"He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all."
William Osler

Medicine

430

Pulmonary Embolism

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Team Notes
Lecture recording
Davidson's 21th

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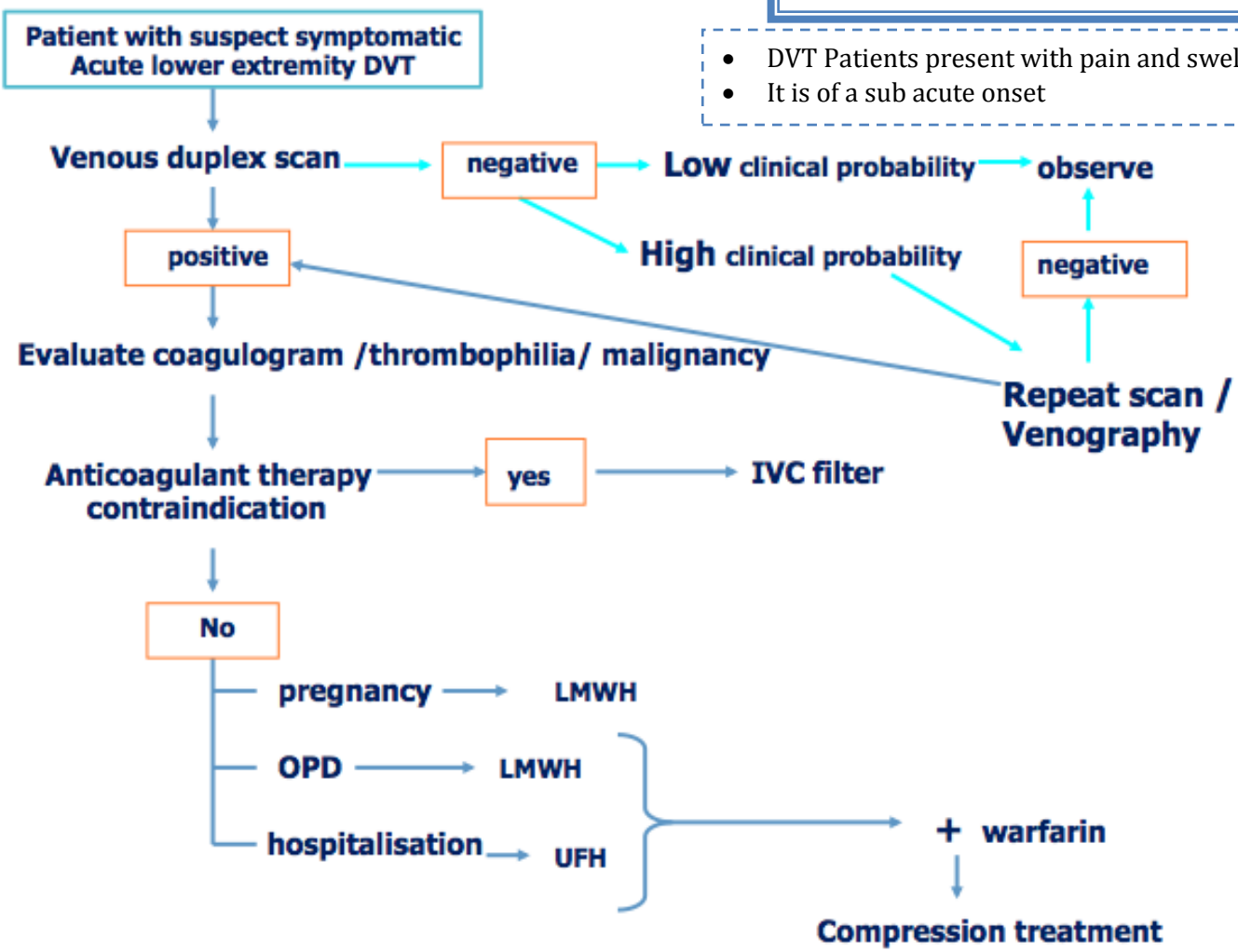
Deep Venous Thrombosis (DVT)

Most Pulmonary embolisms come from DVTs

- DVT Patients present with pain and swelling.
- It is of a sub acute onset



Thrombophilia screening, Factor V leiden, Prot C/S deficiency and Antithrombin III deficiency: (They increase the risk of thrombosis, and you suspect them when your patient has these predispositions)

- Idiopathic DVT < 50 years
- Family history of DVT
- Thrombosis in an unusual site (upper limb)
- Recurrent DVT

Congenital Risk Factors:

- Factor V laden
- Protein S, Protein C deficiency
- Antithrombin 3 deficiency
- Anti-phospholipid syndrome
- SLE Patients

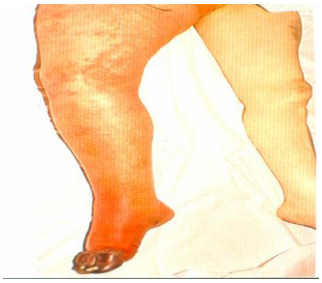
Recommendation for duration of warfarin :

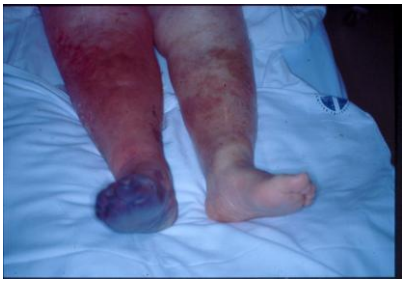
- (3-6) months first DVT with reversible risk factor
- At least 6 months for first idiopathic DVT
- 12 months to lifelong duration of treatment, for recurrent DVT or first DVT with irreversible risk factors (malignancy or thrombophilic state)

Catheter directed-thrombolysis:

- Consider in: Acute < 10 days iliofemoral DVT.
- Long-term benefit in preventing post-phebitic syndrome is unknown

