Pulmonary embolism

Objectives:

- Epidemiology
- Pathophysiology
- Diagnosis
- Massive PE
- Treatment

Team Members: Fatima AlTassan, Jawaher abanumy, Abdulrahman thekry, khalid aleidan

Team Leader: Nawaf Alkhudhayri

Revised By: Maha AlGhamdi

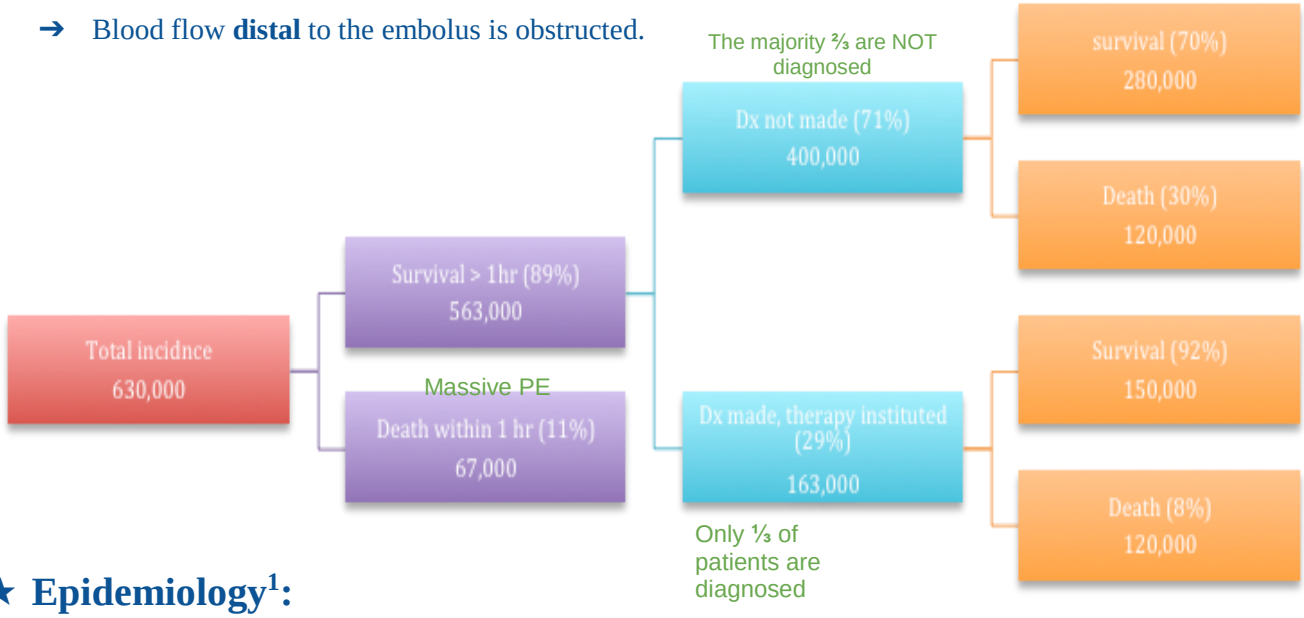
Resources: 435 team + Davidson + kumar + Recall questions step up to medicine.

- Editing file
- Feedback

Overview

video 1: 23 minutes

- **Pulmonary embolism (PE)** and **deep venous thrombosis (DVT)** are considered as a continuum of one clinical entity **(venous thromboembolism)** diagnosing either PE or DVT is an indication for treatment.
- A **P.E.** occurs when a **thrombus** "usually formed in the **systemic veins** or *rarely* in the **right heart (**<10% of cases)" in another region of the body dislodges and embolizes to the **pulmonary vascular tree** (pulmonary arterial system) via the **right ventricle (RV)** and **pulmonary artery.**
  - ➔ Blood flow **distal** to the embolus is obstructed.



★ Epidemiology[1]:

- 11% of patients die within one hour. Because of massive pulmonary embolism.
- Over **317,000** deaths were related to VTE in six countries of the European Union (with a total population of **454.4** million) in 2004. Of these cases:
  - **34%** presented with sudden fatal PE
  - **59%** were deaths resulting from PE that remained undiagnosed[2]
  - Only **7%** of the patients who died early were correctly diagnosed with PE before death.
  - For this reason it is important to correctly diagnose patients since it ↓ mortality & ↑ survival
- **Incidence of pulmonary embolism per year in the united states[3]:**

50,000 individuals die from PE each year in USA, the incidence of PE in USA is 500,000 per year.

---

[1] **Graph explanation**: 11% of PE patients die within 1 hr. because of massive PE. (Note: Massive PE= SHOCK + HYPOTENSION, the rest (89%) survive after 1 hr.: 71% of the later are misdiagnosed with mortality rate of 30%" and 29% are diagnosed with mortality rate of 8%

[2] Undiagnosed = you give them the treatment then they go home & develop another clot and die because of it

[3] Dx: diagnosis

★ Risk factor for venous thrombosis[4]: heretriad: (VIRCHOW'S TRIAD: Endothelial injury, venous stasis, hypercoagulability)

- Stasis, (due to long journeys in a plane or car, heart failure, immobility)
- Injury to venous intima (connective tissue diseases ex: SLE, Marfin syndrome)
- Alterations in the coagulation-fibrinolytic system.[5] (pregnancy, inherited coagulopathies)

★ Risk factors for DVT[6]: here

Patient factors	Surgical conditions	Medical conditions	Haematological disorders
- Advanced age >60 **- Obesity** **- Pregnancy** **- Oral contraceptive pills** **- Postpartum** **- Prolonged immobility:** bed rest, long-distance travel **- Varicose veins.** **- previous Hx of DVT or PE.**	**- General anesthesia** [7] **- Major trauma and surgery:** لذلك نعطي المرضى بعد العمليات **prophylaxis** especially pelvic surgery (orthopedic procedures) and **Lower limb.**	**- Cardiac and respiratory diseases:** especially Congestive heart failure.[8] **-Malignancy,** **Patient comes with multiple PE and when we dig deeper we will find malignancy somewhere.** **- Nephrotic syndrome**	**- Coagulation problems:**[9] Protein C and S deficiency, Antithrombin III deficiency , factor V leiden - Thrombophilia[10]: It needs an insult to trigger PE as smoking or being pregnant. - Antiphospholipid antibody/ lupus anticoagulant.

★ Source of emboli:

DVT		Other sources
Lower extremity DVT	Upper extremity DVT	
PE is the major complication of DVT(>95%). - **Most** pulmonary emboli arise from thromboses in the **deep veins of lower extremities** above the knee (iliofemoral DVT) we have to treat them. - **calf vein thrombi** have a **low incidence** of embolizing to the lungs and we usually just monitor them.[11] - Pulmonary emboli can also arise from the **deep veins of the pelvis.** This thrombi will either detach or go all by one to occlude other places like pulmonary art	- **"Axillary thrombosis"** is a **rare** source of emboli. - (it may be seen in **IV drug abusers** due to foreign material).	**Thrombus in other vein:** - Renal, Uterine, Right cardiac chamber **Other sources of emboli :** - Fat embolism (due long-bone fractures) - Amniotic fluid embolism (during delivery) - Air embolism (due to trauma to thorax) - Septic embolism (IV drug use) -In lupus anticoagulant PE can be caused from an artery.

