

COVID coagulopathy: mechanisms, clinical cases, monitoring and therapeutics

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Introduction

Very high cumulative incidence of thrombotic complications in critically ill COVID-19 patients

Dutch university hospitals:

- 184 ICU patients receiving thromboprophylaxis followed up for 14 days:
- CI of VTE **49%** (95% CI 41-57%); ie confirmed diagnoses of PE, DVT, CVA, MI, arterial embolism
- The majority of VTE were **PE (87%)**
- 43% discharged alive

French university hospitals:

- Prospectively compared COVID (n=150), and non-COVID ARDS (n= 233) patients
- 64 (53%) COVID patients developed clinically relevant thrombotic complications, mainly PE (16.7%), despite thromboprophylaxis as per standard of care.

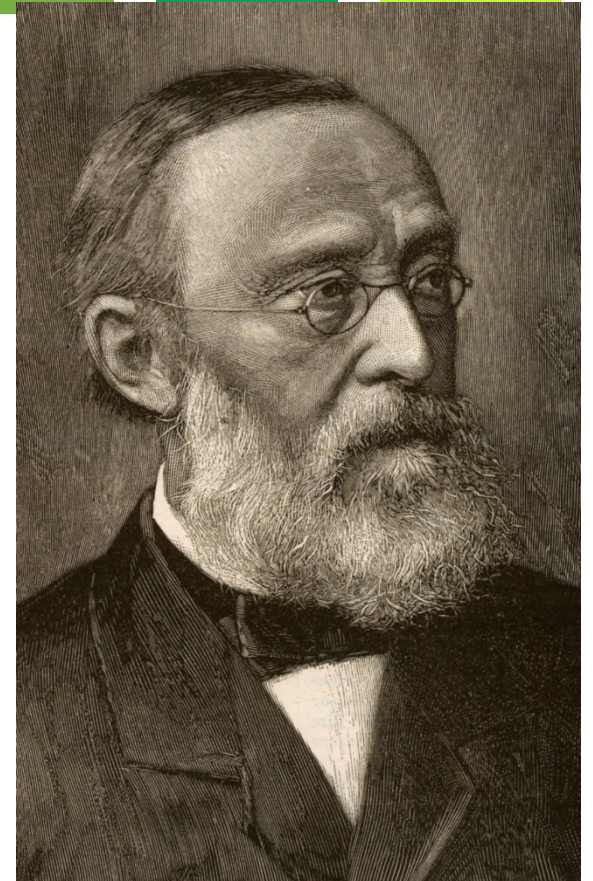
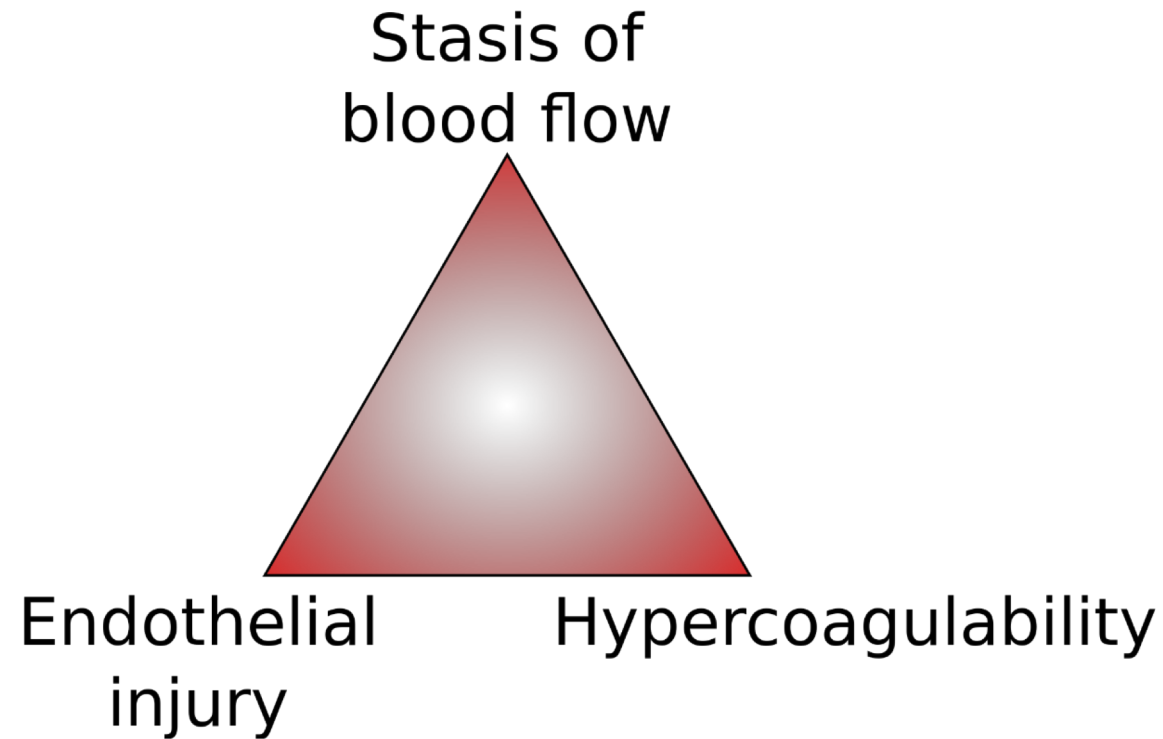
Compared with non-COVID ARDS patients, significantly more thrombotic events ($p < 0.008$)





Virchows Triad:

3 main factors contributing to thrombosis



Rudolf Virchow 1821- 1902



Evidence from autopsy findings in COVID-19

7 COVID lungs **vs** 7 lungs of influenza ARDS lungs **vs** 10 healthy aged matched control lungs

Key findings:

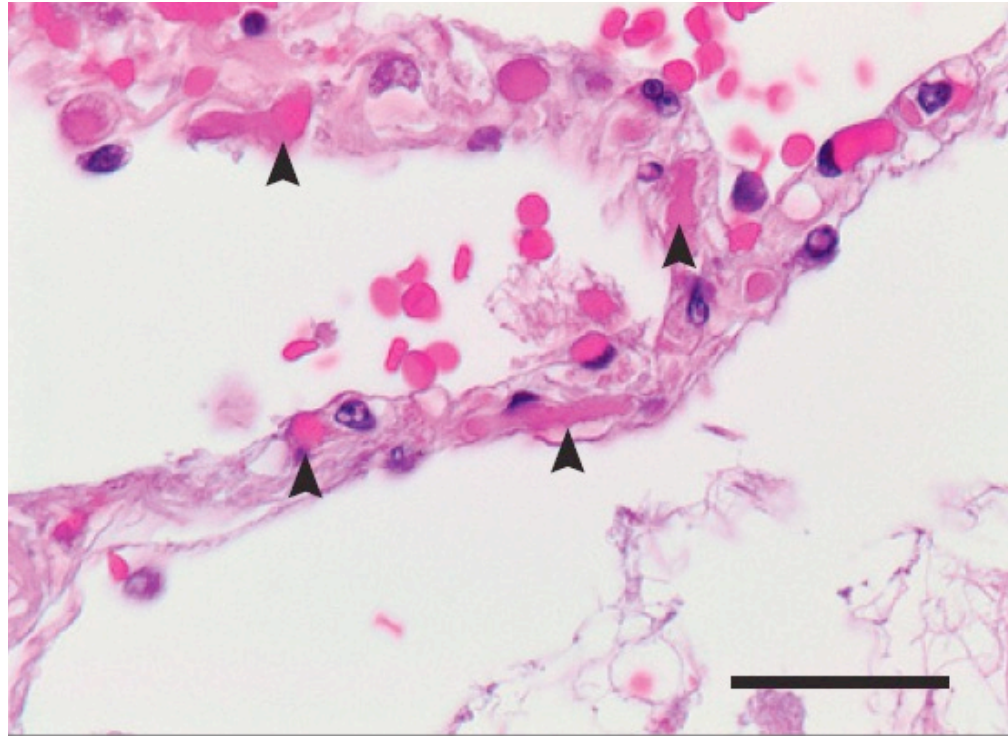
- Lungs from COVID patients: distinct vascular changes with severe endothelial injury, intracellular virus and disrupted cell membranes
- Widespread thrombosis with microangiopathy
- Alveolar capillary microthrombi 9 x as prevalent, new vessel growth 2.7 x prevalent as in patients with influenza (both $P < 0.001$)



Ackermann et al NEJM, May 21 2020.
DOI: [10.1056/NEJMoa2015432](https://doi.org/10.1056/NEJMoa2015432)