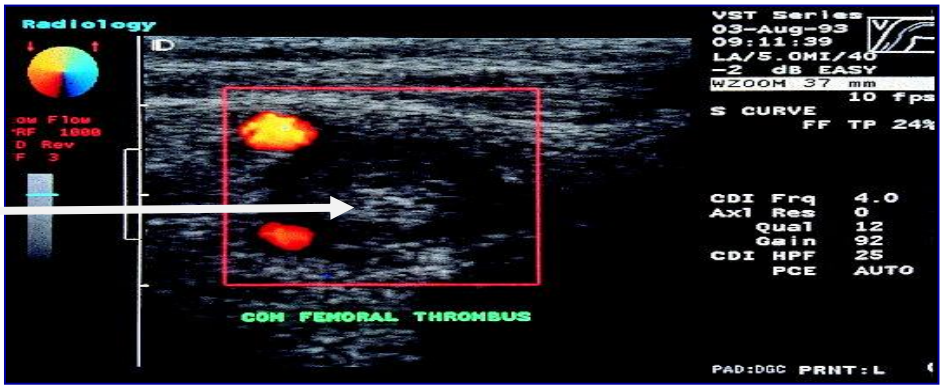
Phlegmasia cerulea dolens
venous gangrene





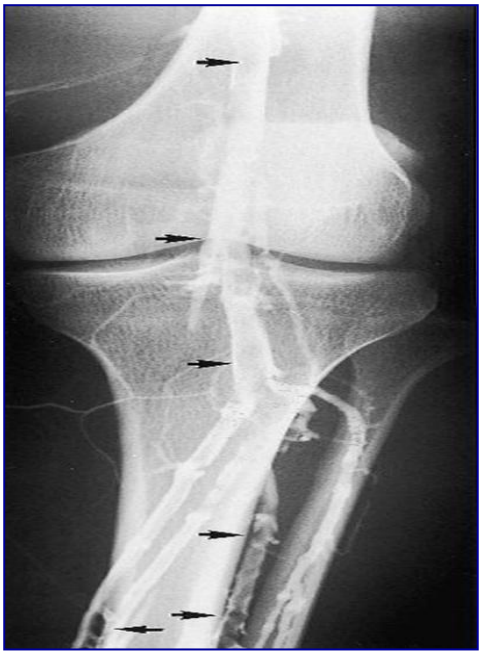
Color duplex scan of DVT.
Color Doppler Ultrasound of leg veins is the investigation of choice in patient with suspected DVT.

This whitish thing is a clot surrounded by the vein.



• Risk factor for venous thrombosis:
- Stasis
- Injury to venous intima
- Alterations in the coagulation-fibrinolytic system

• Source of emboli:
-Deep venous thrombosis (>95%)
-Other veins:
- Renal
-Uterine
-Right cardiac chambers



Venogram showing DVT.
Not needed most of the time!
(Rarely used)

Risk factors for DVT **(very imp to ask in Hx)**
- General anesthesia: sedation, muscle relaxing (atonia)
- Lower limb or pelvic injury or surgery
- Congestive heart failure
- Prolonged immobility
- Pregnancy (VTE is a leading cause of mortality)
- Postpartum
- Oral contraceptive pills
- Malignancy
- Obesity
- Advanced age
- Coagulation problems

Clinical features of PE

- Sudden onset dyspnea.
  - differential diagnosis: pneumothorax, MI, pulmonary edema
- Pleuritic chest pain.
  - Differential diagnosis: pneumonia , pneumothorax , muscular pain
- 3) Hemoptysis
  - Not common in PE but you should consider it.
  - Differential diagnosis: Pulmonary edema, pneumonia , bronchiectasis
- Clinical clues cannot make the diagnosis of PE; their main value lies in suggesting the diagnosis

VTE (venous thromboembolism) is difficult to diagnose, but some points may be helpful in approaching the proper diagnosis by considering the following:
- Is the clinical presentation consistent with PE ?
- Does the patient have risk factors of PE?
- Is there any alternative diagnosis that can explain the patient's presentation?

Clinical presentation of PE varies depending on the size, number, and distribution of emboli, and the underlying cardio-respiratory reserve.
A recognized risk factor is present in between 80% and 90% of patients, the presence of one or more risk factors may multiply the risk

Risk factors of VTE	Examples
Surgery	**- Major abdominal or pelvic surgery** **- Hip / knee surgery** **- post – operative intensive care**
Obstetrics	**- Pregnancy** **- puerperium**
Cardio-respiratory diseases	**- COPD** **-Congestive Heart Failure** **- other disabling disease**
Lower Limb Problems	**- Fracture** **- Varicose Veins** **-stroke / spinal cord injury**
Malignancies	**-abdominal / pelvic** **-advanced / metastatic** **-concurrent chemotherapy**
Miscellaneous	**-increased age, Trauma - Immobility** **-previous proven VTE - Thrombotic Dz**

Signs & symptoms of PE

Signs or symptoms observed in patients with thromboembolism			
		Study	
		Stein et al., % (n= 117)	Anderson et al., % (n= 131)
Pulmonary embolism	Dyspnea	73	77
	Tachypnea	70	70
	Chest pain	66	55
	Cough	37	—
	Tachycardia	30	43
	Cyanosis	1	18
	Hemoptysis	13	13
	Wheezing	9	—
	Hypotension	—	10

Signs or symptoms observed in patients with thromboembolism			
		Study	
		Stein et al., % (n= 117)	Anderson et al., % (n= 131)
Pulmonary Embolism	Syncope	—	10
	Elevated jugular venous pulse	—	8
	Temperature >38.5°C	7	—
	S-3 gallop	3	5
	Pleural friction rub	3	2

Signs or symptoms observed in patients with thromboembolism			
		Study	
		Stein et al., % (n= 117)	Anderson et al., % (n= 131)
Deep vein thrombosis	Swelling	28	88*
	Pain	26	56
	Tenderness	—	55
	Warmth	—	42
	Redness	—	34
	Homan's sign	4	13
	Palpable cord	—	6

Different clinical features:

	Acute Massive PE	Acute Small/medium PE	Chronic PE
Symptoms	Faintness/ collapse/ crushing central chest pain/ apprehension sever dyspnea	Pleuritic chest pain/ restricted breathing/ haemoptysis	Exertional dyspnea/ late symptom of pulmonary hypertension or right heart failure
Signs	Major circulatory collapse: Tachycardia, hypotension, ↑ JVP, right ventricular gallop rhythm, Loud P2, severe cyanosis, ↓ urinary output	Tachycardia, pleural rub, raised hemidiaphragm, crackles, effusion (often blood-stained), low grade fever.	Maybe minimal early in disease. Later: RV heave, Loud P2. Terminal: sign of right heart failure.

