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Pulmonary Embolism

LECTURE IN INTERNAL MEDICINE
FOR IV COURSE STUDENTS

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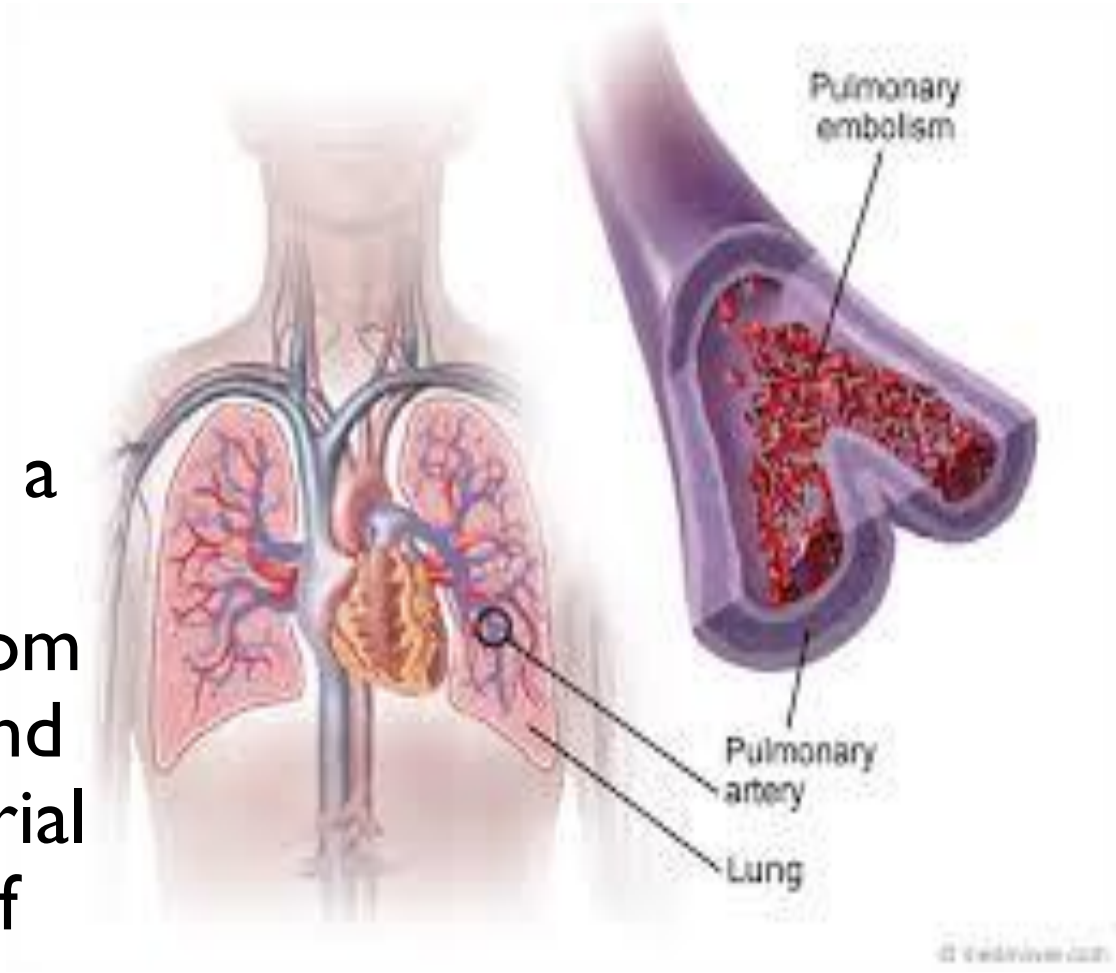
2019

DEFINITION

- **Pulmonary embolism (PE)** is a blockage of the pulmonary artery or one of its branches, usually occuring when a venous thrombus becomes dislodged from its site of formation and embolizes to the arterial blood supply of one of the lungs



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EPIDEMIOLOGY

- **Venous thromboembolism (VTE)** encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE)
- It is the third most frequent cardiovascular disease with an overall annual incidence of 100–200 per 100 000 inhabitants
- VTE may be lethal in the acute phase or lead to chronic disease and disability, but it is also often preventable

https://www.portailvasculaire.fr/sites/default/files/docs/2014_esc_guidelines_ep_eurheartj-ehu283.pdf

EPIDEMIOLOGY

The epidemiology of PE is difficult to determine because it may remain asymptomatic, or its diagnosis may be an incidental finding;

in some cases, the first presentation of PE may be sudden death

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PREDISPOSING FACTORS

HYPERCOAGULABILITY

- Cancer
- Pregnancy
- Postpartum status(<4 wks)
- Oral contraception
- Antiphospholipid antibodies
- Genetic mutations
  - Factor V Leiden mutation
  - Prothrombin gene mutation
  - Factor VIII mutations
  - Protein C deficiency
  - Protein S deficiency

VENOUS STASIS

- Bed rest >48 hrs
- Cast or external fixator
- Recent hospitalization
- Long distance automobile or air travel

VESSEL INJURY

- Recent surgery requiring endotracheal intubation
- Recent trauma requiring hospitalization