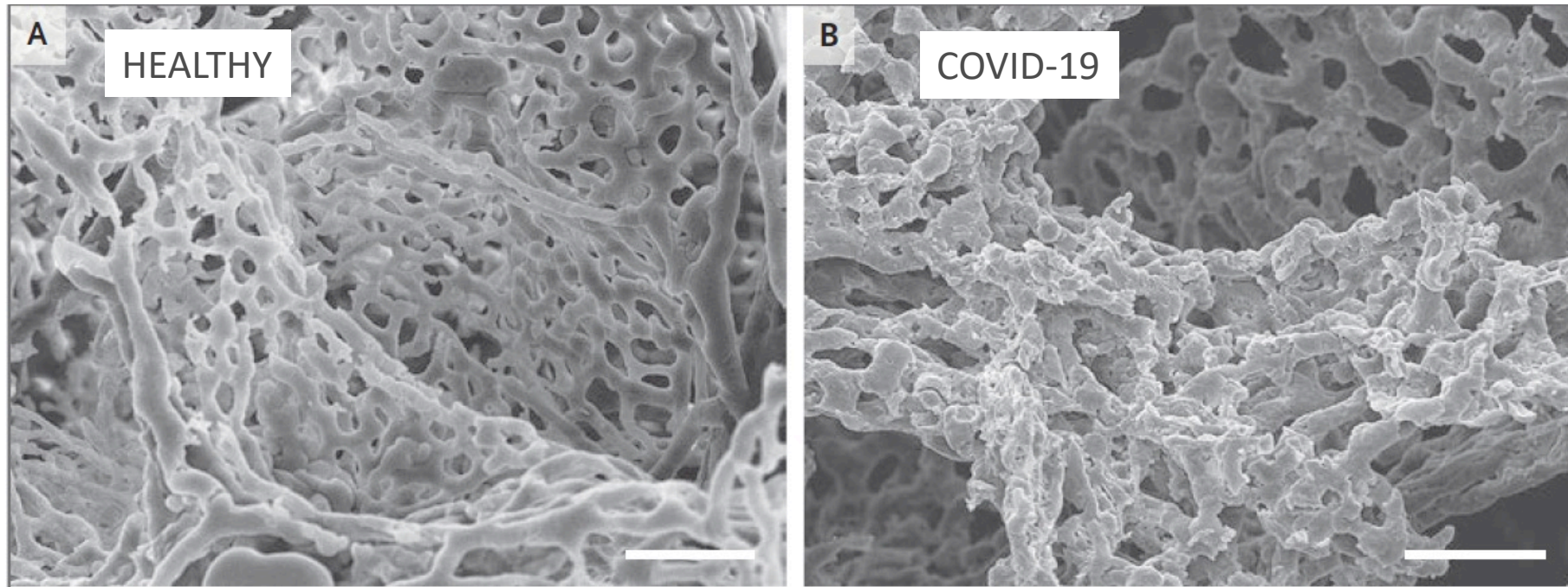
Microthrombi in the lung inter-alveolar septa



Arrowhead: multiple fibrinous microthrombi in alveolar capillaries
Intra alveolar space: extravasated RBC and loose fibrin network
Thickened alveolar septa

Ackermann et al NEJM, May 21 2020. DOI: [10.1056/NEJMoa2015432](https://doi.org/10.1056/NEJMoa2015432)

Alveolar vascular plexus of healthy lung vs COVID 19



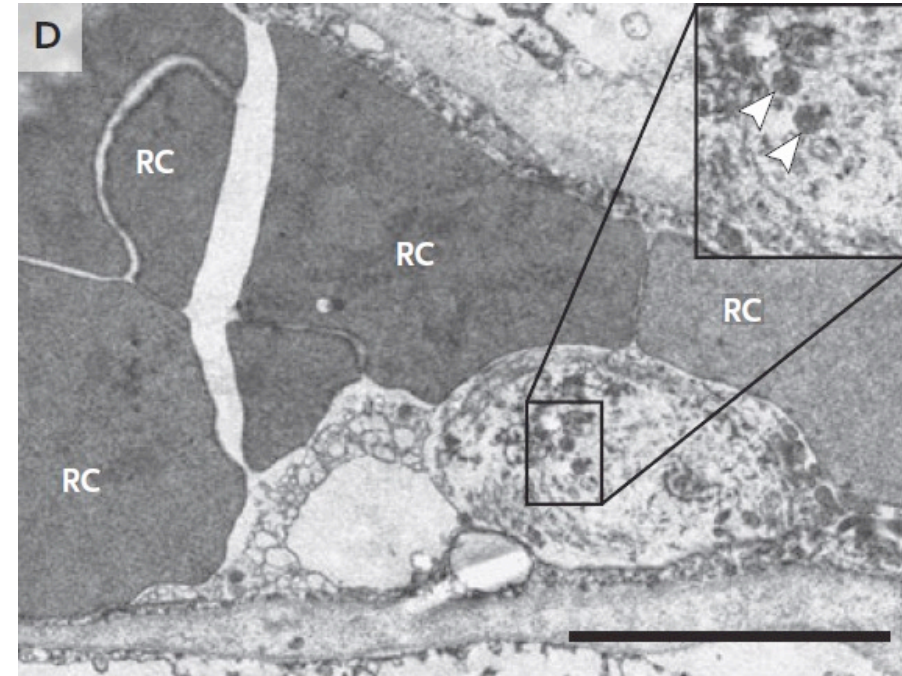
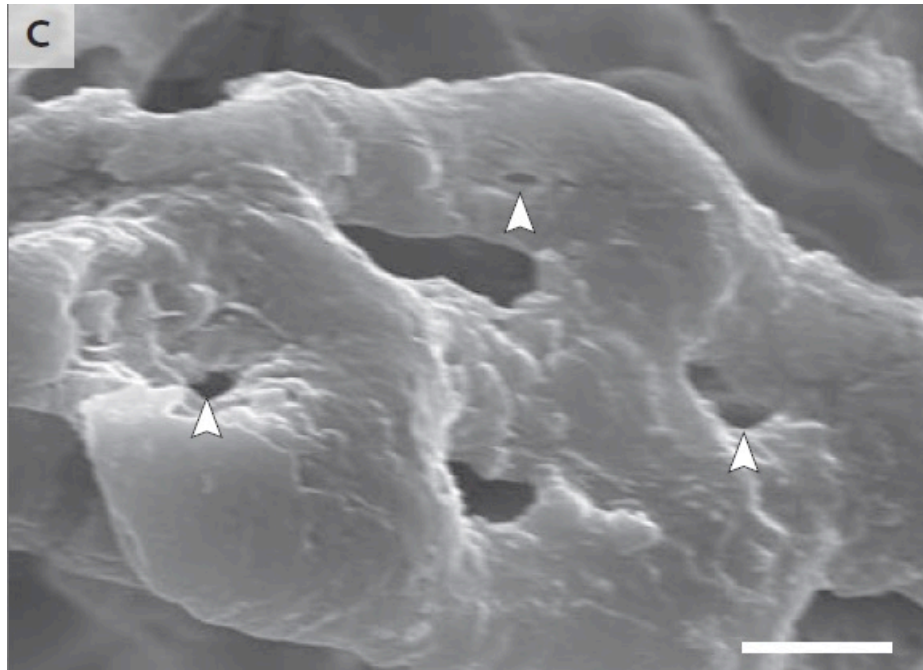
Electron microscopy of microvascular corrosion casts: 3D visualisation showing normal and abnormal microvessels



Ackermann et al NEJM, May 21 2020.
[DOI: 10.1056/NEJMoa2015432](https://doi.org/10.1056/NEJMoa2015432)

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EM: High magnification of pulmonary microvasculature in COVID

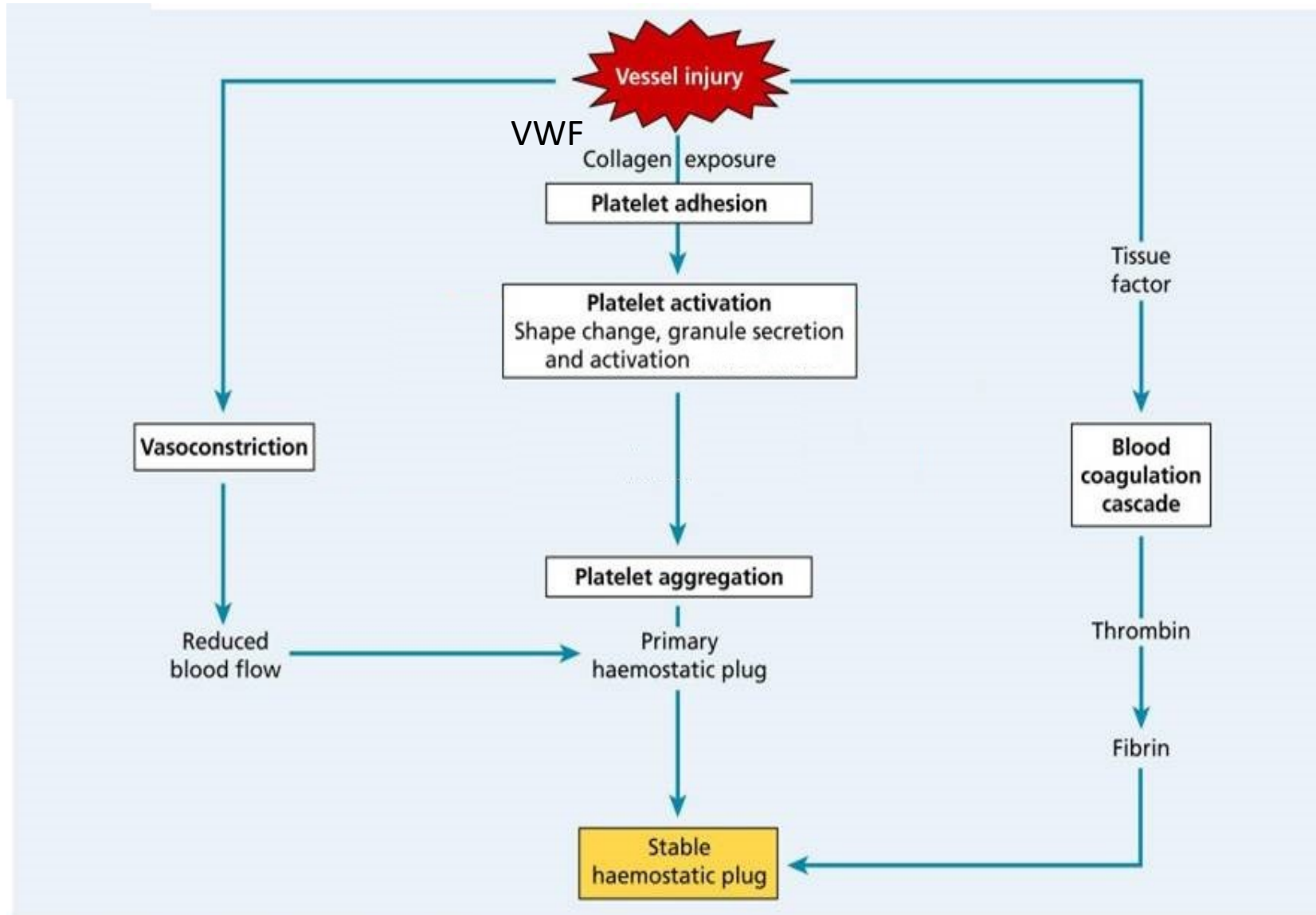


C: Damage to normal capillaries is due to new vessel formation via intussusceptive (non-sprouting) angiogenesis (white arrow); significantly higher in COVID lungs vs influenza : **60.7** +/- 11.8 per field vs **22.5** +/-

D: Ultrastructural destruction of endothelial cells (cell swelling, loss of contact with BM), SARS-CoV-2 virus within the endothelial cell.

