VENOUS THROMBOEMBOLISM

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Pulmonary embolism and deep venous thrombosis

spectrum of one disease

venous thromboembolism

PE is not a disease
it is a complication of DVT

79% PE → DVT LL

50% DVT → PE

Pathophysiology

Virchow triad

primary mechanism

venous stasis, vessel wall injury, hypercoagulable state

most DVT is occult
usually resolves spontaneously without complication

DVT

- Patients of gynecologic surgery, major trauma, indwelling venous catheters (any location)
- most often lower extremities
- nearly always starts in the calf veins
- involved in all cases of symptomatic spontaneous lower extremity DVT
- already has propagated above the knee in 87% of symptomatic patients before the diagnosis is made

DVT

In the absence of prophylaxis DVT may be demonstrated in :

- General medical patients placed at bed rest for a week (10-13%)
- Patients in medical ICU (29-33%)
- Patients with pulmonary disease in bed for >3 days (20-26%)
- Patients admitted to a CCU after MI (27-33%)
- Patients who are asymptomatic after CABG (48%)

BELIEF

calf vein DVT is only a minor threat

DVT of the calf is a significant source of PE

often causes serious morbidity/ death.

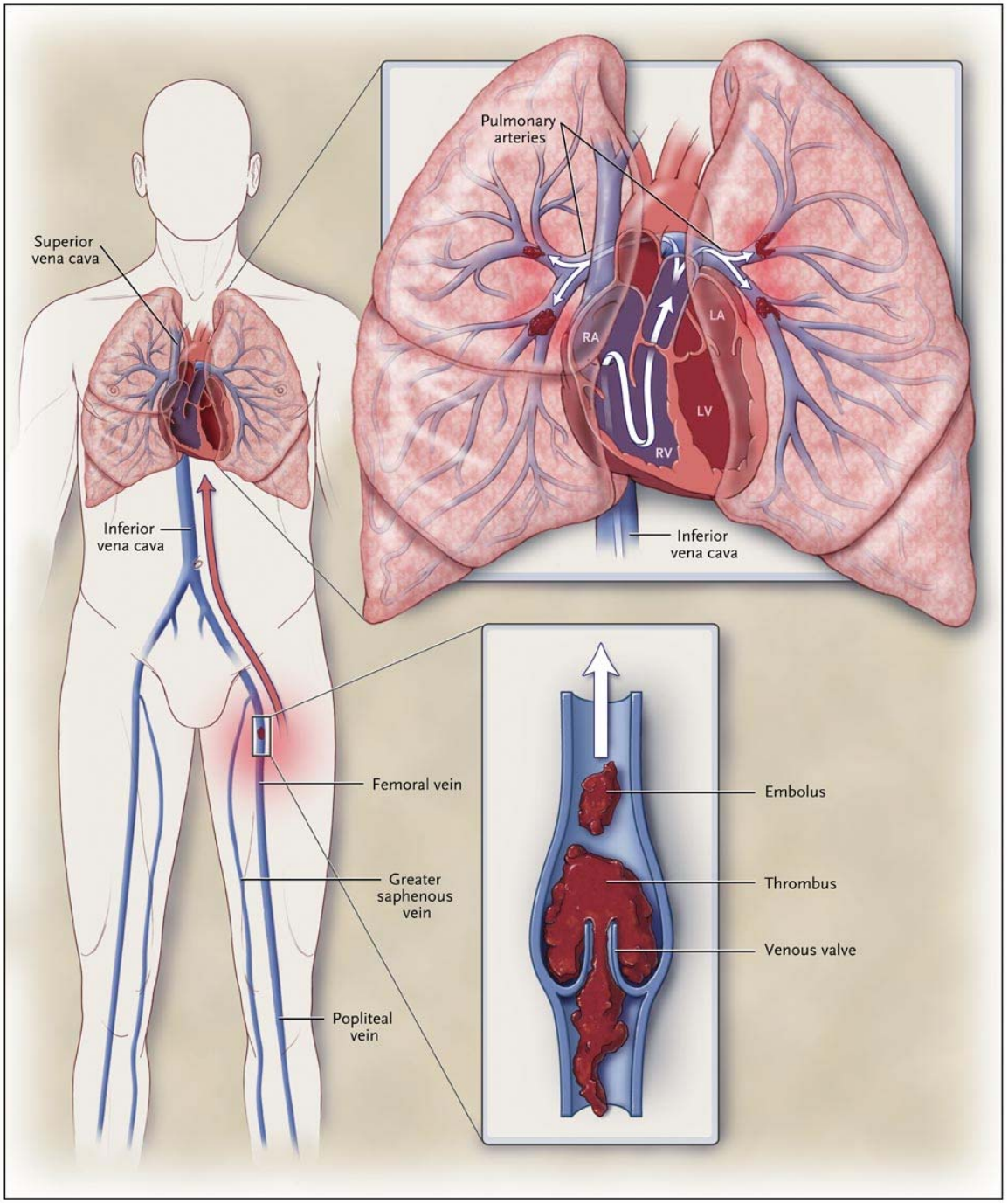
1/3 of massive PE ⟹ only source in calf veins

Mortality/Morbidity

- Unexpected death from massive PE is second only to SCD
- 10% of patients who develop PE die within first hour
- 30% die subsequently from recurrent embolism
- Patients who survive acute PE are at high risk for recurrent PE
- 70% develop pulmonary hypertension and chronic cor pulmonale

Natural history of PE

- usually arise from thrombi originating in deep venous system of LL
- rarely may originate in the pelvic, renal, upper extremity veins
- After traveling to the lung, large thrombi lodge at the bifurcation of the MPA or lobar branches
- Smaller thrombi continue distally occluding smaller vessel periphery
- Most emboli are multiple
- lower lobes > upper lobes


Pulmonary arteries
Superior vena cava
RA
LA
LV
RV
Inferior vena cava
Inferior vena cava
Femoral vein
Greater saphenous vein
Popliteal vein
Embolus
Thrombus
Venous valve

Causes

- General
  - Age (>40)
  - Immobilization longer than 3 days
  - Pregnancy / postpartum period / Major surgery
- Medical
  - Cancer pancreatic; bronchogenic; GUT
  - Previous DVT / Stroke / AMI / CHF / Sepsis / NS / UC
- Trauma
  - Multiple trauma
  - CNS/spinal cord injury / Burns / LL fractures

Causes

- Vasculitis
  - SLE / Behçet syndrome / Homocystinuria
- Hematologic
  - Polycythemia vera / Thrombocytosis
  - Inherited disorders of coagulation/fibrinolysis
  - Antithrombin III deficiency
  - Protein C,S deficiency / Factor V Leiden
- Drugs/medications
  - Iv drug abuse / OC / Estrogens /Heparin-induced thrombocytopenia

Risk factors of VTE

Genetic Disorders and Thromboembolic Risk

- Recurrent thromboembolism
- Young
- Apparently unprovoked episodes
- Thrombosis in an unusual location (cerebral, mesenteric, portal)

History (DVT)

- The bedside diagnosis is insensitive and inaccurate
- Many patients asymptomatic
- Edema, principally unilateral, is most specific symptom
- Massive edema with cyanosis and ischemia rare
- Leg pain (50%) Tenderness (75%)
- Pain can occur on dorsiflexion of the foot (Homans sign)
- Clinical S/S of PE as primary manifestation (10%)
- Pain/tenderness poorly correlate with location,extent
- Warmth or erythema of skin

Physical (DVT)

- Edema, principally unilateral
  - Tenderness, if present, usually confined to calf muscles or along the course of the deep veins in the medial thigh.
- Homans sign
  - Discomfort in the calf muscles on forced dorsiflexion of the foot with the knee straight
  - found in > 50% of patients without DVT
- Venous distension
  - Superficial thrombophlebitis : 40% have DVT
- Fever: may have fever, usually low grade

Superficial thrombophlebitis

Often associated with DVT in 2 specific settings

- In absence of coexisting venous varices and no obvious etiology
- Involvement of the greater saphenous vein above the knee, especially if it extends to the saphenofemoral junction