---

[4] **Put in mind not only PE**

[5] Hypercoagulable state : inherited conditions (Protein c, antithrombin 3, factor V leiden deficiency) > if patient is young or recurrent DVT you need to investigate these.

[6] **you have to ask the PT. about all of these when PE is suspected**

[7] When we give them muscle relaxants → muscle atonia (Muscles are no longer able to pump the blood)

[8] Because of stasis

[9] **(inherited conditions),**"you need to investigate these" and if the patient is young or has recurrent DVT

[10] is a condition where the blood has an increased tendency to form clots

[11] But in many patients these thrombi progress into the proximal veins, increasing the incidence of PE.

Keep in mind: **absence of DVT does NOT exclude PE**! . sometimes the whole clot (instead of parts of it) travels to the lungs. In this case, the legs won't show any sign of thrombosis when examined.

★ Clinical features: You can ssuspecte PE by asking about the symptoms + risk factors

- **Most often, PE is clinically silent.**
- **Sudden onset of unexplained** (1) **dyspnea,** is the most common,and often the only symptom of pulmonary embolism.
- (2) **Pleuritic chest pain** (Sharp & can be Pinpointed with one finger) and (3) **Hemoptysis** "Not diagnostic" are present only when **infarction** has occurred.
- All of them are classical presentations but, THEY ARE NOT specific for PE. That's why PE is usually missed.

Table 3 Clinical characteristics of patients with suspected PE in the emergency department (adapted from Pollack et al. (2011)).

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

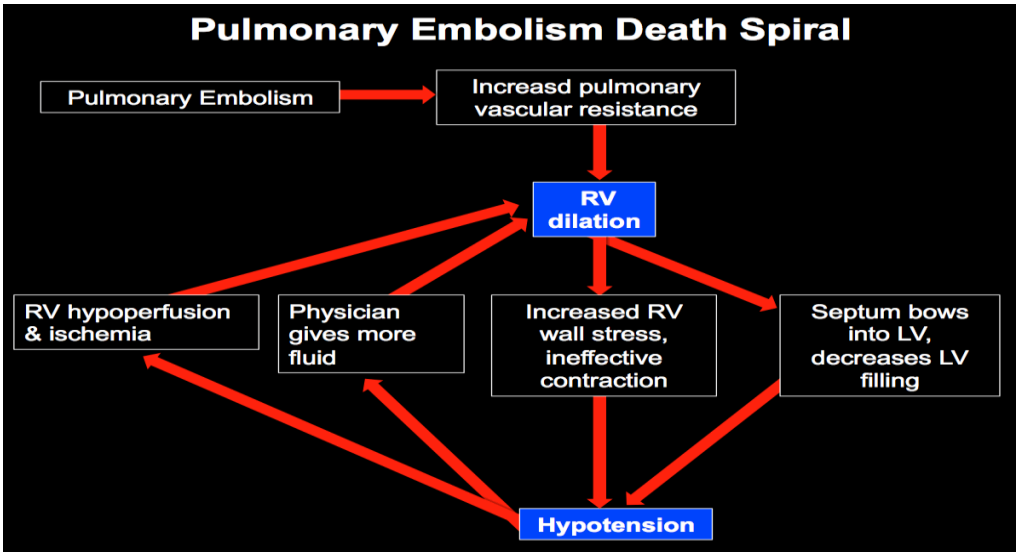
DVT: deep vein thrombosis.

- Clinical clues are not specific that means we cannot make the diagnosis of PE based on them; their main value lies in suggesting the diagnosis[12] .

★ **There are three typical clinical presentations of pulmonary embolism:** (summarised in this table **here**)

1. Acute Massive Pulmonary Embolism

- massive means major hemodynamic effect (shock & hypotension), not reversed to the size.
- It is a catastrophic entity which often results in acute right ventricular failure and death
- Frequently undiscovered until autopsy
- Fatal PE typically leads to death within one to two hours of the event



When a physician gives more fluid this increases the amount of blood going to the heart, but this extra volume cannot pass through the pulmonary vessels because of the clot, this increases RV pressure leading to RV dilatation.

[12] which must be confirmed or rejected by the investigations.

- **Pathophysiology:** Pulmonary Embolism death spiral:

  - DVT or any thrombus that embolizes through the **systemic circulation** into the **RA → RV → pulmonary artery → occlusion of the vascular bed→↑ pulmonary resistance and pressure →↑RV pressure**[13] **→ acute obstruction of RV outflow →↓preload →↓cardiac output → acute right ventricular failure → death** see above "PE death spiral"
  - **Hypoxemia ensues → stimulating vasoconstriction → increase in PAP**
  - In patients without cardiopulmonary disease, occlusion of **25-30** % of the vascular bed **increase in Pulmonary artery pressure** (PAP)
  - **More than 50%** of the vascular bed has to be occluded before PAP becomes substantially elevated
  - When **obstruction approaches 75%,** the **RV** must generate systolic pressure in excess of 50mmHg to preserve pulmonary circulation
  - The normal RV is unable to accomplish this acutely and eventually fails.[14] In cor pulmonale there is pulmonary hypertension but the increase in pressure is chronic and gradual so the RV can accommodate..

- **Symptoms:**
  - crushing central chest "ischemic[15]" pain, - severe dyspnea, - shocked[16], -Faintness or syncope.

- **Signs:**
  - tachycardia , - severe cyanosis, **- hypotension,** -↑ JVP, - widely split loud P2 , - RV gallop rhythm with heave, - ↓urinary output.

2. Acute Small/Medium Pulmonary Embolism

- **Pathophysiology:**
  DVT or any thrombus that embolizes through the **systemic circulation** into the **RA → RV → pulmonary artery**[17] **→ Occlusion of segmental (terminal) pulmonary artery → infarction**[18] +\- **effusion**[19].

- **Symptoms:**
  - pleuritic chest pain , - breathlessness, - hemoptysis[20].

- **Signs:**
  - tachypnea , - sinus tachycardia , - localized pleural rub , - coarse crackle , - low grade fever.

---

[13] RV cannot tolerate high pressures like the LV (RV → volume chamber / LV → pressure chamber)
[14] rapid RV dilatation and dysfunction which is clinically manifest as hypotension and cardiogenic shock.
[15] due to lack of coronary blood flow.
[16] apprehensive, pale and sweaty.
[17] This highlighted sequence constant in all the 3 presentation.
[18] There is ventilation but there is no perfusion → dead space "infarction" → impaired gas exchange →hypoxemia. After some hours NO surfactant → alveolar collapse.
[19] If there was it may be blood-stained.
[20] often 3 or more days after the initial event.

3. Multiple recurrent (chronic) Pulmonary Embolism

- **Pathophysiology:**
  - Multiple chronic occlusions of pulmonary vasculature → pulmonary hypertension → right heart failure.
- **Symptoms:**
  - exertional dyspnea, -weakness, - late symptoms of HF and pulmonary HTN: angina and syncope.
- **Signs:**
  - RV heave, - loud P2, - at the end stage: signs of right ventricular overload[21].

★ Diagnosis:

We can use ECG - CXR – ABG - ECG - D-dimer – Spiral CT – V/Q – Echo – Angio

- The symptoms and signs of small/medium PE are often subtle and nonspecific, so the diagnosis is often delayed or even completely missed.
- The diagnosis of Acute massive PE should be explored whenever oxygenation or hemodynamic parameters are severely compromised without explanation.
  - CXR
  - ABG
- Significant hypoxemia is almost uniformly present when there is a hemodynamically significant PE
  - V/Q
  - Spiral CT
  - Echo
  - Angio

1. Arterial blood gas (ABG)[22],[23]:

- **Massive EP:**

  Significant hypoxemia is almost uniformly present when there is a hemodynamically significant PE.

