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Coagulation disorders – pulmonary embolism

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1. Haemostasis

Haemostasis is defined as a balance to maintain the fluidity of blood vessels while forming a hemostatic plug, in case of vascular injury. The result of this process is **fibrin** which traps the blood cells in the blood-forming clot. It is academically divided into different steps but most of them are happening simultaneously in vivo:

A. Vasoconstriction

B. Primary haemostatic plug

I. Adhesion

II. Activation and secretion

III. Aggregation

C. Secondary hemostasis-coagulation cascade

I. Initiation- extrinsic pathway+ common pathway

II. Amfiplication- intrinsic pathway+ common pathway

III. Propagation

D. Regulation

- Antiagregation
- Anticoagulation
- Fibrynolytics

(a) Vasoconstriction

Represents a local response aiming to stop the bleeding and facilitate platelet adhesion. Substances that are primarily involved in the vessel vasoconstrictions are endothelin, serotonin (5-HT) from endothelium and thromboxane (TXA) from platelets.

(b) Primary haemostatic plug

The creation of a primary plug is initiated by collagen exposed by damaged vessel endothelium, this causes a platelet activation (role of von Willebrand factor) and degranulation (granules containing- adenosine diphosphate (ADP), serotonin, thromboxane A, factor V, factor XIII, fibrinogen). This leads to enhanced vasospasm and aggregation of more platelets.

(c) Secondary hemostasis - coagulation cascade

Taking it from the end. What do we want to achieve? The goal is to end up with **fibrin** stabilizing the primary plug. This happens through activating FIBRINOGEN into FIBRIN (which can polymerase and form the stabilizing mesh), this step is mediated by Thrombin (f IIa).

The coagulation cascade

The coagulation cascade is a series of enzymatic reactions that turn inactive precursors into active factors. The result of the cascade is the production of fibrin, a protein that binds platelets and other materials in a stable clot.

There is the "**classic model**" which is more applicable in vitro. We need to understand it to be able to interpret the laboratory tests and imagine the effects of drugs. In this model, the cascade has two initial pathways: **the extrinsic** (tissue factor-mediated) and **the intrinsic** (contact system-initiated). These two pathways converge to become the **common pathway** with the activation of factor X.

In extrinsic the damaged vessel releases the tissue factor (f III) and this together with factor VII (f VII), which circulates in the blood, activates factor X (f Xa).

In the intrinsic pathway, where factor XII is activated by kallikrein, the cascade gradually activates factors XI, IX and VII to activate factor X.

The common pathway starts by activating factor X, which in combination with Ca2+ ions and activated factor V (thromboxane) causes the desirable activation of factor II (prothrombin), activating it to thrombin (f IIa). Thrombin acts by changing fibrinogen into fibrin. An important plug stabilizing factor is XIII.

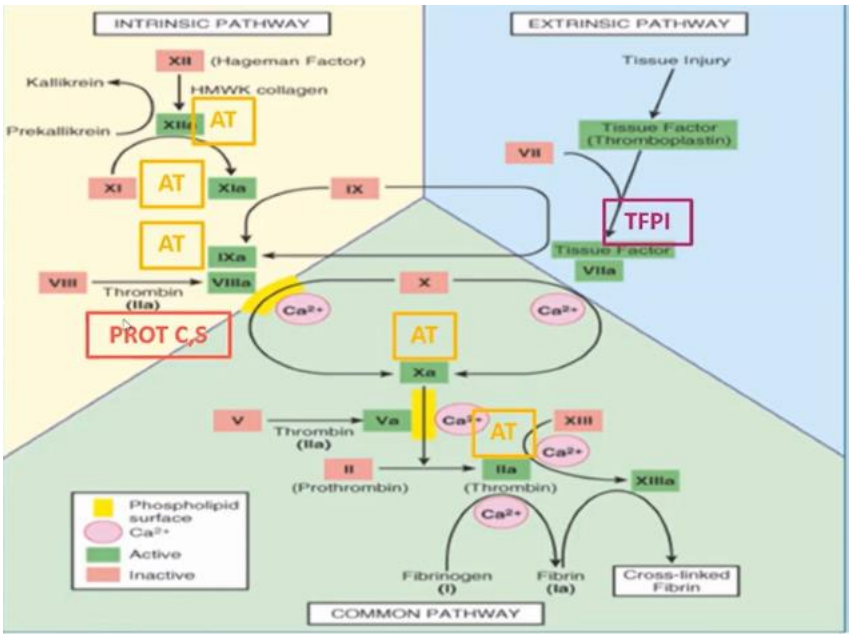

Figure 1: Coagulation cascade and its physiological regulators

Evidence supports the understanding that the intrinsic pathway is not a parallel but it augments thrombin generation primarily initiated by the extrinsic pathway. More physiological is **the cellular model** ("in vivo model") of coagulation, which includes:

I. Initiation phase

Tissue injury and collagen exposure (tissue factor) is called an extrinsic pathway. Initiated when prothrombin is activated to thrombin (f IIa), this is called an initial thrombin burst.

II. Amplification stage

Factor IIa does all the job, it activates fibrinogen to fibrin, activates intrinsic pathway and activates cofactors (f V, f VIII-f IX, f XIII).

(d) Regulation

The clotting mechanism is balanced by opposing reactions.

- In primary haemostasis the physiological **antiaggregatory agents** (endothelium-prostaglandins-PG2- NO, heparin sulphate)
- In secondary haemostasis the physiological **anticoagulants** (Tissue factor platelet inhibitor-TFPI, Antithrombin-AT, protein C, S)
- System to dissolve the clot
- tPA (tissue plasmin activator) activates plasminogen to plasmin which cuts the fibrin mesh creating the fibrin degradation products (FDP), one of the fibrin degradation products is D-dimers