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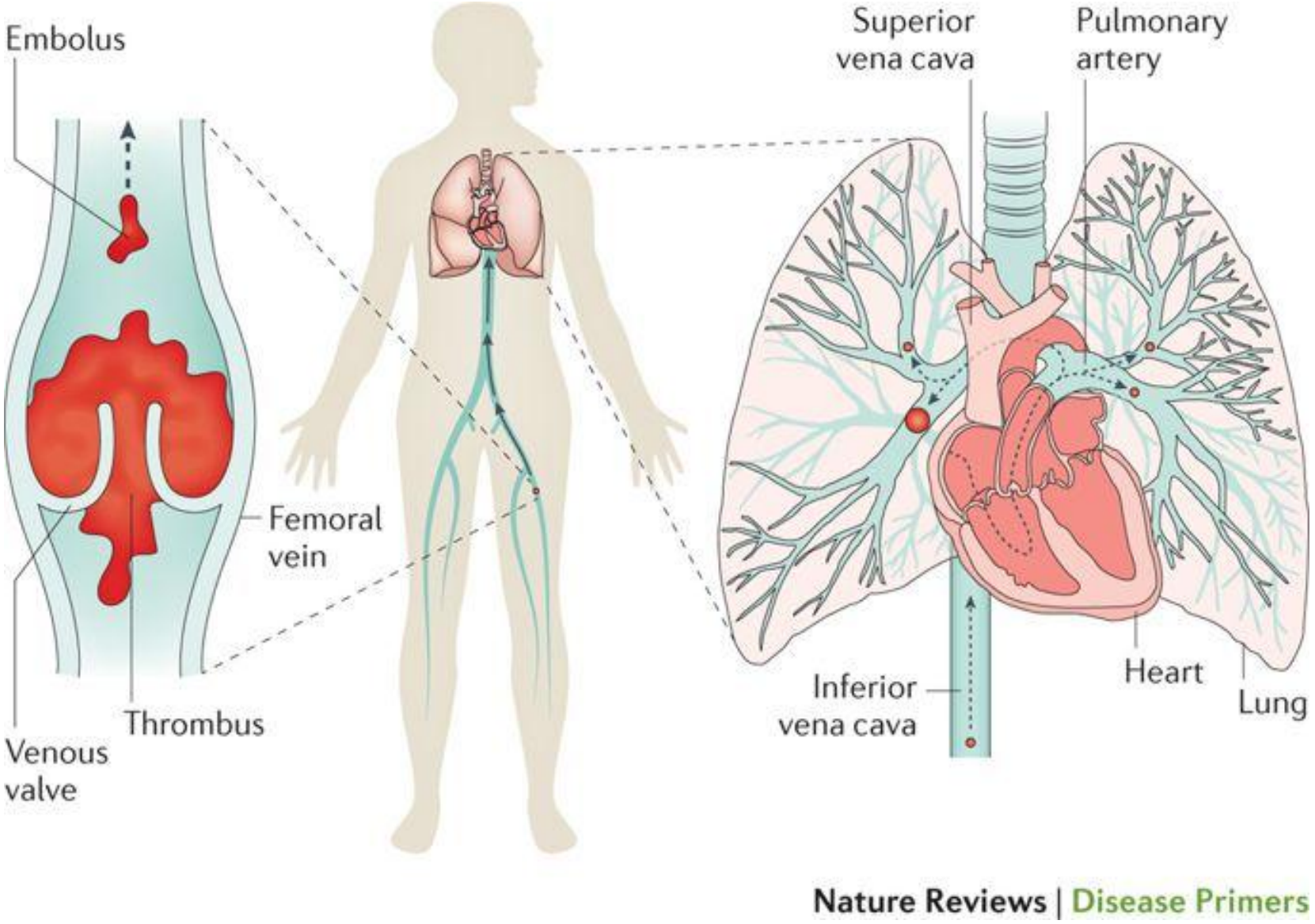
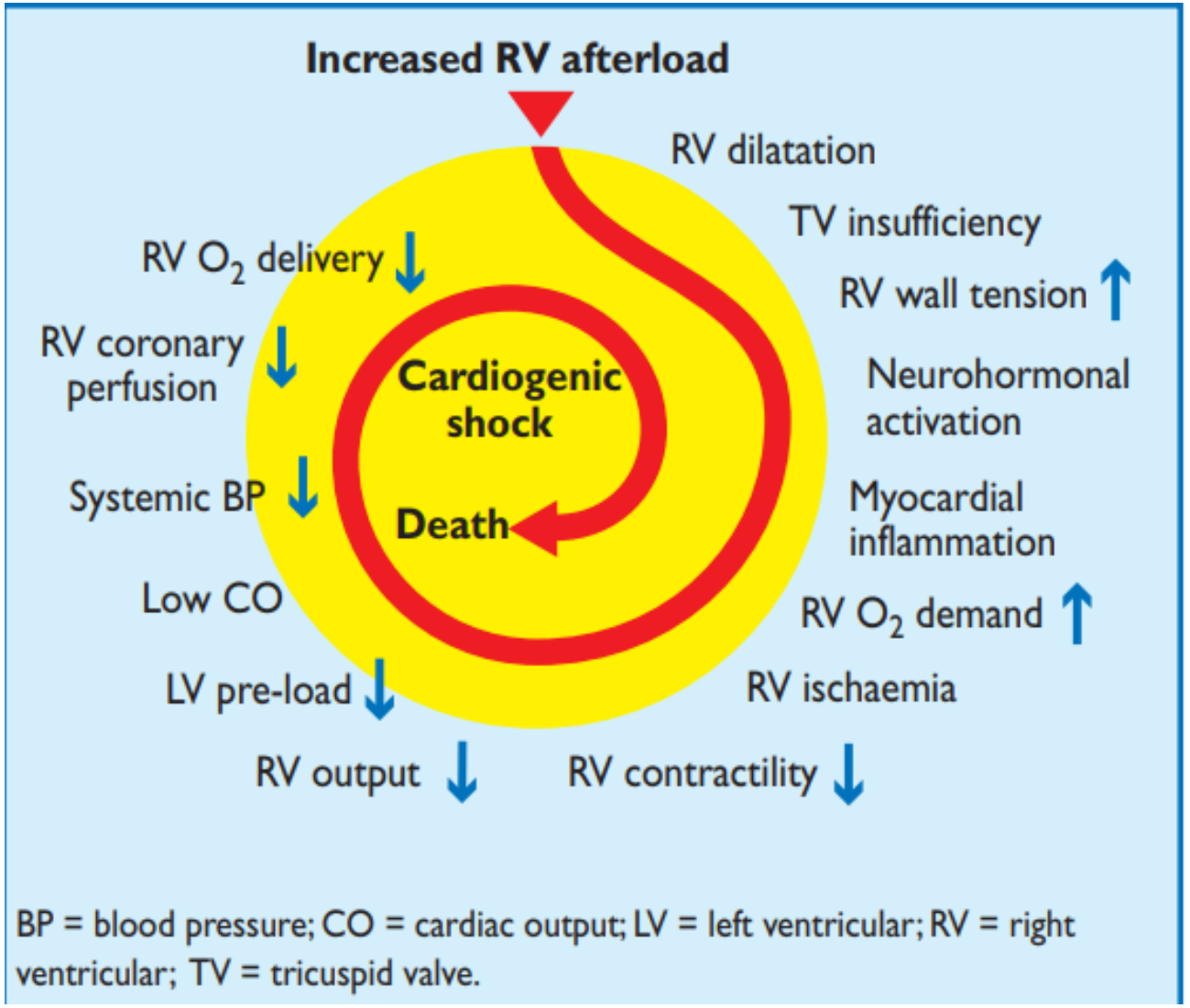
PATHOPHYSIOLOGY



http://deko4halloweenguenstig.info/dvt-drug-treatment-2018-46fdc/

PATHOPHYSIOLOGY

Key factors contributing to haemodynamic collapse in acute pulmonary embolism



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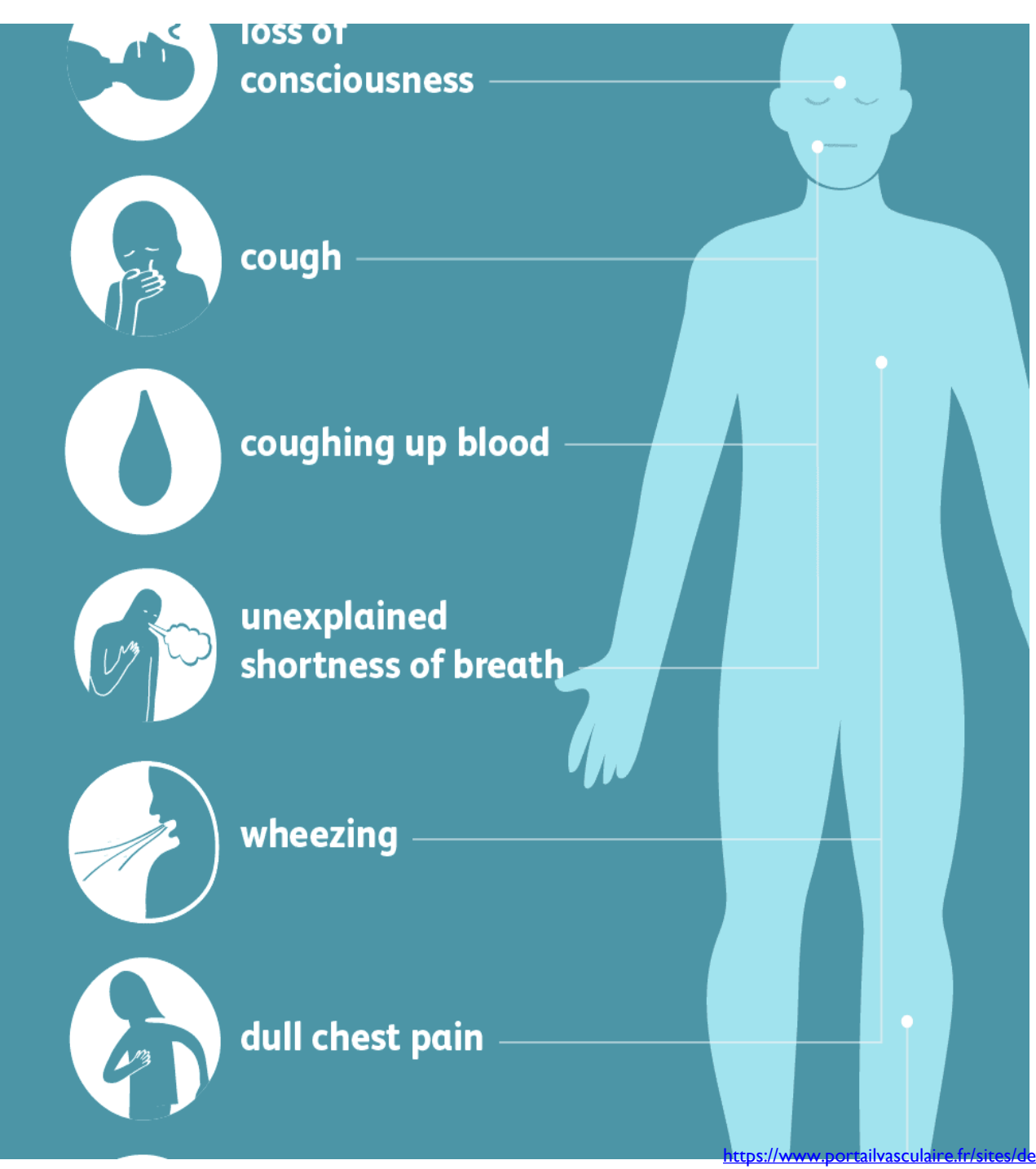