Direct viral effects and perivascular inflammation contribute to the endothelial injury

Haemostasis: The big picture

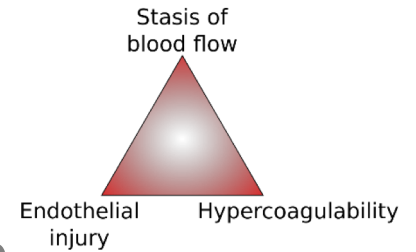


From: *Essential Haematology*, 6th Edn. © A. V. Hoffbrand & P. A. H. Moss.
Published 2011 by Blackwell Publishing Ltd.

Limited by fibrinolysis

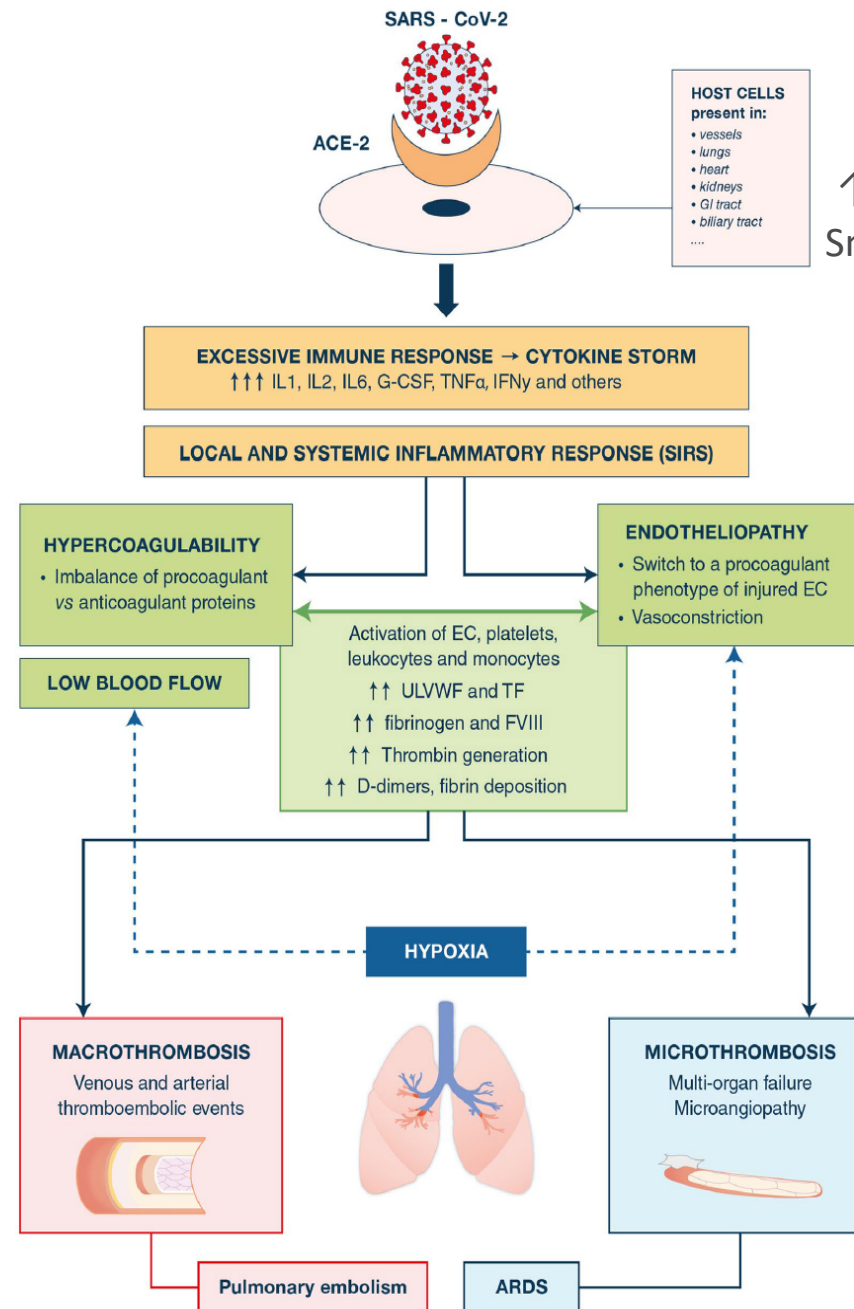


COVID Endothelial injury/endotheliopathy



- Leads to switch of endothelial membrane from anticoagulant surface to procoagulant phenotype
 - Release of ultralarge vWF multimers which bind platelets to damaged endothelial membrane
 - Over-expression of tissue factor (TF) which triggers the coagulation cascade
 - Imbalance of procoagulant vs anticoagulant proteins leading to
 - **HYPERCOAGULABILITY**
- Worsened by **STASIS** due to local vasoconstriction due to damaged endothelium and hypoxia
- All three components of Virchows triad contributing to thrombosis are met

COVID and Haemostasis: Role of Inflammatory response



↑ density of ACE-R in lungs, heart, veins and arteries
Smooth muscle linings of arteries in brain*

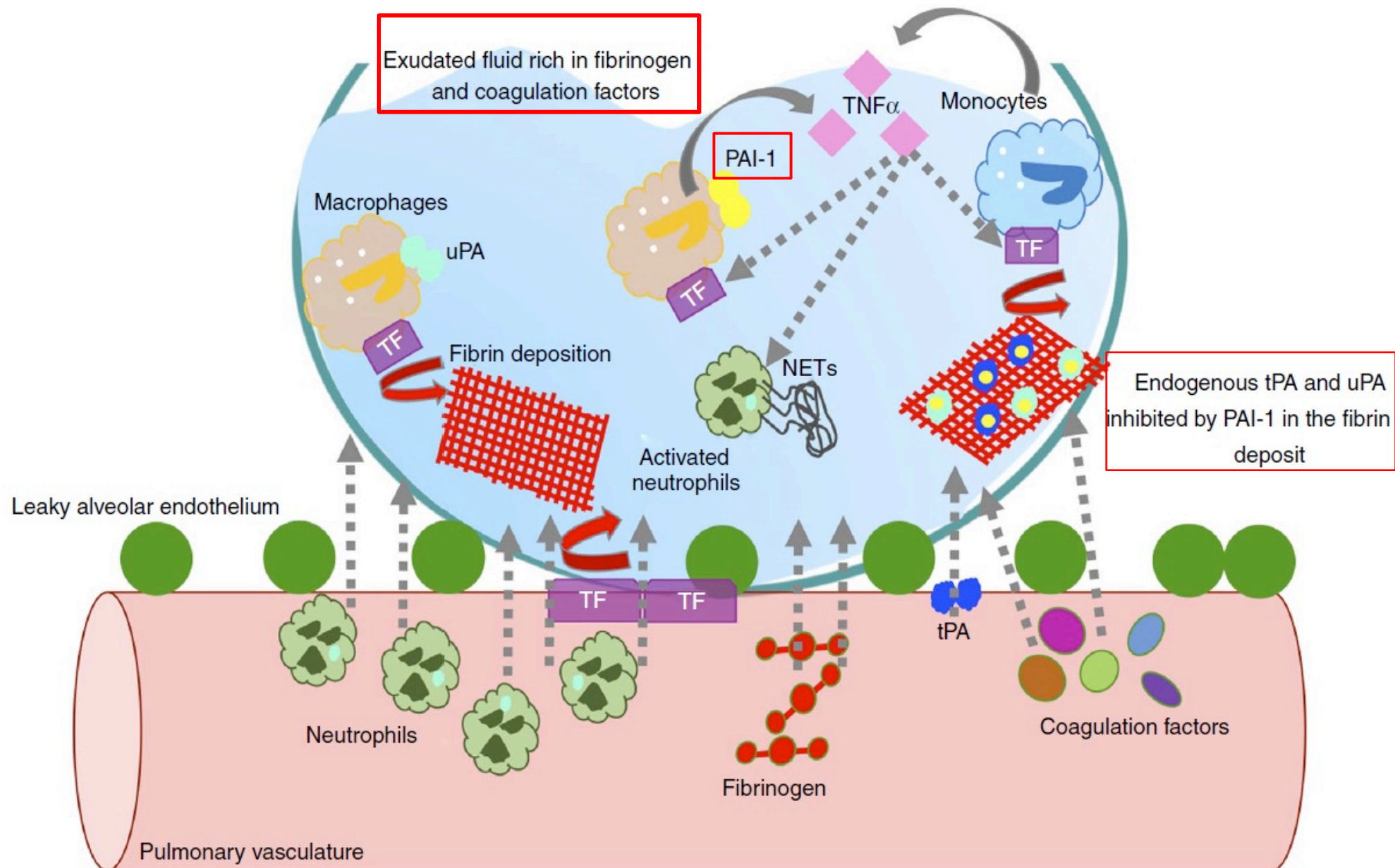
Macrothromboses:
Often unusual presentations
Strokes in young patients,
MI in absence of culprit lesion
Limb ischaemia

COVID microangiopathy distinct from DIC
(uncommon) & TTP

Intensive Care Med

<https://doi.org/10.1007/s00134-020-06088-1>

*Hamming et al. J Pathol 2004





FIBRINOLYTIC SYSTEM ABNORMAL: hypofibrinolysis

A consistent finding in ARDS: deposition of fibrin in air spaces and lung parenchyma
COVID-19 patients:

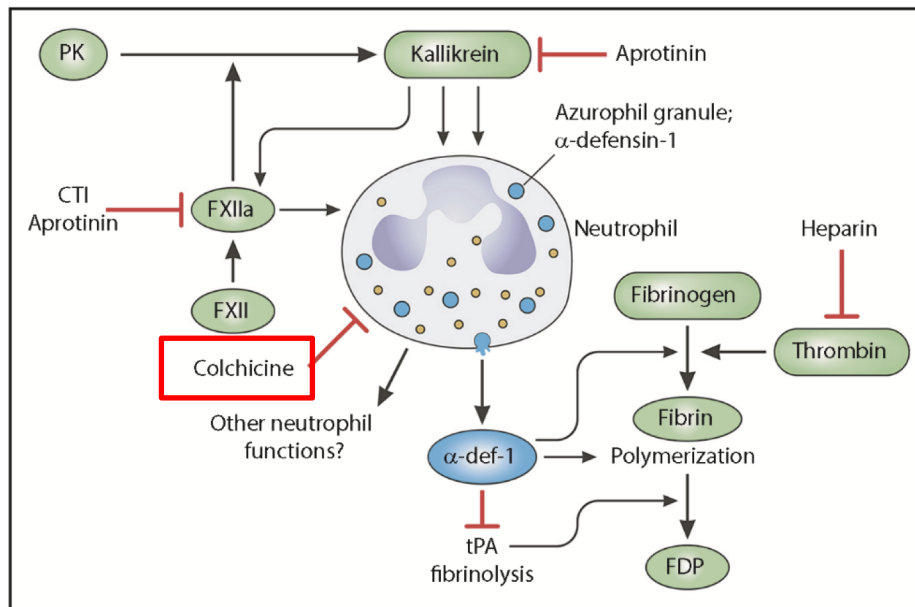
- Fibrin deposits in lungs, due to dysregulation of coagulation and fibrinolytic systems:
 - Tissue factor (TF) is exposed on damaged alveolar endothelial cells, leukocyte surfaces – promoting fibrin deposition
 - Significantly elevated levels of **plasminogen activator inhibitor 1 (PAI-1)** from lung epithelium and endothelial cells prevent fibrinolysis

Whyte CS et al. J Thromb Haemost. 2020;00:1–8.

With thanks to Dr Jaco Joubert UFS

Inflammation is linked to thrombosis

- Inflammation and thrombosis integrated and mutually reinforcing processes
- IL6, powerful proinflammatory cytokine, induces **Tissue Factor** expression and thus thrombin generation.
- **α defensins**, antimicrobial proteins released from activated human neutrophils on clot formation, accelerate fibrin polymerization, incorporate into clots and **impede fibrinolysis**; demonstrated in mouse model



Contact system of coagulation sends defensins to the rescue

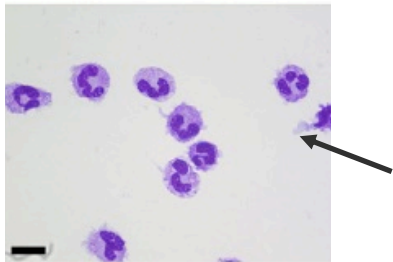
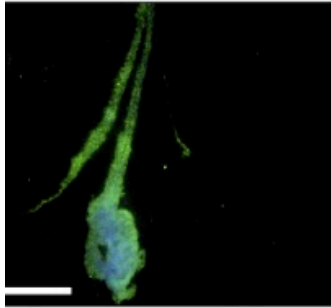
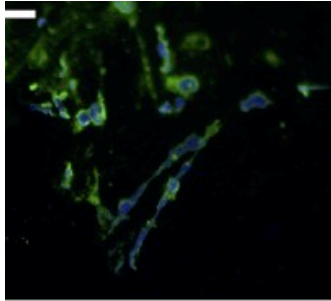
L. D. Healy, O. J. T. McCarty, Blood, 2019,



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Role of neutrophil extracellular traps



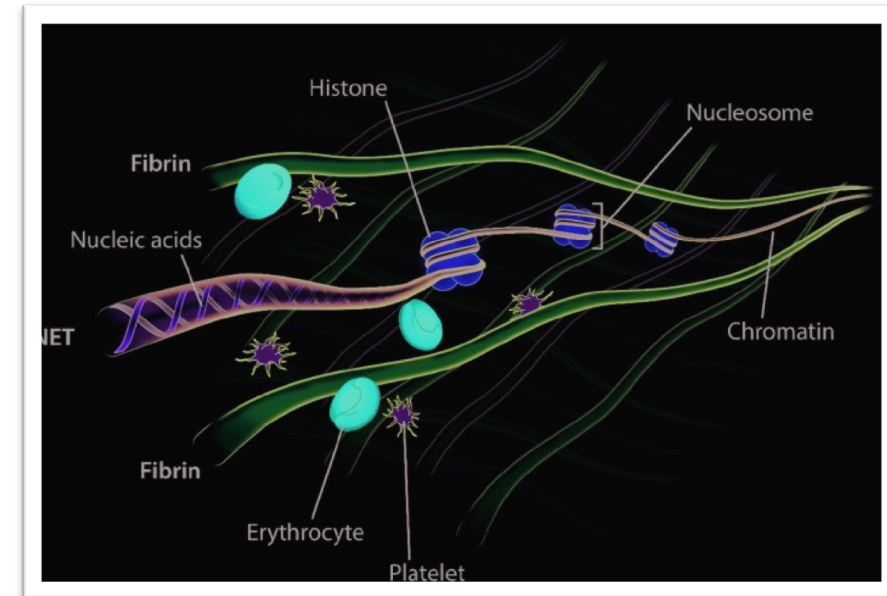
Septic shock with DIC

Green Stain: myeloperoxidase

Blue stain: DNA

In response to infection/acute inflammation, neutrophils:

- Release their content including DNA, histones, granule content/enzymes
- forms a large net-like extra cellular structure to trap pathogens
- Large procoagulant surface:
 - Activates platelets and contact phase of coagulation
 - Promote thrombus formation in microvessels
 - Play a major role in immunothrombosis
 - Link inflammation, coagulation and thrombosis in multiple conditions at multiple sites

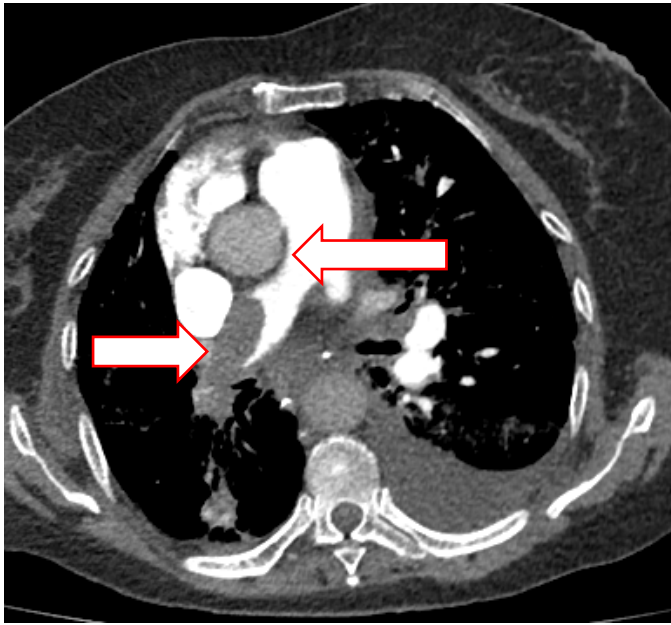


<https://doi.org/10.1016/j.thromres.2019.09.036>

Journal of Thrombosis and Thrombolysis (2020) 50:54–67

<https://doi.org/10.1007/s11239-020-02134-3>

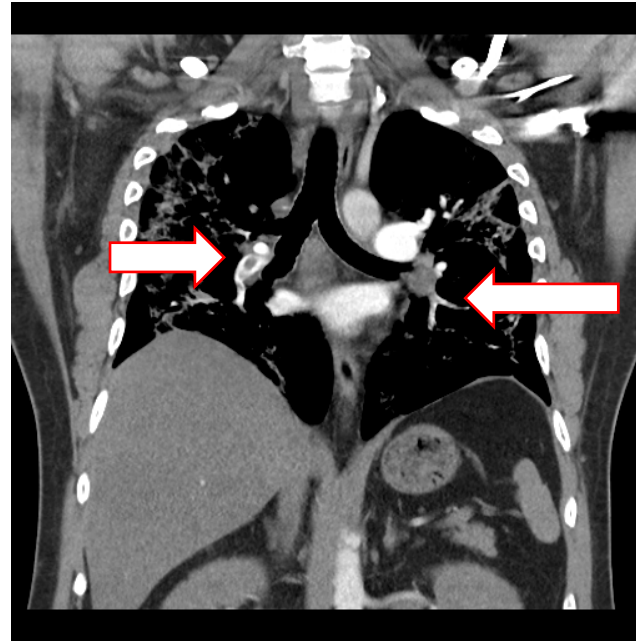
Clinical spectrum of VTE



Sudden deterioration

58 year old woman
New diabetes and obese
5 days shortness of breath, cough
sO2 84% RA
Started HFNO/proning on Day 7
On therapeutic dose enoxaparin
Deterioration on Day 11