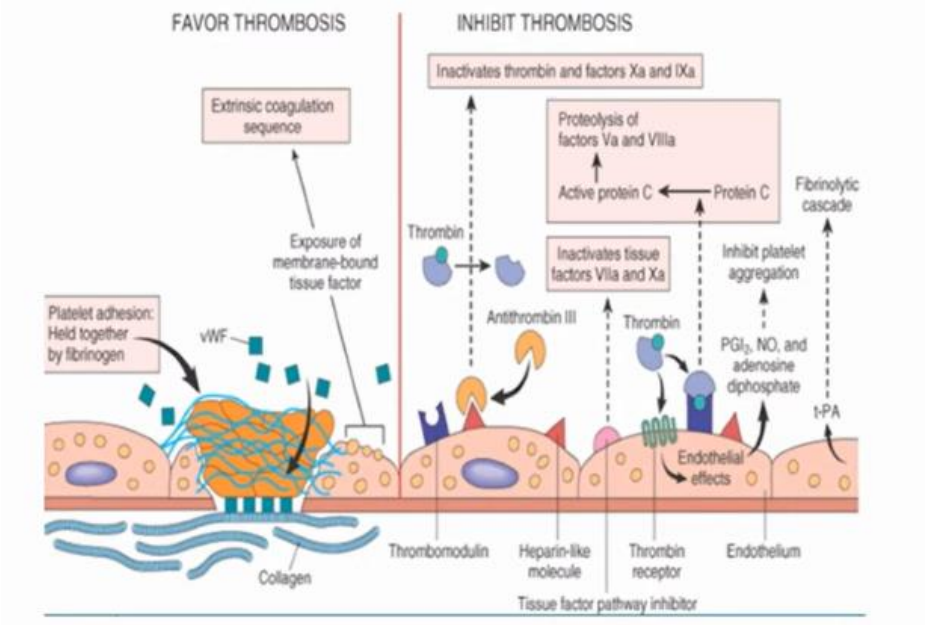

Figure 2: Factors favouring and inhibiting thrombosis

Drugs affecting the coagulation system

1. **Antiaggregant/antiplatelets**

   I. **COX 1 inhibitors**- non-steroidal anti-inflammatory drugs-(NSAID´s), acetylsalicylic acid (ASA)

   II. **P2Y12 ADR receptor inhibitors –**Clopidogrel, Prasugrel (both p.o)

Both are irreversible inhibitors of the platelet P2Y12 adenosine diphosphate receptor (ADR). Inhibition of this receptor prevents the downstream activation of the glycoprotein IIb/IIIa receptor complex, which leads to reduced platelet aggregation.

   III. **Glycoprotein IIb/IIIa** (membrane of platelets) inhibitor –Abciximab, Tirofiban (i.v.)

2. **Anticoagulants**

   I. Heparin

Chemically it is a mixture of polysaccharides. Heparin binds to antithrombin, increasing its effect by 1000 x.

- unfractionated (UFH)- extracted from pig gastric mucosa, binds to antithrombin, causing its conformational change, half time 90 min, possible antagonist protamine (1mg protamine to 100 IU UFH), monitor by using aPTT (aim 1,5-2,5 x normal aPTT), risk of heparin-induced thrombocytopenia (HIT)

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- low molecular weight heparin (LMWH) -**enoxaparin, dalteparin**- produced by enzymatic/ chemical degradation of heparin, better bioavailability, longer half time (1x daily s.c), greater activity against Xa also partially affects f IIa, cause less inhibition of platelet function (less HIT risk), renal excretion (dosage reduction in renal failure), cannot be completely neutralized by protamine
- **fondaparinux**- synthetic pentasaccharide, an indirect inhibitor of f Xa, contraindicated in severe acute kidney injury, can be used in HIT

   II. vitamin K antagonists- coumarins

Warfarin inhibits the enzyme vitamin K epoxide reductase, blocking the hepatic synthesis of the active, reduced form of vitamin K. Vitamin K-dependent coagulation factors are **II, VII, IX, X and protein C, protein S**. When warfarin is used regular monitoring is necessary. This is done by prothrombin time PT/ international normalized ratio INR (goal INR of 2 to 3) extrinsic pathway of the coagulation cascade. Warfarin interacts with a broad range of medications and food (metabolization by C-P450). Substances that increase, or decrease the effect of warfarin are summoned here:

https://www.remedirx.com/wp-content/uploads/2016/06/Warfarin-DDI-Reference_Bimonthly-Resource-FINAL-061716.pdf.

It is not suitable for acute therapy of PE or DVT. In case of extensive or life-threatening bleeding: stop coumarins; administer fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) and vitamin K

III. Non-vitamin K antagonist oral anticoagulants (NOACs)

- Direct thrombin inhibitors- dabigatran (Pradaxa)
- Factor X inhibitors- rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Savaysa)

In comparison to warfarin, NOACs have more predictable pharmacokinetics, fewer drug interactions, shorter half-lives, and quicker onset of action. Factor Xa catalyses the activation of prothrombin into thrombin, all NOACs exert an anti-thrombin effect and prevent the activation of fibrinogen into fibrin. They do not require regular monitoring but also lack routine tests for monitoring. For the events of life-threatening haemorrhage, specific antidotes are available (idarucizumab- PRAXBIND is a dabigatran antidote and andexanet alfa for factor Xa inhibitors, Aripazine is a new universal NOAC antidote that binds to both factor Xa inhibitors and dabigatran through hydrogen bonds- phase 2 trials are ongoing). NOACs are not suitable for patients with artificial valves.

IV. Thrombolytic agents

- Recombinant tissue-type plasminogen activator (tPA- alteplase), streptokinase (SK), recombinant human urokinase (UK), alteplase – has a high affinity to fibrin, binds to coagulum and in the presence of fibrin activates plasminogen to plasmin, half-life time is 5 minutes.

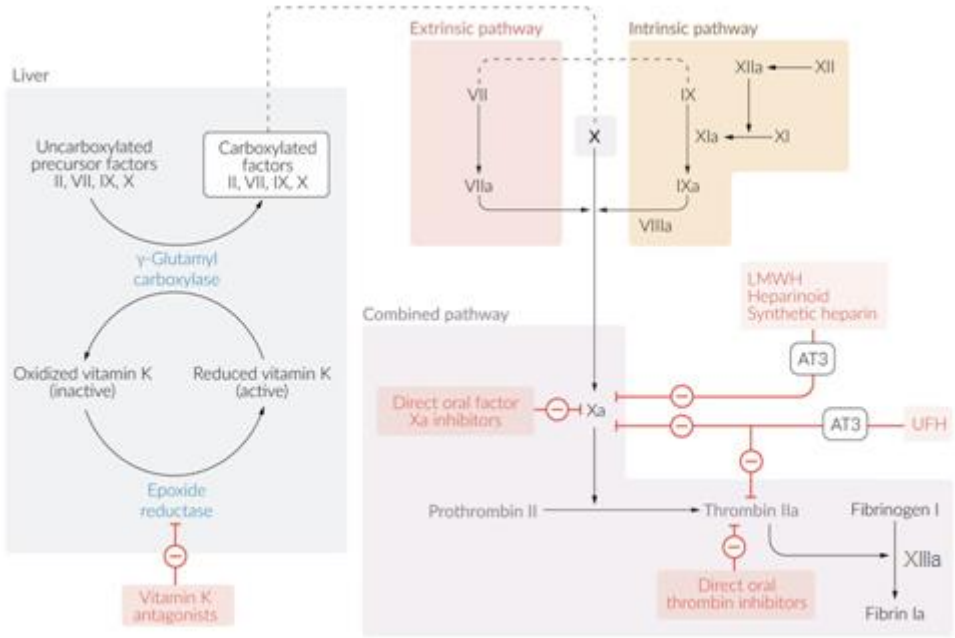


Figure 3: Drugs affecting the coagulation cascade

Laboratory testing

Used to identify patients at risk of bleeding or thrombosis or to effectively monitor/manage the treatment. In emergencies (e.g., life-threatening bleeding- rapid) changes in laboratory values could be established by bedside tests.

