient to begin spontaneously breathing in the case of a failed intubation. Benumof et al. however in 1997 showed that critical haemoglobin desaturation will occur prior to return of spontaneous ventilation following administration of suxamethonium 1.0mg/kg in patients with a non-patent airway.

Suxamethonium may in fact be associated with quicker desaturation than with non-depolarisers. The current evidence suggests that the use of suxamethonium results in a faster onset of haemoglobin desaturation than rocuronium, most likely due to the increased oxygen requirements associated with muscle fasciculation.

TIME TO HEMOGLOBIN DESATURATION WITH INITIAL $F_{A}O_2 = 0.87$



A question that needs to be posed is whether it really is an advantage for a muscle relaxant to wear off rapidly. Patients who require emergency intubation often have a dire need for a secure airway to be established – simply allowing the relaxant to “wear off” and the patient to begin spontaneously breathing again does nothing to alter their situation and may hamper further attempts at intubation or the establishment of a surgical airway.

Sugammadex

No discussion on the debate of the fate of suxamethonium would be complete without mentioning—sugammadex. A γ -cyclodextrin specifically designed to encapsulate and inactivate rocuronium thereby reversing the effects of neuromuscular blockade from rocuronium. In addition to its action on rocuronium, sugammadex also appears to have some crossover effect on vecuronium, and pancuronium. Sugammadex has great potential in achieving quick recovery from rocuronium-induced paralysis within a few minutes.

For immediate rescue reversal of block after administration of 1.2 mg/kg of rocuronium a dose of sugammadex (16 mg/kg) results in complete recovery within a mean of 1.6 min (range 0.7–6.9 min). Rocuronium–sugammadex sequence had significantly quicker offset of neuromuscular blocking agent effect compared with suxamethonium.

With lower dose rocuronium-induced (0.6 mg/kg) shallow neuromuscular block (TOF 2/4), a range of sugammadex doses of 1.0–4.0 mg/kg result in a median time to recovery of less than 3 minutes.

Sugammadex and deep neuromuscular blockade

Sugammadex provides the anaesthetist with the ability to safely reverse from any level of neuromuscular blockade. This means that deep paralysis could be maintained right up till the end of surgery without fear of having to prolong anaesthesia whilst waiting until the return of two twitches of the TOF to allow reversal with neostigmine.

Laparoscopic surgery is one area where the ability to maintain a deep level of block can bring safety benefits to the patient by improving intraoperative conditions for the surgeon. Over the last decade there has been a significant increase in the number and types of surgery that can be performed laparoscopically. The combined aims of the surgeon and anaesthetist are to do no harm, practice safe surgery, and produce an enhanced recovery for the patient. Major bowel surgery and the majority of gynaecological surgery are now routinely being performed using a laparoscopic technique. Avoiding large abdominal incisions brings real benefits to patients in terms of enhanced recovery.

The anaesthetist has a key role to play in assisting to provide optimal operating conditions for the surgeon right up until the end of surgery. There is evidence that provision of deep NMB can improve the operating conditions for surgeons, in particular the working space in laparoscopic surgery, with improved outcomes for patients. A deeper block prevents sudden unexpected patient movement, increases the working space, lowers intra-abdominal pressure and may reduce postoperative pain. Nonetheless, routine use of sugammadex has been limited by high cost, a feature accentuated by the fact that higher doses are required to reverse complete paralysis when rocuronium plasma concentrations are high.

Rocuronium anaphylaxis

Sugammadex binds rocuronium. Studies have demonstrated that once encapsulated, a rocuronium–sugammadex complex is formed and the epitope of the rocuronium molecule is concealed. Current evidence in clinical practice remains at a case report level. Most of these describe an improvement in clinical condition following the administration of large doses of sugammadex immediately, or soon after the recognition of rocuronium induced anaphylaxis. Once an allergic process and mast cell activation have been triggered it is unlikely that encapsulation of the rocuronium will affect the anaphylactic cascade.

Prolonging apnoeic desaturation time

Rapid sequence induction carries the risk of hypoxemia if laryngoscopy is prolonged especially in high-risk patients. Bag and mask pre-oxygenation is normally used to extend the apnoea time; however, arterial desaturation may still rapidly occur. Transnasal humidified rapid insufflation ventilatory exchange (THRIVE) is a new technique that provides modest CPAP during pre-oxygenation and crucially also continuous oxygenation of the pharyngeal space throughout the apnoeic period. In elective surgery, THRIVE provides apnoea times as long as 60 minutes due to apnoeic oxygenation. High-flow devices likely increase the apnoea window by both splinting the upper airway via positive pressure and improving gas exchange through flushing of dead space. THRIVE may prolong the safe apnoea window and thus allow for a smoother, less-pressured approach to definitive airway management in patients with difficult airways.

How to do it - Poor man's THRIVE

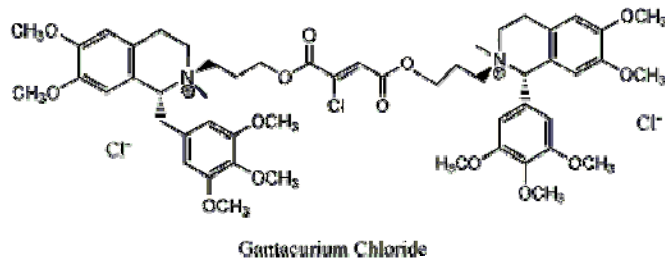
Ensure patient is pre-oxygenated with nasal cannula in situ (15 L/min oxygen flow rate) Administer induction agent maintain the nasal cannula flow rate to 15 L/min and administer oxygen via bag-mask valve as well. If SpO₂ <95% consider apnoeic oxygenation with positive pressure with BVM with PEEP valve with coexistent administration of oxygen at 15 L/min via nasal cannulae - alternatively, abandon apnoeic oxygenation and provide 6 gentle ventilations/minute (<15cmH₂O) if the risk: benefit of apnoea is unfavourable) maintain a patent airway until the time of intubation using: 2-handed face-mask technique with jaw thrust nasopharyngeal airway(s) oropharyngeal airway remove the mask at the time of intubation, but continue to oxygenate via the nasal cannulae this has been termed "NO DESAT" (nasal oxygen during efforts securing a tube).

New muscle relaxants and reversal agents on the horizon

Despite a propensity for adverse side-effects, the depolarizing drug suxamethonium remains the only rapid onset, ultrashort duration muscle relaxant available for clinical use. Although it has been suggested that the development of a non-depolarising replacement for suxamethonium represents the 'holy grail' of muscle relaxant research, efforts to date have been largely unsuccessful with many potential compounds exhibiting significant side-effects in preclinical testing, and most drugs introduced into the marketplace having an onset of action that is too slow, a duration of action that is too long, or a profile of cardiopulmonary side-effects that limit clinical utility

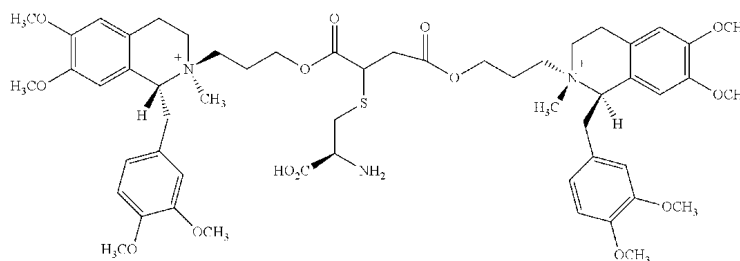
Gantacurium

Gantacurium is a diester derivative of chlorofumaric acid belonging to the family of tetrahydroisoquinoliniums. It has a fast onset of action of 1.5 min with spontaneous recovery of the train-of-four (TOF) ratio to 0.9 in 10–14 min. It is being considered as a replacement for suxamethonium. Gantacurium is degraded non-enzymatically to inactive derivatives by the endogenous amino acid, L-cysteine, in the plasma. L-cysteine conjugates with the central double-bond carbons in gantacurium causing alkaline hydrolysis. This drug is associated with less histamine release than suxamethonium. Its neuromuscular blocking effects can rapidly be antagonized by anticholinesterases, or cysteine. Injecting L-cysteine at the onset of complete paralysis rapidly produces recovery of neuromuscular function. Phase 2 and preclinical trials ongoing.



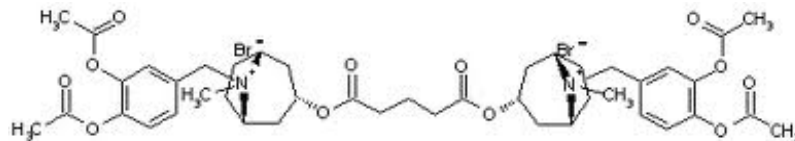
CW002

The unique pharmacology of gantacurium has led to the development of related compounds with an intermediate duration of action that can be rapidly reversed by intravenous injection of L-cysteine, even in the absence of spontaneous muscle recovery. One of these compounds is CW002, a nonhalogenated, symmetrical benzylisoquinolinium fumarate diester, which exhibits an intermediate duration and reversal by L-cysteine. It is an exciting new molecule that interacts more slowly with endogenous cysteine to produce an intermediate duration, but can be reversed at any time by exogenous L-cysteine.



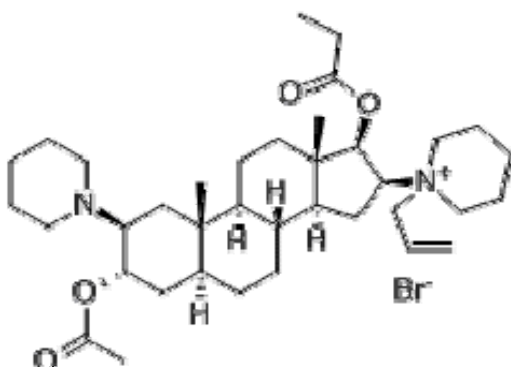
TAAC3

TAAC3 is an ultrashort non-depolarizing tropinyl diester neuromuscular blocking agent. It is faster in onset and shorter in duration of action than suxamethonium, and it is noncumulative. Its pharmacologic profile is benign. Among all neuromuscular blocking compounds acting alone, it came closest to beating suxamethonium. However, it failed the toxicity test. The culprit appears to be a very transient nephrotoxic metabolite, produced by a "Hofmann-like" elimination process.



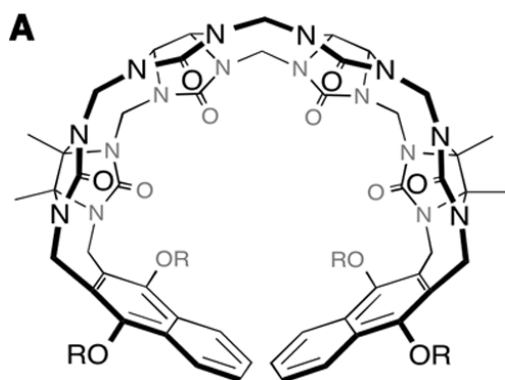
Rapacuronium

Rapacuronium is an aminosteroid, nondepolarising neuromuscular blocking agent. At the recommended dose for endotracheal intubation (1.5 mg/kg), an intravenous bolus of rapacuronium has a rapid onset (approximately 1.2 to 1.8 minutes) and short duration of action (10.2 to 16.5 minutes). Due to risk of fatal bronchospasm it was withdrawn from the United States market by Organon on March 27, 2001, less than 2 years after its FDA approval in 1999.

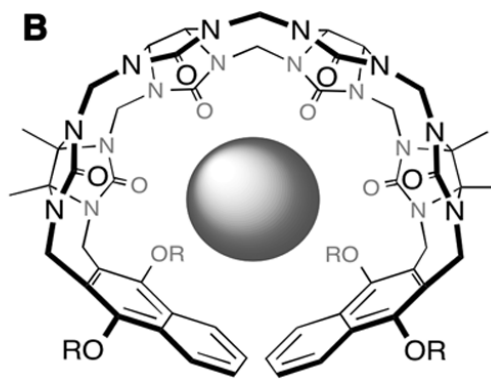


Calabadiion

Calabadiions are acyclic tetrameric derivatives of Cucurbituril, a class of complex molecules that have been characterized as 'molecular containers'. They are able to flex the glycoluril oligomer backbone, expand its cavity, and thereby accommodate molecules with a range of size. Previously used as components of drug delivery vehicles, molecules in the Cucurbituril family such as calabadiion have now been shown to cover the quaternary amine sites for both benzylisoquinolinium and steroidal NMBDs to prevent binding to neuromuscular nicotinic receptors. Although similar to sugammadex in terms of rapid reversal at any time without the need for antimuscarinics, the mechanism of action for calabadiion appears to be somewhat more specific: changing affinity of the NMBA for neuromuscular nicotinic receptors as opposed to enveloping and removing free NMBA from the motor end plate.



Calabadiion 2: R = (CH₂)₃SO₃Na
Molecular Formula: C₆₂H₆₈N₁₆Na₄O₂₄S₄
Molecular Weight: 1641.51



Calabadiion 2•rocuronium

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Notes

Is there still a place for the Peripheral Nerve Stimulator in Non-depolarising Neuromuscular Blockade?

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BACKGROUND

The use of a peripheral nerve stimulator (PNS) post non-depolarising neuromuscular blockade (NDNMB) appears in many anaesthesia guidelines, yet monitoring neuromuscular function is still not universally practiced when NDNMB are administered. In addition to this, the reversal of residual block is far from routinely administered and misinformation regarding optimal muscle relaxant management is still widespread. The question is why 40 years after the PNS devices became readily available, is there such a discord between editorial opinion regarding the optimal management of neuromuscular blocking drugs (“...*objective neuromuscular monitoring should be used whenever a NDNMB is administered...*”¹⁵) and actual day-to-day clinical practice?^{2,3,4,5,6,7,8}

The 2013 ASA practice guidelines for post-anaesthesia care recommend the following with regards to neuromuscular function¹:

“Assessment of neuromuscular function primarily includes physical examination and, on occasion, may include neuromuscular blockade monitoring. The original literature indicated that neuromuscular blockade monitoring is effective in detecting neuromuscular dysfunction (Category B2-B evidence); new literature is insufficient to further evaluate these findings. The consultants and ASA members agree that assessment of neuromuscular function identifies potential complications, reduces adverse outcomes, and should be done during emergence and recovery.”

However, a survey conducted in 2010 to compare the differences in neuromuscular monitoring across the Atlantic concluded that its use is far from routine and that 19.3% of European and 9.4% of American respondents never use neuromuscular monitors. Another interesting finding was that routine pharmacological reversal was reportedly used by only 18% and 34.2% of European and American anaesthetic practitioners respectively.²

DEFINITION AND CONTEXT

Residual neuromuscular blockade is defined as *inadequate neuromuscular recovery as measured by objective neuromuscular monitoring*. Current opinion defines residual or persisting paralysis as a measured train-of-four ratio of less than 0.9 (TOF <0.9) in the recovery unit.³

The incidence of residual neuromuscular blockade (TOF <0.9) in the recovery unit varies widely between studies, with reporting frequencies between 2-64%³, with likely estimates of around 40%¹³. Based on studies examining morbidity from residual paralysis, a rough estimate of 1-3% of these patients would be expected to develop clinically apparent events such as hypoxaemia and airway obstruction.^{3,7,11} Considering the large percentage of patients estimated to have residual blockade, it could be easily inferred that most patients tolerate residual block of modest depth without untoward results. However, there exists a small population of patients, particularly those with existing limited physiological reserve, where residual neuromuscular blockade has serious consequences.¹¹ One suspects that the low complication rate of residual blockade causing clinically apparent respiratory compromise is just the tip of the iceberg. There is a strong likelihood that many additional patients would have had some difficulty or discomfort, managed to compensate, and did not need specific intervention. It is possible that rigorous management of residual blockade would lead to more comfortable and satisfied patients in the recovery room who could be more rapidly discharged.⁷

TOF nerve stimulation using a PNS was introduced in the early 1970s and consists of four supramaximal stimuli delivered to a nerve at 0.5 second intervals (2Hz). The muscular response to the 4th stimulus is compared with that of the 1st and the fade of force of muscle contraction provides the basis for evaluation. Commonly used sites are that of the adductor pollicis muscle of the thumb (ulnar nerve) and the corrugator supercilii and orbicularis oculi muscles of the eyebrow (facial nerve). Early studies suggested that by visual or tactile observation (‘subjective’ or ‘qualitative’ assessment) a TOF

ratio of 0.7 was considered compatible with normal respiratory function and should be the target prior to tracheal extubation. It was later recognised that human senses could not appreciate the difference between a TOF ratio between 0.4–0.7 and thus 'subjective' monitoring could not identify residual blockade reliably. The term "blind paralysis" was used for TOR ratio values in the range 0.4 to 0.7.^{7,8}

In the 1990s it was appreciated that patients could have signs and symptoms of residual paralysis despite having a TOF ratio >0.7. This was largely due to the previously poorly recognised effects of neuromuscular blockade on upper airway patency and swallowing. For example, various muscle groups were still weak (e.g. pharyngeal muscles) even with a TOF >0.7. There was mounting evidence that even 'mild' residual blockade mattered and had deleterious effects such as hypoxia, hypercarbia, atelectasis and airway obstruction. This reassessment of the target for adequate neuromuscular recovery led to the **current recommendation to increase the TOF ratio to >0.9**.^{7,8,10} This more stringent ratio was arrived at after several studies demonstrated an increased risk of aspiration and pharyngeal dysfunction at TOF ratio <0.9 and impaired inspiratory flow and partial airway obstruction at TOF <0.8.³

'Subjective' or 'qualitative' assessment of the TOF ratio has been found to be less accurate than 'objective' or 'quantitative' monitoring which involves the use of a stimulator coupled with a measuring device that displays a numerical value of the response.⁷

ADVERSE EFFECTS OF RESIDUAL NDNMB

Table 1. Adverse effects of Residual NDNMB³

SYMPTOMS & SIGNS	TOF RATIO
Profound symptoms of muscle weakness • Visual disturbances, severe facial weakness, difficulty speaking and drinking, generalised weakness, patient distress	<0.70 - 0.75
Increased risk of aspiration • Swallowing dysfunction, delayed initiation of swallowing reflex	<0.8
Increased risk of postoperative pulmonary complications • Atelectasis or pneumonia • Prolonged ventilator weaning and increased intubation times	<0.7 <0.9
Upper airway obstruction	<0.8
Impaired hypoxic ventilatory drive	<0.7

INVESTIGATIONS TO DETERMINE RECOVERY FROM NDNMB

The ideal test would not require an awake, cooperative patient and would be easily applied, reliable and inexpensive.¹¹

Clinical tests

Table 2. Diagnostic attributes of the Clinical Tests: Sensitivity, Specificity, Positive and Negative Predictive Values of an Individual Clinical Test for a TOF <0.9⁴

Clinical Test	Sensitivity	Specificity	PPV	NPV
Inability to smile/swallow/speak	0.21 - 0.29	0.80 – 0.85	0.47	0.64
General weakness	0.35	0.78	0.51	0.66
Inability to maintain head lift x 5s	0.19	0.88	0.51	0.64
Inability to sustain hand grip x 5s	0.18	0.89	0.51	0.63

- *Sensitivity = the number of true positives divided by the sum of true positives + false negatives.*
- *Specificity = the number of true negatives divided by the sum of true negatives + false positives.*
- *True positives are positive for the test and have TOF <0.9.*
- *False negatives have a negative test but TOF <0.9.*
- *True negatives have a negative test and a TOF >0.9. (i.e. not <0.9)*
- *False positives have a positive test and a TOF >0.9.*
- *A positive test result means the inability to smile, swallow, speak, general muscle weakness etc.*

In practice most clinicians rely on clinical signs or tests of muscle weakness to determine the presence of residual neuromuscular blockade prior to tracheal extubation. These clinical criteria would include assessment of a patient's ability to maintain adequate head lift, jaw clench, grip strength and vital capacity. However, available evidence does not support this belief as studies have shown that even a

5 second head lift is possible with a TOF ratio of <0.5 and thus is an unreliable predictor of neuromuscular recovery. As noted in the table above⁴, the sensitivity and positive predictive values of all the tests were low for predicting TOF ratios <0.9 . The 2 best clinical tests used for confirmation of TOF <0.9 were sustained head lift and hand grip, with specificity of 0.88 and 0.89 respectively.

Subjective Neuromuscular Monitoring

TOF, as described previously, can be conducted subjectively as either a TOF count or TOF ratio when there is already a TOFC of 4. Tactile assessment of the movement of the patient's thumb against the observer's fingers is slightly more accurate than the visual assessment, but not significantly so.⁴ However, neither method is reliable at detecting fade and the majority of evaluators are unable to detect fade when TOF ratios are >0.4 .¹¹

Double Burst Stimulation (DBS) is another method of neuromuscular monitoring and usually measured in a subjective manner. DBS improves detection of fade up to TOF 0.6, which is significant, but still doesn't eliminate the incidence and degree of residual NDNMB.

Tactile evaluation of TOF and DBS fade reduces the incidence and degree of postoperative residual paralysis compared with clinical criteria to assess readiness for tracheal extubation.⁴

Objective Neuromuscular Monitoring

Objective measurement of neuromuscular activity is the only way of accurately assessing for residual NDNMB. In general it is conducted by quantitative measurement of the strength of muscle contraction in response to peripheral nerve stimulation produced by 2 stimulating electrodes. Each measurement technique measures the force of contraction either directly or by a factor that is proportional to the force.¹¹

Table 3. Different types of objective neuromuscular monitoring devices¹¹

Device	Sensor	Measures	Notes
Mechanomyography (MMG)	Force transducer	Force of muscle contraction	Widely considered gold standard Rarely used due to elaborate setup and bulkiness
Electromyography (EMG)	Electrodes	Amplitude of compound muscle action potential	Affected by electrocautery Some experts consider as gold standard
Kinemyography (KMG)	Piezoelectric polymer sensor in groove between thumb and index finger	Movement of muscle (which generates voltage in sensor)	Less reproducible than EMG
Phenomyography (PMG)	High-fidelity narrow-bandwidth microphone placed alongside muscle	Sound intensity	Low clinical use and unclear future
Acceleromyography (AMG)	Piezoelectric crystal	Acceleration of muscle (which generates voltage in crystal)	Reliably detects TOF ratios Can overestimate compared with EMG

It is important to bear in mind that the problem of residual NMB will not be completely resolved with routine use of neuromuscular monitoring. Studies have shown that a TOF ratio of >0.9 may still have up to 50% of the receptors occupied.¹⁰ It would make sense then to add a margin of safety to the normal pharmacokinetic elimination of NDNMBs by routinely administering reversal of NMB with neostigmine (or sugammadex).¹⁰

Site of Neuromuscular Monitoring

Adequate recovery from NDNMB depends on return of neuromuscular function in muscles that contribute to airway tone and breathing. The diaphragm strength recovers earlier than the upper airway muscles which are particularly sensitive to NDNMB. Upper airway muscles contract in synchrony with the diaphragm to ensure airway patency and diaphragm strength alone does not imply an intact respiratory system. Geniohyoid, masseter and upper oesophageal muscles and that of adductor pollicis have similar recovery times and therefore the adductor pollicis muscle response to ulnar nerve stimulation can be used as a validated guide for recovery. Movement of the eyebrow

(orbicularis oculi and corrugator supercilii muscles) in response to facial nerve stimulation recovers early, much like the diaphragm, and earlier than the upper airway muscles or adductor pollicis. It follows that facial nerve stimulation should not be used to guide reversal and recovery.¹³ It should also be noted that dose and timing of reversal is based on recovery of adductor pollicis. It is expected that when 4 twitches are present at the eyebrow, the adductor pollicis count will be fewer and the risk of residual paralysis higher.¹³

PHARMACOLOGICAL REVERSAL AGENTS

It is good practice to always consider giving reversal agent, unless there is objective neuromuscular monitoring demonstrating a TOF >0.9. However, giving neostigmine to fully recovered patients may actually decrease upper airway muscle activity and tidal volume. Alternatively, studies showed a 37% incidence of residual paralysis (TOF <0.9) 2 hours after a single intubating dose of intermediate acting NDNMB when no reversal was administered.⁴

Clinicians often underestimate the time required and significant variability in the time to onset and duration of reversal drugs to fully antagonize the effects of NDNMBs. Given after a TOFC of 2, the average time to adequate reversal is 15 minutes, with some patients demonstrating residual paralysis (TOF <0.9) after 30 minutes!⁴

Reversal of NDNMB should not be attempted until evidence of spontaneous recovery of neuromuscular function has occurred (i.e. there is at least 1 response to TOF stimulation). When using anaesthetic techniques that potentiate NDNMB (e.g. inhalational volatiles), adequate spontaneous recovery of TOF count of 4 should be established before giving reversal. When using anaesthetic techniques that do not potentiate NDNMB (e.g. TIVA), a minimum TOFC of 2 should be established.⁴

It is important to remember the estimated physiological correlations with TOF:

Table 4. Train of four count and physiological correlation

TOF count	% neuromuscular blockade at muscle
4	0-75%
3	75%
2	80%
1	90%
0	100%

Reversal suggestions in clinical practice.⁴

No neuromuscular monitor or peripheral nerve stimulator

- Pharmacological reversal should be administered routinely
- Administered only when there is return of spontaneous muscle activity present

Peripheral nerve stimulator – subjective (visual, tactile) assessment

- TOFC of 0 or 1 → delay reversal
- TOFC of 2 or 3 → give reversal
- TOFC 4 with fade → give reversal
- TOFC 4 with no perceived fade → give reversal (consider low dose neostigmine - 20mcg/kg)

Quantitative evoked muscle response (eg. AMG, KMG, EMG)

- TOFC of 0 or 1 → delay reversal
- TOFC of 2 or 3 → give reversal
- TOF < 0.4 → give reversal
- TOF 0.4 – 0.9 → give reversal (consider low dose neostigmine – 20mcg/kg)
- TOF > 0.9 → no reversal recommended

Sugammadex

Sugammadex is a modified gamma-cyclodextrin (ie. cyclic sugar) reversal agent that has become available throughout many countries and is being trialled for approval in many others. Chemically it has a negatively charged lipophilic core surrounded by hydrophilic periphery. It is unique as a selective relaxant binding agent (SRBA) that selectively binds aminosteroid NDNMBs (rocuronium > vecuronium > pancuronium). A dose of 2mg/kg, when given at TOFC 2, will reliably produce TOF >0.9 in 2 minutes. There is no biotransformation and elimination is by renal excretion only.¹¹

Sugammadex is an expensive drug. (In the UK, 2013, the estimated cost of reversal of NMB with sugammadex for a 75 kg person was £60 for 2 mg/kg, £120 for 4 mg/kg and £360 for 16 mg/kg vs £0.71 for spontaneous recovery from suxamethonium.) However, studies have shown that use of sugammadex can be cost-effective by reduced incidence of post-operative residual paralysis, reducing operative time, post-operative recovery stay and also decreased side-effects associated with the use of suxamethonium.¹⁶

Its availability and cost are limiting more widespread use but its ability to rapidly reduce neuromuscular blockade and thereby reduce the incidence and extent of residual blockade which will make sugammadex an important drug in the anaesthetist's armament in the future.

NEUROMUSCULAR BLOCKERS

The following factors have been shown to contribute to residual neuromuscular blockade:¹¹

1. The use of NDNMB
 - a. NDNMB should only be used when clinically indicated⁴
2. Dose
 - a. High dose NDNMB (3-4 ED95) used for modified rapid sequence inductions will prolong the duration (50-300%) of blockade compared with normal dose (1-2 ED95)³
 - b. Dosing should be individualized based on surgical necessity, patient factors and presence of coexisting disease⁴
3. Type
 - a. The use of long acting NDNMB (e.g. pancuronium) is associated with a 3-fold increased risk of TOF <0.7 in the post-operative period.¹⁴ Intermediate-acting NDNMB should be used whenever feasible.⁴
4. Depth
 - a. Routine maintenance of deep intra-operative paralysis (TOFC zero and PTC 0-5) is associated with residual neuromuscular blockade.¹⁴
5. High risk patients
 - a. Special attention to careful NDNMB use must be taken in patients who are high risk of residual paralysis and post-operative pulmonary complications: those with neuromuscular disease, respiratory disease, sleep apnoea, the elderly and the obese.¹⁴
 - b. Consider or avoid factors that prolong neuromuscular blockade – inhalational agents, opioids, acidosis, hypothermia, hypercarbia, hypoxia.¹¹

CONCLUSION

Careful neuromuscular management may reduce the risk of postoperative residual weakness and its associated complications. Incomplete recovery from NDNMB continues to be a problem in modern post-anaesthesia care units and given that this is a potentially preventable patient safety problem it is important that all safeguards should be used to reduce its incidence.

In light of this, take note of the following key considerations:^{8,10, 13}

- Remember that postoperative residual neuromuscular paralysis is an important clinical problem and although usually well tolerated, can pose a significant threat to patient wellbeing, particularly in high risk patients. Anaesthesia educational programmes should emphasise the use of neuromuscular monitoring and the indications for neostigmine administration.
- It is not possible to exclude with certainty potentially clinically relevant postoperative residual paralysis by
 - o Any clinical test or combinations thereof. Clinical tests cannot reliably exclude the presence of residual paralysis.
 - o Tactile or visual evaluation of the response to TOF.
- Good evidence-based practice dictates that anaesthetists should ideally confirm that the TOF ratio is >0.9 before sending the patients to the recovery room
 - o Due to lack of availability of objective monitors and the inaccuracy of subjective analysis, a more conservative approach should be used for subjective assessment of TOF count. A count of 4 twitches of adductor pollicis should be ascertained prior to administration of reversal.
- Routine administration of pharmacological reversal.
- Be alert to, and ready to treat, residual neuromuscular blockade.

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The Recovery Room...

A safe haven, or a disaster waiting to happen?

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This was published as an editorial in the SAJAA in 2009.

The measure of a good anaesthetic may well differ, depending on whether you are the patient, the surgeon, the anaesthesiologist, or the postoperative nursing staff. Ultimately, however, the patient should be the judge of whether his or her anaesthetic was a good experience. An essential part of this experience is the recovery process which is continual, and may last for up to a few days. The less serious, non-life-threatening adverse events such as postoperative pain, nausea and vomiting, drowsiness and dizziness have been shown to be predictors for patient satisfaction and level of postoperative functioning.

Marshall and Chung (1) divided the recovery process into three phases:

- Early recovery, which lasts from the discontinuation of anaesthesia until patients have recovered their protective reflexes and motor functions. This usually takes place in the high-dependency atmosphere of a recovery room (PACU)
- Phase 2, which is when the crucial decision is made to discharge the patient from recovery room to the ward. During this period there is continued clinical recovery, and in day cases home readiness is achieved
- Phase 3, which is the phase of full recovery, including psychological recovery

The early recovery phase is the process of immediate concern, both from the point of view of patient safety, as well as patient satisfaction. Interestingly, "fast-tracking" (bypassing the recovery room) has been studied, particularly in the context of ambulatory surgery. The objective of this is to decrease recovery time and therefore costs, particularly nursing costs. Song et al(2) studied these costs, and concluded that bypassing the recovery room decreased recovery time without compromising patient satisfaction, BUT the overall nursing workload and the associated costs were no different.

The *South African Society of Anaesthesiologists'* (SASA) guidelines to safe anaesthetic practice state the following about the recovery of patients:

GENERAL PRINCIPLES

The anaesthesiologist should be readily available during the period of recovery from anaesthesia until such time as the patient is deemed fit for transfer from the recovery area.

1. Recovery from anaesthesia must take place under appropriate supervision in an area designed for this purpose.
2. This area should be either in the theatre itself or close to where the anaesthetic was administered.
3. The staff working in this area must be appropriately trained. When the need arises the staff must be able to contact the anaesthesiologist or his/her designate promptly.
4. It is desirable for patients to have regained consciousness and be in a stable state before they are transported any distance.
5. If patients have to be transported within and from the operating suite while not fully recovered, they must be on a suitably designed trolley/bed capable of head-down tilt. The bed or trolley should be provided with oxygen, a means of inflating the patient's lungs, equipment for suctioning and an appropriate monitor. They must be accompanied by staff able to deal with the problems that may occur during transport.

The SASA guidelines also emphasize the following:

- **Staffing**
It is the responsibility of the institution to ensure that the staff appointed to the recovery room is trained and competent. The recovery staff must be available at all times.
A registered or enrolled nurse trained and competent in recovery room care must be present at all times.
An appropriately trained registered nurse experienced and competent in recovery room work should be in charge.
The ratio of nursing staff trained in recovery room care to patients needs to be flexible so as to provide no less than 1:2 patients, and one to each patient who has not recovered protective reflexes.
- **Management and supervision**
Written protocols for safe management should be established.
A written routine for checking the equipment and drugs must be established.
Observations should be recorded at appropriate intervals and should include at least: state of consciousness, colour, respiration, oxygen saturation, pulse and blood pressure and level of pain. The record should form part of the patient's clinical notes.
All patients should remain until the anaesthesiologist considers it safe to discharge them from the recovery room, according to validated criteria, which includes the return of protective airway reflexes, stable cardiovascular and respiratory function, full reversal of neuromuscular blockade, absence of nausea and vomiting and absence of pain.
- **The anaesthesiologist is responsible for:**
Supervising the recovery period and authorising the patient's discharge
Accompanying the patient to the recovery room and adequately handing him/her over to the nursing staff who will document the patient's condition on arrival and subsequent course in recovery
Providing appropriate written and verbal instructions and information to the recovery room staff for each case
Specifying the type of apparatus and the flow rate to be used in oxygen therapy
Remaining in the facility until the patient meets the criteria detailed above, or delegating this responsibility to another anaesthesiologist or intensivist.

Patient safety issues in the recovery room

The important issues as outlined in the SASA guidelines include the equipment and staffing, and the observations that are recorded. In addition, the patient remains the responsibility of the anaesthesiologist, and must be discharged by the anaesthesiologist from the recovery room. The American Society of Anaesthesiologists has emphasized the recovery room process by allocating "standards" to each step of the process, with standard 5 being the "discharge of the patient from the recovery room by a physician".

In recent years, many mishaps have occurred in recovery rooms in South Africa, many relating to hypoxia, with disastrous consequences such as hypoxic brain damage or death.

The recommended observations (originally proposed by Aldrete) should include:

- Activity – the ability to move voluntarily or on command
- Respiration – the depth and quality of respiration
- Circulation – the blood pressure in relation to the preanaesthetic level
- Level of consciousness
- Oxygen saturation, with or without oxygen supplementation

These are largely based on the types of complications that tend to occur in the recovery room. The incidence of complications in numerous studies (3) has been found to be >20%. The major complications include:

- Nausea and vomiting (incidence of 10%)
- Respiratory (**the need for airway support being the commonest**)
- Circulatory (hypo- and hypertension and dysrhythmias)

Chung et al compared adverse events in elderly and young patients coming for ambulatory surgery (4). On average the elderly patients spent a longer time undergoing surgery, and a shorter time in the recovery room. The rate of intra-operative events was much higher in the older patients, in that they

had 5 times more cardiovascular events. However, in the recovery room, the younger patients experienced a 4-fold increase in adverse events compared with their elderly counterparts, with an adjusted odds ratio of 0, 43. The commonest adverse events were pain, and nausea and vomiting.

Therefore how do we ensure a safe and satisfactory recovery period for our patients, regardless of whether they are in-patients or being done as ambulatory cases?

1. Recovery rooms need to be properly equipped as per the SASA guidelines.
2. Staffing of recovery rooms MUST be in accordance with SASA guidelines. The staff allocated must be dedicated only to the recovery room, and should not have any other duties.
3. Protocols must be in place, and observations must be recorded.
4. The anaesthesiologist needs to discharge the patient from the recovery room. It is suggested that the Modified Aldrete Scoring system be used for determining when patients are ready for discharge from the recovery room. A score of 9 or >9 is required for discharge.

Modified Aldrete Scoring System

Activity: able to move voluntarily or on command	4 extremities	2
	2 extremities	1
	0 extremities	0
Respiration	Cough/deep breathing	2
	Dyspnoea/shallow	1
	Apnoea	0
Circulation – BP within mmHg of preop level	20mmHg	2
	20-50 mmHg	1
	50 mmHg	0
Level of consciousness	Fully awake	2
	Arousable on calling	1
	Not responding	0
Oxygen saturation	Sats >92% on room air	2
	O2 required for sats >90%	1
	Sats < 90% despite oxygen	0

The most important parameter of all is the oxygen saturation, as this reflects an adequate cardiorespiratory system, as well as whether there are undesirable effects such as shivering and pain.

5. The patient must also be pain-free, and
6. There must be no nausea and vomiting.

The Paediatric patient

Caring for a paediatric patient after anaesthesia has the same requirements as adults, with the following additions:

- Recovery staff experienced in recovering paediatric patients
- An emergency equipment cart with paediatric equipment, including intraosseous lines
- A drug chart with paediatric drug dosages

The controversial issue is whether parental presence should be allowed in the recovery room. In areas which have both paediatric patients and adults, it is not advisable. Occasionally, if a child is inconsolable after emergence and all physiological parameters are stable, then the parents *MAY* be allowed into the recovery room, provided the nursing staff are comfortable with this.

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Notes

End of Life Medical Practices

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As things stand currently in South Africa, end of life decision making presents a dilemma between ethical issues and the law, from the point of view of medical practitioners.

There are various end of life medical practices that need to be explored. These are:

- Assisted suicide
- Living wills and advance directives
- Passive euthanasia / withdrawing and withholding treatment

Assisted suicide / Active euthanasia

This is currently illegal in South Africa, but not necessarily unethical. It also engenders heated and emotional debate. One of its proponents is Archbishop Emeritus Desmond Tutu, who stated “I revere the sanctity of life – but not at any cost. I confirm I don’t want my life prolonged. I can see I would probably incline towards the quality of life argument, whereas others will be upset if I said I wanted assisted dying. I would say I wouldn’t mind actually.”

In 2015 Mr Stransham-Ford brought an application to court in Pretoria, requesting that a medical practitioner assist in ending his life, which was medically untenable. The court ordered that he was entitled to be assisted by a doctor in ending his life, and that the doctor would not be considered to have acted unlawfully. The court stated that this case dealt with the right to life and the right to dignity, as well as the sacredness of the quality of life. The court recommended that similar cases should be heard on a case by case basis. This judgment has changed the law, and is currently being appealed. The results of this appeal may have far-reaching ramifications for future anaesthetic practice and decision-making.

Living wills / advance directives

This comprises instruction given by a competent adult in anticipation of becoming a patient and lacking capacity. It usually entails refusal of treatment, and furthers the ethical principle of autonomy (to rule oneself). Hence it is ethically acceptable, and patients have a constitutional right to have their living wills honoured. In addition, a patient’s contemporaneous decision to refuse medical treatment is valid in South African law, so a prospective decision to refuse medical treatment is also legally acceptable. An advance directive, is, however, not legally enforceable. An advance directive can also take the form of a lasting power of attorney, which allows a person to appoint someone else as a healthcare proxy. Not all health care practitioners are comfortable in carrying out the advance directives of a patient, and may delegate to a willing colleague.

From an ethical perspective, an advance directive / living will is valid if the following 4 conditions are met:

- The patient must have issued the directives when he/she was >18 years.
- The patient had the mental capacity to make medical decisions.
- The patient was fully informed about everything pertaining to refusal of the treatment. It is preferable that the instructions are not too restrictive and pertain to a specific disease or condition.
- There is no evidence that the patient has changed his/her mind about the directive.

The over-riding principle in carrying out the advance directives of a patient are to act in that patient’s best interests.

Passive euthanasia / withdrawing and withholding treatment

This means withholding or omitting treatment in a conscious or unconscious patient, which results in that patient’s death. In South Africa this is acceptable ethically and legally as it allows the natural process of death to follow its course, BUT the act must alleviate suffering. In other words, the **intention** is very important, in that the act must relieve suffering and not solely accelerate death. The decision must be taken by the senior clinician who is in charge of the patient’s care, taking into account the views of the patient or the patient’s family.

Notes

Preoperative Fasting Guidelines in the Age of ERAS

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Traditionally anaesthetists have starved their patients from midnight. This became standard practice due to a fear of aspiration on induction of anaesthesia. However times have changed and we now realise aspiration fears in healthy patients undergoing elective surgery are largely unfounded. All major anaesthetic bodies now advocate a 6 hour fast for solids and 2 hours for clear fluids. ERAS has taken this one step further and advocates preoperative carbohydrate loading the night before and 2 hours before induction. Let us look at the evidence for this evolution.

CURRENT GUIDELINES

Anaesthesia Societies currently advocate the following:

- 2 hours fasting for clear fluids
- 4 hours fasting for breastmilk
- 6 hours fasting for solids, formula and non-human milk

Clear fluids include water, fruit juice without pulp, carbonated beverages, tea and coffee and drinks such as Powerade, Game and Oros. Tea and coffee can include milk provided it is less than 1/5th the total volume of the drink. Patients are not cancelled for sucking on a boiled sweet, chewing gum or smoking preoperatively. Milky drinks are not considered clear fluids.

This includes the European Society of Anaesthesia, the Association of Anaesthetists of Great Britain and Ireland, the Canadian Anaesthesia Society, the Scandinavian's anaesthetic society, Australian and New Zealand College of Anaesthesia and our own SASA.

The American Society of Anaesthesia qualifies this a bit further and says it allows a 6 hour fasting time for a "light meal" such as toast but prefers an 8 hour fasting time for meals with meat or fat.

As a patient if you were to go to sasaweb.co.za and click on patient information, they advise you to not eat for 6 hours preoperatively but that you are allowed to drink small volumes of water up to 2 hours preoperatively, and to discuss this with your anaesthetist.

We know now that 6 hours is adequate time for a gastric emptying for a solid meal and 2 hours for clear fluids. Starving the patient for any longer than this in fear of gastric aspiration is not necessary. This also results in improved patient well-being both psychologically and physiologically.

FACTORS INFLUENCING GASTRIC EMPTYING

Gastric emptying takes 6 hours for solid food on average and 90 minutes for liquids. Intake of higher volumes will speed up gastric emptying at an exponential rate (i.e. the fuller the stomach the faster it will empty).

Various factors can slow gastric emptying down.

1. Physiological
 - Food of high caloric density
 - Fatty food, and to a lesser degree proteins
 - Intake of cold food (but only for about ten minutes)
 - Ethanol intake (higher concentrations, i.e. spirits)
 - Fear, apprehension, pain and trauma (increased sympathetic tone and endogenous opiates)
 - Intake of acidic solutions (particularly low molecular weight acids)
 - Hypertonic solutions (water with a low osmololality is absorbed very rapidly)
 - Hormones (gastrin promotes emptying whereas cholecystokinin, secretin and gastric inhibitory peptide inhibit emptying)
2. Drugs (opiates, anticholinergics, beta agonists, L-Dopa, tricyclic antidepressants)
3. Stomach and oesophageal surgery
4. Mechanical obstruction (e.g. pyloric stenosis, distal gastric carcinoma)

5. Acid-peptic diseases (GORD, gastric ulcer disease)
6. Pathology resulting in gastroparesis
 - Autonomic neuropathy (e.g. diabetics)
 - Connective tissues diseases (scleroderma, Ehlers-Danlos)
 - Neurodegenerative diseases (Parkinsons)
 - Mitochondrial disease
 - Metabolic (hypokalaemia, hypercalcaemia, hypocalcaemia, hypomagnesaemia, hypothyroidism, uraemia, hepatic encephalopathy, hyperglycaemia and acidosis – diabetic ketoacidosis)
 - Idiopathic

Pregnancy per se does not delay gastric emptying. Labour however may (pain, anxiety and exogenous opiates), and most pregnant patients report increased symptoms of reflux.

EVIDENCE FOR CURRENT GUIDELINES

A Cochrane database review was conducted in 2003 on studies in gastric emptying and preop fasting guidelines in adult patients. They found that patients allowed to drink water up to 2 hours preoperatively did not have increased gastric volume or decreased gastric pH on induction regardless of the volume of fluid ingested.

Subsequently a Cochrane database review on the paediatric population was conducted in 2009. In 2543 children only one aspiration occurred. Children permitted clear fluids up to 2 hours preoperatively did not have increased gastric volume or decreased gastric pH on induction. In addition they were better behaved, less thirsty and hungry and more comfortable.

ERAS

The Enhanced Recovery of Anaesthesia Society takes the preop fasting guidelines on step further. While they stick to the standard 6 hour fasting period for solids and 2 hours for liquids, they advocate carbohydrate loading in the preoperative period. This is in the form of a carbohydrate drink (12,5% maltodextrin) of which 800ml (100g carbohydrates) must be ingested the night before and 400ml (50 g carbohydrates) must be ingested 2-3 hours before induction of anaesthesia. Such a drink is available in South Africa from Nestle.

Please note that the ERAS guidelines (and therefore the preoperative carbohydrate drink) are intended for adults undergoing major elective surgery. In minor surgery the benefit is primarily patient well-being. The patients receiving this drink should also not have delayed gastric emptying (i.e. gastroparesis, GORD, achalasia etc.).

Pathophysiology

Surgery is an insult to the body and gives rise to a surgical stress response. During this surgical stress response there is an increase in counter regulatory hormones (cortisol, glucagon, growth hormone and catecholamines). These hormones put the body into a catabolic state where amongst other effects protein is broken down as a source of glucose. This causes two important factors which may result in perioperative complications.

Firstly the body enters a state of insulin resistance and at times even hyperglycaemia. Studies have found a significant association between the magnitude of insulin resistance and complications. And if the patient develops “diabetes of injury” with fasting plasma glucose more than 7 mmol/l or random level more than 11.1 mmol/l in a general surgery ward, there is an 18 fold increase in in hospital mortality, length of stay and infection risk.

Secondly the catabolism of protein causes protein loss in your patient. A healthy individual can lose up to 2,4kg of wet skeletal muscle after elective open abdominal surgery. This may lead to an increase in complications such as postop respiratory complications. These protein losses are 50% higher in insulin resistance patients. Keep in mind that some may start with a poor reserve (diabetics, the elderly and patients with malignancies) and this protein loss may be even more devastating in this population.

Starving a patient for a prolonged period (i.e. npo from midnight) may shift them into this catabolic state preoperatively already. This will increase insulin resistance, patient discomfort and could decrease intravascular volume in patients receiving mechanical bowel preparation. This may worsen the postoperative outcome.

Animal studies have shown that the administration of carbohydrates preoperatively improved perioperative insulin resistance and animals coped with stress much better if it was sustained in the fed rather than fasted state.

The Evidence for preoperative carbohydrate drinks

Preoperative discomfort:

Hausel et al (Anaesthesia and Analgesia 2001) took 252 ASA 1 and 2 patients. They were divided into 3 groups (npo vs placebo vs carbohydrate drink). There were no adverse events. The carbohydrate group had the least hunger and anxiety of the 3 groups.

PONV

Hausel et al (British Journal of Surgery 2005) randomised 172 patients to placebo or carbohydrate drink preoperatively for laparoscopic cholecystectomy. There was a decrease of incidence of PONV in the carbohydrate group.

Perioperative insulin resistance and preservation of muscle mass:

A large number of studies have been performed by O Ljungqvist from Sweden. In 1994 he published a study in the Journal of American College of Surgery. 12 patients with similar preoperative insulin sensitivity were divided into two groups. One group received a glucose infusion preoperatively whereas the other group were kept traditionally npo. He demonstrated a decrease in postoperative insulin resistance in the group given the glucose infusion.

In 1998 Ljungqvist et al published a study in Clinical Nutrition. He took 14 patients going for elective colorectal surgery and gave 7 a preoperative carbohydrate drink and the other 7 were kept npo. The group given the carbohydrate drink demonstrated less insulin resistance.

In 1999 Ljungqvist et al published again in Clinical Nutrition. This time he took 16 patients going for total hip replacement and once again the group given the carbohydrate drink demonstrated less insulin resistance postoperatively.

In 2005 Ljungqvist et al took 6 healthy volunteers and sequentially tested their insulin resistance in different settings, i.e. traditionally npo, carbohydrate drink the night before, carbohydrate drink in the morning and carbohydrate drinks both night before and in the morning. The last two groups demonstrated less insulin resistance.

Ljungqvist et al published in the British Journal of Surgery in 2007. This time the study looked at 12 patients undergoing colorectal resection who were divided into two groups. The one had a low carbohydrate intake preoperatively and the other a high carbohydrate intake. The high carb group demonstrated improved perioperative insulin resistance and a whole body protein balance.

Other groups such as Wang et al and Yuill et al have also studied preoperative carbohydrate drinks and found a decrease in perioperative insulin resistance.

Breuer et al in Anaesthesia and Analgesia 2006 however did not find this. He took ASA 3 and 4 patients going for elective cardiac surgery and found that the preoperative carbohydrate drink may be cardioprotective but it does not affect perioperative insulin resistance.

Ljungqvist published a review in Current Opinion in Anaesthesia 2015 where he concluded that preoperative carbohydrate administration resulted in decreased insulin resistance, was protein sparing with improved muscle function and preserved immune response. Therefore it would improve clinical outcome.

Theoretically this attenuation of insulin resistance and preservation of muscle mass should translate into a decrease in perioperative complications and reduced length of stay and therefore improve clinical outcome.

This is where our problem comes in as other reviews of the literature have however not been as favourable.

The Cochrane database review in 2014 looked at 1976 participants in various trials in total and they found that in many studies there was a lack of adequate blinding (i.e. bias). Furthermore length of stay was only decreased by 0,3 days and there was low quality evidence for that. 2 studies demonstrated decreased time to passage of flatus and 3 trials demonstrated an improvement in peripheral insulin sensitivity. However there was no increase or decrease in postoperative complications. They felt that there was a need for further well designed studies in this field. Significantly though there was no incidence of aspiration pneumonitis.

Awad et al (including Ljungqvist) also did a review in 2013 based on the methods of the Cochrane database review and had the same result. "Preoperative carbohydrate drinks may be associated with a decreased length of stay in patients undergoing major abdominal surgery; however, the included studies were of low to moderate quality." There was no difference in length of stay in minor surgery or orthopaedic surgery.

In the ERAS guidelines themselves carbohydrate loading is strongly recommended but they acknowledge the evidence level is low.

Controversial patient groups

Obesity

Harter et al in Anaesthesia and Analgesia 1998 compared 256 fasted patients (75 obese and 157 lean). They found that in otherwise healthy patients who were obese, there was no increased incidence of combined high volume, low pH stomach contents when fasted.

Maltby et al in the Canadian Journal of Anesthesia 2004 studied 126 patients who were obese and ASA 1 or 2. They also could not demonstrate an increase in gastric volume or lower pH in these patients on induction. They concluded that obesity per se should not be considered a risk factor for pulmonary aspiration and that healthy obese patients should be allowed to drink clear liquids until two hours before elective surgery.

Diabetes

Gustafsson UO et al in Acta Anaesth Scand 2008 studied the gastric emptying time of 25 type 2 diabetics vs 10 healthy control subjects. They were given a carbohydrate rich drink with paracetamol 1.5g. The diabetic patients demonstrated elevated glucose patients at the 2 hour mark but this returned to normal at 3 hours. There was no difference in gastric half-emptying time. They concluded that preoperative carbohydrate rich drinks could be safely used in diabetics but that these drinks should be given 3 hours preop, not 2 hours.

CONCLUSION

The ERAS protocol strongly advocates the use of carbohydrate rich drinks in elective patients undergoing major elective surgery. This is despite low quality evidence. This approach is does not appear to cause harm as no patients have aspirated on this protocol. This also appears safe in otherwise healthy obese patients and diabetics without gastroparesis. However further well designed studies are necessary to determine if this practice actually has clinically relevant outcomes (e.g. reduced length of stay). Currently the use of these drinks much be weighed up against the cost incurred by the patient/hospital. We can all however make more of an effort to avoid prolonged starvation times which are unnecessary and potentially detrimental to the postoperative outcome of our patients.

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Notes

One Lung Ventilation Physiology; How to do it

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Department of Anaesthesia and Perioperative Medicine
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"One lung ventilation cases take your breath away, that's for sure. And while you're struggling with that lung that keeps coming up, you'll be taking your patient's breath away, too.

Lung isolation is the most consistent pain in the neck in anaesthesia. Just when you think you've finally got the lung down, a patient comes along who didn't read the book. You'll do everything right, and that lung WILL NOT GO DOWN! It won't deflate for love or money. Then the next day a patient comes whose lung goes down, and in close concert with the lung, the saturation goes down, never to rise again. Ay caramba, what a challenge!"

CHAPTER 38: "The lung's not down, you idiot" – Lung isolation
L Cooper and A Sewell in
"ANESTHESIA UNPLUGGED"

One lung ventilation (OLV) is one of the most important topic you will encounter during your training.

It is not just important!

It is essential knowledge!

Understanding of the physiology of OLV rests with prior knowledge and understanding of some basic respiratory physiology.

INTRODUCTION

The separation/isolation of one of the body's major paired organs – the lungs – is unique in the practice of anaesthesia. The fascinating pathophysiological changes that occur during OLV and manipulation of physiology, pharmacology, and technology/equipment make the cornerstone of thoracic anaesthesia.

The late development of thoracic surgery as a discipline is something of an accepted and not often mentioned fact. It was due to both the inability of the patient to cope with the rapid development of the respiratory distress as soon as the chest was open and the inability of the surgeon to operate within the given time-frame on such a rapidly moving surgical field.

Better understanding of pulmonary physiology; developments in pharmacology with its newer volatiles and the arrival on the scene of muscle relaxants; advances in technology with development of tubes and fibreoptics; understanding of the limits and limitations of surgery; as well as understanding of the role that patient's fitness plays in the ability to withstand the ordeal of the whole process, all these contributed to the advancement and development of thoracic anaesthesia as a discipline on its own (although very much still in the shadow of cardiac anaesthesia!!!).

Lung cancer, multi-drug resistant tuberculosis, extension of indications for OLV beyond thoracic surgery, and the increased expectations and demands of both patients and surgeons (read: minimally invasive surgical techniques) continue to push forward – hence, the prescription in the anaesthetic trainees' curricula of thoracic anaesthesia skills, particularly, OLV.

INDICATIONS/CONTRAINDICATIONS OF OLV

OLV is a well-established anaesthetic technique that is increasingly being used for both pulmonary and non-pulmonary intrathoracic procedures.

With rising demands for various VATS (video-assisted thoracoscopic surgery) procedures due to the perceived benefits and the generally increased interest in minimally access surgery, one needs to recall the indications and potential contraindications to performing OLV.

INDICATIONS

Not only is OLV part of the **Domain 4** in the “*Curriculum for Trainees in Anaesthesiology*” (see page 12 in the Feb 2014 edition!).

It is also required for surgery within the thoracic cavity, either on the lung itself, or on the nearby structures (oesophagus, pleura, tumours in the mediastinum, thoracic aorta: dissection/aneurysm, thoracic spine, autonomic nervous system: sympathectomy for hyperhydrosis, minimally invasive cardiac surgery, or radiofrequency ablation for atrial fibrillation).

Previous classification of the indications for OLV into: absolute and relative, seems to be fading away. The indications for OLV nowadays, are as follows:

- for surgical exposure;
- for lung protection (from blood, pus, or air);
- for ventilation in situations like:
 - o bronchopleural fistula or
 - o independent lung ventilation.

CONTRAINDICATIONS

Difficult to conceptualize that there might be contraindications to OLV!

Have you considered:

- tracheal tears;
- tumours in the trachea or eroding from the oesophagus; or
- those patients with poor lung function that might not be able to maintain oxygenation during OLV !?!

PHYSIOLOGY/PATHOPHYSIOLOGY

Change in position from standing to supine, associated pre-existent cardiorespiratory diseases, neuraxial block, induction of anaesthesia, muscle paralysis, instrumentation of the airway, change in position from supine to lateral, mechanical ventilation, surgery, OLV, all of these, have significant effects on respiratory function.

The resultant modified physiology may translate in extreme changes in lung volumes, lung mechanics, and control of breathing. Anaesthetic challenges range from common problems such as reducing atelectasis and maintaining ventilated lung volume, to minimizing the ventilation/perfusion abnormalities and preventing/reducing the risk of acute lung injury. Applying sound rationale and basic physiologic principles may lead to safe delivery of good anaesthetic technique and survival of your patient.

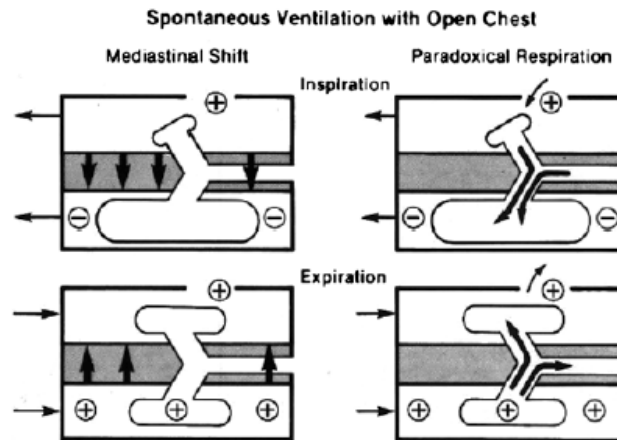
What follows in this section is a brief, mostly pictorial, outline of well-known basic respiratory physiology and pathophysiology of OLV.

Early attempts at thoracic surgery were discouraged by the rapidly developing respiratory distress in the patient and a fast moving surgical field that made it impossible for the venturing surgeon to operate. These were explained by the *Pendel-luft* and *Mediastinal shift*.

Pendel-luft literally translates as “air pendulum”. In the context of lung physiology as it was understood at the beginnings of thoracic surgery, *pendel-luft* was a somewhat paradoxical air movement from both the outside environment as well as the collapsed (operative) lung during inspiration. During expiration, air would move from the dependent lung towards both the outside as well as the collapsed operative lung.

Mediastinal shift occurs through a similar process where the negative inspiratory pressure pulls the mediastinal structures towards the dependent non-operative lung. During expiration, the positive intrathoracic pressure pushes the mediastinum across into the open thorax.

These two phenomena explain the difficulty of performing intrathoracic surgical interventions and may be responsible for the development of hypoxia and hypercapnia.



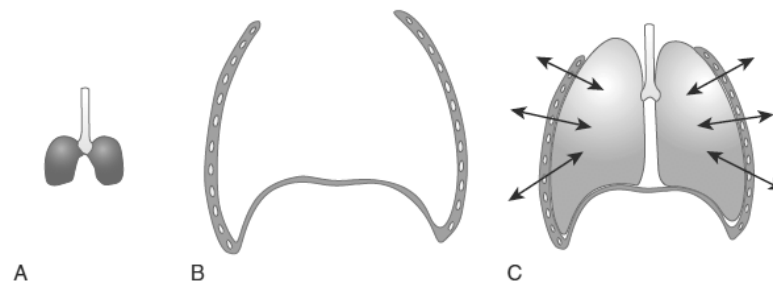
From P Slinger modified from Benumof

Should probably be mentioned now the re-kindled interest in awake thoracic surgery in certain high-risk patients. What is being emphasized by the proponents of this technique, is the lack of anaesthetic agents' influence on the very mechanisms that act to compensate for pathophysiological changes induced by the surgical pneumothorax:

- intact hypoxic pulmonary vasoconstriction (HPV) that minimizes the ventilation/perfusion abnormalities;
- reduction in atelectasis in a spontaneously breathing patient in the dependent regions;
- maintenance of diaphragmatic action, and, as a result, better maintenance of lung volumes;
- better oxygenation in the lateral position, even in the presence of surgical pneumothorax;
- unhindered (by the anaesthetic agents) central nervous system responses to the hypercapnoea and the reduced tidal volume; and,
- the advantage (some would mention!) of avoiding the risks of general anaesthesia.

PHYSIOLOGY

Understanding of respiratory physiology is essential and might be refreshed by starting from the "macro-elements" of the lung mechanics and moving towards the "circulatory" aspects. Lung mechanics is out there for all to see:



From WC Wilson and JL Benumof

When the lungs are removed from the chest, their elastic recoil causes them to collapse (see A: resting state of normal lungs). Opening the chest to the atmosphere (and removing its contents) will make the chest to expand (as in B: resting state of normal chest wall).

The lung volume that exists at the end of a normal expiration is the **functional residual capacity (FRC)**. At FRC the elastic forces of the lung and chest wall are equal and acting in opposite directions, thus, maintaining the equilibrium (like in C: respiratory system at the end of expiration). Pleura might be considered to represent the interface between these opposing forces (the elastic recoil of the lung and the expanding chest wall).

FRC is a central concept in respiratory physiology. It is also a key element around which the practice of anaesthesia seems to revolve.

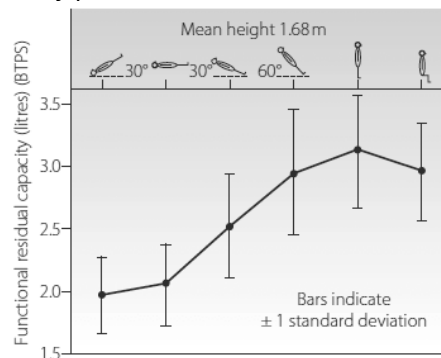
There are numerous **factors affecting FRC**:

- gender: for the same height, females have an FRC less 10% than males;
- age: FRC increases with age (16 ml/year);
- height: FRC increases linearly with height;
- obesity: FRC decreases with increasing body weight;
- diaphragmatic muscle tone;
- posture: in the supine posture FRC is reduced by 20 – 25%;
- lung disease; and, of course,
- anaesthesia.