Massive Pulmonary Embolism

- 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

- Hemodynamic compromise (shock = hypotension)
- Disregarding the size of the embolus, what induces hypotension is considered Massive

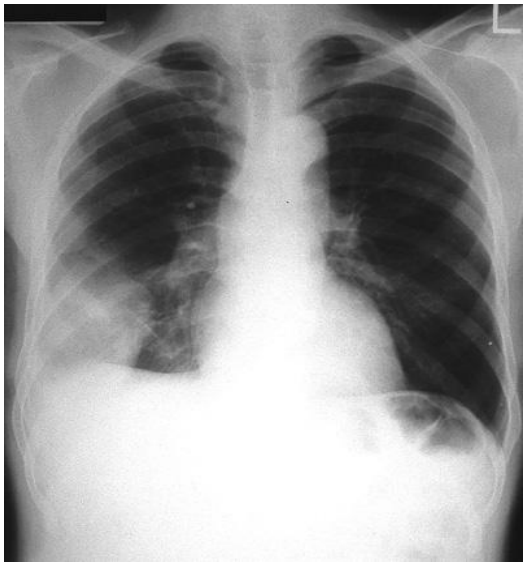
Pathophysiology

- Massive PE causes an increase in PVR (pulmonary vascular resistance, which is normally low) → right ventricular outflow obstruction → decreased left ventricular preload → Decreased CO
- In patients without cardiopulmonary disease, occlusion of 25-30 % of the vascular bed → increase in Pulmonary artery pressure (PAP)
- Hypoxemia ensues → stimulating vasoconstriction → increase in 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

Diagnosis of PE

- CXR
- ABG
- ECG
- V/Q
- Spiral CT
- Echo
- Angio (Gold Standard)
- Fibrin Split Products/D-dimer

CXR (chest X-ray)



- Chest radiograph showing a pulmonary infarct in the right lower lobe.
- This patient had low-grade fever, hemoptysis, and pleuritic chest pain.
- The ventilation-perfusion scan was read as high probability due to the pulmonary embolism.
- A pleural-based density in the lower lobe with the convexity directed toward the hilum signifies pulmonary infarction.
- This sign is also known as Hampton's hump."

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

The chest radiograph is nonspecific for the diagnosis of pulmonary embolism and cannot be used to confirm the diagnosis. The existence of underlying lung disease may also influence the chest radiographic appearance of pulmonary embolism.

ABG (arterial blood gases)

In PE, the patient has Hypocarbia (a state of reduced carbon dioxide in the blood "or hypocapnia") & hypoxemia, sometimes big clots reflect hypercapnia.

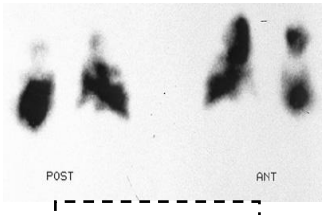
V/Q scans. (ventilation-perfusion scanning) is less commonly used.

The use of ventilation perfusion scan in diagnosing pulmonary embolism		
High Probability	Intermediate probability	Low probability
=2 large segmental (>75% of a segment) perfusion defects without corresponding ventilation or radiographic abnormalities or substantially larger than matching ventilation or radiologic abnormalities or =2 moderate segmental (>25% and <75% of a segment) perfusion defects without matching ventilation or chest radiographic abnormalities plus one large unmatched segmental defect or =4 moderate segmental perfusion defects without matching ventilation or chest radiologic abnormalities	Scans that do not fall into normal, very low, low, or high probability categories	Nonsegmental perfusion defects Or Single moderate mismatched segmental perfusion defect with normal chest radiograph Or Any perfusion defect with a substantially larger abnormality on chest radiograph Or Large or moderate segmental perfusion defects involving no more than four segments in one lung and no more than three segments in one lung region with matching or larger ventilation/radiographic abnormalities Or More than three small segmental perfusion defects (<25% of a segment) with a normal chest radiograph Very low probability Three or fewer small segmental perfusion defects with a normal chest radiograph Normal No perfusion defects present

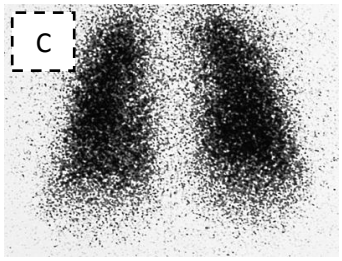
Explanation:
The criteria used for interpreting ventilation-perfusion scans are listed in the schedule above. In patients suspected to have pulmonary embolism, this study is ordered routinely. The perfusion scan is usually performed first. Macroaggregates of albumin labeled with technetium-99m are injected, and images are obtained in anterior, posterior, and right and left lateral and oblique views. If the perfusion scan is normal, there is no need to perform a ventilation scan. Defects in perfusion are assessed and quantified. The ventilation scan is performed by inhalation of a radioactive gas, usually 133 Xe is mixed with air. The patient breathes this radioactive mixture until a state of equilibrium has been reached between the spirometer and lungs, then the patientbreathes room air. Images taken in this wash-out phase are useful in detecting ventilation abnormalities. (Adapted from the PIOPEDInvestigators [14].)

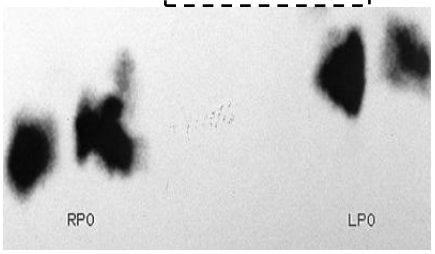
Cont. V/Q

- High-probability ventilation-perfusion scan.
- A and B, Multiple large segmental and subsegmental perfusion defects are seen bilaterally.
- C, The corresponding ventilation image was normal. The patient was treated for pulmonary embolism.