Axillary/subclavian vein thrombosis

PE occurs in 10% of patients

Fatal or massive PE is extremely rare

Causes:

Thoracic outlet compression

Catheter-induced thrombosis

Pulmonary artery catheters

History (PE)

- symptoms nonspecific
- high index of suspicion required
- classic triad
- (hemoptysis, dyspnea, chest pain) <20%

History (PE)

MC symptoms

dyspnea (73%), pleuritic chest pain (66%), cough (37%), hemoptysis (13%)

Atypical symptoms

- Seizures
- Syncope
- Fever
- Productive cough
- Wheezing
- Decreasing level of consciousness
- New onset atrial fibrillation

Physical (PE)

- 96% have tachypnea
- 58% develop crackles
- 53% have accentuated second heart sound
- 44% have tachycardia
- 43% have fever
- 36% have diaphoresis
- 34% have an S3 or S4 gallop
- 32% have thrombophlebitis
- 24% have lower extremity edema
- 23% have a cardiac murmur
- 19% have cyanosis

Clinical Syndromes of Pulmonary Embolism

Classification	Presentation	Remarks
Massive PE	Systolic BP ≤ 90 mm Hg for at least 15 minutes or requiring inotropic support	•Dyspnea: usually most notable symptom •transient cyanosis common •chest pain unusual •signs of pulmonary hypertension such as loud P2, RVS3,TR
	or pulselessness	
	or persistent profound bradycardia (heart rate 40 bpm)	
	plus	
	right or left main pulmonary artery thrombus or "high clot burden"	
Submassive PE	•Hemodynamically stable but moderate or severe right ventricular dysfunction •RV dilation or systolic dysfunction •Elevation of BNP/ pro-BNP •new complete or incomplete RBBB, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion ● Myocardial necrosis is defined as elevation of troponin I / T	•nonspecific symptoms of unexplained dyspnea /substernal discomfort •Risk for recurrent PE: even with adequate anticoagulation. •If RV dysfunction still persists: thrombolysis or embolectomy to be considered

Clinical Syndromes of Pulmonary Embolism

Classification	Presentation	Remarks
Small to moderate PE	Normal hemodynamics and normal right ventricular size and function	•No cardiac biomarker release •normal RV function adequate anticoagulation •excellent clinical outcome
Pulmonary infarction	•Caused by a tiny peripheral pulmonary embolus which usually lodges in peripheral pulmonary arterial tree near the pleura. •Pleuritic chest pain, often not responsive to narcotics •Low-grade fever •Pleural-rub, hemoptysis	•Tissue infarction usually occurs 3 to 7 days after embolism. •often includes fever, leukocytosis, an elevated ESR, radiological evidence of infarction

Lab Studies

- WBC count may be normal or elevated
- Clotting study results are normal in most
- ABG has zero / negative predictive value in a typical population in whom PE is suspected clinically
- Other etiologies that masquerade as PE are more likely to lower the PO_2 than PE
- pulse oximetry is extremely insensitive, is normal in the majority of patients with PE

Lab Studies

D-dimer

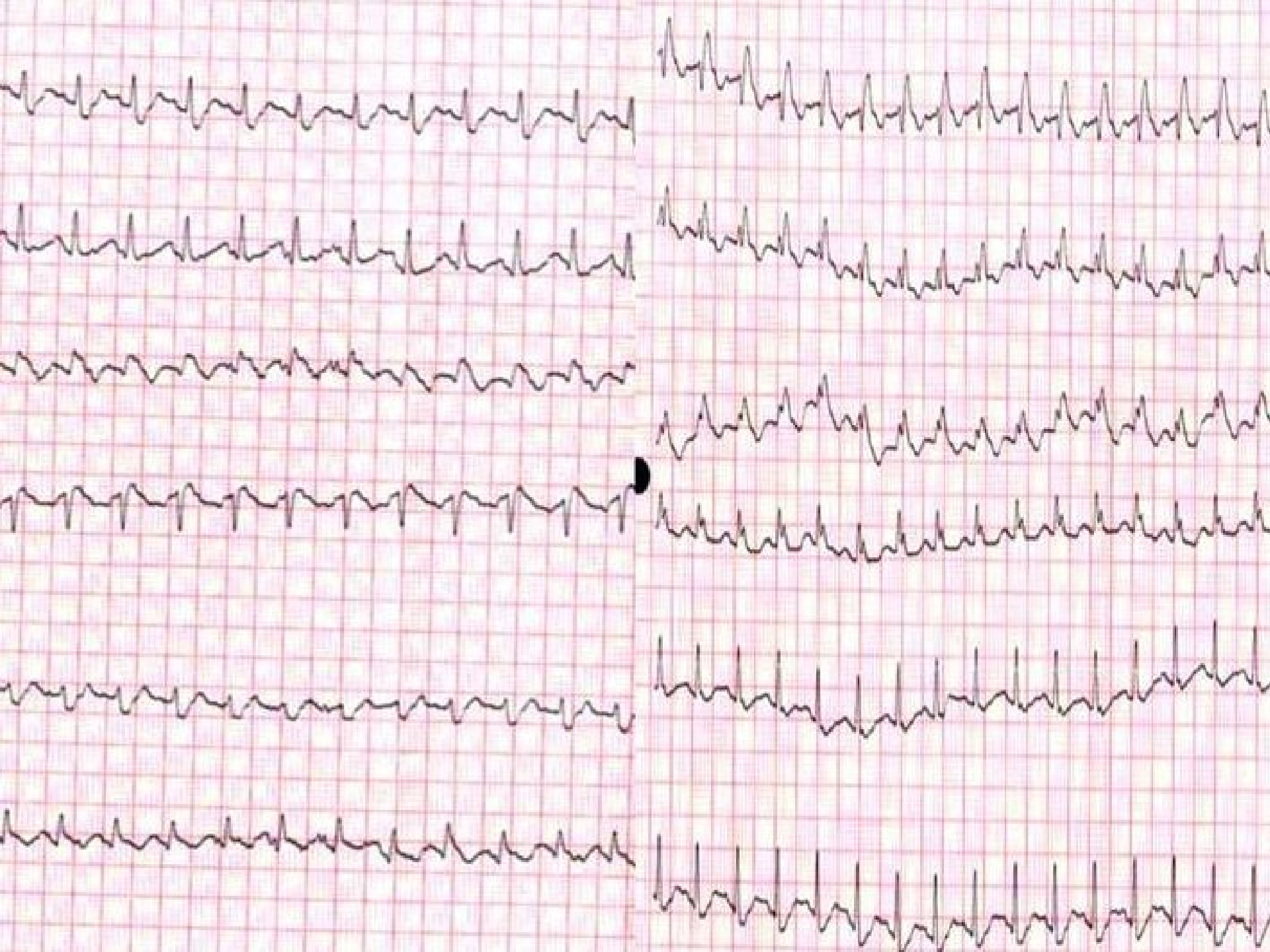
- degradation product produced by plasmin-mediated proteases of cross-linked fibrin
- level is elevated in trauma, recent surgery, hemorrhage, cancer, sepsis
- assays have low specificity for DVT, sensitivity 98%
- should only be used to rule out DVT, not to confirm
- D-dimer results should be used as follows:
  - A negative D-dimer assay result rules out DVT in patients with low-to-moderate risk
  - All patients with a positive D-dimer assay result and all patients with a moderate-to-high risk of DVT require a diagnostic study

GENETIC FACTORS

- Protein S, protein C, antithrombin III, factor V Leyden, antiphospholipid antibodies, homocysteine levels
- rare causes of DVT
- Laboratory investigations for these are primarily indicated when:
  - DVT is diagnosed in patients < 35 years
  - when thrombosis is detected in unusual sites