Of some scientific interest can be the following formula for working out the FRC of a particular patient:

$$FRC = (5.95 \times \text{height}) + (0.019 \times \text{age}) - (0.086 \times BMI) - 5.3$$

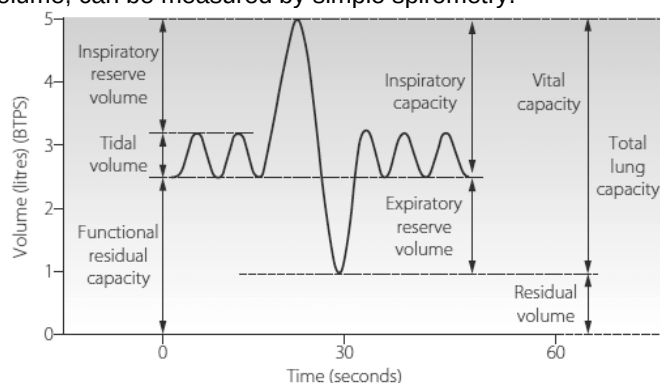
Of probably more interest is going to be the following diagram of studies of Dr. Nunn and his co-workers of the FRC in different body positions.



From AB Lumb

The expiratory reserve volume (ERV) is part of the FRC and it can be defined as the additional volume of gas/air that can be consciously exhaled beyond the tidal volume V_T . What is left in the lungs following forced expiration is the residual volume (RV).

All these lung volumes: V_T , inspiratory capacity, vital capacity VC, inspiratory reserve volume, expiratory reserve volume, can be measured by simple spirometry.



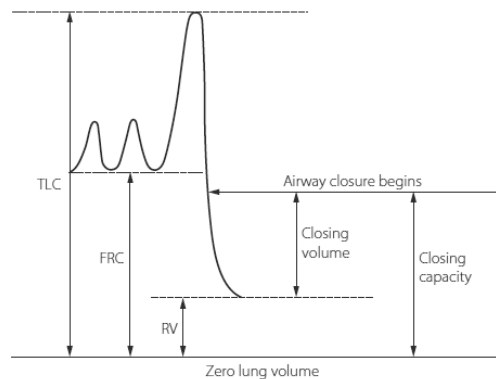
From AB Lumb

There are two reasons why maintenance of gas in the lungs at the end of expiration (FRC) is important/beneficial:

- (1) conservation of energy: inflating an already open (inflated) lung is easier than when the lung is collapsed (deflated); and
- (2) desaturation. Although perfusion in the lungs is phasic (systole-diastole), it amounts to almost a continuous flow due to the high frequency but small amplitude oscillations. While ventilation is different: low frequency but wide amplitude oscillations (inspiration-expiration), potentially leading to complete collapse of the lungs with each respiratory cycle. Blood would be flowing from the collapsed/closed alveoli (containing no O_2) with low SpO_2 . This would mix into the overall blood flow from the lungs and cause oxygen desaturation with every exhalation.

Of specific interest is the relationship between **FRC** and the **closing capacity**.

Reduction in lung volume below a certain level results in airway closure with relative or total underventilation in the dependent parts of the lung. The lung volume below which this effect becomes apparent is called **closing capacity (CC)**.

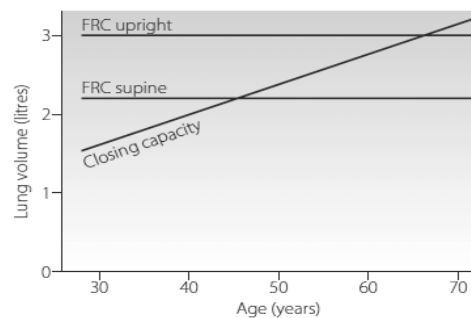


From AB Lumb

The closing capacity seems to be independent of body position, but the FRC changes markedly with position (as we've seen in one of the diagrams above).

Closing capacity increases linearly with age and is less than FRC in young adults but increases to become equal to FRC at a mean age of 44 years in the supine position and 75 years in the upright position.

And here is another well-known, representation of Nunn's classic diagram.



From AB Lumb

Total lung capacity (TLC) and FRC contain this fraction – residual volume (RV) - that cannot be measured by simple spirometry.

RV, FRC and TLC can be measured by:

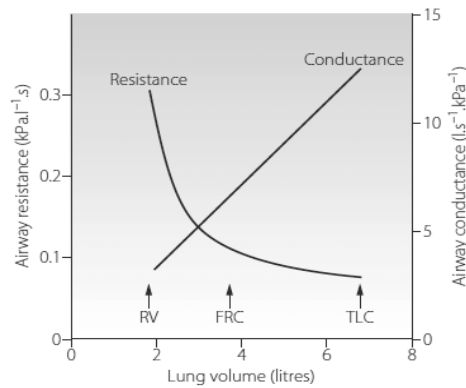
- nitrogen wash out;
- helium dilution; and
- total body plethysmography.

Only total body plethysmography allows for the measurement of the volume of gas trapped within the lung distal to closed airways.

Gas flow along pulmonary airways is complex and consists of a varying mixture of both laminar and turbulent flow. That is quite easy to visualize/understand, particularly as there are frequent divisions of variable lengths of the airways (as one goes down the tracheobronchial tree).

In normal lungs, **respiratory resistance** is controlled by changes in airway diameter, mainly in small airways and bronchioles and changes in lung volume.

When the lung volume is reduced, there is a proportional reduction in all the structures, including the air-passages. If the bronchomotor tone remains constant, airway resistance is an inverse function of the lung volume. In general, increasing lung volume decreases airway resistance.



From AB Lumb

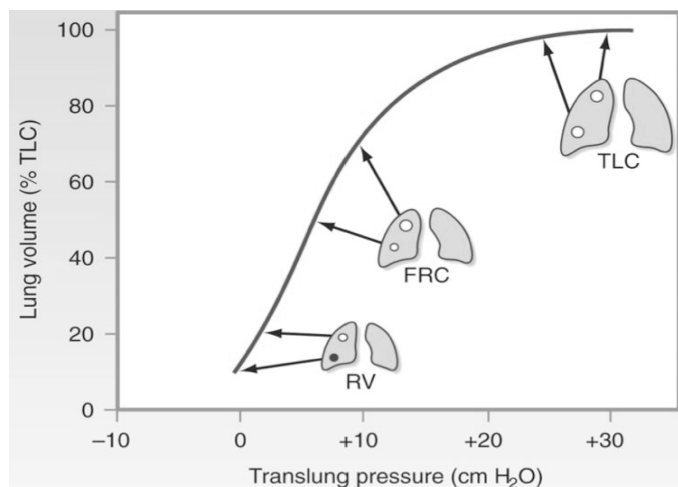
There is a direct relationship between lung volume and the maximum expiratory flow rate that can be attained. At low lung volume, flow-related airway collapse occurs more readily. Expiratory flow-related airway collapse leads to air trapping distal to the collapsed airway, increasing the residual volume and FRC.

Thus, in general, increasing lung volume decreases airway resistance and helps to prevent gas trapping. This is achieved by applying **continuous airway positive pressure (CPAP)** to the spontaneously breathing patient or **positive-end expiratory pressure (PEEP)** to the paralyzed, ventilated patient.

The transmural (transpulmonary) pressure gradient is the difference between intrathoracic (or pleural) pressure and alveolar (airway) pressure.

Ventilation is not uniformly distributed in the lung, due to a number of factors, of which gravity is most easily understood.

If the chest (lung) is upright, the alveoli near the apex of the lung are more expanded than the alveoli at the base. The alveoli at the apex have a larger volume than those in the dependent parts of the lung (at the base) - except at total lung capacity. The expanded alveoli at the apex of the lung are closer to the top of the pressure:volume curve. They are stiffer than the alveoli at the bases of the lung that are more compliant.

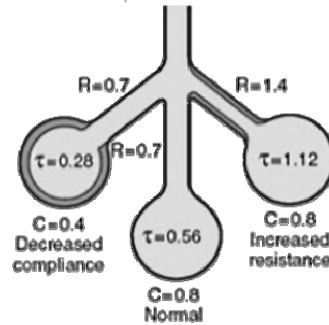


From BM Koeppen and BA Stanton

In addition to the gravitational effects of the distribution of ventilation, the ventilation in the terminal respiratory units is also not uniform. This is caused by variable airway resistance (R) or compliance (C), and it may be describe by the **time constant (τ)**.

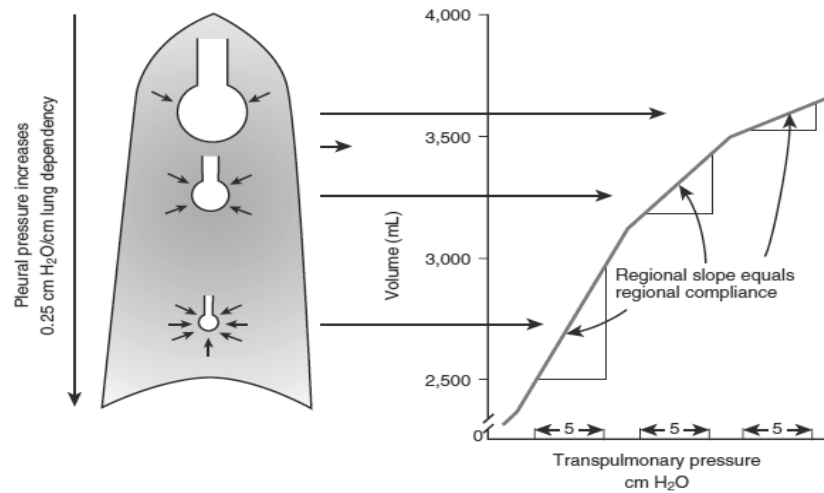
$$\tau = R \times C$$

Alveolar units with long time constants fill and empty slowly. Thus, a unit with increased airway resistance or with increased compliance will take longer to fill and longer to empty.



From BM Koeppen and BA Stanton

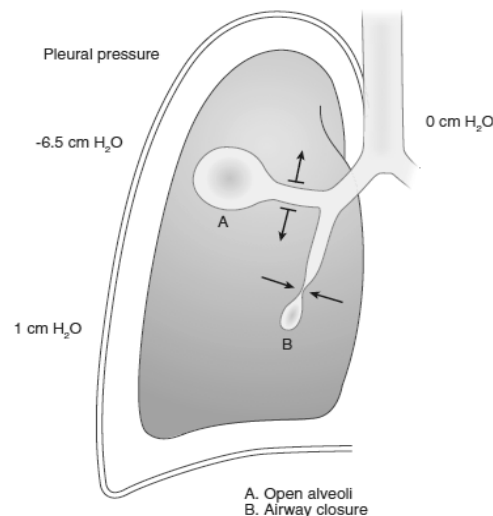
To have a better understanding, one should think of the relationship between lung volume and alveolar pressure (compliance) as being applied to various horizontal strata in the lung – regional differences in lung ventilation.



From WC Wilson and JL Benumof

Increasing pleural pressure down the lung leads to a decrease in alveolar volume from the top of the lung to the bottom. The dependent small alveoli receive the largest share of the tidal volume (they are on the steep portion of the curve). Or, said somewhat differently, during tidal breathing the lower zones ventilate more than the upper zones.

Below a certain lung volume, some alveoli tend to close and only re-open at a considerably greater lung volume and to a much higher transmural pressure gradient than that at which they closed – **recruitment**.



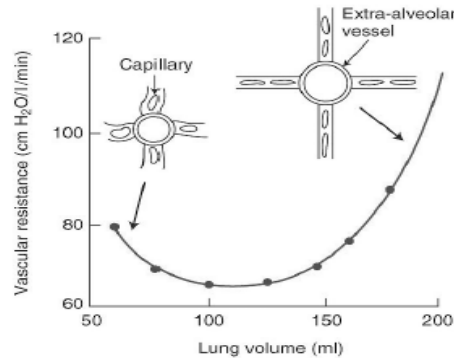
From BP Kavanagh and G Hedenstierna

Airway pressure is atmospheric, i.e. 0 cm H₂O. In the upper regions of the lung, pleural pressure is sub-atmospheric keeping the airways open. In the lower regions of the lung, in contrast, airway pressure is less than pleural pressure and so, causes airways closure. This can be potentially exacerbated by absorption of gas behind the occluded airways.

Closure of the airways during expiration is normal.

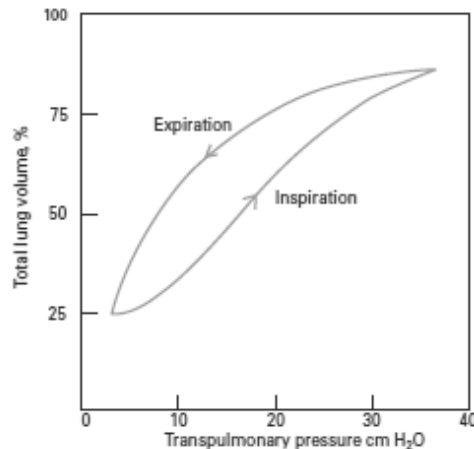
The transmural pressure gradient has an important influence on many aspects of pulmonary function and its "horizontal stratification" confers **regional differences** on airway closure, ventilation/perfusion ratios and gas exchange.

Lung volume also has an influence on the **vascular resistance** of the pulmonary vessels. At low lung volume the resistance is high because of compression of the extra-alveolar vessels. At high volume, the capillaries are stretched and their caliber is reduced.



From West

If the lungs are slowly inflated and then, slowly deflated, the pressure/volume curve during inflation differs from that obtained during deflation. This phenomenon is known as **hysteresis**.



From MG Levitzky

For air to flow into the lungs, a pressure gradient (ΔP) must be developed to overcome the elastic resistance of the lungs and chest wall to expansion. The relationship between ΔP and the resultant volume increase ΔV of the lungs and thorax is independent of time and is known as **total compliance** C_T .

$$C_T = \frac{\Delta V}{\Delta P}$$

$$\frac{1}{\text{Total compliance}} = \frac{1}{\text{compliance of the lung}} + \frac{1}{\text{compliance of the chest wall}}$$

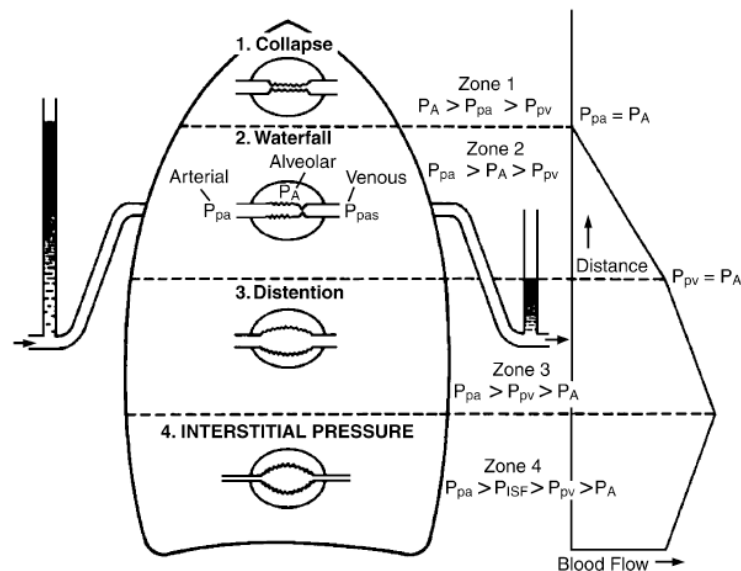
Pulmonary circulation is a low-pressure (5 to 10-fold lower than the systemic circulation) and low-resistance (the vessels are shorter and wider) circulation. As a result, gravity as well as other, non-gravitational factors, contribute to an uneven distribution of blood flow in the lung.

Contraction of the heart/right ventricle imparts kinetic energy to the blood in the main pulmonary artery. As this energy is dissipated in climbing a vertical hydrostatic gradient, the absolute pressure in the pulmonary artery P_{PA} decreases by 1 cm H₂O for each cm of height up the lung. Based on such gravitational distribution of pulmonary artery pressure, as well as the effect of alveolar distension with respect to lung volume, West divided the lung into his famous zones.

This system (**West zones**) is based on the principle that perfusion to the alveoli depends on the pressures in the pulmonary artery P_{PA} , pulmonary veins P_{PV} and alveolus P_A .

In the apex (zone I) pulmonary artery pressure P_{PA} is less than alveolar pressure P_A and as a result, there is no perfusion. Ventilation of such a zone is dead space ventilation, like when ventilating with large tidal volumes.

Below the apex, in zone II, the pulmonary vein pressure P_{PV} is less than alveolar pressure P_A and the veins are collapsed except during flow, like in a "vascular waterfall". Perfusion occurs only when there is flow, when P_{PA} is more than P_A .



From KP Grichnik and JA Clark

In zone III, both arterial and venous pressures exceed alveolar pressure. As a result, there is perfusion throughout systole and diastole and during the whole respiratory cycle (both inspiration and expiration).

In zone IV, as a result of gravity compressing the lung and the lung vessels therein (increases in interstitial pressure P_{ISF}), there is also a reduction in perfusion, particularly due to increases in vascular resistance.

Both ventilation and perfusion are essential elements for normal functioning of the lung.

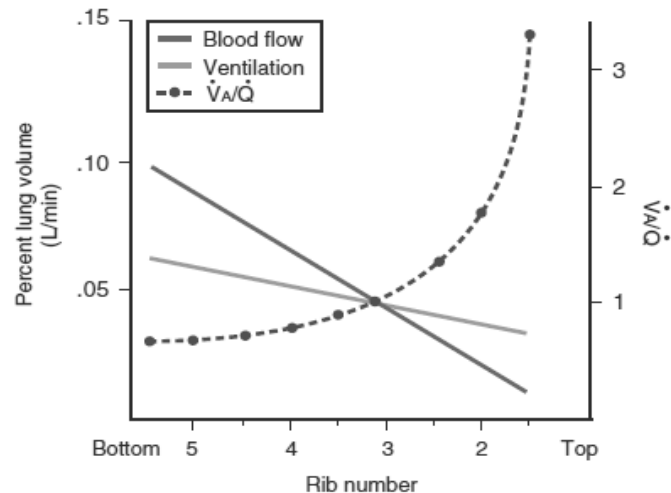
The **ventilation/perfusion ratio (V/Q ratio)** is defined as the ratio of ventilation to blood flow.

In normal resting individuals, alveolar ventilation (4 L/min) is slightly less than pulmonary blood flow (5 L/min), giving a ratio of about 0.8

Both blood flow and ventilation fall with distance up the lung. If the blood flow (perfusion) and ventilation are expressed in liters per minute percentage alveolar volume, the two figures can be divided to produce the ventilation-perfusion (V/Q) ratio. And that can be represented graphically with respect to the number of ribs.

At the base of the lung the V/Q ratio is low (0.6) suggesting greater perfusion than ventilation. This increases to the apex (3.3) where there is greater ventilation than perfusion.

V/Q ratio reflects gas exchange in a lung region.



From WC Wilson and JL Benumof

If ventilation and blood flow are mismatched, both O_2 and CO_2 transfer are impaired.

Ideally, ventilation and blood flow are uniformly distributed. This is not the case, even in normal, healthy individuals. Factors such as age, position/posture, depth of breathing, they all alter the V/Q relationship in a dynamic fashion.

In patients with cardiopulmonary disease, mismatching of pulmonary blood flow and alveolar ventilation is the most frequent cause of systemic arterial hypoxaemia.

Hypoxic pulmonary vasoconstriction (HPV) is a compensatory mechanism that diverts blood flow away from hypoxic lung regions towards better oxygenated regions. The major stimulus for HPV is low alveolar oxygen tension and is more potent when it affects a smaller lung region. Older volatile anaesthetics were thought to inhibit HPV, whereas iv-based anaesthetics as well as the newer volatiles including sevoflurane and desflurane, have little effect.

PATHOPHYSIOLOGY

Physiology, as it has been highlighted above, suffers modifications and responds to:

- changes in position;
- administration of anaesthetic agents, including muscle relaxants;
- alterations of various parameters like blood pressure (perfusion), lung volumes (dead space ventilation, airway closure); and
- exclusion of half the function – as it happens in OLV.

OLV is one of the most challenging techniques of anaesthetic practice.

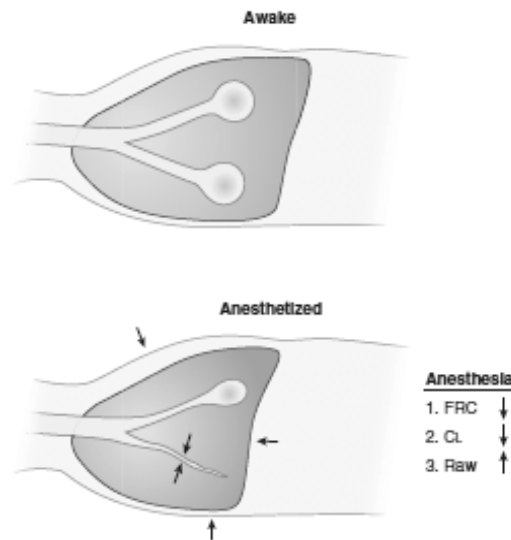
Anaesthesia

Anaesthesia, whether the patient is breathing spontaneously or is mechanically ventilated, impairs respiratory function.

Impaired oxygenation occurs in most anaesthetised individuals, and this is why supplemental oxygen (0.3 to 0.5) is used intraoperatively. Mild to moderate hypoxaemia lasts from a couple of seconds to minutes.

Beyond the OT, the respiratory complications attributed to anaesthesia can persist. Postoperative respiratory complications can be encountered in 1-2% of any surgical intervention with an incidence of up to 20% after major abdominal and thoracic surgical procedure.

FRC is reduced by almost 1L by moving from upright to supine position. Induction of anaesthesia further decreases the FRC by 0.5L, bringing the FRC closer to RV. General anaesthesia causes a fall in FRC (by approx. 20%) whether breathing is spontaneous or controlled, and whether the anaesthetic is intravenous or inhaled. This is a major contributor to lower oxygenation. Muscle paralysis (in the context of general anaesthesia) does not cause additional decrease in FRC.



From PB Kavanagh and G Hedenstierna

Anaesthesia induces a cranial shift of the diaphragm with atelectasis and airway closure leading to a decreased compliance and increased respiratory resistance.

Atelectasis is an important cause of hypoxaemia.

Certain manoeuvres help prevent /minimize atelectasis:

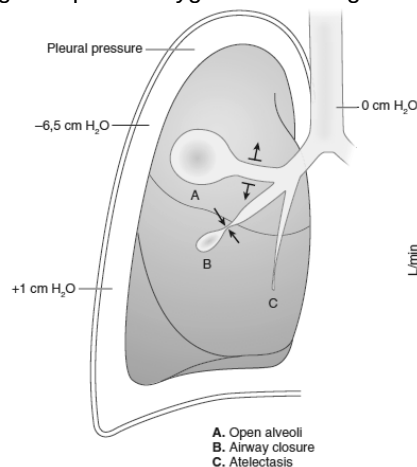
- application of PEEP (5-10 cm H₂O) – considerably – can improve oxygenation (carefully titrated, since high levels of PEEP may reduce venous return and compromise cardiac output leading to further desaturation);
- recruitment manoeuvres – like a VC manoeuvre - may reverse/reduce atelectasis (40 cm H₂O for 7-8 seconds might suffice, although there are numerous other variations);
- minimizing gas resorption by ventilating with a gas mixture of 60% N₂ (i.e. 40% O₂); and
- maintaining muscle tone – sometimes this may be tricky.

Anaesthesia reduces FRC and this, leads to increases in airway closure. The reduction in ventilation in non-atelectatic areas is caused by airway closure. Taken together, atelectasis and airway closure in the face of maintained perfusion (low V/Q ratio regions) explain (in a proportion of 75%) the impairment in oxygenation.

A three-compartment lung model:

- (1) normal V/Q ratio regions;
- (2) regions of airway closure; and
- (3) atelectatic areas;

describes the factors contributing to impaired oxygenation during anaesthesia.



From BP Kavanagh and G Hedenstierna

Anaesthesia impairs CO_2 elimination and oxygenation of the blood.
Reduced CO_2 elimination is due to reduced minute ventilation.
Impaired blood oxygenation during anaesthesia is more marked with increasing age, obesity and smoking.

Patient position

Though OLV may be required in a supine patient, the lateral position is most commonly used for thoracic surgery.

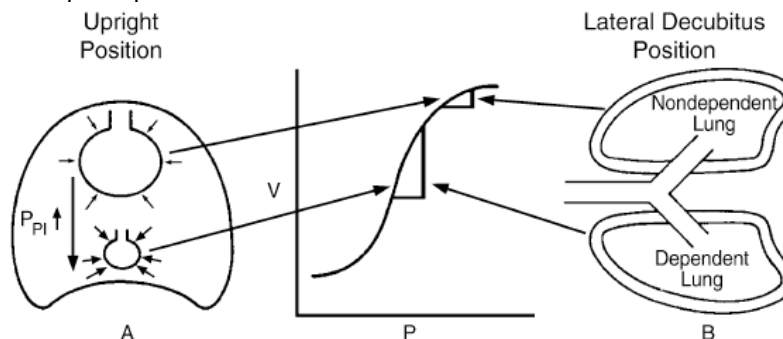


From JWW Gothard

This position significantly affects ventilation and perfusion in the lungs.

With the assumption of lateral position in an awake patient, the non-dependent lung behaves as the superior portion of the upright lung, and the dependent lung behaves as the inferior portion of the upright lung.

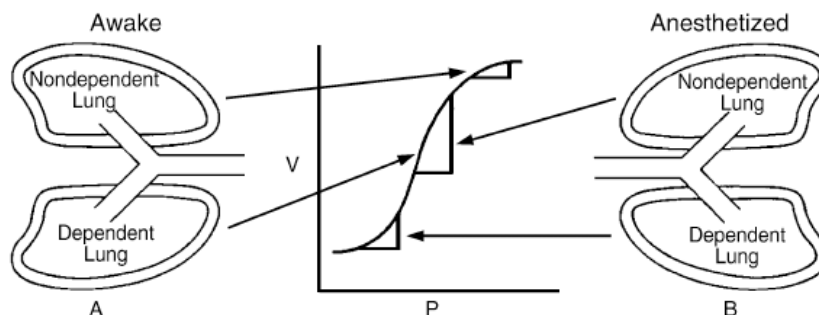
The dependent lung is on a steep portion of the pulmonary compliance curve, and the nondependent lung is on a less compliant portion on the curve.



From KP Grichnik and JA Clark

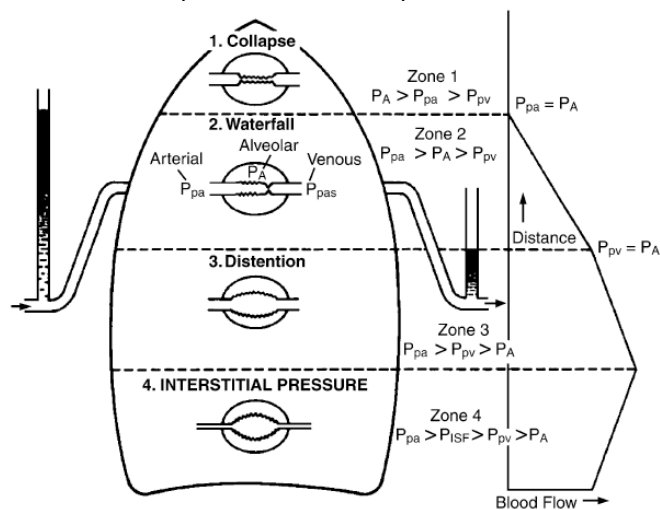
With the induction of anaesthesia and in the lateral position, the non-dependent lung moves to a more compliant portion, and the dependent lung moves to a less compliant portion of the pulmonary compliance curve.

The loss of muscle tone in the chest wall and the diaphragm associated with general anaesthesia causes gravity to affect the lung volumes. The volume of the dependent lung is decreased by the weight of the mediastinum above and the cephalad movement of the diaphragm from the weight of the abdominal contents. FRC increases for the non-dependent lung and declines for the dependent lung with 55% of the tidal volume directed to the non-dependent lung. Perfusion changes little, and as a result, a significant V/Q mismatch is introduced.



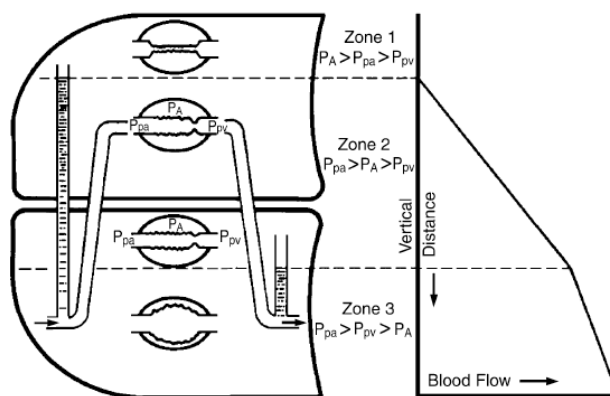
From KP Grichnik and JA Clark

It is probably worth drawing the attention upon the fact that oxygenation during OLV is better preserved in the lateral versus the supine or semi-lateral position.



From KP Grichnik and JA Clark

Just comparing the heights over which the distribution of the 4 West zones happens in the lateral decubitus position versus the supine position shows a wider spread for the lateral position.



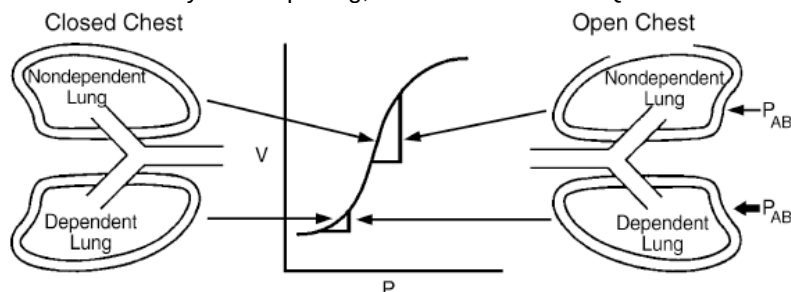
From KP Grichnik and JA Clark

In the supine position the vertical height of the lung is less allowing for blood flow distribution in greater proportion to the non-dependent lung and thus attenuating the hypoxic pulmonary vasoconstriction and leading to hypoxaemia.

The open chest

Opening the non-dependent hemithorax of a lateral, anaesthetized, paralyzed patient, leads to further redirection of ventilation to the non-dependent lung. The dependent lung experiences the full weight of the mediastinum, and improper positioning may further limit the lung movement. The dependent lung has a decreased FRC and as a result, decreased compliance.

Since perfusion is not affected by chest opening, there is increased V/Q mismatch.



From KP Grichnik and JA Clark

One lung ventilation

During OLV, although only one lung is ventilated, both lungs are perfused. Perfusion of the collapsed, non-ventilated lung leads to shunting (although less than anticipated), impairment of oxygenation, and hypoxaemia.

Ceasing ventilation to the non-dependent lung removes the better ventilated lung, leaving the challenge of ventilating the low-volume, low-compliance dependent lung. Mean airway pressure cannot be allowed to increase unchecked because eventually it leads to increased pulmonary artery pressure and further shunting through the non-dependent lung.

The introduction of OLV results in changes in airway resistance and mean airway pressure and they can be accentuated by external compression from the mediastinum and diaphragm, suboptimal positioning, surgical packing, lung separation devices as well as endobronchial secretions.

With collapse of the non-dependent lung during OLV, perfusion to the non-dependent lung continues, and this leads to a large increase in V/Q mismatch (shunt fraction). This right-to-left shunt through the non-ventilated lung is in addition to the normal 5% of shunt that exists in the contralateral, ventilated lung.

HPV is believed to be the most important determinant of pulmonary blood flow in the non-dependent, non-ventilated lung. The 40-50% of cardiac output that would be expected to flow through the non-ventilated lung is actually reduced to 20-30% by HPV.

HPV begins within few seconds and is maximal at 15 minutes. With moderate hypoxia the response is sustained, but in severe hypoxia, it quickly declines.

HPV inhibition by anaesthetic agents is well recognized, the newer agents are less inclined to affect it. Hypothermia, as well as haemodilution and increased left atrial pressure also inhibit the HPV. Surgical retraction may aid HPV by increasing pulmonary vascular resistance in the operative lung.

MANAGEMENT OF OLV

OLV has enabled remarkably complex intrathoracic surgical procedures and with the increased use of minimally invasive techniques, it is becoming a common occurrence in daily anaesthetic practice. However, OLV is associated with postoperative pulmonary complications in about 20% of cases.

Historically feared for its high rate of hypoxaemia, OLV is now recognized as an important cause for the development of acute lung injury (ALI).

Management of OLV revolves around management - prevention and treatment - of these two complex/difficult issues:

- hypoxaemia, and
- lung injury.

HYPOXAEMIA

The incidence of hypoxaemia during OLV is currently reported to be around 5%. It is generally thought that the incidence of hypoxaemia during OLV is decreasing. Studies from the 1970s and before suggest that the incidence of hypoxaemia during OLV was in the range of 25-40%.

There is no agreed standard for the definition of hypoxaemia during OLV. An arterial oxygen saturation below 90% with an F_{IO_2} of 1.0 is commonly accepted as a level at which some intervention by the anaesthetist is required.

Prediction of hypoxaemia

A number of factors may be helpful in predicting oxygenation during OLV:

- side of the operation: better during left thoracotomy, when the larger right lung is the dependent, ventilated lung;
- lung function abnormalities: good preoperative pulmonary function was found to be predictive of poor OLV oxygenation – paradoxical effect;
- distribution of perfusion between the two lungs relating to position (oxygenation is better in the lateral decubitus than supine);
- the size and location of pulmonary pathology (patients with large, central pulmonary masses will have better oxygenation than patients with small peripherally located lesions).

Management

It is probably safe to assume that **improving the pulmonary function** prior to surgery/OLV will decrease the risk of potential complications both during and after the procedure, and will improve oxygenation during OLV.

Clinical experience suggests that the most common treatable cause of hypoxaemia during OLV is malpositioning of the isolating lung device or malfunctioning due to blockage from secretions or blood.

Monitoring lung separation thus becomes essential whenever problems are encountered.

Once a particular device has been selected and placed, its good functioning and position should be monitored to confirm good lung isolation and whenever there is a change in position.

Nowadays, technology allowed a progress from the clinical confirmation of placement of the device, to the fiberoptic confirmation of proper positioning of the respective device.

Clinical examination with auscultation and inspection, sometimes fails to identify malpositioning.

Fiberoptic inspection remains the gold standard for the optimal positioning of the lung isolation device.

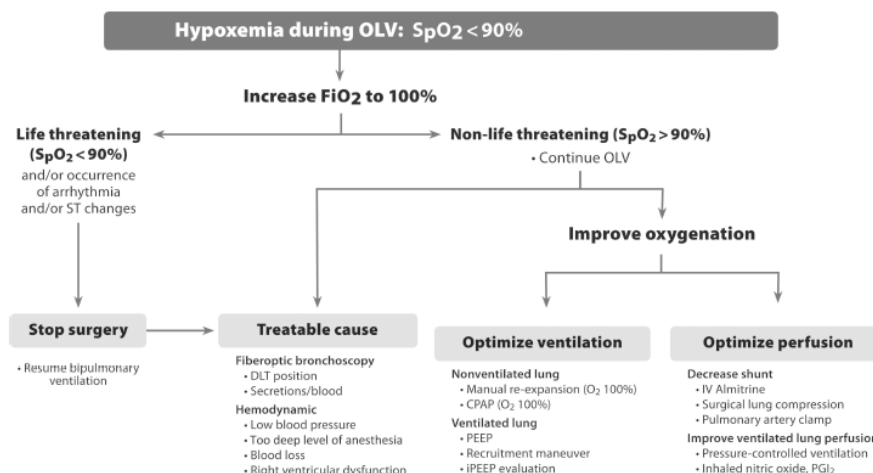
Some even advocate the use of ultrasound to confirm good/appropriate positioning of the device chosen for lung isolation.

Haemodynamic conditions also need to be assessed and steps might need to be taken since a low cardiac output might lead to impaired oxygenation. Fluid loading and appropriate titration of vasopressors/inotropic agents is sometimes all that needs to be done.

As OLV induces increases in right ventricular afterload, intraoperative assessment of ventricular function may be useful. Transoesophageal echocardiography (TOE) is probably the best intraoperative monitoring technique to use during OLV. Signs of right ventricular dysfunction that can be observed are: right ventricular dilatation as well as paradoxical septal motion.

Ventilation strategy is important in order to decrease the incidence of hypoxaemia during OLV. This includes the following steps:

- increasing the F_{IO_2} – this is effective in immediately treating hypoxaemia. In shunt fractions greater than 40% this might not lead to improved oxygenation. The shunt fraction during OLV is around 20-30% leaving room for increasing oxygenation.
- assessing haemoglobin levels – oxygenation during OLV depends not only on the magnitude of the shunt fraction, but also on the oxygenation of the shunted blood. Increased oxygen extraction (either because of low cardiac output or increased oxygen expenditure) and low haemoglobin levels can lead to a decrease in oxygenation;
- administration of CPAP or high frequency jet ventilation to the non-dependent lung – although it may not be well tolerated by the surgeon in certain circumstances (like VATS!);
- compression of the non-dependent lung in the surgical field or ligation of its pulmonary artery can significantly improve oxygenation by reducing the shunt
- administration of PEEP and recruitment manoeuvres to the ventilated lung;
- re-expansion of the operative lung (two-lung ventilation);
- modulation of perfusion with interventions like nitric oxide and almitrine – mentioned just for historical interest - has not been very efficient and has limited clinical application.



From H Roze, M Lafargue

LUNG INJURY

Post-thoracotomy acute lung injury occurs in 5-15% of cases, the greater the extent of the surgical intervention, the greater the incidence.

ALI and the acute respiratory distress syndrome (ARDS) are the leading cause of death after thoracic surgery.

The pathophysiologic mechanisms that underlie the development of ALI after OLV are different for the ventilated lung and the collapsed lung.

In the perioperative period patients are at risk of developing several types of lung injury:

- atelectasis;
- pneumonia;
- pneumothorax;
- bronchopleural fistula;
- acute lung injury ALI; and/or
- acute respiratory distress syndrome ARDS.

Anaesthetic management can cause, exacerbate or ameliorate most of these injuries.

Lung-protective ventilation strategies using physiological tidal volumes and appropriate levels of PEEP can decrease the extent of the injuries.

The very existence of ALI as an independent entity, has been replaced in the latest ARDS consensus criteria (Berlin definition) by the term "mild ARDS".

Acute respiratory distress syndrome			
Timing	Within 1 week of a known clinical insult or new/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		
	Mild	Moderate	Severe
Oxygenation ^b	$200 < \text{PaO}_2/\text{FiO}_2 \leq 300$ with PEEP or CPAP ≥ 5 cmH ₂ O ^c	$100 < \text{PaO}_2/\text{FiO}_2 \leq 200$ with PEEP ≥ 5 cmH ₂ O	$\text{PaO}_2/\text{FiO}_2 \leq 100$ with PEEP ≥ 5 cmH ₂ O

This only underlines the fact that ALI is the same disease as ARDS, just of a different degree on the scale of oxygenation.

Pathophysiological considerations

Atelectasis occurs frequently after surgery and general anaesthesia – in up to 90% of patients. It is a pathological state that has both direct and indirect effects on the development or aggravation of lung injury.

Caused either by compression, gas resorption or impairment in the surfactant, atelectasis has a number of consequences:

- decreased lung compliance – with resultant effects on the lung mechanics;
- impaired oxygenation;
- increased pulmonary vascular resistance; and,
- the development of acute lung injury.

Direct, stretch-independent effects include:

- a propensity to infection due to impaired alveolar macrophage function; and
- local hypoxia and hyperoxia.

Atelectasis causes local alveolar hypoxia due to collapse of alveoli and systemic hypoxaemia due to increased pulmonary shunt. An increase in F_{IO_2} causes hyperoxia in the aerated lung. Alveolar hypoxia can induce inflammation, and alveolar hyperoxia can worsen atelectasis by absorption and lead to an excess of reactive oxygen species, all contributing to ALI.

Indirect, stretch-dependent effects include mechanical stress-induced injury that, interestingly, is maximal in the non-atelectatic regions of the lung, as there is a shift of tidal volume to the aerated lung units with subsequent over-inflation.

There is concern that lower tidal volumes (advocated by protective ventilation strategies) might predispose to atelectasis and, as a result, to ALI. Techniques like recruitment manoeuvres and application of appropriate PEEP, combined with low tidal volumes have a well established role in prevention/management of lung injury during anaesthesia. Following anaesthesia, application of low F_{IO_2} (where appropriate) and CPAP after tracheal extubation decreases atelectasis and leads to better respiratory function in the postoperative period.

One lung ventilation patients are heterogeneous both with respect to the underlying pathology and surgical procedure. They can both predispose or cause ALI.

The classical description of ALI:

- onset 1 up to 3 days following pneumonectomy;
- high associated mortality (25-50%);
- greater frequency after right compared with left pneumonectomy;
- female gender
- prolonged OLV;
- high intraoperative pressures;
- pre-existing lung injury (trauma, infection, chemotherapy);
- excessive fluid infusion;
- pre-operative alcohol abuse; and
- resistance to standard therapies.

ALI also occurs after lesser resections, like lobectomies, where it has a much lower mortality. Interestingly enough, in the majority of the unilateral ALI cases, the affected lung was the non-operative (the ventilated) lung where the endothelial damage seems to play a key role (ARDS-type mechanism).

Lung volumes and lung mechanics are significantly altered by the breach of the pleural interface with thoracotomy. Of particular importance seems to be the alteration in the normal relationship between FRC and CC. CC is an intrinsic property of the lungs of a particular patient (with or without a particular pathology). FRC is the balance point between the inward recoil of the lungs and the outward recoil of the chest wall. With the surgical pneumothorax FRC stops to exist in the collapsed lung. The ventilated lung (with all the compression from the surroundings) depends on the positive airway pressure to stay above residual volume.

The end-expiratory lung volume of the ventilated lung becomes dependent on the respiratory rate, tidal volume, I:E ratio, and PEEP.

The ventilated lung becomes distended and subjected to strain (even at low lung volumes) and induces an inflammatory response – ARDS.

Hypercapnia (permissive hypercapnia) is an accepted consequence of lung protective ventilation in patients with ARDS. Its beneficial effects are mainly biological and consist of attenuated lung injury as a result of inhibition of the endogenous xanthine oxidase pathway.

Mechanisms of lung injury in the ventilated lung

Injury at high lung volumes (volutrauma) has been documented with excessive end-inspiratory lung volumes (due to either large tidal volumes or gas trapping in the setting of inadequate expiratory time or excessive PEEP).

High ventilating pressures during large tidal volume OLV are also harmful. High peak pressures need to be avoided during OLV, but these values do not seem to be reflected at intra-bronchial level, probably due to the increased airflow resistance of the lung isolation devices.

Pressure-control ventilation (that does reduce peak pressures) does not seem to be much different from volume-control ventilation.

Alveolar recruitment manoeuvres intentionally create high alveolar pressures to expand (open lung ventilation) the low compliance alveolar units. This may result in regional over-distention of the high compliance units.

Recruitment manoeuvres are an integral part of lung protective ventilation strategies.

Re-expansion of the collapsed alveoli may be harmful, as stress and strain is amplified at the interface between the aerated regions of the lung and those that are collapsed.

Injury at low lung volume (atelectrauma) is common in ventilated lung since atelectasis is common in the dependent lung tissue as a result of both extrinsic compression and oxygen absorption. Atelectasis predisposes the patient to lung injury due to worsened lung compliance and oxygenation

which demand greater ventilating pressures and an increase in F_{IO_2} .

Capillary shear stress is described as the disruption of the capillary endothelium, alveolar epithelium, or sometimes, all the layers. Lungs exposed to high pulmonary flow (as happens during OLV – due to HPV, gravity, or surgical manipulation) experienced decreases in compliance and increases in vascular resistance

Biotrauma includes cytokine release, over-expression of inflammatory mediators and prolonged activation of neutrophils.

Oxidative injury because of reactive oxygen species is a well known component of ARDS.

Mechanisms of lung injury in the collapsed lung

Atelectasis/recruitment is harmful to the collapsed lung. While atelectasis per se does not induce any injury, lung expansion from collapse produces significant stress and strain and creates shear forces in the adjacent regions.

Hypoperfusion/ischaemia-reperfusion injury worsens the lung injury by increasing microvascular permeability and lung oedema. In this context, oxidative stress seems to be directly proportional to the duration of OLV.

Biotrauma with its cytokine and inflammatory mediators release is more intense in the collapsed lung than in the ventilated lung and is also dependent on the duration of OLV.

Surgical trauma/manipulation depends on whether the lung is retracted or resected. Manipulation, obviously seems to have more impact leading to interstitial oedema, microhaemorrhages and microatelectasis.

Systemic factors affecting both lungs

Neutrophil activation, cytokine and reactive oxygen species release are not localized but result in systemic effects with cross-talk with the contralateral lung.

Surgical trauma modulates the inflammatory response, again with systemic effects.

Overhydration (large perioperative fluid load) seems to influence the glycocalyx systemically.

Disruption of the lymphatic flow with impairment of fluid clearance is also affecting the severity of lung injury.

Management

Anaesthetic technique may influence the severity of lung injury following OLV.

Protective OLV and volatile anaesthesia appear effective in reducing ICU admission, length of hospital stay, and adverse outcomes.

Volatile anaesthetics have immune-modulating effects. They act as pre- and post conditioning agents and induce lung protection by inhibiting the expression of pro-inflammatory mediators.

Although initially promoted due to their lack of effect on HPV, intravenous anaesthetic agents do not seem to be superior to the volatiles and the choice of anaesthetic agents has not yet been proven to substantially affect clinical outcomes.

OLV is not physiological and results in injury even if managed with lung protective strategies. OLV should therefore be “administered” only when required and in the smallest “dose” (duration) necessary.

Overhydration should be avoided since it worsens lung injury

Optimization of lung compliance lessens lung injury. This entails:

- recruitment manoeuvres;
- appropriate PEEP;
- bronchodilation and bronchial toilet.

Application of CPAP to the collapsed lung – even during thoracoscopic procedures (low level PEEP will not impair surgical exposure).

Protective ventilation to the ventilated lung is essential to reduce lung injury. This consists of:

- low tidal volume ventilation: 4-5 ml/kg;
- PEEP (5-10 cm H₂O) must be routine to restore end-expiratory lung volume;
- respiratory rate and minute ventilation must be targeted to allow mild hypercapnia;
- maintain an F_{IO2} low enough to obtain an SpO₂ above 90%.

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Notes

Anaphylaxis in Anaesthesia

Overview and key challenges for the anaesthetist and allergist

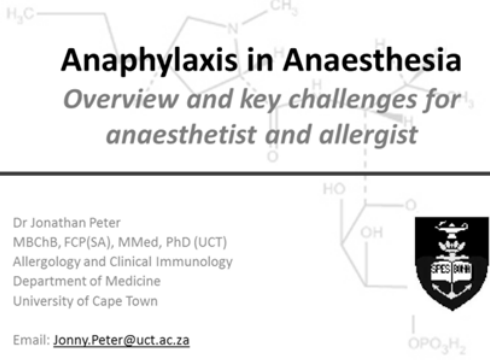
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Anaphylaxis in Anaesthesia
Overview and key challenges for anaesthetist and allergist

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Overview

- Why care?
- Challenges of peri-operative anaphylaxis
 - Making and confirming the diagnosis
 - Connecting with the allergist and identifying the offender
 - Allergy labeling
- How do drugs cause hypersensitivity?
- Getting to the bottom of it
 - All available information
 - The common offenders (Antibiotics, NMBA, NSAIDs and other)
 - *In vitro* and *in vivo* testing and limitations
- Understanding the options, planning the next surgery and feedback



Why care?

- Anaphylaxis is severe and life-threatening
- Incidence of severe reactions vary 15-fold but likely about 1-2:10000 general anaesthetics
- Mortality between 1.4-9% in anaphylaxis associated with anaesthesia
- Usually repeat surgery a requirement thus a plan must be made!

Mertes P et al. *J Allergy Clin Immunol* 2011
Gibb N et al *Br J Anaesthesia* 2013
Reitter M et al *Allergy* 2014
Saager L et al *Anesthesiology* 2015



Making the diagnosis – lots going on?

- Multiple drugs given in short period
- Non allergic effects of anaesthetic drugs may mimic features of anaphylaxis
- Delayed recognition of anaphylaxis in anaesthetised, surgically draped
- Underestimation of severity and consideration of other more common causes of hypotension and difficulties with ventilation

Dippenaar JM & Naidoo S *CACI* 2015



Case 1

Adverse events during anaesthesia

box 1. Causes of severe adverse events during anaesthesia

- Exaggerated pharmacological effect, e.g. hypotension during extradural anaesthesia or with propofol; bradycardia and hypotension after opiates
- Anaphylaxis to one of the i.v. NMBA's or anaesthetic drugs
- Adverse reaction to another administered drug e.g. drug with pre-medication; antibiotic with induction; analgesic, e.g. NSAID rectally or opiate intra-operatively
- Latex rubber allergy
- Reaction to intravenous infusion, e.g. colloid, blood, plasma
- Allergy to other substance given, e.g. chlorhexidine or a diagnostic dye
- Problem with anaesthetic technique, e.g. intubation
- Autonomic parasympathetic effects, e.g. during laparoscopy, peritoneal traction, arthroscopy, squint surgery, dental surgery
- Blood loss
- Medical (non-allergic) cause, e.g. septicemia; cardiac; severe asthma, pneumothorax; air embolus
- Malignant hyperthermia

Ewan PW et al *Clinical & Exp Allergy* 2009



Clinical presentation of anaphylaxis

Table 1. Anaphylaxis due to intravenous induction agents in general anaesthesia

Clinical features	Frequency (%)	Route of administration:
Cardiovascular collapse	88	IVI – cardiovascular collapses usually minutes
Bronchospasm	36	Rectal: cutaneous more common, up to 30 minutes delay
Angio-oedema (facial, periorbital, perioral)	24	Skin e.g. latex - delayed
Angio-oedema (generalized)	7	
Other cutaneous features		
Erythema	45	
Itch	13	
Urticaria	8	

Data from Fisher and Baldo [7, 8].

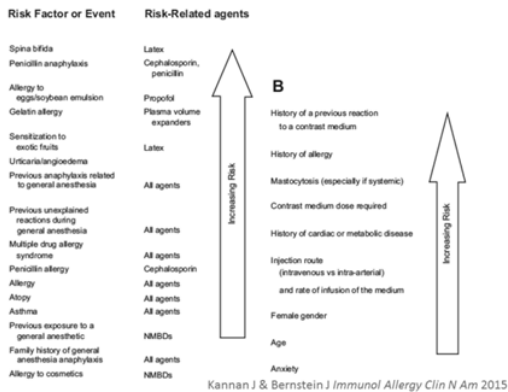
Essential for anaesthetist to THINK about the diagnosis and initiate treatment early
Consideration of risk factors also useful to identify high risk patient

Ewan PW et al *Clinical & Exp Allergy* 2009

Time of onset as a diagnostic clue

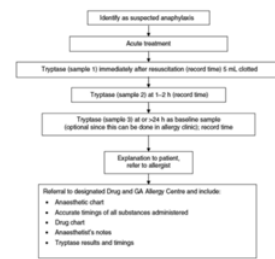
Within minutes of induction	Intra-operative	Towards end of surgery/recovery
NMBAs	I.v. NSAID/paracetamol	Rectal NSAID
Intravenous anaesthetics	Intravenous opiate	Intravenous opiate
Intravenous opiate	Intravenous antibiotic	Colloid
Intravenous antibiotic with induction	Local anaesthetic	Reversal agents
	Colloid (> 15 min from start of infusion)	Latex rubber allergy
	Latex rubber allergy	
	Dyes/contrast media	
	Chlorhexidine	
	Povidone iodine	
Technical anaesthetic problem	Surgical problem	

Ewan PW et al *Clinical & Exp Allergy* 2009

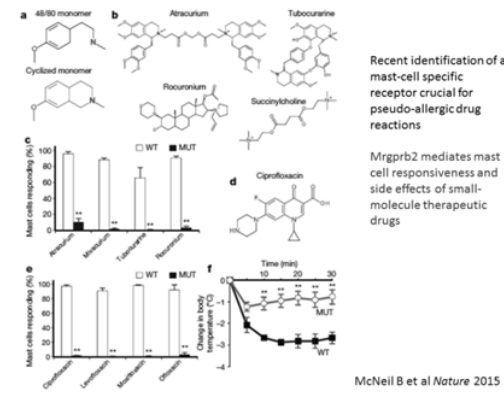
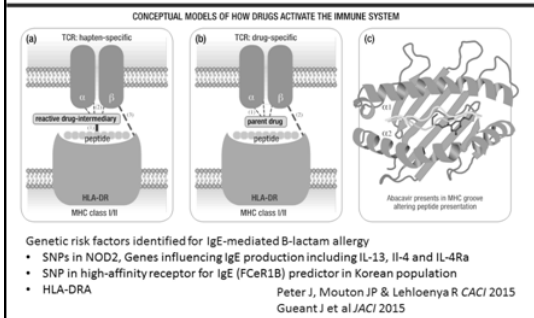


Tryptase measurement

- Tryptase only biomarker
- Blood up to 6 hours from event may be useful
- Excellent PPV >90% (no effect of CPR)
- NPV only ~50% (Low sensitivity)
- Baseline level required



Models of pathogenesis



Getting to the bottom of it?

- Raising awareness amongst anaesthesiologist to think anaphylaxis and confirm with tryptase measurements
- Know the common offending agents, and be aware of the rarer ones
- Get as much information and insist on the anaesthetic records – this can be difficult

Case 2

-

- Gonzalez-Estrada A et al *JACI Pract* 2015
Guyer AC et al *JACI Pract* 2015
Laxenaire MC et al *Br J Anaesthesia* 2001

Berroa F et al. *Anaesthesia & Analgesia* 2015

- 

- Succinylcholine
- $$\left[\text{N}^+ \text{---} \text{CH}_2 \text{---} \text{CH}_2 \text{---} \text{O} \text{---} \text{C}(=\text{O}) \text{---} \text{CH}_2 \text{---} \text{CH}_2 \text{---} \text{C}(=\text{O}) \text{---} \text{O} \text{---} \text{CH}_2 \text{---} \text{CH}_2 \text{---} \text{N}^+ \right]_2$$

Demographics, characteristics (age, years), laboratory findings (skin test and biopsy, serology and viral antibody titers), delay diagnosis, delay between reaction and diagnostic approach (in month); Delay in re-exposure, delay between diagnostic approach and re-exposure (in month); +, positive result; -, negative result; NA, not available due to insufficient serum.

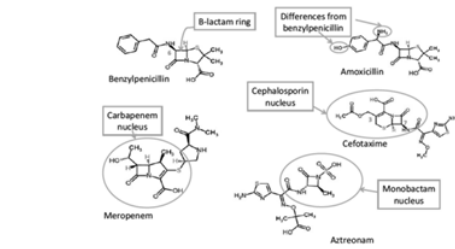
Leysen J et al. *Clinical & Exp Allergy* 2014

NSM, natural killer cell; AA, arthritis; FNA, fine needle aspiration; 1, second, second or third exposure; Delay diagnosis, delay between infection and diagnostic approach (in months); Delay exposure, delay between diagnostic approach and re-exposure (in months); +, positive result; -, negative result; U, unreliable; NA, not available due to insufficient amount; IgG test, total IgG; Mm, myoglobin; A, atrepanium; C, clasticarum; M, streptococcus; S, streptococcus; V, streptococcus; NSMMA, streptococcus myoglobinase.

Leysen J et al. *Clinical & Exp Allergy* 2014

- Ewan PW et al *Clinical & Exp Allergy* 2009
Hagau N et al *Allergol Int* 2016
Macy E *Curr Allergy Asthma Rep* 2014

Molecular structure and immunogenicity



Mirakian R Clin Exp Allergy 2015

Case 3

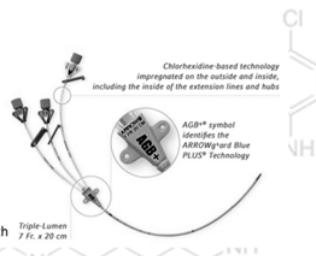
Chlorhexidine hypersensitivity

Skin prick testing

Negative propofol, rocuronium, PPL, MDM, ceftriaxone

Positive chlorhexidine and Specific IgE elevated to chlorhexidine

May cause up to 5% of anaphylaxis associated with anaesthesia



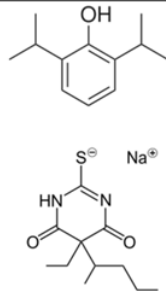
Abdallah C J Anaesthesiol Clin Pharmacol 2015
Antunes J et al Allergol Immunopathol (Madr) 2014
Odedra KM, et al. Postgrad Med J 2014

Opiates

- Anaphylaxis to narcotics is rare
- Non IgE-mediated non-specific histamine release most common mechanism (rate and dose related), but reports are available of IgE-mediated anaphylaxis to both morphine and fentanyl
- Most reactions flushing, urticaria, pruritus, and mild hypotension
- Morphine > fentanyl
- No utility of diagnostic testing

Propofol and other hypnotics

- Several cases of anaphylaxis to barbiturates (thiopentone)
- Non-IgE mediated mechanisms implicated
- Etomidate and ketamine reactions very rare
- Propofol can cause IgE-mediated reactions (2 isopropyl groups as antigenic epitopes)
- Issue around egg and soy allergy debunked!



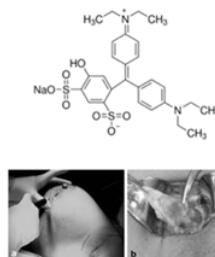
Latex

- Previously a major reason for peri-operative anaphylaxis but now most hospitals have latex-free policies
- High risk patients were those with multiple surgeries and certain foods
- Cross reactions with kiwi, banana, chestnut, and avocado
- Mostly IgE-mediated reactions that occur during the maintenance phase of anaesthesia
- Specific IgE testing routinely available and good diagnostic accuracy



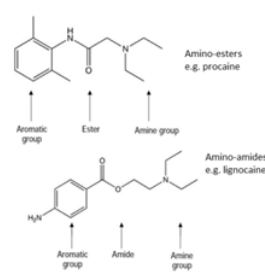
Dyes

- Increase intra-operative use for lymph node biopsy
- 1-2% reported incidence of allergy (0.15-1.1% with severe anaphylaxis)
- Similarity of isosulfan blue found in cosmetics, soaps, antifungals and paper industry materials
- SPTs possible (25mg/ml), possible diverse CAST



Local anaesthetic agents

- Very uncommon, except delayed hypersensitivity reactions to amino-esters
- Study of 157 patients referred for LA-associated drug reactions found no IgE-mediated reactions
- Sensitivity of SPTs low, must progress to IDT and subcutaneous challenge



Classification of NSAID hypersensitivity

Hypersensitivity reactions	Time of reaction	Clinical manifestation	Type of reaction	Underlying disease	Potential mechanism
Aspirin-exacerbated respiratory disease (AERD)	Immediate*	Rhinitis/asthma	Multiple NSAIDs hypersensitivity	Asthma/ rhinosinusitis/ nasal polyps	COX-1 inhibition
Urticaria exacerbated cutaneous disease (AECB)	Immediate*	Urticaria/angioedema	Multiple NSAIDs hypersensitivity	Chronic urticaria	COX-1 inhibition
Multiple NSAIDs-induced urticaria/angioedema (MNSAID-UA)	Immediate*	Urticaria/angioedema/anaphylaxis	Multiple NSAIDs hypersensitivity	None	Unknown, presumably related to COX-1 inhibition
Single NSAIDs-IgE allergy	Immediate* (usually within 1 h)	Urticaria/angioedema/anaphylaxis	Single drug induced	Anaphylaxis	IgE mediated
Single NSAIDs-T cell reaction	Non-Immediate*	Fixed drug eruptions Severe bullous skin reactions Mandibular drug eruptions Pneumonitis Aseptic meningitis Nephritis Contact and photocontact dermatitis	Single drug induced	Usually none	T cell-mediated (Type IV) Cytotoxic T cells NK cells Other

*Reaction occurs from minutes to hours after exposure. In the case of multiple hypersensitivity reactions the intervals between drug intake and reaction can take even longer.

*Reaction occurs from hours to more than 24 h after exposure.

Ayuso P et al 2013 Clin Exp Allergy

What to do with NSAID reactions?

- Consider cross intolerance versus single drug, with different pathophysiology

- Referral as benefit from detailed investigation which invariably requires safe use of provocation testing to determine offending and safe NSAIDs

1) Non-Selective COX Inhibitors (Conventional NSAIDs)

i) Salicylates: Aspirin, Diflunisal.
ii) Pyrazolone Derivatives: Phenylbutazone, Oxphenbutazone.
iii) Indole Derivatives: Indomethacin, Sulindac.
iv) Propionic Acid Derivatives: Ibuprofen, Naproxen, Ketoprofen, Flurbiprofen.
v) Arthritis Acid Derivatives: Mefenamic acid.
vi) Aryl-Acetic Acid Derivatives: Diclofenac.
vii) Oxycam Derivatives: Piroxicam, Tenoxicam.
viii) Pyrrole-Pyrrole Derivatives: Ketorolac.

2) Preferential COX-2 Inhibitors:

Nimesulide, Meloxicam, Nabumetone.

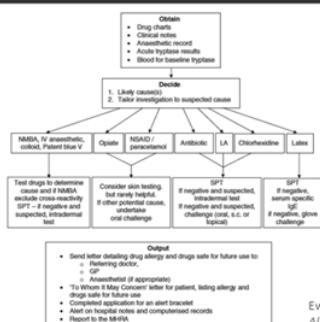
3) Selective COX-2 Inhibitors:

Celecoxib, Rofecoxib, Valdecoxib.