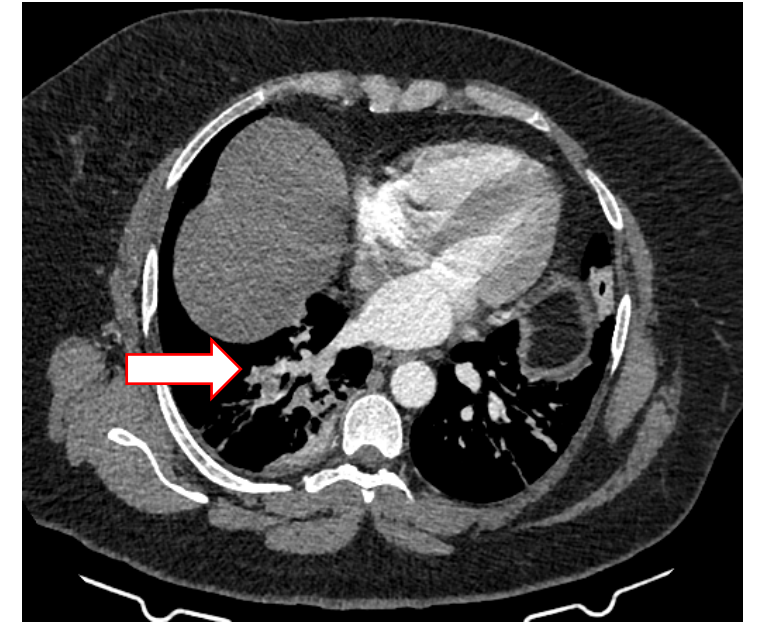
CTPA: massive central clot with almost no perfusion of the RLL



DVT and persistent hypoxia

36 year old man
Hypertension; MI with PCI and stents; smoker; overweight
17 days SOB, myalgia, swollen left calf
sO2 90% FMO2
D-dimer > 5; CRP 76
Therapeutic dose enoxaparin

CTPA: bilateral pulmonary emboli



Typical symptoms, milder Covid

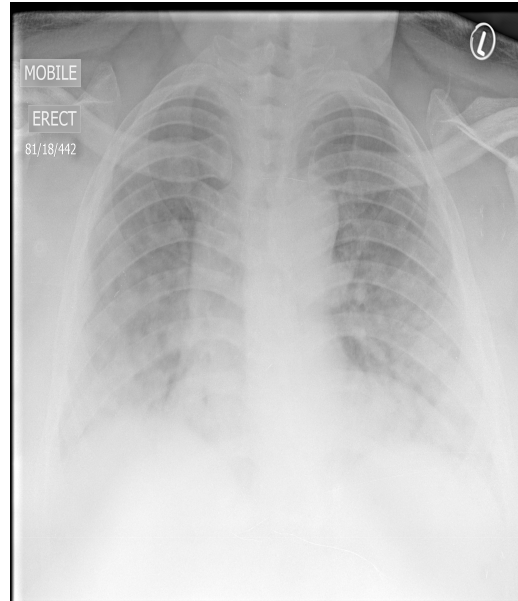
45 year old woman
Rectal carcinoma; abdominoperineal resection
Represented 1 day later: SOB, right pleuritic chest pain, cough, fever
sO2 90% R/A

CTPA: right lower lobe PE

Arterial thrombosis

Limb ischaemia

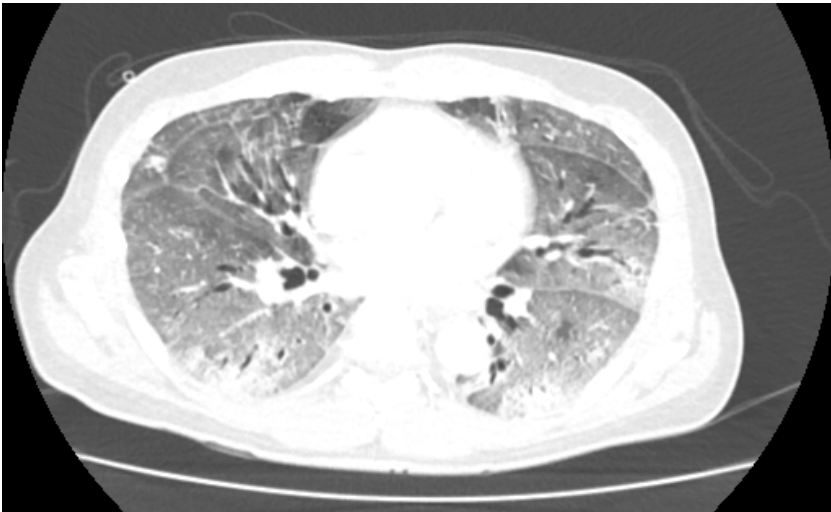
44 year old man
New diabetes; obese
Diagnosed Covid 26 June
CTICC: sudden onset painful left leg
sO₂ 88% NRM; pulse 120
Lactate 4.9
Pulseless and cold left foot
CTA not performed
Anticoagulation started: clexane 120 BD
For conservative management



Arterial thrombosis

Mesenteric ischaemia

58 year old man
Hypertension and smoker
Confirmed Covid
CTICC: sudden onset abdominal pain on
day 4 (was on clexane prophylaxis)
sO2 85% NRM
Lactate 3.1; CRP 266; ferritin > 1500
Epigastric tenderness

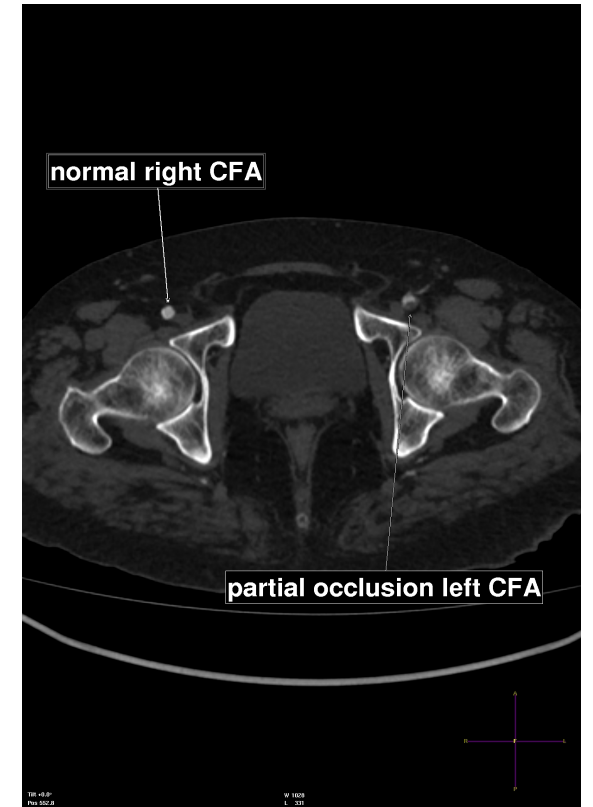
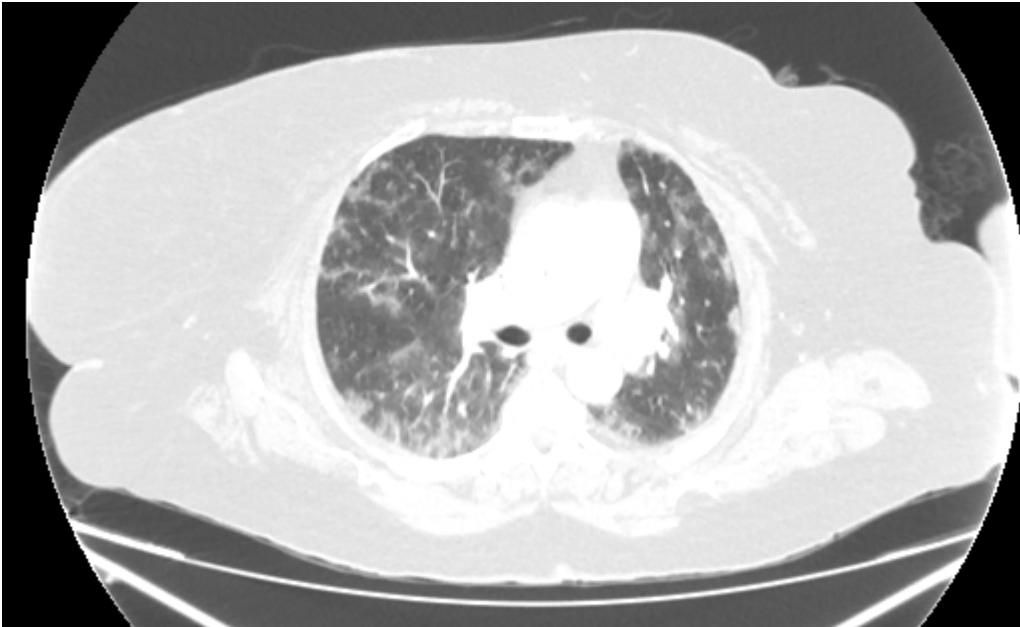


CT abdomen: proximal SMA occlusion; PV thrombosis, splenic infarcts

Arterial thrombosis

CFA occlusion

72 year old woman
Hypertension and diabetic
Confirmed Covid
Sudden onset left leg pain D18
Absent pulses



CT abdomen: acute thrombus left CFA extending into proximal SFA with cut off of popliteal artery

Arterial thrombosis

Thrombosed aorta

42 year old man

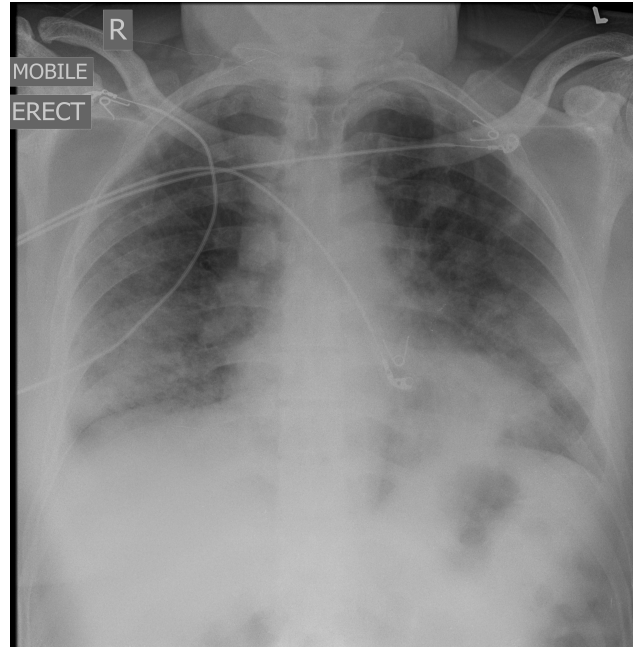
Hypertension

Severe Covid

On therapeutic anticoagulation

Sudden onset loss of sensation and
weakness in legs

D-dimer 0.52 → >5.2



**CTA: complete
thrombotic occlusion of
infrarenal aorta**





Haemostatic monitoring of COVID patients:

- Minimal panel of haemostasis tests:
 - **prothrombin time** (not INR which is insensitive)
 - **Fibrinogen**
 - **platelet count** (also NB for HIT)
 - **D-dimers**
- High fibrinogen and D-dimer levels reflect the hypercoagulable and inflammatory state
- Recommend monitoring with anti – Xa levels to ensure therapeutic levels.
- Could viscoelastic tests on whole blood eg TEG better explore hypercoagulability and predict thrombotic events in this setting?