Prothrombin time (PT)

- measures the time it takes plasma to clot when exposed to tissue factor and phospholipid in recalcified citrated patient plasma,
- **assess extrinsic pathway (II, V, VII, IX) and common pathway**
- the result is measured in seconds, normal range of 11- 15 s
- INR international normalised ratio (patient's PT to a control PT), normal range 0,7-1,2

prolonged e.g., in warfarin therapy

Activated partial thromboplastin time (APTT)

- measures time to clot formation when citrated plasma is exposed to negatively charged substances (e.g., kaolin), prothromboplastin and calcium
- **assesses the intrinsic and common pathways** of coagulation
- prolonged e.g., in heparin therapy, haemophilia A, B, von Willebrand disease
- normal range 26-40s
- another option for monitoring full-dose unfractionated heparin is to use anti-factor Xa activity (sometimes called "anti-Xa")

Thrombin time (TT)

- measures the final step of coagulation, the conversion of fibrinogen to fibrin
- citrated plasma in the presence of thrombin
- prolonged if fibrinogen levels are low or if an anticoagulant that inhibits thrombin is present in the sample
- not routinely used
- heparin, LMWH, direct thrombin inhibitors (e.g., bivalirudin or argatroban) prolong
- in contrast, oral direct Xa inhibitors, danaparoid, fondaparinux, and warfarin do not prolong TT
- normal range 14-19 s

plasma anti-Xa – monitor LMWH effect

Disorder	PT	APPT	TT	FDPs	Platelets	Fibrinogen
Thrombocytopenia	→	→	→	→	↓	→
DIC	↑	↑	↑	↑	↓	↓
Heparin therapy	↑	↑	↑	→	→*	→
Warfarin therapy	↑	↑	→	→	→	→
Hepatic failure	↑	↑	↑	→	→	↓
Massive blood transfusion	↑	↑	↑	→	↓	→
Primary fibrinolysis	↑	↑	↑	↑	→	↓

↑, Increase; ↓, decrease; →, no change.

Table 1: Clotting times, platelets, and fibrinogen changes in different clinical situations

Fibrinogen

- precursor of fibrin
- abnormally low levels can result in impaired clot formation and increased bleeding risk
- 1,5-4,0 g/l

D-dimers

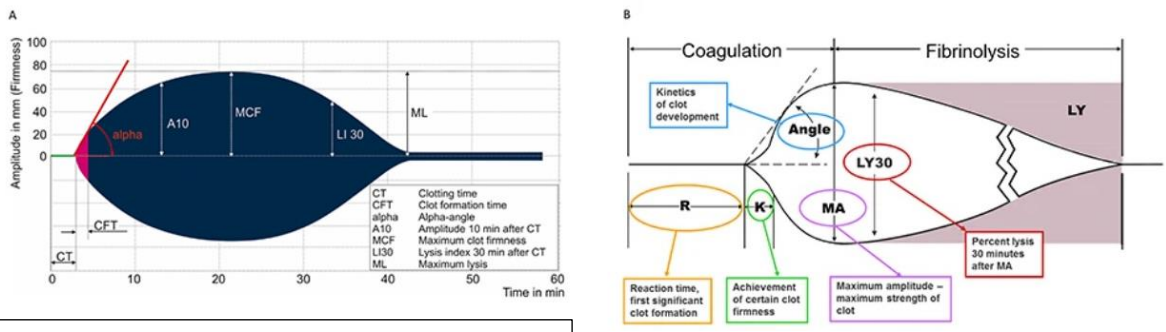
- fibrin degradation product (or FDP), a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis
- high negative predictive value in PE
- normal range 0-0,5 g/l
- elevated also postoperatively, after trauma, in pregnancy and elderly

Example of ROTEM machine, source: https://www.werfen.com/na/en/c

ROTEM/TEG

- viscoelastic measurement of haemostasis testing
- point of care, “bed-side” method
- INTEM, EXTEM, and FIBTEM for different coagulation pathways

Examples of thrombelastography and therapeutic suggestions source:



https://litfl.com/thromboelastogram-teg/
https://www.emra.org/emresident/article/teg-and-

Inherited bleeding disorders

Haemophilia A

- X-linked recessive bleeding disorder
- a chromosomal mutation resulting in a deficiency or absence of coagulation **factor VIII**
- varying severity, clinical presentation: spontaneous, postoperative, or posttraumatic bleeding, bleeding into joints, soft tissue
- prevalence of about 1 in 5000 live male births
- initial diagnostic testing: coagulation profile (prothrombin time/INR, activated partial thromboplastin time (aPTT), platelet count, and a von Willebrand factor assay) all of which are all usually normal in haemophilia except the aPTT which is often prolonged in moderate-to-severe disease
- factor VIII has a half-life time about 12 hours-> must be administrated 2x daily to maintain therapeutic levels
- synthetic vasopressin(desmopressin) i.v, s.c or intranasally causes a 3-5 x increase in factor VIII (useful in mild haemophilia not in severe cases)
- complications:
    - synovitis and arthropathy secondary to recurrent hemarthrosis
    - delayed post-traumatic bleeding
    - increased risk of intracranial haemorrhage
    - development of fVIII antibodies (difficult management, even high doses of factor VIII may not be clinically significant)