4) Analgesic-Antipyretics with Poor Anti-inflammatory Action

i) Paracetamol Derivative: Paracetamol (Acetaminophen).
ii) Pyrazolone Derivatives: Metamizol (Dipyrone), Propiphenazone.
iii) Benzoxazine Derivative: Nefopam.

Allergist's role

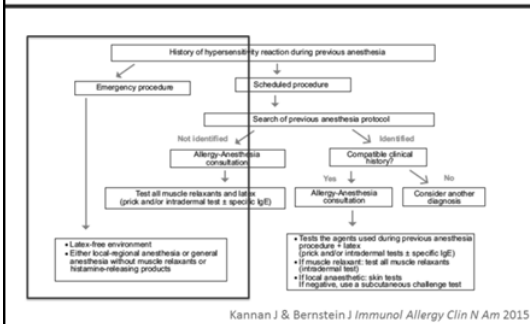


Ewan PW et al Clinical & Exp Allergy 2009

Planning the next surgery

- If offender and safe alternative identified - easy
- Beware of high risk patients and possibility of rare multiple sensitivities
- Beware of concomitant medication use e.g. beta-blockers
- If no causative agent confirmed (30-40%) need to consider:
 - Is surgery absolutely necessary?
 - Can an entirely different set of drugs be used?
 - Avoid common offenders e.g. no antibiotics, NMBA
 - pre-operative antihistamines and corticosteroids (controversial)
 - Medic alert

Emergency situation



Kannan J & Bernstein J Immunol Allergy Clin N Am 2015

End

Notes

Pericarditis and Anaesthesia for Pericardiectomy

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Pericardial Anatomy:

The pericardium encloses the heart and great vessels. The parietal pericardium is a fibrinous layer while the visceral pericardium is a serous layer. The pericardial space normally contains about 20 - 50 mls of fluid, an ultrafiltrate of plasma.

Pericardial Function:

Mechanical: protection against acute dilatation, mediation in diastolic coupling between ventricles, involved in ventricular pressure volume relationship. (Acts as a hydrostatic system allowing for the Frank-Starling mechanism to act uniformly)

Membranous: Lubrication, barrier to infection.

Ligamentous: Prevention of acute cardiac displacement.

The normal pericardium is relatively non-compliant. Elevation of intra-pericardial pressure may result from disease of the pericardium causing fluid accumulation or pericardial thickening (constriction) or acute chamber enlargement e.g. RV infarction. Pericardial collections may become quite large without compromising cardiac function if they occur slowly. Rapid fluid accumulation causes tamponade. Loculated collections may cause specific cardiac chamber compression.

1) ACUTE PERICARDITIS:

Aetiology:

Malignancy	
Myocardial infarction	15 - 20% of patients, usually within first week or Dressler's syndrome 2 -3-months later
Postcardiotomy	10 - 90 days after cardiac surgery (in 17.8% of surgical pts)
Trauma	
Uraemia	
Idiopathic	
"Infective"	esp AIDS (opportunistic), viral , tuberculous (this acute phase responds well to medical treatment). Fungal pericarditis usually requires medical therapy and pericardiectomy for successful treatment.
Collagen - vascular diseases	SLE where acute pericarditis is common but tamponade is most unusual.
Metabolic disorders	
Contiguity	

Clinical Presentation:

(need at least 2 of the 4 major criteria with ↑ inflammatory markers for diagnosis of acute pericarditis)

Pain*: Three types of pain may occur singly or in combination	a) Pleuritic chest pain radiating to back and trapezius muscle, influenced by body position, usually more or less continuous (unlike ischaemia). b) Pericardial pain which is substernal like myocardial infarction pain c) rarely a pain synchronous with the heart beat felt at the left sternal border and shoulder.
Dyspnoea	
Low grade fever	
Friction rub*	over precordium (best heard left of sternum) is pathognomonic.(elicit by listening with the patient in various positions).
Signs of tamponade	
Arrhythmias	usually atrial

Investigations:

Cardiac enzymes	Usually normal
ECG*	early: ST elevation in std limb and precordial leads late: -T wave inversion, PR baseline depression. Usually no Q waves.
CXR	normal or cardiomegaly from effusion. Occasionally left pleural effusion.
Inflammatory markers	Take time to manifest e.g. ↑C-reactive protein
ECHO	sensitive and specific for effusions*.
Pericardiocentesis	Diagnostic and/or therapeutic

Treatment:

Treat cause and analgesia/steroids. Purulent effusions usually need surgical drainage and aggressive antibiotic therapy. HIV-associated tuberculous pericarditis is associated with a mortality of 40% at 6 months despite TB treatment.

Recurrent Pericarditis generally begins with an active phase followed by a gradual reduction in number and severity of the flare-ups until it burns out. It is usually treated with NSAIDs, steroids or colchicine (1-2 mg/day) or rarely other immunosuppressants such as azathioprine. Only rarely pericardiectomy may be considered.

2) CONSTRICTIVE PERICARDITIS:

Aetiology: May result from an acute or chronic condition.

Post-surgical constrictive pericarditis: may occur 1 - 204 months after surgery (mean 23months, Median ?). The operative mortality of pericardiectomy varies, but recent indications suggest that it may be decreasing to around 6%. In one of the larger series about 80% of cases were subjected to pericardiectomy and about 75% of these benefitted, however mortality at 30 days was 11%.

Other causes of constrictive pericarditis:

<i>Infection - tuberculous esp</i> <i>Idiopathic</i> <i>Neoplasms</i> <i>Uraemia</i> <i>Post - irradiation</i> <i>Rheumatic</i> <i>Myocardial infarction</i> <i>Sarcoidosis</i> <i>Post-cardiac transplantation</i> <i>Familial Mediterranean Fever</i>	<i>Rheumatoid, autoimmune</i> <i>Wegener's granulomatosis</i> <i>Amyloid</i> <i>Hypereosinophilic syndrome</i> <i>Haemorrhagic disorders</i> <i>AICD pacemaker</i> <i>Trauma</i> <i>Myxoedema</i> <i>Retroperitoneal/mediastinal fibrosis</i> <i>Familial Pericarditis</i>	<u>Drugs:</u> <i>Methysergide</i> <i>Practolol</i> <i>povidone – iodine</i> <i>Phenytoin</i> <i>Isoniazid</i> <i>Hydrallazine</i> <i>procainamide</i> <i>Anticoagulants</i> <i>Minoxidil</i>

There are interesting case reports of an ingested toothpicks and IV needles causing constrictive pericarditis after migration into the pericardium.

Clinical Presentation and investigation:

Symptoms:

Leg and abdominal swelling, anorexia, wasting (because of low output + hepatic congestion). Dyspnoea is common, but there is usually no orthopnoea, paroxysmal nocturnal dyspnoea or pulmonary oedema (unless other cardiac disease also present).

Signs:

Pulse: Paradoxical pulse occurs in about 1/3.

Jugular Venous pressure: a) raised, prominent y descent followed by steep ascent (diastolic shock on palpation). B) Kussmaul's sign: increase in venous pressure in inspiration.

Heart Sounds: Pericardial Knock (diastolic, early 3rd heart sound - occurring 0.06 - 0.12 sec after aortic valve closure due to sudden ventricular filling) in 40% of patients.

Abdomen: Hepatomegaly (non-pulsatile) and ascites (Chylous ascites due to constrictive pericarditis has been described), splenomegaly. Occasionally jaundice.

Lungs: Usually little or no pulmonary venous congestion. (Pulmonary oedema is rare because the decrease in cardiac output occurs before the pulmonary venous pressure gets to 25mmHg).

RV waveform: Diastolic dip and prominent y descent.

Haemodynamic measurements:

RAP	=	PCWP	=	PAD	=	Pressure plateau
(right atrial pressure)		(wedge)		(pulm art diastolic pressure)		
(Square root pattern)						

Investigations:

ECG: P mitrale, QRS low voltage, T wave inversion. Electrical alternans usually absent. Atrial fibrillation in 25%. Significant RVH or LVH on ECG means that constriction is unlikely.

CXR: Non-specific cardiomegaly if any at all. In about 50% pericardial calcification (and this usually points to constriction rather than myocardial disease). CT or MRI can show up pericardial thickening and calcification.

ECHO: May be normal or abnormal. Positive diagnostic indications for CP are a) septal notch (sudden ventricular septum shift because of asymmetrical filling of the ventricles) b) During inspiration the septum shifts toward the LV and during expiration it shifts towards the RV (discordant filling). c) biatrial enlargement which is usually only moderate. d) Pericardial thickening (absence is not an exclusion criterion).

Doppler flow studies are useful in differentiating from restrictive cardiomyopathy as in CP early diastolic filling is discordant. Tricuspid velocity is increased in inspiration and mitral velocity decreased.

CT and MRI, endomyocardial biopsy may be useful in selecting patients requiring surgery and detecting existing myocardial atrophy.

Differential diagnosis: Myocardial restriction, endomyocardial fibrosis, chronic rejection of transplanted heart. I know of at least one recent patient in our unit who had an exploratory thoracotomy in an attempt to exclude pericardial constriction as a reason for his cardiac failure.

PERICARDIECTOMY:

History: Description goes back to Avenzoar (1113-1162). The First successful pericardiectomy for constrictive pericarditis was performed in 1926 by Fischer and Schmieden but Churchill who did it in 1928 is often given the credit. Mc Gaughan (1985) and Bashi (1988) recommended early surgery before marked constriction causes myocardial damage.

Procedure:

High risk procedure: Mortality 5 - 15%. The Bombay group had an early mortality of 21/112 patients from December '63 to May '87. This was related to the degree of preoperative disability. Preoperative high right atrial pressure, hyperbilirubinaemia, renal dysfunction, atrial fibrillation, pericardial calcification (not all series), thoracotomy approach and partial pericardiectomy were significant mortality risk factors in Chowdhury's series of 395 patients (Jan85 to Dec 2004) and only 7 cases were done on bypass after major vessel injury or bleeding. The survivors had significantly improved NYHA functional class as confirmed in other studies. Post irradiation pericardiectomy has a very high in-hospital and late mortality (>50%) probably because of radiation induced myocardial damage, including coronary artery damage, myocardial fibrosis, conduction disturbances and valve dysfunction. This will be less with the modern radiation techniques. Old age, low serum sodium and abnormal LV systolic function are also associated with a bad outcome in other series. Our own mortality figures confirm the great difficulty of this procedure.

Pericardiectomy may be done via thoracotomy (less safe if severe calcification involves the right ventricle of atrium, but this route is possibly desirable if there is purulent pericarditis and may provide better access to the left ventricle) or sternotomy, usually with CPB on standby. The pericardium (and if necessary the epicardium) is carefully stripped off. Dissection may be very difficult leading to cardiac compression, impaired output and arrhythmias. Haemorrhage may be catastrophic. Heparinization makes bleeding worse. Usually the right atrium and venae cavae are left till last. Unequal release of the ventricles may lead to severe pulmonary oedema. The coronary arteries may be damaged. Often this procedure is given to junior surgeons to do making it more hazardous. A high speed burr has occasionally been used to remove calcified pericardium. Sometimes cross hatching is the best result that can be achieved.

How much pericardium to take is controversial -all or just enough. Sometimes patients return for a second pericardiectomy, to remove remaining pericardium (probably localised pericardial constriction leading to RV outflow tract obstruction). Recent series suggest a worse outcome for partial procedures.

Monitoring: Basically the same as any major cardiac case - Arterial line, large bore IV line, Central venous line, lines for inotropes, urinary catheter, temperature etc. Continuous Cardiac output catheter or monitoring may be particularly useful especially since these patients do not always improve spectacularly, but often deteriorate over the first 24-48 hours post-op and management of haemodynamics is difficult. Transoesophageal echo monitoring is very useful. Intra-aortic balloon pumping should be considered early rather than too late. Recovery of function may take weeks. ECMO has been used successfully to bridge this period. Post operatively delayed mitral regurgitation and tricuspid regurgitation have been reported, presumably occurring as the heart dilates.

We have had one patient die after spontaneously rupturing the right atrium about 2 hours following return to the ICU after an initial excellent response to stripping. We have also been totally unsuccessful in stripping the pericardium with a poor outcome. One of our patients presented with pulmonary oedema and severe mitral regurgitation which completely resolved on pericardiectomy and he had a very good operative result.

Anaesthesia guidelines: Prevent bradycardia, maintain the preload, afterload and contractility. How you achieve this is probably immaterial.

RARE FORMS OF CONSTRICTIVE PERICARDITIS:

Effusive-constrictive, localized, transient, occult, and constrictive pericarditis with normal pericardial thickness, have been described.

3) PERICARDIAL EFFUSION:

If fluid accumulates slowly the effusion may be large without haemodynamic consequences. In trauma 200-300ml may cause tamponade because of rapid accumulation.

Symptoms: Usually painless, unless bloody.

Signs: Usually some tachycardia, apical impulse difficult to feel and heart sounds distant. A pericardial rub may occasionally still be present. Usually there are no murmurs. If tamponade is present, then the corresponding signs will be present (see below).

ECG: usually non-specific. Electrical alternans if the position of the heart changes excessively during the cardiac cycle.

CXR: Usually cardiomegaly. An associated left pleural effusion is common. (Exclude a large LA).

ECHO: Effusions can be clearly delineated. Ultrasound is also useful for guided needle aspiration. Usually the atria and ventricles are small. TOE is especially good at picking up LA, RA and RV collapse and can differentiate tamponade from RV failure (but tamponade is a clinical diagnosis and may be present even with a negative echo).

Invasive tests: angiography etc. are seldom necessary these days.

Treatment: Treat cause. Pericardiocentesis if the effusion is large. Open drainage or pericardial window may be necessary. These can be done under local anaesthesia, using the subxiphoid approach (GA also used) or thoracoscopically under local or general anaesthesia. Current reports have indicated that subxiphoid balloon pericardiectomy provides a useful less invasive alternative to surgery. The laparoscopic approach has also been used successfully. Placement of a pericardioperitoneal Denver shunt under local anaesthesia is another possibility. Chylous pericardium may require ligation of the thoracic duct in addition to a pericardial window to prevent re-accumulation of the fluid.

CARDIAC TAMPONADE:

Cardiac tamponade develops when the pressure in the pericardial cavity rises to a level equal to that in the heart during diastole. The right atrium and ventricle are compressed first, especially during diastole and later throughout the cycle as the intra-pericardial pressure rises. When the left heart also becomes affected, the pulsus paradoxus becomes evident. Tamponade occurs in about 3% of post cardiac surgery patients. Medical patients usually have uraemia or malignancy.

Clinical signs: a) Hypotension and reflex tachycardia. b) Elevation and equalization of left and right sided filling pressures. The Y descent of the JVP wave becomes less prominent = plateau. c) Exaggerated BP response to IPPV in ventilated patients giving an early marked increase in ejection on inspiration as the lungs are filled. In the spontaneously breathing patient pulsus paradoxus = pulse pressure decrease of 15-20mm on inspiration occurs (by definition >10% fall in systolic or >10mmHg). Kussmaul's sign is usually absent. d) Cessation of drainage from chest tubes. e) In severe tamponade impaired coronary bloodflow may lead to ischaemia.

CXR - widened mediastinum, cardiomegaly, but the heart may be small if the tamponade is acute. Usually the lung fields are clear and the pulmonary vessels not prominent.

ECG - decreased voltage, electrical alternans, sometimes myocardial ischaemia.

ECHO - Effusions can be clearly delineated. Clotted blood is more difficult to identify. RA and LA collapse well shown.

Angiography - definitive diagnosis.

Differential Diagnosis: In postsurgical patients: low cardiac output syndrome and the numerous other causes of postoperative hypotension. Cardiac enlargement and heart failure usually is associated with bilateral pleural effusions.

Treatment: Urgent. **Early diagnosis and drainage** is important. Support the circulation with volume and inotropes and especially maintain the rate (Isoprenaline used to be very useful in this situation). Reduce intrapericardial pressure by drainage pericardiocentesis or in the postsurgical patient reopen the chest, evacuate clots and control sites of bleeding. The chest can be reopened in the ward if necessary. Usually relief of the pressure improves the patient's condition rapidly - the pressure volume curve is steep so even removing a small volume produces marked improvement.

PERICARDIOCENTESIS: Best done under fluoroscopic control. Use an 18 gauge needle or larger with short bevel. Enter in the subxiphoid region and direct needle toward the left shoulder about 30° posteriorly. Attaching an ECG electrode (chest lead) to the needle with alligator clips will indicate contact with the myocardium as the ST segment will become acutely elevated. Concurrent CVP measurement is also useful as it may demonstrate acute relief of tamponade by falling significantly. ECHO guidance is also useful. A catheter may be left in for prolonged drainage. Fluid should be sent for laboratory investigation (including culture).

References (some recent ones)

1. Grocott HP, Gulati H, Srinathan S, Mackensen GB. Anesthesia and the patient with pericardial disease. *Canadian Journal of anaesthesia* (2011) 58:952-966 (*nice review*)
2. Faisal F, Syed and Bongani M, Mayosi. A Modern Approach to Tuberculous Pericarditis. *Progress in Cardiovascular Diseases*, Vol. 50, No. 3 (November/December), 2007: pp 218-236
3. Michael Bergman, Janos Vitrai, Hertzal Salman. Constrictive pericarditis: A reminder of a not so rare disease. *European Journal of Internal Medicine* 17 (2006) 457-464
4. Schwefer m et al. Constrictive Pericarditis, still a diagnostic challenge: comprehensive review of clinical management. *European journal of cardiothoracic Surgery* (2009)36:502-10
5. Tokuda et al. Outcome of pericardiectomy for constrictive pericarditis in Japan: A nationwide outcome study. *Ann Thoracic surgery* (2013)96:571-6

Notes

When can anaesthesia *justifiably* be cancelled or delayed in the face of an electrolyte derangement?

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Electrolyte disturbances can cause multiple organ system dysfunctions during the perioperative period. Of particular relevance to the anaesthetist is impairment of the central nervous system, cardiovascular system and neuromuscular function.

Physiology

Resting Membrane Potential

An action potential occurs as a result of ionic currents flowing through cell membranes. The resting membrane potential is the membrane potential at which the electrostatic gradient balances the concentration gradient for a specific ion.

When a membrane is permeable to several different ions, the Goldman-Hodgkin-Katz equation is used to calculate the membrane potential. This incorporates the concentrations of all ions influencing resting membrane potential (sodium, potassium and chloride) both inside and outside of the membrane, the permeability of the membrane to the ions as well as the polarity of the electrical charge of each ion.

The resting membrane potential (-90mV) is also influenced by the Donnan effect which describes the uneven distribution of trapped anions over the cell membrane to create a membrane potential as well as the Na^+/K^+ -ATPase pump. Cell membranes contain Na^+/K^+ -ATPase pumps to actively transport sodium out of and potassium into cells in a 3:2 ratio. Activity of this enzyme is increased by hormones, including catecholamines, insulin and aldosterone and by ion flux. In large nerve cells and striated muscle cells, restoration of electrolyte equilibrium can take up to 20% of the total metabolic requirement of the cell.

Action Potential

In nerve cells, depolarization occurs due to rapid influx of sodium through voltage-gated sodium channels. This is reversed by movement of potassium out of the cell through voltage-gated potassium channels. A change in potassium concentration gradient or the Na^+/K^+ -ATPase enzyme will influence the movement of potassium out of the cell.

Almost all cell membranes also have voltage-gated calcium channels which act alongside or even in place of sodium channels particularly in smooth and cardiac muscle. Since cardiac cell action potentials are triggered by both fast sodium channels and slow calcium channels, which open more slowly and stay open longer than fast sodium channels, the action potential in cardiac muscle is slower and has a plateau. This plateau is also contributed to by the reduced potassium ion permeability that occurs immediately after the onset of the action potential – this does not occur during skeletal muscle action potentials. Importantly, the influx of calcium ions into the cell plays an important role in triggering muscle contraction.

Spontaneous Rhythmicity

Specialised pacemaker cells have a higher resting membrane potential (-50mV) to allow automatic membrane depolarization. Because of this higher resting membrane potential, not all the sodium and calcium voltage-gated channels are closed allowing these ions to leak into the cell increasing the membrane potential until a threshold potential (-40mV) is reached. An action potential is then generated through the opening of L-type calcium channels. This less negative resting membrane potential is also responsible for inactivating the fast sodium channels which would create a faster and greater amplitude action potential. The phase 0 upstroke is less rapid and of lower amplitude than that in other cells (just above 0mV) and does not have a plateau. Initially the flow of sodium and calcium inwards is opposed by the outflow of potassium through the repolarizing potassium channels. This opposition gradually diminishes allowing the membrane potential to increase. At the end of each action potential the membrane becomes very permeable to potassium allowing the membrane potential to return to its resting state.

Sodium

Intracellular (mmol/l)	Interstitial Fluid (mmol/l)	Plasma (mmol/l)
10	145	142

Usually plasma sodium concentration is kept within narrow limits by the action of vasopressin on water homeostasis.

Both hypernatraemia and hyponatraemia can exist in hypovolaemic, euvolaemic or hypervolaemic states.

Hypernatraemia (Plasma Na^+ >145mmol/l)

Hyperosmolality occurs whenever total body solute content increases relative to total body water. It is usually associated with hypernatraemia. Hypernatraemia is nearly always due to hypotonic fluid loss or retention of large quantities of sodium. Because thirst is highly effective in preventing hypernatraemia, this is most commonly seen in those unable to drink, the very old and young, and those with a reduced level of consciousness.

Clinically neurological signs predominate due to cellular dehydration. Restlessness, lethargy and hyperreflexia may progress to seizures, coma and death. Symptoms correlate more closely with the rate of movement of water out of the brain than with the actual level of hypernatraemia. Rapid decreases in brain volumes can rupture cerebral veins causing intracerebral or subarachnoid bleeds. After 24-48 hours, intracellular osmolality begins to rise, slowly returning neuronal water content to normal.

Anaesthetic considerations

Morgan and Mikhail suggest that elective surgery should be postponed in patients with significant hypernatraemia (>150mmol/l) until the cause is established and fluid deficits are corrected. The *Oxford Handbook* suggests no elective surgery if Na^+ >155mmol/l or hypovolaemic. *Stoelting* suggests that surgery be delayed until hypernatraemia has been corrected or at least until symptoms have resolved.

Should emergency surgery be required the following recommendations are made:

- Frequent sodium measurements will be required perioperatively.
- Invasive blood pressure monitoring may be useful as hypovolaemia will accentuate any vasodilation or cardiac depression from anaesthetic agents thus predisposing to hypotension and hypoperfusion. Fluids, vasopressors or even inotropes may be required.
- Decreases in the volume of distribution of many drugs means that the doses of most intravenous agents should be reduced while a reduction in cardiac output may enhance the uptake of inhalational anaesthetics.

Hyponatraemia (Plasma Na^+ <135mmol/l)

This usually reflects water retention from an increase in total body water or loss of sodium in excess of water. Hyponatraemia has been associated with higher morbidity and mortality in observational studies. Whether the hyponatraemia is causal or rather indicative of serious underlying pathology is not clear.

Clinically once again the signs of hyponatraemia are primarily neurological and related more to the rapidity at which hypo-osmolality develops. Usually mild hyponatraemia (Na^+ > 125mmol/l) is asymptomatic. When sodium falls below 120mmol/l, serious manifestations of hyponatraemia such as cerebral oedema, lethargy, confusion, seizures, coma and death occur.

Slowly developing hyponatraemia allows for gradual compensatory loss of intracellular solutes restoring cell volumes to normal.

Anaesthetic Considerations

Morgan and Mikhail recommend that plasma sodium concentrations > 130mmol/l are safe for general anaesthesia. The *Oxford Handbook* suggests cancelling elective surgery if symptomatic or if Na^+ <120mmol/l. *Stoelting* recommends correcting hyponatraemia prior to surgery if possible, especially if symptomatic.

Should emergency surgery be required the following recommendations are made:

- Corrective therapy should continue during surgery and into the postoperative period.
- Induction and maintenance of anaesthesia carry a high risk of hypotension, thus fluid, vasopressors and inotropes should be available prior to induction and invasive blood pressure monitoring should be considered.
- Significant cerebral oedema may be seen intraoperatively as a reduction in anaesthetic requirements or postoperatively as confusion or somnolence

Potassium

Intracellular (mmol/l)	Interstitial Fluid (mmol/l)	Plasma (mmol/l)
159	4	4

Potassium is the principal intracellular cation. Only 2% of total body potassium is extracellular. Despite this, body potassium homeostasis is driven to maintain the extracellular potassium content at the expense of total body potassium content.

When total body potassium is depleted, serum potassium concentration reflects this deficit in a linear fashion up until a deficit of 500mEq (a 70kg person has a total body potassium of about 3 500 mEq).

Hypokalaemia (Plasma $K^+ < 3.5$ mmol/l)

The contribution of potassium to the resting membrane potential can be predicted by the Nernst equation. This predicts the electrical potential difference across a membrane that will just balance the concentration gradient for a specific ion. In its simplified form this is:

$$V_K = 61.5 \log [K^+]_{\text{outside}} / [K^+]_{\text{inside}} \text{ at } 37^\circ\text{C}$$

Because the resting membrane potential is proportional to the logarithm of the ratio of the external to the internal potassium concentrations, small changes in extracellular potassium concentrations have a large impact. When this ratio is altered nerve cell function will be affected.

In acute hypokalaemia, the resting membrane potential is more negative, resulting in reduced nerve cell excitability and thus generalised weakness, ileus and even respiratory muscle weakness.

In the myocardial conducting system a more negative resting membrane potential increases the number of activated fast sodium channels and thus increasing the rapidity of the upstroke velocity during phase 0. There is also an increase in automaticity (slope of phase 4) which increases the occurrence of arrhythmias. Acute decreases in extracellular potassium thus increase excitability and predispose to ventricular fibrillation and catecholamine induced arrhythmias.

Chronic changes in potassium affect both the intracellular and the extracellular environment and thus do not influence the resting membrane potential.

Anaesthetic Considerations

While physiologically the risk of arrhythmias seems clear, the actual clinical risk is more controversial. Also the perioperative morbidity associated with hypokalaemia is unproven.

The decision to treat hypokalaemia preoperatively should be based on the chronicity and severity of the defect. When total body stores of potassium are low, small intravenous boluses of potassium are unlikely to reduce risk and may even cause harm due to diminished potassium regulatory states such as diabetes of renal failure or even due to an administration error.

Miller states that no studies have shown increased morbidity or mortality for patients undergoing anaesthesia with a potassium of at least 2.6 mmol/l. However, should the patient have other clinical risk factors, such as cardiac failure or digoxin use, correction of hypokalaemia prior to anaesthesia may be critical. Hypokalaemia predisposes the heart to digoxin toxicity which may result in heart block, supraventricular tachycardias or other arrhythmias. Plasma K^+ levels > 4.0 mmol/l are recommended in these patients.

Thus the decision to delay elective surgery should be based on:

- Rate at which hypokalaemia developed – chronicity is suggested by an elevated bicarbonate
- Presence of secondary organ dysfunction
- Level of hypokalaemia
- Urgency of surgery – if possible replace potassium in the 24 hours prior to surgery

Intraoperative management in hypokalaemic patients should include:

- Vigilant ECG monitoring
- Potassium replacement intravenously if arrhythmias do develop
- Avoid worsening hypokalaemia – through the administration of insulin, glucose, beta agonists, bicarbonate, diuretics, or through hyperventilation induced respiratory alkalosis
- Increased sensitivity to nondepolarising neuromuscular blockers may be seen. Dosage should be reduced and a nerve stimulator used to monitor effect and reversibility of these drugs.

Hyperkalaemia (Plasma $K^+ > 5.5 \text{ mmol/l}$)

Acute hyperkalaemia reduces the ratio of external to internal potassium concentrations, elevating the resting membrane potential and reducing the gap between resting membrane potential and the excitability threshold. Thus more conduction occurs resulting in paraesthesia and spontaneous motor activity. This eventually results in fatigue and weakness. Skeletal muscle weakness is generally not seen until plasma $K^+ > 8 \text{ mmol/l}$

Once again, gradual hyperkalaemia results in increases in both the intracellular and extracellular potassium concentrations, leaving the ratio of intracellular to extracellular potassium concentration unchanged thus exerting less effect on the resting membrane potential.

Cardiac manifestations are primarily due to delayed depolarization and are consistently present when $K^+ > 7 \text{ mmol/l}$. Contractility appears relatively well preserved. In the SA node, the less negative resting membrane potential increases the number of inactivated sodium channels thus reducing the rapidity of the upstroke velocity in phase 0. There is a longer period of irritability and reduced automaticity (A more gradual slope in phase 4). At very high potassium concentrations the slope of phase 0 is so reduced that adjacent cells cannot be depolarised, and the heart thus stops in diastole.

Anaesthetic Considerations

The level at which hyperkalaemia should be treated is controversial but tends toward conservative recommendations. *Morgan and Mikhail* recommend treatment of hyperkalaemia when $K^+ > 6 \text{ mmol/l}$. The *Oxford Handbook* states that elective surgery should not be considered in hyperkalaemic patients and if life-saving surgery is required hyperkalaemia should be treated first. *Stoelting* suggests that serum potassium should be below 5.5 mmol/l for elective surgery. Clinical signs and symptoms do not correlate predictably with potassium serum concentrations and there is little evidence on which to select such a threshold.

Intraoperative management in hyperkalaemic patients should include:

- Careful monitoring of the ECG
- Avoid succinylcholine
- Avoid metabolic or respiratory acidosis which may increase the shift of potassium extracellularly.
- Avoid infusion of potassium containing solutions
- Monitor neuromuscular function as hyperkalaemia may accentuate the effect of nondepolarising muscle relaxants.

Calcium

Intracellular (mmol/l)	Interstitial Fluid (mmol/l)	Plasma (mmol/l)
0.5	1.5	2.5

A normal 70kg adult has about 1,2 kg of calcium, 99% of which is located in bone. The normal total calcium concentration in plasma is about $2.25\text{--}2.55 \text{ mmol/l}$. Fifty percent of this is ionised, 40% is bound to serum proteins and 10% is bound to anions. The intracellular ionised calcium concentration is at least 1000 times lower, about $0.00013\text{--}0.0013 \text{ mmol/l}$. This is maintained as the cell membrane is poorly permeable to calcium ions and cells have powerful mechanisms to extrude, sequester and buffer calcium. Plasma ionised calcium is physiologically active and is maintained within a narrow range ($1.0\text{--}1.25 \text{ mmol/l}$) through the influence of parathyroid hormone, vitamin D and calcitonin.

Calcium is essential for many biological processes. Of particular interest to the anaesthetist is its effects on the myocardium, vascular smooth muscle and blood coagulation.

In addition to calcium release from the sarcoplasmic reticulum, in cardiac myocytes, calcium also diffuses intracellularly through T tubules. This improves myocardial contractility as myocardial cells contain a poorly developed sarcoplasmic reticulum which does not store as much calcium as skeletal muscle cells do. Since T tubules open directly into the interstitium of the cardiac muscle, the strength of myocardial contractility is greatly dependant on the extracellular calcium ion concentration. An excess of extracellular calcium ions would stimulate the cardiac contractile process leading the heart toward spastic contraction due to the direct role that extracellular calcium plays on contractility. Fortunately, extracellular calcium is tightly regulated and so this is seldom a clinical concern.

Similarly, in vascular smooth muscle, calcium plays a vital role in contraction. When the cytoplasmic calcium levels rise, more calcium binds with the regulatory protein calmodulin to activate a protein kinase which then phosphorylates myosin, activating the smooth muscle actin-myosin complex resulting in vasoconstriction.

In coagulation, calcium influences both platelets and clotting factors. Thromboxane A₂ formation increases cytoplasmic calcium within platelets stimulating the actin-myosin complexes and thus driving the shape conformation required by platelets for coagulation. Calcium is also essential for several enzymatic steps required during the coagulation pathway.

The effect of calcium on neuromuscular transmission is unpredictable. Generally, nondepolarising muscle relaxants seem to be potentiated by both hyper- and hypocalcaemia.

Hypocalcaemia (Plasma Ca⁺⁺<1mmol/l)

Low extracellular calcium levels lower the threshold potential allowing voltage-gated Na⁺ channels to open with very little increase in membrane potential. This can result in highly excitable nerve fibres and tetany. Guyton theorises that this is due to the calcium ions themselves altering the electrical state of the ion channel by binding to the exterior surface of the channel increasing the change in resting membrane potential required to trigger an action potential. In pacemaker cells, a decrease in extracellular calcium concentration will diminish the amplitude of the action potential and the slope of the action potential increasing the period of irritability and reducing automaticity thus increasing the risk of arrhythmias.

Life threatening complications frequently occur if ionised calcium levels drop below 0.5mmol/l. Neuromuscular irritability causing laryngeal spasm and bronchospasm may develop. Hypocalcaemia can cause hypotension, cardiac failure (reduced contractility) and bradycardia. Hypocalcaemia may result in digoxin insensitivity. Cardiac irritability resulting in arrhythmias such as PVCs and VF may occur. Only very low ionised calcium concentrations would impair coagulation – less than 0,6mmol/l

Anaesthetic Considerations

Stoelting suggests that symptomatic hypocalcaemia should be treated preoperatively, and further decreases in ionised calcium intraoperatively should be avoided.

Should emergency surgery be required the following recommendations are made:

- The potentially additive effects of drugs used in anaesthesia, particularly the volatile agents, must be remembered when anaesthetising a patient with hypocalcaemia. Greater amounts of myocardial depression and hypotension should be expected.
- The action of nondepolarising muscle relaxants may be prolonged and should thus be monitored with a nerve stimulator.
- Alkalosis should be avoided to prevent further decreases in ionised calcium.

Recently, awareness that calcium may play a role in cell damage related to reperfusion injury has made anaesthetist reconsider the role of routine calcium administration. Correction of significant hypocalcaemia should be titrated against measured plasma ionised calcium concentrations wherever possible.

Hypercalcaemia (Plasma Ca⁺⁺>1.5mmol/l)

The symptoms associated with hypercalcaemia correlate with both the magnitude and the rapidity of the increase in plasma calcium.

Common presentations include anorexia, nausea, vomiting and polyuria. Hypertension may be present initially due to vasoconstriction but is usually followed by hypovolaemia.

Hypercalcaemia increases the threshold potential required to trigger action potentials in pacemaker cells. This increases the period of irritability which may result in arrhythmias. Digitalis sensitivity and even cardiac arrest may occur. While these changes are potentially lethal, they are fortunately rarely

seen under anaesthesia.

There have been sporadic reports of wide spread thrombosis in hypercalcaemic patients. Generalised muscle weakness and hyporeflexia are characteristic, and may result in a prolonged effect of nondepolarising neuromuscular blockers.

Anaesthetic Considerations

While there is no literature that supports any cut off value above which plasma calcium value would make anaesthesia unacceptably dangerous, hypercalcaemia should be corrected if possible prior to anaesthesia administration. This should include restoration of intravascular volume prior to induction and increasing urinary excretion of calcium with loop diuretics.

Should emergency surgery be required the following recommendations are made:

- Haemodynamic monitoring may be advisable if emergency surgery is proceeding during the ongoing management of hypercalcaemia with fluid resuscitation and diuretics.
- Ionised calcium levels should be monitored
- Saline diuresis should be continued
- Hypovolemia should be avoided
- Ventilation should be controlled to avoid respiratory acidosis. Acidosis reduces calcium binding to albumin thus increasing the ionised calcium ion fraction.

Conclusion

In conclusion, while electrolyte derangements may increase the risk of adverse events – particularly involving excitable tissues, the decision to delay surgery should be made after consideration of the following:

- Are the derangements acute or chronic?
- Is the patient symptomatic?
- Are there associated significant ECG changes?
- Are there other comorbidities increasing risk – such as digoxin use or cardiac failure?

If emergency surgery is required, the following anaesthetic considerations should guide management of the patient:

- Consideration of the underlying cause of the electrolyte imbalance as well as the patient's hydration state prior to induction
- Vigilant monitoring for arrhythmias and haemodynamic effects of electrolyte derangement
- Regular measurement of electrolytes in the perioperative period
- Early correction of electrolyte imbalances when indicated
- Avoid worsening of electrolyte imbalances through drug or fluid administration or alteration of pH
- Consideration to the effect of the electrolyte imbalance or related fluid states on anaesthetic drugs administered

Recommended Reading

- Stoelting – Fluid, electrolyte and acid base disorders
- Morgan & Mikhail – Management of patients with fluid and electrolyte disturbances
- Oxford handbook of anaesthesia
- Potassium and anaesthesia; JE Tetzlaff, JF O'Hara, MT Walsh; Can J Anaesth; 1993, (40),227-246
- Calcium and the anaesthetist; IM Aguilera, RS Vaughan; Anaesthesia; 2000, (55), 779-790
- Calcium; Prof James; 2005 Part 1 ARC

The Perioperative Management of Diabetes

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1. Introduction

Diabetes Mellitus (DM) is the most common metabolic disorder worldwide and the prevalence is increasing rapidly!^{2,5}

Diabetes leads to a magnitude of complications, which includes, accelerated atherosclerosis renal impairment, coronary vascular disease, peripheral vascular disease, cerebrovascular disease and neuropathy. Subsequently, the surgical patient with diabetes is at higher risk of perioperative morbidity and mortality and is subjected to longer hospital stays.²

The reasons for this excess morbidity and mortality is multifactorial and includes, increased risks of hypoglycaemia and hyperglycaemia, infective complications (both surgical site infections and systemic infections), medical complications, which includes acute kidney injury, acute coronary syndromes, acute cerebrovascular events, hospital acquired diabetic ketoacidosis (DKA), inappropriate use of variable rate intravenous insulin infusions (VRII), management errors when converting from intravenous insulin to usual medication, complex polypharmacy, misuse of insulin and multiple comorbidities.^{2,3}

With this set of notes I will be discussing practical perioperative management regimes.

2. Assessment of glycaemic control pre-operatively³

Assessment of the adequacy of glycaemic control is very important and will determine whether a patient is suitable for elective surgery or whether the patient will need optimisation of current treatment. The risks of proceeding when control is suboptimal should be balanced against the urgency of the procedure.

Chronic glycaemic control is assessed by measurement of HbA1C, and the following is recommended by the Joint British Diabetes Societies for inpatient care (JBDS – IP)³

- For elective surgery the HBA1C should be less than 69 mmol/mol or 8,5 %
- Consider referral to the diabetes specialist team* in the following circumstances:
 - o All patients with hypoglycaemia unawareness
 - o Those with HbA1C greater than 69 mmol/mol (8.5%) where it is felt that further optimisation is safely achievable

* In the UK, problematic diabetic patients are referred to a dedicated diabetes specialist team, in our setting the patient will be referred to Internal medicine or Endocrinology.

3. Acute perioperative glycaemic control^{2,3,5}

For many years the fear of undetected hypoglycaemia during general anaesthesia was the major influence in determining blood glucose concentrations. High glucose values were tolerated on the basis that "permissive hyperglycaemia" was safer than rigorous blood glucose control with the associated risk of hypoglycaemia.³

We know now that poor acute perioperative glycaemic control as defined by elevated perioperative CBG's are associated with a worse outcome.²

There is considerable in vitro work to show the deleterious effects of hyperglycaemia. High glucose concentrations have been shown to impair reactive endothelial nitrous oxide generation, increase expression of leukocyte and endothelial adhesion molecules, decrease complement function, impair neutrophil chemotaxis and phagocytosis and enhance the synthesis of inflammatory cytokines.

The overall effect of these glucose-induced changes is to enhance inflammation and increase vulnerability to infection. The concentration of glucose at which these deleterious effects can be shown is surprisingly uniform, usually greater than 9 or 10 mmol/L, which is similar to the values at which clinical infections become more common.³

In the virtual absence of clinical studies in general surgery, and considering the basic biological data on the harmful effects of hyperglycaemia, the JBDS – IP recommends the following:³

- In the **preoperative, anaesthetise or sedated patient**, blood glucose should be maintained in the range **6 – 10 mmol/L** with up to 12 mmol/L being acceptable.
- This recommendation is approximately concordant with the position statement of the American Association of Clinical Endocrinologists and American Diabetes Association (5.9 – 10.0 mmol/L) and minimises the risks of hyperglycaemia and hypoglycaemia. It also reduces the risk of variability in blood glucose, which is more likely to occur if the target is less than 6.1 mmol/L and has been associated with worse outcomes.
- In the **awake post-operative patient** a range from **4 – 12 mmol/L** may be acceptable.

4. Chronic perioperative glycaemic control^{1,2,3,5}

Poor chronic perioperative glycaemic control as defined by and elevated HbA1C is associated with a worse outcome.²

This has been demonstrated in both elective and emergency surgery including spinal, vascular, colorectal, cardiac, trauma, breast, orthopaedic, neurosurgical and hepatobiliary surgery. One study showed that the adverse outcomes include a greater than 50% increase in mortality, a 2.4-fold increase in the incidence of postoperative respiratory infections, a doubling of surgical site infections, a threefold increase in postoperative urinary tract infections, a doubling in the incidence of myocardial infarction, and an almost twofold increase in acute kidney injury.¹

Measuring HbA1C allows identification of patients at higher risk of complications. An elevated HbA1C will help to identify patients that may require a higher level of care postoperatively.²

A patient who has chronic poor glycaemic control is more likely to suffer perioperative dysglycaemia and subsequently have a higher incidence of surgical site infection, systemic infections and other medical complications. These patients are also more likely to be managed with a VRIII and subsequently be exposed to all the inherent risks associated with VRIII usage.²

An elevated pre-operative HbA1C is associated with poorer outcomes whether diabetes has been diagnosed or not. There may be a role for routine measurement of HbA1C at pre-operative assessment in undiagnosed patients with risk factors for diabetes.³

Aldam et al commented on this: “We suggest that preoperative HbA1C values should be determined in all patients undergoing major surgery, and also in all elective surgical patients with diabetes. Not only will this strategy diagnose DM in some patients with undiagnosed DM, it may also influence the timing of elective surgery”⁵

Good long-term preoperative glycaemic control is associated with improved outcomes.³

It allows selected diabetic patients to be safely managed without a VRIII (i.e. manipulation of normal diabetes medication), and therefore promotes day surgery, shorter length of hospital stays and shorter periods in which iatrogenic complications may occur.²

5. Perioperative diabetes management plan^{1,3}

Factors that will be influencing the choice of peri-operative diabetes management:³

- The duration of starvation
- The timing of surgery (a.m. or p.m.)
- The usual treatment regimen of the patient (insulin, tablets, diet)
- The diabetes control prior to admission
- The presence of co-morbidities
- The likelihood that the patient will be capable of self-managing their diabetes during the immediate post-operative period

The aim is to avoid hypo- or hyperglycaemia during the period of fasting and the time during and after the procedure, until the patient is eating and drinking normally.¹

5.1. Management of an anticipated short starvation period (only one missed meal)^{1,3}

Patients with good control (HbA1C less than 69 mmol/mol, 8.5%) who are undergoing surgery with a short starvation period can often be managed by manipulating the patient's normal medication using the guidance provided in Tables 1 and 2. These tables are a pragmatic approach to the pre-operative management of all the available classes of agents used to treat diabetes.

5.2. Principles for the safe manipulation of diabetes medication³

At present there is only one randomised study comparing the effect of manipulating the dose of diabetes medication preoperatively. The perioperative manipulation of diabetes drugs is therefore based on experience, physiology and pharmacological principles. These principles include the following:

- Patients with type1 diabetes will always require background insulin to prevent ketosis
- Diabetes medication can broadly be subdivided into two categories:
 - o Drugs that lower blood glucose levels:
 - These include insulin and the sulphonylureas
 - These drugs are associated with hypoglycaemia in the fasted state, and will always require perioperative dose manipulation
 - o Drugs that prevent blood glucose from rising:
 - e.g. metformin, GLP-1 analogues, DPP-IV inhibitors, SGLT2 inhibitors
 - These drugs will never or rarely cause hypoglycaemia in the fasted state, and will only require dose manipulation if there are other concerns
- In basal – bolus insulin regimens and the continuous subcutaneous insulin infusion (CSII), the basal component provides the background insulin, whilst the bolus component provides the insulin to deal with the glucose load from meal times:
 - o Perioperative manipulation will always involve avoidance of the bolus dose associated with meals
 - o Minor reduction of the basal dose is prudent to avoid hypoglycaemia that may be associated with lack of snacking/ lack of early morning breakfast
 - o In patients on premixed insulin, halving the insulin dose with the omitted meal has been widely used

5.3. Management of an anticipated long starvation period (more than one missed meal)³

Most of these patients will require a VRIII, which will be discussed shortly !

For a type 1 diabetic patient normally on a basal bolus regime that requires a VRIII, the recommendation is that the long-acting analogue (Glargine/Lantus®, Degludec/Tresiba®, Detemir/Levemir®) should be continued with the VRIII during the peri-operative period. Evidence shows that this reduces the risk of rebound hyperglycaemia when the VRIII is discontinued. The dose of long acting insulin that the patient takes when they are well should be reduced by 20% whilst they are in hospital.

Table 1 Guideline for peri-operative adjustment of insulin (short starvation period – no more than one missed meal).

Insulin	Day before admission	Day of surgery		Whilst a VRIII is being used*
		Surgery in the morning	Surgery in the afternoon	
Once daily (e.g. Lantus [®] , Levemir [®] , Tresiba [®] , Insulatard [®] , Humulin I [®] , Insuman [®])				
Evening	Reduce dose by 20%	Check blood glucose on admission	Check blood glucose on admission	Continue at 80% of usual dose
Morning	Reduce dose by 20%	Reduce dose by 20%; check blood glucose on admission	Reduce dose by 20%; check blood glucose on admission	Continue at 80% of usual dose
Twice daily				
Biphasic or ultra-long acting (e.g. Novomix 30 [®] , Humulin M3 [®] , Humalog Mix 25 [®] , Humalog Mix 50 [®] , Insuman [®] Comb 25, Insuman [®] Comb 50, Levemir [®] , Lantus [®]) by single injection, given twice daily	No dose change	Halve the usual morning dose; check blood glucose on admission; leave evening meal dose unchanged	Halve the usual morning dose; check blood glucose on admission; leave the evening meal dose unchanged	Stop until eating and drinking normally
Short-acting (e.g. animal neutral, Novorapid [®] , Humulin S [®] , Apidra [®]) and intermediate-acting (e.g. animal isophane, Insulatard [®] , Humulin I [®] , Insuman [®]) by separate injections, both given twice daily	No dose change	Calculate total dose of morning insulin(s); give half as intermediate-acting only in the morning; check blood glucose on admission; leave evening meal dose unchanged	Calculate total dose of morning insulin(s); give half as intermediate-acting only in the morning; check blood glucose on admission; leave evening meal dose unchanged	Stop until eating and drinking normally
Three to five injections daily				
	No dose change	Basal bolus regimens: Omit morning and lunchtime short-acting insulins; keep basal unchanged* Premixed morning insulin: Halve morning dose and omit lunchtime dose; check blood glucose on admission	Give usual morning insulin dose(s); omit lunchtime dose; check blood glucose on admission	Stop until eating and drinking normally

*If the patient requires a VRIII then the long-acting background insulin should be continued but at 80% of the dose the patient usually takes when he/she is well.

Taken from P Barker, PE Creasey, K Dhatariya, N Levy, A Lipp, MH Nathanson, N Penfold, B Watson T Woodcock. Peri-operative management of the surgical patient with diabetes 2015. *Anaesthesia* 2015; 70:1427–1440

Example of a variable-rate intravenous insulin infusion prescription. Glucose concentration is usually measured in capillary blood.

Glucose concentration; mmol.l ⁻¹	Standard rate (use unless otherwise indicated)		Reduced rate (e.g. insulin-sensitive patients (i.e. < 24 IU.day ⁻¹))		Increased rate (e.g. insulin-resistant patients (i.e. > 100 IU.day ⁻¹))	
	No basal insulin	Basal insulin continued	No basal insulin	Basal insulin continued	No basal insulin	Basal insulin continued
< 4	0.5 IU.h ⁻¹ + give 100 ml glucose 20% intravenously	STOP + give 100 ml glucose 20% intravenously	0.2 IU.h ⁻¹ + give 100 ml glucose 20% intravenously	STOP + give 100 ml glucose 20% intravenously	0.5 IU.h ⁻¹ + give 100 ml glucose 20% intravenously	STOP + give 100 ml glucose 20% intravenously
4.1–6.0	0.5 IU.h ⁻¹ + consider 50 ml glucose 20% intravenously	STOP + consider 50 ml glucose 20% intravenously	0.2 IU.h ⁻¹ + give 50 ml glucose 20% intravenously	STOP + consider 50 ml glucose 20% intravenously	0.5 IU.h ⁻¹ + give 50 ml glucose 20% intravenously	STOP + consider 50 ml glucose 20% intravenously
6.1–8.0	1 IU.h ⁻¹	1 IU.h ⁻¹	0.5 IU.h ⁻¹	0.5 IU.h ⁻¹	2 IU.h ⁻¹	2 IU.h ⁻¹
8.1–12.0	2 IU.h ⁻¹	2 IU.h ⁻¹	1 IU.h ⁻¹	1 IU.h ⁻¹	4 IU.h ⁻¹	4 IU.h ⁻¹
12.1–16.0	4 IU.h ⁻¹	4 IU.h ⁻¹	2 IU.h ⁻¹	2 IU.h ⁻¹	6 IU.h ⁻¹	6 IU.h ⁻¹
16.1–20.0	5 IU.h ⁻¹	5 IU.h ⁻¹	3 IU.h ⁻¹	3 IU.h ⁻¹	7 IU.h ⁻¹	7 IU.h ⁻¹
20.1–24.0	6 IU.h ⁻¹	6 IU.h ⁻¹	4 IU.h ⁻¹	4 IU.h ⁻¹	8 IU.h ⁻¹	8 IU.h ⁻¹
> 24.1	8 IU.h ⁻¹	8 IU.h ⁻¹	6 IU.h ⁻¹	6 IU.h ⁻¹	10 IU.h ⁻¹	10 IU.h ⁻¹
> 24.1	Ensure insulin is running and that the measured blood glucose concentration is not artefactual					

Taken from P Barker, PE Creasey, K Dhatariya, N Levy, A Lipp, MH Nathanson, N Penfold, B Watson T Woodcock. Peri-operative management of the surgical patient with diabetes 2015. *Anaesthesia* 2015; 70:1427–1440

Table 2 Guideline for peri-operative adjustment of oral hypoglycaemic agents (short starvation period – no more than one missed meal).

Agent	Day before admission	Day of surgery		Whilst a VRILL is being used
		Surgery in the morning	Surgery in the afternoon	
<i>Drugs that require omission when fasting owing to risk of hypoglycaemia</i>				
Meglitinides (e.g. repaglinide, nateglinide)	Take as normal	Omit morning dose if nil by mouth	Give morning dose if eating	Stop until eating and drinking normally
Sulphonylurea (e.g. glibenclamide, gliclazide, glipizide)	Take as normal	Omit morning dose (whether taking once or twice daily)	Omit (whether taking once or twice daily)	Stop until eating and drinking normally
<i>Drugs that require omission when fasting owing to risk of ketoacidosis</i>				
SGLT-2 inhibitors* (e.g. dapagliflozin, canagliflozin)	No dose change	Halve the usual morning dose; check blood glucose on admission; leave evening meal dose unchanged	Halve the usual morning dose; check blood glucose on admission; leave the evening meal dose unchanged	Stop until eating and drinking normally
<i>Drugs that may be continued when fasting</i>				
Acarbose	Take as normal	Omit morning dose if nil by mouth	Give morning dose if eating	Stop until eating and drinking normally
DPP-IV inhibitors (e.g. sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin)	Take as normal	Take as normal	Take as normal	Stop until eating and drinking normally
GLP-1 analogues (e.g. exenatide, liraglutide, lixisenatide)	Take as normal	Take as normal	Take as normal	Take as normal
Metformin (procedure not requiring use of contrast media†)	Take as normal	Take as normal	Take as normal	Stop until eating and drinking normally
Pioglitazone	Take as normal	Take as normal	Take as normal	Stop until eating and drinking normally

*Also omit the day after surgery.

†If contrast medium is to be used or the estimated glomerular filtration rate is under $60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$, metformin should be omitted on the day of the procedure and for the following 48 h.

VRIII, variable-rate intravenous insulin infusion; SGLT-2, sodium-glucose co-transporter-2; DPP-IV, dipeptidyl peptidase-IV; GLP-1, glucagon-like peptide-1.

Taken from P Barker, PE Creasey, K Dhatariya, N Levy, A Lipp, MH Nathanson, N Penfold, B Watson T Woodcock. Peri-operative management of the surgical patient with diabetes 2015. *Anaesthesia* 2015; 70:1427–1440

6. Variable Rate Intravenous Insulin Infusions (VRIII) ^{2,3,4}

6.1. Background

Prior to the publication of Alberti's paper in 1979, the perioperative management of the surgical patient with diabetes was haphazard, and was associated with an unacceptable level of morbidity and mortality. Alberti's Glucose, Insulin, Potassium (GIK) regimen was based on sound scientific principles. Therefore since 1979, the gold standard for controlling the metabolic consequences of diabetes during surgery and starvation has been the simultaneous intravenous administration of glucose, insulin and potassium ³

It involved infusing a 500 ml bag of 10% glucose at 125 ml/hr (to minimise catabolism associated with starvation and surgical stress), with 10 units of insulin and 1 g potassium chloride added to the bag. If the patient's CBG fell out of the range of 5 – 10 mmol/L, the whole bag of fluid was discarded and a different amount of insulin was added. The Alberti regime was therefore both intensive and wasteful and had the potential for error with the number of additives to the fluid bag. ³

Variable rate insulin regimens became possible in the 1980's as a result of reliable infusion pumps and the widespread availability of rapid accurate monitoring of blood glucose concentrations. Insulin and glucose could be administered separately by infusion pumps with the rate of insulin infusion adjusted according to the circulating glucose value. ⁴

Subsequently by 1993, the Alberti regime had become superseded by the regime in which the

substrate and the insulin were separated into 2 separate infusions. This regime was previously called a 'sliding scale' and remains the most widely used and reliable method of controlling the metabolic consequences of starvation and surgery in the patient with diabetes. The term 'variable rate intravenous insulin infusion' (VRII) is now preferred as the term 'sliding scale' is ambiguous and may also be applied to variable intermittent boluses of subcutaneous insulin.³

The VRII is an offshoot of the Alberti GIK (glucose insulin potassium) regime and was never subjected to rigorous scientific studies before its widespread introduction. In theory, the VRII has the potential to achieve excellent glycaemic control.²

Unfortunately in reality, the use of VRII is associated with patient harm and death!²

Fairly recent studies from the critical care environment, which includes the van den Berghe studies; the efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) and the NICE–SUGAR studies, have demonstrated that the use of the VRII is associated with hypoglycaemia and death.²

Repeated national UK audits have also demonstrated that it is associated with harm in the ward environment, and that patients on the VRII are often either hypoglycaemic or hyperglycaemic.

- This may be because of the fact that approximately one in 20 patients are having three or less CBG measurements per day.
- Furthermore, issues with either delayed establishment of the VRII or delayed administration of subcutaneous insulin after discontinuation of the VRII, have been identified and both potentially leads to DKA.²

The advice is therefore to avoid the use of the VRII when and where possible. Despite these concerns, there is currently no other viable option for managing diabetes in the surgical patient who has a prolonged starvation period, and in these patients the use of the VRII is justified with the aim of preventing the deleterious effects of hyperglycaemia and DKA in the patient with type1 Diabetes.²

6.2. JDBS – IP indications for the use of a VRII³

- Patient with Type 1 diabetes undergoing surgery with a starvation period greater than 1 missed meal
- Patient with Type 1 diabetes undergoing surgery who has not received background insulin
- Patient with Type 2 diabetes undergoing surgery with a starvation period greater than 1 missed meal and who develops hyperglycaemia (CBG > 12mmol/L)
- Patients with poorly controlled diabetes as defined by HbA1C > 69 mmol/mol (>8.5%)
- Most patients with diabetes requiring emergency surgery

6.3. Practicalities related to the VRII³

- Make up a 50ml syringe using 50 units (0.5 ml) of Soluble Human Insulin (e.g. Human Actrapid®) and add 49.5ml of 0.9% sodium chloride
- A patient with a VRII needs at least 2 cannulae – one dedicated for insulin and glucose, and the other for anaesthetic drugs and additional fluids

6.4. Advantages of VRII³

- Flexibility for independent adjustment of fluid and insulin
- Accurate delivery of insulin via syringe driver
- Allows tight blood glucose control in the intraoperative starvation period

6.5. Disadvantages of VRII^{2,3}

- Hypoglycaemia
 - Subcutaneous insulin administered by the patient just prior to or at the same time as the variable rate insulin protocol is commenced, leading to hypoglycaemia
 - Hypoglycaemia may be fatal if the glucose infusion or enteral feeds are discontinued but the insulin infusion is continued
- Hyperglycaemia
 - Failure to monitor blood glucose regularly or to adjust the rate of insulin infusion appropriately may lead to either hyper- or hypoglycaemic incidents

- DKA
 - o May result from insulin omission in fasting patients, usually with type 1 diabetes
- Prolonged hospital stay
- Delays in return to normal diabetes medication
- Hyponatraemia
 - o It is well recognized that the use of the VRIII is associated with hyponatremia because of insufficient saline in the substrate solution
- Iatrogenic complications
 - o Up to tenfold insulin overdoses resulting from miscalculation or mispreparation of insulin containing infusions
 - o Administration of either insulin and/or glucose containing solutions without using an electronic infusion control device
 - o Incorrect setting of infusion pumps and syringe drivers leading to over or under infusion of insulin and/or glucose

7. Fluid management^{1,4}

There is a limited evidence base for the recommendation of optimal fluid management of the adult diabetic patient undergoing surgery. It is now recognised that Hartmann's solution is safe to administer to patients with diabetes and does not contribute to clinically significant hyperglycaemia.¹

Lactate is a 3-carbon compound and glucose is a 6-carbon compound. In one litre of Hartmann's solution, the 29 mmol of lactate would yield 14.5 mmol of glucose at most. This assumes that the biosynthetic pathways of gluconeogenesis are 100% efficient, that one litre of Hartman's solution is given instantaneously and that no lactate is oxidised. The initial glucose distribution space is the extracellular fluid volume, which in a 70 kg patient would be 12–15 litres. Therefore, the maximum increase in glucose concentration with one litre of Hartmann's would be about 1 mmol/l and in clinical practice the effect on blood glucose will be much less.⁴

7.1. Fluid management for patients requiring a variable rate intravenous insulin infusion¹

The aim is to provide glucose as a substrate to prevent proteolysis, lipolysis and ketogenesis, as well as to optimise intravascular volume status and to maintain plasma electrolytes and glucose within the normal range.

It is important to avoid iatrogenic hyponatraemia from the administration of hypotonic solutions. Glucose 5% solution should be avoided. The substrate solution to be used should be based on the patient's current electrolyte concentrations. There is no clear evidence that one type of balanced crystalloid fluid is better than another, half-strength 'normal' saline combined with glucose is, theoretically, a reasonable compromise to achieve these aims.

The initial fluid should be glucose 5% in saline 0.45% pre-mixed with either KCl 0.15% (20 mmol/l) or KCl 0.3% (40 mmol/l), depending on the presence of hypokalaemia (< 3.5 mmol/l). Fluid should be administered at the rate that is appropriate for the patient's usual maintenance requirements which is usually 25–50 ml/kg/day (approximately 83 ml/h for a 70 kg patient).

Very occasionally, the patient may develop hyponatraemia without signs of fluid overload. In these circumstances, it is acceptable to prescribe one of the following solutions as the substrate solution:

- Glucose 5% in saline 0.9% with pre-mixed potassium chloride 0.15% (20 mmol/l)
- Glucose 5% in saline 0.9% with pre-mixed potassium chloride 0.3% (40 mmol/l)

Additional Hartmann's solution or another balanced isotonic crystalloid solution should be used to optimise intravascular volume status.

7.2. Fluid management for patients NOT requiring a variable rate intravenous insulin infusion¹

The aim is to avoid glucose-containing solutions unless the blood glucose is low.

It is important to avoid hyperchloraemic metabolic acidosis therefore Hartmann's solution should be used to optimise the intravascular volume status. If the patient requires prolonged postoperative fluids (> 24 h), a VRIII should be considered.