  Low Oxygen sat on 100% O2 mask

  Markedly abnormal with ↓PaO2 "arterial **hypoxaemia**[24]" and ↓PaCO2[25]. Respiratory alkalosis (pH is high), the body will compensate leading to Metabolic acidosis.
- **small/medium PE: normal** or ↓PaO2 or ↓PaCO2
- **Multiple recurrent PE: Exertional** ↓PaO2

---

[21] -↑ JVP, - widely split loud P2 , - RV gallop rhythm with heave,

[22] test measures the acidity (pH) and the levels of oxygen and carbon dioxide in the blood from an artery.

[23] levels are **NOT** diagnostic for PE.

[24] Significant hypoxemia is almost uniformly present when there is a hemodynamically significant PE. **Hemodynamically PE** = unstable **PE** ("massive" **PE**).

[25] Due to hyperventilation.

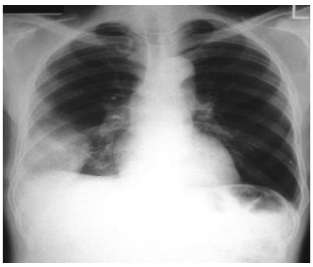
2-Chest X-ray (CXR)[26],[27]: here

So you will see (1) atelectasis (2) plural effusion yet not common (3) Plural based opacity.

- **Massive EP:** Usually normal, but sometimes there are **oligaemia and dilatation (enlargement) of the pulmonary artery**[28]**.**

- **Small/medium PE:** here
  - **linear shadow (opacity)**→ "refers to previous scars", and **Atelectasis,**
  - **Hampton's hump**[29] (pleural based peripheral **Wedge shaped** opacity due to infarction[30]) **and Westermark's sign** (focal peripheral hyperlucency 2ry to regional **oligaemia**), both are **rarely seen,**
  - signs of **pleural effusion**: blunted costophrenic angle,
  - **Raised hemidiaphragm.**[31]

- **Multiple recurrent PE:** may be **Normal**, but sometimes there might be:
  - Enlarged pulmonary artery trunk,
  - Enlarged heart, prominent right ventricle
  - Oligemic lung.



E.g. of CXR showing pulmonary infarction in right lower lobe:

A patient had **low-grade fever**, **hemoptysis**, and **pleuritic chest pain. ventilation-perfusion scan** was done and the read shows **high probability** for pulmonary embolism.

On CXR: A signifies pulmonary infarction in the right lower lobe seen as A **pleural-based density** in the lower lobe with the convexity directed toward the hilum **"Wedge shaped"**

- **This sign is also known as ? "Hampton's hump."**

---

[26] usually **Normal. so it's Not diagnostic,** but it is the most useful in **excluding alternative diagnoses, e.g.** pneumonia or pneumothorax

[27] You may see some ischemic changes. However Normal appearances in a symptomatic patient should raise the suspicion of PE, as should bilateral changes in a patient presenting with unilateral pleuritic chest pain

[28] Fleischner sign

[29] E.g. Pleural-Pulmonary opacities.

[30] **Infarction is not usual in PE..WHY?**
The Lung has: 1- **Dual blood supply**: intercostal arteries & bronchial artery (which comes from the systemic circulation, from the aorta). 2- **lower Oxygen consumption** than that in the heart.

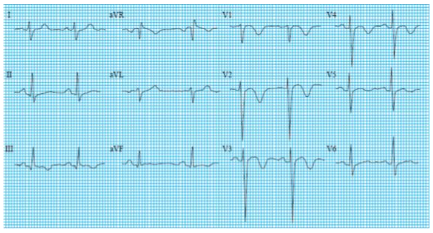
[31] Atelectasis elevate the diaphragm.

3. ECG[32],[33]:

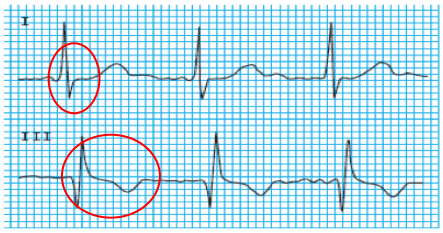
- **Massive EP[34]:**

- The 'classic' ECG pattern (S_1 , Q_3, T_3 anterior T-wave inversion[35])[36] is rare and it's only suggestive NOT diagnostic
- Right Bundle Branch Block (RBBB).

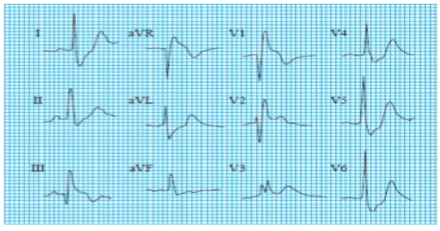
- **small/medium PE: sinus tachycardia.**



T-wave inversion



S_1, Q_3, T_3 pattern

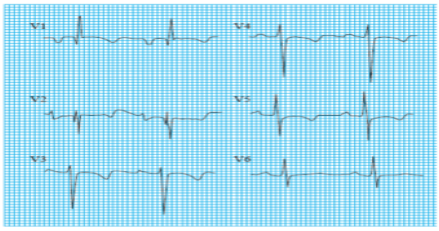


Right Bundle Branch Block (RBBB).

- S wave (Lead I), **Narrowed QRS** (incomplete right bundle branch block.), **Wide QRS** (Complete bundle branch block.)

- Normal duration of QRS = 0.02

right



ventricular strain

- **Multiple recurrent PE:**

can be **NORMAL** or show signs of:

- **Pulmonary hypertension,**
- **RV hypertrophy and strain.**

---

[32] Non-specific findings.

[33] often **Normal,** but is useful in **excluding alternative diagnoses**, E.g. Acute myocardial infarction and pericarditis.

[34] These findings are an evidence of right ventricular strain due to larger emboli

[35] Due to Ischemic changes (Right side is dilated).

[36] The number represent the number of lead where u can see the change.

4. D-dimer[37]: here

- fairly sensitive test (90% to 98%) with low Specificity.
- An **elevated** D-dimer is of limited value, as it may be raised in a variety of conditions including PE.[38] (**negative**, you can rule out a clot/PE. but if it is **positive**, this does not help you.)
- If results are **NORMAL OR LOW** (< 500 ng/mL, measured by ELISA) and **clinical suspicion (risk) is low**, have a high negative predictive value **(PE is very unlikely)** and further investigation is usually unnecessary
- **Disregarded** the result if it is **NORMAL** in **high-risk patients,** and further investigation is mandatory even.[39]

5. Spiral CT pulmonary angiography (CTPA):

Helical (spiral) computed tomography scan of the chest with IV contrast[40], **is the first-line diagnostic test** + **Has replaced V/Q scan.**

- **Its advantages:**

- have a sensitivity of **83%** and specificity of **96%**, with a positive predictive value of **92%**.[41]
- Visualizing the distribution and extent of the emboli[42],
- Highlighting an alternative diagnosis[43],

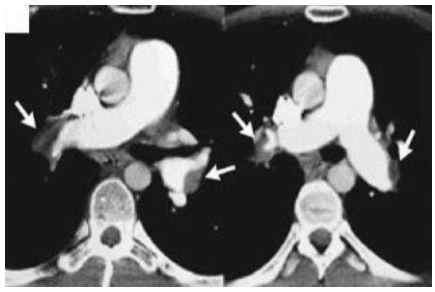
- **Its disadvantages:**

- As the contrast media may be **nephrotoxic**, care should be taken in patients with renal impairment,
- Should be avoided in those with a history of **allergy** to iodinated contrast media.