PE: SYMPTOMS

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CLINICAL CHARACTERISTICS OF PATIENTS WITH SUSPECTED PE IN THE ER

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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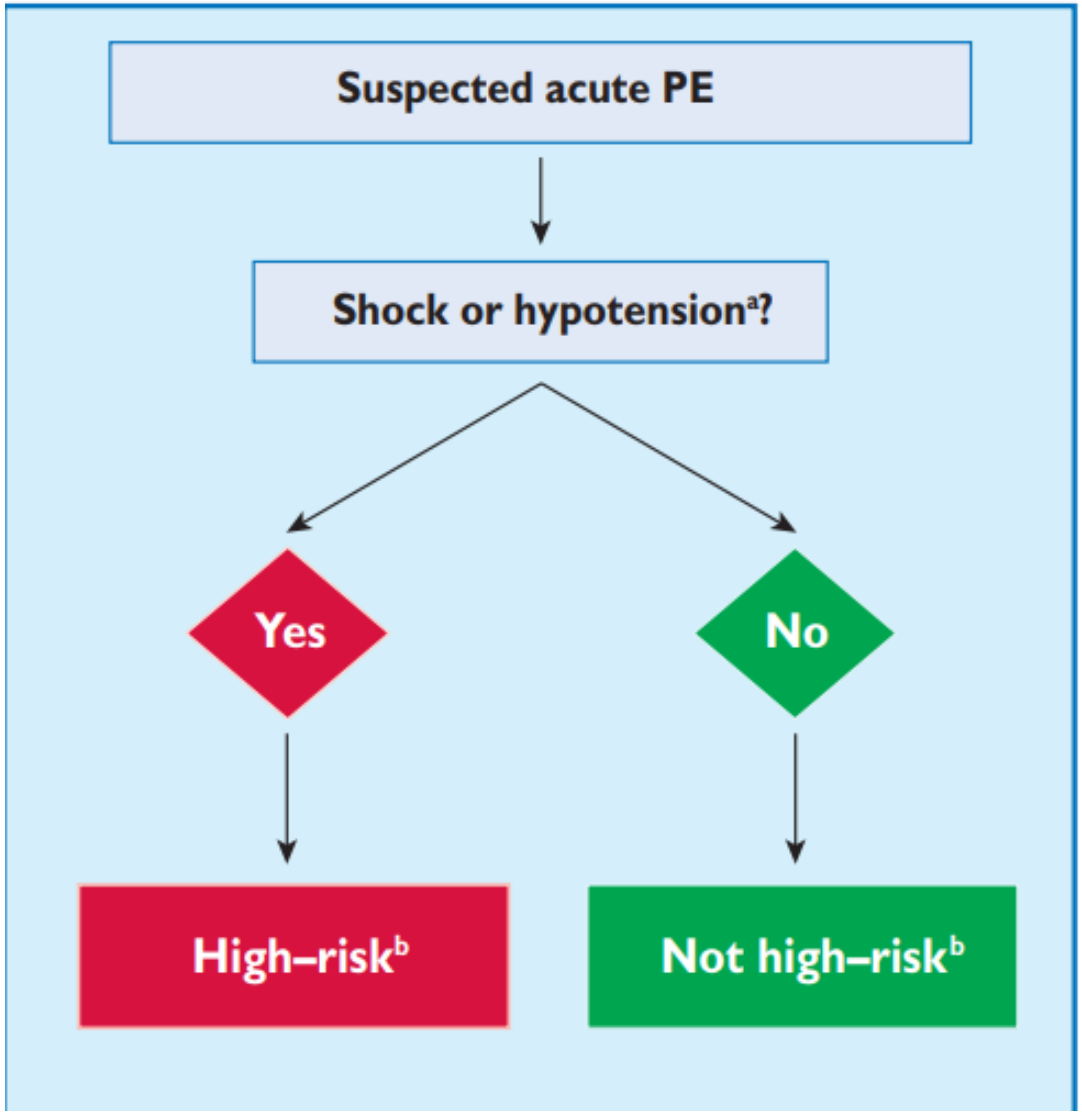
INITIAL RISK STRATIFICATION OF ACUTE PE

- **a** Defined as systolic blood pressure (SBP) < 90 mm Hg, or a systolic pressure drop by ≥40 mm Hg, for >15 minutes, if not caused by new-onset arrhythmia, hypovolaemia, or sepsis
- **b** Based on the estimated PE-related in-hospital or 30-day mortality



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PE: CLINICAL PROBABILITY

Wells rule	Original version[95]	Simplified version[107]
Previous PE or DVT	1.5	1
Heart rate ≥100 b.p.m.	1.5	1
Surgery or immobilization within the past four weeks	1.5	1
Haemoptysis	1	1
Active cancer	1	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Clinical probability		
Three-level score		
Low	0–1	N/A
Intermediate	2–6	N/A
High	≥7	N/A
Two-level score		
PE unlikely	0–4	0–1
PE likely	≥5	≥2

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PE: CLINICAL PROBABILITY

Revised Geneva score	Original version[93]	Simplified version[108]
Previous PE or DVT	3	1
Heart rate 75–94 b.p.m. ≥95 b.p.m.	 3 5	 1 2
Surgery or fracture within the past month	2	1
Haemoptysis	2	1
Active cancer	2	1
Unilateral lower limb pain	3	1
Pain on lower limb deep venous palpation and unilateral oedema	4	1
Age >65 years	1	1
Clinical probability		
Three-level score		
Low	0–3	0–1
Intermediate	4–10	2–4
High	≥11	≥5
Two-level score		
PE unlikely	0–5	0–2
PE likely	≥6	≥3

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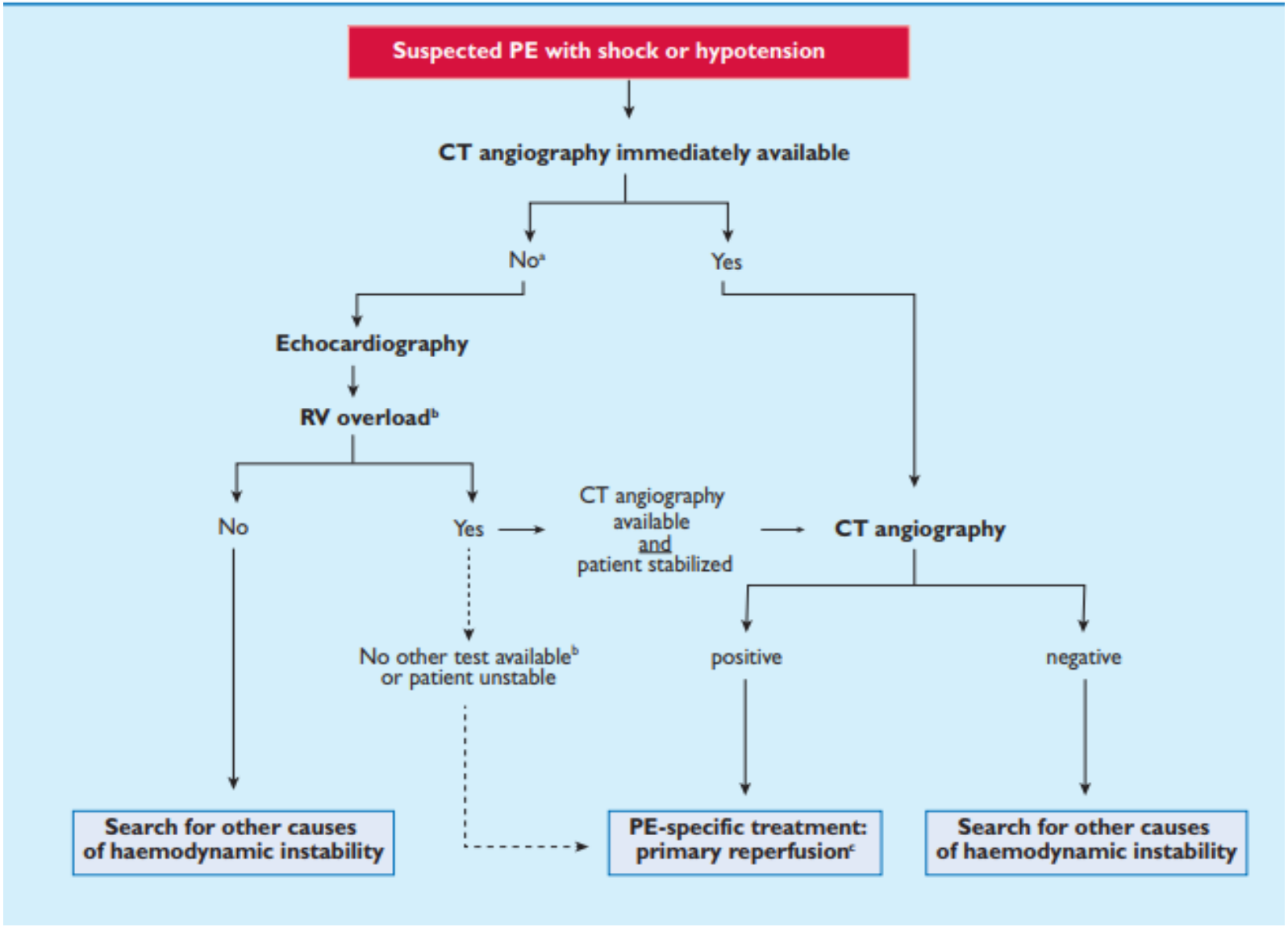
DIAGNOSTIC ALGORITHM