8. Management of perioperative hyperglycaemia and hypoglycaemia^{1,2,3}

8.1. Hyperglycaemia:¹

Perioperative hyperglycaemia is defined as CBG > 10 mmol/litre

If the CBG exceeds 12 mmol/l and insulin has been omitted:

- Measure capillary blood ketone levels if possible (point-of-care devices are available in the UK!)
- If the capillary blood ketones are > 3 mmol/l or there is significant ketonuria (> 2+ on urine sticks) the patient should be treated as having diabetic ketoacidosis (DKA). See section on DKA under emergency surgery
- If DKA is not present, follow the guidelines below

8.2. Treatment of pre-operative hyperglycaemia (CBG > 12mmol/L with blood ketones < 3mmol/L or urine ketones < 3+).³

- Type 1 diabetes:
 - Give subcutaneous (SC) rapid acting analogue insulin (i.e. Novo- rapid®, Humalog® or Apidra®), using a specific insulin syringe
 - Assume that 1 IU will drop the blood glucose by 3mmol/L
 - Recheck CBG 1 hour later to ensure it is falling
 - If surgery cannot be delayed commence a VRIII
- Type 2 diabetes:
 - Give 0.1 units/kg of SC rapid acting analogue insulin (i.e. Novo- rapid®, Humalog® or Apidra®), using a specific insulin syringe
 - Recheck CBG 1 hour later to ensure it is falling
 - If surgery cannot be delayed or the response is inadequate, commence a VRIII

8.3. Treatment of intra-operative hyperglycaemia in a patient with type-1 diabetes¹

- Give SC rapid-acting insulin (e.g. Novo- rapid®, Humalog® or Apidra®) up to a maximum of 6 IU using a specific insulin syringe
- Assume that 1 IU will drop the CBG by 3 mmol/l
- The CBG should be checked hourly and a second dose considered only after 2 h

8.4. Treatment of intra-operative hyperglycaemia in a patient with type-2 diabetes¹

- Give SC rapid-acting insulin (e.g. Novo- rapid®, Humalog® or Apidra®) 0,1 IU/kg up to a maximum of 6 IU using a specific insulin syringe
- The CBG should be checked hourly and a second dose considered only after 2 h
- A VRIII should be considered if the patient remains hyperglycaemic

8.5. Treatment of post-operative hyperglycaemia (CBG > 12mmol/L with blood ketones < 3mmol/L or urine ketones < 3+)³

- Type 1 diabetes:
 - Give SC rapid acting analogue insulin (e.g. Novo- rapid®, Humalog® or Apidra®)
 - Assume that 1 unit will drop blood glucose by 3mmol/L
 - Take advice from the patient about the amount of insulin normally required to correct a high blood glucose
 - Recheck the blood glucose 1 hour later to ensure it is falling
 - Repeat the subcutaneous insulin dose after 2 hours if the blood glucose is still above 12mmol/L. In this situation the insulin dose selected should take into account the response to the initial dose – consider increasing the dose if the response is inadequate
 - Recheck the blood glucose after 1 hour. If it is not falling consider introducing a VRIII

- Type 2 diabetes:
 - o Give 0.1 units/kg of subcutaneous rapid acting analogue insulin
 - o Recheck blood glucose 1 hour later to ensure it is falling
 - o Repeat the subcutaneous insulin after 2 hours if the blood glucose is still above 12 mmol/L. In this situation the insulin dose selected should take into account the response to the initial dose – consider doubling the dose if the response is inadequate
 - o Repeat the blood glucose after another hour. If it is not falling consider introducing VRIII

8.6. Hypoglycaemia ³

Perioperative hypoglycaemia is defined as capillary blood glucose less than 4 mmol/litre.

8.7. Management of peri-operative hypoglycaemia

N.B. patients on diet alone are not at risk of hypoglycaemia and are excluded from the guideline below:

- If CBG is 4 – 6 mmol/L and the patient has symptoms of hypoglycaemia: Consider giving 50 – 100ml of 10% dextrose as a stat IV bolus and repeat the CBG after 10 minutes.
- If CBG is less than 4 mmol/L; give 75 – 100ml of 20% glucose and repeat the capillary blood glucose after 10 minutes.
- Try to avoid stopping the VRIII in type 1 diabetic patients. If it is stopped recommence as soon as the blood glucose rises above 5 mmol/L.
- Persistent hypoglycaemia should be appropriately referred urgently.
- Increase frequency of blood glucose monitoring until normoglycaemia has been achieved and then revert to monitoring blood glucose hourly until the patient is eating and drinking.

9. Continuous Subcutaneous Insulin Infusion Pump (CSII) ^{7,3}

The primary goal of insulin pump therapy is to mimic physiological insulin replacement in patients with type 1 diabetes

9.1. Principles of insulin infusion

The insulin pump is a small, battery-operated, programmable device which aims to mimic physiological insulin delivery over 24 hours with basal and bolus insulin infusions of rapid acting insulin analogues (Novorapid®, Humalog®, Apidra®). The pump is programmed to administer a basal infusion of insulin, which can be changed and stopped at any time. The pump also has built in calculators, which help with the dosing accuracy of additional bolus insulin that will accompany meals.

9.2. Basal and bolus insulin

The basal rate is programmed to deliver small doses of insulin as a constant infusion over 24 hours. Potentially by acting as a 'very long acting' insulin, the pump provides very stable insulin administration and excellent blood glucose control in the fasted state. The mealtime bolus dose is required when the patient is having a meal.

9.3. How it all works

Most commonly, the user wears a disposable metal or plastic, subcutaneously inserted cannula, which is held in place on the skin surface and changed every 2 – 3 days, to prevent problems from erratic absorption at the insertion site. The cannula is connected to the pump via a long flexible plastic tube. The insulin is held in a glass or plastic syringe within the pump. Some pumps contain built in continuous glucose monitoring system devices (CGMS), with the ability to measure interstitial glucose if an additional subcutaneous sensor is worn.

9.4. The disadvantages of insulin pump therapy

Only short-acting insulin is infused in the insulin pump. Disconnection, occlusion or cessation of pump therapy will render the pump-user relatively insulin deficient within 1 hour and absolutely insulin

deficient within 4 hours, with a severe risk of hyperglycaemia and ketosis. There are also cosmetic and psychological barriers to be considered for some people who prefer to remain on multi dose injections (MDI).

Recommendations for management of people with type1 diabetes on insulin pump therapy perioperatively.

The CSII may be continued peri-operatively if the starvation period is short (i.e. one missed meal. The following should be noted if the CSII will be used peri-operatively:

- Patients should remain on their basal insulin rate until they are eating and drinking normally.
- The infusion set should be changed the day before surgery and enough time should be allowed to check two CBG readings several hours apart, to ensure the infusion set is functioning correctly.
- A plastic infusion set is preferred for surgery because of the risks of subcutaneous metals with diathermy.
- The infusion site should be distant from the site of the surgery, away from the field of diathermy and should be readily accessible by the anaesthetist at all times. (The infusion site is usually on the abdomen, thighs or buttocks.)
- Do not give bolus insulin doses via the CSII.
- If the CBG decreases below 4 mmol/litre, hypoglycaemia should be treated as discussed earlier. As a result of the relatively slow absorption of insulin from the subcutaneous site, it is not necessary to stop the basal insulin infusion at this point, because it is unlikely to have an effect on glucose control for up to 2 hours. However, if the blood glucose becomes difficult to manage, or hypoglycaemia is recurrent, the pump should be stopped and a VRIII should be started.
- Monitor CBG hourly.
- Peri-operative hypotension can decrease skin perfusion and reduce insulin absorption therefore normal hydration and blood pressure must be maintained.
- Mealtime boluses should only be recommenced once the patient is eating and drinking normally in the postoperative period.

Usage of the CSII is contraindicated in the following circumstances. The pump should be stopped and a VRIII should be started:

- Major surgery
- Emergency surgery
- Abdominal surgery with expected significant postoperative ileus
- Prolonged starvation time (missing more than meal)
- Procedures that will expose the patient to ionizing radiation or electromagnetic fields

When a VRIII has been used, the CSII should only be restarted once the patient is eating and drinking normally. The VRIII should be discontinued 30 minutes after the first mealtime bolus.

10. Emergency surgery and Diabetic Ketoacidosis ^{1,3,7}

10.1. Background

Diabetic patients often present with surgical emergencies. The release of high levels of catabolic hormones in response to the crisis will lead to hyperglycaemia and will complicate the clinical situation. Many emergencies result from infection, which will add further to the hyperglycaemia. By definition there may be no opportunity for pre surgery optimisation. Generally, the emergency patient will require a VRIII. The HbA1C should be measured to assess the level of chronic glycaemic control as this may influence subsequent diabetes management. Consult ICU timeously when you anticipate that postoperative critical care may be needed. 3

Glycaemic management for patients undergoing emergency surgery: ¹

- Check the CBG regularly (hourly as a minimum whilst acutely unwell)
- Check for ketonaemia (> 3.0 mmol/l) or significant ketonuria (> 2+ on urine sticks) if the CBG exceeds 12 mmol/l.

There are three ways of managing diabetes in the patient requiring emergency surgery: ¹

1. Modification of normal medication ^{1,3}

This is only possible if the patient is physiologically well and is being operated on a scheduled

list, for example a regular trauma list for minor hand surgery, or evacuation of retained products of conception on a regular Gynaecology list. 1 The same principles outlined in tables 1 and 2 may be used for these cases – provided there is the opportunity for patient education. The blood glucose should be closely monitored and if it rises above 10mmol/L a VRIII should be commenced and continued until the patient is eating and drinking. 3

2. **Use of a VRIII** ¹

This should be the default technique to manage a patient undergoing emergency surgery because of the unpredictability of the starvation period caused by the erratic nature of emergency lists.

3. **Use of a fixed-rate intravenous insulin infusion** ¹

This should only be used if the patient requires immediate surgery and has concurrent Diabetic Ketoacidosis (DKA). The aim is for the patient to be taken to the operating theatre with a CBG of 6–10mmol/l (6–12 mmol/l may be acceptable), without overt DKA, and having been adequately resuscitated. Operating on a patient with DKA carries significant mortality and should be avoided if at all possible.

This is the ideal place to highlight some facts about DKA: ⁷

10.2. Definition

Diabetic ketoacidosis (DKA) consists of the biochemical triad of ketonaemia (ketosis), hyperglycaemia and acidaemia.

10.3. Pathophysiology

DKA usually occurs as a consequence of absolute or relative insulin deficiency that is accompanied by an increase in counter regulatory hormones (i.e. glucagon, cortisol, growth hormone, catecholamines). This type of hormonal imbalance enhances hepatic gluconeogenesis and glycogenolysis and results in severe hyperglycaemia. Enhanced lipolysis increases serum free fatty acids that are then metabolised as an alternative energy source in the process of ketogenesis. This results in accumulation of large quantities of ketone bodies and subsequent metabolic acidosis. Ketones include acetone, 3-beta-hydroxybutyrate and acetoacetate. The predominant ketone in DKA is 3-beta-hydroxybutyrate.

There are several mechanisms responsible for fluid depletion in DKA. These include osmotic diuresis due to hyperglycaemia, vomiting which is commonly associated with DKA and eventually, inability to take fluid in due to a diminished level of consciousness. Electrolyte shifts and depletion are in part related to the osmotic diuresis. Hyperkalaemia and hypokalaemia need particular attention.

10.4. Diagnosis

- Ketonaemia ≥ 3.0 mmol/L or significant ketonuria (more than 2+ on standard urine sticks)
- Blood glucose > 11.0 mmol/L or known diabetes mellitus
- Bicarbonate (HCO_3^-) < 15.0 mmol/L and/or venous pH < 7.3

10.5. General management issues:

10.5.1. Fluid administration and deficits

There is universal agreement that the most important initial therapeutic intervention in DKA is appropriate fluid replacement followed by insulin administration.

The main aims for fluid replacement are:

- Restoration of circulatory volume
- Clearance of ketones
- Correction of electrolyte imbalance

The typical fluid and electrolyte deficits are shown below. An adult weighing 70kg that presents with DKA may be up to 7 litres in deficit. This should be replaced with crystalloid. The aim of the first few litres of fluid is to correct any hypotension, replenish the intravascular deficit, and to counteract the effects of the osmotic diuresis with correction of the electrolyte disturbance.

Typical deficits in DKA in adults

Water – 100ml/kg

Sodium – 7 – 10 mmol/kg
Chloride – 3 – 5 mmol/kg
Potassium – 3 – 5 mmol/kg

10.5.2. Insulin therapy

Administration of a Fixed Rate Intravenous Insulin Infusion (FRIII):

- Indicated if the patient is still ketotic or acidotic (ketones greater than 0.6 mmol/L and/or HCO_3^- less than 15 mmol/L)
- Add 50 units soluble insulin (Actrapid®/Humulin S®) in a 50 ml syringe using 0.9% sodium chloride
- Calculated on 0.1 units / per kilogram body weight / per hour (see table below to assist)

Insulin has several effects, but the following are the most important when treating DKA:

- Suppression of ketogenesis
- Reduction of blood glucose
- Correction of electrolyte disturbance

An example of a Fixed Rate Intravenous Insulin Infusion (FRIII)

Weight in kg	Insulin dose per hour (Units)
60 – 69	6
70 – 79	7
80 – 89	8
90 – 99	9
100 – 109	10
110 – 119	11
120 – 130	12
130 – 139	13
140 – 150	14
> 150	15 (any dose higher should be on the advice of the Diabetes Specialist Team)

10.6. Metabolic treatment targets

The recommended targets are

- Reduction of the blood ketone concentration by 0.5mmol/L/hour □
- Increase the venous bicarbonate by 3.0mmol/L/hour □
- Reduce capillary blood glucose by 3.0mmol/L/hour □
- Maintain potassium between 4.0 and 5.5mmol/L

If these rates are not achieved, the FRIII rate should be increased.

10.7. Intravenous glucose concentration

The management should be focused on clearing ketones as well as normalising blood glucose. It is often necessary to administer an intravenous infusion of 10% glucose in order to avoid hypoglycaemia and to permit the continuation of a FRIII to suppress ketogenesis. Introduction of 10% glucose is recommended when the blood glucose falls below 14.0mmol/L. It is important to continue 0.9% sodium chloride solution to correct circulatory volume. It is often necessary to infuse these solutions concurrently. Glucose should be continued until the patient is eating and drinking normally.

11. Restarting of 'normal' medication in the postoperative period ^{1,3}

Any surgical procedure induces significant neuroendocrine stress, which results in increased insulin resistance with consequent hyperglycaemia. During the postoperative period, nutrition may be delayed or interrupted by additional investigations or procedures. Glucose control may therefore be

unpredictable and difficult during this period ³

Patients who had emergency surgery done are at particularly high risk in the post-operative period. Catabolic stress and infection predispose to hyperglycaemia and ketogenesis and it is crucial to maintain glycaemic control to optimise the outcome. ³

Acceptable blood glucose levels during the postoperative period (JBDS-IP - Sept 2015) ³

- In the awake patient not on a VRIII: 4 – 12 mmol/L
- If a VRIII is used, the acceptable range remains 6 – 12 mmol/L

11.1. Transferring from a VRIII to subcutaneous insulin or oral treatment ^{1,3}

If the patient has type-1 diabetes and a VRIII has been used, it must be continued for 30 – 60 minutes after the patient has had their first dose of subcutaneous insulin. Premature discontinuation of the VRIII is associated with iatrogenic DKA. ¹

11.2. Restarting oral hypoglycaemic medication ³

Recommence oral hypoglycaemic agents at pre-operative doses once the patient is ready to eat and drink. Be prepared to withhold or reduce sulphonylureas if the food intake is likely to be reduced.

Metformin should only be recommenced if the estimated glomerular filtration rate (eGFR) is greater than 60 ml/min/1.73 m². More about Metformin a little bit later!

11.3. Restarting subcutaneous insulin for patients already established on insulin ³

Conversion to subcutaneous insulin should be delayed until the patient is able to eat and drink without nausea or vomiting. Restart the normal pre-surgical regimen. Be prepared to adjust the doses because the insulin requirement may change as a result of post-operative stress, infection or altered food intake. The transition from intravenous to subcutaneous insulin should take place when the next meal-related subcutaneous insulin dose is due e.g. with breakfast or lunch.

11.4. For the patient on basal bolus insulin ³

There should be an overlap between the end of the VRIII and the first injection of fast acting insulin. The fast acting insulin should be injected subcutaneously with the meal and the intravenous insulin and fluids discontinued 30 to 60 minutes later. If the patient was previously on a long acting insulin analogue such as Lantus[®], Tresiba[®], or Levemir[®], this should have been continued and therefore the only action should be to restart the patient's normal short acting insulin at the next meal. If the basal insulin was stopped in error, the insulin infusion should be continued until the patient's usual background insulin has been given. If the basal insulin is normally taken once daily in the evening and the intention is to convert to subcutaneous insulin in the morning, give half the usual daily dose of basal insulin as isophane (e.g. Insulatard[®], Humulin I[®]) in the morning, this will provide essential background insulin until the long acting analogue can be recommenced. Check for blood or urine ketones and check glucose levels regularly (e.g. every 4 to 6 hours) during this transition phase.

11.5. For the patient on a twice-daily fixed- mix regimen ³

The insulin should be re-introduced before breakfast or before the evening meal. Do not change to subcutaneous insulin at any other time. The VRIII should be maintained for 30 to 60 minutes after the subcutaneous insulin has been given.

11.6. For the patient on a continuous subcutaneous insulin infusion (CSII pump) ³

As discussed earlier, the subcutaneous insulin infusion should be recommenced at the patient's normal basal rate. The VRIII should be continued until the next meal bolus has been given. Do not recommence the CSII at bedtime.

11.7. Resumption of normal diet ¹

The key to successful management of the surgical patient with diabetes is resumption of the patients' usual diet. This allows resumption of normal diabetes medication. Hospital discharge is only feasible once the patient has resumed eating and drinking.

12. Other perioperative anaesthetic considerations

12.1. Use of regional anaesthesia ¹

Local anaesthetic techniques (neuraxial blocks and peripheral nerve blocks), reduces the risk of postoperative nausea and vomiting when used as the sole anaesthetic. Furthermore, when used as part of the multimodal analgesic technique during general anaesthesia, they have opioid-sparing actions, with resultant reduction of opioid-related side effects. The downside however, is that evidence suggests that patients with diabetic autonomic neuropathy, are more prone to epidural abscesses and haemodynamic instability after central neuraxial blockade. There is also a possible increased risk of neuropathy after peripheral nerve blocks in this group of patients.

12.2. The Enhanced Recovery Partnership Programme and diabetes ^{1,3}

The Enhanced Recovery Partnership Programme has particular relevance for patients with diabetes. This programme employs a selected number of evidence-based interventions, which promote earlier resumption of normal diet, earlier mobilisation, and reduced length of hospital stay. The aim of this pathway is to maintain the patients in a state of as little metabolic stress as possible. The Enhanced Recovery Partnership Programme recommends the administration of complex carbohydrate drinks prior to surgery, in order to reduce insulin resistance and to promote recovery. This may compromise blood glucose control and is not applicable for diabetic patients who are due to have their diabetes controlled perioperatively by manipulation of their medication. However, the recommended oral carbohydrate load will benefit patients who will be treated with a VRILL.

12.3. The safe use of Insulin ³

Errors in insulin prescribing are very common and insulin has been identified as one of the top five high-risk medications in the in-patient environment in the UK. The wide range of preparations and devices available for insulin administration (currently more than 60) increases the potential for error. The following is recommended: Insulin should be prescribed using the brand name, written out in full. Abbreviations such as 'u' or 'iu' should not be used as it may lead to dose errors and misinterpretation. Always use a specific insulin administration device e.g. insulin syringe or insulin pen to draw up or to administer insulin.

12.4. Dexamethasone ^{1,3}

All glucocorticoids have the potential to cause hyperglycaemia. The use of dexamethasone for the treatment of post-operative nausea and vomiting is controversial in people with diabetes because the advantages of allowing earlier resumption of normal diet may be outweighed by the complication of prolonged hyperglycaemia. If it is decided that the possible benefits of earlier resumption of normal diet outweigh the disadvantages of hyperglycaemia, it should be ensured that CBG is measured hourly for at least 4 hours after the administration of dexamethasone.

12.5. Glucose meters ⁵

The FDA in the USA allows a 20% error for glucose meters at concentrations above 100-mg/ dl (5.6 mmol/litre) and a 15% error for values below 100 mg/dl. Therefore, a measured concentration of 4 mmol/litre will have an actual value between 3.4 and 4.6 mmol/litre, while a measured concentration of 12 mmol/litre will have an actual value between 9.6 and 14.4 mmol/litre. In addition, measurement of glucose values with assay strips, glucose meters and by arterial gas analysis overestimates concentrations at low values. Many factors commonly found in surgical patients may also affect the measurement of glucose, which includes, poor peripheral perfusion, anaemia, increased bilirubin, increased uric acid as well as drugs such as paracetamol, dopamine, and mannitol.

12.6. Metformin ³

Metformin is an effective drug used to treat type 2 diabetes. It primarily works by preventing gluconeogenesis, and therefore the risk of hypoglycaemia in the starved state is low. It is renally excreted and renal impairment may lead to accumulation, which is associated with an increased risk of lactic acidosis. A number of guidelines available for the use of metformin (NICE CG66 Type 2 diabetes May 2008 and BNF 68 March 2015) recommend withdrawing treatment peri-operatively.

Evidence for this approach is however lacking and there is some evidence that perioperative continuation of metformin is safe. The JBDS-IP (September 2015) recommends that Metformin should be continued when patients are undergoing procedures with a short starvation period (1 missed meal only) and if they have a low risk of developing acute kidney injury. Metformin should however be stopped if the starvation period will be prolonged (more than 1 missed meal), and if the patient has a high risk of developing AKI. If the decision has been made to stop metformin, it should be stopped when the preoperative fast begins and restarted post-operatively once the patient has resumed normal eating and drinking.

12.7. Radio-opaque contrast and metformin ³

Contrast induced nephropathy is the development of renal impairment as a complication of radiological investigation using contrast media. Risk factors include advanced age, cardiac impairment, and pre-existing renal impairment, particularly in patients with diabetes. Guidance produced by the UK Royal College of Radiologists in 2015 states “that there is no need to stop metformin after contrast in patients with a creatinine within the normal reference range and/or eGFR of 60 ml/min/1.73m². If the creatinine is above the reference range or the eGFR is below 60, any decision to stop the metformin for 48 hours following contrast medium administration should be made in consultation with the referring clinician”

12.8. Non-steroidal anti-inflammatory drugs (NSAID's) ³

Regular NSAID's provide excellent analgesia for many post-operative patients and can have useful opioid-sparing effects, particularly in patients undergoing day case and other minor surgery. However, there are several additional considerations in patients with diabetes:

- Gastro-intestinal:
 - o Patients already taking regular aspirin to prevent coronary thrombosis, have an increased risk of gastrointestinal haemorrhage. NSAID-induced gastritis and diarrhoea may predispose to dehydration
- Renal:
 - o NSAID's impair the redistribution of renal blood flow in the presence of hypovolaemia and may worsen renal function. This is especially important if prescribed concurrently with drugs that modulate the Renin-Angiotensin-Aldosterone system
- Oedema:
 - o NSAID's may increase the risk of oedema, especially if given concurrently with Glitazones

13. Conclusion

To conclude, a summary of the main JBDS-IP (Sept 2015) recommendations pertaining to the perioperative management of the diabetic patient ²

1. *Promote day surgery and day of surgery admission when and where possible – if a patient is not in hospital it is less likely for iatrogenic harm to occur.*
2. *Promote self-medication if possible – many patients are often more knowledgeable than medical staff about their medical condition, and they have a vested interest to self-medicate properly*
3. *Avoid the use of sliding scales / VRIII when and where possible – modification of the patient's usual diabetes medication is preferable*
4. *Indications for the use of a VRIII include poor glycaemic control and anticipated prolonged starvation*
5. *Every hospital should have guidelines to promote the safe use of a VRIII*
6. *Maintenance fluid to be used with a VRIII should be 5% glucose in 0.45% saline with either 0.15% or 0.3% KCl - to prevent iatrogenic hyponatraemia and hypokalaemia*
7. *The ideal CBG should be 6 – 10 mmol/litre; an acceptable CBG is 4 – 12 mmol/litre*
8. *Prevent neuroglycopenia in the unconscious state by measuring the CBG hourly*
9. *An elective surgical patient should have an HbA1C of < 8.5% (69 mmol/mol) where practically possible.*

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Informed Consent- Pitfalls

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This lecture contains excerpts from an article in press for the SA Family Practice journal:

“**The Health Professions Act (56 of 1974)** of South Africa is the law under which we as anaesthesiologists and anaesthetists in South Africa practise. This law states that we are required to inform our patients of the costs of their treatment. Likewise, the Consumer Protection Act informs us of the following:

- We are required to give our patients a written quotation;
- We may not charge more than this quotation;
- This “financial consent” needs to be obtained preoperatively;
- This transaction should preferably be in writing;
- This consent can be obtained by another person acting on the patient's behalf.

Insofar as ethical and legal consent for anaesthesia in adult patients is concerned, we are bound by the **National Health Act (61 of 2003)**. This replaced our previous legislation in South Africa which had a very paternalistic attitude to informed consent from patients. The National Health Act embodies the ethical principle of patient autonomy, which is the right to decide for oneself.”

Why is informed consent necessary from the ethical perspective? Essentially the whole issue hinges on the principle of Autonomy. (Autos = self; Nomos = rule) Autonomy thus implies freedom from the control of others (liberty) and freedom from excessive personal limitations (capacity) and is simply the right to decide for oneself. Beauchamp and Childress in “The Principles of Biomedical Ethics” discuss two important issues – the Principle of Autonomy and Respect for Autonomy. Their theories of autonomy involve understanding, reasoning and choice, and that autonomous action is described as acting intentionally, with understanding and without controlling influences that determine one's actions. Insofar as choice is concerned there are definitely factors that affect choice such as ignorance (what is the procedure? what is on the consent form?), coercion, (by family or the Community) temporary or partial incapacity and others. Beauchamp and Childress also allude to the consequences of respect for autonomy, which are Informed Consent, truth telling (full disclosure) and confidentiality. A contentious issue when considering autonomy is its limitations. These may be those affecting the individual, such as immaturity, incapacity, irrationality, ignorance and imposition (coercion and exploitation), as well as those affecting the community such as endangering public health, potential harm to others and competition for limited resources.

“Obtaining informed consent from a patient is a process, and not merely a signature on a piece of paper or a form. It entails the following:

- Assessment of the patient's age (must be >18 years) and decisional capacity. The latter is usually fairly straightforward in adults, but can be somewhat of a challenge in children, when one applies the Children's Act 38 of 2005.
- Description of the proposed anaesthetic intervention, incorporating risks, benefits and consequences, as well as costs, if applicable. One needs to check that the patient understands the information.
- The patient makes a decision and communicates this, and signs in writing to this effect.
- All communication must be in a language that the patient understands and in a manner that takes into account literacy.
- The patient must be reminded that consent may be withdrawn at any time. The consequences of withdrawal need to be understood.

When adult patients lack decisional capacity (which may be for a variety of reasons), The National Health Act (NHA) mandates that the following process be followed:

- An advance directive must be sought. If not available or not applicable, then the following surrogates may consent on the patients behalf, provided the patient has not previously knowingly refused the exact same treatment (anaesthetic):
 - A proxy, mandated in writing (power of attorney)
 - A person authorised by law or a court order;
 - The patient's spouse or partner;
 - Parent;
 - Grandparent;
 - Adult child;
 - Brother or sister.
- If none of the above options are available and the treatment is urgent to prevent either death or irreversible damage to the patient (and the patient has not previously refused the exact same treatment), then the emergency treatment may be performed without consent. It is recommended that consent is sought afterwards, in these circumstances.

In patients who are < 18 years of age, the **Children's Act (38 of 2005)** applies, when deciding on informed consent for anaesthesia. Legally, the consent of the parent or guardian is required if the child is < 12 years of age, or over that age but is of insufficient maturity or is unable to understand the benefits, risks and social implications of the treatment.

If a child is older the 12 years, then the Children's Act states as follows:

- A child may consent to his or her own medical treatment or to the medical treatment of his or her child IF the child is over the age of 12 years AND the child is of sufficient maturity and has the mental capacity to understand the benefits, risks, social and other implications of the treatment. This would apply to epidural analgesia, for example.
- A child may consent to the performance of a surgical operation on him or her or his or her child if the child is over the age of 12 years AND the child is of sufficient maturity AND has the mental capacity to understand the benefits, risks, social and other implications of the surgical operation and the child is duly assisted by his or her parent or guardian. This applies to consent for surgery and anaesthesia.

In the case of an emergency then the following applies:

- The superintendent of a hospital or the person in charge of the hospital in the absence of the superintendent may consent to the medical treatment of or a surgical operation on a child if the treatment or operation is necessary to preserve the child's life and is so urgent that it cannot be deferred.
- A High Court or children's court may consent to the medical treatment of or a surgical operation on a child in all instances where another person that may give consent in terms of this section refuses or is unable to give such consent.

In all matters pertaining to children the overriding ethical principle is that the decisions that are made must be IN THE BEST INTERESTS OF THE CHILD.

Other ages for consent in children as per the Children's Act 38 of 2005(4) include the following:

- Female circumcision is banned.
- Male circumcision may only be carried out in a male >16 years with his consent, unless it conforms to religious practices or is medically necessary.
- Virginity testing may only be performed in children > 16 years under strict conditions."

What applies in the case of an adult who is not of sound mind? **The Mental Health Care Act (17 of 2002) and its regulations (of 2003)** govern issues pertaining to informed consent in this group of patients as follows:

- An involuntary mental health care user, an assisted mental health care user, a state patient or a mentally ill prisoner who is capable of consenting to treatment or an operation, must decide whether to have the treatment or an operation or not.
- If a mental health care practitioner deems a user to be incapable of consenting to treatment or an operation, due to mental illness or intellectual disability then a curator, if a court has appointed one, a spouse, next of kin, a parent or a guardian, a child over the age of 18, a brother or sister, a partner or associate, may consent to the treatment or operation.
- The head of the health establishment where the mental health user resides may only grant consent to treatment or an operation if none of the above persons are available and attempts have been made to locate them and this is confirmed in writing; the relevant alternatives have been discussed with the head of the health establishment concerned and he/she is satisfied that this is the most appropriate intervention or the medical practitioner who is going to perform such operation recommends the treatment or operation.

All of the above must be documented in the clinical record of the mental health care user.

One of South Africa's most progressive Acts insofar as informed consent is concerned is **The Choice on Termination of Pregnancy Act (92 of 1996)** and its various amendments. This Act states as follows:

- A pregnant female of any age may consent to the termination of her pregnancy at various stages, depending on specific factors; these are divided up into 3 groups: <12 weeks; 13-20 weeks; >20weeks gestation.
- In the case of a pregnant minor, she is advised to consult with her parents/guardian/family members but **does not have to AND** the identity of the woman shall remain confidential.

What about consent for procedures resulting from this termination, for example a hysterectomy? This is open to interpretation, but legalprecedence indicates that ALL procedures as a direct result of the termination are covered by the original consent. Some would say that the Act even covers consent for caesarean sections, in the section of the Act that deals with pregnancies of > 20 weeks and where the life of the mother or the foetus is at risk.

The big debate is how detailed does the discussion on "benefits, risks and consequences" need to be, in terms of all of the various acts?

If one consults with the Medical Protection Society, they will tell you that patients need to be informed on absolutely every "risk and consequence" i.e. complication, regardless of how uncommon this is, unless they specifically say "I do not want to know." The latter, however, may possibly be looked at as invalidating the consent, as it is no longer "informed". The Australian National Health and Medical Research Council has stated: "Known risks should be disclosed when an adverse outcome is common even though the detriment is slight, or when an adverse outcome is severe, even though its occurrence is rare."

Should we inform our patients of ALL of the risks?

In the past the tendency has been to only warn/inform the patient about the minor (and usually more common) morbidities. The South African Acts that govern consent, as well as the Medical Protection Society dictate that we should inform our patients of the minor morbidities (common with slight detriment), as well as the severe adverse outcome/s, even though its/their occurrence is rare.

Practically the reasonable way to do this would be by means of an information booklet, which according to our Act, needs to be "in a language that the user understands and in a manner which takes into account the user's level of literacy".

Does this extensive information have the effect of creating anxiety in the patient? Inglis and Farnell in Australia showed that there was no increase in anxiety levels when detailed information was made available. Thus in the current medico legal climate, patients should rarely have detailed information about the risks of anaesthesia or surgery withheld on the grounds that they are likely to suffer adversely from such information.

In addition, the perception of risk is modified by a number of factors when informing patients:

- Probability of occurring (perspective with everyday living)
- Severity
- Vulnerability (lack of control by the patient)
- Controllability (loss of conscious choice)
- Familiarity (previous anaesthetics)
- Acceptability and dread (expected norms)
- Framing and presentation (90% survival rather than 10% mortality)

Thus one needs to take these factors into account when informing the patient in a positive manner, looking at the mortality and morbidity results of best practice.

Are we ethical in approaching our patient's death?

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The patient who I anaesthetised has died - what do I do ethically? What do I need to do medicolegally?

Current practice appears to indicate the following thought processes:

- Depends if intra- or post-op....do I even know that the patient has died?
- Depends if elective or emergency
- Depends if trauma-related
- Depends on patient's preoperative status
- Depends on whether the anaesthetic was uneventful or not.....anticipated problems
- How informed was the consent?
- Do I know what to do?
- Am I STILL under the impression that only patients who die < 24 hours after the onset of an anaesthetic need to be reported?
- Do I know what the law says?
- Have I kept a good and accurate contemporaneous record?
- Do I know which forms to complete and how detailed must it be?
- What do I tell the family?

The Law and the Deceased

Three important Acts govern procedures that need to be followed after one's patient dies. They are:

- Births and Deaths Registration Act (51 of 1992)(BDRA)
- Inquests Act (58 of 1959)
- The Health Profession Act (56 of 1974)

If one does not comply with these one is guilty of a criminal offence.

The relevant portion of the **Births and Deaths Registration Act (51 of 1992)** states: "If a medical practitioner is of the opinion that the death was due to other than natural causes, he shall NOT issue a certificate and shall inform a police officer as to his opinion in that regard." For practical purposes this means completing a D28 form, as well as a GW7/24 form. It also means that a medicolegal postmortem needs to be conducted, and as this is the law, **one does not need consent from the family.**

The **Inquest Act (58 of 1959)** states: "Any person who has reason to believe that any other person has died and that death was due to other than natural causes, shall, as soon as possible, report accordingly to a Policeman, unless he has reason to believe that a report has been or will be made by any other person." This has the same implications as the Births and Deaths Registration Act.

And finally, the **Health Profession Act (56 of 1974)** with its **amendment from 2007** states as follows: "The death of a person undergoing, or as a result of, a procedure of a therapeutic, diagnostic or palliative nature, or of which any aspect of such procedure has been a contributory cause, shall not be deemed to be a death from natural causes, as contemplated in the Inquest Act, 1959 (Act 58 of 1959), or the Births, Marriages and Deaths Registration Act, 1992 (Act No 51 of 1992)."

This means that in this type of death a medico-legal post-mortem AND inquest (paper or formal) must be held.

The purpose of all of this legislation is to protect the public and to protect medical practitioners.

Ethics and “anaesthetic” deaths

The legal requirements must be fulfilled, with completion of the required paperwork, and a medicolegal postmortem. The family needs to understand this, and that their opinion and/or consent are both irrelevant, regardless of social or religious beliefs. They need to be informed in a caring but practical manner.

The entire anaesthetic and surgical team should meet with the family, and give an honest and unified explanation of what transpired. This may at times be very, very difficult, particularly in the case of children, fit patients for elective surgery (unexpected death) and patients where one genuinely made a mistake and the patient died.

The entire theatre team should be debriefed, with psychological and emotional backup for each individual if necessary. All departments should have a debriefing policy. This is vital, as some anaesthetists may not be “fit” to go straight back to work, depending on what the circumstances were surrounding the patient’s death.

We all need to be cognisant of conducting ourselves ethically to our deceased patients, the patient’s family, as well as our colleagues.

Triaging of Emergency Surgical Cases

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The concept of triage

Triage is derived from the French word ***trier***, which means 'to sort', or 'to sieve' and is a tool that guides the process of prioritising treatment and evacuation of patients in mass casualty situations. Its aims are to give the right patient the right care at the right time, in the right place. Accurate triage rapidly identifies patients needing the most urgent interventions as well as those that can wait longer for treatment. It also flags patients that are so severely injured that survival is unlikely, and in whom use of scarce resources is probably futile.

Triage is applicable not only in pre-hospital, mass casualty situations, but also in hospital emergency departments. It is a dynamic process that must be repeated frequently as the patient's condition changes, for the better or worse. When applied correctly, triage tools form an important component of clinical risk management in the emergency care setting.

All triage systems have the same basic structure with some variations. This structure comprises priority levels that inform or prescribe actions or interventions that are time and management specific. Priority levels are commonly used in conjunction with colour coding which enhances their visual impact in a stressful and busy environment.

For example:

RED- a patient whose life is in immediate danger and requires immediate treatment. This may include patients with airway obstruction or severe breathing problems.

YELLOW- a patient whose life is not in danger. Surgical or medical intervention is required within 2- 4 hours. This may include patients with intra-abdominal bleeding or complicated (open) fractures.

GREEN- a patient with minor injuries who will eventually require treatment (within 24 hours).

BLUE- expectant. A patient who is either dead or so severely injured/ill that they are unlikely to survive with the resources available.

Triage beyond the emergency unit

Acute surgical cases are evaluated in the emergency or trauma unit where they are assigned a triage category based on the South African Triage Scale (SATS) system. This system was developed in 2004 by the Cape Triage Group, a multidisciplinary panel of health professionals whose ambit was to develop a triage tool appropriate for local conditions. SATS triage categories are shown below:

<u>Colour</u>	<u>Status</u>
RED	Immediate priority (resuscitation cases)
ORANGE	Very urgent priority (potentially life/limb threatening pathology)
YELLOW	Urgent priority- significant pathology
GREEN	Delayed priority- minor injury/illness
BLUE	Dead

Once admitted to the ward and booked on an emergency list awaiting surgery, patients effectively 'lose' their triage category and, unless severely ill, may languish on the emergency list until their clinical status deteriorates enough to warrant 'jumping the queue' or, indeed, 'crashing' and elective list. By actively triaging admitted surgical cases based on their initial clinical status and on the likely natural history of their condition, decisions on which cases are prioritised for theatre can be made timeously regardless on their position in the queue for emergency theatre.

As perioperative physicians, anaesthetists are strategically placed to participate in the triaging of emergency surgical cases by assigning peri-operative risk and instituting optimisation strategies to modify individual patient's risk in conjunction with surgical colleagues.

Emergency surgery: scheduling of emergency cases

There have been many studies examining the process of decision making in the medical environment but few of them have looked at decision making when scheduling of emergency surgery. Decisions around the scheduling of emergency cases have consequences not only for the operating theatre, but for the hospital as a whole and for the patients in its care (viz. length of hospital stay, delays in surgical management leading to increased morbidity and mortality etc).

Decision making in the hospital environment has a number of unique qualities that separate it from similar functions in other societal institutions. It involves a strong focus on restoring patient health; it is responsive to change in both the patient's clinical status and the changing availability of hospital resources; time constraints are non-negotiable and there may be significant personal consequences associated with decisions made. This is especially true in the operating theatre environment, and for this reason, the scheduling of surgery (and emergency surgery in particular) has been described as a complex activity fraught with potential conflict.

Models for decision making, particularly in the context of surgery, follow **decision theory** which describes an ability to comprehensively consider information from diverse sources, especially in situations of great uncertainty. This theory manifests in the form of two models, namely:

- a) Queuing theory and
- b) The Poisson distribution model.

Under **queuing theory**, management of emergency cases operates on the basis of "first come first served" whereby priority is determined by chronology only. In the context of patient health outcomes, this approach is illogical and potentially harmful. In contrast the **Poisson distribution model** is particularly apt at representing a particular event, like emergency surgery. It describes a discrete probability distribution that expresses the probability of a given number of events occurring at a fixed interval of time and/or space if these events occur with a known average rate and independently of the time since the last event. The Poisson distribution model thus allows for the random arrival of patients, independent from the arrival of other patients and supposes independence from the state of the hospital system. This model is effective where emergency surgical cases are selected based on a set of clinical priorities rather than their position in an emergency list queue.

When managing unplanned surgical cases, there are many factors that influence the decision making process, namely:

1. Clinical need for urgent and timely treatment;
2. The ambiguity and bias that surrounds the determination of clinical urgency;
3. The dynamic nature of acute surgical emergencies coupled with the changing demands for theatre space and other resources;
4. The potential for disruption of planned (elective) surgical lists;
5. The burden of emergency surgical cases at any one time.

It is with the above in mind that, over the past ten years or so, several institutions have attempted to improve risk-management and communication between health professionals by instituting **urgency categorisations tools** for emergency surgical cases based on the concept of triage. The aim of this approach is to prioritise cases according to surgical acuity rather than booking chronology on the emergency list.

Urgency Categorisation tool models

Examples of urgency categorisation models include:

1. The NCEPOD classification (2004):

IMMEDIATE – Immediate life, limb or organ-saving intervention – resuscitation simultaneous with intervention. Normally within minutes of decision to operate.

A. Life-saving

B. Other e.g. limb or organ saving

URGENT – Intervention for acute onset or clinical deterioration of potentially life-threatening conditions, for those conditions that may threaten the survival of limb or organ, for fixation of many fractures and for relief of pain or other distressing symptoms. Normally within hours of decision to operate.

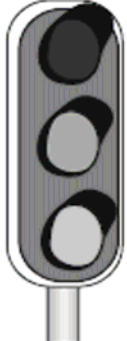
EXPECTED – Patient requiring early treatment where the condition is not an immediate threat to life, limb or organ survival. Normally within days of decision to operate.

ELECTIVE – Intervention planned or booked in advance of routine admission to hospital. Timing to suit patient, hospital and staff.

2. The Acute Surgery Priority System introduced by the NSW Health Surgical Services Task Force (Australia):

< 15 minutes	Immediate life threatening. The patient is in immediate risk loss of life, shocked or moribund, resuscitation not providing positive physiological response.
< 1 hour	Life threatening. The patient has a life-threatening condition but is responding to resuscitative measures.
< 4 hours	Organ/limb threatening. The patient is physiologically stable but there is immediate risk of organ survival or systemic decompensation.
< 8 hours	Non-critical, emergent. The patient's is physiologically stable but the surgical problem may undergo significant deterioration if left untreated.
< 24 hours	Non-critical, non-emergent, urgent. The patient's condition is stable. No deterioration is expected.
< 72 hours	Semi-urgent, not stable for discharge. The patient's condition is stable. No deterioration is expected but the patient is not suitable to be discharged.

3. The traffic light colour coding system (Finland)

Colour code	Priority/maximum allowed delay to surgery	Timing of surgery	Example
	 Start as soon as possible; Any hour of the day delay to surgery < 8 h	 Usually not between 22.00 and 08.00 hours	 Ruptured abdominal aortic aneurysm Perforated hollow viscus organ Acute appendicitis
	Early operation required; maximum delay 8–24 h	Usually not between 22.00 and 08.00 hours	Acute cholecystitis Acute adhesive small bowel obstruction (not strangulated)
	Non-elective operation required; maximum delay 24–48 h	Usually not between 22.00 and 08.00 hours	Skin grafting (open abdomen) Tracheostomy Cholecystectomy after mild biliary pancreatitis

All these models have the following features in common:

- An category and/or a colour code that assigns cases a variable degrees of urgency;
- An indication of time or maximum delay within which an emergency case must be operated upon;
- Examples of type of cases appropriate for each urgency category

The Groote Schuur Emergency Surgery Triage System (GSEST)

Colour Code	Urgency category	Parameters
Red	Immediate	Immediate life-saving operation, resuscitation simultaneous with surgical treatment e.g. resuscitative laparotomy, ruptured aortic aneurysm, threatened airway, cord prolapse, foetal bradycardia
Orange	Urgent	Operation as soon as possible after resuscitation (within 1 to 2 hours) - e.g. ruptured ectopic pregnancy, leaking aortic aneurysm, cranial decompression, positive DPL in multiple trauma, threatened limb
Yellow	Expedited	Operation within 6 hours of booking e.g. compound fractures, appendicitis, incarcerated hernia/intestinal obstruction, EUA for non-accidental injuries
Green	Emergent	Operation not immediately life or limb saving but to be done within 24 hours of booking e.g. ORIF of simple fractures, bleeding haemorrhoids, I&D abscess
Blue	Scheduled	Semi-urgent cases, to be done within 72 hours. Operation during in-hours on next available slate if possible

The GSEST was developed and introduced by the Department of Anaesthesia, Groote Schuur Hospital (GSH) in 2010. The system uses colour codes identical to those utilised by the South African Triage Scale (SATS), a triage tool used in all emergency units in South Africa.

In conjunction with the introduction of the urgency categorisation tool, the manual booking of cases on a white board was substituted by a computerised booking system with the GSEST colour coding of patients linked to an electronic display screen.

Reasons for the introduction of the GSEST mirrored those of other institutions using similar urgency categorisation tools, namely the inefficient use of emergency theatre, overburdened emergency surgical lists, a lack of adequate communication and conflict between members of the surgical and anaesthetic teams around issues of emergency list management and case prioritisation.

One aspect differentiates the GSESTs from other urgency categorisation tools. The GSESTs incorporate an ***anaesthetic triage registrar (ATR)*** as an addition to the emergency theatre team. At GSH, the anaesthetic triage registrar is usually a senior trainee in the final year of their specialist training. The ATR's role is to assess all emergency surgical cases as they are booked on the emergency list. Their function is to primarily ascertain anaesthetic risk and to suggest optimisation strategies on patients with co-morbid conditions that may have an effect on the conduct of anaesthesia. Management decisions are communicated and discussed with surgical colleagues responsible for the care of the patient in the ward. ATRs provide a continuum of contact between the patient, surgeon and the emergency theatre team. They effectively 'close the loop' on one of the factors that may impact negatively on patient outcome: communication breakdown between surgeons and the team responsible for running the emergency theatre.

Final thoughts

It is difficult to ascertain whether the use of urgency categorisation tools directly affect patient outcome. They are useful as management tools around which specific decisions are made concerning the timing of surgery for patients booked on an emergency list. Studies have shown time and again that the timing of emergency surgery has a significant impact on patient outcome for a variety of surgical conditions (e.g. acute appendicitis). Using these tools to effectively prioritise emergency cases ensures that scarce resources are used effectively and delay induced morbidity and mortality is curtailed.

References

On request

Notes

Sepsis stuff What's new?

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Sepsis is not a specific illness, but is a syndrome of physiological, pathological and biochemical abnormalities that are induced by infection. The true incidence is unknown, but it is, almost certainly, the leading cause of mortality and critical illness worldwide. The incidence of sepsis is increasing, due to a combination of aging populations, with more comorbidities, and greater recognition. In survivors, long term physical, psychological and cognitive disabilities have a significant impact on health care (recent estimates suggest it accounts for more than 5.2% of US hospital costs), as well as a costly social burden. Early recognition may result in improved outcomes, yet there remains no validated diagnostic test and no gold standard definition. An added challenge to diagnosing sepsis is that infection is seldom confirmed microbiologically by the time treatment is commenced – culture-positive sepsis is only found in 30-40% of cases. Although sepsis is a life threatening syndrome, the mortality rate from sepsis is decreasing, probably due to improved care of the septic patient: earlier antibiotics, lung protective ventilation, glycaemic control, increased intensivist staffing, more aggressive resuscitation, conservative fluid strategies. A recent study in JAMA⁽¹⁾ showed that from 2000 to 2012, the absolute mortality decreased from 35% to 18.4% (an annual rate of decrease of 1.3% and a relative risk reduction of 47.5%).

In February 2016, a new definition for sepsis and septic shock were proposed, and have come to be known as “Sepsis-3”. These definitions have caused controversy in the critical care community and the Sepsis-3 publications are a hot topic. Here is a recap of what's gone before and a reflection of how thinking has changed over the past 25 years. I will cover some of the older definitions of sepsis, as these terms are still frequently used, and I will highlight the process behind the 2016 definition.

History of Sepsis

In case you have some time on your hands, and have an interest in history...here is how it all began!

Sepsis was described over 2000 years ago - the term “Sepsis” was first introduced by Hippocrates (460-370 BC). Its origins are from the Greek word “Sipsi” which means to make rotten. The concept of septicaemia was described by Ibn Sina (979-1037 BC) where blood putrefaction was associated with fever. The modern view of sepsis is thanks to Ignaz Semmelweis (1818-1865), who recognised that puerperal sepsis was caused by “decomposed animal matter that entered the blood stream” and attributed this to medical students performing gynaecological examinations immediately after pathology class. By introducing handwashing in chlorinated lime solution prior to performing gynaecological examinations, he reduced the mortality rate from 18% to 2.5%. Tragically, his techniques and deductions were ridiculed and he was dismissed from his post in Vienna. Ironically, he died in a lunatic asylum from sepsis due to infected wounds, which had likely been inflicted upon him during his internment in the asylum. Louis Pasteur (1822-1895) discovered bacteria, and identified them as the organisms responsible for causing putrefaction. Joseph Lister (1827-1912) introduced sterilisation of equipment and his techniques were refined by Robert Koch (1843-1910) who introduced steam sterilising.

In 1914, the link between the source of infection as a cause of sepsis was made by Hugo Schottmüller (1867-1936) who stated that “Sepsis is present if a focus has developed from which pathogenic bacteria, constantly or periodically, invade the blood stream in such a way that this causes subjective and objective symptoms”.

Even today, with all the technology and investigations available, sepsis can be surprisingly difficult to define and there *still* is no “gold standard” definition. In 1991, a committee was convened with the goal of standardising the definition of sepsis. It was chaired by Roger Bone and has become labelled as “Sepsis-1”.

“Sepsis-1”⁽²⁾

What has been recently termed “Sepsis-1” is, in fact, the 1992 consensus document from the ACCP and SCCM (the American College of Chest Physicians and the Society of Critical Care Medicine). The document was entitled “Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis” and was convened to address the issue of terminology and definitions surrounding sepsis. Terms such as bacteraemia, septicaemia, septic shock and sepsis were being used interchangeably – causing confusion, and hampering the understanding of sepsis and its sequelae. This consensus document proposed a whole host of definitions, and was, perhaps, most famous for proposing the terms SIRS (Systemic Inflammatory Response Syndrome) and MODS (Multi Organ Dysfunction Syndrome). This document was drawn up by a panel of experts and, unlike the current definition, did not base the definitions on outcome data.

SIRS is the presence of **two or more of**:

- **Temperature** >38°C or <36°C
- **Heart rate** >90 beats/min
- **Respiratory rate** >20/min or PaCO₂ <32mmHg (4.3kPa)
- **White blood cell** count >12000/mm³ or <4000/mm³ (or 10% immature neutrophils (bands).

The changes seen in SIRS should represent an acute change from baseline, in the absence of other known causes for such abnormalities. SIRS may reflect an appropriate, adaptive, host response that may become damaging to the host.

SIRS is the term used to describe a systemic inflammatory response. The clinical response may be identical whether the precipitant is infectious, or non-infectious, in aetiology (e.g. burns, pancreatitis, polytrauma). When SIRS is due to a confirmed infectious process, it is termed **sepsis**. Thus, **sepsis is SIRS in response to an infection** (see Figure 1).

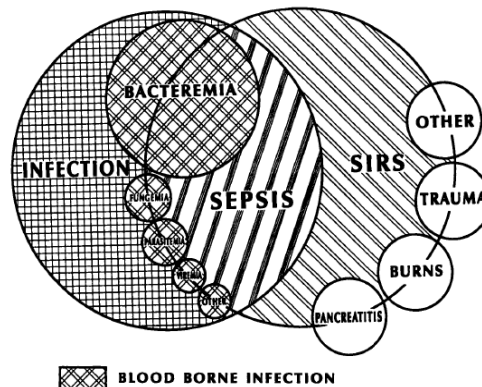


Figure 1. Relationship of SIRS, sepsis and infection.

From Bone R et al⁽²⁾ without permission.

The idea behind defining SIRS was to provide a practical approach for use in both clinical and research settings, since, up until this time, there was no uniformity for the definition of sepsis. SIRS is a clinical description, and there is concern that it may miss some septic patients who do not fulfil SIRS criteria (i.e. who are SIRS-negative). The danger lies in the fact that a SIRS-negative septic patient might be inappropriately investigated or treated.

Sepsis-1 stated that sepsis is the leading cause of death in non-coronary ICUs. Although, this is perhaps true, it is probably more accurate to blame the cause of death on the dysregulated response to infection, rather than the infection itself. The development of organ dysfunction (e.g. renal failure, acute lung injury) is a frequent complication of SIRS and has been termed MODS (multi-organ **dysfunction** syndrome). MODS occurs in about 30% of patients with sepsis, but it can also be due to a non-infective precipitant (where inflammatory mediators are the chief culprits). It is important to appreciate that the dysfunction may not be as a result from the infection itself, but rather from the generalised inflammatory reaction; i.e. the threat to life is less related to the underlying illness, and more to the progressive physiological deterioration of the interdependent organ systems. The term organ *dysfunction* has been chosen as it represents the state when organ function is no longer capable of providing homeostasis. Organ dysfunction may be absolute or relative i.e. the patient may have a cardiac output and oxygen delivery that are within “normal limits”, yet still has inadequate

tissue oxygenation. MODS replaced an earlier term "Multiple Organ Failure" which implied an irreversible state. MODS can be subdivided into:

- **Primary MODS:** when organ dysfunction is directly attributable to the insult – e.g. polytrauma with MODS due to pulmonary contusion, renal failure from rhabdomyolysis, coagulopathy from massive transfusion.
- **Secondary MODS:** where the organ dysfunction does not occur in direct response to the insult, but as a consequence of the host response. This usually evolves after a latent period following the inciting injury or event e.g. ARDS secondary to pancreatitis.

Other terms defined in the Sepsis-1 consensus include:

- **Infection:** a microbial phenomenon characterised by an inflammatory response to the presence of microorganisms, or the invasion of normally sterile host tissue by those organisms. (Quite clearly, this is far from a perfect definition. Consider, for example, infection with *Clostridium difficile* when colonic overgrowth may precipitate toxic megacolon. This is obviously an infection, but the colon is far from a sterile environment!!).
- **Bacteraemia:** the presence of viable bacteria in the blood. [Similarly applied terms include viraemia, fungaemia and parasitaemia].
- **Septicaemia:** presence of microorganisms or their toxins in the blood. *This term was felt to be outdated by Sepsis-1, who recommended that its use be eliminated.* And yet we still hear it on a daily basis, 25 years later! Don't let it come out of your mouth in a viva!! ;)

Sepsis-1 proposed that the clinical construct of sepsis should be seen as a continuum, in terms of the degree of severity. In order of severity they defined:

1. **Sepsis:** SIRS plus infection
2. **Severe sepsis:** sepsis associated with organ dysfunction, hypoperfusion abnormality or sepsis-induced hypotension. Hypoperfusion abnormalities include lactic acidosis, oliguria and acute alterations of mental status.
3. **Sepsis-induced hypotension:** systolic blood pressure (sBP) <90mmHg or a reduction of ≥ 40 mmHg from baseline, in the absence of other causes for hypotension (e.g. cardiogenic shock). Sepsis-induced hypotension is a subset of severe sepsis.
4. **Septic shock:** sepsis-induced hypotension that persists despite adequate fluid resuscitation, along with presence of hypoperfusion abnormalities or organ dysfunction.

CARS, MARS, SIRS and CHAOS

– a new hypothesis for the pathogenesis of the disease process ⁽³⁾

This article proposed adding new terms to describe the systemic reaction to sepsis: in addition to SIRS, these includes compensatory anti-inflammatory response syndrome (CARS) and mixed antagonists response syndrome (MARS) to the set of clinical definitions developed in Sepsis-1. Simply put, SIRS is a proinflammatory condition, CARS is an anti-inflammatory state, and MARS is a mixed pro- and anti-inflammatory state. These ultimately can lead to CHAOS:

Cardiovascular compromise / shock – SIRS predominates
Homeostasis – a balance between CARS and SIRS (i.e. MARS)
Apoptosis (cell death) – death with minimal inflammation
Organ dysfunction – SIRS predominates
Suppression of the immune system – CARS predominates

Roger Bone, the chair of the Sepsis-1 consensus committee, and widely revered as the father of sepsis in the modern era, was the lead author in this landmark publication from 1997. Up until this period much of the focus had been on sepsis being, predominantly, a state of proinflammation. This led to a slew of anti-inflammatory agents being tested in clinical trials of SIRS and sepsis, many of which had negative, or even harmful, results. The failure of such clinical trials would suggest that "non-proinflammatory responses" might play a role in the human setting (e.g. compensatory anti-inflammatory responses and mixed pro- and anti-inflammatory responses), this would explain why targeting anti-inflammatory agents did not translate into clinical benefit. This article highlights the complexity of the sepsis process and suggests that it involves an imbalance between pro- and anti-inflammatory responses. It also explains that proinflammatory mediators are not just "bad guys" and that lower levels of proinflammatory mediators are crucial to combat pathogens and promote healing.

Sepsis-1 introduced the concept that MODS may result from a generalised inflammatory response,

rather than solely from the infection. By 1997 it was recognised that the common pathway underpinning MODS was systemic cytokine release precipitating a massive inflammatory reaction. Identifying a specific cytokine as the culprit has been impossible, and it was appreciated that cytokine release is an important, **appropriate** response to infection, with a subtle balance of both pro- and anti-inflammatory mediators that keep each other "in-check". Failure to achieve homeostasis is due to an imbalance between the pro- and anti-inflammatory mediators; this will result in either predominantly a proinflammatory reaction (SIRS), or a compensatory anti-inflammatory reaction (CARS); both of which have clinical sequelae, termed CHAOS.

Sepsis-1 was correct in its assumption that there is a massive inflammatory response underlying both SIRS and MODS; but it would appear that, early on, after the initial release of proinflammatory mediators, there is a compensatory anti-inflammatory reaction (CARS), that may even exceed the proinflammatory response in magnitude. The CARS response can be seen as an attempt to damp down the inflammatory excess. Using an anti-inflammatory agent either during a necessary proinflammatory phase, or during the CARS phase, may cause harm and could explain why treating sepsis with an anti-inflammatory agent has never been successful. Such a simplistic treatment approach fails to take cognisance of the body's attempt to restore homeostasis. It was proposed that, in most people, the body can achieve a balance between pro- and anti-inflammatory mediators, thereby restoring homeostasis. However, in some patients, this balance is not achieved and this results in MODS and potential tissue damage.

Bone proposed 5 stages to the development of MODS:

1. Local reaction at the site of infection / injury
2. Early systemic response
3. Massive systemic inflammation
4. Excessive immunosuppression
5. Immunologic dissonance.

Stage 1.

The initial response to the injury/infection is the development of a proinflammatory state, localised to the area of damage, designed to limit new damage and heal the existing damage. This is shortly followed by a localised compensatory anti-inflammatory response, the aim of which is to limit the proinflammatory mediators to ensure that they do not cause harm.

Stage 2.

There is spill-over of proinflammatory mediators into the systemic circulation, this is part of the normal response to infection. It is suggested that this spill over is a signal that the local environment is unable to contain the insult and there is stimulation of the compensatory systemic anti-inflammatory response. Organ dysfunction is rare in this stage.

Stage 3.

Failure to regulate the proinflammatory response results in a systemic reaction, or SIRS. This is characterised by endothelial dysfunction, activation of the coagulation system, vasodilatation and shock. Organ dysfunction will result unless homeostasis can be quickly restored.

Stage 4.

Immunoparesis has been described in sepsis, and it is likely that this occurs due to an inappropriate compensatory anti-inflammatory reaction syndrome (CARS), leading to marked immunosuppression. CARS is characterised by the reduced expression of human leucocyte antigen (HLA)-DR expression, to <30% of normal.

Stage 5.

The final stage of MODS is termed "immunologic dissonance", which is an inappropriate response of immunomodulation and may be caused by either overwhelming inflammation, or persistent immunosuppression; both of which lead to an increased risk of death.

“Sepsis-2” (4)

Sepsis-2 is the consensus definition proposed from a conference involving several European and North American Societies (the International Sepsis Definitions Conference, convened in 2001). The rationale behind the conference was that, in the 10 years since Sepsis-1, there had been great progress in the understanding of the pathophysiology and pathobiology of sepsis, and it was felt, in the light of such advances, that the Sepsis-1 definitions needed major revision.

The conference findings were published in 2003 and, interestingly, opined that the 1991 Sepsis-1 concepts were robust definitions, and that introducing biomarkers to help to define and diagnose sepsis was premature. In essence, it means that they didn't think that Sepsis-1 needed changing!

However, the Sepsis-2 group raised concerns that the SIRS criteria was too non-specific to be useful in the diagnosis of sepsis and published an expanded list of possible signs and symptoms of systemic inflammation that reflected clinical experience (see Table 1). However, the group concluded that none of the signs/symptoms is specific for sepsis.