★ **In combination with clinical suspicion, guides treatment:**

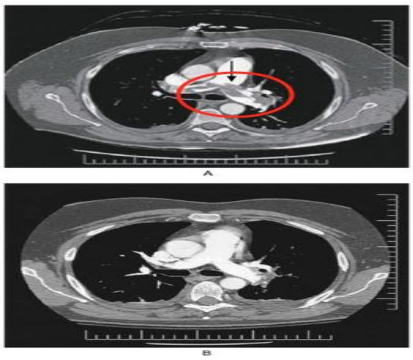
- Data suggest that a **negative Spiral CT** is an adequate criterion for excluding PE in patients with a **non-high clinical probability of PE.**
- If **negative** with **high** clinical probability (there is a 5% incidence of PE) so, do V\Q scan.

What if there wasn't a CT?
Treat with your clinical suspicion, start with anticoagulation & do the CT when it available (Stop the anticoagulation if negative).



P.E before treatment:
saddle clot

After treatment with thrombolytics



[37] is a specific degradation product released into the circulation when cross-linked fibrin undergoes endogenous fibrinolysis, levels can be elevated in patients with PE and DVT.

[38] Any cause of clot or increased bleeding can elevate the d -dimer level. E.g. myocardial infarction, CHF, pneumonia, sepsis and postoperative.

[39] Other circulating markers that reflect right ventricular micro-infarction, such as troponin I and brain natriuretic peptide, are under investigation.

[40] Dark color = clot.

[41] **increased by simultaneous visualization of the femoral and popliteal veins.**

[42] Can visualize very small clots (as small as 2 mm)

[43] E.g. consolidation, pneumothorax or aortic dissection.

6. Color Doppler ultrasound of the leg veins:

Remains the investigation of choice in patients with suspected **DVT**[44] (performed for the detection of **clots in pelvic or iliofemoral veins**) but can be used in patients with **suspected PE**[45].

- **Interpretation of results:**

1. If there is **a positive result,** treat with **IV anticoagulation** (heparin); treatment of DVT is the same as for PE.
   - Keep in mind that with this approach, a false positive ultrasound will result in anticoagulation of some patients who do not have DVT or PE. Also, a negative result is not helpful, as patient may still have a PE despite no DVT on ultrasound.

2. This test is very helpful when positive, but of **little value when negative** (negative results occur in 50% of patients with proven PE).

7. Ventilation-perfusion lung scan (V/Q):

- Traditionally, this **was** the **most common** test used when PE is suspected, but it has been replaced by helical CT as the initial study of choice.[46]

- Plays an important role in diagnosis when there is a **contraindication to helical CT** (spiral CT scan) or in centers which are inexperienced in performing helical CT scans:
  - Radiation is much less than the CT safer in pregnancy,
  - May be particularly useful when the chest x-ray is clear and when there is no underlying cardiopulmonary disease.
  -

- To know how it performed see here: investigation of lung diseases , but in short:

1. Patient will **inhale radioactive** → take a photo →OK all the areas are **ventilated** now.

2. Then they give them **I.V contrast** → see if there is match or mismatch*.

*If area is ventilated but not perfused → **mismatch** (clot). (Remember for the results to be useful we need a healthy lung to start with, if a patient is already diagnosed with COPD the lung is destroyed so the V/Q is not helpful)

[44] Not PE

[45] particularly if there are clinical signs in a limb, as many will have identifiable proximal thrombus in the leg veins.

[46] WHY we stop using it in the same way that we used to do? Because: it is Time consuming, requires patient cooperation and it is Not available (in all hospitals).

- **Interpretation of results:** can be either **NORMAL**, **low-probability, intermediate probability, or HIGH-PROBABILITY** (treatment guidelines based on PIOPED study):

Prospective investigation of pulmonary embolism diagnosis results

Scan category	PE present	PE absent	PE uncertain	No angiogram	Total
High probability	102	14	1	7	124
Intermediate probability	105	217	9	33	364
Low probability	39	199	12	62	312
Near normal or normal	5	50	2	74	131
Total	251	480	24	176	931

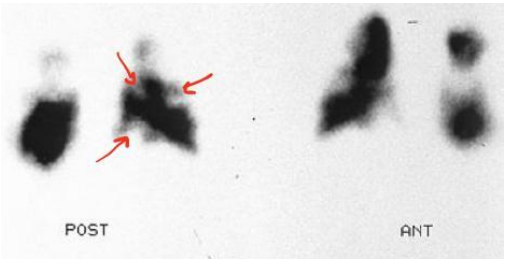
- A **NORMAL** V/Q scan virtually rules out PE,**no** further testing is needed, **but** a scan is almost **never "normal" in anyone**.

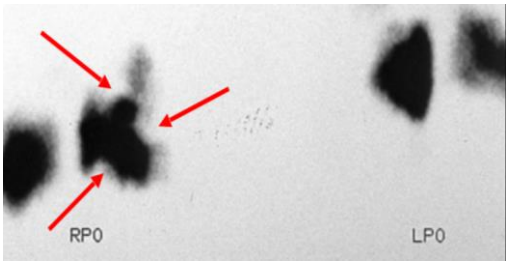
- A **HIGH PROBABILITY** V/Q scan confirms PE very high sensitivity for PE; **treat with heparin.**
- If there is **low or intermediate probability,** we need to do further tests:

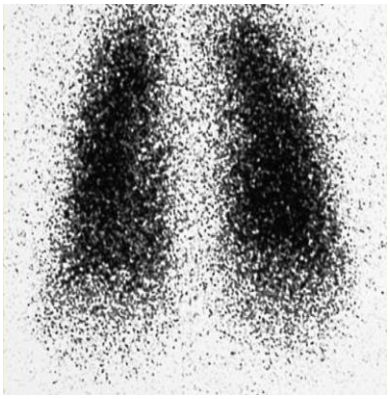
- **clinical suspicion** determines the next step:

  ★ If **clinical suspicion is high**, → **pulmonary angiography** is indicated. Alternatively, perform a **lower extremity duplex ultrasound** to avoid pulmonary angiography.
  - If the **duplex is positive**, treatment for DVT is the same as for PE[47].
  - If the **duplex is negative/uncertain**, then pulmonary angiography is indicated to exclude PE.

Pic: High-probability ventilation-perfusion scan. The arrows show defects/mismatch →







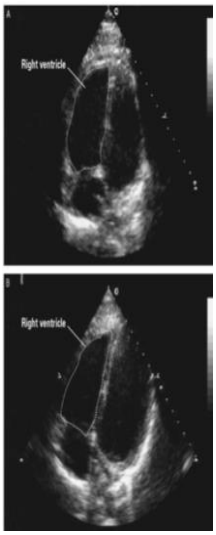
[47] It will be discussed later.

8. Bedside echocardiography:

extremely **helpful in the differential diagnosis**[48] and assessment of acute circulatory collapse.