ECG

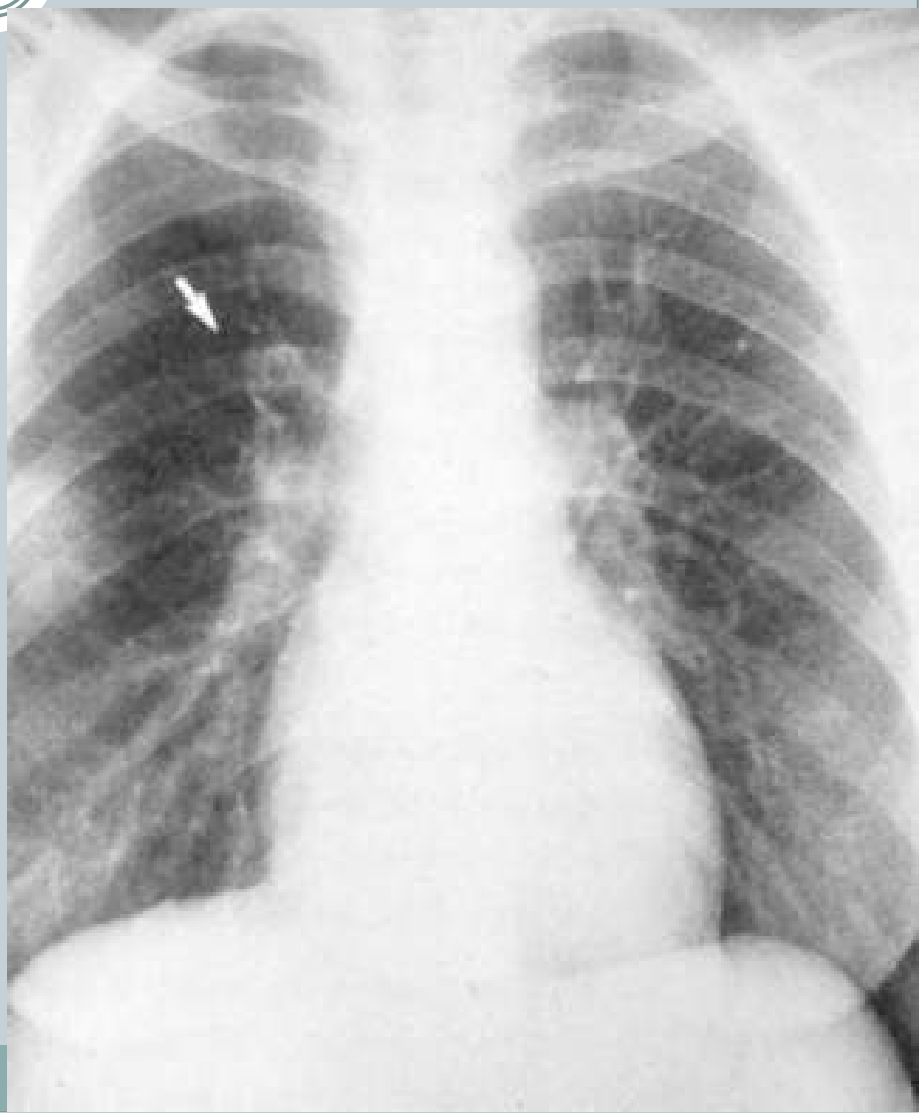
- most common ECG abnormalities of PE are tachycardia and nonspecific ST-T wave abnormalities
- classic findings of right heart strain and acute cor pulmonale are P pulmonale, RAD, RBBB, S1-Q3-T3 pattern, AF
- 25% ECGs of patients with proven PE have no changes



- Initial CxR **NORMAL**

- May show collapse, consolidation, pleural effusion, elevated diaphragm
- Pleural based opacities with convex medial margins known as Hampton's Hump

Westermark sign – Dilatation of pulmonary vessels proximal to embolism along with collapse of distal vessels, often with a sharp cut off



Ventilation-perfusion (V/Q) scanning

Important when CTA not available

- indicated whenever diagnosis of PE is suspected and no alternative diagnosis can be proved.
- Screening V/Q is indicated for most patients with DVT even without symptoms of PE.
- repeat V/Q scan is indicated before stopping anticoagulation in a patient with irreversible risk factors for DVT and PE
- reference "post treatment" V/Q scan can serve as a new baseline for comparison

V/Q Scanning

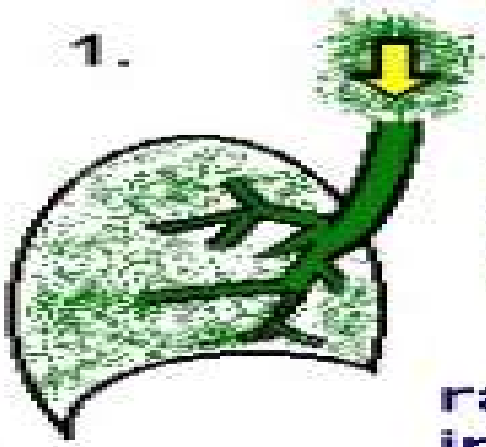
unless the scan shows normal perfusion, the patient must not be abandoned without a definitive test to rule out PE or a definitive test to prove an alternative diagnosis

V/Q Scanning

- ventilation part is inhalation of Krypton 81m, which has short half life and is pure gamma emitter and assessed under gamma camera
- perfusion part is achieved by injecting with technetium 99m, coupled with macro aggregated albumin which sticks in pulmonary capillaries
- An embolus shows up as a cold area when patient is placed under gamma camera

V/Q Scanning

1. radioactive compound inhaled into airspaces of lung.
in a normal lung, this will distribute evenly to all regions.

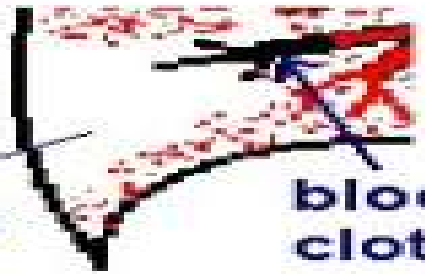


2. radioactive compound injected into vein. Travels to lung tissues in blood vessels.

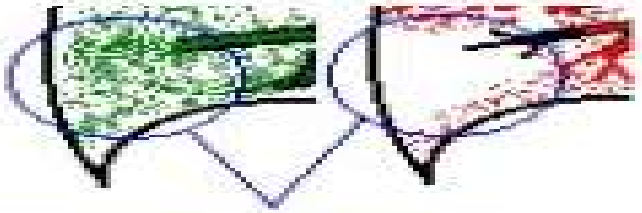
(pulmonary embolus is a blood clot in a pulmonary artery)

no injected material reaches this region

blood clot



3. "mismatch" of inhaled and injected compounds on the lung scan images = pulmonary embolus



Normal V/Q scan

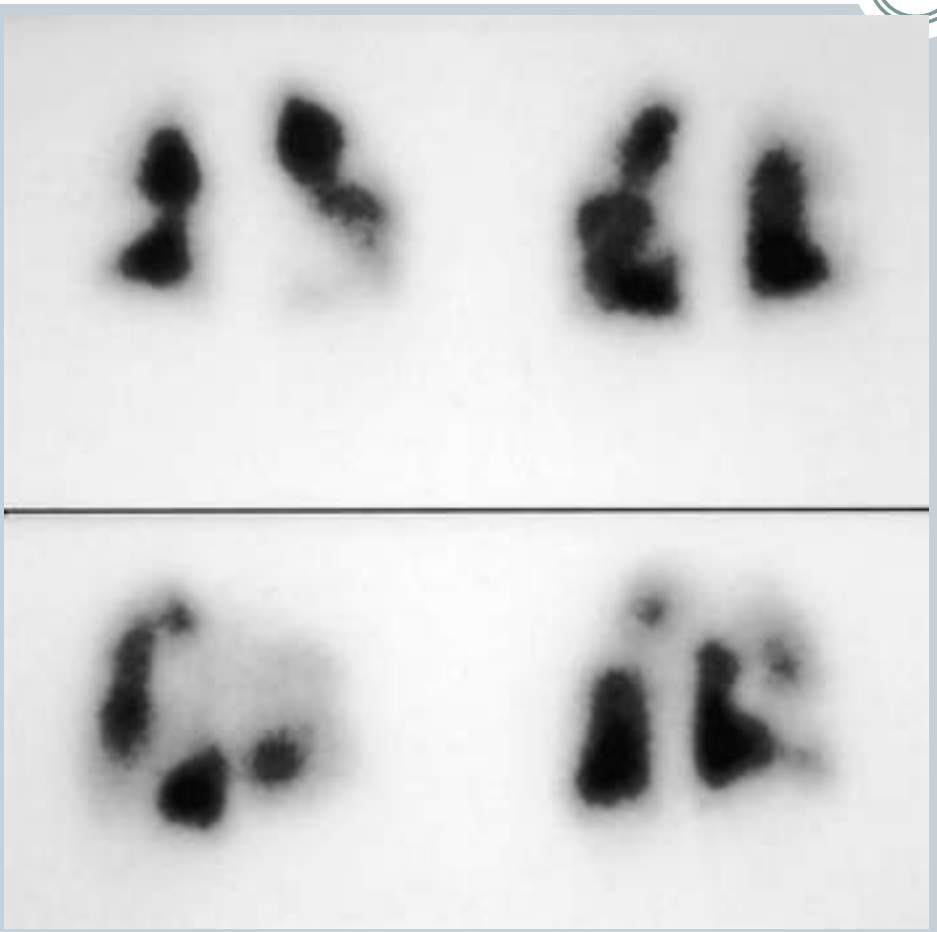
- No perfusion defects are seen.
- approx 1 of every 25 patients sent home after normal scan has PE