Covid-19-associated coagulopathy “CAC”

COVID-19-associated coagulopathy

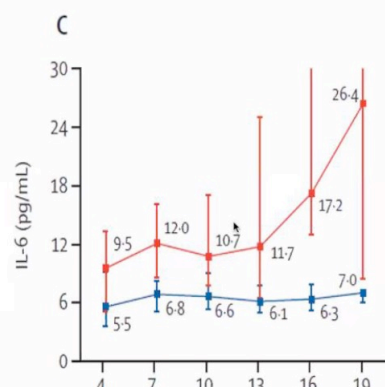
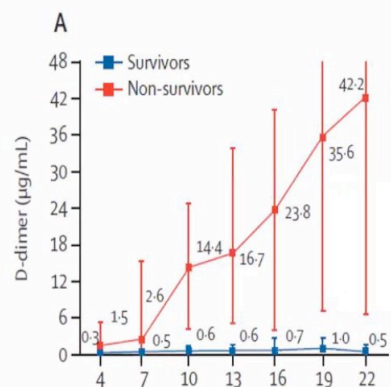
Summary of findings
1. Coagulopathy is manifest as elevated fibrinogen, elevated D-dimers, and minimal change in PT, aPTT, and platelet count in early stages of infection
2. Increasing IL-6 levels are correlated with increasing fibrinogen levels
3. Coagulopathy appears to be related to severity of illness and resultant thromboinflammation and not intrinsic viral activity
4. Elevated D-dimer at admission is associated with increased mortality
5. Rising D-dimer after admission precedes multiorgan failure and overt DIC - Noted to start at 4 d after admission in nonsurvivors - Longer duration of hospital stay associated with increasing D-dimer and development of sepsis physiology
6. Bleeding manifestations are not common despite coagulopathy

“CAC” distinct from DIC and Thrombotic microangiopathy

Connors and Levy, *Blood* 4 June 2020
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D Dimer and risk of in-hospital death

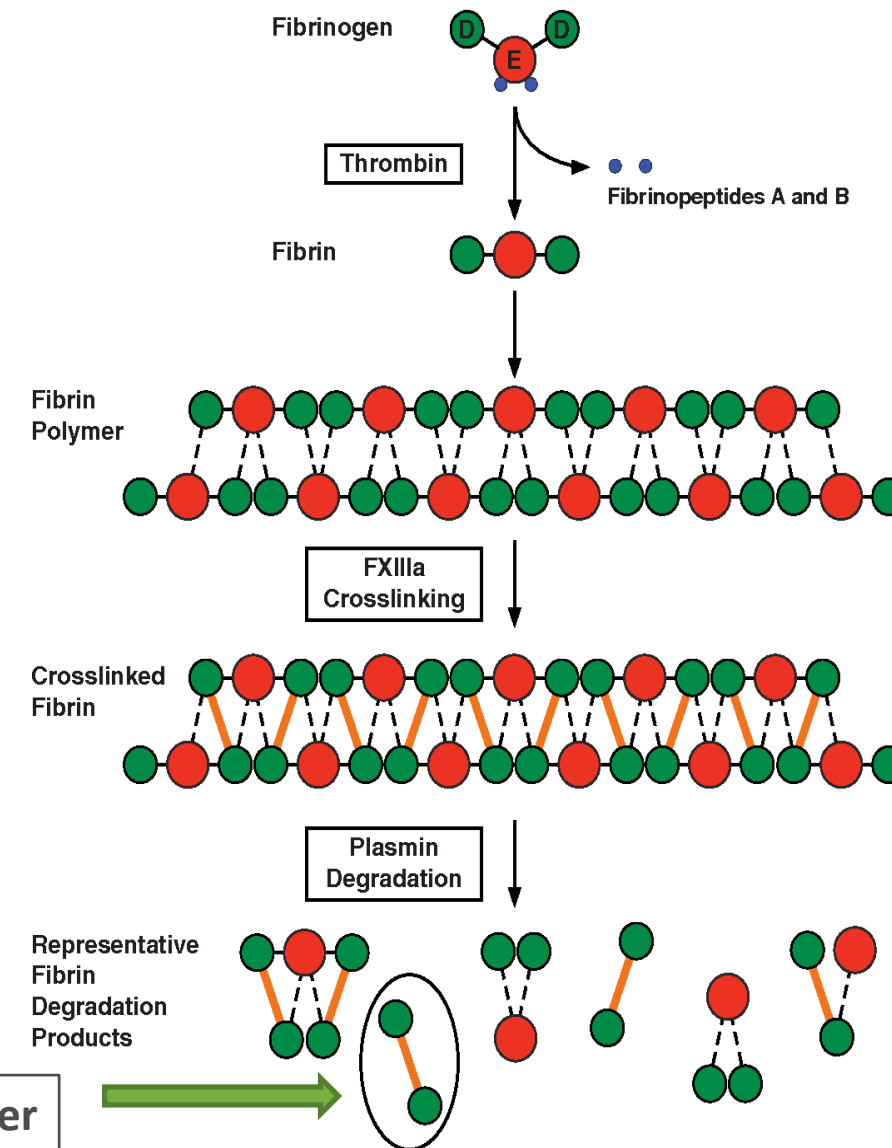
	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
D-dimer, µg/mL				
≤0.5	1 (ref)	..	1 (ref)	..
> 0.5	1.96 (0.52-7.43)	0.32	2.14 (0.21-21.39)	0.52
> 1	20.04 (6.52-61.56)	<0.0001	18.42 (2.64-128.55)	0.0033

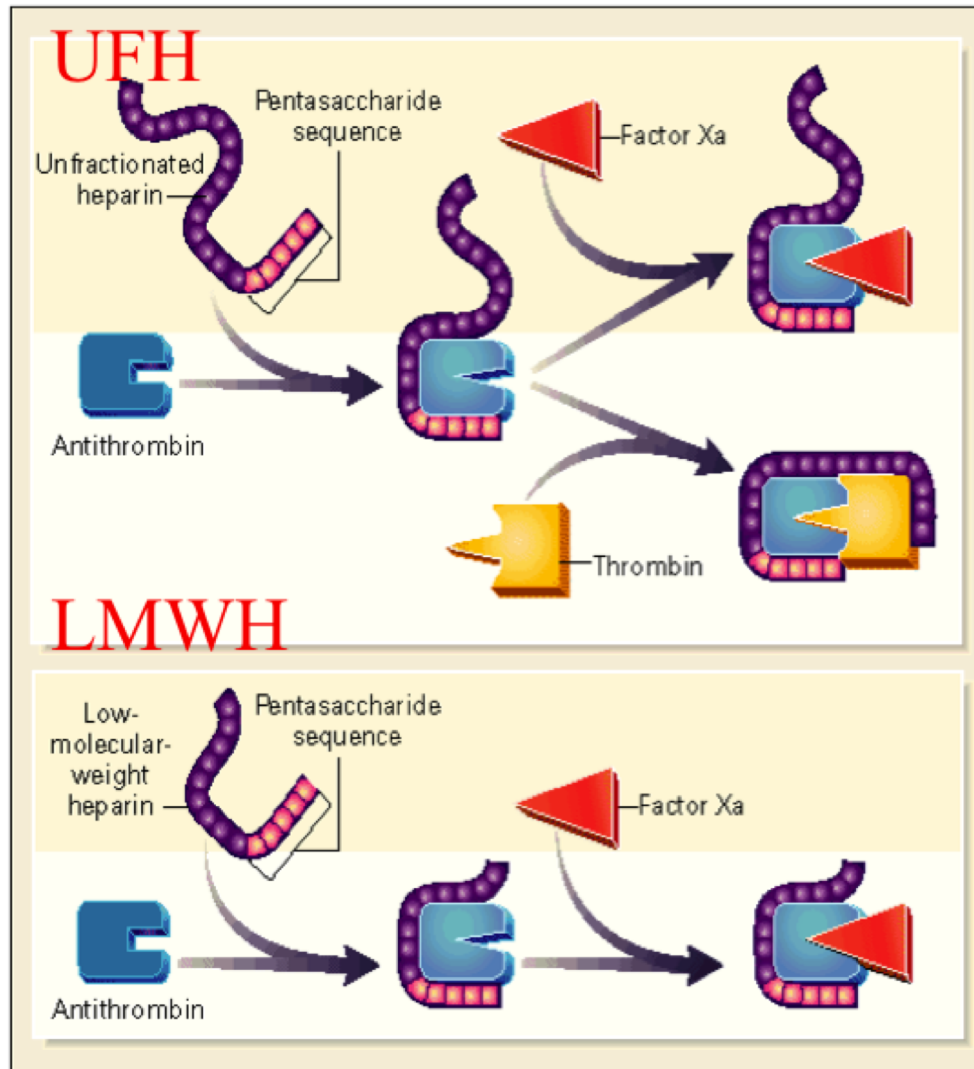


Feizhou et al, Lancet 2020

D-Dimer testing

- D Dimer is end product of plasmin degraded cross-linked fibrin
- Increased levels indicates fibrin polymer breakdown by plasmin.
- High negative predictive value but many causes for increased levels (low specificity) including pregnancy, malignancy, recent surgery.
- NHLS D Dimer assay measures 0.2-5.25 mg/l (normal < 0.25 mg/l)
- Named from having D fragments of fibrin protein joined by a covalently bound cross link