A & B





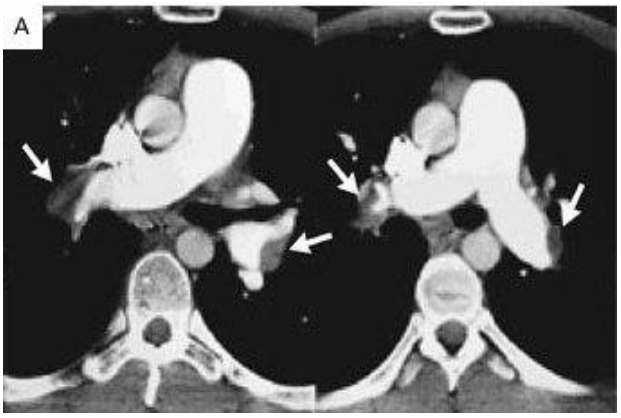
Prospective investigation of pulmonary embolism diagnosis results

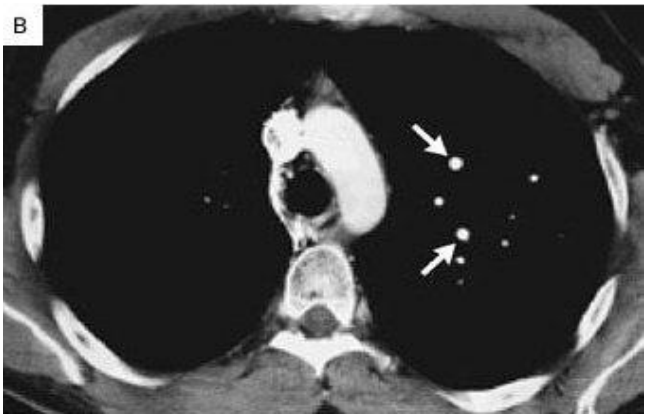
Scan category	PE present	PE absent	PE uncertain	No angiogram	Total
High probability	102	14	1	7	124
Intermediate probability	105	217	9	33	364
Low probability	39	199	12	62	312
Near normal or normal	5	50	2	74	131
Total	251	480	24	176	931

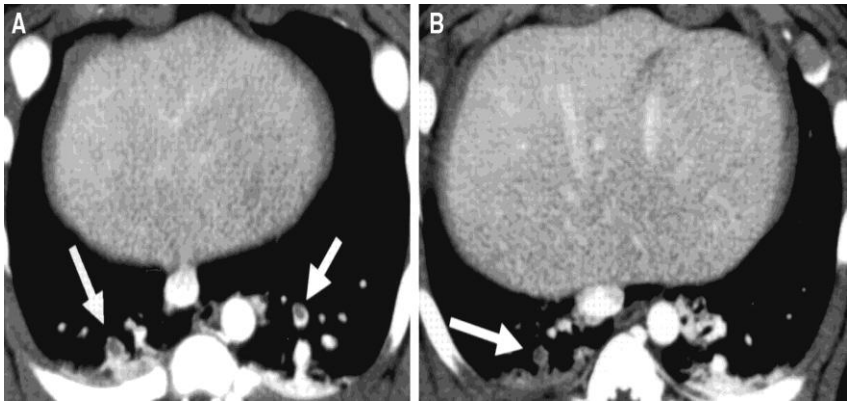
Explanation :

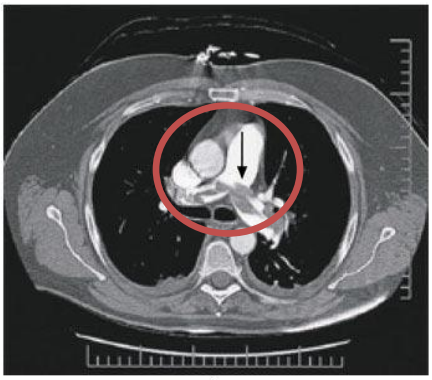
This prospective study was designed to study the accuracy of ventilation-perfusion (õ/õ) scan in the diagnosis of pulmonary embolism. Results of õ/õ scan were compared with pulmonary angiography, which was used as a gold standard. From the results it is obvious that more than two thirds of patients have scans of low or intermediate probability that are nondiagnostic. Although a high-probability scan usually indicates pulmonary embolism, only a minority of patients with pulmonary embolism have a high-probability scan. Near-normal lung scans make the diagnosis of pulmonary embolism very unlikely. (Data from the PIOPED Investigators [14].)

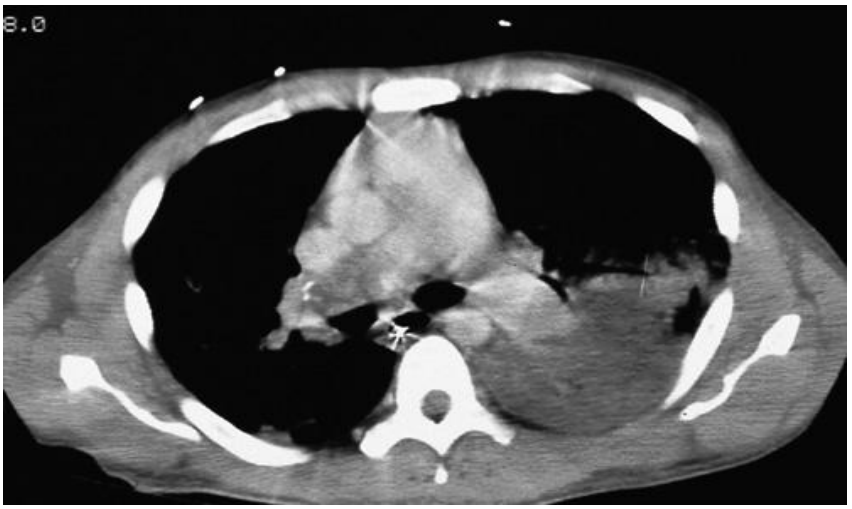
Spiral (Helical) CT (Most commonly used nowadays)