Table 1. Diagnostic criteria for sepsis

Infection	Documented or suspected or some of the following:
General variables	Fever (core temperature $>38.3^{\circ}\text{C}$)
	Hypothermia (core temperature $<36^{\circ}\text{C}$)
	Heart rate $>90/\text{min}$ or $>2\text{SD}$ above normal value for age
	Tachypnoea
	Altered mental status
	Significant oedema or positive fluid balance ($>20\text{mL/kg}$ over 24 hours)
	Hyperglycaemia (plasma glucose $>7.7\text{mmol/L}$) in the absence of diabetes
Inflammatory variables	Leucocytosis (white cell count $>12\,000/\mu\text{L}$)
	Leucopaenia (white cell count $<4000/\mu\text{L}$)
	Normal white blood cell count with $>10\%$ immature forms
	Plasma C-reactive protein (CRP) $>2\text{SD}$ above normal
	Plasma procalcitonin (PCT) $>2\text{SD}$ above normal
Haemodynamic variables	Arterial hypotension (sBP $<90\text{mmHg}$, MAP $<70\text{mmHg}$, or an sBP decrease of $>40\text{mmHg}$ in an adult, or $<2\text{SD}$ below normal for age)
	Mixed venous saturation $>70\%$
	Cardiac index $>3.5\text{L/min/m}^2$
Organ dysfunction variables	Arterial hypoxaemia ($\text{PaO}_2/\text{F}_2\text{O}_2 <300$)
	Acute oliguria (urine output $<0.5\text{mL/kg/h}$ or 45mmol/L for at least 2h)
	Creatinine increase $>0.5\text{mg/dL}$ ($>44.2\mu\text{mol/L}$)
	Coagulation abnormalities (INR >1.5 or aPTT $>60\text{secs}$)
	Ileus
	Thrombocytopenia (platelet count $<100\,000/\mu\text{L}$)
	Hyperbilirubinaemia (plasma total bilirubin $>70\text{mmol/L}$)
Tissue perfusion variables	Hyperlactataemia ($>1\text{mmol/L}$)
	Decreased capillary refill or mottling

Perhaps the main recommendation of Sepsis-2 was the development of a staging system for sepsis, which they termed PIRO. PIRO is a mnemonic for:

- **Predisposing conditions**
 - E.g. pre-existing state of health, genetics, religious and cultural factors, sex and age; all of which may influence both incidence and outcome and the approach towards therapy.
- **Infection / insult**
 - Site of infection, extent of infection (e.g. bilateral pneumonia is likely to be more severe than localised pneumonia), infecting organisms (the host response to gram negative organism differs from the response to gram positives).
- **Response of the host**
 - SIRS, shock, other signs of sepsis
- **Organ dysfunction**
 - The need for a qualitative description of the development and progression of organ dysfunction (e.g. Sequential Organ Failure Assessment (SOFA) score). Sepsis-2 went on to recommend the use of a scoring system, such as SOFA, when defining organ dysfunction.

I have to admit, I have found little utility for PIRO – it's quite a nice framework, but with little practical use and it never really took off in critical care.

The Surviving Sepsis Campaign Guidelines⁽⁵⁾

The Surviving Sepsis Campaign Guidelines (SSCG) were initially released in 2001, and most recently expanded in 2012. Unlike Sepsis-1 and -2, these guidelines proposed a framework for the treatment and management of the septic patient. The 2001 guideline (and its expansion) were in an attempt to curb the high mortality seen with severe sepsis and septic shock (in excess of 25%). These guidelines did not make any alterations to the definitions in Sepsis-1 and -2, but they made a distinction between *definitions* and *therapeutic targets*.

For example:

- Septic induced hypotension is **defined** as sBP <90mmHg, or MAP <70mmHg, or a decrease in sBP >40mmHg (or less than 2 SD below normal for age) in the absence of other causes of hypotension. However, the **therapeutic target** is a MAP threshold $\geq$ 65mmHg.

I will not expand further upon the Surviving Sepsis Campaign Guidelines (they are a lecture in their own right), but I do suggest that you familiarise yourself with them!

Summary so far:

- 1991 consensus conference ("Sepsis-1") – sepsis resulted from hosts response (SIRS) to infection, introduced MODS and proposed definitions for infection and its sequelae. The idea behind the definition SIRS was to provide a practical approach that could be used in both clinical and research settings, as, up until this time, there was no uniformity as to the definition of sepsis.
- 1996 – CARS, MARS, SIRS and CHAOS proposal reflected on the pathobiology of sepsis.
- 2001 task force ("Sepsis-2") – recognised limitations with the 1991 definitions, expanded list of diagnostic criteria but did not offer alternatives because of the lack of supporting evidence. Introduced the concept of PIRO.
- 2001 & 2012 - Surviving Sepsis Campaign Guidelines introduced therapeutic targets for the treatment of septic shock.

ICU Scoring Systems

Before I continue with the sepsis story to date, I need to introduce the concept of scoring systems, so that the newest guidelines make sense! Multiple scoring systems are utilised in the critically ill patients; examples include:

- **Outcome prediction models** such as APACHE I-IV (Applied Physiology and Chronic Health Evaluation) and SAPS II (Simplified Acute Physiology Score).
- **Organ dysfunction scores** such as LODS (Logistic Organ Dysfunction System), MODS (Multi Organ Dysfunction Score) and SOFA (Sepsis-related Organ Failure Assessment Score).
- **Severity assessment scores based on workload** such as TISS (Therapeutic Intervention Scoring System) and NAS (Nursing Activities Score).

Scores may be useful to predict outcome, quantify the severity of organ dysfunction and disease, and help to assess resource use. They are widely used in benchmarking, auditing and research. Such scoring systems have been used to predict mortality for individual patient use, but care must be taken with this extrapolation: remember, they have been designed in particular patient subgroups and geographical locations, and may not be generalisable to an individual patient in your ICU. Although organ dysfunction scores (such as SOFA) may correlate with outcomes, this is not the purpose for which they were developed. APACHE and SAPS are more appropriate tools for predicting outcomes. They are far better at predicting outcome for a population than for individual patients.

SOFA score⁽⁶⁾

For the purpose of this lecture, the SOFA score (Sepsis-related Organ Failure Assessment) needs to be expanded upon. It was first described in 1996 and you can see from the acronym expansion that the SOFA score was originally designed for application to septic patients, although it is widely applied to non-septic patients. The intention behind the design of SOFA was not to predict outcome, but to

rather describe a sequence of complications in the critically ill. It is frequently used as a daily tool in the critically ill to chart the patient's progress. 6 organ systems (neurologic, cardiovascular, respiratory, coagulation, renal, hepatic – note: there is no score assigned for gastrointestinal dysfunction) are scored from 0 to 4, depending on the degree of dysfunction in each system, where 0 is normal organ function and 4 is the most severely deranged organ function (see Table 2). The total score can range from 0 to 24 and is determined by the worst value in each 24-hour period.

Table 2. SOFA score (1996) ⁽⁶⁾

SOFA score	1	2	3	4
Respiration: PaO ₂ / F _i O ₂ (mmHg)	<400	<300	<200 With respiratory support	<100 With respiratory support
Coagulation: Platelets x10 ³ /mm ³	<150	<100	<50	<20
Liver: Bilirubin (μmol/L)	20-32	33-101	102-204	>204
Cardiovascular*: Hypotension	MAP<70mmHg	Dopamine ≤5, or dobutamine (any dose)	Dopamine >5, or adrenaline or noradrenaline ≤0.1	Dopamine >15, or adrenaline or noradrenaline >0.1
Central nervous system: Glasgow Coma Score	13-14	10-12	6-9	<6
Renal: Creatinine (μmol/L) or urine output	110-170	171-299	300-440 or <500ml/day	>440 or <200ml/day

* Adrenergic agents administered for at least 1h (doses in μg/kg/min)

So...now what?

It is apparent from the above summary that the definition of infection and its sequelae have remained static for over 20 years, despite considerable inroads into the understanding of sepsis.

What have been the recent concerns and considerations? Many of the issues arise from the fact that SIRS criteria play such a big role in the definition of sepsis. It has been frequently demonstrated that the presence of SIRS is almost ubiquitous in hospitalised patients – this includes benign conditions which may or may not be related to the presence of infection. More concerning, however, is that SIRS may miss some septic patients who do not fulfil SIRS criteria (i.e. are SIRS-negative, but have severe sepsis). Since sepsis has such a high mortality, it's a disaster if a septic patient who is SIRS-negative is inappropriately treated, hence it needs a definition that is **extremely sensitive** so that septic patients are not missed. A retrospective study of the ANZICS ICU adult database was performed by Kaukonen et al (2015) ⁽⁷⁾, looking at over 100 000 patients with infection and organ failure. They found that, when sepsis is defined using 2 or more SIRS criteria, it excludes 1 in 8 similar patients (with organ failure and infection) who have SIRS-negative sepsis. Surprisingly, despite the fact that these patients might have a delay in appropriate treatment, they had a lower (but still substantial) mortality when compared to patients with SIRS-positive sepsis (8.5% mortality if SIRS-negative compared to 18.3% mortality if SIRS-positive in data from 2013). Prior to the Kaukonen study it was believed that using SIRS criteria to define severe sepsis was associated with an excellent sensitivity but low specificity (i.e. it was designed to have good *face validity*). The Kaukonen study demonstrates that SIRS criteria lacks both specificity and sensitivity for diagnosing severe sepsis.

Remember:

Sensitivity: the ability of a test to recognise true positives

Specificity: the number of true negatives correctly identified

For a condition with a high mortality (such as sepsis), a high sensitivity would be more important than a high specificity, to ensure that cases aren't missed. However, SIRS was never designed to be specific – this is part of the reason that the Sepsis-2 greatly expanded the diagnostic criteria to include other indicators of infection, such as biomarkers!

Further criticisms for SIRS come from the apparent arbitrary cut-off for ≥2 of the SIRS criteria used to define sepsis. Why ≥2? One might think that, if 2 SIRS criteria were significant, the odds ratio for mortality would markedly increase once 2 criteria are reached (i.e. when the definition of SIRS is met).

This is not the case. Mortality increases 13% with each additional SIRS criteria, without a transitional increase when SIRS is met (Figures 2 and 3). This suggests that SIRS lacks **construct validity** – it does not reflect the severity of the disease process.

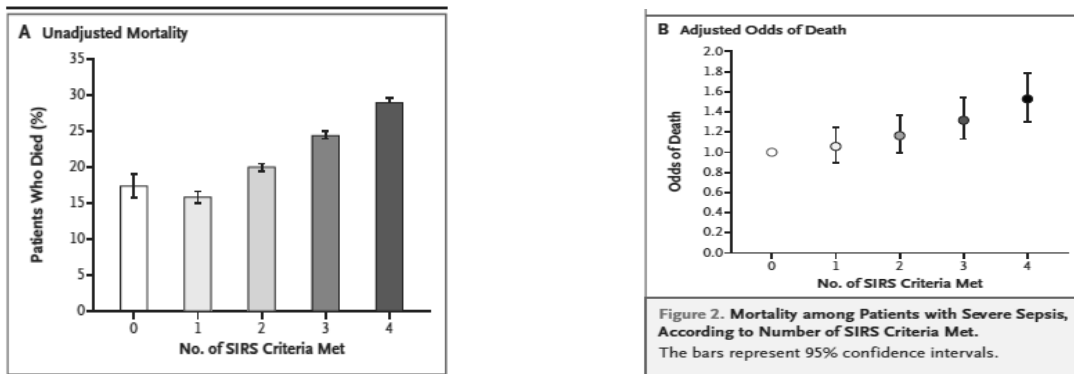


Figure 2 and 3. Unadjusted and adjusted mortality according to number of SIRS criteria.

Notice that when 2 criteria is reached, there is no marked increase in mortality.

Taken, without permission from Kaukonen KM et al ⁽⁷⁾.

Concerns with old definitions:

1. SIRS-negative sepsis may be missed
 - 1 in 8 patients with infection and organ dysfunction are missed, as the criteria is not sufficiently sensitive
 - In addition, it is estimated that 4 out of 5 ICU patients have SIRS criteria in the absence of infection.
2. Arbitrary cut off of ≥ 2 SIRS criteria.
3. SIRS terminology does not provide any explanation for the understanding of the disease process (i.e. it lacks face validity), and the parameters are arbitrarily simplified (e.g. heart rate of 90/min is not a physiologically significant threshold).
4. Previous definitions don't consider advances in the understanding of pathophysiology and epidemiology.
5. Previous definitions (in the words of Mervyn Singer) "describe a vague syndrome without pinning down what we mean at the bedside – lack of standardisation and much confusion".

In 2015 a task force of experts was assembled from the European Society of Intensive Care Medicine and the Society of Critical Care Medicine with the aim of standardising sepsis definitions that would be applicable to both clinical practice and research. The brief was to **differentiate sepsis from uncomplicated infection** and to update definitions of sepsis and septic shock so that they were consistent with the improved understanding of the pathobiology of sepsis. In February 2016, a series of articles was published in JAMA. These 3 articles form what has become termed "Sepsis-3".

The first article described the development of the new definition:

Developing a new definition and assessing new clinical criteria for septic shock. For the 3rd international consensus definition for sepsis and septic shock (Sepsis-3)

Shankar-Hari M et al. JAMA 2016; 315(8):775-787 ⁽⁸⁾

The strength behind the new definition is that it is more evidence based than the previous 2 iterations (Sepsis-1 and -2), which were largely developed by expert conjecture. The 2016 consensus definition includes a systematic review and meta-analysis to complement expert deliberations.

The systematic review showed that there was great variability in the criteria that is currently used to identify septic shock; and the meta-analysis demonstrated heterogeneity in mortality. After the systemic review, the Delphi process was used to reach a consensus definition of septic shock and related clinical criteria. The Delphi method is, in essence, a communication technique which uses a panel of experts who answer questionnaires in multiple rounds in order to achieve a majority

agreement. The Delphi method was used to come up with the clinical variable that should be used in the definition of sepsis and septic shock. These variables then were tested and validated in cohort studies (see Seymour paper⁽⁹⁾).

The second article explains how the clinical criteria were assessed prior to being recommended in the new consensus document:

Assessment of Clinical Criteria for sepsis for the 3rd International Consensus Definition for Sepsis and Septic Shock (Sepsis-3)

Seymour CW et al. JAMA 2016; 315(8):762-774⁽⁹⁾

In the assessment of clinical criteria, there were 4 steps:

1. 1.3 million electronic health records from Southwest Pennsylvania were scrutinised in order to identify patients with suspected infection.
2. From this cohort, clinical variables were identified which could be used to define sepsis.
3. These clinical variables were grouped into a novel set of criteria which could easily be identified at the bedside. This novel set of criteria became termed qSOFA (quick SOFA).
4. qSOFA was then validated in hospital cohorts, looking at how it would predict in-hospital mortality, or ICU length of stay ≥ 3 days.

The premise is that qSOFA can **identify sepsis amongst patients with suspected or confirmed infection**. In this way, we can recognise which patients are at increased risk of dying from their infection. The qSOFA score is comprised of 3 variables:

- **Respiratory rate ≥ 22 breaths/min**
- **Glasgow Coma Scale ≤ 13** (note that this has been changed in the final construct of qSOFA)
- **Systolic Blood Pressure ≤ 100 mmHg**

1 point is scored for each of the above variables, with a range of scores from 0-3. Interestingly, and perhaps somewhat surprisingly, during the model building of the novel set of criteria, serum lactate did not meet the pre-specified statistical thresholds for inclusion in qSOFA, and did not improve the predictive ability of qSOFA.

qSOFA was compared against 3 other scoring systems for its ability to predict in-hospital mortality. These scoring systems were SIRS, SOFA, and Logistic Organ Dysfunction System (LODS). The ability of qSOFA to predict mortality, depended on whether the cohorts were in ICU, or outside ICU:

- Outside the ICU, in patients with suspected infection, the predictive validity for in-hospital mortality of qSOFA was statistically greater than SOFA, SIRS and LODS. The area under the receiver operating curve (AUROC) for qSOFA was 0.81 (95%CI 0.80-0.82), which was greater than SOFA (AUROC 0.79; 95%CI 0.78-0.80; $p < 0.001$).
- In ICU patients with suspected infection, the predictive validity for in-hospital mortality of SOFA was not significantly different than the more complex LODS, but was statistically greater than SIRS and qSOFA. AUROC for qSOFA 0.66 (95%CI 0.64-0.68) vs SOFA (AUROC 0.74; 95%CI 0.73-0.76; $p < 0.001$)

What this means is that **qSOFA is better at predicting in-hospital mortality in patients with suspected infection who have not yet been admitted to ICU** when compared to 3 other scoring systems. Within the ICU cohort, qSOFA is better at predicting mortality than SIRS, but is not as good as SOFA. Why does qSOFA underachieve in ICU patients? This may be because, in the critically ill patient, sepsis is difficult to diagnose because of pre-existing organ dysfunction, treatments administered prior to admission to ICU, and ongoing organ support (use of vasopressors, sedation and mechanical ventilation). The SOFA score should be used to predict in-hospital mortality in patients with suspected infection who are in the ICU. SIRS performs badly in predicting mortality in patients both in, and out of, the ICU.

In patients outside ICU, in-hospital mortality is increased 3-14x if they have ≥ 2 qSOFA points, compared to patients with < 2 qSOFA points. This led to the task force recommending the use of qSOFA in non-ICU settings. Patients with ≥ 2 qSOFA points are at greater likelihood of having an adverse outcome, and this should act as a flag to increase monitoring in this group. The greater the qSOFA score, the greater the likelihood of death:

- 1 criterion: 2-3% risk of death
- 2 criteria: 8% risk of death
- 3 criteria: $> 20\%$ chance of death

Strengths of qSOFA are that it aids in the early recognition of sepsis (which is crucial since early

detection and treatment are vital). Its simplicity lies in the fact that it is a clinical diagnosis and can readily be done at the bedside, without relying upon laboratory values that may not be readily available, either due to resources or a delay in obtaining the results.

Note that, a popular mnemonic for qSOFA is **HAT**

- Hypotension
- Altered mental state
- Tachypnoea

The third article proposes the new definitions and recommendations:

3rd International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Singer M et al. JAMA 2016; 315(8): 801-810 ⁽¹⁰⁾

The task force concluded that the previous definitions were inadequate. The old definition using SIRS criteria focussed on inflammatory excess and the misleading assumption that sepsis follows a continuum through severe sepsis to shock. SIRS is inadequate (in terms of sensitivity and specificity) for being the basis on which to define sepsis. It's now well established that both pro- and anti-inflammatory responses are activated early in sepsis and that non-immunological pathways also play a major role. SIRS does not necessarily indicate a dysregulated, life-threatening response, as it has poor discriminatory ability (it is present in many hospitalised patients who do not develop an infection, or have a bad outcome). SIRS should no longer be used to identify septic patients.

The new definitions and recommendations:

- **Sepsis: life-threatening organ dysfunction caused by a dysregulated host response to infection.**
 - They even introduced a definition for the lay public! "Sepsis is a life-threatening condition that arises when the body's response to infection injures its own tissues".
 - **Organ dysfunction:** an increase in the total SOFA score of ≥ 2 points. This is associated with a mortality of $>10\%$. It should be assumed that the baseline SOFA score is 0, unless the patient is known to have pre-existing organ dysfunction prior to the onset of infection (note that the pre-existing dysfunction may be either acute, or chronic).
 - The new clinical criteria for sepsis is: **suspected or documented infection and an acute increase of ≥ 2 SOFA points** (where SOFA score is a proxy for organ dysfunction).
- **Septic shock:** a subset of sepsis with profound circulatory, cellular, and metabolic abnormalities and associated with a higher risk of mortality than sepsis alone. Clinically identified by the need for vasopressors to maintain a MAP ≥ 65 mmHg, and serum lactate level >2 mmol/L in the absence of hypovolaemia. This is associated with an in-hospital mortality of $>40\%$. (Previous consensus definitions of 1991 and 2001, described septic shock as a state of cardiovascular dysfunction associated with infection and unexplained by other causes).
- The terms **severe sepsis, sepsis syndrome and septicaemia**, should no longer be used. Severe sepsis is now redundant in the new framework, as the new definition of sepsis incorporates the old definition of severe sepsis.
- qSOFA is ≥ 2 of:
 - Systolic blood pressure ≤ 100 mmHg
 - Altered mentation (GCS <15)
 - Respiratory rate ≥ 22 /min

Note that the final recommendation for qSOFA was to use altered mentation (rather than a GCS ≤ 13 , as used in the Seymour paper). Predictive validity of qSOFA was unchanged when a GCS <15 was used, and it simplifies the score further. Outside of the ICU (for example in the emergency department, out-of-hospital, or in general hospital wards), qSOFA should be used to **screen patients with suspected infection who are likely to develop sepsis** (by definition, sepsis is a complication of infection and is associated with a poor outcome).

qSOFA is ideal for use in the pre-ICU environment as it is based on clinical variables and does not rely on laboratory testing (such as is necessary with SOFA). A positive qSOFA, should be a bedside prompt to the clinician to place the patient where they can be more closely monitored (e.g. in and ICU) and to ensure adequate and timely treatment. **A full SOFA score can then be performed.**

- Infection should be suspected in any patient with unexplained organ dysfunction.

The beauty of qSOFA is its ability to be easily measure outside the ICU, e.g. by nurses, paramedics etc. and enables the rapid detection of the at risk patient. However, it must be emphasised that both qSOFA and SOFA are not intended to be stand-alone definitions of sepsis. If severe infection is suspected and ≥ 2 qSOFA or >2 SOFA criteria are not present, further investigations or treatment of infection should not be delayed whilst waiting for the patient to become qSOFA-positive!

In the definitions of septic shock, hyperlactataemia is a marker for disease severity; higher levels of lactate predict mortality. Although lactate reflects cellular dysfunction or metabolic stress in sepsis, it also occurs under other circumstances such as: hepatic dysfunction (lactate is, in part, cleared by the liver), accelerated glycolysis (e.g. as seen with exogenous use of adrenaline and other β -adrenergic agents), impaired aerobic respiration and inadequate tissue oxygen delivery. Hence lactate is sensitive, but not specific.

The Sepsis-3 criteria for septic shock are:

- **fluid resistant hypotension**
- **the need for vasopressors**
- **hyperlactataemia $>2\text{mmol/L}$**

In the Surviving Sepsis Campaign Guidelines database, the presence of all 3 criteria (and a lactate of $>4\text{mmol/L}$, which is the value used in SSCG) is associated with an in-hospital mortality rate of 49.7%, if a serum lactate of $>2\text{mmol/L}$ is used (as in Sepsis-3), the mortality rate is 42.3%.

The guidelines proposed a framework in which qSOFA can help to detect patients with sepsis and septic shock (Figure 4).

Figure. Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock

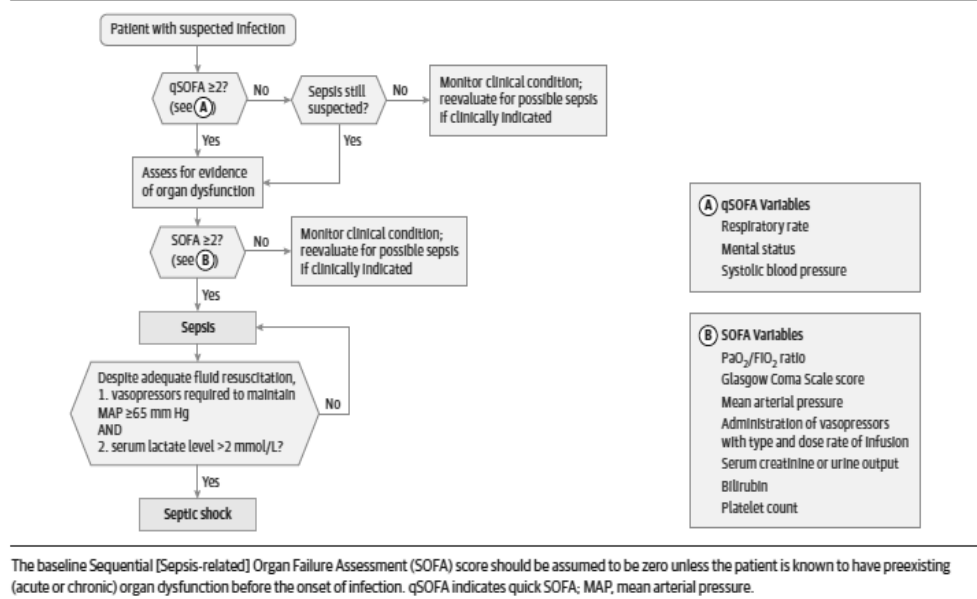


Figure 4. The proposed clinical model of identifying patients with sepsis and septic shock. From Singer et al ⁽¹⁰⁾, without permission.

Limitations of qSOFA include the need for prospective validation in other countries, the initial validation was performed, retrospectively in the US and Germany. It must also be recognised that the recommendations are for adult patients only.

Remember: qSOFA is not used to detect infection. It should be used in patients outside of the ICU setting, in whom an infection is suspected. It predicts which of these patients are at risk of developing sepsis and dying. Importantly, if you are concerned that a patient has a severe infection, you should not withhold treatment for sepsis just because the criteria for qSOFA are not reached.

Criticisms of Sepsis-3, and the future ^(11,12)

As mentioned above, whether or not Sepsis-3 is applicable to settings outside the US remains to be validated. There has yet to be a prospective validation of Sepsis-3 in any setting.

Not every patient with a positive qSOFA should be treated for sepsis – for example, patients with a pulmonary embolus, fat embolism syndrome or pancreatitis would also have a positive qSOFA score (a similar lack of specificity was also a criticism of the SIRS criteria).

qSOFA may over-estimate the mortality associated with pneumonia. The CURB65 score is a well validated prognostic model for community acquired pneumonia. CURB65 score points for

- **C**onfusion
- **U**rea >7mmol/L
- **R**espiratory rate >30/min
- **B**lood pressure (systolic BP<90mmHg or diastolic BP ≤60mmHg)
- **≥65** years of age

The CURB65 score ranges from 0-5, with respective mortality rates of 0.6% to 28%.

By way of example: if a patient has normal mental status, urea of 5mmol/L, respiratory rate of 25 breaths/minute, BP of 95/65 and is 60 years old, they score 2 on qSOFA (with a mortality rate of 8%) but on CURB65 they score 0 (predicted mortality of 0.6%) and could be sent home on oral antibiotics.

Following the Kaukonen paper ⁽⁷⁾ (as earlier described) SIRS was highly criticised for lack of sensitivity. However, although SIRS misses 1 in 8 patients with sepsis, it picks up 7 out of 8 (88%) – it has been proposed that this should be interpreted as being highly sensitive for organ dysfunction! Due to the high mortality associated with sepsis, a high sensitivity is more desirable than specificity, and it is argued that SIRS should still be used to alert the physician to the possibility of life threatening organ dysfunction.

The requirement of 2 qSOFA points will likely select a more severely ill group of patients, this may be detrimental in middle and low income countries where there are huge efforts to try to raise awareness of sepsis, and to treat early - early intervention in severe infection might be delayed whilst waiting for two qSOFA points to be reached. In these settings, patients with, for example, isolated hypotension, or a reduced level of consciousness, will be classified as uncomplicated infection and therapy may be delayed.

An elevated lactate level is now only used to define septic shock, and is not part of the organ dysfunction criteria used to define sepsis. This supposition would suggest that patients with hyperlactataemia, but without hypotension, are not at a higher risk of death!

Although it is nice to have a consensus definition, a problem with this definition is that it isn't clinically useful. Quite clearly, Sepsis-3 is a work in progress, and, as our knowledge increases (and the hunt for new diagnostics continues), definitions will likely be expanded in the forms of Sepsis-4 and further sequels! It already appears that including changes in mental state adds very little value to qSOFA, thus further simplification of the index may ensue.

In the light of the new definitions, it is now unclear how we should interpret previous studies that used older definitions (for example: Rivers' Early Goal Directed Therapy in Sepsis study, and the trio of publications that followed it, ProCESS, PROMISE and ARISE).

At the crux of the current definitions of sepsis and septic shock is the presence of infection. Confirming infection can be exceptionally difficult and negative microbiological cultures are common in patients who, clinically, have sepsis. New technologies such as mass spectrometry and Matrix-Associated Laser Desorption Ionisation-Time of Flight(!!) (MALDI-TOF) will hopefully enhance our ability to diagnose infection. Hopefully, in the future, a genomic approach will be established to provide rapid microbial diagnostics, biomarkers will likely play a role.

What I need to know...in a nutshell

SIRS is the presence of **two or more of**:

- **Temperature** >38°C or <36°C
- **Heart rate** >90 beats/min
- **Respiratory rate** >20/min or PaCO₂ <32mmHg (4.3kPa)
- **White blood cell** count >12000/mm³ or <4000/mm³ (or 10% immature neutrophils (bands))

The old definitions:

- **Sepsis:** SIRS plus infection
- **Severe sepsis:** sepsis associated with organ dysfunction, hypoperfusion abnormality or sepsis-induced hypotension. Hypoperfusion abnormalities include lactic acidosis, oliguria and acute alterations of mental status.
- **Sepsis-induced hypotension:** sBP<90mmHg or a reduction of ≥40mmHg from baseline, in the absence of other causes for hypotension (e.g. cardiogenic shock). Sepsis-induced hypotension is a subset of severe sepsis.
- **Septic shock:** sepsis-induced hypotension that persists despite adequate fluid resuscitation, along with presence of hypoperfusion abnormalities or organ dysfunction.

Sepsis was defined as SIRS in response to infection. This definition has recently been challenged because SIRS is felt to lack sensitivity. The concern is that SIRS-negative patients may not be treated for severe infection.

The new definition (Sepsis-3)

- **Sepsis: life-threatening organ dysfunction caused by a dysregulated host response to infection.**
- **Septic shock:** a subset of sepsis with profound circulatory, cellular, and metabolic abnormalities are associated with a higher risk of mortality than sepsis alone. Clinically identified by the need for vasopressors to maintain a MAP ≥65mmHg, and serum lactate level >2mmol/L in the absence of hypovolaemia. This is associated with an in-hospital mortality of >40%.
- The terms **severe sepsis, sepsis syndrome and septicaemia**, should no longer be used.
 - The term sepsis is now reserved for what was previously known as severe sepsis.
- qSOFA should be used to predict which patients with an infection are at high risk of complications / dying.
- qSOFA is ≥2 of the following
 - Systolic blood pressure ≤100mmHg
 - Altered mentation (GCS<15)
 - Respiratory rate ≥22/min
- qSOFA should be used to prompt the clinician to perform further tests and to move the patient to an area where they can be monitored closely for signs of deterioration.

qSOFA **does not** mean that infection should not be treated until the qSOFA reaches 2 – Sepsis-3 introduces new definitions; it does not make assumptions or recommendations about treatment.

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Notes

ECG Interpretation

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Notes

Notes

Anaesthesia for Tonsillectomy

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ANAESTHESIA FOR TONSILLECTOMY

Tonsillectomy remains one of the commonest surgeries performed during childhood. The predominant indication is for sleep disordered breathing (SDB), and in particular obstructive sleep apnoea (OSA). In our approach to anaesthesia for tonsillectomy we can consider the following questions:

- How can we identify those patients at increased risk of adverse events in the peri-operative period who require in-patient admission?
- What is the optimal anaesthetic technique for a tonsillectomy?
- What are the anaesthetic challenges surrounding the child with bleeding post-tonsillectomy?

IDENTIFYING PATIENTS AT INCREASED RISK OF PERI-OPERATIVE ADVERSE EVENTS

Whilst the overall mortality from adenotonsillectomy remains low, recent studies have reported a number of cases where children have died within the first 24 hours post surgery in the post anaesthesia care unit (PACU), on the ward, and at home [Cote, 2015]. Although deaths due to haemorrhage may not be preventable, the concern relates to death, due to apnoea, which should be entirely preventable with appropriate monitoring and intervention.

The American Academy of Paediatrics has issued guidelines [Marcus *et. al.*, 2012] regarding the diagnosis and management of patients with obstructive sleep apnoea following a review of over 3000 articles. They have defined high-risk patients as the following:

- Age < 3 yrs
- Severe OSA on polysomnography (oxygen saturation <80% during polysomnography or postsurgery or apnoea/hypopnea index > 24 per hour)
- Cardiac complications related to OSA
 - Right ventricular hypertrophy
 - Pulmonary hypertension
 - Cor pulmonale
- Significant hypercapnia during polysomnography (PECO₂ ≥ 60 mmHg)
- Failure to thrive (<3rd percentile)
- Obesity (> 95th percentile)
- Craniofacial anomalies
- Neuromuscular disorders

Identification of sleep breathing disorders and OSA in the pre-operative period allows appropriate peri-operative management, including the use of reduced opioid doses and adequate post-operative monitoring. Signs and symptoms of OSA should be elicited through history and physical examination (Table 1).

Table 1: Symptoms and Signs of OSAS

History

Frequent snoring (≥3 nights/wk)
 Laboured breathing during sleep
 Gasps/snorting noises/observed episodes of apnea
 Sleep enuresis (especially secondary enuresis)[†]
 Sleeping in a seated position or with the neck hyperextended
 Cyanosis
 Headaches on awakening
 Daytime sleepiness
 Attention-deficit/hyperactivity disorder
 Learning problems

Physical examination

Underweight or overweight
 Tonsillar hypertrophy
 Adenoidal facies
 Micrognathia/retrognathia
 High-arched palate
 Hypertension

[†] Enuresis after at least 6 months of continence

Table from American Academy of Pediatrics
2012 Guidelines

Polysomnography

- Gold standard for diagnosis of sleep breathing disorders, but expensive and often unavailable
- American Academy of Otolaryngology Head and Neck Surgery Foundation guidelines [Bough et. al. 2011] regarding additional indications for polysomnography prior to tonsillectomy in children, includes:
 - o Obesity
 - o Trisomy 21
 - o Muscular disorders
 - o Sickle-cell disease
 - o Mucopolysaccharidoses
 - o Discordance between tonsil size and severity of reported SDB
- Apnoea-Hypoxia Index ≥ 10 associated with an increased risk of post-operative respiratory complications [McColley et.al., 1992]

Overnight Oximetry

- Desaturation $<80\%$ indicates severe OSA [Nixon et. al., 2004]

Combined Sleep Clinical Record (Figure 1) & McGill Oximetry Score (Figure 2)

- Combination allows accurate classification of SDB severity in about two-thirds of patients 12 yrs or younger who are referred for suspected OSA when PSG testing not an option [Villa et. al. 2015]
- Overnight oximetry mis-classifies approximately two-thirds of children with moderate-to-severe disease into mild OSAS or primary snoring [Villa et. al. 2015]

Figure 1 Sleep Clinical Record Page 1

Sleep Clinical Record

DATE: _____

Patient

Date of birth _____
Age (years) _____ Weight (Kg) _____ Height (Cm) _____
BMI (Kg/m²) _____ percentile BMI _____

Age at symptom onset (years): _____ Duration of disease (years): _____
Name: _____ Surname _____

NOSE

- 1) Septum nose deviation: YES/NO
- 2) Nasal cartilage hypotonia (see figure below): YES/NO
- 3) Orbicular muscle hypotonia (see figure below): YES/NO
- 4) Nasal airway patency: YES/NO
Perform the "sniff test"; obstruction of nasal airflow is based on physical examination by audible nasal congestion as a patient inhales forcibly 4 times through the right and left nostril, while the clinician compresses the contralateral nostril.

Figure 2 McGills Oximetry Scoring System

- A. Number of episodes with oxygen saturation dropping to 85-89%
- B. Number of episodes with oxygen saturation dropping to 80-84%
- C. Number of episodes with oxygen saturation dropping $< 80\%$

Drops in Oxygen Saturation	Oximetry Score	Oximetry Grade
AND (1-2 A, 0 B, 0 C)	1	Inconclusive
AND (A+B ≥ 3 , 0-3 B, 0 C)	2	Mild OSA
OR (1-3 C, B > 3)	3	Moderate OSA
> 3 C	4	Severe OSA

- **If polysomnography is unavailable; clinical suspicion and the presence of OSAS-associated morbidity should be used to identify children with moderate-to-severe OSAS that may potentially be missed by oximetry testing**
- **'High-risk' patients should be admitted post-operatively for pulse oximetry and apnoea monitoring and then re-evaluated to determine whether additional treatment is needed**

Recommended reading: Cote C. Anesthesiological considerations for children with obstructive sleep apnoea. Current Opinion in Anesthesiology 2015;28:327-332

Pulmonary Hypertension & Cor Pulmonale

"Syndrome of cor pulmonale consequent to upper airway obstruction... noisy, stertorous respirations, somnolence, clinical and electrocardiographic evidence of right ventricular hypertrophy, radiological findings of cardiomegaly, and occasionally pulmonary oedema and right heart failure"
[Ainger, 1968]

A clinical history and examination with findings suggestive of pulmonary hypertension or cor pulmonale warrant an ECG and ECHO. In addition, it has long been noted that children with severe pulmonary hypertension may merely present with failure to thrive (weight <3rd percentile) in addition to SBD, due to the increased work of breathing, but neither respiratory failure nor heart failure [Blum et. al., 2004].

A chest radiograph may show evidence of cardiomegaly or other features consistent with pulmonary hypertension or right ventricular hypertrophy, but may be normal. The ECG may show evidence of right ventricular hypertrophy and right heart strain, but may also be normal.

- **The use of investigations should be at the discretion of the clinician but it is important to recognise that other additional risk factors, such as chronic lung disease, multi-level airway obstruction and trisomy 21, as well as other features increase the risk of pulmonary hypertension**
- **In patients with severe pulmonary hypertension or cor pulmonale, anaesthetic vigilance, invasive arterial blood pressure and post-operative PICU monitoring is advisable**

Recommended reading: Galante D. Intraoperative Management of pulmonary arterial hypertension in Infants and children. Current Opinion in Anesthesiology. 2009. 22:378-382

ANAESTHETIC TECHNIQUE

Pre-medication

Reduction in anxiety and a smooth induction can have a beneficial effect on the reduction of post-operative emergence delirium and pain. Midazolam 0.3 – 0.5 mg.kg⁻¹ or clonidine 3 – 4 mcg.kg⁻¹ can be given. Caution must be applied in patients with pre-existing OSA as the sedation and loss of airway tone may precipitate an obstructive and/or apnoeic event and hypoxia. In these patients clonidine is preferable due to the relative preservation of airway tone. If there is any concern then the patient should be monitored and observed after the pre-medication is given.

Induction

If there are no concerns with the airway then either an intravenous induction or inhalational induction is appropriate, but it may be prudent to maintain a spontaneously ventilating technique if there is concern about airway obstruction or other features suggestive of a potentially difficult airway.

Airway

All of the tonsillectomies at our institution are electively intubated, preferably with a cuffed tube, although there are some institutions where these procedures are performed with laryngeal mask airways (LMA). The benefit of a cuffed endotracheal tube includes better access for the surgeons, relative sealing of the trachea to minimise soiling of the airway with blood and secretions, prevention of pollution of the operating room with volatile gases, and preventing the leakage of high-concentration oxygenation into the airway thereby reducing the chance of airway fire with the use of electrocautery.

The benefit of an LMA may include a smoother “extubation”, reduction in the incidence of adverse respiratory events compared with intubation in a child with an upper respiratory tract infection [Tait et. al, 1998]. However, the LMA will not provide the same surgical exposure and the risk of converting to an ETT varies from 6.8% - 20% [Lalwani et. al. 2013; Peng et. al. 2011]. LMA failure is more likely in younger patients and with controlled versus spontaneous respiration [Lalwani et. al. 2013].

Whether the airway is secured with an ETT or LMA, it is important to be vigilant when the mouth gag is inserted as it may kink or dislodge the airway. Ultimately, the choice of airway will depend on the preference and experience of the surgeon and the anaesthetist.

Neuromuscular Blocking Agents

In our institution muscle relaxation is not routinely given for intubation for tonsillectomies, and unless a short-acting NMBA is given, it may in fact delay the end of the procedure whilst waiting for the patient to be suitable for the administration of reversal agents.

Maintenance

Anaesthesia is usually maintained using isoflurane, and either positive pressure ventilation, or spontaneous ventilation, if suitable. In children with a significant history or risk of PONV or at risk of malignant hyperthermia or anaesthesia induced rhabdomyolysis, a TIVA technique may be considered.

Analgesia

Pain post-tonsillectomy can be significant. Occurring both immediately, subsiding and then peaking again at day 3-4, and it may last up to 11 days. A multi-modal approach with an opioid sparing technique has the benefit of reducing side-effects including post-operative nausea and vomiting, upper airway obstruction and apnoeas. It remains unclear whether the surgical technique affects the degree of postoperative pain after tonsillectomy.

Paracetamol

- Loading dose IV 15-20 mg.kg⁻¹, PR 40 mg.kg⁻¹

NSAIDS

- May be as effective as opioids in reduction of post-tonsillectomy pain, whilst minimising respiratory depression [Kelly et al., 2015]
- Latest Cochrane review suggests it is not possible to rule out increased risk of bleeding [Lewis, 2013]
- May be prudent to give NSAID at the end of the procedure once haemostasis achieved
- In our institution we give 1 mg.kg⁻¹ diclofenac PR unless contra-indicated

Dexamethasone

- Cochrane review concludes that a single dose of dexamethasone significantly reduces the incidence of PONV in the first 24 hrs and reduces analgesic requirements [Steward DL, 2011]
- Optimal dose unknown, but doses of 0.5 mg.kg⁻¹ may increase risk of bleeding [Czarnetzki, 2008]
- In our institution we commonly give 0.15-0.25 mg.kg⁻¹

Clonidine

- Cochrane review of clonidine pre-medication and post-operative analgesia in children (4/11 studies involved tonsillectomies) suggests 4 mcg.kg⁻¹ is likely to have beneficial effect on postoperative pain [Lambert P et al., 2014]
- No delayed discharge in ambulatory patients [Reimer, 1998]
- In our institution if a clonidine pre-med has not been given then clonidine 1 mcg.kg⁻¹ may be given as an alternative by slow intravenous injection, although this requires signed consent from the caregiver

Dexmedetomidine

- Meta-analysis showed it may be as effective as use of opioids in prevention of post-operative pain and emergence delirium [He XY et al. 2013]
- Less respiratory depression compared with opioids, but optimal dose unknown and expensive!

Ketamine

- Limited evidence from small studies that intravenous ketamine improves pain management in PACU and early post-operative period [Dahmani et al, 2011]
- Ketamine (0.5 – 1 mcg.kg⁻¹) administered locally into the tonsillar bed decreases PACU and early (6-24 hr) pain intensities, as well as PACU analgesic requirements [Dahmani et al., 2011]

Gabapentin

- May reduce need for analgesics during 24 hours post-operatively [Hwang et al., 2015]
- Optimal dose unknown and further good quality clinical trials needed

OPIOIDS

Intra-operative fentanyl

- Dose: 0.5 – 1 mcg.kg⁻¹ IV during or after induction

Intra-operative morphine

- Dose: 0.1 mg.kg⁻¹ IV

OPIOIDS IN PATIENTS WITH OSA

- Children with recurrent hypoxia as a result of OSA have an increased sensitivity to opioids
- Opioid doses should be reduced to $\frac{1}{3}$ to $\frac{1}{2}$ of standard doses

[Brown, 2006]

There is no consensus on the optimal postoperative analgesia for breakthrough pain in children post-tonsillectomy/adenotonsillectomy.

Codeine

[Lauder and Emmott, 2014]

- Weak opiate drug which elicits its analgesic effects mainly via metabolism to active metabolites
- Significant inter-individual pharmacogenetics of CYP450 metabolism
- 3 deaths of children in US who received codeine after an elective adenotonsillectomy can be attributed to definite ultra-rapid metabolizer phenotype
- Often prescribed as mixed preparation and therefore increased risk of inadvertent paracetamol toxicity

Tramadol

- Overall evidence regarding tramadol for postoperative pain in children is low or very low and should be interpreted with caution due to small studies and methodological problems [Schanbel et. al., 2015]
- Risk-benefit analysis was not possible as adverse events poorly reported [Schanbel et. al., 2015]
- Single case-report of respiratory depression in child with OSA following adenotonsillectomy after tramadol 1 mg.kg^{-1} for breakthrough pain [Orliaguet et. al., 2015]

Valoron (Tilidine hydrochloride) Drops

- In our institution valoron drops are the only routinely available non-intravenous opiate
- Dose: 2.5 mg.kg^{-1} PRN 4 – 6 hourly
- The dose should be reduced in obese patients and those with OSA

Local Anaesthesia

A number of different medications have been injected into the tonsillar bed in an effort to reduce post-operative pain with varying success. Topical application or injection of local anaesthetics into the tonsillar bed may have a modest effect on post-operative pain. [Grainger & Saravanappa, 2008]

However, there are reports of several adverse events, including life-threatening upper airway obstruction as a result of local anaesthetic infiltration and vocal cord paresis. [Bean-Lijewski, 1997]

Infiltration with local anaesthesia is not routinely practiced in our institution.

NON-PHARMACOLOGICAL OPTIONS

Honey

[Hwang et. al, 2016]

- Reduction in pain scores on day 1 and reduced analgesic intake for first 5 postoperative days
- Significantly increased tonsillectomy bed wound healing vs placebo during first 2 weeks after surgery
- Further good quality studies needed to confirm these results

Acupuncture

- Less pain, less analgesic drug consumption, and higher patient/parent satisfaction with analgesic treatment scores [Gilbey, 2015]
- Further large well-designed trials are required

Anti-emetics

Children undergoing adenotonsillectomy are at increased risk of post-operative vomiting (POV).

- Multimodal analgesia and minimising long acting opioids will reduce the incidence POV
- Dexamethasone: Single dose between $0.15\text{--}1 \text{ mg.kg}^{-1}$ halves the risk of vomiting [Steward et. al., 2011]
- Ondansetron: optimal dose 0.15 mg.kg^{-1} (Early vomiting NNT = 2.82, late vomiting NNT = 3.67) [Figueredo & Canosa, 1998]
- In one small study hyper-hydration with 30 ml.kg^{-1} compared with 10 ml.kg^{-1} of crystalloid has been shown to decrease the incidence of POV [Elgueta et. al., 2012]
- Acupuncture may also be of benefit [Shin et. al., 2016]

Recommended reading: Association of Paediatric Anaesthetist of Great Britain & Ireland 2009
Guidelines on Post-Operative Vomiting in Children

Extubation

- One of the conundrums is whether to “extubate deep”, avoid coughing, straining, and hence decreased risk of bleeding or whether to “extubate awake” in the patient with an obstructed airway to minimise the risk of airway obstruction, laryngospasm and hypoxia. The evidence from a single center observational study suggests: [Bajjal et. al., 2015]
- There does not appear to be a difference in the incidence of major respiratory complications between awake (10.4%) vs deep (10.7%) extubation
- Trend towards awake extubation in severe OSA patients confirmed on polysomnography, although there was no difference in major respiratory complications in severe OSA group if extubated awake vs. deep

Ultimately, the decision must be tailored to the patient and the recovery facilities available and suctioning under direct vision should be undertaken to avoid the potentially lethal “coroners clot.”

Early Post-Operative Negative Behaviour (ePONB)

The incidence of ePONB following adenoidectomy and/or tonsillectomy can be as high as 91%.

[Somaini, 2014]

One of the challenges can be to differentiate between true emergence delirium (ED), which is self-limiting, and pain which will likely require further analgesia. The presence of ‘abnormal facial expression’, ‘crying’ and ‘inconsolability’ has a high sensitivity and specificity to detect pain. The association of ‘no eye contact’ and ‘no awareness of surroundings’ has a high sensitivity to identify ED during the first 15 minutes after awakening.

[Somaini, 2016]

Further confusing the matter is that pain is also a risk factor for ED.

Although ED is self-limiting treatment must be undertaken if there is a risk of the child injuring him/herself. A number of medications have been shown in studies to be useful in the prevention of ED. Clonidine and melatonin premedication appears to be better than midazolam, dexmedetomidine has been found to be superior to a propofol bolus at the end of surgery or the continuous administration of ketamine, and dexamethasone has also been found to be as effective as paracetamol-codeine in preventing ED*.

*Recommended reading: Dahmani et. al. Emergence delirium in children: an update. Current Opinion in Anaesthesiology. 2014.27:309-315

“THE BLEEDING TONSIL”

“The bleeding tonsil” is an infrequent, yet serious complication, which presents the anaesthetist with the following issues:

1. Potentially difficult airway
2. Full stomach due to swallowed blood
3. Anaemia & hypovolaemia
4. Recurrent anaesthetic

Primary bleeding: Within first 24 hr, occurs in <1% of patients

Secondary bleeding: Usually 5-12 days following tonsillectomy and often due to disruption of the healing clot, occurs in up to 4% of patients

Factors associated with an increase in the incidence of post-tonsillectomy haemorrhage include:

- Surgical technique
- Age > 5 yrs
- Chronic tonsillar infection
- Pre-operative use of aspirin
- NSAIDS

Anaesthetic Technique

When presented with a child with a post-tonsillectomy bleed it is difficult to determine the preoperative blood loss as much of blood is swallowed. It is therefore important to assess the volume status of the child and resuscitate the child with adequate intravenous access to minimise the risk of haemodynamic instability on induction. In the majority of cases it will be possible to evaluate the volume status, and to determine the haemoglobin and haematocrit, to request a group & screen and coagulation studies if indicated. This must be balanced against the necessity to stop the bleeding and investigations should not delay emergent surgical treatment.

In anticipation of a potentially difficult airway, two large bore suction devices should be available and the ENT surgeon must be present should emergent access to the airway through the anterior neck be required. The position for intubation should be optimised and pre-oxygenation performed as best as possible. A retrospective cohort study showed that 9.9% of patients suffered a hypoxaemic episode and most of these occurred during extubation or emergence. [Fields et. al., 2010]

Inhalational induction in the left lateral position or rapid sequence induction?

There is no strong evidence to suggest whether an inhalational induction in the left lateral position or a rapid sequence induction is preferable, although in a survey of UK anaesthetists 93% favoured an RSI over an inhalational induction in the bleeding tonsil. [Moore, 2012]

The benefit of an inhalational induction in which spontaneous respiration is maintained and blood and clots drain away from the airway must be balanced against the potential risk for pulmonary aspiration, the difficulty of a mask induction in an uncooperative child and the potential haemodynamic stability if high inspired concentrations of volatiles are used or a deep plane of anaesthesia is reached. An intravenous RSI may be easier to manage in the uncooperative child, although pre-oxygenation/denitrogenation may not be, and allows for rapid securing of the airway, which will minimise the risk of aspiration. However, the supine position may allow blood and clots to accumulate, there may be necessity for bag valve ventilation if the patient becomes hypoxic when apneic and there is potential for haemodynamic instability on induction dependent on the hypnotic agent and doses used. ketamine 1 - 2 mg.kg⁻¹ or etomidate 0.3 mg.kg⁻¹ may provide the most optimal haemodynamics in this situation. Prior to extubation a large bore nasogastric tube should be introduced orally to decompress the stomach. The patient should be extubated once they are awake and normal gag and cough reflexes have returned.

Recommended reading: Fields R et.al. Anesthetic Management of the Bleeding Tonsil. Pediatric Anesthesia. 2010: 982-986

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Transfusion Strategies

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The discussion of transfusion strategies is an endlessly broad topic. The following current concepts in transfusion strategies according to the latest literature will be discussed here. Please also see 2015 Refresher course topics of Massive Transfusion and Current concepts in Trauma discussed.

The focus of this talk will be:

1. The pathophysiology of Trauma induced coagulopathy
2. Component therapy: Is 1:1:1 the answer?
3. Transfusing the critically ill

Trauma

Trauma is the leading cause of death and disability worldwide, contributing significantly to the global burden of disease. The World Health Organization estimate injury responsible for more than 5 million deaths per annum - more than the mortality of HIV, malaria and TB combined. Of the 3 components of the Triad of Death, coagulopathy is still the leading cause of death. Bleeding accounts for 30-40% of mortality in the trauma patient. Hypothermia lead to

- ☐ Platelet responsiveness
- ☐ Platelet sequestration in liver/spleen
- ☐ Function factors XI/XII and
- Alters fibrinolysis

The low pH in acidosis strongly affects factors V, VII and X, inhibits thrombin generation and at a pH of 7.2 lead to decreased contractility and increase incidence of dysrhythmias.

With coagulopathy as the major cause of death in trauma, what can we do to prevent coagulopathy? To be able to prevent coagulopathy, we need to understand the pathophysiology of Acute Trauma Coagulopathy (ATC) and Trauma Induced Coagulopathy (TIC)

It is crucial in the survival of the severely injured trauma patient to rapidly treat and prevent Trauma Induced Coagulopathy (TIC).

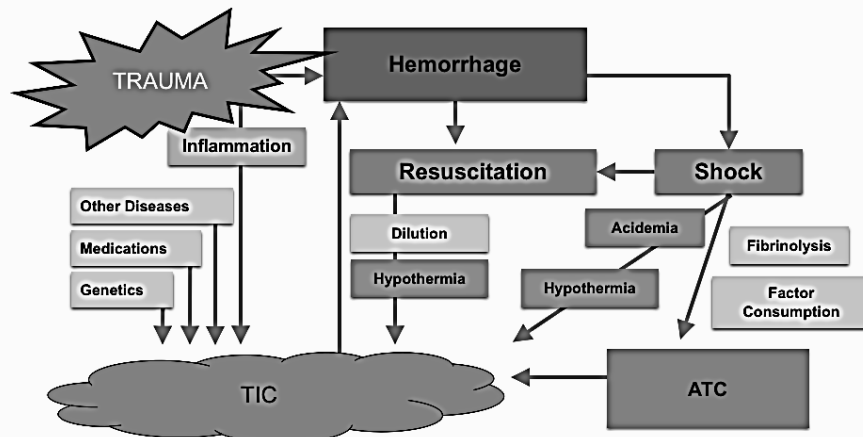
Acute Trauma Coagulopathy (ATC)

In a third of patients that is severely injured, ATC is already present by the time of hospital admission. This contributes significantly to hemorrhage. ATC is associated with an increase in massive transfusion, increased hospital stays and mortality.

The major trigger of ATC is systemic hypo-perfusion after major haemorrhage. Hypo-perfusion leads to expression of thrombomodulin on the endothelial cells. Thrombin binds to thrombomodulin and this complex of thrombin-thrombomodulin activates protein C. Activated Protein C (APC) leads to further coagulation limitations by inhibiting activated factor V and VIII. This enhances fibrinolysis by depletion of plasminogen activator inhibitor 1 (PAI-1) and accelerates plasmin formation. Thrombin gets diverted from cleaving fibrinogen for clot formation, now to binding to thrombomodulin. This reduces the activation of thrombin-activatable fibrinolysis inhibitor (TAFI) that leads to further hyper-fibrinolysis. This complex process leads to early coagulopathy due to hyper-fibrinolysis and systemic anticoagulation.

ATC is defined as a reduction in clot strength at 5 min on rotational thromboelastometry (ROTEM) (Clot amplitude - 35 mm) with minor changes in prothrombin time (PT) and partial thromboplastin time (PTT).

TRAUMA INDUCED COAGULOPATHY (TIC)



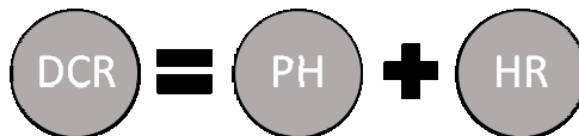
Adapted from: Hess JR, Brohi K, Dutton RP; et al. The coagulopathy of trauma: a review of mechanisms, J Trauma 2008 654 748-754.

Trauma Induced Coagulopathy (TIC)

ATC is further exacerbated by hemodilution, hemorrhage, acidosis & hypothermia. This gives rise to a multifactorial process - the global failure of the coagulation system to maintain adequate haemostasis after trauma. In TIC there are varying degrees of dysfibrinogenaemia, hyper-fibrinolysis, endothelial dysfunction and impaired platelet activity, dependent on the magnitude of trauma, and severity of haemorrhagic shock.

Damage control resuscitation (DCR) is associated with improved outcomes although the mechanisms of how it corrects TIC have yet to be fully understood. DCR is different from the conventional resuscitation in the early correction of coagulopathy and metabolic derangements and is focused on hemostatic potential.

The 2 key components are Permissive hypotension (PH), a fluid management strategy that targets subnormal blood pressure till surgical control of bleeding confirmed and hemostatic resuscitation (HR). Hemostatic resuscitation is the early goal directed blood product transfusion with less crystalloid solutions and with the concept of damage control surgery (DCS) has got survival benefit in patients with severe hemorrhage. An in depth discussion these concepts and of the topic of Massive Transfusion was done in 2015 ARC.



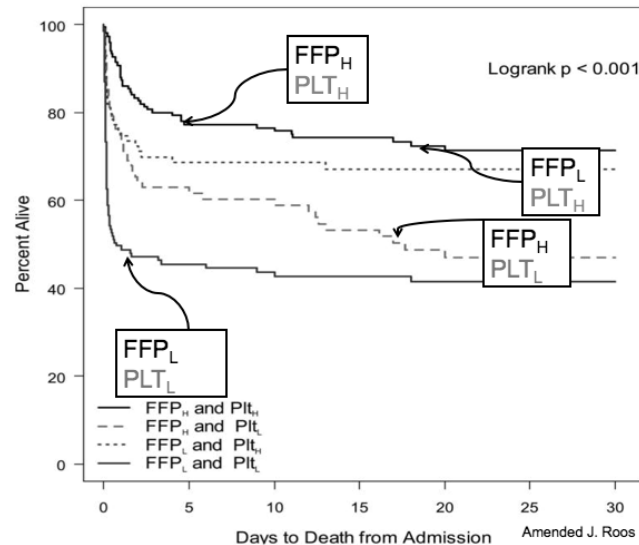
Component therapy: Is 1:1:1 the answer?

From the pathophysiology discussed above, it is clear that the coagulopathy of trauma need to be treated early to prevent further mortality and morbidity. But which blood components should be used? There is a lot of controversy in current literature about the timing and ratios to which blood components should be administered.

Emerging current trends in the treatment of coagulopathy is the use of high ratio fresh frozen plasma(FFP) and platelets to red blood cells (RBC), together with the correction of hypothermia and acidosis. Antifibrinolytic drugs like tranexamic acid in the prehospital setting and the use of recombinant activated factor VII and prothrombin complex concentrates(PCC) is still under investigation.

Holcomb et al showed in their study of 466 civilian patients, who required massive transfusion, (2008) the benefit of transfusing higher FFP and platelets ratios. The specific emphasis is on higher platelets more than higher FFP's if you look at the diagram below. Overall survival by increased amounts of

plasma and platelets specific emphasis on high platelets had mortality benefit. This lead to investigation of a more balanced resuscitation protocol in massive transfusion.



2 Important studies were published recently that I want to highlight. The PROMMT (2013) and The PROPPR(2015) trials were both multicenter studies that look at component therapy and mortality.

	PROMMT	PROPPR
Yr	2013	2015
Study	Prospective observational	RCT
Intervention	Plasma:RBC (1:1)	Plasma:Plts:RBC (1:1:1)
Control	Plasma:RBC (1:2)	Plasma:Plts:RBC (1:1:2)
Cohort	905	680
Primary endpoint	In hospital mortality	24h/30d ☐
Outcomes	Higher plasma:RBC ratio's decreased 6h mortality in patients receive >3 blood products No associated after 24h of survival	No significant difference @ 24h/30d 1:1:1 earlier hemostasis and decreased mortality due to exsanguinations in 24h

In the PROMMT (Prospective, observational, multicenter, major trauma transfusion) study, higher plasma and platelet ratios early in resuscitation were associated with decreased mortality in patients who received transfusions of at least 3 units of blood products during the first 24 hours after admission. The survivors at 24 hours, the subsequent risk of death by day 30 was not associated with plasma or platelet ratios.

In 2015 Holcomb's group published another study: PROPPR (Pragmatic, Randomized Optimal Platelets and Plasma Ratios which compared 2 different regimes of transfusion: the FFP:platelet:RBC ratio of 1:1:1 versus 1:1:2. Although there was no difference in mortality in the two groups, the 1:1:1 group achieved earlier hemostasis and less exsanguination compared to the 1:1:2 group. The authors of the PROPPR trial concluded that in severe trauma patients there is support to use a more balanced technique utilizing the 1:1:1 regime should be considered. Of importance is that there was no increase in ARDS or other transfusion related complications detected.

Other components

Prothrombin complex concentrates (PCC) is a source of vit K dependent coagulation factors. It leads to the reduction in the use of blood products and is used off-label in the trauma setting. Although the animal models and retrospective reviews look promising, there is no prospective data to support the use of PCC in the trauma setting with regard to outcome benefit currently.

Recombinant Activated factor VII (rFVIIa) enhance the formation of fibrin from fibrinogen by a thrombin burst. There is not enough evidence to use it as a standard treatment of bleeding in trauma and due to the expense not used in our setting.

Take home messages from trauma

- The trauma patient presenting to you already have a coagulopathy
- Damage control resuscitation =Permissive hypotension + hemostatic resuscitation improve mortality
- Early resuscitation with high ratio's like 1:1:1 is probably the way forward

Ongoing research and unanswered questions?

- Should we transfuse patients with severe trauma in the pre-hospital setting?
- The PATCH trial will answer weather the use of Tranexamic Acid pre-hospital will increase the survival of severely injured patients
- Use of PCC and rFVIIa in trauma

Critical care and transfusion

Anemia is a common problem in Intensive Care Units (ICU). More than 40 percent of patients in ICU will receive one or more RBC transfusions during their stay in ICU estimated to several studies. ICU is the one place where benefit/risk should be carefully weighted before any action is taken.

Red blood cells

Indications for transfusion of RBC include acute hemorrhagic shock with instability, inadequate oxygen delivery and a Hemoglobin of <7g/dL. Hb of 7 is the accepted threshold after the TRICC (Transfusion Requirements in Critical Care) trial done in 1999. This trial assigned patients to restrictive strategy (Hb <7) vs the Liberal strategy (Hb <10) and found that the restrictive strategy had decreased mortality.

What about the patient that is critically ill and has ischemic heart disease? In the TRICC trial, there was a trend to better outcome in the liberal group (Hb < 10) but it was not statistically significant. Larger trials are needed to answer this question and most clinical trials up to date excluded these patients.

The Transfusion requirements after cardiac surgery (TRACS) trial was compared post cardiac surgery patients with a Hematocrit of 30% vs >24%. There was no difference in mortality and severe morbidity in the two groups. The number of RBC's transfused was an independent risk factor for clinical complications.

Blood transfusions in septic patients

Since the Rivers trial in 2001, blood transfusion is part of the protocols of severe sepsis and septic shock. The Surviving Sepsis guideline advocates a hematocrit of 30% in the first 6hrs of septic shock with hypoperfusion despite fluids and vasopressors.