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Haemophilia B

- hereditary X-linked chromosomal disorder
- deficiency or absence of coagulation **factor IX**
- varying severity
- spontaneous, postoperative, or posttraumatic bleeding, bleeding into joints, soft tissue
- incidence is 1 in 20,000 to 1 in 30,000 live male births
- family history of haemophilia in 70% of cases
- initial diagnostic testing: coagulation profile (prothrombin time/INR, activated partial thromboplastin time (aPTT), platelet count, and a von Willebrand factor assay) all of which are all usually normal in haemophilia except the aPTT which is often prolonged in moderate-to-severe disease
- definitive testing: factor IX activity
- complications: hemophilic arthropathy (the result of chronic synovitis and hemarthrosis)
    - increased risk of intracranial haemorrhage

Von Willebrand Disease

- bleeding disorder caused by quantitative or qualitative defects in von Willebrand factor (vWF) activity (plays a role in platelet adhesion to damaged subendothelium as well as in stabilizing factor VIII in plasma)-> defective platelet function, factor VIII deficiency
- vWD is the most common inherited bleeding disorder (prevalence of 0.1%-1% in the general population)
- 3 types- different severity
- laboratory tests showing abnormalities in von Willebrand factor and/or factor VIII
- clinical presentation: mucocutaneous bleeding (gingiva, nose-epistaxis, oral and gastrointestinal mucosa, menorrhagia, GI bleeding), ecchymoses, hematomas, and/or petechiae, haemarthrosis is rare

Acquired bleeding disorders

Vitamin K deficiency

- f II, VII, IX, X, protein C, protein S
- deficiency due to: inadequate stores, malabsorption, oral anticoagulant drugs
- test: PT and APTT prolonged
- clinical presentation: bruising, haematuria, gastrointestinal or cerebral bleeding

Haemorrhagic disease of newborn (1 mg i.m.- vit. K to newborns)

Liver disease

- vitamin K deficiency (intra/extrahepatic cholestasis)
- reduce the synthesis of coagulation factors
- thrombocytopenia (hepatosplenomegaly, portal hypertension/ folic acid deficiency)
- functional abnormalities in fibrinogen and platelets

DIC

- a syndrome characterized by systemic intravascular coagulation with loss of localization (activation of blood coagulation, which generates intravascular thrombin and fibrin, resulting in the thrombosis of small- to medium-sized vessels) and ultimately organ dysfunction and severe bleeding
- microthrombi formation, platelet consumption, and subsequent exhaustion of all clotting factors, which causes hemorrhagic manifestations
- a mixture of initial thrombosis followed by a bleeding tendency

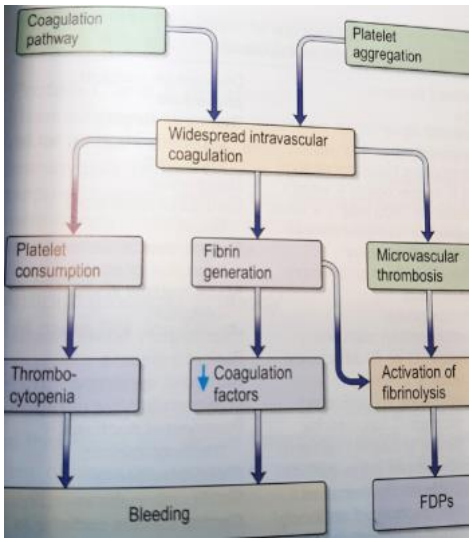

Figure 4: DIC pathogenesis

- hypercoagulation and hyperfibrinolysis
- causes: malignant disease, septicemia (e.g., G- or meningococcal infection), haemolytic transfusion reactions, obstetric causes (e.g., placental abruption, amniotic fluid embolism), trauma, burns, surgery, acute pancreatitis, snake bite...

- clinical features depend on severity: acutely ill patient in shock, bleeding (epistaxis, venepuncture, ecchymosis, haematuria, hemoperitoneum, hemothorax...), thrombotic manifestation (neurological dysfunction-altered mental state, acute renal failure-oliguria, hemoptysis, pulmonary thromboembolism, purpura fulminans - skin necrosis...)
- in severe cases prolonged PT, APTT, TT, low fibrinogen levels, high levels of fibrin degrading products (e.g., D-dimer)
- therapy: treatment of the underlying cause, supportive therapy with transfusions of platelet concentrates, FFP, and/or cryoprecipitate in patients with severe bleeding
- therapeutic doses of heparin should be considered in cases of DIC in which thrombosis predominates

Inherited prothrombic disorders

I. Venous:

Leiden mutation (factor V mutation)

Antithrombin (AT) deficiency

Protein C deficiency

Protein S deficiency

II. Arterial:

Antiphospholipid antibody syndrome

- autoimmune disease, idiopathic or acquired (SLE, acute infection e.g., malaria, medication e.g., phenytoin)
- circulating antibodies deactivate anticoagulant proteins and activate platelets -> paradox of prolonged clotting times and prothrombotic tendency
- clinical presentation:
  - recurrent fetal loss in 2nd or 3rd trimester
  - thrombocytopenia
  - skin lesions
  - haemolytic anaemia

Acquired prothrombotic factors

Obesity

Malignancy

Immobilization

Dehydration

Peroral Contraceptives

Hormone Replacement Therapy

Pregnancy and postpartum

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2. Pulmonary embolism

Thrombophilia

= inherited/ acquired defects of haemostasis leading to a predisposition to arterial or venous thrombosis

Thrombosis

1. **Arterial**
    - association of atheroma plaque -> rupture -> platelets adhere to damaged vessel- “white thrombus” formation-> embolization+/- obstruction
    - Risk factors related= same as to atherosclerosis
    - occurs in areas of turbulent flows- bifurcations of arteries
        - in the heart (prosthetic valves, left ventricle -after myocardial infarction, left atrium- mitral valve disease)
2. **Venous (ad pulmonary embolism)**

(a) Definition and etiology of pulmonary embolism

Pulmonary embolism (PE) is the obstruction of one or more pulmonary arteries by solid, liquid, or gaseous masses. In most cases, the embolism is caused by blood thrombi, which arise from the deep vein system in the legs or pelvis (**deep vein thrombosis**- DVT) and embolize to the lungs via the inferior vena cava. This condition causes a redistribution of blood in the lungs, which impairs ventilation-perfusion matching (V/Q mismatch) and gas exchange. There are both respiratory (increased dead space, hypoxemia, hyperventilation) and hemodynamic consequences (increased pulmonary vascular resistance, increased right ventricular afterload) from PE. In addition, the humoral and reflex mechanisms contribute to pulmonary arterial constriction.