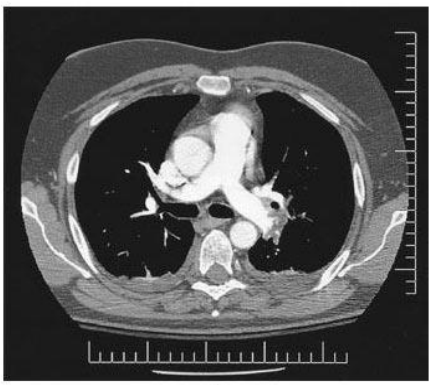








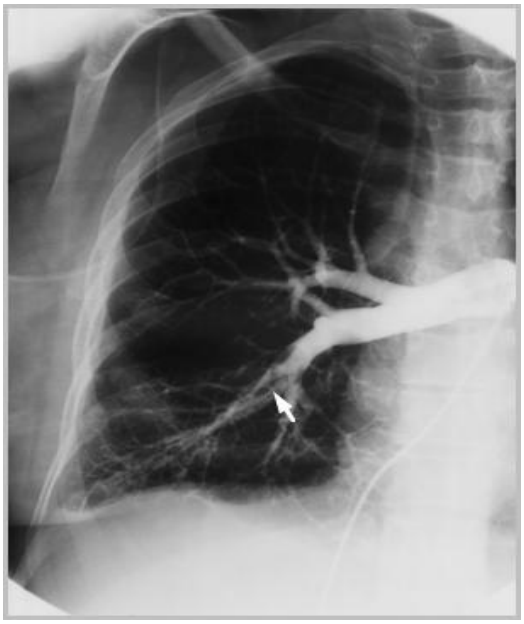




- A, Computed tomographic scan demonstrating infarcted lung on left and large clot in the right main pulmonary artery.
  B, Autopsy specimen from same patient demonstrating organized clot in right main pulmonary artery.
- The patient presented with chronic dyspnea and hemoptysis and later died from complications of severe pulmonary hypertension. Patients with moderate to severe pulmonary hypertension may be considered for thromboendarterectomy. The operative mortality has decreased to approximately 5% with improvement in technique.
- Patients may experience dramatic relief of symptoms.
- Life-long anticoagulation is required to prevent recurrence.

Angio, or CT pulmonary angiogram

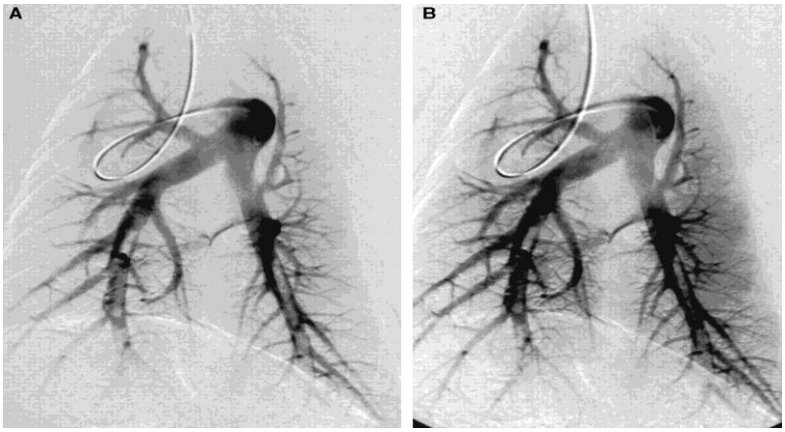
It has the advantage of visualizing the distribution and the extent of the emboli, or highlighting alternative diagnosis as consolidation, pneumothorax, and aortic dissection .



- **Pulmonary angiography remains the diagnostic gold standard for pulmonary embolism.**
- Access to the pulmonary artery is obtained via transvenous catheter placement.
- The diagnosis is confirmed by persistent filling defect or abrupt cut-off of flow.
- Abrupt cut-off of flow to the right and left upper lobe vessels is seen in this patient.

Echocardiography.

Helpful in differential diagnosis and assessment of acute circulatory collapse.



Fibrin Split Products/D-dimer

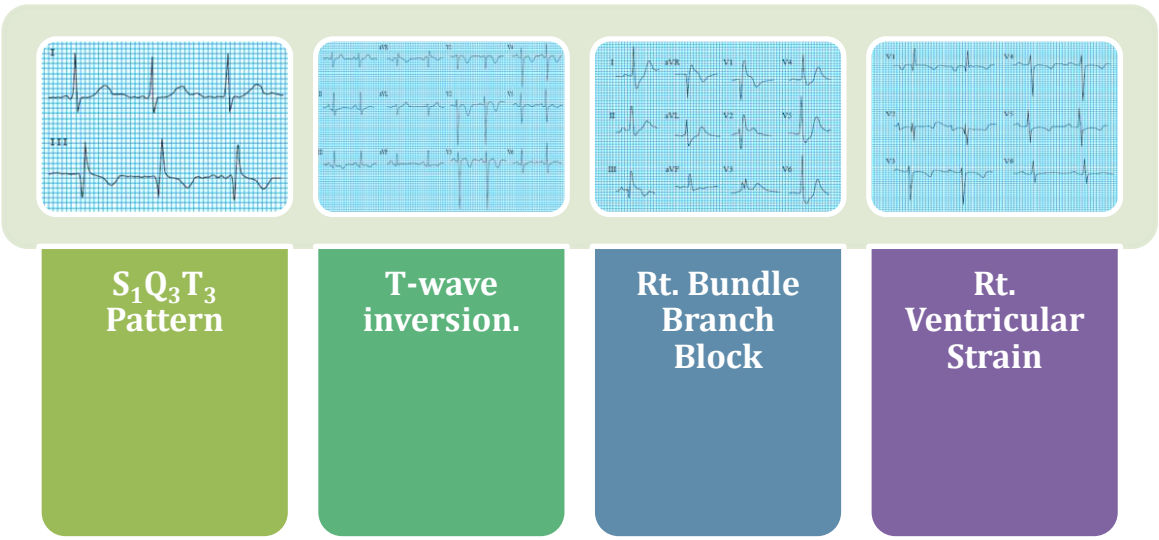
it's increased in the presence of any kind of thrombosis .
If the value is negative, it makes the diagnosis of PE less likely.