High-probability scan

- ≥2 segmental perfusion defects with normal CXR /ventilation
- ≥2 segmental perfusion defects where CXR abnormalities and ventilation defects are substantially smaller than perfusion defects
- ≥2 subsegmental and one segmental perfusion defect with normal CXR and normal ventilation
- ≥4 subsegmental perfusion defects with normal CXR and normal ventilation

In most settings, high-probability scan may be considered positive for PE

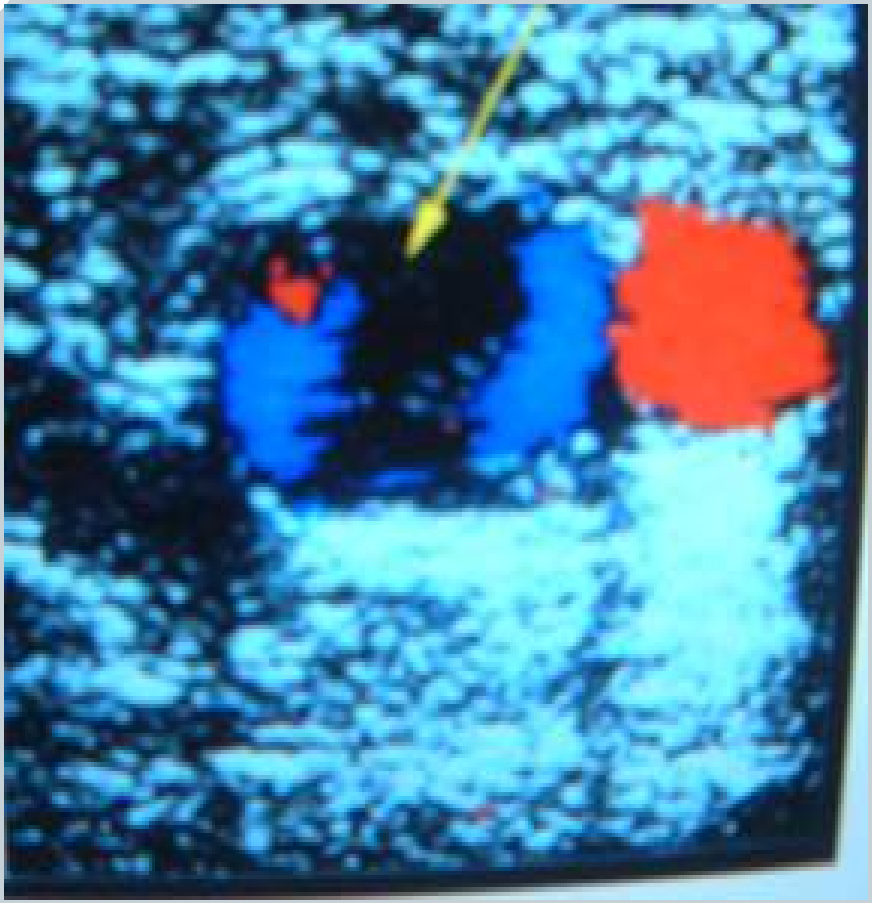
V/Q Scanning



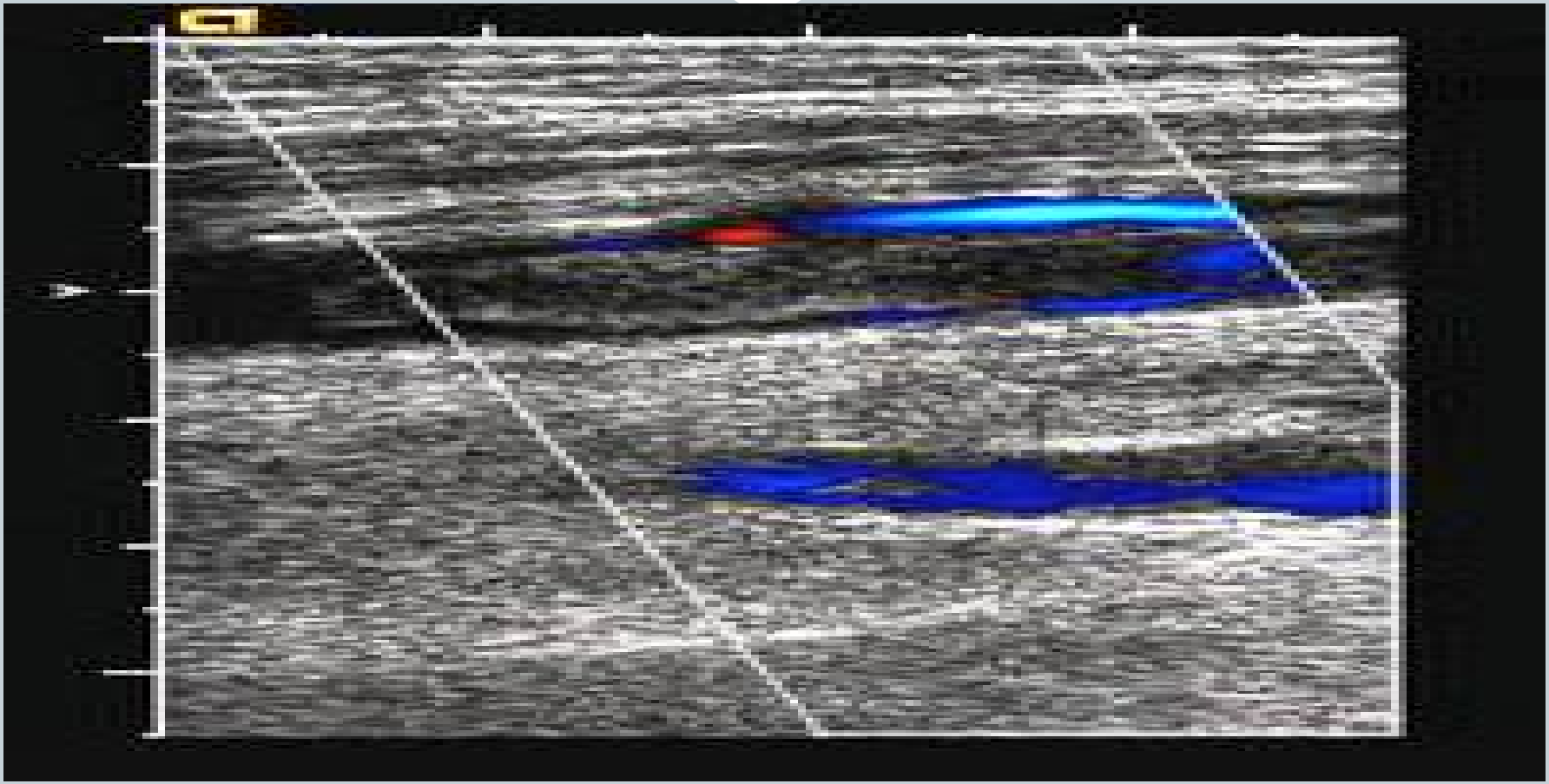
Perfusion Mismatch Ventilation

Duplex ultrasonography

- major USG criterion for detecting VT is failure to compress the vascular lumen
- Sensitivity for proximal vein DVT is 97%
- Sensitivity is 73% for calf vein DVT
- Overall specificity is 95%.
- primary disadvantage is its inherent inaccuracy in the diagnosis of calf vein thrombosis