★ In massive PE:

- **Acute dilatation of the right heart** is usually present,
- A clot in the right ventricular outflow tract. May be visible,
- Vigorously contracting left ventricle.



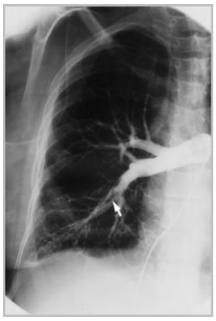
Pic: Trans esophageal Echo: One of the investigations that we use in ICU patients.
A-before treatment
B- after treatment

9. Conventional pulmonary angiography:

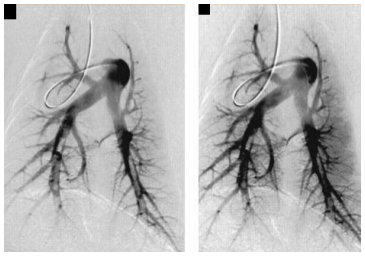
It is the is the gold standard test in detecting PE, but it has been largely suspended by CTPA[49] **or MRI.**

- Definitively diagnoses or excludes P.E but **is invasive**[50]**.**
- **Contrast** injected into pulmonary artery branch after percutaneous **catheterization** of femoral vein.
- The diagnosis is confirmed by persistent filling defect or abrupt cut-off of flow.

◆ Consider when:
noninvasive testing is equivocal, and risk of anticoagulation is high, or if the patient is hemodynamically unstable and embolectomy may be required.

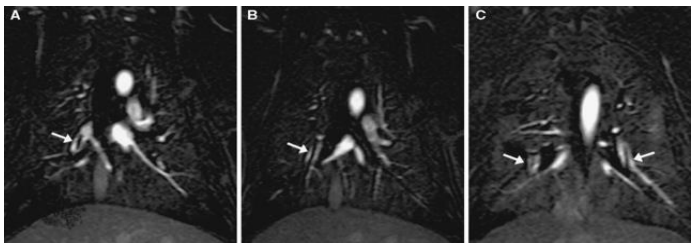


Pic: **Abrupt cut-off of flow** to the right and left upper lobe vessels is seen in this patient.



10. MR imaging: here

CT is better, but MR imaging can be used if CT angiography is contraindicated.



[48] E.g. left ventricular failure, aortic dissection and pericardial tamponade, can also be identified.
[49] but is still useful in selected settings or to deliver catheter-based therapies.
[50] Angiography is rarely performed because it carries a 0.5% mortality.

★ Treatment:

- **General measures:**

Start treatment immediately in high suspicion you don't need to confirm the PE.

★ **All patients should receive high-flow oxygen (60-100%)[51] to correct hypoxemia.** Patients with pulmonary infarcts require bed rest and analgesia[52].

★ Circulatory shock[53] should be treated with intravenous fluids or plasma expander[54], but inotropic agents[55] are of limited value.

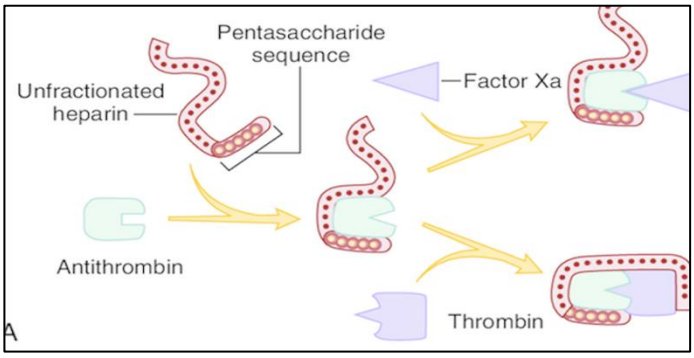
○ Anticoagulation:[56]

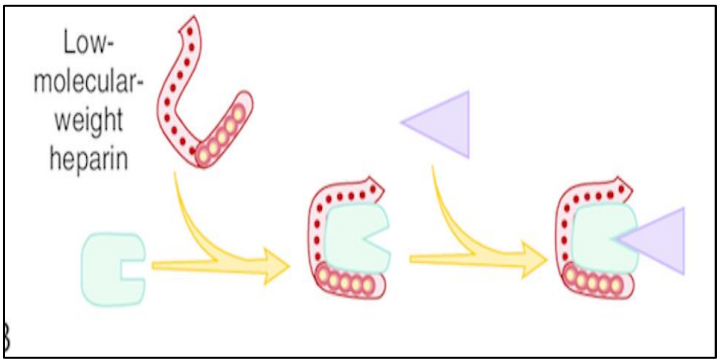
Anticoagulation should be commenced immediately in patients with a high or intermediate probability of PE[57]

★ Acute anticoagulation therapy with **HEPARIN** (either unfractionated or low-molecular-weight) **to prevent another PE.**

- Heparin acts by promoting the action of antithrombin III.
- The dose is based on the patient's weight.
- should continue for **at least 5 days** (usually continued for 5–7 d), during which time an oral anticoagulant is commenced.
- **Platelet count** should be monitored at **least every 3 d** during initial heparin therapy[58],
- **Therapeutic APTT** should correspond to plasma heparin level of **0.2–0.4 IU/mL**.
- After initiating heparin therapy, **repeat APTT every 6 h** for first 24 h and then **every 24 h** when therapeutic APTT is achieved **(The goal is an APTT of 1.5 to 2.5 times control).**

*Extra pictures





[51] unless they have significant chronic lung disease.
[52] should be used with caution in the hypotensive patient.
[53] very ill patients will require care on the intensive therapy unit.
[54] Diuretics and vasodilators should also be avoided, as they will reduce cardiac output.
[55] As the hypoxic dilated right ventricle is already close to maximally stimulated by endogenous catecholamines. Even that, sometimes they're required improve the pumping of the right heart are sometimes required.
[56] (Anticoagulation (Heparin\warfarin) prevents further clot formation but does not lyse existing emboli or diminish thrombus size.)Thrombolytics = dissolve already formed.
[57] may be safely withheld in those with low clinical probability, pending investigation.
[58] Due to HIT syndrome

- **Oral anticoagulant (WARFARIN[59] – a vitamin K antagonist –)** is usually begun immediately and the heparin is tapered off as the oral anticoagulant becomes effective

  -**Heparin** can be stopped[60] after 4–5 d of **warfarin** therapy when **INR is in 2.0–3.0 range** for at least 24 hours.
- **Warfarin 5 mg/d** can be started on **day 1 of therapy;** there is no benefit from higher starting doses.
- Oral anticoagulants are **continued for 6 weeks to 6 months,** depending on the likelihood of recurrence of venous thrombosis or embolism. In some situations, such as after **recurrent embolism**, lifelong treatment is indicated.
- Regular measurement of the INR is required throughout the duration of anticoagulation.

Drugs that decrease warfarin requirement	Drugs that increase warfarin requirement
Phenylbutazone	Barbiturates
Metronidazole	Carbamazepine
Trimethoprim-sulfamethoxazole	Rifampin
Amiodarone	Penicillin
Second- and third-generation cephalosporins	Griseofulvin
Clofibrate	Cholestyramine
Erythromycin	
Anabolic steroids	
Thyroxine	

Why?

1-narrow therapeutic index of warfarin and

2- its propensity to **interact with other drugs** and food

(table: Important drug interactions with warfarin: you don't have to memorize it).