Types of emboli:

- thromboembolism
- septic embolism
- venous air embolism
- fat embolism
- amniotic fluid embolism
- tumour embolism
- foreign material embolism (e.g., silicone, broken catheters, guide wires, vena cava filters, embolization coils, and endovascular stent components)

Acute and Subacute vs. Chronic

PE can be characterized as acute or chronic. PE is pathologically characterized as acute when the embolus is situated centrally within the vascular lumen or if it occludes the vessel, usually causing distension of the vessel. An embolus is chronic if it is eccentric and contiguous with the vessel wall, it reduces the diameter by more than 50%, and there is evidence of recanalization within the thrombus.

Hemodynamically stable vs. unstable PE

Hemodynamically unstable PE is also called "massive" or "high-risk" PE. It is that which results in hypotension and/or persistent tachycardia (heart rate over 100 beats per minute with signs or symptoms of shock). Hypotension is defined as a systolic blood pressure <90 mmHg or a drop in systolic blood pressure of ≥40 mmHg from baseline for a period >15 minutes or hypotension that requires vasopressors or inotropic support and is not explained by other causes such as sepsis, arrhythmia, left ventricular dysfunction from acute myocardial ischemia or infarction, or hypovolemia. Although hemodynamically unstable PE is often caused by large (ie, massive) PE, it can sometimes be due to small PE in patients with underlying cardiopulmonary disease. Thus, the term "massive" PE does not necessarily describe the size of the PE as much as its hemodynamic effect. Patients with hemodynamic instability due to PE are at risk of obstructive shock.

Hemodynamically stable PE is defined as PE that does not meet the definition of hemodynamically unstable PE. There is a spectrum of severity within this population ranging from patients who present with small, mildly symptomatic or asymptomatic PE (also known as "low-risk PE") to those who present with mild or borderline hypotension that stabilizes in response to fluid therapy, or those who present with right ventricle dysfunction (also known as "submassive" or "intermediate-risk" PE).

Symptomatic vs. Asymptomatic

Asymptomatic PE refers to finding PE on imaging, without the patient having any clinical symptoms.

(b) Epidemiology, risk factors and clinical presentation

The overall incidence is higher in males compared with females (56 versus 48 per 100,000, respectively). The incidence rises with increased age, especially in women (NÆSS 2007).

Special population:

- Pt. with malignancy- tumour type, location, stage, and time since diagnosis influence VTE risk, in general, 10x higher than the normal population
- Pt. with stroke- deep vein thrombosis (DVT) is common (up to 10 % pt. after stroke)
- Pregnancy

Venous thromboembolism (VTE) is approximately 10 times more common in the pregnant population (compared with non-pregnant women) with an incidence of 1 in 1000 and the highest risk in the postnatal period. Most women with pregnancy-associated VTE will have identifiable risk factors (obesity, age >35 years old, Parity ≥3, smoking, varicose veins, previous pregnancy-related VTE, etc.) All three components

of “Virchow’s triad” of venous stasis, hypercoagulability and vascular damage occur in the course of pregnancy and delivery. The majority of gestational deep vein thrombosis are ileofemoral- often non-detectable by USG, in contrast to those who are not pregnant, in whom the majority are popliteofemoral.

Risk factor	Example
Circulation Stasis	Immobility Prolonged travel Recent surgery Congestive heart failure Obesity
Hypercoagulability	Pregnancy Medication (hormonal contraceptives, hormone replacement therapy, antipsychotics, fibrates...) Severe burns Malignancy (solid tumours, leukaemias, lymphomas) Acute medical illness (e.g., AIDS, SLE, Ulcerative colitis) Hereditary factors (e.g protein C/S deficiency, factor V Leiden)
Endothelial damage	Fracture Previous DVT Trauma
Other	Smoking, Haemolytic anaemias, inflammatory bowel disease...

Table 2: Risk factors of Virchow Triad

Classic Risk Factors for PE: "THROMBOSIS"

Trauma/**T**ravel

Hypercoagulable state/**H**ormone Replace Therapy

Recreational drugs (IVDU)

Older

Malignancy

Birth Control

Obesity/**O**bstetrical

Surgery

Immobilization

Smoking

Clinical presentation

Various (asymptomatic-> cardiac shock), non-specific

- abrupt onset of chest pain
- shortness of breath, dyspnea, cough
- hypoxia, tachypnea
- fever (if pulmonary infarct)
- syncope
- hemoptysis
- Deep vein thrombosis (erythematous, swollen, warm lower extremity)

Feature	PE confirmed (*n* = 1880)	PE not confirmed (*n* = 528)
Dyspnoea	50%	51%
Pleuritic chest pain	39%	28%
Cough	23%	23%
Substernal chest pain	15%	17%
Fever	10%	10%
Haemoptysis	8%	4%
Syncope	6%	6%
Unilateral leg pain	6%	5%
Signs of DVT (unilateral extremity swelling)	24%	18%

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Table 3: Symptoms of PE

(c) Investigation

- clinical assessment of the likelihood of PE

Wells's score should be estimated. The Wells criteria were applied and the score was calculated to determine the probability of PE into a three-level system of:

- Low (score <2)

- Intermediate(score 2 - 6)

- High (score >6)

Risk factor	Score
Clinical signs and symptoms of DVT (objectively measured leg swelling and pain with palpation in the deep-vein region)	3.0
Heart rate >100 beats/min.	1.5
Immobilisation (bed rest, except access to bathroom, for 3 or more days; or surgery in previous 4 weeks)	1.5
Haemoptysis	1.0
Previously objectively diagnosed DVT or PE	1.5
Malignancy (patients with cancer receiving treatment or treatment stopped within previous 6 months or receiving palliative care)	1.0
PE as likely or more likely than an alternative diagnosis (based on clinical information, chest X-ray, ECG and any blood tests required to diagnose PE	3.0

Table 4: Wells score

A low-risk patient (< 2 points) can be worked up with a D-dimer. An intermediate-risk patient (2-6 points) can be worked up with a D-dimer or CT angiogram pending clinical suspicion. A high-risk patient (score > 6 points) should be worked up with a CT angiogram. The only exception to this rule is in very high-risk patients with a classic presentation for PE who have unstable vitals. In these patients, it is appropriate to first treat with heparin while a CT angiogram is being ordered/performed to confirm the diagnosis.

D-dimer — D-dimer is one of the fibrin degradation products (FDP), produced when a blood clot gets dissolved in the body by enzyme plasmin, the level of D-dimer in the blood can rise when there is significant formation and breakdown of fibrin clots in the body

An elevated D-dimer alone is insufficient to make a diagnosis of PE but can be used to rule out PE with high certainty (negative predictive value). D-dimer testing is best used in conjunction with clinical probability assessment.