thrombus in the distal superficial saphenous vein, which is under the artery

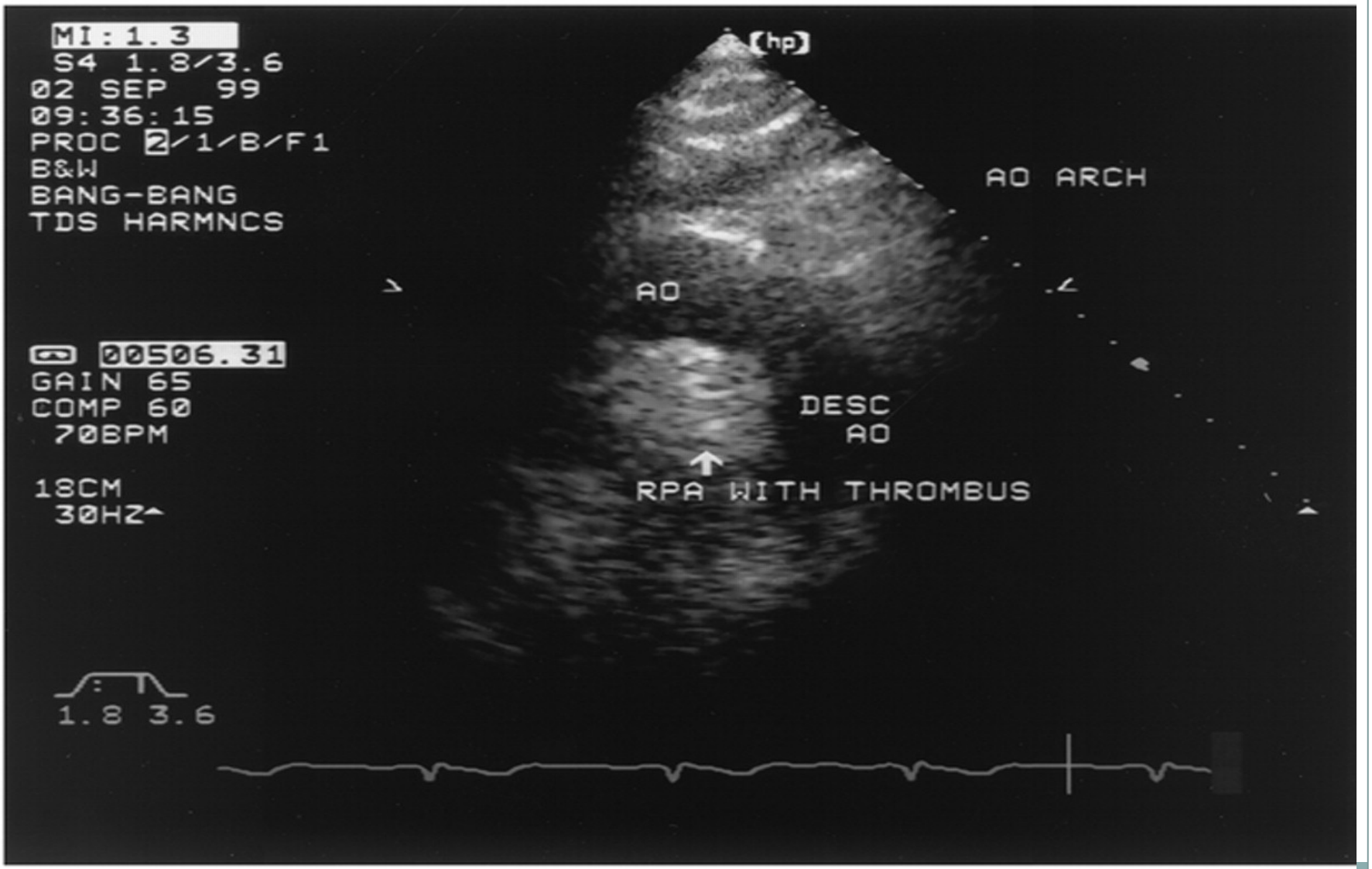


thrombus tip in the superficial femoral vein

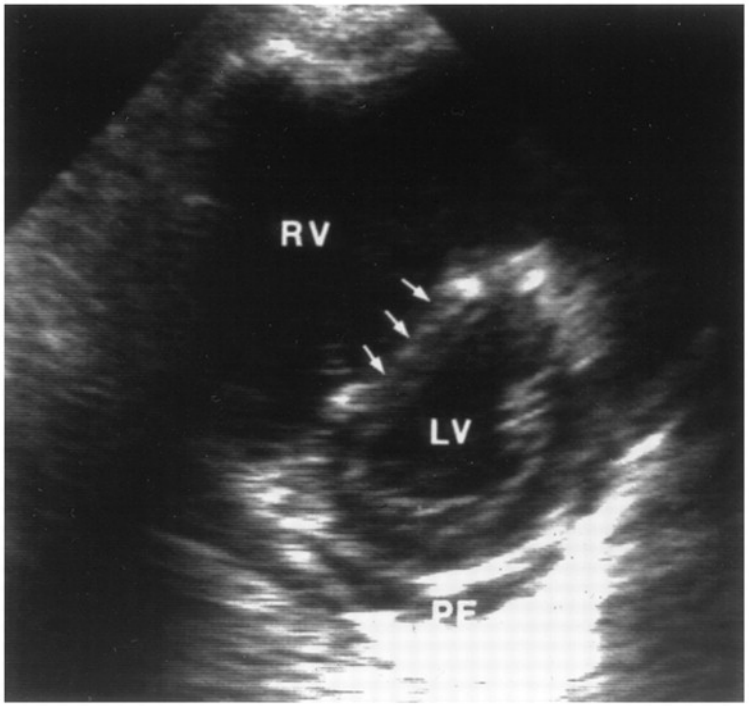
Echocardiography

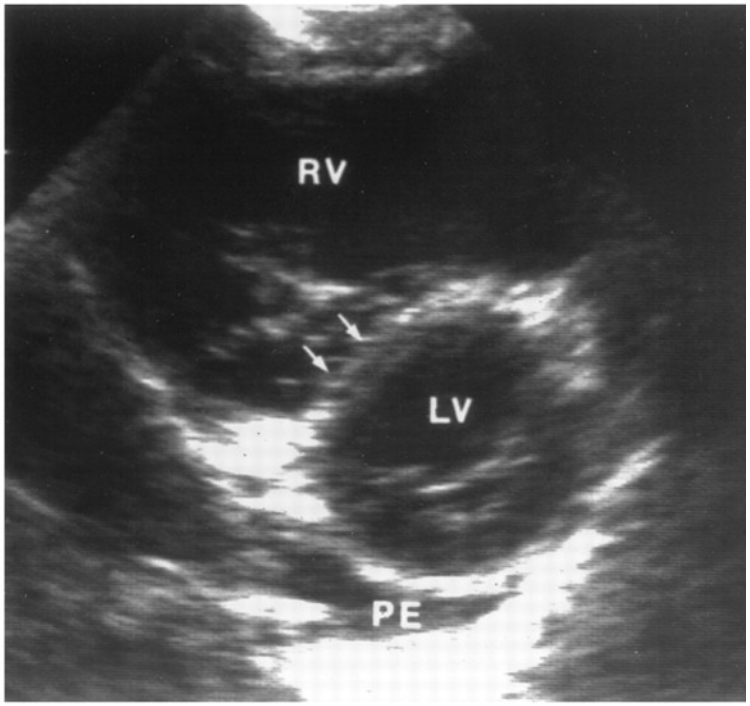
- generally has limited accuracy in diagnosis of PE
- TEE may identify central PE
- sensitivity for central PE is 80%
- Overall sensitivity and specificity for central and peripheral PE is 59% and 77%
- may demonstrate RV dysfunction in acute PE, predicting a higher mortality and possible benefit from thrombolytic therapy

Right main pulmonary artery embolism visualized on transthoracic echocardiography.RPA.