LMWH: improved bioavailability, decreased affinity for heparin binding proteins
More predictable dosing than UFH
Routine monitoring not needed (non COVID)
Excreted renally

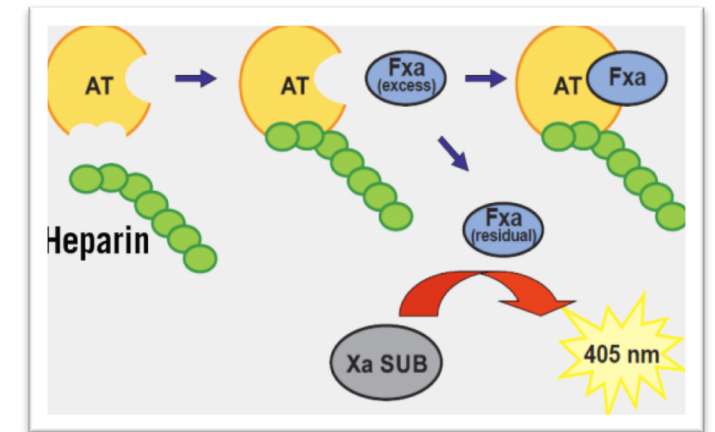


Anti Xa levels for patients on clexane:

- Typically only monitor pregnant, renal failure, paed, extremes of body weight
- In COVID much higher doses are often required to reach a therapeutic range
 - 69 ICU patients:
 - heparin resistance to UFH in 8/10, LMWH suboptimal peak anti-Xa in 5/5
 - Spiked plasma of 12 COVID ICU patients with LMWH: lower anti Xa levels compared to normal control plasma
 - Further studies needed
 - Due to ↑↑ Fibrinogen and Factor VIII; ↓Antithrombin
- Anti X-a monitoring advised in COVID patients

How to monitor & dose using anti-Xa.

- Weight based dosing
- Measure levels after steady state achieved: after 3 doses of 1mg/kg 12 hrly or 2 doses of 1.5 mg once daily
- Timing crucial: concentrations peak at 4 hrs post dose(3- 5 hrs)
- MUST reach lab within an hour
- Adjust dose upwards if levels subtherapeutic (Target **0.6 – 1.2 IU/ml**)
- Not susceptible to interference from $\uparrow$ FVIII or fibrinogen
- Obesity:
 - Under dosing common
 - Increased renal blood flow and glomerular filtration



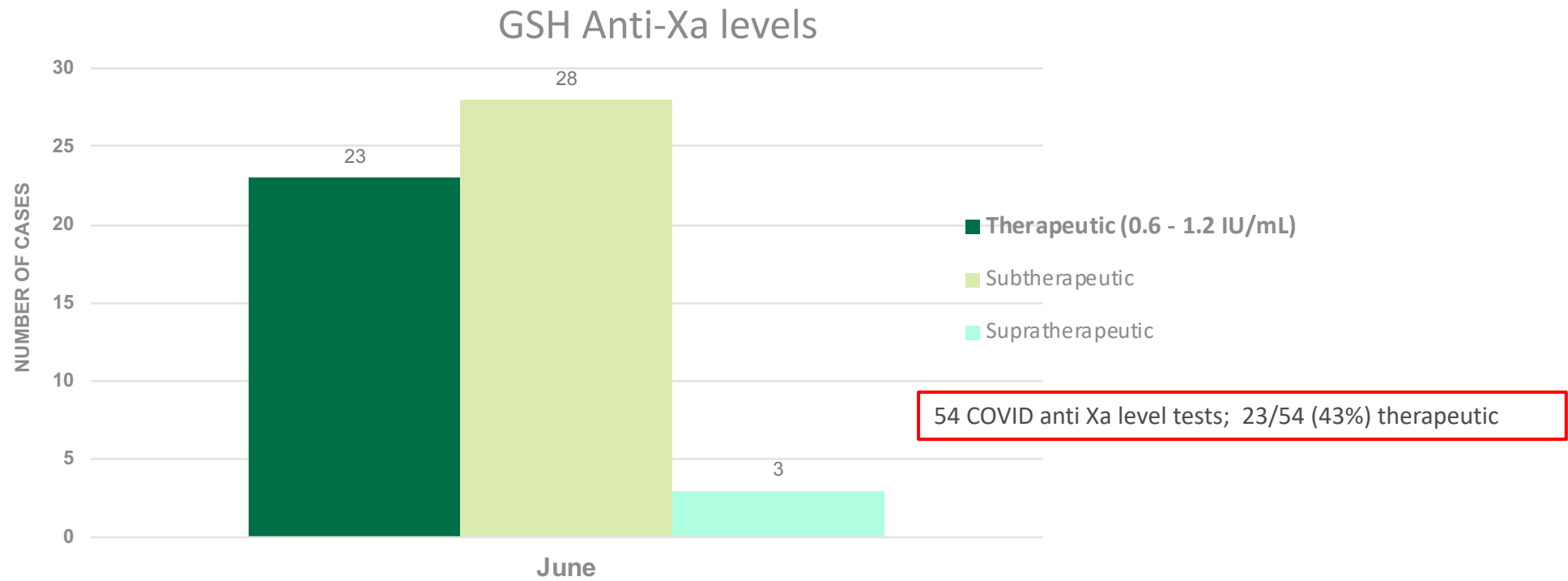
Principles of chromogenic anti-X a assay

Xa SUB = chromogenic substrate

Anti X a levels are inversely proportional to light absorbance



COVID NHLS lab Anti-Xa stats June 2020



May: 27 COVID anti Xa levels received; 18 (67%) therapeutic

No clinical data for these patients yet.

With thanks to: **Dr Jenique Bailly**, Haematology Pathologist and **Ms Zulfa Abrahams**, RXH lab manager

Role of Thromboelastography (TEG)

Studies have shown

1. COVID patients **hypercoagulable** on TEG

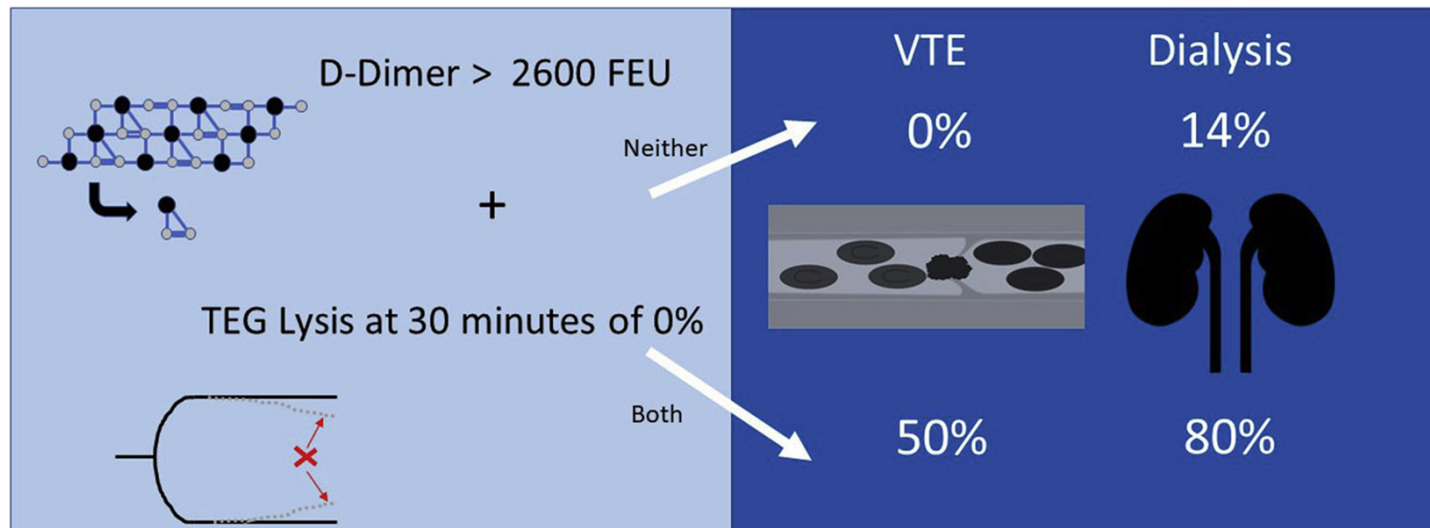
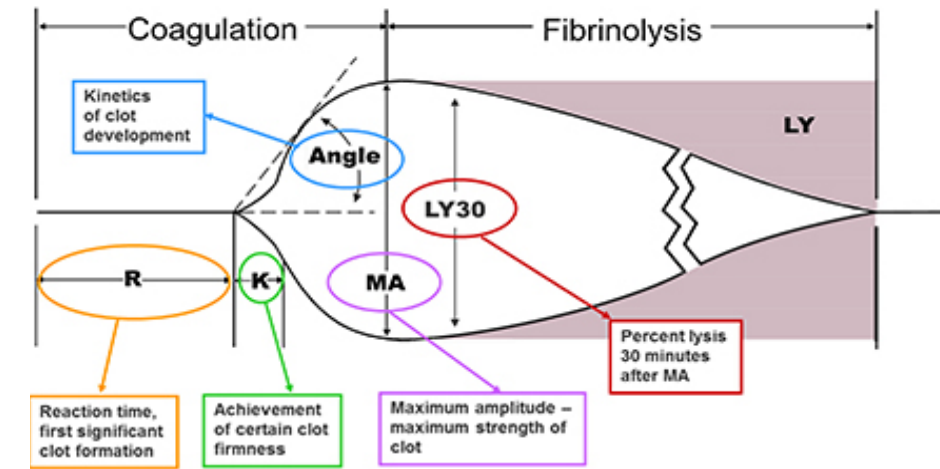
24 patients admitted to ICU

Decreased R and K value (time to fibrin clot formation) and increased MA (strength of clot).