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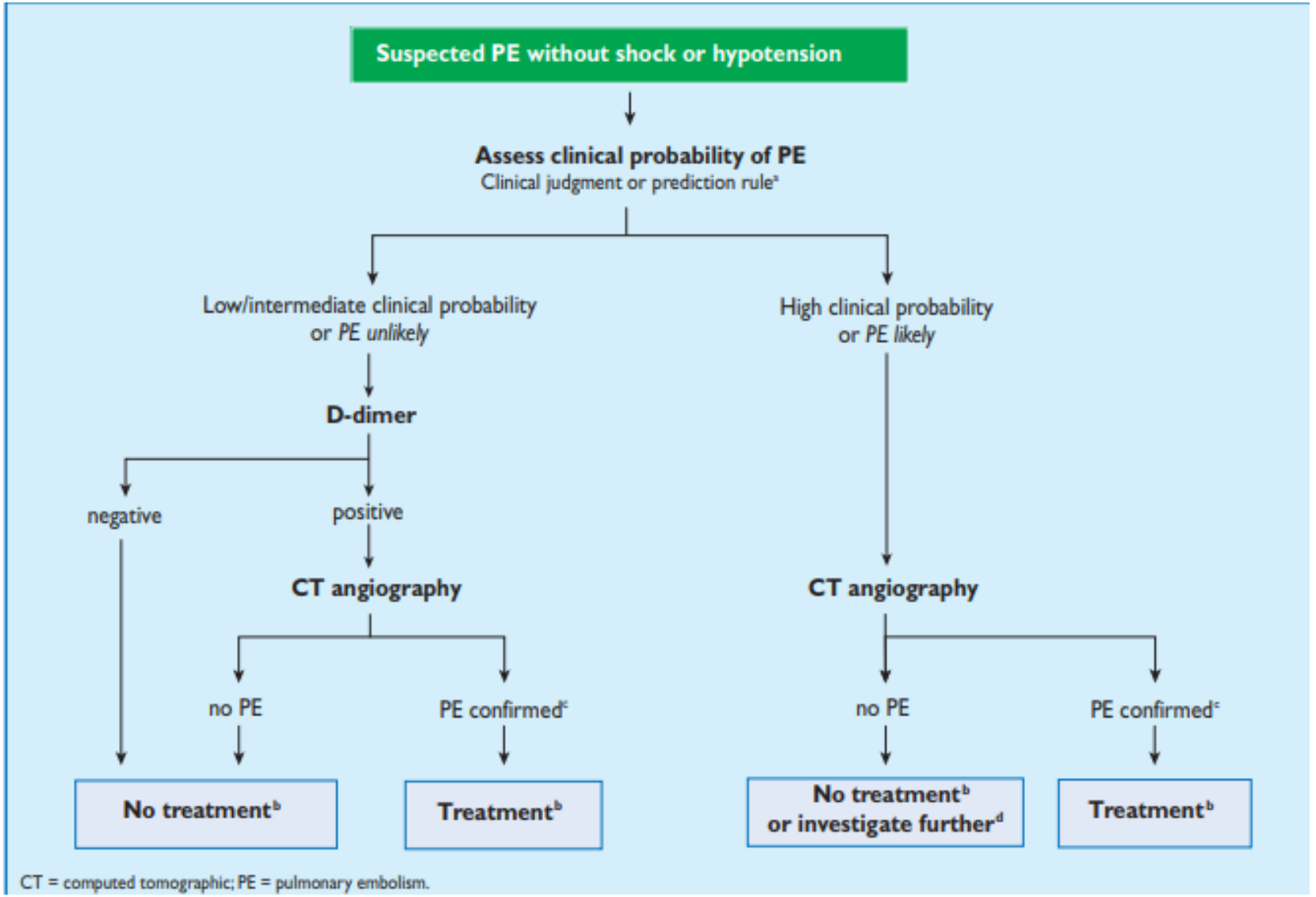
DIAGNOSTIC ALGORITHM



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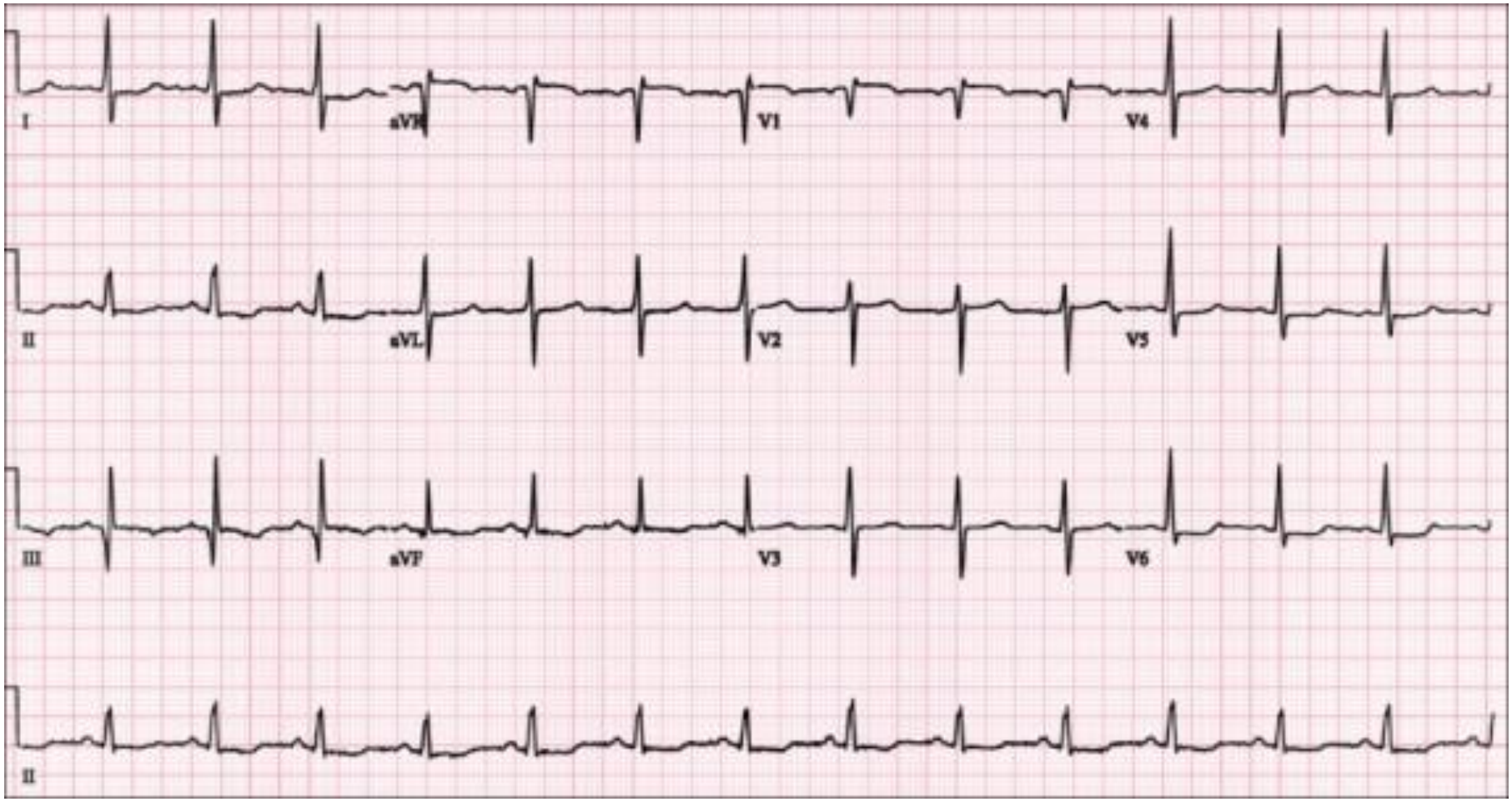
ELECTROCARDIOGRAPHIC FINDINGS IN PULMONARY EMBOLISM



ECG shows an S1Q3T3 pattern

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4613926/

TREATMENT 1.4.