We start the patient on both heparin and warfarin, because heparin has fast onset and will provide immediate results while the warfarin will take 3 to 4 days to start it effect. And then when we measure the INR and it's in the therapeutic range we stop the heparin and continue with the warfarin.

- ★ **NOAC:**
- ★ **Non-vitamin K-dependent New Oral Anticoagulants**
- ★ **Dabigatran**
- ★ **Rivaroxaban**
- ★ **Apixaban**
- ★ **Endoxaban**

[59] Newer thrombin or activated factor X inhibitors offer more predictable dosing and have no requirement for coagulation monitoring; they may ultimately replace warfarin. here

[60] LMWH should be continued for at least 6 months before switching to warfarin in patients with cancer associated VTE.

★ Complications of anticoagulation:

	Complication	Management
Heparin	**Bleeding**	- Stop heparin infusion. - in **severe bleeding**, the anticoagulant effect of heparin can be reversed with **IV protamine sulfate 1 mg/100 units of heparin bolus** or 0.5 mg for the number of units given by constant infusion over the past hour[61]; provide supportive care including transfusion and clot evacuation from closed body cavities as needed.
	Heparin-induced thrombocytopenia and thrombosis[62] Also called HIT syndrome	- Carefully **monitor platelet count during therapy.** (after 3 days of initiating therapy and repeat it after 6 days) - Stop-heparin for platelet[63] counts **<75,000**. - Replace heparin with **direct inhibitors of thrombin**-like **desirudin** if necessary. These agents do not cause heparin-induced thrombocytopenia. Avoid platelet transfusion because of the risk for thrombosis.
	Heparin-induced osteoporosis (therapy >1 mo)	**LMWHs** may have **lower propensity** to cause osteoporosis as compared with **unfractionated heparin**; consider LMWH if prolonged heparin therapy is necessary.
Warfarin	**Bleeding**	- Stop therapy. - **Administer vitamin K and fresh-frozen plasma** for **severe bleeding**; provide supportive care including transfusion and clot evacuation from closed body cavities as needed.
	Skin necrosis (rare)	Supportive care.
	Teratogenicity	Do not use in pregnancy or in patients planning to become pregnant.

[61] Fractionated > ⬇ half-life. LMW > ⬆ half-life > predicted dose response

[62] idiosyncratic reaction: Immune , Not dose dependent.

[63] We measure the platelets because if there are clots being formed the platelets will be used up and their number will decrease

○ Approved thrombolytics for pulmonary embolism:[64]

★ **Recombinant tissue-plasminogen activator: Thrombolytics = dissolve already formed**

100 mg as a continuous peripheral intravenous infusion administered **over 2 h**

★ **Streptokinase:**

250,000 IU as loading dose **over 30 min**, followed by 100,000 U/h **for 24 h**

★ **Urokinase:**

4400 IU/kg as a loading dose **over 10 min**, followed by 4400 IU/kg/h **for 12-24 h.**

◆ Indications:

- Hemodynamically unstable patient (in shock).[65]
- Hypoxia on 100% oxygen
- Right ventricular dysfunction by echocardiography (thrombolysis can reverse this).

◆ Contraindications:

Relative:

- **Recent surgery** within **last 10 d** or **Previous arterial punctures** within **10 d,**
- **Neurosurgery** within **6 months** ,
- **Ophthalmologic surgery** within **6 weeks ,**
- **Bleeding disorder** (thrombocytopenia, renal failure, liver failure)[66],
- **Hypertension** >**200 mmHg systolic** or **110 mmHg diastolic ,**
- **Placement of central venous catheter** within **48 h,**
- **Hypertensive retinopathy** with **hemorrhages** or **exudates Intracerebral aneurysm** or **malignancy,**
- **Cardiopulmonary resuscitation** within **2 weeks,**
- **Cerebrovascular disease,**
- **Major internal bleeding** within the **last 6 months**,
- **Pregnancy** and the **1st 10 days postpartum,**
- **Infectious endocarditis** or **Pericarditis,**
- **Severe trauma** within **2 months,**

Absolute:

- **Active internal bleeding**

We only give thrombolytic to patients with MASSIVE PE and SHOCK. We don't use it with other patients because there is no evidence that it improves survival or outcome, in fact it increases risk of bleeding, but in massive PE the benefits outweigh the outcome because the patient may die without it.

---

[64] **MASSIVE PE = THROMBOLYTICS ,**Speeds up the lysis of clots. There is no evidence that thrombolysis **improves mortality** rates in patients with PE. Therefore, **its use is not well defined at this point**.

[65] (Patients with massive PE with persistent hypotension).

[66] patients must be screened carefully for haemorrhagic risk, as there is a high risk of intracranial haemorrhage.

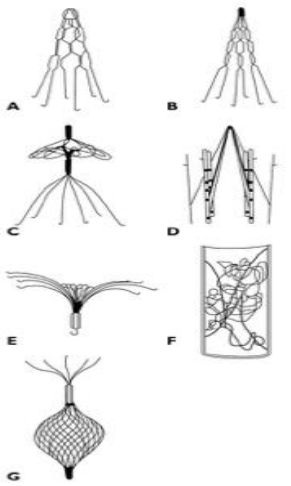
○ Other Treatment Modalities[67]:

★ Surgical embolectomy,

★ Percutaneous catheter-directed treatment[68]:

◆ **Various inferior vena caval (IVC) filters:**

- Use has become more common but reduction in mortality has not been conclusively demonstrated.
- Patients who have IVC filter placed are at higher risk of recurrent DVT (but lower risk of recurrent PE).



● **Indications of IVC include:**

- **Anticoagulation contraindicated** (eg, patients with multiple trauma, active bleeding)
- **Failure of antithrombotic therapy**
- **Complications from anticoagulant** therapy preclude further use
- **Prophylaxis against embolism** from preexisting DVT in patients with poor cardiopulmonary reserve or in patients at high risk to develop DVT.
- Patients with **recurrent PE** undergoing thromboendarterectomy.

● **Complications of IVC filter placement (rare):**

- filter migration or misplacement,
- filter erosion and perforation of IVC wall, and IVC obstruction due to filter thrombosis.