- D-dimer is a specific degradation product released into the circulation when cross linked-fibrin undergoes endogenous fibrinolysis.
- An elevated D-dimer level occurs in number of conditions including PE, Myocardial infarction, Pneumonia and Sepsis.
- Low D-dimer levels(< 500ng/mL measured by ElISA), particularly when clinical risk is low, have a **high negative predicative value** and further investigation are un necessary, but D-dimer level should be disregarded in high risk patient, as other investigation are mandatory even if D-dimer level is normal.

- D-Dimer can tell you if there's a problem or not, but it can't define the problem.
- If levels are high we do further investigations,
- If not then PE in highly unlikely → No further investigations

ECG

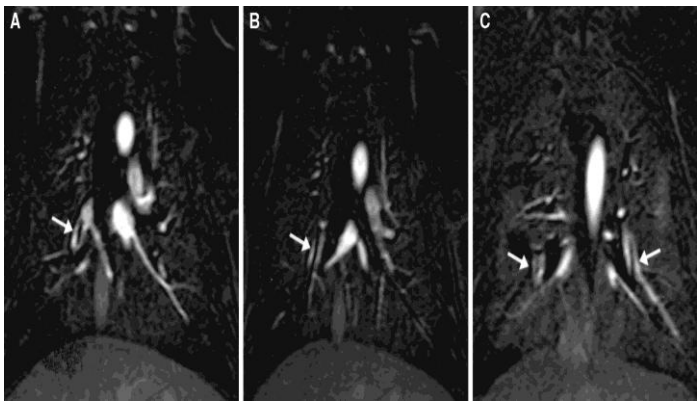
- **Suggestive but not diagnostic,** and it's useful in excluding other differential diagnosis such as acute myocardial infarction and pericarditis.
- The most common abnormalities in PE include **sinus tachycardia and anterior T-wave inversion** but are non-specific.
- Larger emboli may cause right heart strain revealed by an **$S_1Q_3T_3$ pattern, ST-segment and T-wave changes**, or the appearance of **right bundle branch block**



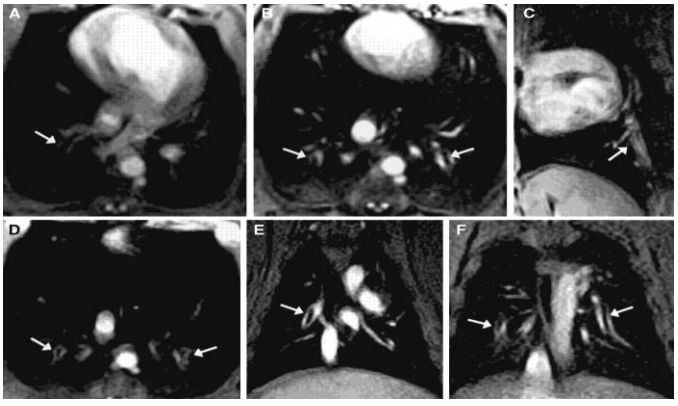
The diagnosis of massive PE should be explored whenever oxygenation or hemodynamic parameters are severely compromised without explanation

- CXR
- ABG: Significant hypoxemia is almost uniformly present when there is a hemodynamically significant PE
- V/Q
- Spiral CT (Most commonly used)
- Echo
- Angiogram (Gold Standard)
- D-Dimer
- BNP
- Troponin

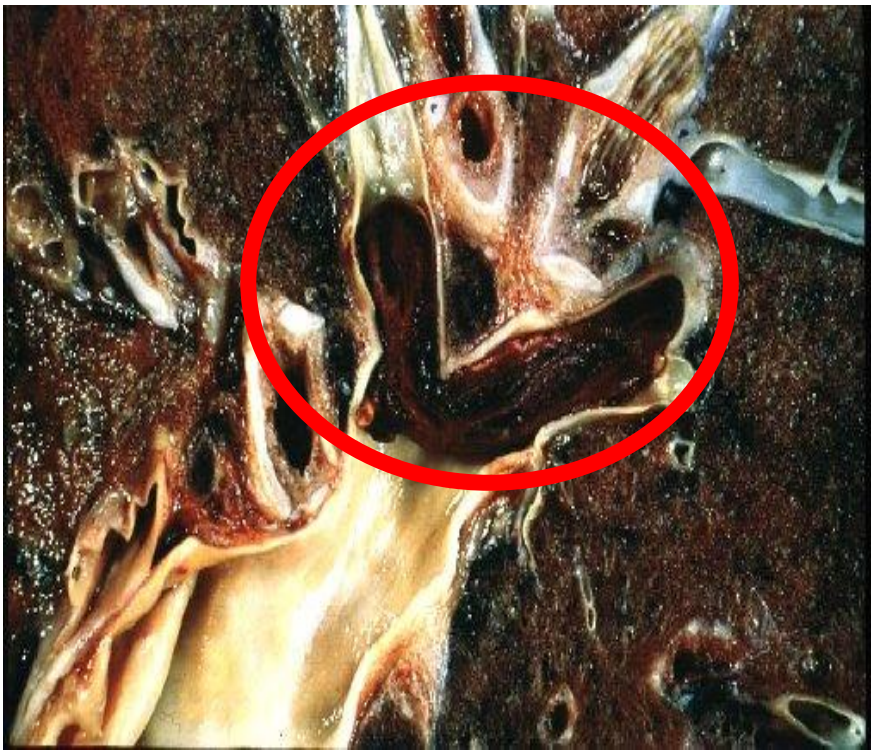
MRA
(Magnetic Resonance Anngeogram)
With contrast