The TRISS (Transfusion Requirement in Septic Shock) trial completed in 2014 showed there is no justification for this practice in sepsis. In this study patients were randomized to a transfusion trigger of Hb 7g/dL or 9g/dL throughout their ICU stay. As in previous studies patients with myocardial ischemia was excluded. The 90-day mortality was similar in both groups. There is no apparent benefit in septic patients for transfusion of a Hb >7g/dL without active bleeding or myocardial ischemia. Experts may conclude that TRISS, ProCESS and ARISE trials invalidate the transfusion of Hb >7 g/dL as part of standard protocols for severe sepsis.

Other blood products

Plasma

The indications for transfusion of plasma are less well established than for RBC. Plasma is needed when there is insufficient hemostasis that outweighs the risk of plasma transfusion.

Platelets

Transfusion of platelets in critically ill is either therapeutic or prophylactic. In special situations like Heparin-induced thrombocytopenia (HIT), Thrombotic thrombocytopenia purpura (TTP) or Disseminated intravascular coagulation (DIC), platelets are reserved for life-threatening bleeds caused by the association with clinical deterioration or the loss of effect.

Surviving sepsis guidelines on blood transfusions (2013)

- Restricting RBC transfusion in adults with severe sepsis/septic shock till Hb < 7 g/dL, transfuse to but not > 9 g/dL in IHD when severe hypoxemia, or active bleeding are not present **(Grade 1B)**
- Advise against erythropoietin (EPO) for anemia with severe sepsis / septic shock. **(Grade 1B)**
- Reserve transfusion of fresh frozen plasma (FFP) for severe sepsis/septic shock who have increased PT, PTT, and/or INR, and who either have active bleeding, or are planned to undergo surgery or invasive procedures. **(Grade 2D)**
- Transfuse platelets prophylactically if $<10,000 / \text{mm}^3$, with no bleeding. In patients at risk for bleeding, a threshold of $20,000 / \text{mm}^3$ is suggested, and active bleeding/ undergoing surgery /invasive procedures, transfusing platelets to $50,000 / \text{mm}^3$ is suggested. **(Grade 2D)**

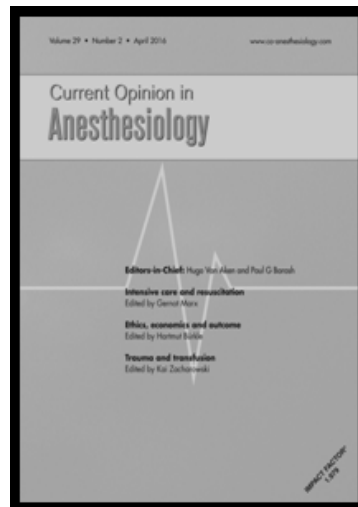
Ongoing research and controversy in ICU transfusion?

- What is the transfusion trigger for a critically ill patient with Ischemic heart disease?
- Should we use leucodepleted blood in the critically ill? Only observational data
- Should we use blood less than 2-3 weeks old?

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Please look at this journal: *Current opinion in Anesthesiology* April 2016 for useful articles on transfusion and trauma.



Risk Assessment Algorithms

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Risk:

noun - a situation involving exposure to danger.

verb - expose (someone or something valued) to danger, harm or loss.

Introduction

Risk is part of every human endeavor, with risk and survival going hand in hand from early evolution. The Chinese symbol for risk infers a combination of danger and opportunity.

Risk stratification has become integral to perioperative anaesthetic work up of any patient before surgery, whether it may be for functional status, physical status, difficult airway assessment, perioperative MI and cardiac arrest, renal failure, morbidity, etc. as we strive to improve anaesthetic safety and identify patients that would most benefit from optimisation or specific intervention.

A patient has to make a choice whether to proceed with an operation, balancing the chances of harm and benefit with each choice. Risk discussion requires clear communication, should be easy to understand and should include all risks that a reasonable patient considers significant. The perception of risk varies for both the patient and the anaesthetist.¹

Assessing risk for course of action –
think **BRAN!**

Benefit

Risk

Alternatives

what would happen if **Nothing** was done

JB Carlisle thoughts on surgery, perioperative morbidity and mortality:²⁻⁴

People avoid things that will kill or incapacitate them, so it is surprising how many people subject themselves to scheduled surgery. Scheduled surgery kills some patients who would otherwise live. Patients most likely to die from other causes are also most likely to be killed by 'curative' surgery on the primary pathology, as some patients with lethal pathologies (cancer, AAA) die from other causes, without the 'lethal' pathology being symptomatic, diagnosed or treated.

Both RCTs and observational data indicate that scheduled surgery increases mortality, sometimes for more than 3 months, with the postoperative survival curve taking more than 1 year to equal the survival of patients who had not had surgery.

Mortality is a good measure of killing, but it is a poor measure of cure, palliation or the maintenance of function. Consequences of surgical intervention are difficult to interpret with little information on quality of life, or how long and good life would be without surgery.

The pre-operative estimation of postoperative mortality and morbidity has three purposes to:

- i) target peri-operative interventions to reduce both morbidity and mortality
- ii) change mortality risk that better matches the value of interventions and use this to better distribute resources
- iii) create a context within which a patient can determine his/her own fate through collaborative decision-making.

Anaesthetic risk stratification

Overall perioperative mortality for all patients 1 month after elective surgery is 1:177 (UK data).¹ Major non-cardiac surgery is associated with an incidence of cardiac death between 0.5-1.5% and have major cardiac complications between 2-3.5%.⁵ Deaths after non-cardiac surgery attributed to vascular etiologies account for up to a third of perioperative deaths. Eight percent of patients presenting for high risk surgery are dead 1 year post surgery.⁶ Emergency surgery is associated with particularly high risk, as cardiac complications are 2-5 times more likely than with elective procedures.¹

The diagnoses of myocardial infarction, heart failure, stroke, and peripheral arterial disease each chronically increase mortality risk ~1.5 times, compared with people who do not have these. In the absence of myocardial infarction (MI) or stroke, the diagnoses of angina and transient ischemic attack multiply risk by ~1.2 times. Renal failure is the fifth co-morbidity that consistently increases mortality risk, by between 1% and 2% for each 1 ml/min decrease in estimated glomerular filtration rate (eGFR), particularly below 75 ml/min. The relative risk increasing by 1.8 – 3.3 times with a reduction in eGFR to 15 ml/min.⁴

In 2005 Khuri et al. listed the following relative important preoperative, intraoperative and postoperative variables for 30-day and long-term mortality⁷

Rank	30-day mortality	Long-term survival
1	Any complication	Age
2	ASA class	Albumin(g/dl)
3	Emergency surgery	Any complication
4	Albumin(g/dl)	ASA class
5	RBC units (intraoperative)	BUN >40 mg/dl
6	Age	History of COPD
7	Sodium < 135 nmol/l	smoking
8	Disseminated cancer	diabetes
9	BUN >40 mg/dl	Functional status
10	SGOT > 40IU/ml	Disseminated cancer

(BUN, body urea nitrogen; SGOT, serum glutaminic oxaloacetic transaminase)

Biccard and Rodseth performed a systematic review in 2013 of intraoperative predictors of perioperative cardiac outcome and identified vascular surgery, emergent/urgent surgery and need for intraoperative blood transfusion as independent intraoperative risk predictors. They confirm the strong association between intraoperative blood transfusion and adverse postoperative cardiac events after non-cardiac surgery. Perioperative transfusion should flag patients as particularly high risk for adverse cardiac events.

Other risk factors identified were fall in mean ABP >20 mmHg for >60min, >30% increase in baseline SBP, tachycardia in recovery room, new onset atrial fibrillation, hypothermia, and remote ischemic preconditioning. These risk factors are potentially modifiable by perioperative physicians and may present opportunities to improve patient outcomes.⁸

Perioperative medicine is rapidly evolving and definitions of what constitutes perioperative cardiac morbidity have evolved over the past decade. New definitions to consider with risk stratification of cardiac patient for non-cardiac surgery are:

- **MACE** - Major adverse cardiac event of death or myocardial infarction (MI).
- **MINS** - Myocardial injury after non-cardiac surgery. A perioperative troponin leak is independently associated with 30-day postoperative mortality (VISION study). Peak troponin T (4th gen.) ≥ 0.03 ng/mL is judged to be diagnostic and attributable to myocardial ischemia, although 80% of patients who have perioperative troponin leak are clinically asymptomatic for myocardial ischemia.

Current validated potential cardiovascular risk predictors for perioperative myocardial infarction are; age, peripheral vascular disease, function status, surgical procedure risk stratification, ASA grading, estimated glomerular filtration rate, surgical Apgar score.⁹

Multivariable analyses have identified combinations of factors that can be used to estimate perioperative risk. Perioperative risk is expressed as the likelihood (in percent) that a patient will suffer a cardiac complication at the time of non-cardiac surgery. This objective clinical outcomes data is invaluable for rational allocation of healthcare resources, informed patient consent and improving patient-centered outcomes (see below).¹⁰

Several perioperative cardiac risk indices/scores have been proposed – Goldman used to be the gold standard with the RCRI (revised cardiac risk index) the most widely used risk indices.

Evolution of risk indices;

1977 – Goldman Index

1986 - Detsky

1999 – Revised Cardiac Risk Index (RCRI) model by Lee and Goldman

2007,14 - ACC/AHA & ECS/ESA surgical risk stratification

2011 – Gupta risk calculator

2013 – ACS NSQIP risk calculator

The later 2 risk models are statistical predictive models. They use a real time point of patient calculator for predicting the likelihood of perioperative cardiac events in patients undergoing non-cardiac surgery as well as morbidity (ACS-NSQIP only). This objective assessment may influence judgement on whether to improve cardiac status perioperatively, or more importantly whether to operate or not.

Risk models should not dictate management decisions but should be regarded as one piece of the puzzle to be evaluated in concert with the more traditional information. The ideal model must be globally validated, accurate, readily available, clinically easy to use and updated every few years.

Original Cardiac Risk Index ^{10,11}

The first cardiac risk index, developed in 1977 by Goldman, et al.

Also known as the Goldman Index.

This multifactorial index for cardiac risk in non-cardiac surgical patients included nine variables associated with an increased risk of perioperative cardiac complications, with 4 classes of risk depending on the total number of points scored.

Risk factors	Points
S3, distended JVP indicating HF	11
MI past 6 months	10
>5 PVC/min before surgery	7
Rhythm other than sinus	7
Age >70 years	5
Emergency surgery	4
Significant aortic stenosis	3
High risk surgery (Intraperitoneal, intrathoracic, aorta)	3
Markers of poor general conditions	3

Revised Cardiac Risk Index (RCRI) ^{10,12}

Also known as the Lee Index, published in 1999.

Appeal of the RCRI is the simplicity, using 6 additive predictors, as a tool to estimate a patient's risk of perioperative cardiac complications.

Compared with the Original Cardiac Risk Index, the RCRI was easier to use and more accurate. The RCRI was used widely in clinical practice, research, and was incorporated in a modified form into the 2007 preoperative cardiac risk evaluation guideline from the American Heart Association and American College of Cardiology (AHA/ACC).

In the derivation of the index, 2893 patients (mean age 66) undergoing elective major non-cardiac procedures were monitored for major cardiac complications.

The cardiac outcomes were: myocardial infarction, pulmonary edema, ventricular fibrillation or primary cardiac arrest, and complete heart block.

The index was validated in a cohort of 1422 similar individuals, aged ≥ 50 undergoing major non-cardiac surgery, which became known as the Revised Cardiac Risk Index. The predictive value was significant in all types of elective major non-cardiac surgery except for abdominal aortic aneurysm surgery.

Lee identified 6 independent variables that predicted an increased risk for cardiac complications;

1. high risk surgery
(intraperitoneal, intrathoracic, suprainguinal vascular surgery)
2. history of ischemic heart disease

(current chest pain, Hx of MI, nitrate Tx, pathological q-waves)
3. history of congestive heart failure
(pulmonary oedema, S3, PND, bilateral crackles, CXR changes)
4. history of cerebrovascular disease
(TIA/stroke)
5. Insulin dependant diabetes
6. Creatinine >176.8 micromol/l

Risk for cardiac death, nonfatal MI, and nonfatal cardiac arrest:

- 0 predictors = 0.4%,
- 1 predictor = 0.9%,
- 2 predictors = 6.6%,
- ≥ 3 predictors = >11%

These 6 RCRI risk factors remain independently associated with the original RCRI outcome definition, MINS, myocardial infarction and cardiac arrest.

Considerations regarding RCRI:

The high-risk category of the RCRI has been associated with short- and long term mortality, but in a meta-analysis it has shown marked heterogeneity around the estimate of mortality. Vascular etiologies of deaths after non-cardiac surgery attributed for 45% of perioperative deaths. Also the type of myocardial infarction after surgery is changing. The incidence of a type 1, plaque rupture, MI is decreasing while type 2, hemodynamic MI, is increasing. It is inappropriate to consider the utility of cardiac risk predictors in predicting all-cause mortality and the original RCRI risk prediction model did not take all-cause mortality into account.

Smaller studies have suggested that some of the traditional RCRI risk factors lose their significance in the presence of intraoperative predictors. However, the largest prospective observational study

suggests that all the RCRI risk factors remain independently predictive of MINS, together with a history of peripheral vascular disease and surgical risk.

RCRI has consistently shown inferior discrimination in vascular surgical patients when compared with its performance in other types of non-cardiac surgery. Three factors have been identified as independent predictors of MACE in vascular surgical patients

- history of coronary revascularization, associated with an independent reduction in postoperative MACE.
- medications to modify risk (B-blockers, Statins)
- chronic obstructive pulmonary disease

Smoking and hypertension are other identified predictors, although they have been less consistently identified and thus their importance is debatable.

Other controversial methodological questions relating to outcomes assessment:

- the cardiac biomarker during this time was creatine kinase (CK) and its MB isoenzyme fraction. CK has now been replaced by the troponins.
- use of a single individual to classify all complications
- inclusion of pulmonary edema as an outcome (given the dynamic perioperative hemodynamics and lung volume changes)

The RCRI has limited clinical application in identifying patients at risk of MACE. It is useful at excluding patients at risk of MACE (through an absence of known cardiac risk factors), but it does not perform adequately in identifying patients at risk of MACE.

2014 ESC/ESA guidelines on non-cardiac surgery: cardiovascular assessment and management.¹³

An evidence-based, stepwise approach for determining which patients would benefit from cardiac testing, coronary revascularization, and cardiovascular therapy before surgery.

Step 1: Urgent surgery

Step 2: active or unstable cardiac conditions

Step 3: what is the risk of surgical procedure of the surgical procedure?

Step 4: what is the functional capacity of the patient?

Step 5: In poor low functional capacity: consider the risk of surgical procedure

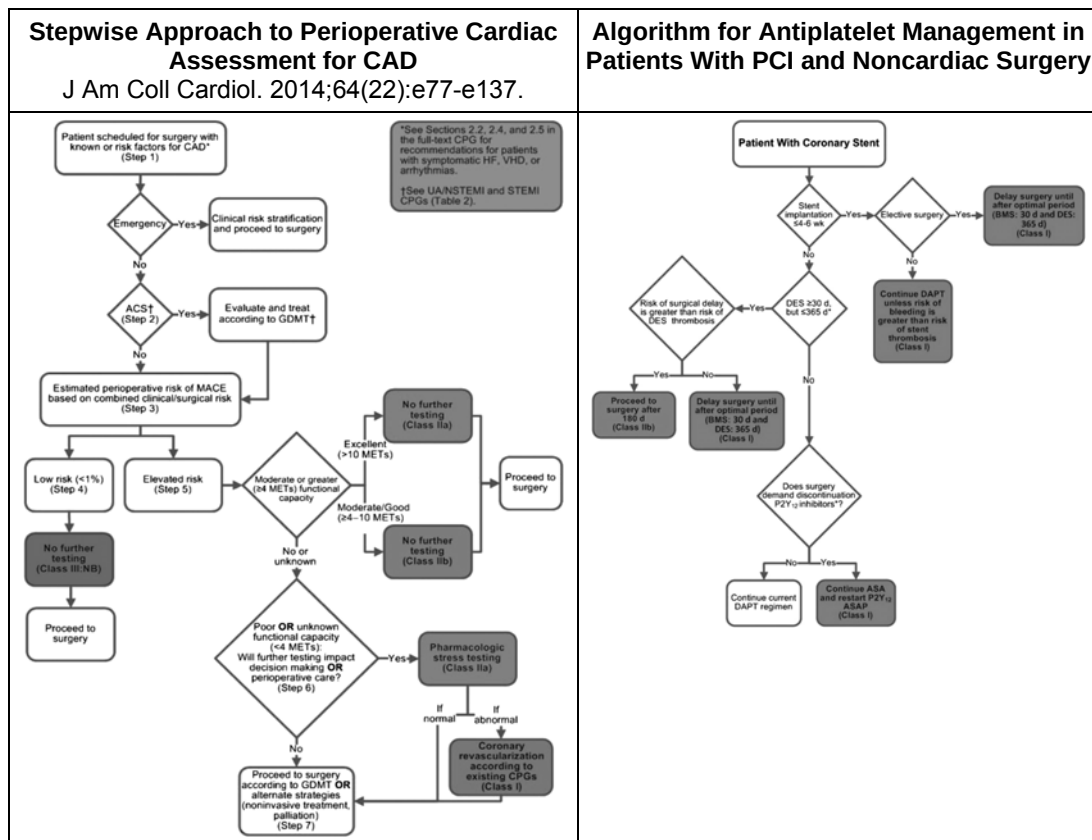
Step 6: consider cardiac risk factors

Step 7: consider non invasive testing

What's new in these guidelines

- i) pre-operatively multi-disciplinary expert team for high risk or known cardiac patients undergoing high risk surgery
- ii) updated surgical risk assessment
- iii) patient risk assessment (RCRI, NSQIP risk score, and recommendations on biomarkers)
- iv) B-Blocker not indicated in all patients, but maybe considered in high risk surgery and patients with risk factors, IHD, or myocardial ischemia
- v) updated recommendations on aspirin, P2Y12 inhibitors and new anticoagulants as well as peri-operative monitoring and concomitant disease sections

2014 ACC/AHA Perioperative clinical practice guidelines: 14



Considerations relating to the 2014 guidelines: 15

- i) This algorithm is aimed more selectively at coronary artery disease & acute coronary syndromes, and should not be considered to risk stratify patients with cardiac failure, valvular heart disease or arrhythmias.
- ii) Surgical grading has been removed from the risk stratification, and built into risk stratification models. (Gupta MICA, ACS –NSQIP risk calculator).
- iii) Importance is placed on predicted risk of MACE. A validated risk-prediction tool can be useful in predicting the risk of perioperative MACE in patients undergoing noncardiac surgery (CLASS IIa, Level of Evidence: B) Risk of MACE is either defined by RCRI or either one of the risk stratification models.
RCRI of 0 or 1 predictor(s) of risk would have a low risk of MACE. Patients with > 2 predictors of risk would have elevated risk.
Gupta MICA calculator uses 5 factors to predict perioperative myocardial infarction and/or cardiac arrest. ACS-NSQIP risk calculator is a universal surgical risk calculator consisting of 20 patient factors plus the surgical procedure to provide predictor of mortality and 8 morbidity factors of which cardiac complications (MACE) are included.
- iv) All patients with a MACE risk of > 1% require an individualised approach to risk stratification and risk reduction. In these patient's functional capacity plays an important role. Those who can perform ≥ 4 METs of activity, require no additional tests. For those whose functional capacity is lower or unknown, additional testing may be indicated if it will influence perioperative care.
- v) As mentioned above, functional capacity is integral to this ACC/AHA algorithm, although there are no prospective, observational data on the efficacy of functional status for MACE in the presence of RCRI. Functional independence seems to have clinical utility, with a 2.75-fold increase in risk for MI and cardiac arrest in patients who are functionally total dependent compared to totally functional independent patients. A limitation with functional dependence is that it is uncommon, with only 7% of the NSQIP patients having been partially or totally dependent.⁹
- vi) Pharmacological stress testing is recommended, should this be clinically indicated
- vii) Heart rate control has been removed as a recommended routine risk reduction procedure in patients at increased risk.

Risk calculators based on the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) system use considerably more risk factors and are tailored to specific surgical procedures.

Gupta myocardial infarction/cardiac arrest (MICA) risk model^{13,14,16}

The NSQIP database was used to determine risk factors associated with intraoperative/postoperative myocardial infarction or cardiac arrest (MICA). This tool includes adjusted ORs for different surgical sites, with inguinal hernia as the reference group.

Over 200,000 patients underwent surgery in 2007, from a 180 hospitals. The primary end point was intra-/post-operative myocardial infarction or cardiac arrest at up to 30 days after surgery. On multivariate logistic regression analysis, 5 factors were identified as predictors of MICA:

- type of surgery
- dependent functional status
- abnormal creatinine
- American Society of Anesthesiologists' class
- increased age

A risk model was developed using these five factors and subsequently validated on a 2008 data set of 257,385 patients.

This model is an interactive risk calculator so that risk can be calculated at the bedside in a simple and accurate way. It doesn't provide a scoring system but provides a model based estimate of the probability of MI or cardiac arrest for an individual patient.

The risk model had a relatively high predictive accuracy (C statistic of 0.874) and outperformed the RCRI (C statistic of 0.747). It must be recognized that it only considers MI/cardiac arrest. Pulmonary oedema and complete heart block are not considered by this risk model, as these data were not captured in the NSQIP database set

ACS - NSQIP universal surgical risk calculator^{13,14,17}

American College of Surgeons (ACS), prospectively collected data on operations performed in more than 525 participating hospitals in the United States. Data on more than 1 million operations have been used to create this risk calculator.

This is a web-based "universal" surgical risk calculator model, consisting of 20 patient factors plus the surgical procedure. From this input, it calculates the percentage risk of a MACE, death, and 8 other outcomes. This risk calculator may offer the best estimation of surgery-specific risk of a MACE and death

This model had excellent performance for mortality (c-statistic = 0.944; Brier score = 0.011 [where scores approaching 0 are better]), morbidity (c-statistic = 0.816, Brier score = 0.069), and six additional complications (c-statistics > 0.8). While more comprehensive than the other risk calculators, it is more cumbersome, which may limit its use.

The MICA calculator outperformed the RCRI in some circumstances, and the newer ACS-NSQIP surgical risk calculator is more comprehensive and procedure specific.

Limitations to the NSQIP-based calculators:

- it has not been validated in an external population outside the NSQIP
- the definition of MI includes only ST-segment MIs or a large troponin rise (>3 times normal); in symptomatic patients
- ASA Physical Status Classification, commonly used by anaesthetists, but known to have poor inter-rater reliability and may be unfamiliar to other clinicians.
- functional status: defined as the best level of self-care by the patient within 30 days prior to surgery. It distinguishes functional status as independent, partially dependent, totally dependent. With partial dependence, the patient requires some assistance with activities of daily living opposed to totally dependent; where the patient requires total assistance for all activities of daily living. A limitation with functional dependence is that it is uncommon, with only 7% of the NSQIP patients having been partially or totally dependent.⁹

Although most non-cardiac surgeries will benefit from a standard "generic" cardiovascular risk prediction model, there are data to suggest that patients with human immunodeficiency virus disease undergoing vascular surgery may benefit from a specific cardiovascular risk prediction models.⁹

The American Society of Anesthesiologists (ASA) Grading⁹

The ASA grading has been shown to be a powerful predictor of postoperative myocardial infarction

and cardiac arrest, with a 9.9-fold increase in risk from ASA II to ASA IV and/or emergency surgery. Unfortunately, the performance of the ASA grading has not been evaluated in the presence of the RCRI in studies of postoperative MACE. It is possible that there may be collinearity between the ASA score and the cardiovascular risk factors.

Functional capacity¹

Exercise tolerance is a major predictor of perioperative risk. Functional status can be assessed objectively or subjectively and expressed in metabolic equivalents of task (MET). Inability to achieve 4 METs is associated with increased perioperative cardiovascular morbidity.

One MET is defined as the resting oxygen consumption of a 40 year old, 70 kg male in the sitting position ~ 3.5 mL O₂ /kg/min. Relationship of anaerobic threshold (AT) to major surgical risk;

- AT > 11ml O₂/kg/min ~ 0,8% mortality
- AT < 11ml O₂/kg/min ~ 18% mortality

Functional capacity is classified as excellent (>10 METs), good (7-10 METs), moderate (4-6 METs), and poor (<4 METs).

Indicators of functional status include the following:

- take care of self; eat, dress, or use the toilet (1 MET)
- walk up a flight of steps or a hill or walk on level ground at 3 to 4 mph (4 METs)
- do heavy work around the house; scrubbing floors, lifting or moving heavy furniture, climb 2 flights of stairs, running briefly, playing golf (4 - 10 METs).
- participate in strenuous sports; swimming, tennis, football and skiing (>10 METs)

Functional status can also be assessed more formally by Duke Activity Status Index and the Specific Activity Scale.

Analyses from the ACS NSQIP dataset have shown that dependent functional status, based on the need for assistance with activities of daily living rather than on METs, is associated with significantly increased risk of perioperative morbidity and mortality.

Frailty assessment¹⁸

Frailty assessment is included in the 2014 ACA/AHA guideline for management of valvular heart disease risk algorithms. Frailty is defined as the ability to perform activities of daily living- independence in feeding, bathing, dressing, transferring, toileting, urinary continence, etc. Published frailty scores are available, but in a limited evaluation the following may be used:

- no frailty (perform all activities of daily living and a 5 meter walk in <6 seconds)
- mild degree of frailty (unable to perform 1 activities of daily living /a 5 m walk in <6 s)
- moderate-to-severe degree of frailty (unable to perform >2 activities of daily living).

Other factors to consider not included in risk models are concurrent medications, obesity, atrial fibrillation and biomarkers.

Obesity

Obese patients are at increased risk for adverse cardiovascular events at the time of non-cardiac surgery. However, obesity has not been shown to be an independent predictor.

Role of biomarkers to improve/modify on RCRI⁹

Biomarkers may provide incremental predictive value.

Routine creatinine screening is currently required for cardiovascular risk stratification.

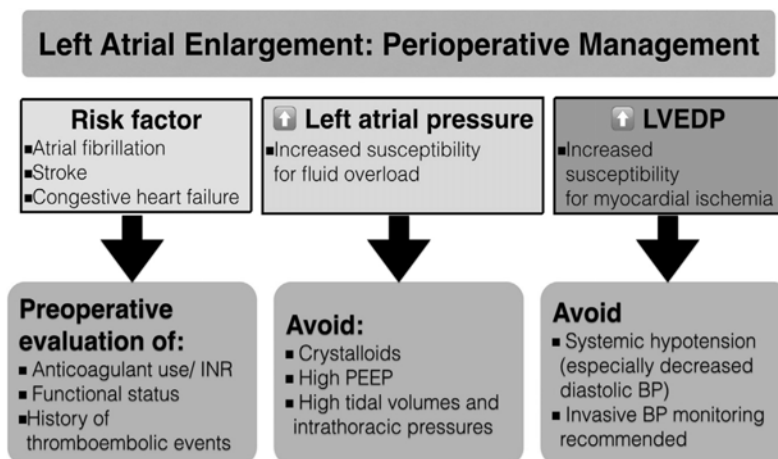
It is thus likely that preoperative biomarker estimation will also be integrated into routine preoperative cardiovascular risk stratification in the future.

- Preoperative B-type natriuretic peptides significantly increase the number of patients correctly reclassified as being at risk of MACE (strong individual data)
- Preoperative risk stratification with troponins is currently controversial. At present the controversy surrounding the significance of troponin as a marker of primary myocardial injury versus troponin release secondary to non-cardiac etiologies.
- Pre- and post-operative patients that could most benefit from BNP or Troponin for early detection of post-operative complications:¹⁴
 - o METS <4
 - o RCRI >1 in vascular surgery or >2 non-vascular surgery
 - o Post-operative APGAR score <7

Atrial fibrillation (AF)

A retrospective, administrative database study demonstrated an association between a history of prior admission for AF and postoperative complications. The risk associated with AF was higher than that associated with a diagnosis of coronary artery disease.¹⁹

Left atrial size and perioperative cardiac risk (Bardia A et al. JCVA 2014;28;6.)



Stratify ischemic stroke risk in patients with nonvalvular AF:

The CHADS₂ score has been validated in multiple nonvalvular AF cohorts. There is an increase in stroke rate of 2.0% for each 1-point increase in CHADS₂ score (from 1.9% with a score of 0 to 18.2% with a score of 6). A limitation of this scoring system is that a score of 1 is considered an "intermediate" risk and those at lowest risk may not be well identified. Furthermore, patients whose only risk factor is a CHADS₂ score of 2 due to prior stroke may have a greater risk than a score of 2 would indicate.

CHADS₂ Congestive heart failure Hypertension Age >75 years Diabetes mellitus prior Stroke/TIA/TE 1 point for each risk factor except 2 points for prior stroke, TIA, TE

The CHA₂DS₂-VASc score has a broader score range (0 to 9) and includes a larger number of risk factors than the CHADS₂.

Women cannot achieve a CHA₂DS₂-VASc score of 0. CHA₂DS₂-VASc index better discriminated stroke risk among subjects with a baseline CHADS₂ score of 0 to 1 with an improved predictive ability.

CHA₂DS₂-VASc score more clearly defines anticoagulation recommendations than the CHADS₂ score.

More patients, especially older women, were redistributed from the low to high-risk categories.

CHA₂DS₂-VASc Congestive heart failure Hypertension Age >75 years* Diabetes mellitus prior Stroke/TIA/TE* Vascular disease Age 65 to 74 years Female Sex 1 point for each risk factor except; *Age >75 years *prior Stroke, TIA, TE *score 2 points each

Scores defining patients on anti-coagulation at elevated bleeding risk.

- HAS-BLED score [hypertension (SBP >160 mm Hg), abnormal liver/renal function, history of stroke/bleeding, labile INRs, elderly age (>65 years), use of drugs that promote bleeding, or alcohol excess].
- RIETE (Computerized Registry of Patients With Venous Thromboembolism),
- HEMORR2HAGES (Hepatic or Renal Dis- ease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Rebleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke),
- ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation)

A score > 3 indicates potentially “high risk” for bleeding and may require closer observation of a patient for adverse risks, closer monitoring of INRs, or differential dose selections for oral anticoagulants or aspirin. HAS-BLED is better at discriminating risk than the HEMORR2HAGES or ATRIA scoring systems are, but all 3 scores had C indexes <0.70 in the receiver operating curves, indicating only modest performance and poor predictive accuracy.

Conduction disturbances:

The presence of supraventricular or ventricular dysrhythmias preoperatively is considered an independent risk factor for adverse postoperative cardiac events. Patients with these arrhythmias are at an elevated risk of experiencing intraoperative and postoperative arrhythmias. However, they are not at increased risk for perioperative fatal or nonfatal MIs.

Bundle branch blocks or first-degree heart block is unlikely to progress to complete heart block perioperatively. Patients with delayed conduction and heart block that are asymptomatic and have no history of syncope do not require implantation of a temporary or permanent pacemaker. Patients with advanced heart block (second-degree Mobitz 2, third-degree) will need a temporary or permanent pacemaker prior to surgery.

Conclusion:

Risk models help with objective patient assessment and should not dictate management decisions but should be regarded as one piece of the puzzle to be evaluated. The ideal model must be globally validated, accurate, readily available, clinically easy to use and updated every few years.

Risk discussion requires clear communication, should be easy to understand. A patient has to make a choice whether to proceed with an operation, balancing the chances of harm and benefit with each choice.

Recommended reading

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- iii) Biccadd BM. Proposed research plan for the derivation of a new cardiac risk index. *Anesth Analg* 2015;120:543–53.

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Neonatal Monitoring

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The same minimum monitoring standards that apply to adult patients, should apply to neonates. It may take some effort from the medical practitioner to ensure that a facility has the appropriate equipment to manage a neonate. The unavailability of such equipment should compel staff involved in the care of a neonate to transfer the baby to a suitable institution, or source the necessary equipment. **SASA's Practice guidelines** can be found on their website¹.

The **ASA Monitoring standards** demand the following:

1. Qualified anaesthesia personnel monitoring the patient
2. Oxygenation, ventilation, circulation and temperature (when changes expected) shall be evaluated regularly. These include:
 - a. Inspiratory oxygen (FiO₂) with low limit alarm
 - b. Arterial saturation by pulse oximetry (SpO₂) with audible pulse and low limit alarm
 - c. Ability to inspect the colour of the patient
 - d. Capnography if at all possible ("EtCO₂")
 - e. Respirometry is strongly encouraged
 - f. Disconnection alarm (if positive pressure ventilation is used)
 - g. Electrocardiography (ECG)
 - h. Blood pressure (BP) and heart rate (HR) at least every 5 minutes
 - i. Presence of a pulse

Neonates are at risk of **hypothermia**, which makes regular monitoring of temperature mandatory for anything but the shortest of cases. Furthermore they may be at risk of **hypoglycaemia**, mandating the measurement of blood glucose.

Invasive monitoring pose special challenges and may have an increased risk-to-benefit ratio. It will be discussed further under haemodynamic monitoring. When monitoring neonates, one has to consider what values to aim for, and this will be alluded to in the following discussion.

1. EVIDENCE

Monitoring standards are mostly based on expert opinion. A review looking at the monitoring of neonates in the intensive care unit (ICU) to assess the evidence for the use of various monitors, concluded that HR, ECG, non-invasive and invasive BP, atrial pressure, SpO₂ and EtCO₂ are monitored frequently in ICU without any evidence. Expert opinion indicates that SpO₂ and EtCO₂ should be monitored routinely in ICU. Invasive BP measurement is indicated in shocked neonates, and HR, ECG and atrial pressure are deemed to be indicated only in specific settings, e.g. after cardiac surgery.²

From this it can be deduced that **ECG** is not a very critical monitor in neonates in the ICU. It does not suggest that ECG has no value in theatre, though. Useful information has been derived from the ECG in the theatre setting where major changes can happen within moments. An example would be a baby having a laparotomy for necrotizing enterocolitis. Incision through the abdominal wall may cause a sudden reperfusion from the abdomen resulting in arrhythmias. Massive transfusion can cause hypocalcaemia, which can manifest as a prolongation of the QT time.

Frequent **clinical assessment** is invaluable, because normal values for neonates are still unclear. Therefore clinical condition together with trends in parameters may have more relevance in an individual patient than a single measured number.²

Table 1: Ranges for normal vital signs

Age	HR (beats per min)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Respiratory rate per min.
Premature	120 – 170	55 – 75	35 – 45	40 – 70
0 – 3 months	100 – 150	65 – 85	45 – 55	35 – 55
3 – 6 months	90 – 120	70 – 90	50 – 65	30 – 45
6 – 12 months	80 – 120	80 – 100	55 – 65	25 – 40
1 – 3 years	70 – 110	90 – 105	55 – 70	20 – 30
3 – 6 years	65 – 110	95 – 110	60 – 75	20 – 25
6 – 12 years	60 – 95	100 – 120	60 – 75	14 – 22
>12 years	55 – 85	110 – 135	65 – 85	12 – 18

2. HAEMODYNAMIC MONITORING

Technicalities of non-invasive BP (NIBP):

Cuff width to limb circumference should be 0.44 – 0.55 for most accurate readings.³ Use of leg and arm for NIBP measurement showed similar accuracy in earlier studies,⁴ but a recent, large study refuted this.

Older studies showed that non-invasive measurement overestimates BP at lower blood pressures. Newer investigations (likely with newer equipment) indicate that NIBP measurements can be reasonably accurate,^{5,4} but others disagree.⁶ It seems that systolic NIBP correlates best with invasive measurements, followed by mean pressure, and that there is poor correlation with diastolic measurements in neonates. In summary, it is therefore reasonable to say that oscillometric measurements of systolic pressure are good as a trend monitor, but may show increasing bias at lower blood pressures.²

$$\text{BP} = \text{CO} \times \text{SVR} = (\text{SV} \times \text{HR}) \times \text{SVR}$$

We routinely measure BP and HR. Cardiac output (CO) is rarely measured, but is likely more important than BP in neonates and premature babies. The relationship between CO and BP implies that, under certain conditions CO will increase when BP is lowered.²

Normal systolic BP for a term neonate in the first 24 hours is 62.6 mmHg, going up to 68.4 mmHg after 36 hours, and to a BP of 72/51 mmHg by the end of the first week of life.⁷

Hypotension in (especially premature) neonates is difficult to define. Minimum mean BP of 30 mmHg, mean BP of gestational age (in weeks), and tenth percentile of age- and birth weight specific reference values are generally used.

Although the extent and duration of hypotension correlates to organ damage in certain studies, hypotension is not a reliable marker of hypoperfusion in neonates.⁵ Several studies (often done on very low birth weight babies) found no association between hypotension and neurodevelopmental outcome. Dempsey found no difference in outcome of hypotensive neonates who had *no* signs of impaired perfusion.

The presence of cerebral autoregulation is unpredictable, and often dopamine may increase the BP without increasing NIRS (near infrared spectroscopy) values. Alderliesten found that low BP was not associated with low cerebral NIRS, or with poor neurodevelopmental outcome. However cerebral NIRS less than 50% was associated with neurodevelopmental outcome.⁸

NIRS is particularly useful in neonates and small children, because limited depth of penetration of NIRS is not a limiting factor in this population. Cerebral values of 60 – 80% are normal, and cerebral

oxygen debt can be expected at values of 35 – 45%. The somatic-cerebral gradient (normal 10 – 15%) is particularly useful. It narrows with sympathetic activation, and can indicate early shock before decompensation.⁹ At the outset of shock, perfusion to “non-essential” tissues (e.g. splanchnic circulation) drops, while “essential” organs (e.g. brain) remains well perfused.

Interestingly, the vessels of the forebrain of very premature babies act like “low-priority” vessels for the first few days of life: they behave like splanchnic vessels and constrict in response to decreased cardiac output.¹⁰

Additional entities that can be monitored to assess haemodynamic status, include:^{10,11,12}

- Capillary refill time (CRT)
- Central-peripheral temperature difference (ΔT_{C-P} – performs poorly)
- Pulsatility index (PI, measured by pulse oximeter). PI shows correlation with SVC (superior vena cava) flow, but BP, CRT and ΔT_{C-P} do not correlate to SVC flow.¹³
- Urine output
- Base deficit, serum lactate
- Arterial ultrasound probes
- Echocardiography
- Pulse wave analysis
- Impedance cardiography
- Dilution techniques
- Laser Doppler

Many of these techniques are still being validated and investigated in neonates.

CRT >3 seconds has been accepted as an indication of poor perfusion in neonates. It is most repeatable when done on the chest. It was found to have 55% sensitivity and 81% specificity to predict low SVC flow.¹¹ A CRT >4 seconds combined with a lactate >4 correlates very strongly with a poor SVC flow.⁵

Neonatal stroke volume has traditionally been regarded as “fixed”, but it is now evident that neonates can alter their stroke volume, and therefore **heart rate** is not in a linear relationship with CO.¹⁴

Urine output is low just after birth, followed by polyuria in the second and third day of life, and then settles into a balance with intake.¹⁴

Laser Doppler uses wavelengths of 770 – 790nm, directed at the skin. The Doppler shift measured gives an indication of average velocity of cells in the microcirculation.¹¹

Central venous saturation (ScvO₂) gives an indication of oxygen extraction, and can be used in cyanotic patients to calculate the oxygen extraction ratio. Normal ScvO₂ varies for different sampling sites, because regional oxygen extraction varies for different organs. Normal for SVC is 70 – 75%, internal jugular vein 65 – 70%, and IVC (measured at the IVC-right atrial junction) 80 – 85%.¹² Femoral venous lines are useful to measure right atrial pressure, but not venous saturation.²

Venous-arterial CO₂ difference may also indicate inadequate perfusion. A cut-off value of 6mmHg has been suggested.¹⁵

3. RISKS OF ARTERIAL AND VENOUS CANNULAE

Some well-known risks of **arterial** cannulation (thrombosis, ischaemia, extravasation) are often augmented in neonates.

Radial arteries have the benefit of collateral supply, but may be technically difficult to cannulate in the very small. The radial BP may be significantly lower than aortic BP after cardio-pulmonary bypass and during use of vasopressors. **Brachial** arteries have no collateral circulation, and median nerve injury has been reported in association with brachial artery cannulation. The **axillary** artery has extensive collaterals, and gives a good indication of aortic pressure. It can be technically difficult to access, and extravasation into the axillary sheath can cause brachial plexus injury.¹⁶

The **femoral** artery has good collaterals, and catheters last longer than radial catheters due to the relative size of the vessel. Extraperitoneal haemorrhage may go undetected.¹⁶ The use of femoral artery catheters of adequately small diameter in neonates are associated with an “acceptable” incidence of perfusion-related complications (2.4 – 25%), and decreased perfusion can usually be reversed by removal of the catheter.¹⁷ Complications increase with increased duration of catheter use, and in smaller patients.

Long-term complications of arterial cannulation in infancy include upper or lower limb shortening due to growth plate arrest.¹⁸

Almost all **venous** thrombi in neonates are associated with indwelling venous cannulae. **Thrombosis** is present in 9 – 30% of neonates with central venous lines, but it may be asymptomatic.^{19,20} The high incidence of thrombosis may be due to newborn’s small vessels, low levels of (coagulation and) inhibitor proteins, and conditions like asphyxia. Insertion site does not seem to determine the risk of thrombosis.²⁰

Misplaced lines include femoral venous lines in the ascending lumbar vein. This is more common on the left due to a less acute angle, and should be suspected if (a) blood can not be aspirated, (b) there is a lateral deviation of the catheter at the level of L4/5 on abdominal x-ray, or (c) abdominal x-ray shows the catheter over the vertebral column, instead of to the right of the midline.

Another concern is placement of the catheter in the right atrium. Although an audit of more than 2000 patients showed no pericardial effusions associated with a catheter tip in the right atrium, but most case reports of pericardial effusions report the presence of the catheter tip in the right atrium at diagnosis of the pericardial effusion. Duration of catheter presence may increase the chance of erosion of the atrial wall.¹⁹

The use of **heparin infusion** (0.5 IU/hr – 0.5 IU/kg/hr) is still recommended among physicians dealing with paediatric patients, since there is evidence that it prevents catheter occlusion and prolongs use of the catheter.²⁰

4. CAPNOGRAPHY

Capnography is extremely useful, and can give information about anaesthetic equipment function, airway and breathing, cardiovascular and metabolic function.^{2,21} Hypocapnia is associated with poor clinical outcome in adults and children.⁷ **Hypo- and hypercarbia** have significant complications in premature neonates: it can cause periventricular leukomalacia, intraventricular haemorrhage, and chronic lung disease. Extreme fluctuation in CO₂ is associated with poor neurodevelopmental outcome.²²

The presence of a leak, and dead space of equipment relative to a neonate’s tidal volume, decrease the **accuracy** of EtCO₂ values. Poor lung function also decreases accuracy.²³ Arterial to end-tidal gradients as low as 3 mmHg, but up to 14.8 mmHg have been recorded. Despite potential for inaccuracy, EtCO₂ values give a very good indication of trends (changes) in neonates.^{22,24}

Main stream capnography (with additional dead space as low as 1ml) and side stream capnography using microsampling (50 ml/min.) are more accurate in neonates than conventional side stream capnography with a sampling rate of 150-200 ml/min.²⁵

Transcutaneous EtCO₂ is very accurate in premature babies, and is particularly useful during transport or high frequency oscillatory ventilation. Unfortunately the probe has to be re-sited regularly to prevent skin damage or burns due to heating.²⁴

5. SATURATION

Both hyperoxia and hypoxia are detrimental in neonates. The risks of retinopathy of prematurity (ROP) and broncho-pulmonary dysplasia (BPD) are well documented, but recent RCT’s²⁶ have found increased mortality in the groups of premature neonates targeted to have a SpO₂ of 85 – 89% (vs. 91 – 95%). Sola et al²⁷ did a critical appraisal of these studies, and their group still recommends a

suggested target range for SpO₂ of 87 – 94% if babies are receiving supplemental oxygen. They also refer to another review, where Sola recommends that neonates of any gestational age never be pre-oxygenated – not even for a short period of time. This may be challenging in clinical practice, and there is no data to prove that the avoidance of short duration hyperoxia is more important than the avoidance of short duration hypoxia.

SpO₂ monitors have bias and a wide range of averaging times. SpO₂ can be accurate within 2% if the SaO₂ is >90%, but at lower saturations (as is common in children with congenital heart disease) the pulse oximeter tends to over read increasingly.² New generation SpO₂ monitors with “signal extraction technology” and means to eliminate motion artifact perform better than conventional monitors, and their use is recommended.^{27,28}

SpO₂ monitors are prone to loss of signal, and many will advise that two pulse oximeters be used during surgery on small children.²⁹ “Wrap-around” probes are advisable. The use of adult “clip-on” probes on a neonate’s foot may decrease perfusion (and accuracy), and may cause pressure damage.

TEMPERATURE:

Thermoregulation is very important in neonates. Clinicians need to be aware that neonates are at higher risk of burn injury, though, and burns sustained with use of forced air warmers have been reported in the literature.³⁰

GLUCOSE:

Neonates may be at increased risk of hypoglycemia, although it may just be part of their physiological adaptation. A healthy fasting neonate will produce lactate and ketones that can be used as energy substrate, sparing glucose. However certain babies, e.g. septic or hypoxic-ischaemic babies, or ones with the perinatal conditions listed in table 2, may be at particular risk of hypoglycemia.^{31,32}

Table 2: Risk factors and incidence of neonatal hypoglycemia

Risk factor	Incidence
Preterm or late preterm infants	15 – 67%
Intrauterine growth restriction (IUGR)	18 – 72%
Very low birth weight (VLBW)	Up to 50%
Extremely low birth weight (ELBW)	Up to 70%
Large for gestational age (LGA)	4 – 38%
Infants of diabetic mothers	Up to 50%

However, hyperglycemia may also be present in certain premature neonates, usually due to a combination of insulin resistance and relative insulin deficiency. Hyperglycemia was associated with retinopathy of prematurity, intraventricular haemorrhage and mortality in retrospective observational studies.³²

There are multiple caveats in monitoring glucose in neonates. In the first place, the definition of hypoglycemia in a neonate is ill defined, and ranges from <1.67 to <3.33 mmol/L (most commonly <2.6 mmol/L). Furthermore, multiple factors can cause inaccuracies of point-of-care testing: haemoglobin concentration (false low glucose with high hematocrit, which is typical of neonates), metabolic acidosis, high oxygen tension (false low glucose in certain monitors), hyperbilirubinemia and oedema. Accuracy of point-of-care devices at low ranges of glucose is limited, and values can have an error of up to 1.1 mmol/L.^{31,32} Therefore any value measured by a point-of-care device <3.2 mmol/L should be considered as potentially hypoglycemic.

6. SUMMARY

Neonates deserve the same minimum monitoring as any other patient receiving anaesthesia, but equipment needs to be appropriate, and the application two SpO₂ monitors is very useful.

In addition, extra vigilance is needed with regard to temperature and glucose monitoring. Neonates, and especially premature babies can suffer from hypo- or hyperglycemia.

With regards to haemodynamic monitoring, the risks of invasive lines should be balanced with the benefit (increased accuracy – especially at low values, ease of blood sampling) and utility (importance of BP versus CO). NIRS is a very useful non-invasive monitor, indicating adequacy of oxygen supply, and multisite application can yield much information.

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What's New in Ketamine?

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Ketamine is well known to anaesthesiologists as the dissociative anaesthetic agent with psychotomimetic side effects.

Over the last decade it has surely made a comeback as a much more versatile therapeutic agent used in various disciplines in the realm of medicine.

Ketamine was first synthesized in 1962 and received FDA approval in 1970 for clinical use. Over the last 50 years it has been proven to be a safe and effective drug. Its usefulness is substantial in remote areas and developing countries where resuscitation equipment is scarce. It is also one of the most commonly used drugs in veterinary medicine and a recreational drug of abuse.

More recently ketamine has been used for:

- Analgesia:
 - o Prevention of opioid induced acute tolerance and hyperalgesia
 - o Prevention central sensitization and wind-up
- Treatment for refractory depression.
- Sedation for traumatic brain injury
- Anti-inflammatory actions
- Treatment for refractory status epilepticus.

Chemical structure

Ketamine is a phencyclidine derivative and a non-competitive antagonist of the NMDA receptor. The NMDA receptor is a member of the glutamate receptor family. It is an ion channel with excitatory properties and ketamine antagonises the NMDA receptor calcium pore. (NMDA = N-Methyl-D-aspartate)

Ketamine is composed of a chlorophenyl ring structure bound to a cyclohexanone ring which serves as a chiral centre. The most common preparation is a racemic mixture of 2 enantiomers. The R(-) form known as ketalar and a S(+) form. The S(+) stereoisomer is 4 times more potent and has twice the analgesic potency than the R(-) form. The S(+) form appears to be cleared more rapidly and has shorter duration of action with a faster recovery than the racemic form. The S(+) isomer is not available in South Africa.

Pharmacokinetics

Ketamine can be given IV, IM orally, rectally, subcutaneously, epidurally and via the transnasal route. Ketamine hydrochloride is highly water and lipid soluble and has a pKa of 7.5.

Ketamine has a rapid onset of action with a relatively short duration when given intravenously.

Peak effect :

- 1-5 min (IV)
- 10-15 min (IMI)
- 15-30 min following the oral route

Ketamine has a poor oral bioavailability (17%) with extensive first bypass metabolism. The intranasal bioavailability is about 50% and intramuscular bioavailability is 93%. It is only up to 30% protein bound and leaves the circulation rapidly being redistributed into tissues.

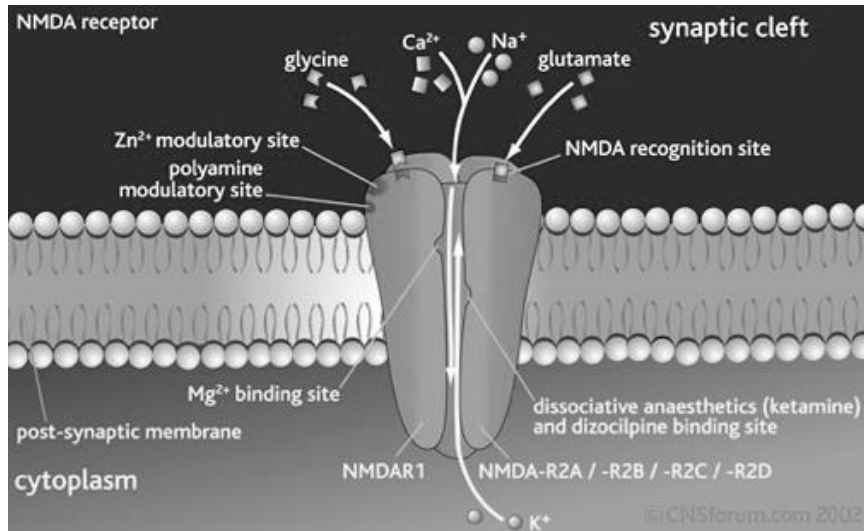
Metabolism is mainly hepatic by the cytochrome P450 system via N-demethylation and mostly metabolized to nor-ketamine an active metabolite but much less potent, which then undergoes renal excretion.

The elimination half-life is 2-3 hours of which 90% is renally excreted.

Repeated doses of ketamine will lead to tolerance, especially to the analgesic effects there-of, which may lead to dependence.

Mechanisms of action

1. Non-competitive antagonist of the NMDA receptor that requires co-activation of 2 ligands (glutamine and glycine). Ketamine has been shown to decrease glutamate driven afferent discharges.



2. Ketamine has some modulatory effects on the opioid receptors. It exerts a central antinociceptive effect through endogenous release of opioids that act on mu and delta receptors which might explain why receiving ketamine requires less opioids. Ketamine also has an effect on the sigma receptor now being a target receptor for antidepressant therapy.
3. Ketamine inhibits the descending inhibitory monoaminergic pain pathways
4. NMDA receptors play an important role in central sensitisation– which leads to an amplification of the response to noiceptive stimuli and a decrease of inhibition leading to hyperalgesia and allodynia and possibly chronic pain or persistent post operative pain. Ketamine inhibits this process.
5. Prevention of wind-up – repetitive noiceptive stimuli are potentiated in the spinal cord before arriving at the pain centres in the brain – which then leads to perceiving more pain.
6. Ketamine also acts as a serotonin and noradrenaline reuptake inhibitor which might add to its antidepressant and analgesic effects
7. Lastly, ketamine has antagonistic effects on the muscarinic receptors.

Pharmacodynamics

• Cardiovascular system

Ketamine is a sympathomimetic; it increases heart rate, cardiac output, systemic as well as pulmonary blood pressures. It stimulates the sympathetic nervous system by inhibiting the neuronal uptake of catecholamines – thereby increasing the circulating concentrations thereof.

The effect of ketamine on rhythm is controversial, animal data suggest ketamine sensitises the myocardium to dysrhythmogenic effects of adrenaline, but it reduced digitalis induced arrhythmias in dogs. The conclusion is that it may have a direct anti-arrhythmic effect on the myocardium but an indirect arrhythmic effect by sympathetic stimulation.

• Respiratory system

Induction with ketamine will maintain the respiratory response to hypercarbic drive. However, a rapid bolus IV has been shown to cause respiratory depression where bag mask ventilation was necessary. Ketamine acts as a bronchodilator – the mechanism being inducing catecholamine release stimulating B2 adrenergic receptors. It also has anticholinergic properties by relaxation of bronchial smooth muscle. However there is no evidence to support the use in acute severe asthma. With ketamine the muscle tone of the tongue and pharynx are maintained together with protective airway reflexes such as coughing, sneezing and swallowing remaining intact and spontaneous breathing continues.

- **Gastrointestinal system**

Ketamine increases salivary gland secretion. In adults it is advised to give a prophylactic antisialogogue. It also increases nausea and vomiting due to the inhibition of neuronal uptake and an increase in serotonergic activity. This can be treated with ondansetron.

- **Musculoskeletal system**

Ketamine may increase skeletal muscle tone. Movements unrelated to noxious stimuli may appear. It can also potentiate muscle relaxants.

- **Eyes**

The effect of ketamine on intraocular pressure remains controversial but it has been concluded that induction with ketamine causes a slight rise in intraocular pressure that is not clinically significant. Ketamine can still safely be used for intraocular procedures but should still be avoided in glaucoma or the open eye.

Side effects

Ketamine's biggest limitation is its unwanted side effects. These are mostly adverse effects on emergence. The most frequently reported are floating sensations, vivid dreams, blurred vision, hallucinations and delirium.

The incidence of hallucinations is 5-30 % and is the lowest in children, it increases from the age of 16 and is more common in females, shorter procedures, larger doses and fast administration of the drug. The prophylactic use of midazolam in adults decreases the severity of psychomimetic phenomena.

In children ketamine administered in high doses IV can cause adverse airway events such as laryngospasm. More commonly in children under 2 or older than 13 years. Interestingly it appears to also to be associated with the administration of anticholinergics and benzodiazepines. Ketamine is a respiratory stimulant that appears to abolish the coupling between loss of consciousness and upper airway dilator muscle dysfunction over a wide dose range.

Well known uses

Induction of general anaesthesia

Doses: IV : 1-2 mg/kg ; IM : 3-5 mg/kg ;

- Unconsciousness is associated with maintenance of airway reflexes and spontaneous ventilation. Consciousness may return within 20 minutes of an anaesthetic dose but full orientation may only be within 60-90min. Amnesia persists for that period although ketamine does not cause retrograde amnesia.
- Induction of acutely hypovolaemic patients. It is important to recognise that it may have cardiodepressant effects if endogenous catecholamine stores are depleted and the sympathetic nervous system's compensatory responses are impaired)
- Ketofol: The combination of sub-anaesthetic doses of ketamine with propofol for total IV anaesthesia has proven more haemodynamically stable than other combinations.
- Infusion regimens using ketamine in children aged (1.5 – 12 years) : the 11-7-5-4 rule (See explanation below)

The regime proposed by Anderson et al ⁷: Loading dose of 2mg/kg followed by an infusion of 11mg/kg/h (0-20 min) then 7mg/kg/h (20-40 min) and then 5 mg/kg/h (40-60min) followed by 4mg/kg/h. (not appropriate in obesity or cardiovascular compromise)

The above regime targets a plasma concentration of 3ug/ml . Children require higher infusion rates than adults and the context sensitive half life is shorter than in adults but increases with increased infusion duration because of return of the drug to the plasma from the peripheral circulation. A large volume of distribution determines the slow return of consciousness. Data suggests that ketamine is more suitable for shorter procedures. A ketamine infusion of longer than 2 hours leads to a prolonged recovery period and is not recommended as a single agent anaesthetic.

Procedural sedation

A propofol-ketamine mixture is becoming increasingly popular for short procedures requiring sedation and analgesia. The optimal dose of each and rate of infusion are unknown. Adding ketamine to propofol will increase the recovery times unless the doses are decreased. Ideal ratios of ketamine to propofol are 1:5 for a 30 min anaesthetic and 1:6.7 for a 90 min anaesthetic.

For sedation in children – especially helpful for the mentally challenged patient or in emergency rooms; suturing a laceration, manipulation of a joint or a change of dressing in a burns patient. Ketamine/midazolam had lower distress scores and pain ratings than fentanyl/midazolam IV for orthopaedic sedations in emergency medicine¹⁷.

IV sedation seems to have a shorter recovery period than ketamine via intramuscular routes (variables in different studies make interpretation difficult because of added midazolam) The average case is prolonged by 20 minutes when given IMI. The IV route is still the preferred route if access can be gained without distressing the child. Anaesthetists still prefer to have IV access but some feel that the IM injection is less traumatic¹⁷.

Benzodiazepines have not been proven to decrease emergence delirium in children and they seem to increase the incidence of oxygen desaturation¹⁸.

Vomiting seems to be a problem, occurring more in older children but some studies neglected to document pre-procedural analgesia or opioids given which might have played a role.

Anticholinergic prophylaxis is not routinely necessary for ketamine sedation in children and midazolam did not reduce the risk of emergence delirium.

Studies have also failed to show any adverse effects with regards to the need for fasting for procedural sedation. No adverse events were shown in 2 large trials. Ketamine is preferred for its preservation of airway reflexes.

Some literature suggest a dose of 0.5-1mg/kg IV and emergency medicine currently recommends 1-1.5mg/kg IV with IM dosing 2-4mg/kg

New developments

Neurocognitive effects

Ketamine is a dissociative anaesthetic agent because of EEG evidence of the dissociation between the thalamo-cortical and limbic systems.

Ketamine has a rapid uptake in the central nervous system due to excellent penetration of the blood brain barrier. The CNS level drops due to redistribution into the peripheral compartment. The thalamus and brainstem send sensory input to the limbic system, which is the processing center that integrates it with information from the sensory association cortex. The limbic system is also important for the development of short and long- term memory. Ketamine depresses these systems, which makes it unable for the CNS to receive or process sensory information and the emotional significance thereof.

This resembles a cataleptic state where even though a patient seems awake: their eyes open, corneal and light reflexes intact with a slow nystagmic gaze, they will be completely unaware of their environment. They can also have various degrees of hypertonus and purposeful skeletal movements independent of surgical stimulation.

Neuroprotection

Ketamine has neuroprotective potential because activation of the NMDA receptor induces cerebral ischemic damage. In rat studies ketamine showed an improvement in neuro-outcomes in head trauma by decreasing plasma catecholamine levels.

Ketamine also attenuated post operative delirium and cognitive dysfunction in patients undergoing cardiac surgery and may produce neuroprotective actions. In other surgical groups it remains unclear. However, there is a concern of mounting evidence from animal studies that even a single or short exposure to clinically relevant doses of ketamine and other commonly used anaesthetic agents may trigger a significant neuroapoptosis response in the developing brain. In a study done on fetal and neonatal rhesus macaque (non human primate), it was shown that 5h exposure of ketamine to these 2

groups initiated neuroapoptoses in the fetus and the neonate. This extrapolates to humans from their 3rd trimester until 6 months of age. This has been reported to cause permanent neurocognitive deficits in the non-human primate.

Ketamine in traumatic brain injury (TBI)

Previously it was thought that ketamine has a harmful effect on patients with traumatic brain injuries. It was reported to cause an elevation in ICP (intracranial pressure) and increased cerebral oxygen consumption. This was documented in the 70's.

The postulated mechanism is large vessel dilatation due to elevated CO₂ in non-ventilated patients, and small vessel vasoconstriction effects related to nitric oxide (NO) synthase inhibition causing a potential increase in cerebral oxygen extraction.

Ketamine does increase cerebral blood flow and metabolism in spontaneously breathing patients and the rise in arterial PCO₂ is the responsible factor for a raised ICP. In patients who are ventilated and sedated, ketamine does not increase intracranial pressure.

There has since been no substantial evidence to support ICP elevations in TBI patients with the use of ketamine in either adults or paediatric patients.

Some studies have shown that ketamine may even decrease the ICP effectively and prevent elevations during potentially stimulating interventions in mechanically ventilated patients with TBI and intracranial hypertension.

Antinociceptive effects (Analgesic actions)

As an analgesic ketamine works at many sites both centrally and peripherally.