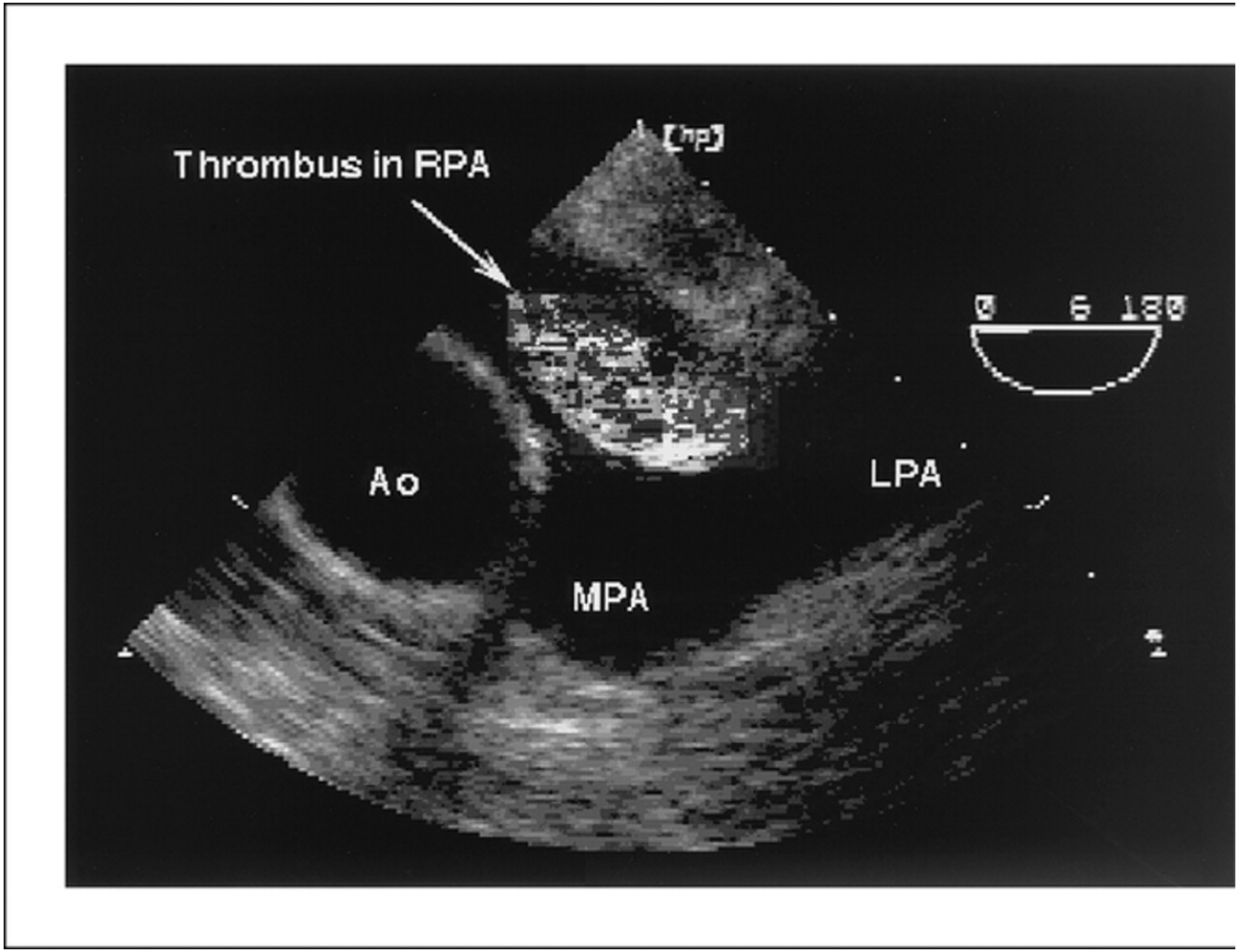


transthoracic echocardiography in patients with massive pulmonary embolism





Transesophageal short-axis view at the level of the pulmonary artery bifurcation, demonstrating thrombus in the right pulmonary artery (RPA).



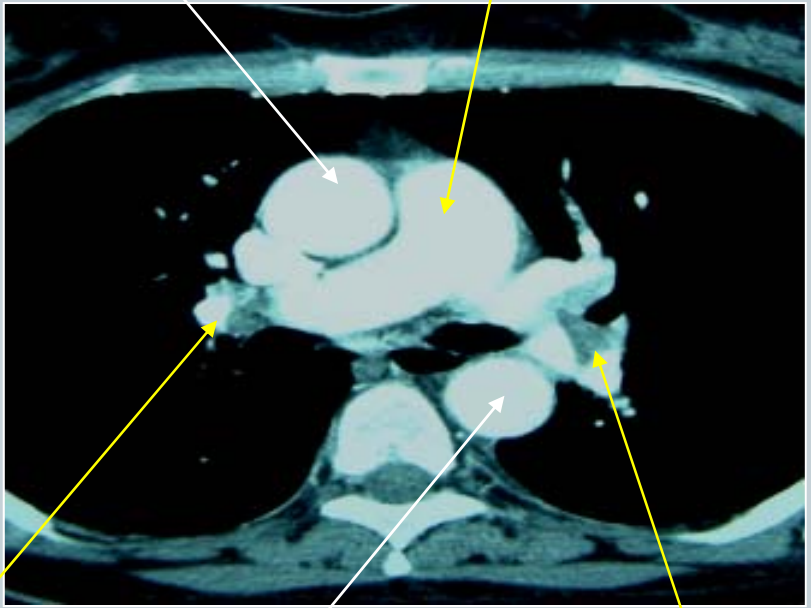
MRI/ MRA

- increasingly been investigated for suspected DVT
- accuracy approaches that of contrast venography
- diagnostic test of choice for suspected iliac vein or inferior vena caval thrombosis when CT venography is C/I
- In 2nd & 3rd trimester pregnancy, more accurate than USG
- In suspected calf vein thrombosis, MRI more sensitive than any other noninvasive study
- MRA is performed using iv gadolinium
- MRI has a sensitivity of 85% and specificity of 96% for central, lobar, and segmental emboli
- MRI is inadequate for the diagnosis of subsegmental emboli

High-resolution multidetector CTA / CTV

- CT venography of LL is performed after scanning of the chest.
- primary utility of CTV is for diagnosis of ileofemoral DVT
- MDCT with intravenous contrast can resolve third-order pulmonary vessels
- an alternate diagnosis may be suggested
- sensitivities for PE reported to be 53-100%
- specificity has been reported to be 78-96%