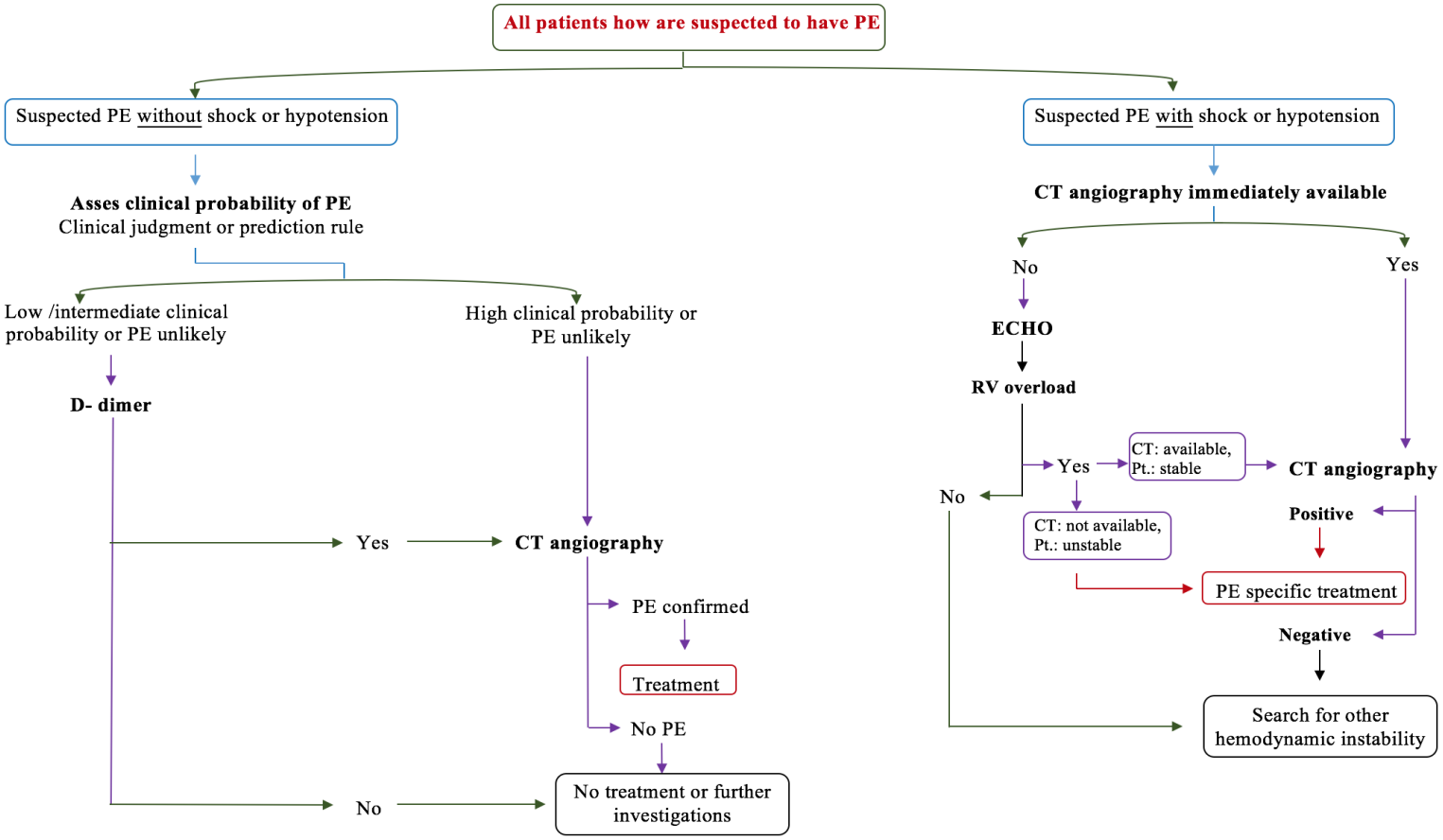
[67] If thrombolytics have failed, this is rescue therapy

[68] Either they suck it or fragment it. (you don't have to know the details this is only to complete the topic)

Conclusions

- PE is common and under-recognized serious medical problem.
- Early diagnosis and treatment are essential for good outcome
- High index of suspicion is needed in high risk patients.

In case of massive (unstable) embolus: You go directly to spiral CT: (A) if it was + treat with thrombolytics and antimutagens. (B) if it was – it's not PE and you have to look for other cause. If you couldn't do spiral CT go for echo to look for RV overload.



- **Features of pulmonary thromboembolism/infarction on chest X-ray**

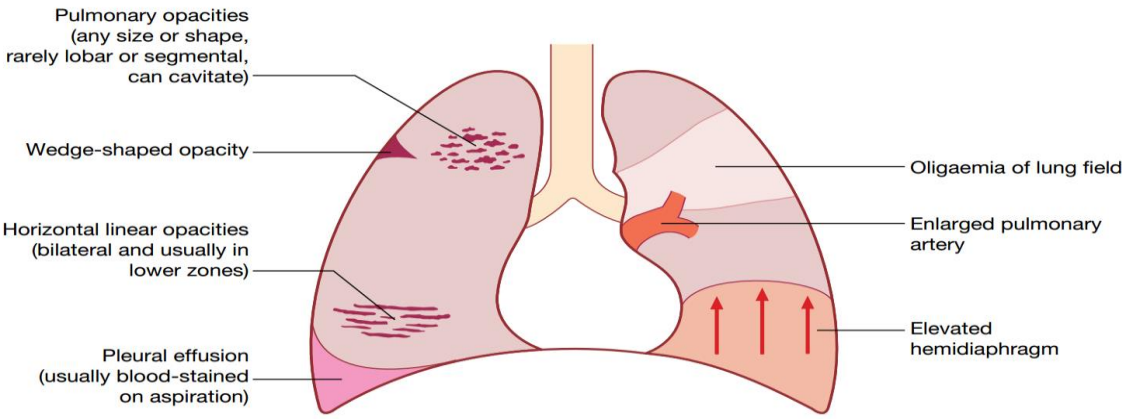


Fig. 19.67 Features of pulmonary thromboembolism/infarction on chest X-ray.

- **Sensitivity of spiral CT, MRI angiography, real-time MRI angiography, for detecting pulmonary emboli:**

Reader	CT	MRA	RT-MRA
1	72.1	79.1	97.7
2	69.8	81.4	97.7
Mean	71.0	80.3	97.7
K	0.86	0.84	1

Am J Respir Crit Care Med 2003

D- dimer assay:

PE

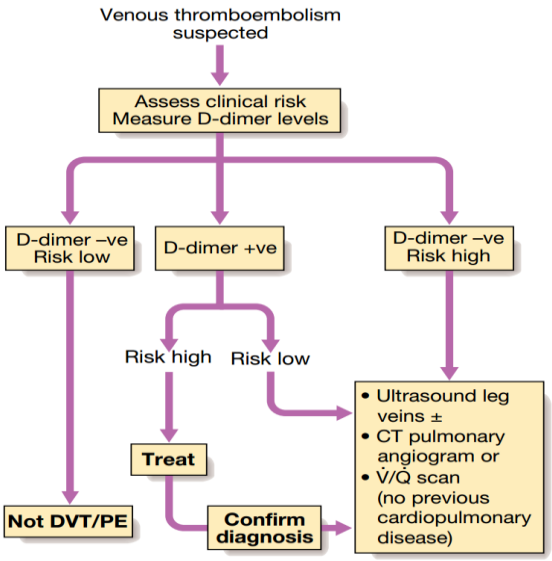


Fig. 19.68 Algorithm for the investigation of patients with suspected pulmonary thromboembolism. Clinical risk is based on the presence of risk factors for venous thromboembolism and the probability of another diagnosis.

- CXR findings in patients with

Chest radiographic findings in patients with pulmonary embolism

	COPD, % (n= 21)	No prior cardiopulmonary disease, % (n= 117)
Atelectasis or pulmonary parenchymal abnormality	76	68
Pleural effusion	52	48
Pleural-based opacity	33	35
Elevated diaphragm	14	24
Decreased pulmonary vascularity	38	21
Prominent central pulmonary artery	29	15
Cardiomegaly	19	12
Westermark's sign*	5	7
Pulmonary edema	14	4

Summary

1. Pulmonary embolism is a medical emergency
2. Diagnosis of DVT or PE is an indication for treatment
3. Lower extremities are the main source of emboli.
4. In severe cases acute cor pulmonale may result
5. Clinical symptoms become more overt as the size of dead space in lung increases.
6. Symptoms of PE are not specific.
7. Most often PE is silent.
8. Dyspnea, pleuritic chest pain , tachypnea are the most common manifestations.
9. Recurrences are common.
10. Spiral CT is the test of choice in diagnosing PE.
11. DVT is diagnosed by ultrasound and clinical suspicion.
12. V/Q scan plays an important role in diagnosing PE if spiral CT is contraindicated.
13. Pulmonary angiography can make a definite diagnosis but, it is invasive.
14. Start therapeutic heparin as initial treatment. Also start warfarin at the same time.