1. As potentiation of opioid analgesia and prevention of hyperalgesia and tolerance
2. As a NMDA receptor antagonist - inhibiting windup and central sensitisation.
3. By activation of descending inhibitory monoaminergic pain pathways.
4. By nitric oxide synthase inhibition – NO is a neurotransmitter involved in central and peripheral nervous systems

Ketamine is not often used as a sole analgesic agent, but it is preferably used in sub-anaesthetic doses with other analgesic agents such as opioids and it may have opioid sparing effects. (Potentiation of opioid analgesia)

Opioids have been reported to cause hyperalgesia and tolerance with long term exposure, especially in patients with intractable cancer pain, trauma or neuropathy. This happens due to opioid receptor desensitization and internalisation. Receptor internalisation occurs because of redistribution of opioid receptors from the plasma membrane to intracellular vesicles and also NMDA receptor opioid release. Pre-treatment with NMDA receptor antagonists may prevent this. Ketamine therefore prevents opioid induced hyperalgesia and acute tolerance. Nor-ketamine, the active metabolite of ketamine (30% of the parent compound) has also been reported to have antinociceptive actions and enhances the effects of morphine. It could possibly maintain potentiation of opioid analgesia and prevent both hyperalgesia and tolerance.

A Cochrane database systemic review showed that ketamine reduced 24hr PCA morphine consumption and post op nausea and vomiting.

Ketamine and Morphine combination PCA's significantly reduced pain scores and cumulative morphine consumption and postoperative desaturation in patients undergoing thoracic surgery. This was less clear in orthopaedic or abdominal surgery.

It may also be a useful adjuvant in palliative care and chronic pain. Opioid requirements were also reduced by 50% in a group of patients with cancer pain.

In a review of ketamine as an adjunct analgesic to opioids comparisons were made between ketamine as a single dose, continuous infusion, PCA and epidural with opioids. The conclusion was that a small dose ketamine is a safe and useful adjuvant to standard practice opioid analgesia. There are several major factors that influence this review and make it difficult to compare the different studies and come to a conclusion.

Studies show the efficacy of low-dose continuous ketamine infusions 0.14–0.4 mg/kg as treatment for neuropathic pain.

Continuous subcutaneous infusions of 0.1mg/kg have also shown to provide sufficient analgesia with minimal side effects in trauma patients.

A sufficiently intense or prolonged painful stimulus causes an extraordinary release of glutamate from peripheral nociceptive afferents onto dorsal horn neurons within the spinal cord. The glutamate released, in turn, stimulates NMDA receptors on second-order neurons that produce the phenomena

of windup and central sensitization. It is reasonable to consider that, by blocking NMDA receptors, one might also be able to block cellular mechanisms supporting windup and central sensitization.

Ketamine is the only potent NMDA-blocking drug currently available for clinical use. An appropriate prolonged infusion of ketamine appears to maintain a level of ketamine in the central nervous system long enough to reverse the effects of the sensitization process and associated pain.

- **Analgesia in children**

Postoperative pain is still very undertreated in children and the memory of pain has been shown to worsen both current and future experiences.

Ketamine for perioperative pain treatment in children: A meta analysis found that ketamine was effective in decreasing the pain intensity and analgesic requirements during the PACU (post anaesthetic care unit) for a 0-2 hour stay but not during the 6- 24 hour period. When used locally during tonsillectomies it did decrease both PACU and early (6-24 hours) analgesic requirements¹⁶. During systemic, local or caudal administration, ketamine had analgesic effects in the PACU period and was not associated with an opioid sparing effect. Ketamine decreased early (6-24hours) pain intensity and non-opioid analgesic requirements only when opioids were not used¹⁶.

- **Chronic post surgical pain: CPSP**

CPSP is the long-term consequences of persistent acute pain following surgery. Repeated excitation of peripheral nociceptors causes modulation to occur which is a reversible change in cell receptor expression and protein signaling cascades in the peripheral and central neurons. Nociceptor modification is a long lasting and often irreversible, change in neurotransmitter expression, cell receptors and neuronal connectivity. It is the likely modification that leads to CPSP.

Ketamine has proven to be a useful adjunct and the initiation of NMDA receptor antagonists exhibits preventive effects by inhibiting central sensitization in the dorsal horn. Ketamine limits wind-up in the CNS, activate inhibitory modulation and reduce opioid induced hyperalgesia.

- **Ketamine for patients with CRPS (Complex Regional Pain Syndrome)**

In a systematic review of RCT for CRPS, a low dose IV infusion of Ketamine for (4,5 days in hospital treatment or 10 consecutive days out of hospital treatment) significantly reduced pain compared to placebo in 2 trials. (One high quality and one low quality trial) They concluded that there was some evidence in treatment for adults with longstanding CRPS with ketamine.

Desensitisation therapy may require repeat treatment cycles in some patients (who initially respond with meaningful relief) to maintain the desired desensitisation effect, particularly if the initial site or source of injury or irritation is still active on some level and capable of maintaining or restarting the initial CRPS.

Most patients receiving more than 35mg/hr maximum ketamine infusion doses were noted to be either nonresponders or to have experienced unwanted side effects resulting in interruption of treatment.

The neurotoxic effects seen in animals after high doses of ketamine might have similar potential effects in humans, but this is not known. Currently it is recommended to avoid using high dose infusions and long duration of treatment. It is proposed to limit the duration of a continuous ketamine infusion treatment to a maximum of 4–5 days and, furthermore, to limit the maximum infusion rate to about 25–50 mg/hr. The conclusion is that the use of a low-dose infusion of ketamine may be a useful option in the treatment of patients with intolerable CRPS but it might not be useful in all CRPS patients.

Ketamine's anti-inflammatory effects

The immune-inhibitory effects of ketamine were found to be partly due to inhibition of transcription factor activator protein-1 and nuclear factor-kB (NF-kB), which regulate the production of pro-inflammatory mediators.

In a study on septic rats, the mortality was reduced with a subanaesthetic dose of ketamine. They showed a significant reduction in the production of tumor necrosis factor alpha and interleukin 6. This has been shown in the clinical setting in patients undergoing coronary artery bypass surgery (CABG) where a low dose ketamine (0,25mg/kg) significantly suppressed intraoperative and

postoperative increases in serum IL-6 and significantly decreased superoxide production. Similarly a dose of 0,5mg/kg attenuated an increase in C-reactive protein, IL6 and IL-10 after cardiac surgery with CPB. This has not been shown in low risk patients undergoing off-pump CABG.

Ketamine as an antidepressant

Studies have investigated the use of ketamine as a rapid antidepressant¹³. Intravenous ketamine seems to be a promising antidepressant and clinical efficacy reported a decrease in suicidal ideations of up to 79% but this is only of transient nature. The recommended long-term use of ketamine has adverse effects and the most concerning is memory impairment. However a recent systemic review has shown that low dosages of ketamine have a procognitive effect and actually improved memory on individuals with treatment resistant depression. It is certainly an area that will be researched further.
^{10,13}

Ketamine for refractory Status Epilepticus.

Ketamine's effect on an EEG is that it abolishes the alpha rhythm and dominates theta activity. At high doses there will be a burst suppression pattern. Ketamine is unlikely to precipitate a generalized convulsion in patients with seizure disorders. EEG evidence of cortical epileptic activity is absent and ketamine is considered to have anticonvulsant activity. It also does not alter the seizure threshold in patients with seizure disorders.

In a retrospective multicenter study from 1999-2012 on patients who had refractory status epilepticus, the authors concluded that ketamine was a relative safe and effective drug to use for refractory status epilepticus. This was after a median dose of 1,5mg/kg as a bolus (maximum 5 mg/kg) followed by an infusion dose median (2,75mg/kg/hr) with a maximum dose of 10mg/kg/hr) No response was observed with a dose lower than 0.9mg/kg/hr¹².

Conclusion

Ketamine has a longstanding track record of being a suitable anaesthetic agent for the haemodynamically unstable patient with the added advantage of providing analgesic effects. However recent advances demonstrate that Ketamine has a much wider range of effects and uses. Importantly neuroprotective and antinociceptive effects makes this agent an important tool in the armamentarium of any anaesthetist.

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Procedural Sedation and Analgesia for the Specialist Anaesthetist

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Introduction

The escalating cost of health care and the availability of modern, less invasive surgical techniques are some of the key factors driving procedural sedation rather than general anaesthesia for therapeutic and diagnostic procedures. Whether specialist anaesthetists are comfortable providing sedation for certain procedures or patients is often no longer in their own hands. In private health care, medical insurers dictate which surgeries will be fully covered when performed under procedural sedation (e.g. dental cases, GIT procedures, etc.) and in the public sector a high turnover surgical service with early discharge (within hours after surgery) will allow scarce resources to be stretched further. The challenge facing the specialist anaesthetist is to meet all of these expectations, but still focus primarily on patient safety and patient satisfaction.

Definitions

Conscious sedation is defined as “A technique in which the use of a drug or drugs produces a state of depression of the central nervous system enabling treatment to be carried out, but during which verbal contact with the patient is maintained throughout the period of sedation. The drugs and techniques used to provide conscious sedation should carry a margin of safety wide enough to render loss of consciousness unlikely.”

Certain procedures may require a state of “**deep sedation**”, where patients do not respond to verbal or simple physical stimuli, and may not maintain a clear airway. This state may not equate to general anaesthesia, but there is a consensus that its supervision requires the same level of training and skill (“monitored anaesthesia care / MAC”). Both conscious sedation and deep sedation / MAC are encompassed in the term “**procedural sedation and analgesia**” or PSA.

The South African Society of Anaesthesiologists describes the continuum of sedation as follows:

	Minimal sedation and anxiolysis	Moderate sedation and analgesia	Deep sedation and analgesia	General anaesthesia
Responsiveness	Responds to verbal stimuli	Purposeful response to verbal or tactile stimuli	Purposeful response only after repeated or painful stimuli	Unable to rouse
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

The following statement by the American Society of Anaesthesiologists must be considered for every sedation procedure: “Because sedation is a continuum, it is not always possible to predict how an individual patient will respond. Hence, practitioners intending to produce a given level of sedation should be able to rescue patients whose level of sedation becomes deeper than that initially intended. Individuals administering moderate sedation and analgesia should be able to rescue patients who enter a state of deep sedation and analgesia, while those administering deep sedation and analgesia should be able to rescue patients entering a state of general anaesthesia. The rescue of a patient from a deeper level of sedation than that intended is an intervention by a practitioner proficient in airway management and ALS. The qualified practitioner corrects adverse physiological consequences

of the deeper-than-intended level of sedation, such as hypoventilation, hypoxia and hypotension, and returns the patient to the originally intended level of sedation.”

The skilled anaesthetist will appreciate that during the course of a single procedure (e.g. bronchoscopy or colonoscopy) it may be necessary to have a patient at different levels of sedation. Initially patient co-operation may be desirable (e.g. to cough or breath hold), but later during more painful or noxious periods moderate to deep sedation and analgesia may be necessary. Additionally, during these periods the absence of patient resistance may facilitate more rapid progress, reducing procedure time and health care costs. At the end of the procedure the patient should ideally recover swiftly so that only minimal sedation is still present upon exiting the procedure room or theatre.

Preparation for sedation

Patient selection and assessment

All patients being considered for PSA should be appropriately selected and fully assessed and evaluated before the procedure. Inadequate pre-sedation assessment is a major factor in sedation-related adverse events and poor outcomes. The assessment should encompass a full history and examination with a review of available medical records. Special attention should be paid to the cardiovascular and respiratory systems, including a focused airway assessment. Relevant special investigations related to the patient's medical condition must be available before commencement of the procedure.

Patients should be classified according to the ASA physical status classification system. ASA I and II patients may be considered for specific procedures outside of an operating room. All ASA III, IV and V patients require higher levels of care and should be sedated in a hospital.

Valid informed consent

Consent for PSA involves a discussion between the patient and the practitioner, where appropriate information is provided and the patient is able to ask questions to assist him/her to understand the risks. Alternative techniques such as local anaesthesia or general anaesthesia should be discussed. Guidelines suggest that this should not occur immediately before the procedure, but this is often problematic as most patients only meet their sedationist / anaesthetist on the day of surgery.

Valid verbal and written consent must be obtained for every PSA. This consent must include an explanation of the procedure, the proposed sedation technique, costs, and an explanation of the risks and benefits. Patients must be informed that the sedation technique may fail and that the procedure may be abandoned, performed under general anaesthesia or performed at a later date. Consent must be obtained for both the procedure and the sedation.

Environmental and clinical setting

The environment where any sedation is performed should be adequately equipped to perform this function, with all the required personnel, equipment and drugs available. Resuscitation equipment must be checked regularly and maintained. The sedationist working in an out-of-hospital location should understand the limitations of his current environment and plan his level of sedation accordingly. Irrespective of the setting, the sedation team must have access to an intensive care setting.

Sedation practitioners may be classified as: single operator sedation practitioners or dedicated sedation practitioners. During brief, minor procedures the single operator sedation practitioner may provide the sedation and perform the procedure, but will require a second person, i.e. an observer, to assist with monitoring the patient.

A three-person sedation team is suggested for all other procedures and should include: an operator, a sedation practitioner and an assistant to the procedure. The sedation practitioner should ideally be an anaesthetist when the procedure is expected to be complex or prolonged, if the patient has co-morbidities or if advanced sedation techniques are to be used.

Monitoring

Patients undergoing PSA are monitored for the following reasons:

- i. to ensure that the appropriate level of sedation and analgesia is being administered
- ii. to pre-empt any adverse events and allow early adjustment of the sedation technique
- iii. to assist in the management of any complications that may arise

The level of sedation and analgesia achieved may be scored clinically on the University of Michigan Sedation Scale, which follows the levels of sedation on the sedation continuum (as per SASA guidelines).

The University of Michigan Sedation Scale		
0	Awake and alert	
1	Minimally sedated	The patient is drowsy and sleepy, but rousable to verbal commands
2	Moderately sedated	The patient may be sleeping, but can be easily roused by light tactile stimulation
3	Deeply sedated	The patient is asleep, and is only rousable by significant physical stimulation or repeated painful stimuli
4	Unrousable	The patient does not respond to significant physical stimulation

The **SASA sedation guidelines of 2015** recommend the following for any PSA:

- Continuous monitoring of heart rate and pulse oximetry
- Intermittent recordings of respiratory rate and blood pressure.
- ECG monitoring and capnography are recommended for: deep sedation, multi-drug sedation and patients with underlying co-morbidities (ischaemic heart disease, respiratory disease, obesity, etc.).

The routine administration of oxygen during sedation is not necessary if adequate monitoring has been applied. Low-flow oxygen via nasal cannula can be used if needed and is less likely to mask significant hypoventilation (newer cannulae allow side-stream capnography on the same device).

BIS monitoring may be utilised and in general values correlate well with the level of sedation, where a score of 65 – 85 implies adequate sedation. The following should be kept in mind:

- i. BIS-sedation is most accurate for propofol and less so with other agents, especially ketamine
- ii. there is no predictable relationship between BIS and analgesia
- iii. there is no predictable relationship between BIS and amnesia (most notably with the benzodiazepines)
- iv. a BIS value indicates what has occurred in the previous 15 – 30 seconds and does not predict what will occur when a stimulus is applied (especially with insufficient analgesia)

All patients scheduled for PSA must have a functioning intravenous catheter placed before the procedure, even if only oral agents will be used.

Agents used in procedural sedation and analgesia

The drugs used in PSA are often used in different dosages than stated on their package inserts, the main reason for this is that multiple drugs are often used and act synergistically (the effect of either drug is greater when used in combination than when used alone).

Broadly the agents used in PSA may be classified as follows:

Oral agents	Benzodiazepines Phenothiazines Butyrophenones Ketamine Chloral hydrate Anti-histamines
Inhalational agents	Nitrous oxide Sevoflurane
Rectal / transnasal agents	Barbiturates Opioids Benzodiazepines Ketamine
Intravenous / intramuscular agents	See Below

The intravenous agents provide numerous advantages. They have a predictable time of onset and are titratable. Ideal agents are short acting and rapidly eliminated, have a wide therapeutic window and minimal inter-patient variability.

Commonly used intravenous agents can be classified as follows:

Drug	Dose	Time to peak effect	Duration of action
SEDATIVES			
a. <i>Benzodiazepines</i> Midazolam	0.05 – 0.1mg/kg	3 – 5 minutes	20-60 minutes
b. <i>Alpha-2 agonists</i> Dexmedetomidine	loading dose of 1 mcg/kg over 10 min	20 minutes	2 hours
Clonidine	1 – 5 mcg/kg	20 – 40 minutes	60 minutes
ANAESTHETIC INDUCTION AGENTS			
Propofol	0.5mg/kg over 3-5 min	2 – 3 minutes	5 – 8 minutes
Ketamine	0.5 – 1 mg/kg	3 – 5 minutes	5 – 10 minutes
Etomidate	0.1mg/kg	2 – 3 minutes	10 – 15 minutes
ANALGESICS			
a. <i>Opioids</i> Fentanyl	0.25 mcg/kg	3 – 5 minutes	30 minutes
Alfentanil	2 – 3 mcg/kg	60 – 120 seconds	5 minutes
Sufentanil	0.02 mcg/kg	5 – 6 minutes	30 minutes
Remifentanil	0.02 – 0.25 mcg/kg/min	60 – 120 seconds	3 – 6 minutes at the end of infusion
b. Tramadol	1 – 2 mg/kg	20 minutes	9 hours
c. <i>Simple analgesics</i> Paracetamol	15 – 20 mg/kg	30 minutes	4 – 6 hours
Diclofenac	1 – 1.5mg/kg	30 – 120 minutes	6 – 8 hours
Paracoxib	40 mg	20 minutes	6 – 8 hours
NOVEL AGENTS			
Remimazolam	0.075 – 0.2 mg/kg	1 – 3 minutes	15 minutes

The **benzodiazepines** are the most commonly used sedative agents and are ideal for simple sedation or as part of advanced sedation techniques. These agents have a good safety record, with excellent cardiovascular stability, but the most common side effect is respiratory depression – particularly in the elderly. The respiratory depression produced has a synergistic effect with other sedative agents, and especially the opioids.

The **alpha-2 agonists** are sedative analgesics with anxiolytic, but not amnestic effects. Unlike the benzodiazepines these drugs have minimal respiratory depressant effects, but at higher doses do cause hypotension, profound bradycardia and even sinus arrest. **Dexmedetomidine** is a highly selective alpha-2 agonist and licensed for use in South Africa in an operating theatre (in a hospital) and in the intensive care setting. Combinations of ketamine and dexmedetomidine are gaining popularity in PSA and dexmedetomidine is increasingly being administered by nasal or buccal route in children.

Propofol is a very effective sedative hypnotic and amnestic, however it has a narrow therapeutic index with deep sedation and may rapidly cause airway obstruction and / or apnoea, and hypotension – therefore propofol should only be used by experienced sedationists and never by single operator sedation practitioners. Propofol may be utilised as small boluses titrated to effect or as a continuous infusion. As propofol has no intrinsic analgesic properties, it is often used in combination with opioids, which further increases the risk for respiratory depression and apnoea. The medium in which propofol is prepared is lipid-based and supports the growth of microorganisms, thus single-use vials should be discarded after each patient and aseptic techniques should be used.

Ketamine is an NMDA receptor antagonist, reducing the presynaptic release of glutamate (an excitatory neurotransmitter). It is available as a racemic mixture of two isomers S(+) and R(-), which is the most commonly used form and is very effective. A single S(+) isomer form is also available. Ketamine is a very popular agent, used by experienced sedationists for a myriad of PSA procedures. It can be administered via multiple routes (iv, im, rectal, buccal, nasal, etc.) and rapidly produces safe sedation, intense analgesia, amnesia, maintains protective reflexes and cardiovascular stability. It is compatible with many other agents, and the sympathomimetic qualities it exhibits when utilised as a general anaesthetic agent are not prominent when practicing PSA.

The thalamoneocortical and limbic dissociation ketamine produces can cause unpleasant dreams, emergence delirium and post-operative agitation – ketamine is thus often administered with a benzodiazepine. Other side effects include: nausea and vomiting, increased production of saliva and tracheobronchial secretions (anti-sialagogues may help – e.g. atropine), ataxia, nystagmus, myoclonus and opisthotonus – though these are rare at dosages used for PSA. Even though ketamine has an excellent safety profile, it should not be used by single operator sedation practitioners.

Ketofol is a mixture of ketamine and propofol commonly administered together in the same syringe. The ratio of ketamine to propofol can range from 1:1 to 1:10 (1:2 and 1:4 being the most popular combinations). The combination allows smaller doses of both drugs to be used, reducing the side effects of both agents. Ketofol can be used as a bolus or as an iv infusion. Ketofol is commonly used in South Africa, and supervised clinical training is recommended.

Opioids are excellent analgesic drugs and produce intense analgesia and some sedation – though they should never be used primarily as sedatives. When used in combination with other agents they increase the incidence of respiratory and cardiac depression. Capnography is recommended when patients are administered a potent opioid, along with full respiratory and cardiovascular monitoring. Naloxone, the specific antagonist, must be available whenever opioids are used.

Remifentanyl is an extremely potent, ultra-short acting opioid, metabolised by non-specific blood and tissue esterases. It is more appropriately administered as a continuous infusion and only in a hospital setting by an anaesthetist. It can be administered as a target controlled infusion (TCI) even in fragile patients for long procedures, however failure of sedation is a real possibility.

Remimazolam is a new benzodiazepine which combines the properties of 2 unique drugs: midazolam and remifentanyl. It acts on GABA receptors (like midazolam), but is metabolised by tissue esterases (like remifentanyl). It has a rapid, more predictable offset of action than other benzodiazepines. It is both faster acting and shorter lasting than midazolam, and has a faster recovery time.

Sedation techniques

Irrespective of the sedation technique used, safe sedation practises are still paramount, including a well-trained sedation team, suitable equipment and adequate monitoring. Describing the possible techniques to the patient before the procedure forms part of informed consent and allows a consideration of all the alternatives.

The main factors determining the choice of sedation technique are:

- the risk / benefit ratio of the technique
- the ASA classification of the patient
- the duration of the sedation required
- the procedure being performed (how extensive and whether analgesia is required)
- the experience of the operator
- the experience of the sedationist
- the environment in which sedation occurs
- any contra-indications to the technique

Simple or standard sedation

Simple sedation is the provision of sedation by a single agent only, e.g. an oral agent, inhalational nitrous oxide in oxygen or titrated doses of a benzodiazepine (e.g. midazolam). The use of any anaesthetic induction agent is considered advanced sedation. Simple analgesics (e.g. Paracetamol) can be added to this technique.

Should a simple sedation technique be insufficient for the procedure or should simple sedation fail – the depth of sedation should only be deepened if : i) the sedationist is experienced enough to manage an advanced technique and, ii) the patient is adequately starved.

Advanced sedation

This technique includes any of the following:

- any combination of drugs administered via any route
- any sedation administered via the intravenous route (with the exception of titrated doses of midazolam up to 0.1mg/kg)
- any inhalational agents, excepting nitrous oxide
- infusion techniques , e.g. target-controlled infusions

The options for administration of intravenous sedation are:

1. a single bolus technique
2. an initial bolus, augmented by further smaller boluses during the procedure (titration)
3. an initial bolus, followed by a continuous infusion
4. target controlled sedation (TCI)
5. patient controlled sedation
6. a combination of the above

The provision of sedation by intermittent boluses is the most commonly used option, especially for brief procedures. During long procedures this technique can be labour intensive and lead to over-sedation of the patient, even if the sedationist is only reacting to patient responses.

Continuous infusions are possible with almost all modern agents. These techniques are less tedious and require a stepwise decrease in infusion rate over time – to avoid accumulation. Infusion rates should also be increased or decreased in response to patient responses to avoid over or under sedation.

TCI uses algorithms and mathematical models to create a variable-rate infusion, designed to maintain a constant plasma level of the sedation agent. Inter-patient variability is a key factor with this technique and the use of secondary agents may lead to over-sedation of the patient.

Patient controlled sedation allows the patient to be the sole provider of anaesthesia (pure bolus technique) or to supplement sedation should they require it (continuous background infusion with small boluses administered by the patient). The pure bolus technique leads to greater patient satisfaction, 10 – 30% lower drug usage and a lower potential of over-sedation. The incidence of over-sedation is higher when a background infusion is used.

Recovery and discharge criteria

All patients recovering from PSA should be monitored by an appropriately trained healthcare professional in a suitably equipped recovery room. Vital signs, level of consciousness, temperature and pain level must be measured and documented at regular intervals. A medical practitioner must still assume overall responsibility for the patient in the recovery area and may not leave the premises until discharge criteria are met.

The Modified Aldrete Scoring System is used for discharge from recovery and the Modified Post Anaesthesia Discharge Scoring System (MPADSS) is used for discharge from hospital.

The modified Aldrete Scoring System		MPADSS	
Characteristic	Score	Vital Signs	Score
Level of Consciousness		BP and Pulse	
Fully awake	2	Within 20% of preoperative baseline	2
Rousable when called	1	Within 20 – 40% of preoperative baseline	1
No response	0	> 40% of the preoperative baseline	0
Oxygen saturation		Activity level	
> 90% breathing room air	2	Steady gait, no dizziness / meets pre-op level	2
Oxygen required to maintain > 90%	1	Requires assistance	1
< 90% even when breathing oxygen	0	Unable to ambulate	0
Circulation and blood pressure		Nausea and vomiting	
Sys BP within 20mmHg of pre-sedation level	2	Minimal: successfully treated with oral medication	2
Sys BP within 20 – 50mmHg of pre-sedation level	1	Moderate: successfully treated with im medication	1
Sys BP > 50mmHg of pre-sedation level	0	Severe: continues after repeated treatment	0
Movement and activity		Pain	
Able to move all extremities on command	2	Acceptability	
Moves 2 extremities on command	1	Yes	2
Doesn't move extremities	0	No	1
Respiration		Surgical bleeding	
Able to breathe and cough freely	2	Minimal: no dressing change required	2
Dyspnoea, or shallow or limited breathing	1	Moderate: up to 2 dressing changes required	1
Apnoea	0	Severe: more than 3 dressing changes required	0
<i>Require score ≥ 9 to exit the recovery room</i>		<i>Score ≥ 9 indicates home readiness</i>	

The ability to take in fluids orally and the ability to pass urine are no longer requirements to ensure home readiness. However, the patient must be advised to contact the responsible physician if no urine has been passed within 8 hours of discharge. A responsible adult must accompany the patient home. The patient and / or carer must be given written and verbal instructions, including the contact details of the physician should complications arise within the first 24 hours after the procedure.

Following PSA the patient may not perform the following for 24 hours:

- drive a motor vehicle
- operate machinery
- drink alcohol
- sign any legal documents

Conclusion

The provision of PSA is a nuanced and specialised field. The perception that sedation is easier and safer than general anaesthesia is false. PSA has a 3 – 9 times greater morbidity rate for the same procedure than general anaesthesia. Not all complications are related to over-sedation – in fact under-sedation (cardiovascular stress, aspiration, failed procedures, etc.) is responsible for approximately 54% of all sedation-related morbidity.

With the escalating cost of healthcare anaesthetists regularly find themselves providing PSA for patients with significant co-morbidities requiring invasive and painful procedures. As litigation against healthcare providers continues to increase, it is essential for all specialist anaesthetists to ensure that they are providing safe, appropriate procedural sedation and analgesia to all their patients.

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Pacemakers, Resynchronisation Therapy and AICDs

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Notes

Notes

Surgical Site Infections

The role of the anaesthetist

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1. Overview

Surgical Site Infections represent one of the most common serious postoperative complications.

A surgical site infection (SSI) is defined simply as *an infection of a surgical wound, occurring within 30 days after an invasive procedure*. SSIs are the commonest infections among surgical patients.

All surgical wounds are likely to become contaminated (via flora from skin or viscera). Contamination may not be noticeable and does not necessarily result in clinical infection – this being determined by the adequacy of the host's defence mechanisms. The most important immune mechanism involved in protecting against SSIs, has been found to be oxidative killing via neutrophil phagocytosis.

The Centres for Disease Control (CDC) classify SSIs into 3 categories: *superficial, deep, and organ space*.

1.1. Superficial SSI

- Diagnosed within 30 days of operation
- Limited to skin and subcutaneous tissue
- Includes at least one of:
 - o Purulent discharge from incision
 - o Organisms isolated on wound culture
- Includes at least one of these signs or symptoms:
 - o Pain or tenderness
 - o Localized wound swelling
 - o Redness

1.2. Deep SSI

- Diagnosed within 30 days of operation, or within 1 year if an implanted device or tissue or organ is involved
- Involves fascial / muscle layer
- Includes at least one of:
 - o Purulent discharge from the deep incision
 - o Spontaneous dehiscence or deliberate opening of fascia by a surgeon when the patient has one of the following:
 - Temperature > 38°C
 - Localized pain / tenderness (unless wound culture negative)
 - Abscess or other sign of infection based on direct examination or exploration or histopathologic or radiologic examination

1.3. Organ Space SSI

- Diagnosed within 30 days of operation, or within 1 year if an implanted device or tissue or organ is involved
- Relates to anatomy opened or manipulated during surgery (excluding the incision)
- Includes at least one of:
 - o Purulent drainage from a drain placed into the organ space
 - o Organisms isolated from fluid or tissues obtained from the organ space
 - o Abscess or other sign of infection on direct examination / histopathology / radiology

2. The scope of the problem

2.1. Incidence

The global pooled incidence of SSI varies between 2 – 5% of all surgical patients. The risk of SSI higher in developing countries than in developed countries. A 2014 meta-analysis by Fan et al. quotes incidences of as low as 1.9% in the US to an 11.8% average in developing countries. The risk increases 10-fold for colonic surgery.

SSIs are the commonest perioperative infections. They may range from local inflammation to fulminant septic shock. Patients who develop SSIs are also at increased risk of readmission to hospital and re-operation. They also contribute to mortality: a recent cohort study found that SSIs were associated with an increased risk of death in addition to increased hospital stay.

SSI after colorectal surgery is the leading cause of postoperative morbidity in this patient group.

Amoran et al. and Awad suggest that over a third of postoperative deaths worldwide are at least in some way associated with an SSI. Moreover, SSIs increase morbidity, hospital stays and have financial implications, increasing the cost of healthcare significantly. Furthermore, we are losing the war on microorganisms, with fewer and fewer antibiotic drugs available to take up arms against a rapidly evolving zoo of dangerous invaders.

The fact is that up to 60% of SSIs are preventable, and that evidence-based techniques exist for several interventions that prevent SSIs.

2.2. Risk of SSI by surgery type

A Cochrane review has investigated the risk of SSI according to type of surgery. The highest risk of SSI has been found with colorectal surgery (40%) and appendicectomy (up to 40%). Various studies have looked at caesarean section and have found differing results, with infection risks ranging between 20% and as high as 80%.

Some other important infection risks include:

Type of surgery	Infection risk
Breast cancer surgery	3 – 15%
Compound fractures	11%
Hernia repair	4%
Intraventricular shunt insertion	1.5 – 38%

2.3. How can we help?

It would be easy to assume that the anaesthetist has, at most, a passive role to play in preventing these nasties. Sure, we give our cefazolin at the start of a procedure and if we're good we wash our hands between every patient contact, possibly with alcohol gel as well. But is this enough? How can we as anaesthetists form an alliance with our surgical colleagues to prevent SSIs most effectively?

An infection avoided is much better than an infection that needs treated, especially considering the rogue's gallery of pathogens ever ready to infiltrate the scene of the crime: As study of SSIs in China by Fen et. Al. reveals that *Staphylococcus aureus* was involved in 14.3% of SSIs in that country, with *Pseudomonas aeruginosa* at 11.9% and *E. coli* contributing 25.9%. Taken as a bloc, half of these organisms were drug-resistant and accounted for more than 70% of SSIs.

The anaesthetist is in a unique position to co-ordinate activities in theatre, which includes preventing SSIs. As such, they have been identified as the ideal person to implement the WHO's Surgical Safety Checklist, for example.

2.4. Summary of variables known to influence surgical site infection risk

2.4.1. Patient factors

- Age: higher risk in elderly patients
- Intrinsic Host Factors / Immune status
- ASA status
- Nutritional state and alcohol use

- Comorbidities
- *S. aureus* colonization
- High BMI
- Stomas
- Smoking
- Hyperglycaemia

2.4.2. Surgical / Procedure-Related Factors

- Anaesthetic Method (GA / LA / RA)
- Timing of antibiotic administration
- Drug Factors
- Hypothermia
- Length of Surgery
- Severity of Surgery
- Type of Surgery
- Wound contamination
- Tissue oxygenation

3. Drug Factors

3.1. Opioids

Opioids are known to suppress immunity as a class effect – particularly with morphine, fentanyl, remifentanyl and pethidine, with an increased incidence of postoperative infections reported where these drugs have been used.

In a prospective, cohort study of 286 patients by Inagi et al. published in 2013, remifentanyl-based anaesthesia was found to be a risk factor for SSI development. Leucocyte and neutrophil counts were shown to be decreased in the arm that received remifentanyl.

An already immunocompromised patient (whether due to DM, HIV or chemotherapy) may be put at further risk with opioid administration, and this may be particularly important in critically ill patients.

3.2. Volatile anaesthetics

All volatiles in current use are known to depress cellular-mediated immunity *in vitro*.

3.3. Nitrous Oxide

The ENIGMA-1 Trial showed that avoiding N₂O resulted in a decreased incidence of postoperative infections.

3.4. Local anaesthetic agents

Lignocaine and bupivacaine, by contrast, exhibit a dose-dependent inhibition of growth of both gram-positive and gram-negative organisms such as *Staphylococcus aureus* and *Pseudomonas*.

4. The Operating Room Environment

The operating room or theatre is not sterile. Patients are not sterile. Healthcare workers are not sterile. The fact is that despite the most thorough preparation, antibiotics and comprehensive sterile manoeuvres and cleaning, the fact is that *all* surgical wounds become contaminated. The type and degree of contamination together with the host's specific internal defensive milieu will determine the outcome.

4.1. Theatre caps

Although their use is universal, there is little evidence for staff to wear disposable headgear except where staff members are in close proximity to the surgical field.

4.2. Suits, scrubs and gowns

Interestingly, there is little to no evidence to show that wearing surgical attire outside of theatre and then returning without changing increases SSIs. The use of an overcoat, however, is recommended.

4.3. Footwear

Overshoes are falling out of favour because hands can be contaminated when overshoes are donned or removed. Special footwear limited to theatre is recommended.

4.4. Face masks

Although facemasks were thought to minimize the transmission of naso- and oropharyngeal pathogens from staff to patient, little evidence has been found to either support or refute the routine wearing of masks – even by surgeons. Despite this, surgical masks are recommended for staff in the direct surgical field. Anaesthesia providers should always wear masks when performing invasive procedures such as epidural and spinal anaesthesia and central line insertions.

Facemasks also play a role in protecting staff. N-95 masks should be used when in contact with high-risk TB cases (both in theatre and in the ward), and patients encouraged to wear one as well.

4.5. Minimizing theatre traffic

It makes sense to limit the amount of staff in theatre to a minimum, and that theatre doors remain closed at all times except for transport of patients.

4.6. Air quality

Air conditioning should meet basic safety standards (> 20 air changes per hour). Temperature should be set between 18 and 22°C and never exceed this. The evidence for colder temperatures is untested and may contribute negatively to hypothermia. Laminar flow is especially important with joint implants (e.g. knee and hip replacements). Positive pressure should be maintained in theatre.

4.7. Personal equipment

Computer keyboards, cell phones, iDevices and stethoscopes are excellent vectors for bacteria and should be cleaned frequently. The use of cell phones in theatre should be kept to a minimum!

4.8. Hand washing –the most important?

- Hand washing may be one of the simplest and most effective ways of preventing the spread of infection in the healthcare environment.
- The anaesthesia provider is an important potential vector for contamination.
- Central lines are particularly at risk, even if they were sited under full aseptic precautions. One study found that over 11% of central line stopcocks were contaminated intraoperatively, and in nearly half of these cases the source was bacteria from anaesthesia providers' hands.
- Washing with soap and water vs. using alcohol-based hand rub have both been shown to be effective. Alcohol hand-rub provides a quick and easy method of hand hygiene and should be used before and after every patient contact.
- Staff with dermatitis / abrasions should cover the affected area(s) appropriately.
- Boxes of gloves and antiseptic gel should be readily available in multiple sites. Ideally, the gel dispenser should be hands-free.

5. Specific Interventional Strategies

5.1. ERAS / Fast-track surgery

The structured approach of ERAS is aimed at attaining faster recovery from surgery, meaning earlier hospital discharge and an earlier return to normal functioning. While it is thought that this may reduce the incidence of SSIs, the impact of ERAS in this regard remains to be shown.

5.2. Using Perioperative Antibiotics Wisely

Most SSIs are the result of Gram-positive skin flora contaminating the wound (mainly *Staphylococcus* and *Streptococcus* species). Gram-negative organisms and anaerobes present a further problem when surgery involves hollow viscera.

The first evidence for antibiotic prophylaxis for SSI prevention was shown in 1961, with many studies confirming this as well as underlining the importance of timing antibiotic administration relative to the first incision. Multiple RCTs and systematic reviews have consistently shown antibiotic prophylaxis to be of benefit in reducing SSIs.

The 2008 UK NICE guidelines recommend a single dose of IV antibiotic prophylaxis before skin incision (or earlier if a tourniquet is used) in the following situations:

- Clean surgery involving the placement of a prosthesis or implant

- Clean-contaminated surgery
- Contaminated surgery

Clean surgery involves no break in aseptic technique, and no breaching of the respiratory, gastrointestinal or genitourinary tracts.

Clean-contaminated surgery involves the oropharynx, sterile genitourinary or biliary tract, the GIT or respiratory tracts, or if there has been a minor breach of aseptic technique.

Contaminated surgery is defined as the presence of acute inflammation, infected bilious secretions, infected urine, or gross contamination from the GIT.

'Dirty' surgery is where established infection is present and therapeutic antibiotics are already being administered.

It is important to note that routine antibiotic prophylaxis, however, is not recommended for clean, uncomplicated surgery that does not involve the insertion of prosthetic material: antibiotics have risks and adverse effects of their own.

Timing of antibiotics

For prophylaxis to be effective, the minimum inhibitory concentration at tissue level must exceed the time period from incision to wound closure. Timing of administration is therefore crucial.

Published guidelines from the National Surgical Infection Prevention Project (2004) are explicit that antibiotics should be administered within 60 minutes of skin incision – the risk of SSI increasing dramatically if antibiotics are given > 2 hrs. before or after surgery. Observational studies demonstrate that infection rate is lowest if antibiotics are given within 30 minutes of incision. It is also important that the agent be given before skin incision; the risk of SSI is two-fold if it is given afterwards.

Antibiotic timing greatly improves when this is administered in theatre rather than in the ward or holding area (improving from 11% to 97% in one study by Kanter et al.) However, it is only recently that the anaesthesiologist has been identified as the most suitable person to be responsible for antibiotic administration. The same study showed that the rate of SSIs fell from 3.8% to 1.4% when antibiotics were made the responsibility of the anaesthesia provider. This has now been recognised by the WHO in that antibiotic prophylaxis is one of the points covered in the Surgical Safety Checklist.

Selection of antibiotic

Regimens should be tailored to [1] the type of surgery (orthopaedic vs colorectal, for example and [2] the wound classification (clean, or clean-contaminated). Furthermore, patients who require modified therapy should be recognised timeously (e.g. penicillin allergy and known MRSA colonisation).

- For cover of Gram-positive skin flora, first-generation cephalosporins remain the agents of choice.
- Additional antibiotics are required where oropharyngeal or gastrointestinal contamination represents a risk. Metronidazole remains the mainstay of anaerobic cover and gentamicin employed for Gram-negative cover. Co-amoxiclav (Augmentin®) is an attractive option as it is a single agent providing "triple cover".
- Where penicillin allergy exists, current guidelines recommend that clindamycin or vancomycin be substituted instead. Vancomycin is also the agent of choice where MRSA colonization is known.

The importance of guidelines

It is recommended that trusts and hospitals have their own published guidelines for prophylaxis, based on the occurrence of local microbes and their antibiotic resistance patterns. These should be formulated in consultation with microbiologists.

To reiterate, we are rapidly losing the war against microbes and no new antibiotics are being developed!

Pharmacokinetic factors

Although cefazolin is commonly used as prophylaxis, it must be remembered that it has a short half-life and that a subsequent dose (or doses) be given with prolonged procedures. This is especially important in cardiothoracic surgery; the standard being that cefazolin be repeated 3-4 hourly. In

addition, many orthopaedic surgery protocols for hip and knee replacement recommend that antibiotics be continued for 24 hours after surgery.

5.3. Skin preparation

While this is not the provenance of the anaesthesia provider, the following are relevant:

- Clipping rather than shaving the skin, and then only if needed. Shaving inflicts damage to the epidermis which is then more easily colonised by topical flora. Folliculitis can result within a single hour. Recent evidence has shown that shaving the skin increases the risk of SSI by a factor of 3. Ideally, no hair removal is optimal and clipping should be restricted to the immediate surgical area. Spread the word that razors are to be banned from the hospital!
- 2% Chlorhexidine-alcohol skin preparations have been shown to be twice as effective to traditional povidone-iodine, and are now standard in most settings. Chlorhexidine works almost instantly, and has a longer duration of action while iodine takes several minutes to be effective. Importantly, the skin prep must not pool around the patient and should be allowed to dry for at least two minutes to ensure efficacy and reduce fire hazards (e.g. from diathermy).
- The surgical wound should be protected with a sterile dressing for 24-48 hours and the patient educated regarding postoperative wound care.

5.4. Temperature management

General anaesthesia is well-known to impair thermoregulation. After induction of GA there is a rapid redistribution of body heat from the core to the periphery. Thermoregulatory vasoconstriction is triggered, decreasing the oxygen tension of subcutaneous tissue.

Hypothermia also has several deleterious effects on immune function, impairing the migration of leukocytes, phagocytosis and cytokine production.

- Both T cell antibody production and nonspecific neutrophil-mediated responses are affected.
- The net effect is an increased risk of SSI – as borne out by the studies that have shown that preventing perioperative hypothermia significantly reduces the incidence of SSIs, “perhaps to an even greater extent than antibiotic prophylaxis” (Forbes & McLean, 2012).
- This effect has been seen both in “clean” surgery (Meling et al, looking at breast, hernia and varicose vein surgery) and “contaminated” surgery (an RCT of 200 patients undergoing colorectal surgery).
- Even mild hypothermia (under 2° C) has been shown to triple the risk of wound infection and to prolong hospitalisation by 20%.

How should we approach perioperative warming? A complete synopsis of all the strategies is beyond the scope of these notes. However, Level 1 evidence supports the use of warmed intravenous fluid and forced-air warmers for preventing hypothermia, and that this should be routine for surgical procedures longer than 45 minutes. Monitoring of core body temperature is now regarded as part of standard monitoring under GA.

5.5. Hyperoxia: friend, foe, or meh?

Inadequate tissue oxygen tension is detrimental to tissue repair / regeneration. Secondly, neutrophils utilize the formation of reactive oxygen species (ROS) to kill pathogens. These include superoxide ions and hydrogen peroxide. When neutrophils ingest foreign debris, they undergo a “respiratory burst” temporarily increasing its oxygen consumption. In theory, a higher tissue oxygen tension would enhance the killing effects of neutrophils. This has been shown *in vitro*, and several studies have also shown an association between low tissue oxygen tension and SSIs.

However, the *in vivo* implications remain controversial.

- Results from prospective RCTs utilising hyperoxia have been conflicting and some have even shown harm. A meta-analysis pooling 2728 patients in seven trials failed to show any difference in the incidence of SSIs between those who received hyperoxia and those who did not.
- Subgroup analyses considering colorectal surgery patients and those who underwent GA *did* suggest a protective effect with hyperoxia however – suggesting that specific patient groups may benefit from hyperoxia. In a single study looking at colorectal surgery, a FiO₂ of 80% vs. 30% was shown to be statistically significant. A study published in 2013 looking at hyperoxia in Caesarean section patients found that administration of 80% oxygen did not improve outcome.
- The PROXI trial randomised 1400 patients undergoing abdominal surgery to receive either 80% or 30% oxygen and also failed to show any improved outcome in the hyperoxia group.

- For studies where high FiO₂ was shown to decrease the risk of SSIs, the difference was *borderline* statistically significant.
- The efficacy of hyperoxia in the absence of antibiotic prophylaxis is unknown, as most studies included standard antibiotic prophylaxis.

As such, current guidelines to prevent SSI only recommend giving sufficient FiO₂ to maintain oxygen saturations above 95%.

5.6. Neuraxial Anaesthesia

Chang et al (2010) proposed that neuraxial as opposed to general anaesthesia is an option to reduce SSI: Three mechanisms have been proposed:

- (1) Neuraxial blockade very effectively blunts the inflammatory and sympathetic response to surgical incision.
- (2) It may also reduce infection via vasodilatation and hence improved tissue oxygenation.
- (3) The superior postoperative analgesia produced prevents or attenuates the autonomic response to pain. It has been found that severe surgical pain will reduce tissue oxygenation by around 15 mmHg.

Chang et al. undertook a population-based study (n = 3081) of surgical site infections in patients undergoing total hip or knee replacement in Taiwan. They postulated that neuraxial anaesthesia may be associated with a lower incidence of SSIs compared to GA in major surgeries. Their study showed that the odds of developing an SSI within 30 days of surgery were 2.21 higher in the GA group as opposed to the neuraxial (epidural or spinal) group.

Epidural analgesia carries a lower risk of some postoperative respiratory complications.

5.7. Glycaemic control: tight or not?

Acute hyperglycaemia leads to several deleterious effects including reduced vasodilatation, impairment of NO generation, chemotaxis, phagocytosis and reduced complement function. The net effect is an increased risk of inflammation and vulnerability to infection.

A 2009 evidenced-based review by Lipshutz et al. noted that, while some studies have shown that tight glycaemic control (targeting between 4.5 and 6 mmol/dL) reduces blood-borne infections, this may occur at an expense of an increase of hypoglycaemic episodes.

While hyperglycaemia is certainly harmful, there is insufficient evidence to support the routine use of tight glycaemic control. Maintaining blood glucose below 10 mmol/dL is more likely to be safe, easy to attain and clinically effective. Glucose should be checked regularly in lengthy major cases and always in diabetics.

5.8. Blood products

Blood transfusion is known to cause immunomodulation and immunosuppression. A meta-analysis has further shown that there is a dose-related, higher incidence of postoperative infections in transfused patients (especially in trauma patients). The risk appears to be greater when older (> 2 weeks) units of blood are used. The use of leucocyte depleted blood or filters is furthermore recommended.

5.9. Pain control

It makes sense that controlling postoperative pain has beneficial physiological effects (decreasing the sympathetic response which has detrimental implications in the tissue bed of a wound – vasoconstriction, reduced tissue perfusion & hence oxygen tension). However, this is yet to be verified.

5.10. Smoking cessation

The cells of smokers live in a hypoxic milieu. For a patient smoking 20 cigarettes a day, smoking will decrease tissue oxygenation from by about 20 mmHg. The risk of SSI is threefold in these patients. This effect reverses quickly after stopping smoking – meaning that even short-term cessation is likely to have a positive effect. That patients should be educated about their risks is obvious. Some authors maintain that smokers should be given supplemental oxygen for a few hours post-surgery, especially if the patient has undergone bowel surgery.

5.11. Asepsis during invasive anaesthetic procedures

Central lines and epidural catheters represent potential sites of entry for bacteria, and guidelines the world over recommend complete barrier precautions when performing these procedures. The

subclavian site is associated with fewer catheter related bloodstream infections, although anaesthesiologists typically place CVCs in the internal jugular. Ultrasound guided techniques may assist in reducing risk, as the use of US typically results in fewer needle insertions.

Chlorhexidine 2% has been shown to have higher efficacy than povidone-iodine. It must be appreciated that chlorhexidine in alcohol carries a high risk of neuronal toxicity and that the operator be scrupulous that needles and catheters are not contaminated with cleaning solution.

Epidural catheter-related infection is fortunately rare but may be catastrophic. Epidural catheters should be removed after 72 hours, the risk of infection rising sharply after this time period.

Peripheral nerve catheters should also be inserted under strict asepsis, though full barrier methods (gown, mask, gloves) are not universally used. It is not known whether PNCs may present a significant source of infection after joint arthroplasty.

5.12. Structuring surgical lists appropriately

“Dirty” cases should be scheduled last on the list. Where not possible, the operating theatre should be ventilated under positive pressure for at least 15 minutes.

6. Summary

- SSIs have major implications for postoperative morbidity
- Preventing SSIs requires a multidisciplinary approach
- The anaesthetist is in a unique position to co-ordinate preventative strategies
- The operating room environment should be optimised to prevent the spread of pathogens as much as possible
- Antibiotic prophylaxis is very effective at reducing but must be tailored appropriately to the type of surgery using the correct antibiotic timeously, within 30 minutes prior to skin incision
- Maintenance of normothermia is crucial. Hypothermia is deleterious and significantly increases the risk of SSIs. Active warming strategies such as forced-air warmers and warmed fluid should be implemented.
- Neuraxial anaesthesia attenuates the inflammatory response to surgical trauma and has a lower incidence of SSIs than GA
- Maintenance of normoglycaemia is important. Tight glucose control risks hypoglycaemia and avoidance of hyperglycaemia (below 10 mmol / dL) may be as effective to reduce SSIs.
- The use of hyperoxia is controversial with equivocal results in the literature. Current evidence does not support its routine use.
- Smoking cessation should be encouraged
- Blood products should be used judiciously and their immunomodulating effects taken into account
- Hand washing is a simple and highly effective way to reduce bacterial contamination.

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Infection control for the anaesthetist

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Infection control in clinical medicine is achieving a steadily increasing amount of attention and interest as the end of the antibiotic era arrives. It is a fact that microbial resistance to current anti-infective agents has reached alarming proportions. This, coupled with the fact that there are no major developments in the antibiotic pipeline, has seen the launch of large programmes driving awareness in infection control, hand hygiene and antibiotic stewardship. It is important to appreciate that many of the programmes, including infection control, have a dual benefit; protection of patients and protection of health care workers.

Hospital acquired infections pose a huge risk to the hospitalized patient population. It has been estimated that in South Africa one in seven hospitalized patients acquire a nosocomial infection!

While the theatre environment has traditionally been seen as one of the most “infection conscious” and clean areas of any hospital, this is sadly not true. While a large amount of effort is focused on sterilization of instruments and drapes, the practice of good infection control has not been optimal. Following discussion started in 2010 the South African Society of Anaesthesiologists produced guidelines for infection control in anaesthesia in 2014. South Africa has thus joined countries like the United Kingdom, Australia, New Zealand, the United States and Singapore in the emphasis of infection control for the anaesthetist.

You need to read the South African guideline!

The legal implications of infection control guidelines

The publication of the South African guideline brings new responsibility to both health care workers and institutions. Hospital employees and medical practitioners need to be aware that ignorance of, or non-compliance with local guidelines or hospital policy may be regarded as negligence. As there is clear evidence that a lack of adherence to infection control policy leads to patient harm, cognizance of the guidelines needs to be taken. Have you introduced the best infection control practices into your own working environment? Have you either intentionally or negligently failed to implement appropriate practices?

A survey of anaesthetists in New Zealand showed that fewer than 44% of practitioners were aware of the content of the local guideline. More than 86% of practitioners split drug ampoules between patients and 41% split multidrug ampoules between patients. This is in clear contravention of their guidelines.

The South African guideline for infection control in anaesthesia

The South African guideline was compiled by a working group representing various areas of expertise including anaesthesia, intensive care, microbiology and virology. Other international guidelines and literature were scrutinized prior to the compilation of the guideline and all chapters reviewed by members of the working group.

The South African guideline encompasses the following:

- An introduction
- An executive summary – a useful overview of the most important points covered
- General principles
- A series of sections dealing with the following issues:
 - o Safe injection practices preventing the contamination of injections and fluids
 - o Hand hygiene guidelines
 - o Anaesthetic equipment decontamination
 - o Prevention of intravascular catheter related infection
 - o Infection control recommendations for regional anaesthesia
 - o Prevention of surgical site infection for the anaesthetist

The highlights of the executive summary and those aspects that most practitioners ignore are highlighted below. All anaesthetic practitioners must be aware of the content of the guideline! You need to read the full guideline!

General principles

- There should be an active infection control programme active in each theatre complex
- Single use devices should be used as such.

Safe injection practices

- Syringes should not be reused or reinserted into a medication vial or solution bag even if for use in the same patient.
- A needle should not be reinserted into a multi-dose vial or solution bag even if for use on the same patient.
- Drug vials should not be shared between patients in any manner whatsoever.
- Multi-dose vials should be used to administer multiple doses of drug to the same patient only.
- Injection ports must be cleaned with alcohol prior to every injection.

Hand hygiene guidelines

- The WHO five moments of hand hygiene is supported. The five moments are:
 - Before patient contact
 - After patient contact
 - Before performing any procedure
 - After any potential contact with fluids
 - After any contact with the patient environment
- Sufficient alcohol based hand rub must be used to ensure adequate decontamination.
- Gloves should be worn whenever potential contact with body fluids or mucous membranes may occur.
- Gloves should be removed prior to touching clinical notes, pens, telephones and other equipment.

Anaesthetic equipment decontamination

- Laryngoscope blades should be cleaned with high-level disinfection as a bare minimum.
- Sterilisation is the advocated means of cleaning laryngoscope blades.
- Magill forceps should be sterilized after each use.

Prevention of intravascular catheter-related infection

- When adherence to sterile technique cannot be guaranteed lines should be removed as soon as possible, and within 48 hours.
- Insertion of a central line is a sterile procedure.
- Connectors and access ports on lines must be cleaned properly prior to connection to or injection.

Infection control recommendations for regional anaesthesia

- Caps, masks, sterile gowns and gloves should always be worn for central neuraxial anaesthetic techniques.
- Where ultrasound is employed a sterile sheath should be used.

Prevention of surgical site infection

Do not give antibiotic prophylaxis for clean, non-prosthetic uncomplicated surgery.
Maintain optimal tissue perfusion and oxygenation.
Consider the use of leucocyte-depleted blood in high-risk patients.

Additional interventions to support patient immunity

The maintenance of body temperature

Every effort should be made to ensure normothermia for all patients presenting for anaesthesia. Hypothermia reduces tissue perfusion and oxygen delivery, impairs neutrophil respiratory burst and oxidative killing.

Perioperative glucose control

Evidence is that blood glucose should be maintained below 10mmol/l at all times. Hyperglycaemia impairs neutrophil chemotaxis and bactericidal activity. This is associated with an increase in wound sepsis and impaired wound healing. Needless to say, hypoglycaemia must be avoided.

Antibiotic prophylaxis

Antibiotics should ideally be administered about 30 minutes prior to skin incision. As pre-operative administration frequently leads to non-administration it is accepted practice for antibiotics to be administered by the anaesthetist in the theatre suite. Administration must be prior to skin incision and is included in the WHO surgical safety checklist.

Controversies and unsupported practices

Numerous references in the literature attest to rituals and practices that cannot be supported and should be discontinued. Sound infection control policy must be evidence based.

Universal or standard precautions

Recommendations are that standard precautions, as defined by the CDC, be adopted for all patient contact. Standard precautions encompass the following:

1. Hand hygiene
2. Appropriate use of personal protective equipment
 - a. Gloves
 - b. Masks
 - c. Goggles
 - d. Gown
3. Appropriate disposal of sharp objects
4. The appropriate cleaning of patient care equipment

The current definition of universal precautions from the CDC (1987), serves to protect health care workers from blood borne pathogens.

Patient preparation for theatre

- There is no evidence that any infection control risk exists from patients wearing their own clothing in the theatre environment.
- The ritual of having patients remove their own underwear is embarrassing and serves no practical purpose whatsoever.
- There is no need for patients to cover their own hair in the operating theatre.
- Getting patients to shower or bath with chlorhexidine based soap prior to major surgery may reduce the incidence of gram-positive wound sepsis.
- Shaving of the surgical site should be discouraged.
- Clipping of hair in the immediate preoperative period may take place if necessary.

Surgical facemasks

- Individuals within 1 meter of the surgical field should wear these, particularly if speaking over the surgical field.
- Facemasks should be worn during the performance of all sterile procedures.
- The mask must cover both nose and mouth.
- Facemasks should always be worn for personal protection during intubation.

Theatre attire

- There is no evidence to support the routine use of theatre caps for staff that are not "scrubbed up".
 - Theatre caps should be worn by all staff in laminar flow theatres
- Clothing worn in theatre needs to be nothing other than "socially" clean.
- Wedding bands need not be removed as part of a standard surgical scrub.

- o Wedding bands are associated with a higher incidence of glove perforation in orthopaedic surgery.
- False fingernails have been proven to harbor pathogens and should not be permitted.
- There is no evidence to show that wearing theatre attire outside of theatre is associated with an increased risk of infection.
- The use of disposable overshoes should be outlawed. Use leads to increased contamination of the hands.
- Visitors to theatre (parents and caregivers) should not be required to dress for theatre, wear cover garments or overshoes.
- Caution is expressed for those taking theatre attire home for cleaning.

Summary

For the purposes of the exam, and clinical practice in general, there needs to be an awareness of the South African guideline for infection control in anaesthesia. It behooves all anaesthetic practitioners to do their utmost to both improve the outcome of patients and to protect themselves as best possible.

It is a sad reality that nosocomial sepsis and pathogens pose a substantial risk to both patients and healthcare workers.

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Perioperative Steroid Use

How to do it

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Introduction

'The need for patients on long-term steroid treatment to increase their dose of glucocorticoids when under stress is a principle that rests in one of the most tranquil corners of medical dogma'. (1)

"...that perioperative glucocorticosteroid supplementation in secondary adrenal insufficiency is an obsolete medical relic". (2)

Early in our anaesthetic careers we learn that patients on chronic steroid therapy must receive supplementary peri-operative steroids in order to avoid severe intra-operative haemodynamic instability and/ or an Addisonian crisis. The physiology behind this dogma remains logical and simple. The administration of exogenous steroids results in a suppression of Adrenocorticotrophin Hormone (ACTH) release from the anterior pituitary leading to deficient adrenal stimulation. The lack of adrenal stimulation results in adrenal atrophy and an inability to produce cortisol when required during stress situations such as surgery leading to the severe unresponsive intra-operative hypotensive state.

Two case reports, both from the early 1950's, are recognized as being the initial description of iatrogenic adrenal insufficiency. (3) Both case reports involved young patients undergoing orthopaedic procedures. The first, a young male patient (34y/o), who had his twice daily 25mg of cortisol withdrawn 48 hours pre-operatively, and the second, a young female patient (20y/o), who had been managed on 100mg cortisol daily & who also had her cortisol withdrawn pre-operatively. (4, 5) Autopsy findings in both patients revealed grossly atrophied adrenal glands. These case reports concluded with a list of recommendations, which became standard practice despite the fact that there may have been numerous other explanations for the patients' deaths apart from adrenal failure.

The first case was complicated by a blood transfusion reaction and both had little or no description of the haemodynamic parameters and neither patient had serum cortisol levels measured before the conclusions were drawn. A number of trials subsequently showed that basal equivalents of the levels of cortisol secreted are adequate in terms of preventing intra-operative haemodynamic instability. (2)

The evidence for peri-operative steroid supplementation, and certainly the initial cases implicating this, as a problem seems to be lacking in terms of large scale trials. Studies done show an association between exogenous steroids and adrenal insufficiency but with little proof that supplementation is beneficial. (6-8). The reality and perception is that by giving steroids a preventable potential complication is easily avoided. Perhaps we should be questioning the rationale behind routine supplementary steroids and certainly acknowledge that the practice of supra-physiological doses of steroids is not necessary. (2) However, until larger studies have been done to examine this question further, it is wise and certainly safer from a defensibility standpoint to follow the current guidelines as they stand.

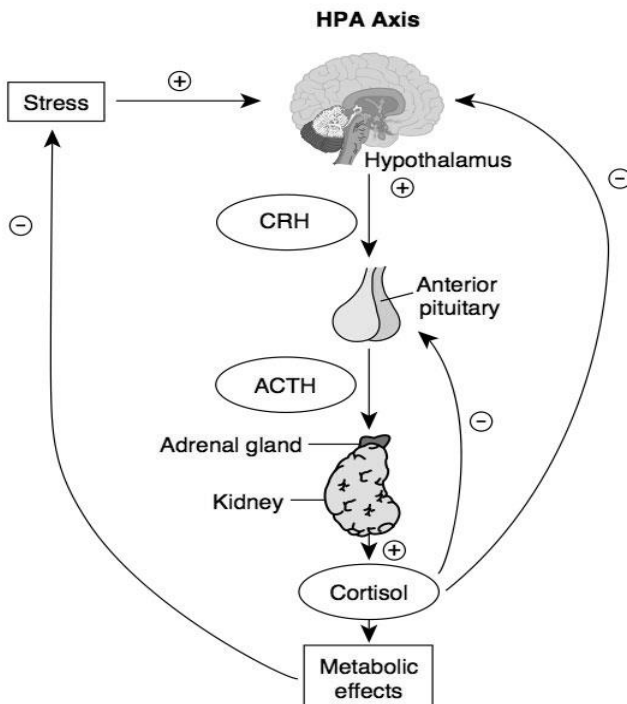
Hypothalamic-Pituitary-Adrenal (HPA) axis physiology & pathophysiology

Corticotrophin Releasing Hormone (CRH) is released by the hypothalamus regulating ACTH secretion from the anterior pituitary. The secretion of ACTH then in turn regulates cortisol release from the adrenal cortex. A normal daily production of cortisol is 5.7mg per square meter body surface area (BSA) (the mythical 75kg 1.8m tall patient would produce roughly 11mg/ day). Earlier studies showed that a maximally stimulated adrenal cortex could produce up to 200-300mg of cortisol/ day under severe stress such as surgery. More recent studies show that this is probably more in the region of 50-100mg/day with surgical stress and varies with the type of surgery. (9)

The release of cortisol varies during the day & in response to stressful situations such as fever, stress, hypoglycaemia and in response to noxious stimuli such as surgery. (9) Surgery is thought to be one of

the most potent stimuli activating the HPA-axis leading to the release of ACTH and hence cortisol. However, during the perioperative period the 3 highest points of ACTH release occur during reversal of anaesthesia, extubation and in the post-operative period. (9)

This system is regulated by a negative feedback/ suppression loop system limiting the unnecessary release of any of these hormones. Negative feedback on both the hypothalamus and anterior pituitary can result from either endogenous glucocorticoid secretion or exogenous glucocorticoid administration. (9)



Excessive ACTH & adrenal hormone secretion, results in the well-known Cushing's syndrome and its typical findings. Cushing's disease refers only to the constellation of symptoms resulting from a pituitary tumour whereas the syndrome may be due to a variety of pathologies.