For patients in whom the risk of PE is thought to be **low**, a normal D-dimer (<500 ng/mL) effectively excludes PE, and typically no further testing is required.

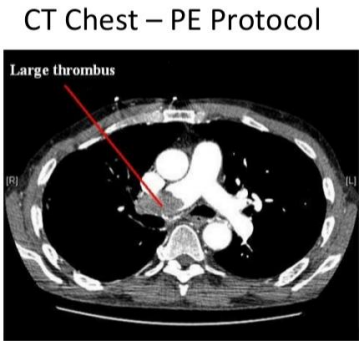
In contrast, an elevated D-dimer (>500 ng/mL) should prompt further testing with diagnostic imaging.

For patients in whom the risk of PE is thought to be **high**, a normal D-dimer is not as helpful for excluding the diagnosis. These patients should undergo diagnostic imaging, preferably with CTPA.

<u>Use D-dimers wisely</u>:

- test *low-risk* patients
- test when you expect it will be negative (to rule out PE)
- don’t test D-dimer if you plan to order a CT regardless
- D-dimers in pregnancy rise in the 2nd and 3rd trimester, and stay high post-partum, are not recommended investigation of suspected acute VTE in pregnancy

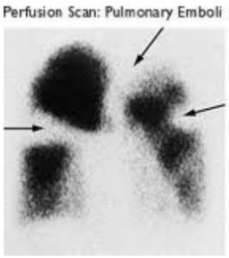
(d) Imagining

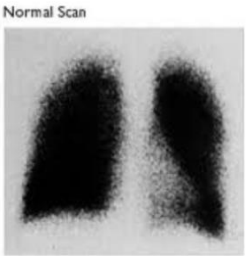


Chest CT with angiography (CTPA)

- A CT scan uses X-rays to build cross-sectional images ("slices") of the body
- cross-sectional images are constructed from measurements of attenuation coefficients of x-ray beams passing through the object studied
- angiography- to check for narrowed or blocked arteries in various vessels of the heart, the aorta and other large blood vessels, the lungs, the kidneys, the head and neck by using contrast
- test of choice in most circumstances, “golden standard”
- suitable for **massive or submassive PE**
- allows adequate visualization of the pulmonary arteries down to at least the segmental level, but cannot rule out subsegmental PE
- be cautious in cases where CTPA results are discordant and clinical judgement
- positive CTPA showing a filling defect confirms the diagnosis of PE

Perfusion scan



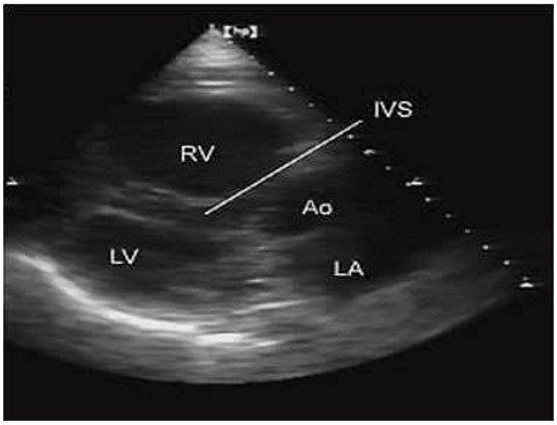


- ↓ pulmonary perfusion without decreased ventilation to a given area (V/Q mismatch)
- reserved for patients in whom **the CTPA is contraindicated** (eg, history of moderate or severe contrast allergy, renal failure, hypotension, advanced heart failure, or inability to tolerate CT scanning due to morbid obesity, pregnancy or when CTCA is inconclusive)
- hemodynamically stable patient and chronic thromboembolic state
- i.v injection of technetium-labelled particles, these block a small fraction of the pulmonary capillaries and thereby enable scintigraphic assessment of lung perfusion (gamma camera)
- risk of further occlusion of pulmonary vessels is only theoretical as the number of capillaries (approx. 300 million) far outnumbers the number of particles injected (usu. 200, 000-500 000) so there is a wide safety margin
- normal chest Xray is useful- then only a perfusion scan is performed
- high frequency of non-diagnostic tests

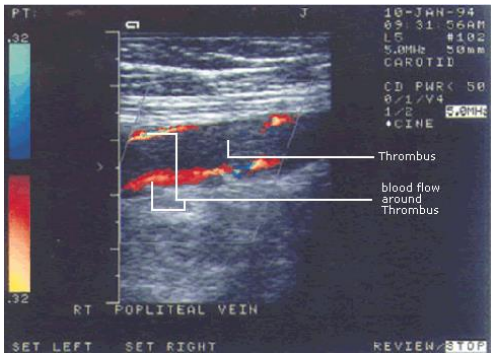
Echocardiography

- Ultrasonography is a technique that uses high-frequency sound waves (1-20 MHz) produced and received by the probes), ultrasound wave is produced by a probe using the piezoelectric effect

- Higher frequency means greater resolution but decreases penetration
- bedside investigation
- presence of a clot in the right heart or new right heart strain
- useful for prognostic purposes in patients with **confirmed** PE
- PE increases the pulmonary artery pressure, which increases right ventricular after-load, resulting in:
  - ✓ Right ventricular dilatation
  - ✓ Hypokineses
  - ✓ Tricuspid valve regurgitation
  - ✓ Ultimately, right ventricular failure



An echocardiogram of a patient with a massive pulmonary embolus. Transthoracic echocardiogram (parasternal view) showing the aorta (Ao), left atrium (LA), a dilated right ventricle (RV) and displacement of the intra-ventricular septum (IVS) into the left ventricle (LV) in a patient with a massive pulmonary embolus



Lower-extremity ultrasound with Doppler

- when neither CTCA nor V/Q scan can be performed or are inconclusive
- evaluate for coexisting DVT
- validated criteria for deep vein thrombosis (DVT)- incomplete collapsibility of the vein

Catheter-based pulmonary angiography

- historically gold-standard confirmatory test
- rarely used, less invasive options available
- contrast is injected under fluoroscopy via a femoral vein catheter introduced into the right atrium and ventricle into the pulmonary outflow tract and then advanced further into each of the main pulmonary arteries
- a bolus of contrast is injected to outline the pulmonary vascular tree
- the disadvantage of this procedure: local bleeding complications, haematoma or pseudoaneurysm in the groin and the general risk (small but definite) of cardiac arrhythmia
- used to guide percutaneous catheter-directed treatment of PE