19.94 Risk factors for venous thromboembolism

Surgery	
• Major abdominal/pelvic surgery	• Post-operative intensive care
• Hip/knee surgery	
Obstetrics	
• Pregnancy/puerperium	
Cardiorespiratory disease	
• COPD	• Other disabling disease
• Congestive cardiac failure	
Lower limb problems	
• Fracture	• Stroke/spinal cord injury
• Varicose veins	
Malignant disease	
• Abdominal/pelvic	• Concurrent chemotherapy
• Advanced/metastatic	
Miscellaneous	
• Increasing age	• Thrombotic disorders (p. 1054)
• Previous proven VTE	• Trauma
• Immobility	

24.17 Factors predisposing to venous thrombosis

Patient factors	**Haematological disorders**
• Increasing age	• Pregnancy/puerperium
• Obesity	• Oestrogen-containing oral contraceptives and HRT
• Varicose veins	• Immobility, e.g. long-distance travel (> 4 hrs)
• Previous DVT	• IV drug use (femoral vein)
• Family history, especially of unprovoked VTE when young	
Surgical conditions	
• Major surgery, especially if > 30 mins' duration	
• Abdominal or pelvic surgery, especially for cancer	
• Major lower limb orthopaedic surgery, e.g. joint replacement and hip fracture surgery	
Medical conditions	
• Myocardial infarction/heart failure	• Pneumonia
• Inflammatory bowel disease	• Neurological conditions associated with immobility, e.g. stroke, paraplegia, Guillain–Barré syndrome
• Malignancy	
• Nephrotic syndrome	

- **Haematological disorders**
  - Polycythaemia rubra vera
  - Essential thrombocythaemia
  - Deficiency of anticoagulants: antithrombin, protein C, protein S
  - Paroxysmal nocturnal haemoglobinuria
  - Gain-of-function prothrombotic mutations: factor V Leiden, prothrombin gene *G20210A*
  - Myelofibrosis
- **Antiphospholipid syndrome**
  - Lupus anticoagulant (more strongly associated with thrombosis than anticardiolipin antibodies)
  - Anticardiolipin antibody

19.93 Features of pulmonary thromboemboli

	Acute massive PE	Acute small/medium PE	Chronic PE
Pathophysiology	Major haemodynamic effects: ↓cardiac output; acute right heart failure	Occlusion of segmental pulmonary artery → infarction ± effusion	Chronic occlusion of pulmonary microvasculature, right heart failure
Symptoms	Faintness or collapse, crushing central chest pain, apprehension, severe dyspnoea	Pleuritic chest pain, restricted breathing, haemoptysis	Exertional dyspnoea. Late symptoms of pulmonary hypertension or right heart failure
Signs	Major circulatory collapse: tachycardia, hypotension, ↑JVP, RV gallop rhythm, loud P_2, severe cyanosis, ↓urinary output	Tachycardia, pleural rub, raised hemidiaphragm, crackles, effusion (often blood-stained), low-grade fever	May be minimal early in disease. Later: RV heave, loud P_2. Terminal: signs of right heart failure
Chest X-ray	Usually normal. May be subtle oligaemia	Pleuropulmonary opacities, pleural effusion, linear shadows, raised hemidiaphragm	Enlarged pulmonary artery trunk, enlarged heart, prominent right ventricle
ECG	$S_1Q_3T_3$ anterior T-wave inversion, RBBB	Sinus tachycardia	RV hypertrophy and strain
Arterial blood gases	Markedly abnormal with ↓PaO_2 and ↓$PaCO_2$. Metabolic acidosis	May be normal or ↓PaO_2 or ↓$PaCO_2$	Exertional ↓PaO_2 or desaturation on formal exercise testing
Alternative diagnoses	Myocardial infarction, pericardial tamponade, aortic dissection	Pneumonia, pneumothorax, musculoskeletal chest pain	Other causes of pulmonary hypertension

(JVP = jugular venous pressure; PE = pulmonary embolism; RBBB = right bundle branch block; RV = right ventricular)

Questions

1. **Which of the following is the best diagnostic test for pulmonary embolism?**
    A. V/Q Scan
    B. Spiral CT
    C. CXR
    D. D-dimer

2. **In which type of P.E are thrombolytics indicated?**
    A. Massive P.E
    B. Acute small P.E
    C. Acute medium P.E
    D. Chronic P.E

3. **Which of the following is a risk factor for P.E?**
    A. Local anesthesia
    B. Congestive heart failure
    C. Infective endocarditis
    D. Analgesics

4. **Patient presents to the ER complaining of dyspnea, chest pain and mild hemoptysis. HR and BP are normal, D-dimer was positive and CT confirmed pulmonary embolism. What is the appropriate next step in management?**
    A. Give O2 and I.V steroids
    B. Give analgesic and discharge
    C. Start patient on heparin
    D. Take for emergency cardiac surgery

5. **A pregnant lady presented to the ER with mild chest pain and was diagnosed to have P.E. Which of the following medications is contraindicated for her?**
    A. Warfarin
    B. Heparin
    C. Aspirin
    D. Paracetamol

6. **A patient complained of mild chest pain, and shortness of breathing during inspiration. He was diagnosed with PE. What is the most likely source of the embolus?**
    A. Renal arteries
    B. Upper extremities
    C. Lower extremities
    D. Axilla

7. **Which of the following have the greatest risk for PE?**
    A. DVT above the knee.
    B. DVT below the knee.
    C. Renal artery thrombus.
    D. Normal delivery in healthy woman**.**

8. **A lady in her late 50s is having recurrent PE for the last 18 months. Which of the following is most probably true about this patient.**
    A. She's on oral contraceptives to control pregnancy.
    B. Recurrent PE is due to her advanced age.
    C. Recent lower limb injury with major surgery fixation.
    D. She could have malignancy somewhere.

9. **A 29-year-old male known diabetes and dyslipidemia. He presented to the ER with sudden SOB for the last 2 hours. Patient's body temperature is 40.2 and on physical examination there's track marks which suggest that the patient is a drug abuser. The patient was diagnosed with PE. What is the most likely source of the embolus?**
    A. Fat embolism due to long bone fracture.
    B. DVT due to sedentary life style.
    C. Air embolism due to trauma.
    D. Septic embolism due to septicemia.

10. **Which of the following is right regarding the treatment of PE?**
    A. Circulatory shock should be treated with inotropic agents.
    B. All patients with PE should receive high flow oxygen.
    C. Heparin is better than NOAC.
    D. Warfarin can be stopped after 4-5 days of Heparin therapy initiation**.**

11. **Which of the following is NOT true regarding PE?**
    A. Early diagnosis and treatment will not affect prognosis.
    B. PE is common and under-recognized serious medical problem.
    C. High index of suspicion is needed in high risk patients. Acute massive PE leads to hemodynamic instability.

Answers: 1. B 2.A 3.B 4. C 5. A 6. C

7.A 8.D 9.D 10.B 11.A