1)Haemodynamic and respiratory support

- Use of vasopressors is often necessary (Epinephrine)
- Administration of oxygen

2)Anticoagulation

- Parenteral anticoagulation (intravenous UFH, subcutaneous LMWH, or subcutaneous fondaparinux)

Low molecular weight heparin and pentasaccharide (fondaparinux) approved for the treatment of PE

	Dosage	Interval
Enoxaparin	1.0 mg/kg or 1.5 mg/kg[a]	Every 12 hours Once daily[a]
Tinzaparin	175 U/kg	Once daily
Dalteparin	100 IU/kg[b] or 200 IU/kg[b]	Every 12 hours[b] Once daily[b]
Nadroparin[c]	86 IU/kg or 171 IU/kg	Every 12 hours Once daily
Fondaparinux	5 mg (body weight <50 kg); 7.5 mg (body weight 50–100 kg); 10 mg (body weight >100 kg)	Once daily

https://www.portailvasculaire.fr/sites/default/files/docs/2014_esc_guidelines_ep_eurheartj-ehu283.pdf

TREATMENT 2.4.

2) Anticoagulation

- **Vitamin K antagonists** (should be initiated as soon as possible, and preferably on the same day as the parenteral anticoagulant)
  - **Warfarin (under international normalized ratio (INR) control-target 2.0-3.0).**

Started at a dose of 10 mg in younger (e.g. ,60 years of age), otherwise healthy outpatients, and at a dose of 5 mg in older

https://www.portailvasculaire.fr/sites/default/files/docs/2014_esc_guidelines_ep_eurheartj-ehu283.pdf

TREATMENT 3.4.

2)Anticoagulation

New oral anticoagulants

Drug	Dosage
Dabigatran	150 mg b.i.d
Rivaroxaban	15 mg b.i.d. for 3 weeks, then 20 mg o.d
Apixaban	10 mg b.i.d. for 7 days, then 5 mg b.i.d.
Edoxaban	(60 mg o.d.; 30 mg o.d. if creatinine clearance 30–50 ml/min or body weight

b.i.d. ¼ bis in die (twice daily)

https://www.portailvasculaire.fr/sites/default/files/docs/2014_esc_guidelines_ep_eurheartj-ehu283.pdf

TREATMENT 4.4.

3) Thrombolytic treatment (streptokinase, urokinase, tenecteplase, t recombinant tissue plasminogen activator);

4) Surgical embolectomy

5) Percutaneous catheter-directed treatment

6) Venous filters (usually placed in the infrarenal portion of the inferior vena cava)

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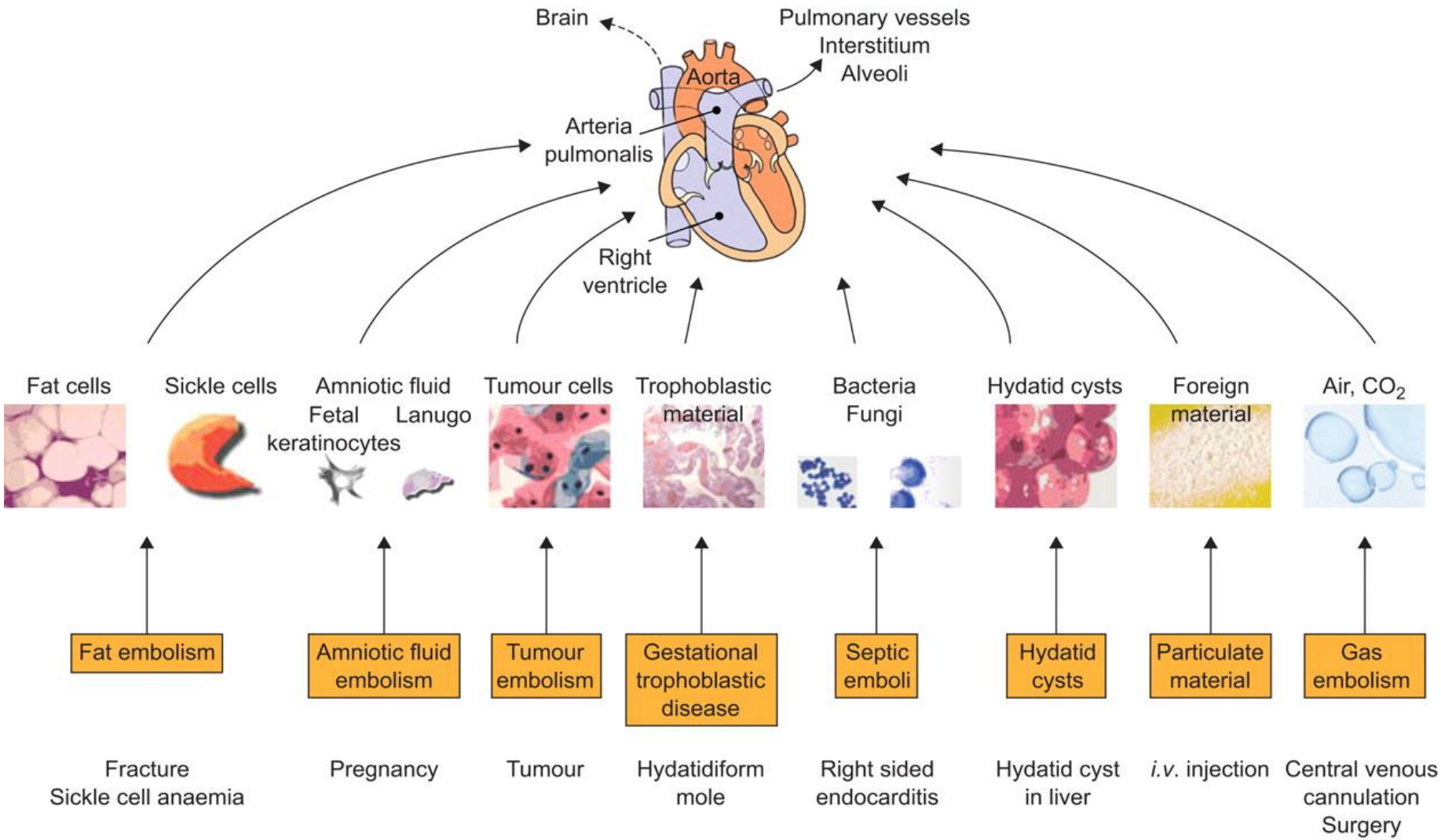
CAUSES: NON-THROMBOTIC PE