Spiral / Multislice CT



Ascending Aorta

Main Pulmonary Artery

Descending Aorta

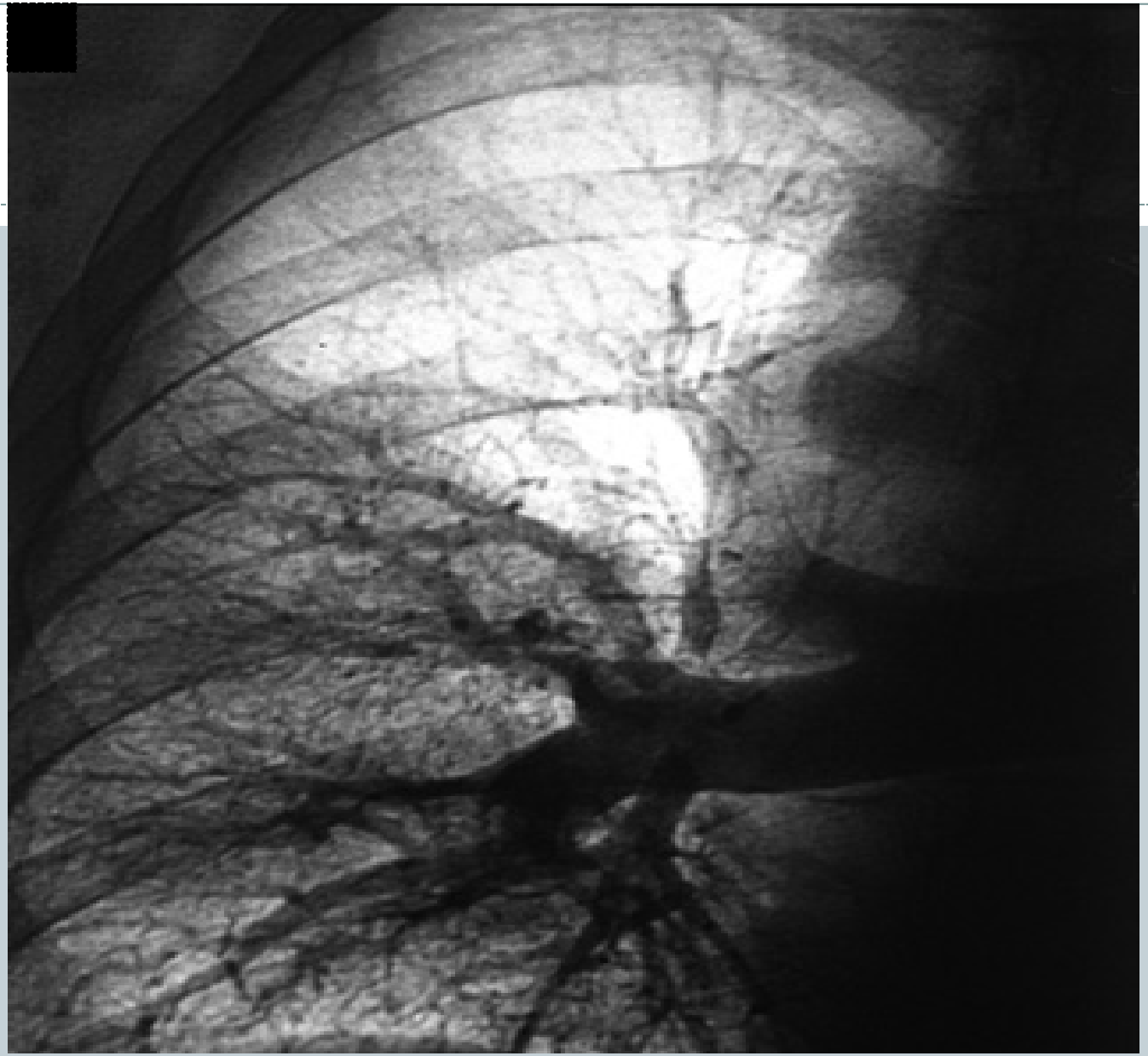
Rt Pulmonary Artery

Lt Pulmonary Artery

Thrombus

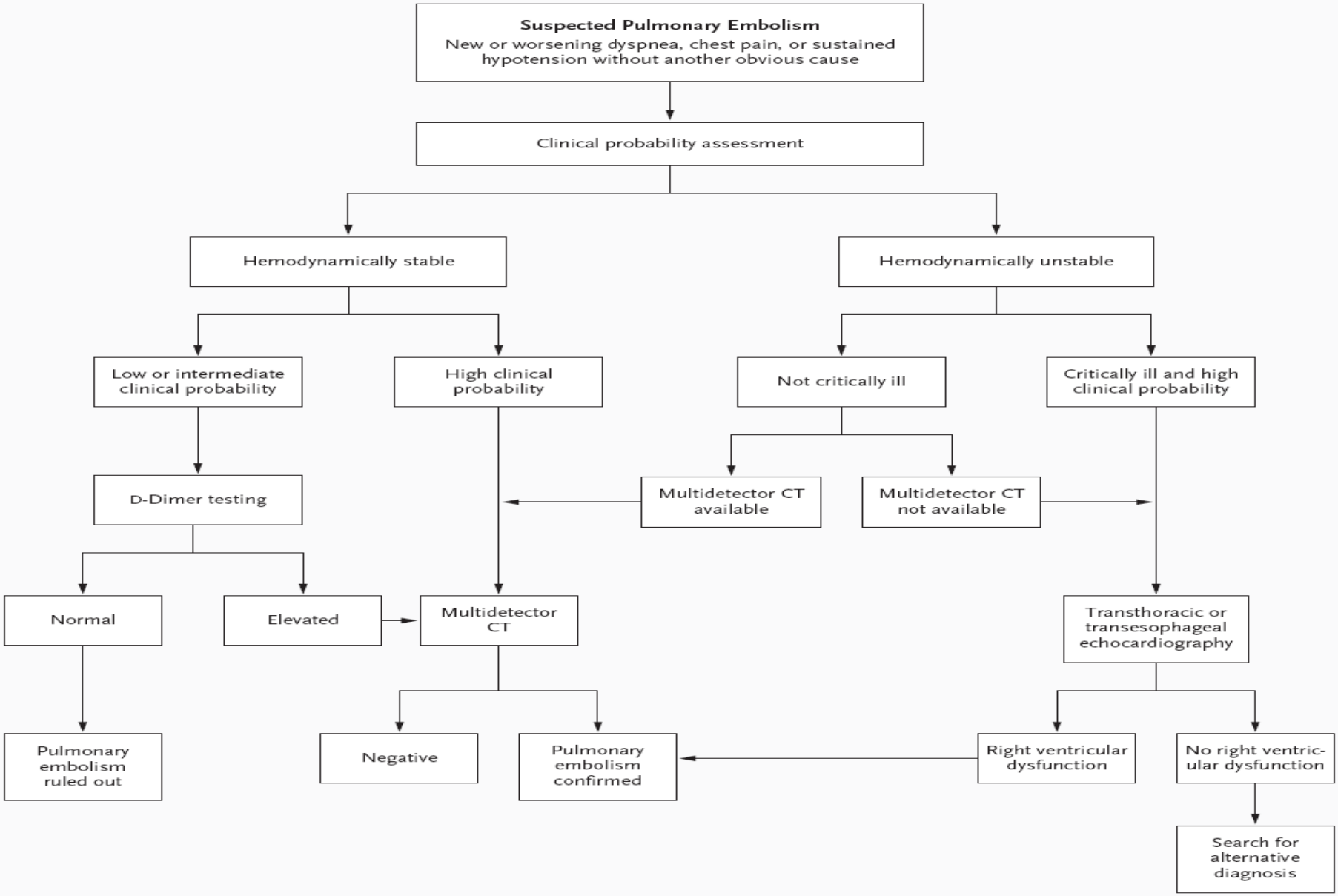
Pulmonary angiography

- criterion standard for the diagnosis of PE
- Positive results consist of a filling defect or sharp cutoff of the affected artery
- Non occlusive emboli have a tram-track appearance
- safe procedure.
- mortality rate < 0.5%
- morbidity rate is < 5%
- Patients with long-standing PAH and RV failure are considered high-risk patients
- Negative pulmonary angiogram findings, even if false-negative, exclude clinically relevant PE



abrupt termination of the ascending branch of the right upper-lobe artery

Diagnostic workup for PE



Complications

- Sudden cardiac death
- Obstructive shock
- Pulseless electrical activity
- Atrial or ventricular arrhythmias
- Cor pulmonale
- Severe hypoxemia
- Right to left intracardiac shunt
- Lung infarction
- Pleural effusion
- Paradoxical embolism
- Recurrent PE
- Permanent leg swelling, discomfort
- Chronic nonhealing ulcerations