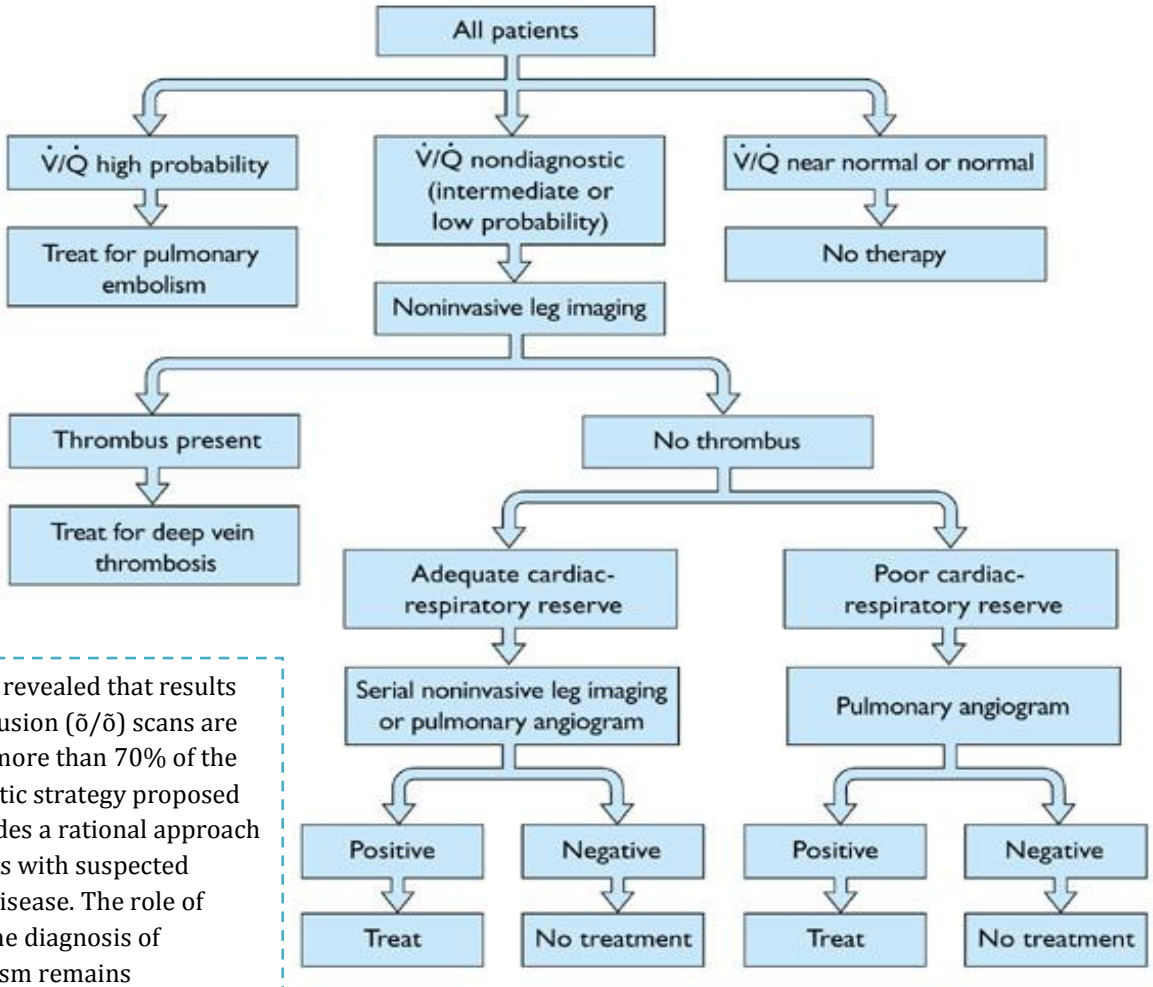
MRA real time



Pulmonary Embolism



Suggested diagnostic strategy for venous thromboembolism



The PIOPED study revealed that results of ventilation-perfusion (õ/õ) scans are non diagnostic in more than 70% of the cases. The diagnostic strategy proposed in the figure provides a rational approach to work up patients with suspected thromboembolic disease. The role of spiral CT scan in the diagnosis of pulmonary embolism remains controversial with a wide range of reported sensitivities (53%–100%) and specificities (81%–100%) [15]. (Adapted from Stein et al.[16].)

Suggested diagnostic strategy for venous thromboembolism → Spiral CT Scan

Treatment

1) Respiratory support
2) Hemodynamic Support
3) Anticoagulation, starting with LMWH (lower Molecular Weight Heparin)

Dosage and monitoring of anticoagulant therapy
After initiating heparin therapy, repeat APTT every 6 h for first 24 h and then every 24 h when therapeutic APTT is achieved
Warfarin 5 mg/d can be started on day 1 of therapy; there is no benefit from higher starting doses
Platelet count should be monitored at least every 3 d during initial heparin therapy
Therapeutic APTT should correspond to plasma heparin level of 0.2–0.4 IU/mL
Heparin is usually continued for 5–7 d
Heparin can be stopped after 4–5 d of warfarin therapy when INR is in 2.0–3.0 range

Important drug interaction with warfarin

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	

- The figure includes only a short list of commonly used agents that are known to have clinically significant interactions with warfarin; several other drugs have pharmacokinetic and pharmacodynamic interactions with warfarin.
- Careful review of medications, alcohol consumption, and dietary factors is mandatory in patients who are on warfarin therapy.

Complications of anticoagulation

	Complication	Management
Heparin	Bleeding	Stop heparin infusion. For severe bleeding, the anticoagulant effect of heparin can be reversed with intravenous 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; provide supportive care including transfusion and clot evacuation from closed body cavities as needed.
	Heparin-induced thrombocytopenia and thrombosis	Carefully monitor platelet count during therapy. Stop-heparin for platelet 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**

	Complication	Management
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.

Major bleeding episodes with the use of heparin are much more likely to occur in patients with identifiable risks for bleeding rather than an excessively long activated partial thromboplastin time per se. LMWH does not affect the APTT to a significant degree; therefore, the APTT need not be routinely measured. Many factors influence the prothrombin time during warfarin therapy. Weekly or biweekly measurements are necessary until the prothrombin time stabilizes. Thereafter, monthly measurements of the prothrombin time may be sufficient.