- diagnosis of PE based on direct evidence of thrombi in 2 projections or defect in the filling of the pulmonary artery branch

Magnetic resonance pulmonary angiography (MRPA)

- imaging option for diagnosis of PE in patients in whom neither CTPA nor V/Q scan can be performed
- a high proportion of inconclusive scans
- no ionising radiation is involved

Other:

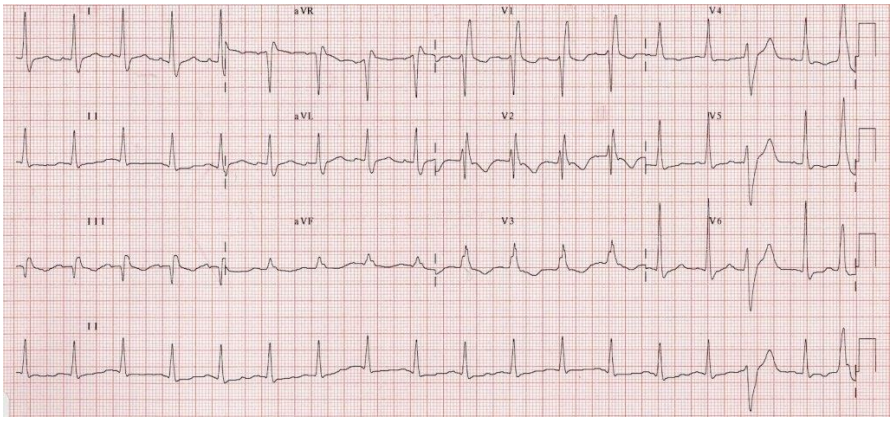
ECG

- visual display of the electrical activity of the heart
- 3 or 12 leads
- to rule out other diagnoses or for stratification of risk
- right ventricle pressure overload and dysfunction
- in hemodynamically unstable patient absence of echocardiographic signs of right ventricle overload or dysfunction practically exclude PE as a cause of hemodynamic instability
- most commonly **nonspecific** ST and T-wave changes, tachycardia

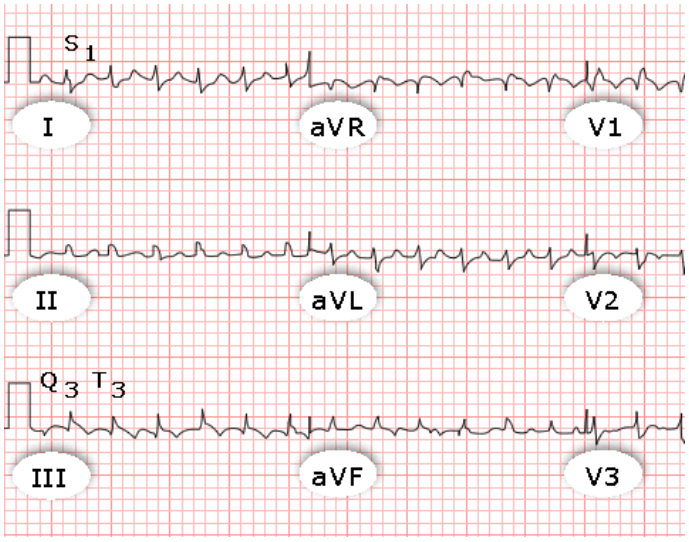
Findings that correlate with cor pulmonale acutum

- sinus tachycardia
- incomplete RBBB
- flipped T waves in the anterior leads
- **S1Q3T3**- deep S wave in lead I, Q wave in III, inverted T wave in III (poor sensitivity & specificity)
- Right ventricular strain pattern – T wave inversions in the right precordial leads (V1-4) ± the inferior leads (II, III, aVF). This pattern is associated with high pulmonary artery pressures (34%)
- Dominant R wave in V1 – a manifestation of acute right ventricular dilatation

- Right atrial enlargement (P pulmonale) – peaked P wave in lead II > 2.5 mm in height



I	aVR	V1	V4
II	aVL	V2	V5
II	aVF	V3	V6
	inferior	anterior	lateral



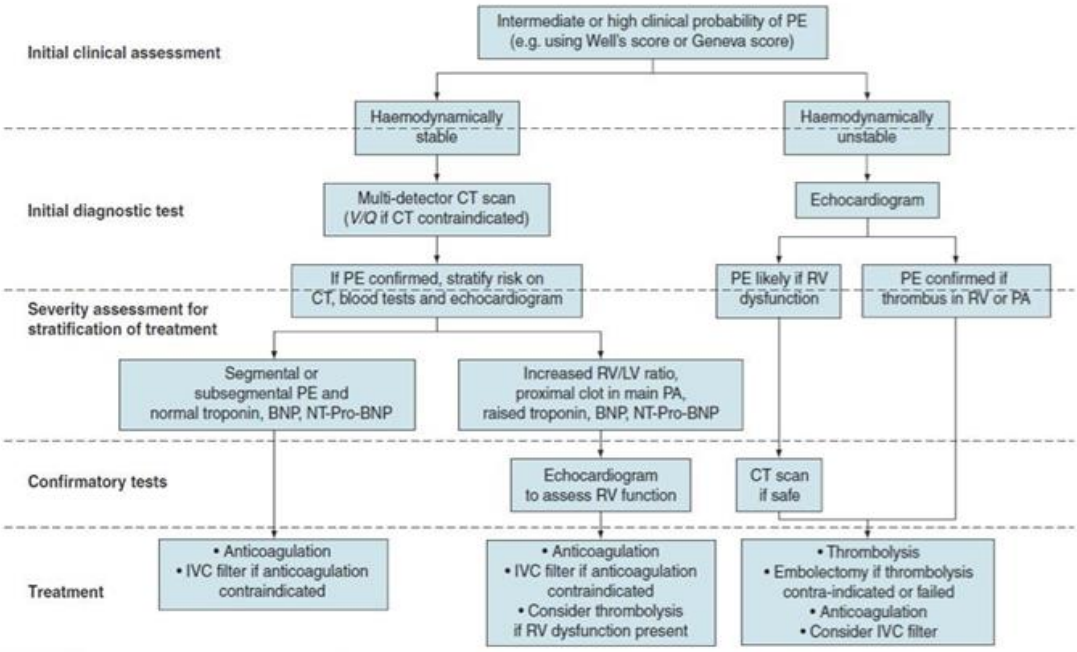
Arterial blood gas analysis

- typically shows evidence of **respiratory alkalosis** with low partial oxygen pressure, low partial carbon dioxide pressure, and elevated pH

	pH	$PaCO_2$	HCO_3
Respiratory Acidosis	↓	↑	↑
Respiratory Alkalosis	↑	↓	↓
Metabolic Acidosis	↓	↓	↓
Metabolic Alkalosis	↑	↑	↑

The diagnosis of PE is based primarily on clinical findings and is confirmed by the detection of an embolism in contrast to CT **pulmonary angiography** (CTPA). Staffing burdens for specific tests (e.g., V/Q scanning and vascular studies of the lower extremities) may impede the clinician's ability to make a timely diagnosis.