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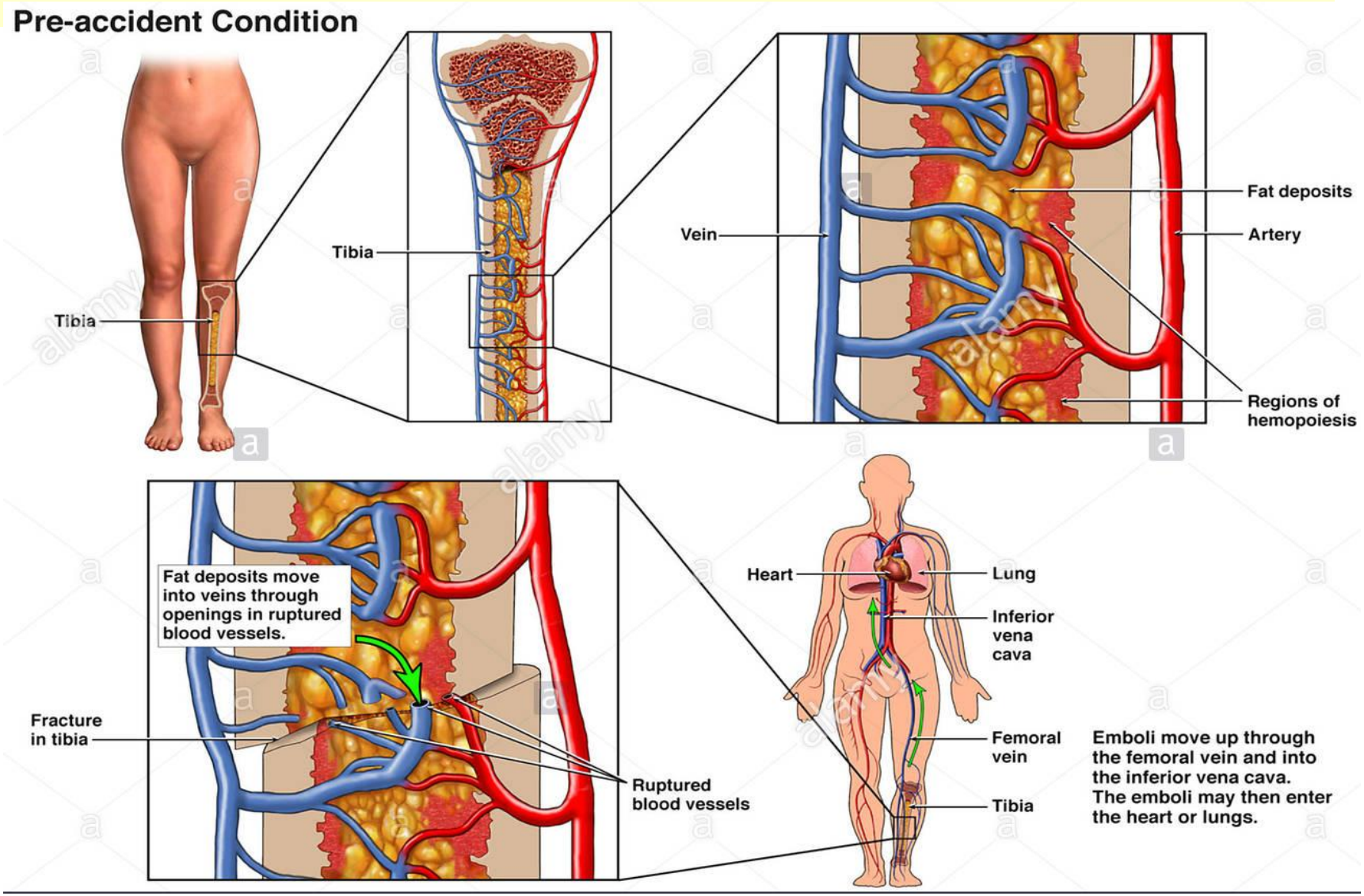
FAT EMBOLISM

- **Fat embolism syndrome (FES)** is a rare clinical consequence of FE, typified by the **triad of pulmonary distress, mental status changes and a petechial rash occurring typically 12–36 hours after injury**
- FE is not limited to skeletal injury
- It is the leading cause of respiratory deterioration in blast victims who survive
- Among the haemoglobinopathies, SCD is commonly associated with pulmonary consequences

https://erj.ersjournals.com/content/34/2/452

FAT EMBOLISM



https://www.alamy.com/development-of-fat-embolism-image7710091.html

CLINICAL SIGNS FA

The clinical diagnosis of FES is one of exclusion, supported by laboratory and radiological investigations

MAJOR

- respiratory distress
- cerebral involvement unrelated to head injury
- petechial rash on the anterior surfaces of the neck, thorax or mucous membranes

MINOR

- tachycardia
- pyrexia
- retinal and urinary changes (anuria, oliguria or fat globules)
- laboratory features including anaemia, thrombocytopenia or high erythrocyte sedimentation rate

https://erj.ersjournals.com/content/34/2/452

DIAGNOSIS

- Diagnosis is facilitated by the presence of haematological and biochemical abnormalities
- Fat globules can be found in blood, urine, sputum, bronchoalveolar lavage (BAL) or even cerebrospinal fluid
- Induced sputum analysis is also a safe and noninvasive test to detect FE in SCD
- In the early stage, atypical radiological findings are bilateral lung infiltrates (chest radiography) or consolidation and ground-glass opacities (computed tomography (CT))

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TREATMENT

- Treatment of FE should primarily be focused on prevention
- **Early immobilisation**, open reduction and internal fixation of fractures have reduced the incidence of FE
- FES is largely self-limiting and is usually associated with a good outcome
- Current treatments are supportive: adequate oxygenation as well as haemodynamic stability, nutrition and prophylaxis of venous thrombosis and stress-related gastrointestinal bleeding
- A beneficial effect of 7.5 mg $\cdot kg^{-1}$ methylprednisolone given six times hourly for 3 days in patients at risk for FES has been reported
- However, the true beneficial effect of corticosteroids either before or after the development of symptoms has not been shown in a well-designed trial

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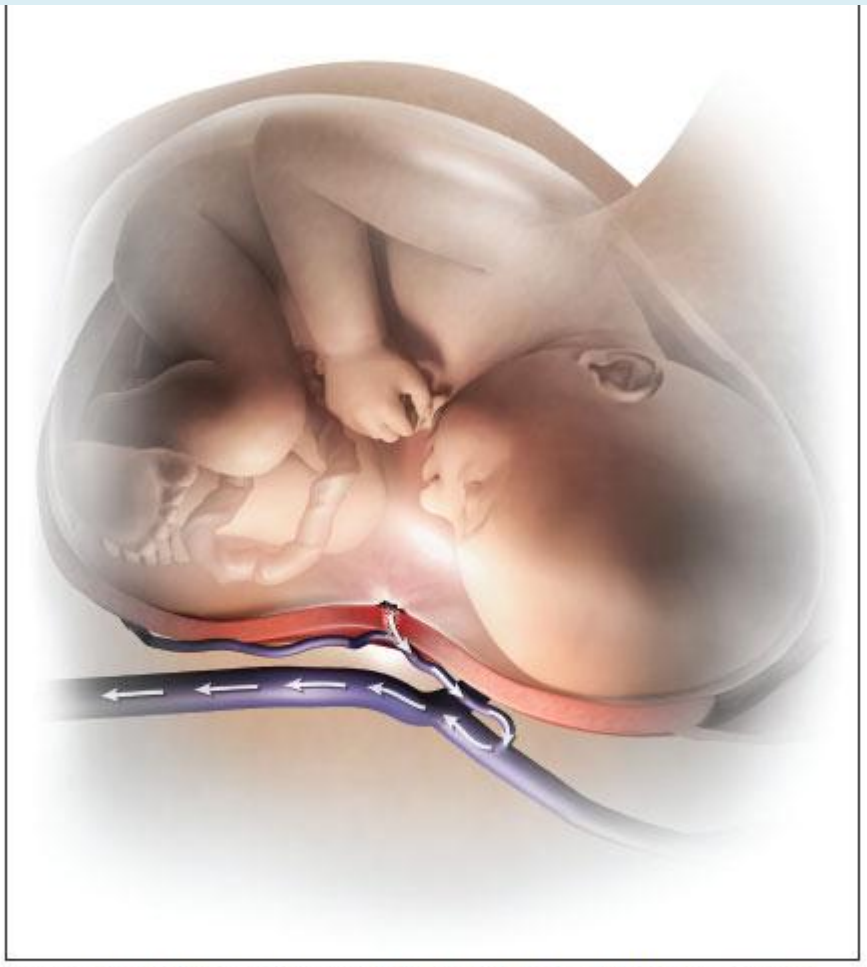
AMNIOTIC FLUID EMBOLISM (AFE)

- The incidence of AFE ranges 1 in 6,000–120,000
- AFE usually occurs during the immediate postpartum period pregnancies



Amniotic fluid embolism is likely caused by amniotic fluid entering the uterine veins. The amniotic fluid triggers an inflammatory and anaphylactoid response that causes cardiopulmonary dysfunction.

https://www.pulmonologyadvisor.com/home/decision-support-in-medicine/pulmonary-medicine/nonthrombotic-pulmonary-embolism-air-amniotic-fluid-fat-tumor/

AMNIOTIC FLUID EMBOLISM (AFE)