Risks and benefits of thrombolytics vs heparin therapy for pulmonary embolism

	Thrombolytic therapy	No difference	Heparin
Improved resolution at 2-4 h after onset of therapy			
Angiography	+	-	-
Pulmonary artery pressure	+	-	-
Echocardiography	+	-	-
Resolution at 24 h			
Lung scan	+	-	-
Angiography	+	-	-

	Thrombolytic therapy	No difference	Heparin
Echocardiography	+	-	-
Pulmonary artery pressure	+	-	-
Resolution at 1 wk and 30 d (lung scan)	-	+	-
Rate of confirmed recurrent pulmonary embolism	-	+	-

	Thrombolytic therapy	No difference	Heparin
Hospital mortality	-	+	-
Late mortality	-	+	-
Less severe bleeding	-	-	+
Less intracranial hemorrhage	-	-	+
Lower cost	-	-	+

The role of thrombolytic therapy in the management of acute thromboembolic disease is unclear. Improvement in hemodynamic parameters and reduction in clot burden have been demonstrated after thrombolysis; however, no improvement in mortality has been demonstrated when compared with conventional anticoagulation. Nonetheless, in selected patients with acute pulmonary embolism and hemodynamic instability, thrombolytics may prove to be life saving. (Adapted from Dalen et al.[18].)

Approved thrombolytics for pulmonary embolism

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
Recombinant tissue-plasminogen activator
100 mg as a continuous peripheral intravenous infusion administered over 2 h

All three US Food and Drug Administration–approved regimens used fixed or weight-adjusted doses. No further dosage adjustments are made. Heparin is resumed after the thrombolytic infusion when the activated partial thromboplastin time is less than 2.5 × control.

Indications and contraindications for thrombolytic therapy in pulmonary embolism

Indications

- Hemodynamic instability
- Hypoxia on 100% Oxygen
- Right ventricular dysfunction by Echocardiography

Thrombolytics may also be used to treat extensive ileofemoral venous thrombosis in selected patients with a low risk of bleeding. Some evidence exists that the incidence of postthrombotic syndrome is reduced if complete thrombolysis is achieved. Often the decision to administer thrombolytic therapy has to be individualized after careful review of potential risks and benefits.

Containdication

- Relative:

- Previous arterial punctures within 10 d
- Recent surgery within last 10 d
- Bleeding disorder (thrombocytopenia, renal failure, liver failure)
- Ophthalmologic surgery within 6 wk
- Neurosurgery within 6 mo
- Placement of central venous catheter within 48 h
- Hypertension >200 mm Hg systolic or 110 mm Hg diastolic
  Intracerebral aneurysm or malignancy
- Hypertensive retinopathy with hemorrhages or exudates
- Cardiopulmonary resuscitation within 2 wk
- Cerebrovascular disease
- Pregnancy and the 1st 10 d
- Postpartum

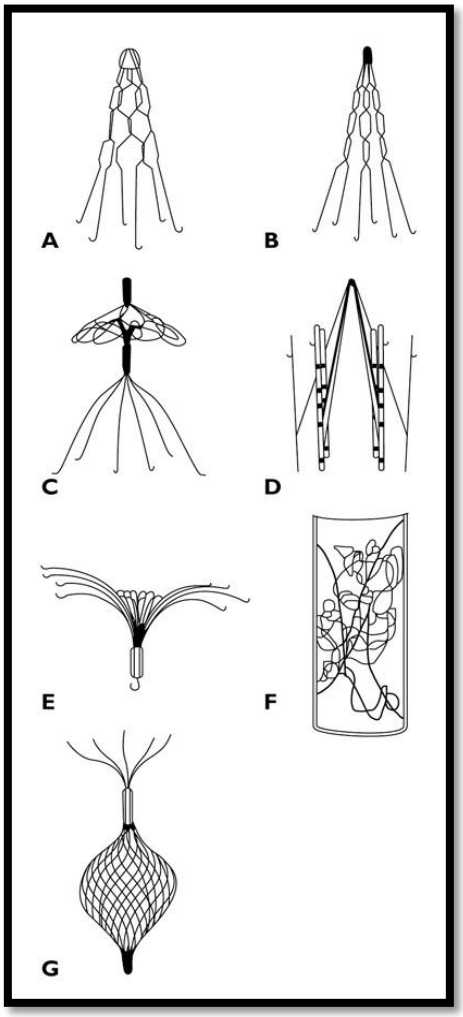
- Major internal bleeding within the last 6 mo
- Severe trauma within 2 mo
- Infectious endocarditis
- Pericarditis

- Absolute

- Active internal bleeding

Indications for inferior vena caval (IVC) filters →

- Absolute contraindication to anticoagulation (eg, active bleeding)
- Recurrent PE despite adequate anticoagulant therapy
- Complication of anticoagulation (eg, severe bleeding)
- Hemodynamic or respiratory compromise that is severe enough that another PE may be lethal.



- ❖ IVC filters are widely used, but randomized controlled trials assessing their efficacy are lacking.
- ❖ The procedure is not difficult to perform in experienced hands; mortality from filter placement is less than 1%.
- ❖ Nonfatal complications that have been reported include misplacement, cellulitis, hematoma, and venous thrombosis Proximal or distal migration of the device may also occur. Erosion of the filter into the vena cava wall has been reported; it usually occurs slowly with very few clinical complications.
- ❖ IVC obstruction and lower extremity venous insufficiency may occur in some patients.
- ❖ If possible, anticoagulation should be used after filter placement to prevent morbidity from deep vein thrombosis in the legs and to prevent clot formation on the filter.
- ❖ Note that IVC filters may lose their effectiveness within a few months due to the development of collateral venous circulation.

Embolectomy

- Embolectomy (ie, removal of the emboli) can be performed using catheters or surgically.
- It should be considered when a patient's presentation is severe enough to warrant thrombolysis (eg, persistent hypotension due to PE), but this approach either fails or is contraindicated.

Conclusion

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