Table 6: PE guideline algorithm



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(e) Management

Asses hemodynamic stability:

a) hemodynamically stable

- ABCD approach
- oxygen if needed
- empiric initial anticoagulation (0-10 days) depending upon the clinical suspicion for PE, risk of bleeding, and expected timing of definitive diagnostic tests
- for those who have contraindications to anticoagulation or have an unacceptably high bleeding risk, placement of an inferior vena cava (IVC) filter should be performed

b) hemodynamically unstable ABCD

- oxygenation and stabilizing the airway with intubation and mechanical ventilation, if necessary
- restoring perfusion with intravenous fluid resuscitation and vasopressor support
- immediate anticoagulation with **unfractionated heparin**
- patient in cardiogenic shock due to PE is managed with **thrombolytic therapy** (alteplase)
- prompt imaging for definitive diagnosis (usually CTPA) when pt. is stabilized

Once the diagnosis is made the patient should be started on **anticoagulation** therapy:

Empiric anticoagulation with heparin is initiated to prevent further thromboembolisms as well as to promote the gradual dissolution of the embolism and the underlying thrombosis.

Options for initial anticoagulation include the following:

- subcutaneous **LMWH** or **fondaparinux** (once daily injections; heparin-induced thrombocytopenia [HIT])
- non-vitamin K antagonist oral (**NOACs**)

Rivaroxaban is the only direct oral anticoagulant for monotherapy (i.e., no pre-treatment with heparin necessary)

OR

- **intravenous unfractionated heparin** (UFH) - patients with severe renal failure, for patients in whom there is a high likelihood that acute reversal of anticoagulation will be needed (e.g., procedure or at increased risk of bleeding) as well as those with hemodynamic instability

Non-vitamin K antagonist oral anticoagulants are not suitable for the treatment of hemodynamically unstable PE or massive iliofemoral DVT. In fulminant PE with shock, resolution of the thrombus with thrombolytic agents or removal in emergency surgery is attempted.

Catheter-directed thrombus removal with or without thrombolysis/ surgical embolectomy:

- hemodynamically unstable PE in whom thrombolytic therapy is contraindicated, fail thrombolysis
- anticoagulant therapy is generally discontinued during the thrombolytic infusion

Definite therapy – oral anticoagulants

- long-term anticoagulant therapy is administered beyond the initial few days of anticoagulation for a finite period of typically three to six months, and up to 12 months

Target INR

1,5 Pulmonary embolism, proximal and calf deep vein thrombosis, recurrence of venous thromboembolism where no longer on warfarin therapy, symptomatic inherited thrombophilia, atrial fibrillation, cardioversion, mural thrombus, cardiomyopathy

3,5 Recurrence of venous thromboembolism while on warfarin therapy, antiphospholipid syndrome, mechanical prosthetic heart valve, coronary artery graft thrombosis

(f) Monitoring and follow up

Therapeutic levels of anticoagulation in patients receiving heparin, warfarin, NOACs –

- Warfarin: increased PT/INR, no change to PTT or TT (routinely monitored)
- Unfractionated heparin a PTT (prolonged) (routinely monitored)
- Direct thrombin inhibitors: prolonged TT, no change to PTT or PT (not routinely monitored)
- Direct factor Xa inhibitors: prolonged PT and PTT, unchanged TT (not routinely monitored)
- development of conditions that affect the half-life of the anticoagulant used (eg, renal failure, pregnancy, weight gain/loss, drug interactions) should also be followed

Complications

- Early complication: recurrence (usually 1 to 2 weeks after initial diagnosis)
- Pulmonary infarction -most cases do not result in infarction due to a large degree of collateral circulation in the lungs, occurs when a patient has a reduction in pulmonary blood flow secondary to decreased cardiac output or obstructive lung disease
- Complications of the therapy itself including bleeding
- Death- due to right ventricular failure, obstructive shock

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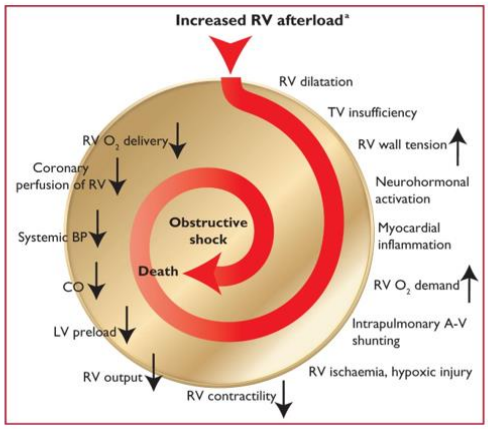

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Sensitivity and specificity, positive and negative predicting value in clinical tests

Sensitivity= true positives/ (true positives+ false negative)

- **measures how often the clinical test correctly identifies the sick patients with the disease** (also known as the "**true positive**" rate)
- highly sensitive test flags almost everyone who has the disease and does not generate many false-negative results
- example: a test with 90% sensitivity will correctly return a positive result for 90% of people who have the disease, but will return a negative result — a false-negative — for 10% of the people who have the disease and should have tested positive

Specificity= true negatives/(true negatives+ false positives)

- measures the test's ability to correctly **generate a negative result** for people who **don't have** the **condition** that's being tested for (also known as the **"true negative"** rate)
- test with high specificity correctly rules out almost everyone who doesn't have the disease and won't generate many false-positive results
- example: a test with 90% specificity will correctly return a negative result for 90% of people who don't have the disease, but will return a positive result — a false-positive — for 10% of the people who don't have the disease and should have tested negative

Positive predicting value = True positives/(true positives + false positives)

- precision rate and measures the proportion of patients who are correctly diagnosed when they test positive

Negative predicting value= True negatives/(true negatives+ false negatives)

- measures the proportion of patients with negative tests being truly disease free

Resources

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