Adrenal insufficiency occurs in response to either the destruction of the pituitary or adrenal glands or due to chronic long-term administration of glucocorticoids. It is thought that Prednisone at 20mg/ day (or its equivalents – see Table 1) for greater than 3 weeks results in the suppression of the HPA-axis. (9) This risk remains for up to 1 year after cessation of steroid therapy. (9) Doses of 5mg/ day or less of Prednisone are thought not to suppress the HPA-axis. (9) The problem lies in the assumed equivocal effects of intermediate doses of prednisone and its affects as well as duration of effect on the HPA-axis.

Table 1: Equivalent doses (10)

Glucocorticoid	Potency	Equivalent dose
Prednisone	1	10mg
Betamethasone	6	1.5mg
Cortisone acetate	0.2	50mg
Dexamethasone	6	1.5mg
Hydrocortisone	0.25	40mg
Methylprednisone	1.25	8mg

An online steroid equivalence convertor can be found by searching for: "MedCalc: Steroid Equivalence Converter". (11)

[As a side note you will come across a number of texts with different doses & duration of therapy of glucocorticoids resulting in HPA-axis suppression. Additionally the fact that there are a number of circulating recommendations implies that there is hardly a consensus on the exact dosing required. (2) I suggest choosing one reputable text and stick to those numbers as you prepare for both the writtens and oral examinations. The glucocorticoid numbers above are taken from Millers Anaesthesia.]

Who needs perioperative steroids?

Patients can essentially be divided into two distinct groups. Those receiving high doses for acute immunosuppression (e.g. transplant patients) and those receiving chronic steroid therapy, in various forms of delivery, as part of their general medical management. In the first group of patients it is essential to continue equivalent doses of steroids through the perioperative period as failure to administer steroids in these patients may have devastating effects (in terms of a donated organ it may result in rejection). Supplementary steroids in these patients is not necessary as immunosuppressive doses are more than sufficient to maintain haemodynamic stability in the face of an acute stress response and their steroid therapy needs to be continued uninterrupted. (1) One author suggests that omitting steroids in these patients is a "hanging offence". (1)

The second group of patients may be receiving steroids of varying doses for a variety of conditions including but not limited to asthma, rheumatoid arthritis, osteoarthritis, various inflammatory diseases and dermatological conditions. This is the group of patients that may or may not require peri-operative steroid supplementation dependent on the dose, duration and route of their steroid therapy. These patients can then be subdivided into three different groups. Those patients with a functionally suppressed HPA-axis, those with a functionally unsuppressed HPA-axis and those with an unknown/intermediate HPA-axis function.

Functionally suppressed HPA-axis

The following patients are assumed to have a functionally suppressed HPA-axis and will require peri-operative steroid supplementation as illustrated in Table 2. (10)

- Any patient who is currently taking more than 20 mg/day of prednisone or its equivalent (eg. 16 mg/day of methylprednisolone, 2 mg/day of dexamethasone, or 80 mg/day of hydrocortisone) for more than three weeks. (12)
- Any patient that clinically has Cushing syndrome.

Table 2: Recommended supplementary steroid dosing.

Patients currently taking steroids	<5mg/ day	Assume no HPA-suppression	No steroid supplements required
	>20mg/ day	Minor surgery e.g. hernia repair	Morning steroid dose only
		Moderate surgery e.g. joint replacement	Use preoperative steroids with 50mg hydrocortisone @ induction & 25mg 8hrly for 24hrs. Resume maintenance thereafter
		Major surgery e.g. oesophagectomy	Use preoperative steroids with 100mg hydrocortisone @ induction & 50mg/ 8hrly for 24hrs; taper by half/ day to maintenance
High dose immunosuppression	Give usual immunosuppressive dose during perioperative period. e.g. Patient on 60mg prednisone gets 250mg hydrocortisone		
Patient stopped taking steroids	>3months ago	No perioperative steroids required	
	<3months ago	Treat as if on steroids	

Functionally unsuppressed HPA-axis

Daily doses of 5mg or less of Prednisone (or its equivalents) taken in the morning do not suppress the HPA-axis. As such the following groups of patients are assumed not to have a suppressed HPA-axis and do not require peri-operative steroids:

- Any patient taking any dose of glucocorticoid for less than 3 weeks. (13)
- Patients receiving morning doses of Prednisone 5mg or less (or its equivalents) for any length of time. (14, 15)
- Patients treated with 10mg Prednisone or less (or its equivalents) every other day. (16-18)

Intermediate HPA-axis function

This is the group of patients that is frequently suggested by the literature to be referred for evaluation of their HPA-axis due to the wide variability in HPA-axis response to more than 5mg Prednisone/ day. It is not possible to predict based upon age, gender, dose or weight which patients have a suppressed HPA-axis. Furthermore patients taking their steroid doses in the evening may also have a variable response to surgical stress and this group should also be considered for testing. (14, 19)

Patients having been on glucocorticoids within the last year should be considered for testing if they have been on any steroid regimen that places them within the functionally suppressed HPA-axis group. (20) This however contradicts a number of texts, guidelines and recommendations that suggest if patients have been off steroids for more than 3 months then they may be assumed to have an HPA-axis that has recovered (3, 10). Again it seems that there is not yet an agreed upon consensus in terms of duration of steroid therapy.

Other than oral steroids the following routes of steroid administration may also result in HPA-axis suppression:

Inhaled Glucocorticoids (IGC)

The effect is dependent on potency, dose, duration, frequency and timing of the inhaled corticosteroids used. It is often confused by the fact that the asthmatic populations studied are frequently given short courses of oral steroids and this needs to be enquired about when evaluating a patient prior to surgery. The risk of suppression is thought to be greatest in children using Fluticasone. (20) Doses causing adrenal suppression in children vary between 500 – 2000mcg/ day and in adults this normally only occurs with Fluticasone doses >750mcg/ day and >1500mcg/ day budesonide or beclomethasone. (20)

Topical Glucocorticoids

Factors increasing the risk of secondary adrenal suppression following topical glucocorticoid application include the following: (20)

- Chronic application
- Application of super-potent topical steroids
- Application of >2g/ day topical steroid
- Application to highly permeable area (genitals/ face) or areas of poor skin integrity
- Application to wide areas increasing absorptive surface area
- Concomitant liver disease
- Young age

Intra-articular and spinal glucocorticoids

Factors influencing the degree of HPA-axis suppression include dose, interval and number of glucocorticoid injections administered. (21, 22) Although described in the literature, the risk of adrenal suppression would appear to be very low in this group of patients and only those exhibiting a Cushingoid appearance or who have received 3 or more intra-articular/ spinal glucocorticoid injections in the 3 months leading up to surgery should be considered as potentially having HPA-axis suppression. (23, 24)

Testing the HPA-axis function

Although frequently suggested in many texts the reality of sending patients for HPA-axis testing in an over-stressed clinical environment is not likely. That said there are a number of texts that go in to great detail discussing HPA-axis testing & it would be valuable to know the physiology & methodology behind the testing. There does appear in the literature to be some disagreement as to the merits of the most commonly used tests. (25)

Static tests of HPA-axis function

Single measurements of serum cortisol and urinary free cortisol

Not able to differentiate between suppressed HPA-axis and normally functioning HPA-axis as levels may overlap in resting states and does not test ability of HPA-axis to increase cortisol levels. (3) Morning (before 8am) serum cortisol is however a good screening test for adrenal insufficiency. In patients on chronic glucocorticoid therapy a morning level of <5ug/dl, after 24hrs off glucocorticoids, suggests HPA-axis suppression and the need for perioperative supplementation. (20) Patients with a morning level >10ug/dl do not require supplementary steroids and may continue on their current dose uninterrupted. It is suggested in patients with morning levels between 5-10ug/ dl that they undergo an ACTH-test or be given empirical glucocorticoid cover.

Random cortisol estimation

Potentially useful in testing during the stressed state to see whether an appropriate response has been mounted by the HPA-axis. (3) Again it is not predictive of response in terms of surgical stress. A cortisol value >25ug/ dl during a stress state reliably indicates normal HPA-axis response (>15ug/dl HPA-axis probably indicates a normal response). (9)

Dynamic tests of HPA-axis function

Insulin tolerance test (ITT)

The ITT is not widely used. It is impractical and probably more dangerous than administering glucocorticoids to a patient. (9) The test is done by administering Insulin intravenously (0.1-0.15U/ kg), to a patient who has been fasted overnight. It results in a predictably rapid decrease in blood glucose levels. When blood glucose levels go below 2.2mmol/L (the level causing neuroglycopenic tissue injury) (3) ACTH and GH should be released from the pituitary as part of a normal response following hypothalamic stimulation. In turn cortisol is released from the adrenals allowing for the entire HPA-axis to be tested. (26) Hypoadrenalism is demonstrated by a peak cortisol level of <500umol/L following symptomatic hypoglycaemia.

Complications that have been reported with the ITT include: Loss of consciousness, seizures, resistant hypoglycaemia, myocardial infarction and even death. (3).

Synthetic ACTH test

Cosyntropin is a synthetic form of ACTH that may be administered in either a high- (250ug) or low- (1ug) dose test. Timing of the test is not important, as the response to cosyntropin in patients with adrenal insufficiency is the same whether done in the morning or the afternoon. (9) A normal response to the high-dose test, measured 30-60mins later, is a rise in serum cortisol to a peak of 18-20ug/dl or greater (Low-dose test rise, 20-30min later, of 17-22.5ug/dl indicates a normal response). Normal responses indicate that no further glucocorticoids are required peri-operatively. (20) A subnormal response indicates inadequate reserve with the need for supplementary steroid cover.

Caution must be taken in patients having recently undergone pituitary surgery. In these patients a normal response to the ACTH-test may be seen up to 4 weeks after pituitary surgery despite ACTH insufficiency and in these patients this test becomes unreliable acutely and empiric therapy should be given. (20, 27)

Urgent & Emergent surgery

Perioperative supplementation should follow the above guidelines. In situations in which the function of the HPA-axis is unknown supplemental steroids should be given based upon the type and duration of surgery as indicated in Table 2. Delaying surgery in order to assess the HPA-axis function is not warranted as the risks of delay outweigh the risks of empirical steroid therapy. (20)

Conclusion

As the first two quotes at the beginning of the article suggest, perioperative steroid cover has gone unquestioned for a long period of time. More recent data suggests that steroid cover is probably given in doses that are too high and often to patients that do not require supplemental steroids. Utilizing HPA-axis testing more frequently may decrease the amount of supplemental steroids given but at the cost of additional resources utilization and higher medical expenditure. Taking a thorough history and examining patient medication charts should detail those patients requiring steroids and those that can simply carry on with their current regimen without additional coverage. It is questionable whether a dose of greater than 5.7mg per square meter BSA is required to avoid intra-operative hypotension and a number of retrospective, prospective and randomized studies support this notion. Unfortunately until a larger randomized and blinded trial is produced we are obliged to continue with the current defensive strategy of steroid supplementation.

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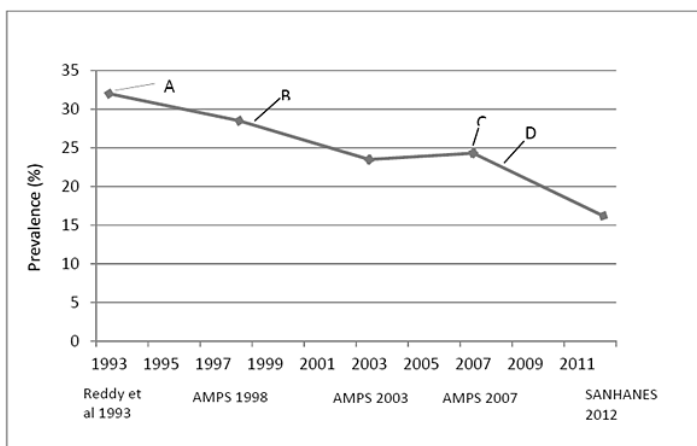
Smoking and Anaesthesia

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1. Incidence

The prevalence of tobacco smoking (16.4% of the population) in South Africa is still high despite declining from 32% over the last 2 decades. These smokers may expose their families to second-hand tobacco smoke. Children are particularly vulnerable to environmental tobacco smoke (ETS). 29.9% of adults revealed exposure to ETS.⁽²⁾



A. Tobacco Products Control Act of 1993; B. Tobacco Products Control Amendment Act No 12 of 1999; C. Tobacco Products Control Amendment Act No. 23 of 2007; D. Tobacco Products Control Amendment Act No. 63 of 2008; AMPS = All media and Product Survey

South African National Health And Nutrition Examination Survey (SANHANES-1) 2012 by the HSRC

Smoking and exposure to ETS causes serious respiratory, cardiovascular disease, has implications for other systems and contributes to an increase in perioperative morbidity.

Smoking has repeatedly been shown to be a univariate and multivariate risk factor for MI, CVA, respiratory failure, ICU admission, pneumonia, laryngospasm and increased use of respiratory therapy services.⁽³⁾

Cigarette smoke contains over 4000 substances that are:

- pharmacologically active, antigenic, cytotoxic, mutagenic, carcinogenic

The smoke consists of a gaseous and a particulate phase.

Gaseous phase (90% of smoke)

mainly nitrogen, O₂, CO₂
CO
carcinogens
ciliotoxins
irritants

Particulate phase

nicotine - main toxic ingredient
carcinogens

2. Systemic Effects

Inadequate delivery to the tissues of usable oxygen is the recurrent theme.

2.1. CVS

Smokers are predisposed to hypertension, ischaemic heart disease, cerebrovascular disease and heart failure. All of these are risk factors for postoperative cardiovascular morbidity and mortality.

Nicotine

(stimulates adrenal medulla → adrenaline
resets carotid body and aortic receptors → higher blood pressure
stimulates autonomic ganglia → increases sympathetic tone)

Decrease myocardial oxygen supply:demand ratio

Incr Myocardial Contractility

increase SBP & DBP
increase heart rate
increase PVR

Decr blood flow

Incr coronary vascular resistance

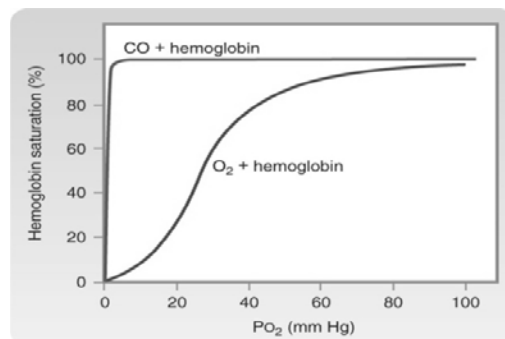
increases intracellular calcium during ischemia
– may exacerbate myocardial cell damage

The half-life of nicotine is 30 – 60min. Three to four hours of abstinence will improve myocardial oxygen supply: demand ratio

Carbon monoxide

Smoke contains 400 parts per million

COHb is elevated: 5 – 15% (normally 0.3 – 1.6%)



ODC shifts left and changes to hyperbolic shape → decr in the oxygen available to the tissues

- high affinity for Hb - 200 x > O₂
- CO binds to the alpha chain of Hb where O₂ does → reduces oxygen carrying capacity
- depletion of 2,3-DPG

Inhibits cytochrome oxidase (required for final oxygen dependent synthesis of ATP in Mtc)

Binds with myoglobin → inactivates mitochondrial enzymes in the cardiac muscle

- **decreases intracellular oxygen transport, usage and has a negative inotropic effect**

The above mechanisms lead to **chronic tissue hypoxia**

With chronically elevated COHb (10 – 15%), a smoker may be close to a point on ODC where any further decrease in PaO₂ will lead to rapid desaturation.

Concentrations above 5% COHb may induce ventricular **arrhythmias** under general anaesthesia.

Half-life of COHb depends primarily on pulmonary ventilation

- At rest: 4 – 6 hrs
- Exercise: 1 hr
- Sleep: 10 – 12 hrs
- Longer in males
- Breathing 100% oxygen: 40 – 80min → significantly expedites CO removal
- Hyperbaric oxygen: 23 min

Abstinence for 12 hours is sufficient to remove carbon monoxide.

Those most at risk are inactive men who smoke heavily before retiring to bed on the night before.

2.2. Respiratory System

Impaired tracheobronchial clearance which leads to **lower airway reactivity**

- hyperviscous mucus with altered elasticity
- cilia damaged by ciliotoxins and become inactive

Increased laryngeal and bronchial reactivity → incr tendency for **breath-holding and laryngospasm** at induction

- damaged epithelium allows incr stimulation of irritant receptors

FEV1 declines three times faster than a non-smoker (60ml/yr)

Increased closing volume (lung volume at which airways collapse and trap air)

- caused by small airway narrowing

Small-airway disease

- decr surfactant

Greater degree of shunt under anaesthesia

- due to altered regional pulmonary mechanics

Increases the likelihood of perioperative hypoxia added to the contribution of both surgery and anaesthesia itself

Higher incidence of **chronic bronchitis and chronic obstructive lung disease**

There is an increase in proteolytic and elastolytic enzymes → Loss of elastic recoil → **Emphysema**

Increased **lung infections**

Incidence of perioperative respiratory events ⁽¹⁾

5.5% in smokers vs **3.3%** in non-smokers

- reintubation, laryngospasm, bronchospasm, aspiration, hypoventilation, hypoxemia
- higher incidence and severity of coughing during emergence from anaesthesia
propofol anaesthesia shown to have less frequency compared to sevoflurane

Relative risk of respiratory event during anaesthesia

- smokers 1.8 times non-smokers
- young smokers 2.3 times
- obese smokers 6.3 times the normal
- young smokers with chronic bronchitis 25.7 times normal

2.3. Haemostatic System

Incr Hct and blood viscosity (secondary to chronic tissue hypoxia)



Incr thrombotic tendency (worsened by exaggerated platelet function and increased plasma fibrinogen)



Incr arterial thromboembolic disease + chronic hypoxia to cardiac muscle

70% greater risk of coronary artery disease

2.4. Gastrointestinal System

Smoking does not increase gastric volume or alter the pH of the gastric secretions

Transient gastroesophageal sphincter incompetence that resolves in 8min of smoking → no increased risk of aspiration.

These patients do have an increased risk of peptic ulcer disease.

2.5. Effect on the Immune System

The compounded detrimental effect of smoking and surgery result in an increased risk of infection and malignancy.

2.6. Effect on the Renal System

Enhanced sympathetic activity increases secretion of ADH → dilutional hyponatremia.

2.7. Effect on Drug Metabolism

Cigarette smoking induces liver microsomal enzymes, increasing the metabolism of certain drugs.

Higher doses of certain analgesics

Fentanyl metabolized faster

Morphine and pethidine have been metabolized quicker in rat models but no difference shown in pethidine clearance in humans

No effect on codeine, paracetamol or NSAIDs

Pharmacokinetics of **benzodiazepines** has not been shown to deviate from non-smokers. However, **larger doses** are required for equivalent effect in non-smokers. This is attributed to decreased end organs response rather than increased metabolism.

Volatile agents

- no change in action
- but increased metabolism potentially leads to higher levels of toxic metabolites
difficult to quantify the extent to which the risk becomes significant

Muscle Relaxants

Small doses of nicotine stimulate the Ach Rc → requiring larger doses of muscle relaxants to block receptors. Reports of the effect on these drugs vary and whether clinically significant is questionable.

2.8. Psychological Aspects of Smoking

Acute withdrawal - anxiety, sleep disturbances, and irritability

Nicotine replacement may alleviate these symptoms

2.9. Effects of Passive Smoking on Anesthesia

Dennis et al showed adverse events (coughing, breath holding, and laryngospasm) during induction was significantly higher in both smokers and passive smokers and there was no difference in the incidence between the two.

Postoperatively, children with a history of passive smoking desaturated significantly more frequently

- no relationship found to COHb level
- possibly due to respiratory infection from increased risk of exposure to microdroplets from respiratory disease of smokers who cough

2.10. The Effect on Postoperative Morbidity

Longer stays in theatre recovery rooms

Higher rate of unplanned admission to HCU/ICU

Postoperative pulmonary complications are 6 x higher in smokers

- highest risk after abdominal and thoracic surgery

Poorer surgical outcome in

- vascular surgery, CABG and colorectal (anastomoses more prone to leak)
- plastic surgical flaps more likely to necrose
- higher rate of rebleed in SAH if patients persist to smoke

3. Management of anaesthesia in smokers

Smoking is partly **responsible for many diseases** requiring surgery (e.g. onco-ENT, thoracic surgery –lung ca, CABG, gastrectomy, bladder cancer and even femoral neck fracture).

Crohn's disease is commoner in smokers and continuing smoking increases their risk of requiring surgery by at least 50%.

The peri-operative course is compromised because smoking **undermines fundamental aims of safe anaesthesia and surgery**

- a safe start, passage through surgery and rapid uncomplicated recovery.

Smoking can **affect surgical outcome**.

3.1. Preop cessation of smoking

The conclusion of a systematic review of 25 studies on smoking cessation was **at least 4 weeks of abstinence reduced respiratory and wound healing complications** ⁽⁷⁾

Even **short-term break (<4weeks)** will influence important parameters although not altering the rate post op pulmonary complications.

Earlier observational studies of short term cessation showed a paradoxical increase in post op respiratory complications. This was possibly associated with increase cough and sputum production after recent cessation. These studies may be limited by confounders and should be interpreted with caution due to methodological problems in determining smoking status and reasons for stopping.

Timing of smoking cessation and effects on physiological recovery

- **12 - 24 hrs:** negate effects of nicotine and COHb
increases physical work capacity by 10 – 20%
- **4-6 days:** ciliary activity recovers but sputum production increases
- **5-10 days:** laryngeal and bronchial reactivity to settle
- **4 weeks:** improvement in small-airway narrowing
- **6 weeks:** sputum volume returns to normal
- **> 8 weeks:** 4 x less pulmonary complication
- **3 months:** tracheobronchial clearance improves
- **6months:** marked improvement: equal incidence of postoperative pulmonary complication as non-smokers

3.2. Preparation

Treat lung infections such as chronic bronchitis.

Prehabilitation: Prescribe bronchodilators, breathing exercises, and chest physiotherapy in symptomatic smokers

ABGs for baseline PaO₂ and PaCO₂ depending on the degree of lung disease and duration and nature of surgery

3.3. Choice of Technique

If general anaesthesia can be avoided, **regional or local anaesthesia** is advantageous for patients with long term respiratory complications of smoking.

Nevertheless neuraxial technique is not without adverse effect

A level above T10 may not be well tolerated (dependent on the degree of the respiratory disease)

- FEV₁, forced midexpiratory flow, forced expiratory flow markedly reduced

3.4. Premedication

Antisialagogue (like glycopyrrolate) to reduce secretions.

Anxiolytic to reduce the psychological effects of stopping smoking

Nebulized 4% lignocaine preop may assist in reducing adverse respiratory sequelae

3.5. General Anaesthesia

Underlying ischaemic heart disease and hypertension should be identified, and considered during the provision of anaesthesia to minimise their risk.

3.5.1. Induction

Airway complications are common especially during facemask ventilation or LMA insertion

- need for intubation should always be anticipated

Preoxygenation will decrease carbon monoxide levels

Any intravenous induction agent is acceptable

Intravenous lignocaine is useful to mitigate laryngospasm during intubation

Alternatively, if nebulized lignocaine not given, spray with 2% lignocaine to anesthetize the larynx and suppress laryngeal hyperreactivity.

Manipulation under light anaesthesia may induce

- coughing, breath holding, laryngospasm, or bronchospasm.

When using induction with volatile agents

- sevoflurane or halothane are least irritant to the airways

3.5.2. Maintenance

Appropriate analgesia and depth of anaesthesia

- regional techniques (e.g. epidural) particularly useful for abdominal or thoracic surgery

Volatiles have bronchodilating effects

Desflurane, however, should be avoided

- stimulates the respiratory irritant receptors
- induces the sympathoadrenal system → higher blood pressure and tachycardia

Ventilator settings should be adjusted towards obstructive lung disease if this has been confirmed or a clinically suspected.

3.5.3. Monitoring

Overestimation of SaO₂ on pulse oximeters

- light absorbance is measured at only 2 wavelengths and cannot distinguish (HbO₂) from COHb
- it combines the saturation of HbO₂ and COHb as the result
- an apparently normal reading can lead to a false sense of security in heavy smokers

CO-oximeters measure a greater numbers of wavelengths and fractional Hb to distinguish between HBO₂, COHb and metHb.

Intermittent **ABGs** to evaluate PaCO₂ - Et CO₂ gradient
greater in smokers and an index of amount alveolar dead space

- approx. 0.9kPa (norm = 0.3 kPa)
- difference worsens with age in smokers

Vigilant **ECG monitoring** - ventricular arrhythmias may occur during anaesthesia in those with CAD.

PNS to monitor neuromuscular block

- since varying reports on the requirement of muscle relaxants

3.5.4. Recovery

Extubation under light anaesthesia may also result in cough, breath holding, laryngospasm, or bronchospasm.

3.6. Post-operative period

Less PONV encountered and is attributed to an antiemetic constituent in smoke.

Supplemental oxygen may be required in the recovery room, while being transported and for some time in the ward.

Administer more analgesics (if appropriate) due to

- anxiety from stopping smoking
- decreased pain threshold
- increased metabolism of the drug

Breathing exercises and chest physiotherapy for symptomatic smokers

- early mobilisation to improve lung function and sputum clearance

4. Anesthesiologists' Role in Advising Smokers

A peri-operative physician's role should extend beyond an isolated interaction with the patient.

The majority of smokers who are having surgery want to quit ⁽³⁾

Surgery may be a 'teachable moment' where there is increased spontaneous smoking cessation

4.1. Interventions

Brief interventions, telephone quit lines, face to face counselling

Very brief smoking advice is less effective but still worthwhile

- accommodated into surgical outpatient practice, anaesthetic pre-assessment clinics, or preoperative assessments

Current best practice advocates the use of nicotine replacement therapy

- doubles the chances of cessation in the future.

Advise smokers to stop smoking during the postoperative ward rounds

- especially in those who had smoking-related problems during anaesthesia. patients found to be especially compliant in those circumstances ⁽⁷⁾

5. Conclusion

In conclusion, patients must stop smoking prior to surgery.

The **best result occurs when the patient stops 8 weeks or more before surgery**. Doing so will significantly reduce perioperative-specific respiratory events and postoperative morbidity, and it will eliminate carbon monoxide and nicotine, improve the clearance of tracheobronchial secretions, decrease small-airway narrowing, and improve immune functioning.

If the patient **does not stop smoking 8 weeks before surgery**, the patient should at least **stop smoking 12 hours before surgery** or, if the surgery is the next morning, the previous evening. This will eliminate problems in tissue oxygen uptake due to carbon monoxide and reduce the cardiac and hemodynamic effects of nicotine.

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Perioperative Management in COPD

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This review aims to offer a practical guide to the perioperative management of COPD patients. These notes are based on, in order of importance and trustworthiness:

- Excellent reviews of the perioperative management of patients with lung disease and lung protective ventilation by Slinger^(1, 2) with Marseu⁽³⁾, though if you've read Slinger's chapter in Millers Anaesthesia you will recognise whole portions of the text as verbatim...why change a good thing?
- A useful description of perioperative issues in COPD by Edrich⁽⁴⁾,
- A CEACCP by Lumb⁽⁵⁾
- Discussions with senior colleagues experienced in thoracic anaesthesia
- My own experience

I was unable to find useful references in the medical literature to solve some of the questions I thought were important to discuss. This implies either that there is no evidence to guide management in these areas, or that I was just not persistent (or smart) enough with my search. The unanswered questions include:

- A concise description of the role of permissive hypercapnea in the intraoperative COPD setting and the parameters to use as targets
- The significance of demonstrating airway reversibility with bronchodilators in the preoperative setting and what this means about potentially delaying a case to 'optimize' the COPD treatment
- Any evidence suggesting superiority of a particular ventilation mode over another for intraoperative use though some reviews mentioned switching to a pressure mode as an option that may be useful intraoperatively⁽⁴⁾ with pressure support advocated if a period of weaning is required⁽⁶⁾.

I will attempt to address these issues again during the lecture.

Background:

A brief background to the disease is necessary to place the intraoperative plan in context.

Definition:

Chronic Obstructive Pulmonary Disease is the most common comorbidity in the thoracic surgery group of patients and causes 10000 deaths per year in the USA⁽⁴⁾. It incorporates 3 separate disease entities:

- Chronic Bronchitis
- Emphysema
- Peripheral airways disease

But the main clinical feature is of expiratory airflow limitation⁽²⁾.

Diagnosis depends on pulmonary function tests findings of a forced expiratory volume in 1 second to forced vital capacity ratio (FEV₁/FVC) of < 0,7 with a suggestive history.

Relevance:

COPD poses cardiovascular challenges for the anaesthetist because of the risk of cardiovascular collapse and the high rates of atherosclerotic disease seen in the population caused by the association with smoking.

However, the risk of Postoperative Pulmonary Complications (PPC), are particularly high in this group and the morbidity, mortality and costs associated with PPCs are significant. In a retrospective cohort audit of 45000 patients that underwent colorectal surgery, 1 in 5 experienced a PPC while only 1 in 100 had a cardiac complication. The costs of treatment of the pulmonary complications were more than that associated with cardiac complications⁽³⁾.

The most common PPC's are:

- Respiratory failure causing CO₂ retention
- Atelectasis
- Pneumonia
- Persistent air leak and pneumothorax⁽³⁾

Of equal importance is the fact that anaesthetists are able to influence the rates of these complications through the institution of accessible interventions.

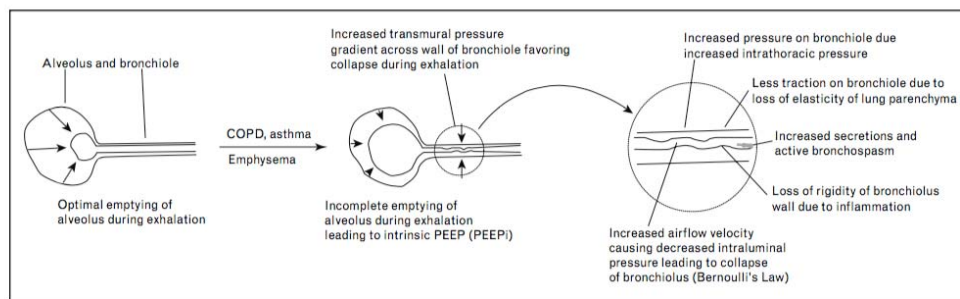
Pathophysiology

Airflow limitation and Dynamic Hyperinflation:

The pervasive feature of COPD is airflow limitation and the factors favouring airway collapse and obstruction during exhalation are:

1. Increasing intrathoracic pressure during expiration
2. Loss of elasticity of lung parenchyma causing less traction
3. Increased secretions and active bronchospasm
4. Loss of rigidity of bronchiolus wall due to inflammation
5. Increased airflow velocity → decreased intraluminal pressures → collapse (Bernoulli)

Figure1 Reduced alveolar emptying in chronic obstructive pulmonary disease, asthma, and emphysema due to pathological changes in the bronchiole wall and altered forces acting to keep it open during exhalation⁽⁴⁾



COPD, chronic obstructive pulmonary disease; PEEP, positive end-expiratory pressure.

The inability to exhale a complete tidal volume, particularly present during times of exertion or during positive pressure ventilation can lead to 'breath-stacking' or 'air-trapping' and the phenomenon of dynamic hyperinflation.

Perioperative CVS Instability:

Cardiovascular collapse at induction or during ventilation is caused by the following mechanism

- PEEP_i becomes increased, leading to raised intrathoracic pressures that impede venous return and thus cardiac output
- Raised intrathoracic pressures are transmitted to the pulmonary arteries via the pulmonary capillary bed causing raised pulmonary vascular resistance that may cause right ventricular strain
- Direct mechanical pressure on the heart may impede diastolic filling of the ventricles despite adequate preload
- A distended right ventricle may shift the inter-ventricular septum causing LV dysfunction⁽⁴⁾

Both the impaired venous return and increased pulmonary pressures appear to play a role.

Cor Pulmonale is also a frequent endpoint of COPD and should be sought out.

Perioperative approach:

I believe it worth asking a series of questions about your patient and their surgery to guide choice of anaesthetic and perioperative interventions. These are:

1. How severe is the COPD? How high is the risk of perioperative complications? And what will this patient's recovery course look like?

2. What can I optimise in order to improve my patient's outcomes without delaying surgery unnecessarily?
3. What will the postoperative analgesic requirements be and how does that change my perioperative management?
4. Where would I like this patient to be post-operatively, and do I have those facilities available?
5. Do I need to perform this case under general anaesthetic or could it be done under regional techniques, and, on balance, which would be better for the patient?
6. What can I do intraoperatively to keep my patient safe through the operation and minimize their risk of postoperative complications?
7. What are my likely postoperative problems and plans to prevent them?

1. How severe is the problem?

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) propose the following grades of severity according to pulmonary function tests⁽⁵⁾:

GOLD criteria for disease severity in COPD

FEV ₁ /FVC	FEV ₁ as % of predicted	GOLD Category (2008)
<0,7	>80	Stage 1 – Mild
<0,7	50-79	Stage 2 - Moderate
<0,7	30-49	Stage 3 - Severe
<0,7	<30	Stage 4 – Very Severe*

*Or FEV₁ < 50% of predicted with respiratory failure

While pulmonary function tests grading severity of disease exist, no single measure correlates with true severity and FEV₁ percentages of predicted values should be interpreted with other information such as effort tolerance or level of disability, frequency and severity of exacerbations, BMI, carbon monoxide transfer factor etc.

Those patients that produce high volumes of sputum should also be identified as they will benefit most from perioperative physiotherapy⁽⁴⁾.

2. What can I optimise?

4 treatable complications of COPD should be sought out and treated pre-operatively⁽²⁾:

- **Atelectasis** – impairs local lung lymphocyte and macrophage function and predisposes to infection
- **Pulmonary oedema** – is difficult to diagnose clinically in COPD and may present very abnormal radiological distributions
- **Bronchospasm**: may be a symptom of CCF or exacerbation of reversible airways disease and should receive max bronchodilator therapy, guided by symptoms. Only 20-25% COPD patients will respond to corticosteroids
- **Respiratory Tract Infections** – that should be tackled with physiotherapy and appropriate antibiotics. Those patients prone to copious sputum production tend to benefit most from physiotherapy, and family members can be taught the techniques required to mobilise and expel secretions.

The Problem of the Perioperative Wheeze:

There appears to be conflicting evidence on the importance of clinical findings suggesting active bronchospasm with some reviews stating a wheeze predicts PPC's while others not^(4, 5). However, there is consensus that active symptoms of bronchospasm or respiratory tract infections should be treated. The duration of treatment of bronchospasm required to "optimize" chronic treatment of COPD is unclear, as is the role of perioperative steroids in COPD patients⁽²⁾.

This calls into question the importance of "reversibility" demonstrated at pre-operative lung function tests by an increase in FEV1 of 10-15% with bronchodilator therapy. Senior clinicians in our department, as always, suggest individualising decisions on delaying surgery in this group of patients.

Patients with reversibility but mild-moderate COPD having elective minor surgery could probably proceed after overnight nebuliser therapy. Those with severe COPD and evidence of reversibility, booked for major surgery, may benefit from an extended period of bronchodilator therapy and physiotherapy to optimise their chances of avoiding serious PPC's. How long the surgery should be delayed while maximal bronchodilator therapy is instituted is unclear and tricky in cancer surgery, but there appears to be little benefit in implementing a programme of intensive physiotherapy for less than a month⁽²⁾.

Of the pre-operative interventions studied, only physiotherapy, prehabilitation and smoking cessation consistently reduce the risk of Post-operative Pulmonary Complications.

Preoperative physiotherapy and prehabilitation:

In our setting, we do not see enough patients more than a month in advance of surgery to engage actively in a meaningful programme of physiotherapy. However, since a fairly high proportion of our COPD related surgery is non-cancer surgery (TB, bronchiectasis, trauma) and thus could be delayed, this is an area for focus and intervention; an opportunity to improve outcomes that we are missing.

Physiotherapy programmes include deep breathing exercise, techniques for expelling of secretions and 'prehabilitation' through graded fitness programmes.

Nutritional status

Poor nutritional status and low albumin may increase the risk of PPC, particularly in the elderly patient presenting for thoracic surgery. Again, this is a difficult problem to tackle in our perioperative setting, but a patient with poor nutritional status and COPD should alert the anaesthetist to the increased risk of airway anastomoses breakdown or other causes of persistent air leaks⁽³⁾.

Smoking cessation

Smoking cessation has been discussed elsewhere in this course, but it is worth reiterating that all interactions with patients should be seen as opportunities for "teachable moments" that could change behaviour⁽⁴⁾.

3. What is the post-op analgesic plan?

As with most anaesthetics the trade off with post-operative analgesia is between the sedative effects and respiratory depression of some systemic analgesics and the logistical requirements and risks of regional techniques.

The risks of opioid induced respiratory depression causing symptomatic hypercapnea are heightened in COPD because of the inherent tendency towards CO₂ retention⁽²⁾.

Recent evidence suggests Thoracic Epidural Analgesia can be employed without detrimental effects on the respiratory mechanics. The improved abdominal wall relaxation and diaphragmatic movement offsets the risk of intercostal muscle paralysis^(2, 3, 7). However, whether or not thoracic epidurals for thoracic, upper abdominal and orthopaedic surgery reduce the risk of PPC's and improve outcomes remains controversial. Slinger interprets the evidence to suggest that Thoracic Epidural Analgesia does improve outcomes^(2, 3).

What I do:

I employ a lower threshold for the use of central-neuraxial blockade, or peripheral regional techniques in the COPD patient than in the rest of the population. However, I would be very reluctant to employ an interscalene or supraclavicular block in a patient with already critical lung mechanics because of the reasons described below.

4. What is the post-op placement plan?

The need for a post-operative high care bed in our department hinges on the fact that we can only offer epidural care and non-invasive ventilation in a high care or ICU environment. If either of these interventions is foreseen, the COPD is severe, or the surgery is extensive, a high care bed is appropriate.

Now that we are committed to a general anaesthetic and positive pressure ventilation...

5. General anaesthetic or regional?

With the previous questions answered, I can now make a final decision on the anaesthetic plan.

Limb and lower abdominal surgery is usually possible under regional or central neuraxial techniques with limited adverse effects on ventilation. However, the risk of respiratory compromise from unintended effects of upper limb blocks may be significant. The effects on respiratory mechanics of the most commonly used brachial plexus block approaches are tabled below⁽⁸⁾:

Approach	% of patients with phrenic nerve block	Note
Interscalene	100% hemi-diaphragmatic paralysis	25% reduction in FEV1 and FVC. In severe COPD this may be critical...avoid!
Supraclavicular	50-67%	Risk of phrenic nerve paralysis may be reduced to near zero with U/S technique
Infraclavicular	0%	Safer in COPD
Axillary	0%	Safer in COPD

What I do:

In severe COPD patients, or in those with active bronchospasm about whom I am concerned, I choose regional techniques over GA wherever possible. I am also reluctant to sedate patients in this category to augment the regional technique, but would usually choose a sedation dose Propofol TCI if absolutely necessary.

Several studies describe the use of non-invasive ventilation, either CPAP or bi-level support (BIPAP) as an intraoperative technique in the patient at risk of intraoperative respiratory failure but not receiving a GA. I am not aware of it being practiced in my hospital, but reports from the literature suggest it is feasible and successful⁽⁹⁾.

6. What can I do intra-operatively?

Goals of intra-operative management are to avoid the likely complications of:

- CVS instability
- Respiratory failure and air-trapping
- Post-operative Pulmonary Complications

The main physiologic insult, as described above, is airflow limitation causing incomplete exhalation during a respiratory cycle. This leads to air-trapping and Auto-PEEP or PEEP_i and ever increasing intra-thoracic pressures. This has adverse effects on the cardiovascular system and ventilatory strategy.

What's the CVS risk?

Cardiovascular collapse at induction or intraoperatively caused by air-trapping and raised intra-thoracic pressures.

How do I mitigate cardiovascular instability?

- In severe COPD patients undergoing GA, I place an a-line pre-induction in order to:
 - o Perform regular, including pre-op, ABG's
 - o Monitor beat to beat changes in BP
- Careful IV induction, and **gentle, low pressure, slow** ventilation.
- Initial BVM may be enough to cause air trapping and precipitous CVS collapse so beware the reservoir bag that appears to be filling slowly ⁽⁴⁾
- Remember: Lazarus syndrome!⁽²⁾

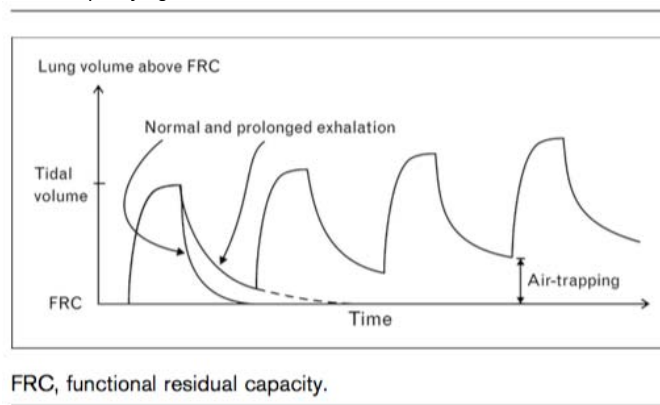
What's the respiratory risk?

- Air-trapping leading to:
 - o Retained CO₂
 - o High airway pressures causing barotrauma and air-leaks/pneumothorax

How do I avoid respiratory complications?

- **Maintain Vigilance for Air-Trapping**
 - o 1st sign may be the manual ventilator bag not filling during BVM
 - o Capnography: up-sloping – implies admixture of air from dead space
 - o Ventilator graphics/direct measurement of flow
 - o Direct measurement of resulting PEEP_i via an expiratory hold (not usually possible with theatre ventilator)
 - o Disconnect patient from ventilator briefly and observe whether BP recovers and PEEP_i is eliminated

Figure 2 Dynamic hyperinflation occurs when mechanical ventilation cycles before prolonged exhalation has reached baseline functional residual capacity again⁽⁴⁾



- **Lung Protective Ventilation and PEEP_i**
 - o Expiratory Time
 - Prolonging expiratory times by reducing respiratory rates allows for improved expiration and reduces the risk of air trapping
 - It is important to increase absolute expiratory time rather than just changing the I:E ratios and thus a lower respiratory rate may be necessary⁽⁶⁾
 - o Inspiratory pressures:
 - Peak pressures >30-40cm H₂O are associated with increased post-operative lung injury
 - Some reviews have suggested high plateau pressures are more important than peak pressures in COPD, but others suggest high peak pressures are also important indicators of post-operative lung injury^(1, 3, 6)
 - Equally, when high inspiratory pressures are required in patients with COPD and bullae, practitioners should remain vigilant of the risk of air leak and pneumothorax and have recourse for insertion of an inter-costal drain
 - o Tidal Volumes of 6-8ml/kg are advocated
 - o PEEP
 - The risk of PEEP_i has been discussed and measures to avoid air-trapping described.
 - Because of movement along the lung compliance curve, application of a small amount of PEEP has been shown to reduce the risk of air-trapping and PEEP_i⁽¹⁻³⁾ in some patients
 - I begin with PEEP of 5cmH₂O and titrate up or down from there.
- **Permissive Hypercapnoea**
 - o Higher than normal ET-CO₂ levels may be tolerated intra-operatively to avoid lung injury
 - o Target pH 7.15-7.2
 - o The hypercapnea may have a protective effect on the lungs, reducing the ventilator associated lung injury and rates of ARDS^(3, 10)

- **Ultra-protective ventilation**
 - o This is definitely not how I do it but its out there and described
 - o Lung volumes of 3ml/kg, with a pumpless extracorporeal lung assist (arterio - venous CO₂ exchanger such as the Novalung) may be beneficial but more use in ARDS than COPD⁽¹⁾
- **Fluids**
 - o Over zealous fluid administration worsens lung injury, while hypovolaemia worsens organ perfusion
 - o A goal-directed fluid plan is advocated with measures of fluid responsiveness integral to decision making⁽³⁾
- **Avoid worsening bronchospasm:**
 - o LMA's may reduce the risk of bronchospasm over ETT's. When using LMA's I am very particular about checking LMA leak pressures to ensure I can generate an inspiratory pressure likely to be sufficient to ventilate the patient
 - o Careful placement of an ETT, with patients deeply anaesthetised
 - o Careful use of drugs that may induce histamine release such as morphine
- **Choice of anaesthetic**
 - o Volatiles cause bronchodilation and sevoflurane may be the most potent bronchodilator⁽²⁾
 - o Desflurane may cause coughing or bronchospasm
 - o Volatiles may imply a lung protective effect in their own right reducing rates of acute lung injury when compared with TCI strategies⁽³⁾.
 - o Wash-out and wake-up may be delayed thus severe obstructive lung disease is a suitable motivator for the use of sevoflurane over isoflurane

7. Post-Operative Period:

What's the risk?

- Post operative pulmonary complication remain common and serious
- Efforts to expand the lungs post-operatively can halve this risk and include:
 - o Physiotherapy
 - o Incentive spirometry
 - o Non-invasive ventilation⁽³⁾

What I do:

- In the very high risk patient, I consider extubating to NIV in the post-anaesthetic high care environment
- Have a low threshold for serial ABG's and chest x-ray

Conclusion:

COPD is a common co-morbidity in the perioperative setting that implies a high risk of post-operative pulmonary complications and intraoperative cardiovascular instability. Pulmonary complications represent a significant contribution to perioperative morbidity and mortality as well as perhaps the largest contribution to post-operative costs⁽³⁾ in some settings.

The anaesthetist is well placed to reduce the risks of anaesthesia and surgery for patients with COPD by:

- initiating pre-operative efforts to reduce risk through
 - o physiotherapy
 - o fitness training
 - o treating infections
 - o encouraging smoking cessation
- ventilating with tidal volumes of 6-8ml/kg and PEEP of <6cm H₂O
- appropriate use of regional techniques
- avoiding fluid overload

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Communicating Risk in Anaesthesia

Dr Sean Dwyer

Private Practice

The following table may help you and your patients get a handle on some of the numbers used to express risk.

Risk	Words	Number of People	SA examples
1:10 10%	Very Common	In your family	Family
1:100 1%	Common	In your street	Year group
1:1 000 0.1%	Uncommon	In a Village	Scarborough
1:10 000 0.01%	Rare	In a Small town	Fish Hoek
1:100 000 0.001%	Very Rare	In a Large Town	Paarl or Stellenbosch
1:1 000 000	Negligible	In a City	Port Elizabeth
1:10 000 000	Negligible	In a Province	KZN

Reference: compiled using information from: Raising the standard: Information for patients. RCA and AAGBI 2003

Mortality risk attributable to anaesthesia itself is about 1:100 000, so you can tell your patients it is very rare (see above).

While anaesthesia is relatively safe, surgery can be dangerous! The European Surgical Outcomes Study showed a median death rate of 3% for elective and 10% for emergency surgery. (Patients ≥ 16yo undergoing non-cardiac surgery over a 7-day period.)

Reference: Irwin M, Kong V. Qualifying and communicating perioperative risk Anaesthesia 2014, 69, 1299-1313

Complications related to General Anaesthesia

Major:

Major Complications	Rate per 10 000 Population
Cardiac arrest	0.5-1.0
Respiratory complications (including airway)	2-200
Cardiovascular complications	Varies, depending on history
Postoperative neurological dysfunction	1 400-5 000 (1:2 to 1:700)
Awareness	3-30
Anaphylaxis	1
Ocular complications	0.08-100 (1:100 cardiac surgery)
Deafness	1 (1:1 000 cardiac surgery)
Peripheral nerve injuries	10-30

Minor

Minor Complications	Rate per 10 000 Population
Postoperative pain	1 000 – 5 000 (1:2)
PONV	2 500 (1:4)
Sore Throat	1 000 – 5 000 (1:2 ETT; 1:5 LMA)
Headache	2 000 (1:5)
Drowsiness and dizziness	2 000 – 5 000 (1:2 to 1:5)
Dental damage	100 (1:100)

Reference: Christina Lundgren refreshed notes 2009: Informed Consent – How informed should it be in 2009

Complications related to Regional Anaesthesia

Complication	Spinal (per 10 000)	Epidural (per 10 000)	Peripheral n block (per 10 000)
Long term neurological damage	1	0.3	1.9
Short term neurological damage	4-80	1-10	200
Haematoma	0.05	0.07	
Cardiac arrest	1.2	0.4	1
PDPH	100	100	
Epidural abscess		0.75 – 5	
Systemic LA toxicity		1	7.5

Reference: Revyl Haylett refresher notes 2011: Risks of Anaesthesia

Notes

Cricoid pressure- Should it be used?

Dr Revyl Haylett

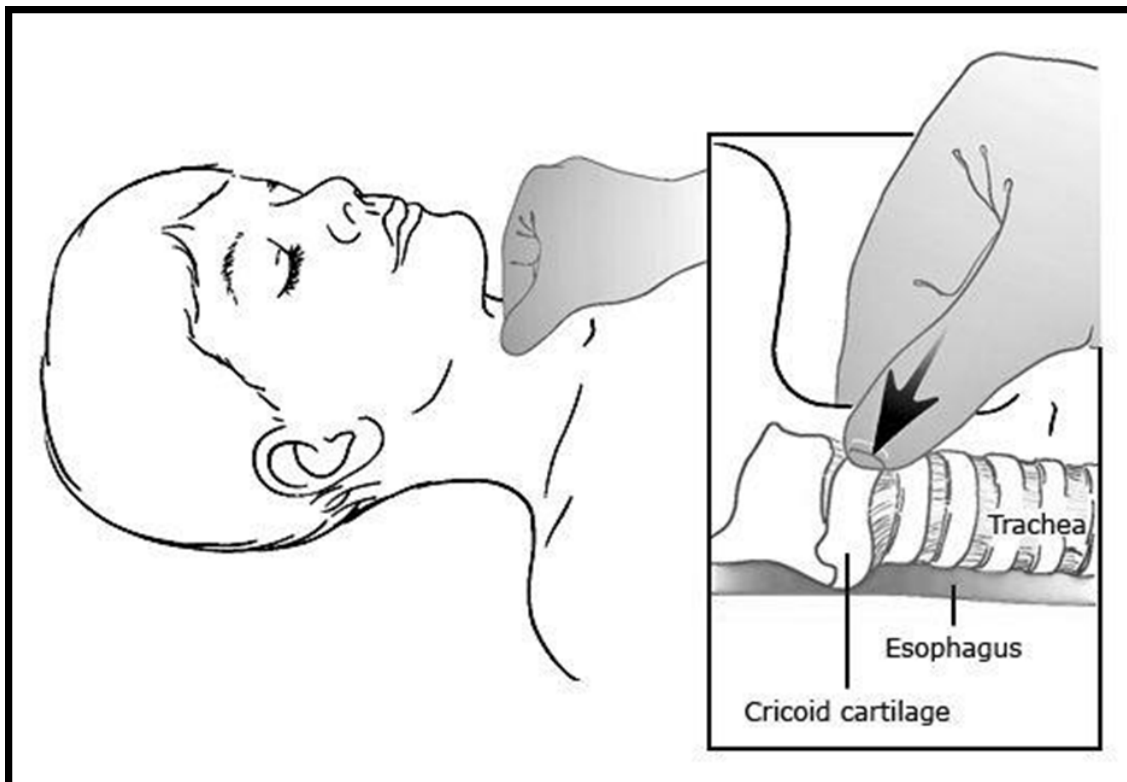
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Rapid sequence induction and intubation (RSII) is a technique used in general anaesthesia designed to reduce the risk of pulmonary aspiration of gastric contents in those patients who are at increased risk of such an event. Because induction of anaesthesia results in the loss of protective airway reflexes, and aspiration is a risk during the interval between loss of consciousness and inflation of the cuff of the endotracheal tube, the components of RSII are employed to protect the airway with a cuffed endotracheal tube as soon after induction of anaesthesia as possible, whilst reducing the chance of passive or active regurgitation.

One of the components of RSII is the application of cricoid pressure – previously inviolate and considered standard of care during anaesthesia induction for patients with high risk for aspiration; but, more recently, the subject of debate and more controversial.

Cricoid pressure

Originally described by Sellick in 1961, the cricoid cartilage is pressed backward by an assistant, using the thumb and index finger, against the underlying cervical vertebrae and occluding the lumen of the oesophagus in order to prevent the regurgitation of stomach contents into the pharynx.



Sellick's initial observation was made using a cadaver model; he then attempted the same manoeuvre during induction of anaesthesia in 26 patients at high risk of aspiration. None of the patients experienced regurgitation or vomiting when cricoid pressure was applied, and three patients had immediate reflux on release of cricoid pressure after tracheal intubation. He also confirmed the value of cricoid pressure in preventing saline that was run into the oesophagus from a height of 100cmH₂O from reaching the pharynx in a patient undergoing gastro-oesophagectomy.

In his report, Sellick described the use of 'firm' pressure but did not quantify the actual force needed to occlude the oesophagus. Based on further cadaver and patient studies, cricoid pressure should be applied at 10 Newtons (1kg) whilst the patient is still awake, and increased to 30 Newtons (3kg) after loss of consciousness. Application of the correct force is vital as using lower force may lead to incomplete oesophageal occlusion, and using excessive force may cause airway compression and limit laryngeal visualisation.

Cricoid pressure should be immediately released if vomiting occurs, to avoid oesophageal rupture.

Important to note is that Sellick described the application of cricoid pressure with the head down, and head and neck in extreme extension so as to tether the oesophagus against the cervical vertebrae; although, in later publications he amended this position to 'slightly extended'. This position is not the standard 'sniff the morning air' position favoured for airway management and may alter the efficacy of the manoeuvre.

Arguments against cricoid pressure

Obstructs laryngoscopy:

Occasionally, Sellick's manoeuvre may obstruct the view of the glottis which may make intubation more difficult, as well as increase the difficulty of placement of a supraglottic airway, fiberoptic intubation and mask ventilation, if such is required during RSII. The evidence in the literature and case reports is contradictory with some documenting worsened laryngeal visualisation with cricoid pressure resulting in increased time to intubation and increased risk for pulmonary aspiration of gastric contents; whilst others showing no difference in laryngeal visualisation or time to intubation.

In a meta-analysis of LMA studies by Brimacombe, it was concluded that cricoid pressure reduced the successful insertion of LMAs from 94% to 67%, and further impeded tracheal intubation via the LMA.

Reduces lower oesophageal sphincter tone:

Cricoid pressure of 20 Newtons in awake volunteers was shown to decrease lower oesophageal sphincter tone from 24 to 15mmHg, and further to 12mmHg when the force was increased to 40 Newtons, with restoration to baseline on release of the pressure. Prophylactic administration of metaclopramide did not prevent this cricoid pressure-induced reduction in lower oesophageal sphincter tone.

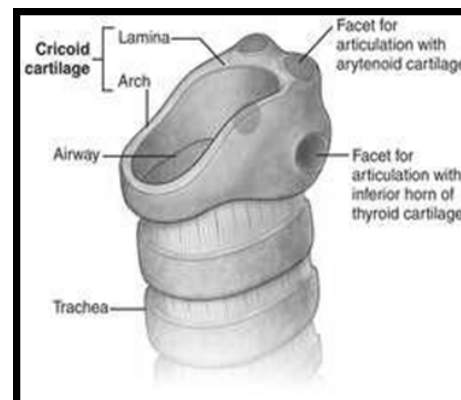
The extrapolation of this concern is that if there was such a response in anaesthetised patients, there would be a risk of gastro-oesophageal reflux; however, this does not necessarily have any bearing on whether there would be any reflux into the pharynx which is, after all, where the regurgitated contents would have to be for the patient to run the risk of aspiration.

It should also be noted that a similar study showed the opposite – that the incidence of gastro-oesophageal reflux was not increased with the application of cricoid pressure.

Incorrect anatomical basis:

The anatomical basis for the theoretical efficacy of cricoid pressure has been disputed recently in both CT and MRI scans which have demonstrated that the oesophagus is located lateral to the midline in approximately 50% of patients (n=51); and that cricoid pressure further displaces the oesophagus laterally in 90% of patients – to the left in 69%, and to the right in 21%. This suggests that the oesophagus could not be occluded by being pinched between the cricoid cartilage and the cervical vertebrae.

When 30 Newtons force is applied to the cricoid cartilage, the cartilage and cervical vertebral body are pressed together and a pressure in excess of 200mmHg is generated posterior to the 10cm² area of the lamina of the cartilage. However, this same force can only prevent regurgitation at pressures up to 40mmHg. This discrepancy can be explained by the fact that the posterior pressure generated by the



manoeuvre is not evenly distributed – the oesophageal portion in the midline will receive greater compression than the lateral areas. When the oesophagus is already in the lateral position (or is moved there by cricoid pressure), the lumen is compressed against the *longus colli* muscle and would also receive less force than if it were being compressed against the bony vertebral body.

Incorrectly performed:

Despite the recommendations with regard to correctly identifying the anatomical position of the cricoid cartilage and the application of the effective amount of pressure, clinicians and assistants are not routinely trained to standardise the technique. In a 1996 survey of 53 anaesthetists and nurse anaesthetists in the US, most of the anaesthetists did not know the definition of a Newton, and all participants were unable to use appropriate force when applying cricoid pressure.

Common errors are to apply pressure to the thyroid cartilage, to use the technique inappropriately and inconsistently, and to remove cricoid pressure either too early (before the airway has been definitively secured) or too late (after the intubator has requested it be removed to facilitate intubation if the glottic view has been obscured).

May cause injury:

Cricoid pressure has been thought to aggravate unstable cervical spine injuries by causing movement at the fracture-dislocation site. Forceful pressure over the fracture site may result in as much motion as direct laryngoscopy, as demonstrated in a cadaver destabilised spine study which showed distraction, angulation and translation of the injured spine when cricoid pressure was applied.

Support for cricoid pressure

- Cadaver studies have shown that cricoid pressure prevents regurgitation of stomach contents (in this case, saline) into the pharynx at oesophageal pressures up to 50cmH₂O. In vivo, intragastric pressures rarely exceed 34cmH₂O (~25mmHg) so a 30 Newton force is more than adequate to prevent regurgitation, regardless of the midline or lateral position of the oesophagus.
- It prevents gastric insufflation during mask ventilation in children and adults - up to 40cmH₂O positive pressure ventilation.
- Cricoid pressure of 30 Newtons effectively occludes the oesophagus, as demonstrated by the failure in passing nasogastric tubes of two different sizes (12 and 20F, 6.7mm and 4mm respectively) into the oesophagus. The use of the Glidescope® video laryngoscope allowed real-time visualisation of the glottis and the oesophageal entrance where the oesophagus was observed to be occluded when cricoid pressure was applied, and patent when cricoid pressure was released. Neither of the nasogastric tube sizes could be passed in any of the study patients whilst cricoid pressure was applied with 30 Newton force; but both sizes could be passed into the oesophagus when the cricoid pressure was released in all the study patients. The results were consistent despite the variable position of the oesophagus whether it was lateral to the glottis or in the midline.

An imaging study with MRI supported this finding. It recommended that the correct anatomic designation for the alimentary tract at the level of the cricoid cartilage should be the *postcricoid hypopharynx* and that it is the oesophagus, originating 1cm below the cricoid ring, that is individually mobile. The study showed that cricoid pressure of 20 to 40 Newtons moved the cricoid cartilage and hypopharynx as a unit (CP unit) which obliterated the lumen of the hypopharynx despite its lateral displacement, and rendered the position of the oesophagus irrelevant in the argument as to whether cricoid pressure prevents regurgitation.

- Sellick's original claim that 'a few seconds' of training would be adequate to ensure appropriate and correct utilisation of cricoid pressure may not be far off – all participants (anaesthetists and nurse anaesthetists) in the survey to ascertain skill level in application of cricoid pressure by clinicians, were able to learn the recommended amount of applied pressure for the manoeuvre, were able to accurately reproduce the pressure required to produce 30 Newtons to within 2 Newtons, and were able to retain this knowledge after three months. The training was simple and not time-consuming; it used an infant scale and

laryngotracheal model to teach position and force required for correct application of cricoid pressure.

- Case reports have documented regurgitation after the release of cricoid pressure.

Advocates of cricoid pressure maintain that it is effective in reducing, but not eliminating, the risk of aspiration. Clinical experience suggests that, on the whole, the application of cricoid pressure is not harmful and may certainly be beneficial; however, as aspiration is a relatively rare event, a study to confirm or refute its efficacy is not feasible. Indeed, it is likely not ethical either as the control group at risk for aspiration would be denied the technique.

This explains its current position in RSII/RSI and other airway management guidelines, despite conflicting evidence regarding its efficacy in preventing regurgitation. It is essentially a low-risk technique that may work in a certain percentage of patients.

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