Identified risk factors include:

- Older maternal age
- Multiparity
- Intense contractions during labor
- Abdominal trauma
- Cesarean section
- Induction of labor
- Placenta previa
- Eclampsia
- Multiple pregnancy
- Early separation of the placenta from the uterus wall

Fetal factors:

- Fetal distress
- Fetal death
- Male baby

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4874066/

PATHOPHYSIOLOGY

- **Poorly understood**
- **Proposed a biphasic model**

Phase 1:

- Amniotic fluid and fetal cells enter the maternal circulation→ biochemical mediators →pulmonary artery vasospasm → pulmonary hypertension → elevated right ventricular pressure → hypoxia→ myocardial and pulmonary capillary damage → left heart failure → acute respiratory distress syndrome

Phase 2:

- → biochemical mediators → DIC→ Hemorrhagic phase characterized by massive hemorrhage and uterine atony

https://www.pulmonologyadvisor.com/home/decision-support-in-medicine/pulmonary-medicine/nonthrombotic-pulmonary-embolism-air-amniotic-fluid-fat-tumor/

CLINICAL PRESENTATION

The classic clinical presentation of the syndrome has been described by five signs that often occur in the following sequence:

- Respiratory distress
- Cyanosis
- Cardiovascular collapse cardiogenic shock
- Hemorrhage
- Coma

https://www.pulmonologyadvisor.com/home/decision-support-in-medicine/pulmonary-medicine/nonthrombotic-pulmonary-embolism-air-amniotic-fluid-fat-tumor/

DIAGNOSIS

AFE is again a diagnosis of exclusion

Four criteria must be present to make the diagnosis of AFE:

- Acute hypotension or cardiac arrest
- Acute hypoxia
- Coagulopathy or severe hemorrhage in the absence of other explanations
- All of these occurring during labor, cesarean delivery, dilation and evacuation, or within 30 min postpartum with no other explanation of findings

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4874066/

DIAGNOSIS

- Continuous pulse oximetry and arterial blood gas
- Serial complete blood counts and coagulation studies
- The chief radiographic abnormalities in AFE are diffuse bilateral heterogeneous and homogeneous areas of increased opacity, which are indistinguishable from acute pulmonary edema
- A 12-lead ECG
- Lung scan may demonstrate some areas of reduced radioactivity in the lung field
- Increased **serum tryptase**, **urinary histamine** concentrations and **significantly lower complement concentrations** suggest an anaphylactoid process
- Few studies have evaluated the diagnostic accuracy of serum **sialyl Tn** (STN), a fetal antigen present in meconium and amniotic fluid, detected through the use of TKH-2 monoclonal antibody

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4874066/

TREATMENT 1.2.

General

Maintaining vital signs

- The initial goal is the rapid correction of maternal hemodynamic instability (correction of hypoxia and hypotension)
- Correcting coagulopathy — Blood and blood products, including fresh frozen plasma (FFP), platelets and cryoprecipitate, must be available and administered early in the resuscitation phase of AFE

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4874066/

TREATMENT 2.2.

Pharmacological

- **Epinephrine** may be the first-line agent of choice
- Inotropic support like **dopamine** or noradrenaline
- **Hydrocortisone**
- **Oxytocin**: decreases inflammation by suppressing migration of polymorphonuclear leukocytes and reversing increased capillary permeability
- Other antifibrinolytic drugs, such as **aminocaproic acid and tranexamic acid**

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4874066/

TUMOR EMBOLISM (TE)

Pulmonary intravascular tumor emboli are seen in up to 26% of autopsies of patients with solid malignancies, although the diagnosis is rarely made before death

Carcinoma of the prostate gland, digestive system, liver, and breast is most commonly implicated

https://www.portailvasculaire.fr/sites/default/files/docs/2014_esc_guidelines_ep_eurheartj-ehu283.pdf

TE: Pathophysiology

- Macroembolism is a feature of primary tumor sites that are connected by the vena cava to the right ventricle
- Tumor emboli possess an unusual level of resistance to recanalization and are therefore more likely to lead to progressive, irreversible obstruction
- Most cases of microembolism show a vascular tissue reaction with intimal proliferation and fibrosis

https://erj.ersjournals.com/content/34/2/452

TE:CLINICAL SIGNS

TE suspected in patients:

- complain of unexplained dyspnoea and developed cor pulmonale

The most common symptom is subacute progressive dyspnea which occurs in 57–100% of cases over a span of weeks to months

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TE DIAGNOSIS

- Even in patients known to have a malignancy, the correct diagnosis is made in as few as 6% *ante mortem*
- TE has a lack of specific radiological features and mimics pneumonia or interstitial lung disease
- A normal chest radiograph with hypoxemia in a patient with a malignancy might even suggest the presence of TE

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TE TREATMENT

- The prognosis is poor and the median survival from diagnosis is a few weeks
- **Surgical cure by resection** of the primary tumor has been reported in patients with atrial myxoma, renal cell carcinoma and choriocarcinoma
- **Chemotherapy is rarely indicated**, although favourable results have also been reported in patients with choriocarcinoma and breast cancer

https://erj.ersjournals.com/content/34/2/452

Case Report 1.10.

- **A 30-year-old** female working as a courier and previously well was referred to the facility with acute onset of **severe dyspnoea and central chest pain**
- She presented with a 4-day history of **dry cough and malaise,** which had not responded to prescribed antibiotics.
- There were **no known risks** for PTE; history of preceding loss of consciousness, trauma, weight loss, or fever; or significant past personal and family medical histories

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5167281/

Case Report 2.10.

The findings on examination

- Tachycardia (120 beats/min)
- Tachypnea (32 breaths/min)
- Hypoxia on room air
- Normal blood pressure
- Apyrexia
- The chest and cardiac exam findings were unremarkable, apart from an accentuated second heart sound

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5167281/

Case Report 3.10.

- Arterial blood gas analysis showed a mild respiratory alkalosis
- Her ECG showed a sinus tachycardia and features of right ventricular strain
- The rapid HIV antibody test was negative and CBC, liver function tests, urea, creatinine, electrolytes, and INR were normal
- The D-dimer was 0.34 mg/L (normal < 0.25 mg/L), fibrinogen was 1.2 mg/L (range: 2.0–4.0 mg/dL), and the C-reactive protein was mildly elevated

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5167281/

Case Report 4.10.

- An ECHO showed severely dilated right heart chambers with elevated right ventricular systolic pressures of 115 mmHg (range: 15–25 mmHg) and moderately impaired right ventricular systolic function
- The pulmonary artery was severely dilated
- The left heart was normal
- Doppler ultrasound of the lower limbs and abdomen did not show evidence of thrombi; however, lymph nodes were noted in the porta hepatis and para-aortic region