2. **Fibrinolysis shutdown** correlates with VTE in severe COVID infection

44 patients: TEG showed elevated MA, low clot lysis at 30 min

Complete lack of clot lysis at 30 min in 57% of patients which **predicted VTE**, especially together with raised D Dimer



Rationale for anticoagulant thromboprophylaxis

1. High risk and incidence of VTE in Covid

Critically ill (ICU)	Acutely ill (non-ICU inpatients)
Range: 20 to 59% (n = 800; majority thromboprophylaxis)	Range: 6 to 22% (n = 521; > 70% on prophylactic heparin)
<i>Failure rate of anticoagulant thromboprophylaxis in non-Covid RCTs: 6 to 16%</i>	<i>Higher than general medical inpatients: < 1% symptomatic VTE</i>

Lower incidence of arterial thrombotic events

14/1419 (1%) in Spanish hospital cohort
3 ACS; 8 stroke; 3 limb thrombosis

Rationale for anticoagulant thromboprophylaxis

2. Elevated D-dimer and obesity associated with worse outcomes and may be predictive of VTE

- Majority of our patients with severe Covid are overweight
- Positive predictive value of D-dimer $6 \times \text{ULN} > 44\%$ in one study

3. Challenging to screen and diagnose VTE in Covid:

- IC issues, dynamic disease, unstable patients (proning)



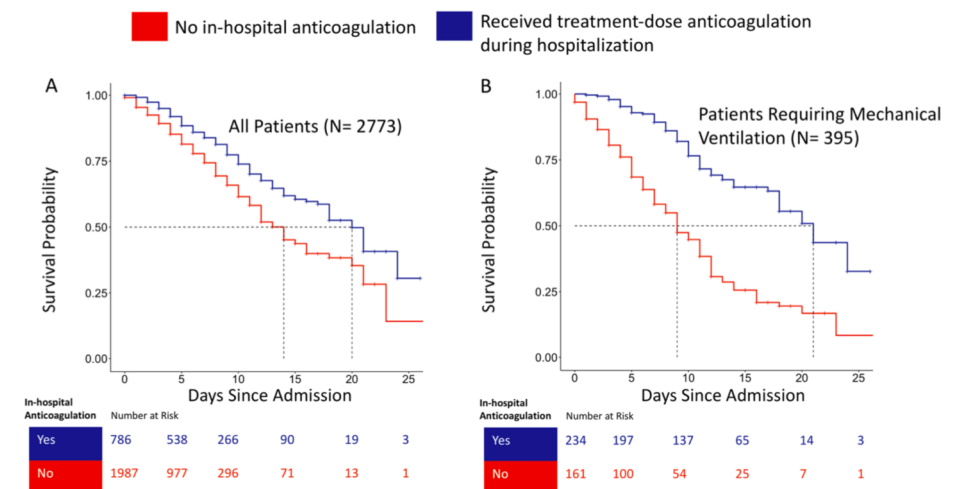
Rationale for anticoagulant thromboprophylaxis

4. Observational studies suggest lower mortality in certain patients treated with heparin

Retrospective Chinese cohort; n = 449, unclear if in ICU
20% absolute lower mortality associated with heparin use if D-dimer > 6 x ULN

Patients with	28-day mortality		Univariate analysis	
	Treating with heparin, %	Nontreating with heparin, %	Odds ratio (95% CI)	P value
D-dimer > 6 ULN (n = 161)	32.8	52.4	0.442 (0.226-0.865)	.017
D-dimer > 8 ULN (n = 150)	33.3	54.8	0.412 (0.207-0.817)	.011

Retrospective US cohort; n = 2,773
Overall in-hospital mortality with AC 22.5% vs 22.8%
Lower mortality in IMV patients on AC (29 vs. 62%)



Our practice and uncertainties

Prophylaxis

- All inpatients with Covid (and suspected Covid) pneumonia

Therapeutic anticoagulation

- Severe hypoxia (requiring NRM or HFNC oxygen to maintain sats); or
- D-dimers > 1.5 mg/L
- Patients with clinical suspicion of VTE (unexplained deterioration)

Uncertainties:

- What is the optimal dose of LMWH for prophylaxis?
- Dosing in obesity and who/how to monitor?
- Impact on outcomes: is there harm?



International Guidance: diagnosis, prevention and treatment of VTE in hospitalised COVID patients

Diagnosis of VTE:

- Particularly problematic due to infectious risks
- Bedside U/S or ECHO useful but lack sensitivity and sensitivity:
 - value of routine screening uncertain
- Uncertain regarding : risk stratification for VTE, optimal intensity & duration for anticoagulation prophylaxis incl post –discharge Rx
- Advised standard- of- care objective testing for VTE based on clinical suspicion
- not routine screening based on elevated D dimer

Carefully assess bleeding risk (NOTE: renal function, platelets <25) LMWH preferred agent

Entity	Outpatient prophylaxis	Inpatient non ICU prophylaxis	ICU prophylaxis	Obesity in ICU	Post discharge Prophylaxis
ISTH(May 2020) Expert consensus	Inpatient only	Routine dose or Intermediate dose (30% of experts)	Routine dose, Intermediate dose in high risk patients (50% of experts)	50% ↑ in prophylactic dose Therap. dose should NOT be considered for 1° prevention**	LMWH or rivaroxaban x 14 days (50% experts) 30 days (20% respondents)
Chest (23 June) Expert consensus	Not mentioned	Routine dose prophylaxis LMWH > UFH preferred over DOAC Do not consider aspirin as alternative to LMWH	** Recommend standard dose LMWH prophylaxis & against antiplatelet agents for VTE prevention		Routine post-discharge prophylaxis NOT recommended (await data)
NIH (May 2020)	Not advised unless clear indications	Routine VTE prophylaxis only. antiplatelet therapy as per standard of care in non COVID	Standard dose. Increased dose only in clinical trials		Routine post-discharge prophylaxis NOT recommended unless high risk (score: age and D-Dimer)

VTE TREATMENT: as per standard protocols. Recurrent VTE: ↑ dose by 30%

Thrombolysis as per standard protocols

** awaiting results of randomised controlled trials

DOACS: concomitant therapy e.g. antivirals can affect pharmacodynamics and ↑ bleeding risk, CI in renal failure

Management of anticoagulation in COVID-19

COVID-19+	Coagulation tests	Standard-dose VTE PPX	Escalated-dose* VTE PPX	Therap. dose anti-coagulation
Outpatient		Consider†		
Inpatient	X			
Ward	X	X		
ICU	X		X	
Confirmed VTE	X			X
Presumed PE‡	X			X
ARDS	X		X	

1. Ambulatory/Outpatients: Consider standard prophylaxis dose LMWH: morbid obesity or past Hx of VTE, case by case basis
2. Escalated dose prophylaxis: (eg 50% of therapeutic dose)* No data to support this except in small studies in obese patients

PPX: Prophylatic dose. **Therap** dose: Therapeutic dose

UCT Haematology COVID study: recommendations for clexane dosing

Recommended low molecular weight heparin dosing in COVID19 patients (enoxaparin/clexane)

Prophylaxis

Body weight

- Dose

<60kg

40mg subcut once daily (od)

60 - 80 kg

60 mg subcut once daily (od)

80 > < 100 kg

40 mg subcut twice daily (bd)

>100 kg

50mg subcut twice daily (bd)

target anti-Xa level

0.2–0.5 iU/ml (4-6 hrs post dose)

Therapy

<60kg

Body weight in mg bd

60 - 80kg

60mg subcut twice daily (bd)

80 - 100 kg

80 mg subcut twice daily (bd)

> 100 kg

100mg subcut twice daily (bd)

target Anti Xa level

0.6-1.2 IU/ml (4 hrs post dose)

AntiXa levels guide dosing

If level is subtherapeutic, increase dose by 20-30% and repeat anti X a level.

Clinical trails

1. Protective Effect of Aspirin on COVID-19 Patients (PEAC)

Randomized to:

Standard Rx vs Standard Rx + aspirin 100mg od until 14 days post D/C discharge

Outcomes: Clinical recovery time, length of time of RT-PCT positivity

China, study completion, June 2020

2. Anti-Coronavirus Therapies to prevent progression of COVID-19 Trial (ACT COVID 19)

Complex study design. Outpatients various groups incl colchicine vs control; aspirin vs control

Inpatients various groups: Interferon B vs standard of care, Colchicine vs standard of care, aspirin + rivaroxaban vs standard of care (Canada)

3. STudy of Alteplase for Respiratory failure in SARS-Cov2/COVID-19: STARS Trial

open label phase IIa trial using tPA to treat COVID-19 related ARDS

- Two different dosing regimens of tPA will be used to test for efficacy in improving oxygenation at 48 hours from study enrollment



Conclusions

COVID causing a unique endotheliopathy and coagulopathy

1. Associated markedly increased risk of venous and arterial thrombosis
2. All angles of Virchow's Triad are met; mechanisms partly elucidated
3. Profound and life threatening clinical sequelae
4. Essential role of haemostatic monitoring including anti-Xa
5. Local and international approach to anticoagulation
6. Many uncertainties still exist in this evolving scenario.
7. Good data from randomised clinical trials needed to guide therapy

Comments from Prof Vernon Louw