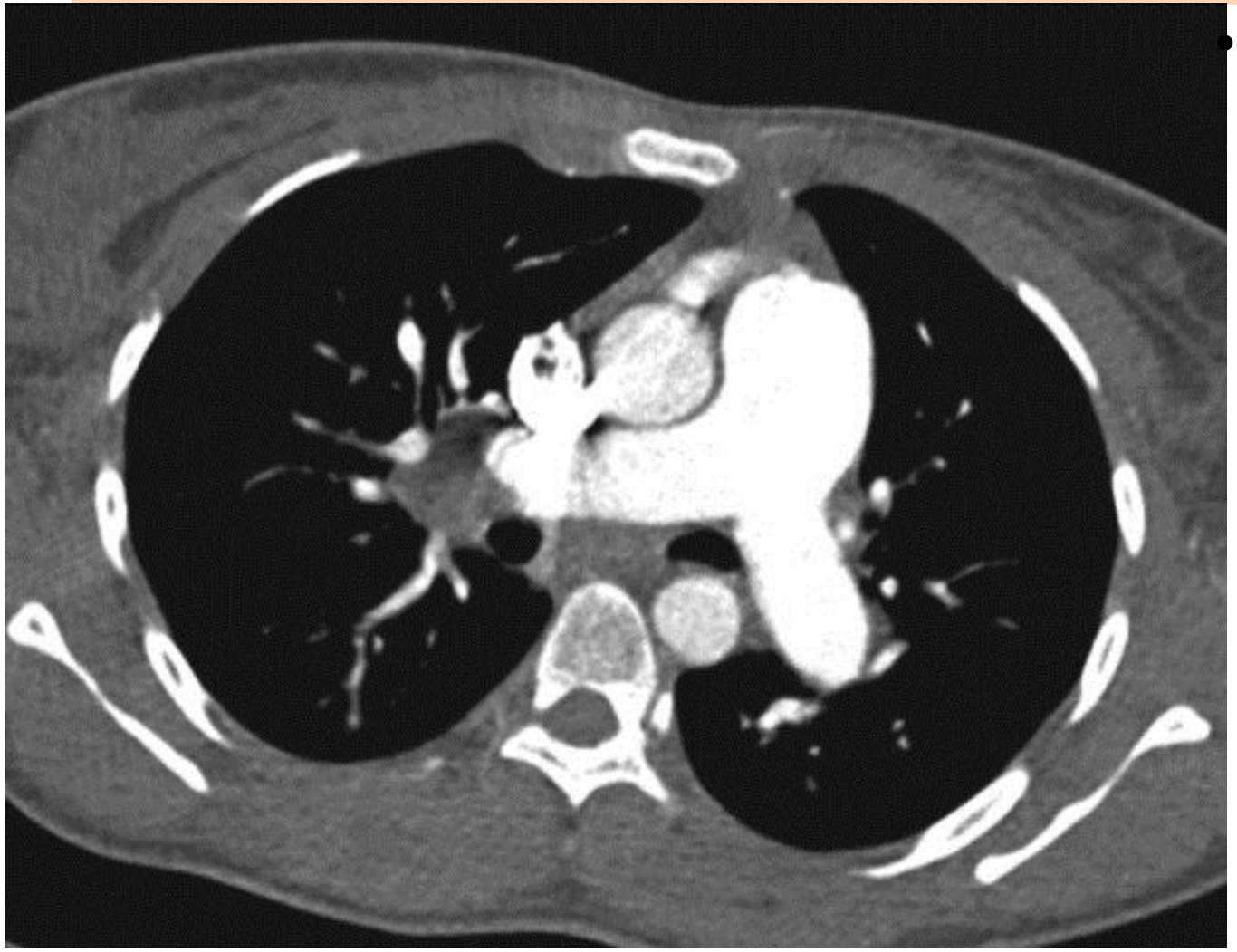
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5167281/

Case Report 5.10.

- The computed tomography (CT) pulmonary angiogram confirmed features of pulmonary hypertension, while also revealing extensive mediastinal adenopathy
- Significantly, the CT scan did not show evidence of intraluminal pulmonary thrombi or features of parenchymal lung disease

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5167281/

Case Report 6.10.



- An axial contrasted CT scan of the chest showing enlarged main pulmonary trunk suggesting pulmonary hypertension and extensive mediastinal lymphadenopathy

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5167281/

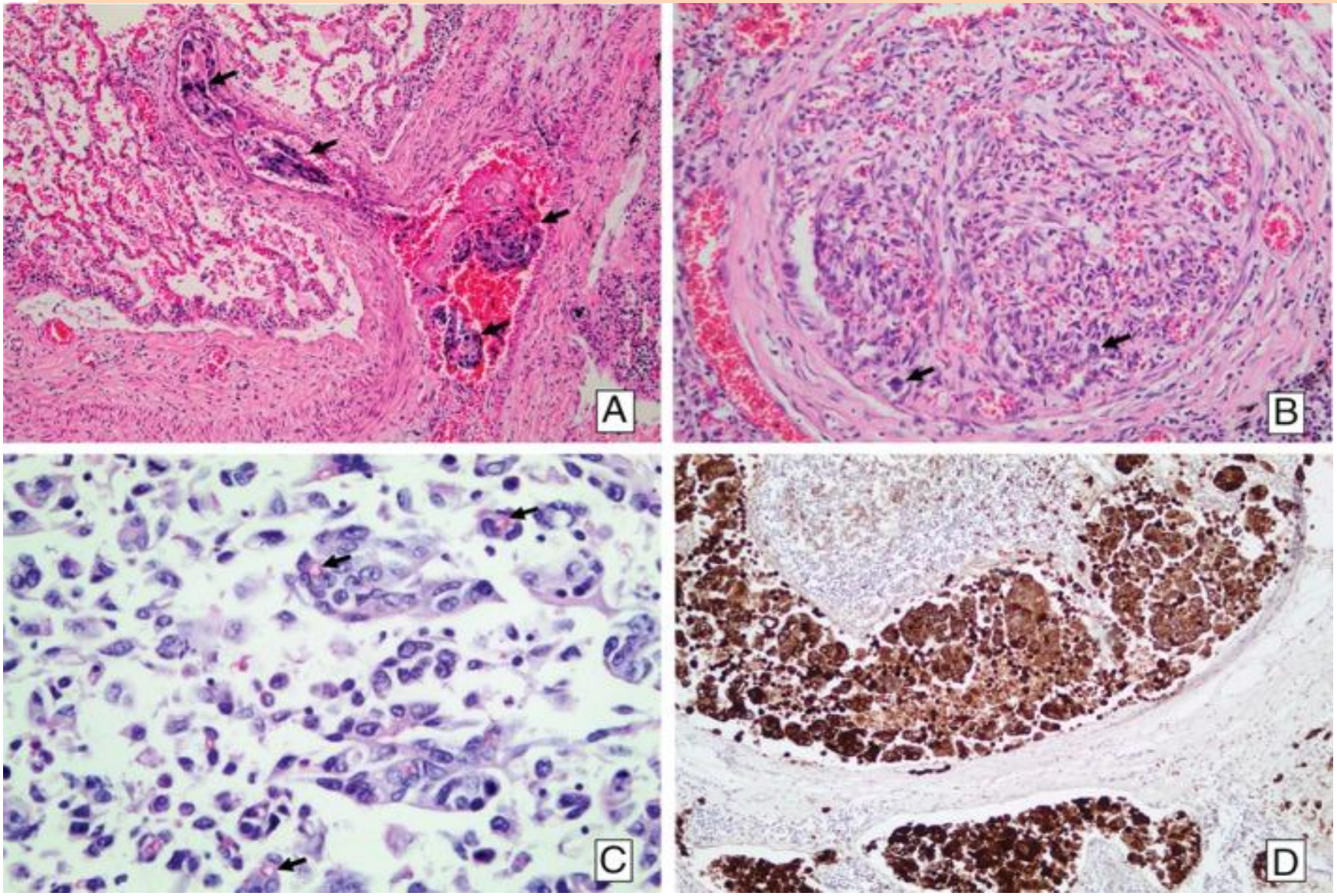
Case Report 7.10.

- During the next 24 h, she developed cardiovascular instability characterized by **recurrent discrete episodes of hypotension and hypoxia** without arrhythmia, necessitating intermittent non-invasive positive pressure ventilation and fluid resuscitation with good inter-episode clinical response
- After the second such episode, she was thrombolysed for suspected new massive pulmonary thromboembolism and admitted to the intensive care unit
- On the 65th hour from hospital admission and after a period of clinical stability, she suffered a **recurrent episode of hypotension and hypoxia, and demised despite prolonged resuscitation**
- A post-mortem examination macroscopically showed **generalized lymphadenopathy and prominent small pulmonary vessels**
- Microscopic examination of the enlarged mediastinal lymph nodes showed a poorly differentiated adenocarcinoma, which was also found in the peri-pancreatic and peri-adrenal soft tissue and invading the diaphragm.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5167281/

Case Report 8.10.

Examination of the lungs demonstrated multiple organized tumor emboli occluding the pulmonary vessels



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5167281/

Case Report 9.10.

- Immunohistochemistry performed was positive for CK20 and negative for CK7, which is typical for colorectal adenocarcinomas
- Macroscopic examination of the gastrointestinal system, however, failed to localize a macroscopic lesion in the gastrointestinal tract
- In addition, CDX-2 (usually positive in colorectal adenocarcinomas) tested negative in this patient
- The post-mortem was unable to identify conclusively a primary location for this disseminated malignancy

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5167281/

Case Report: Conclusion 10.10.

- Pulmonary tumor emboli is typically an end-stage manifestation of malignancy, and the prognosis with or without therapy is generally poor after onset of symptoms
- The patient was a young, previously healthy female with no suggestive medical or family history
- She presented with rapid onset fatal cor pulmonale due to pulmonary tumor embolism from an occult carcinoma of an unknown origin, which is extremely rare
- Most cases of pulmonary tumor embolism occur in patients with established malignancies

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5167281/


The End