MANAGEMENT

- CPR and ACLS protocols are of no value in patients whose cardiac arrest is due to PE
- since obstruction of the pulmonary circuit prevents oxygenated blood from reaching the peripheral and cerebral circulation
- emergency cardiopulmonary bypass or emergency thoracotomy

MANAGEMENT

- Oxygen (even when arterial PO_2 is perfectly normal, because increased alveolar oxygen may help pulmonary vascular dilatation)
- Anti coagulation
- Thrombolysis
- Surgery

Anticoagulation

- Heparin augments natural anticoagulant AT III and prevents conversion of fibrinogen to fibrin
- prevents extension of the thrombus
- is associated with complete lysis in < 10%
- does nothing to dissolve clot that has developed
- single most important treatment that can be provided
- greatest contribution to the mortality rate is ongoing embolization of new thrombi

Newer and older parenteral anticoagulants

	RB006	Heparin	LMWH Enoxaparin, dalteparin, tinzaparin	Fondaparinux
Target	FIXa	FIIa, FIXa, FXa, FXIa	FXa, FIIA	FXa
Administration route	Intravenous, subcutaneous	Intravenous, subcutaneous	Subcutaneous	Subcutaneous
Half-life	Intravenous : >24 hr	30-150 min	3-6 hr	12-17 hr
Renal Clearance	None	Minimal	100%	100%
Routine coagulation monitoring	No	Yes	No	No
Antidote	RB007	Protamine	Protamine (partial)	None
Potential for Immune HIT	No	High	Low	No

New oral anticoagulants

Drug (class)	Half-life (h)	Bio-availability (%)	Renal elimination	Oral dosage
Dabigatran (DTI)	14-17	6	80%	b.i.d.
Rivaroxaban (anti-Xa)	5-13	>80	33% (unchanged) 33% as inactive metabolites	o.d.
Apixaban (anti-Xa)	8-15	50-85	25	b.i.d.
Endoxaban (anti-Xa)	10	50	33	o.d.

Rationale for fibrinolysis in VTE

- Provides a 'head start' in pulmonary reperfusion compared with standard therapy with anticoagulation alone
- Reverses RV failure due to pressure overload & prevents hemodynamic collapse due to worsening RV dysfunction
- Restores systemic arterial perfusion pressure
- Improves pulmonary capillary blood flow and gas exchange
- Reduces thrombus burden in the pulmonary arteries and deep veins of the pelvis and lower extremities
- ↓ risk of developing chronic pulm HTN

Thrombolytic Therapy

does not prevent

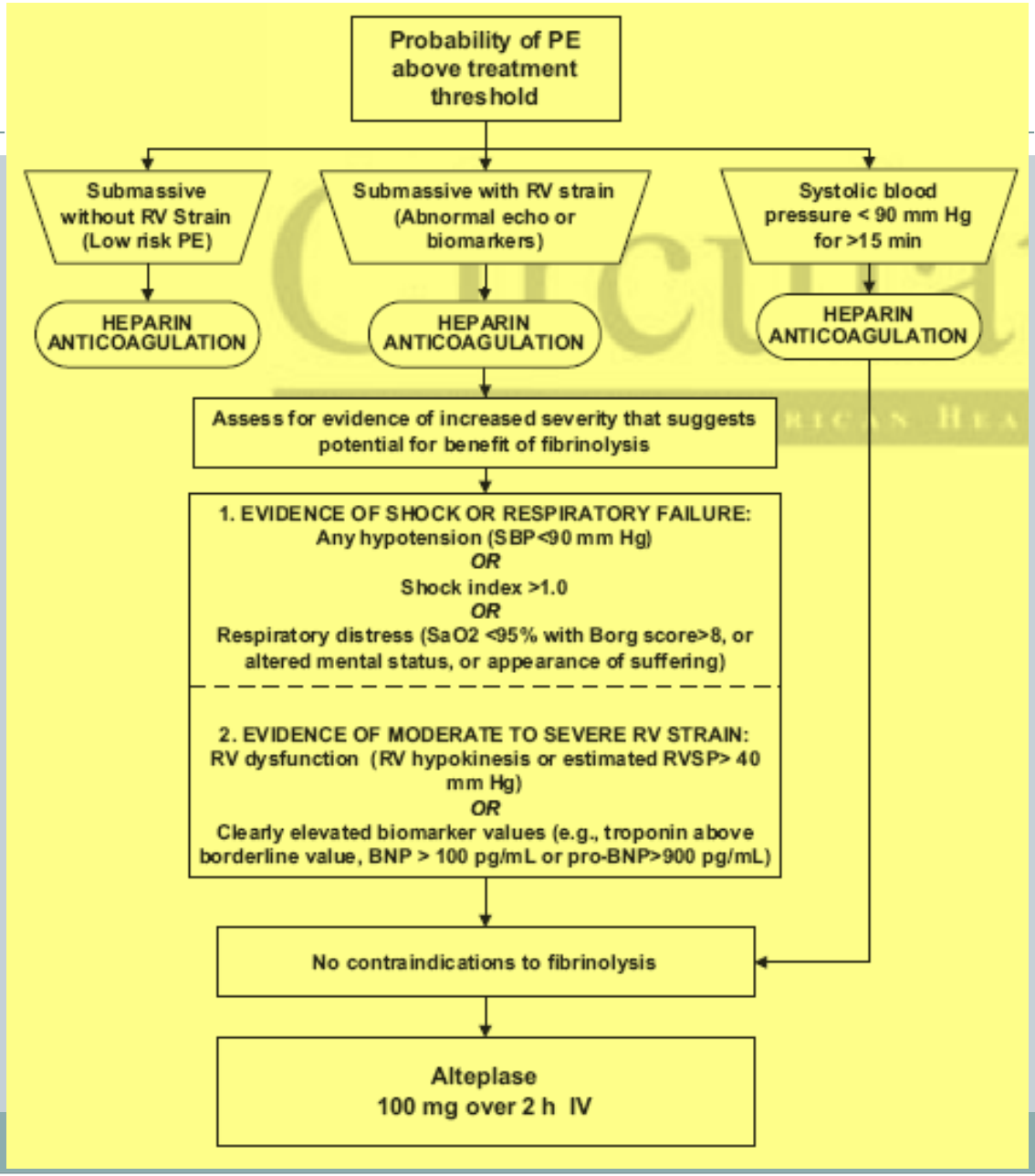
- clot propagation
- rethrombosis
- subsequent embolization

Window period of 14 days

Thrombolytic agents

Streptokinase	250,000 U as a loading dose over 30 min, followed by 100,000 U per hour over 12-24 h
	Accelerated regimen: 1.5 million IU over 2 ht
Urokinase	4,400 U/kg of body weight as a loading dosing over 10 min, followed by 4,400 U/kh/h over 12-24 h
	Accelerated regimen: 3 million U over 2 h
Alteplase	100 mg over 2 h
	Accelerated regimen: 0.6 mg/kg over 15 min
Reteplase	Two bolus injections of 10 U 30 min apart
Tenecteplase	30 to 50 mg bolus over 5-10 sec adjusted for body weight
	<60 kg: 30 mg ≥60 to <70 kg: 35 mg ≥70 to <80 kg: 40 mg ≥80 to <90 kg: 45 mg ≥90 kg: 50 mg

Suggested treatment algorithm for use of fibrinolytics



massive or submassive PE and C/I to fibrinolytic therapy or failed fibrinolysis

Alternative	Strengths	Limitations
Surgical embolectomy	• Effective in patients with large centrally located thrombi • Preferred after failed fibrinolysis • Preferred for patients with paradoxical embolism, persistent right heart thrombi, 'clot-in-transit', or hemodynamic or respiratory compromise requiring cardiopulmonary resuscitation	• May not be effective for smaller peripherally located thrombi • May not be widely available • Requires median sternotomy and cardiopulmonary bypass
Catheter-assisted embolectomy	• Effective in patients with large centrally located thrombi • Useful in patients with contraindications to fibrinolysis and surgical embolectomy • Useful if surgical embolectomy is unavailable	• Requires the administration of iodinated contrast • Volume of contrast administered may worsen right ventricular failure • Associated with risk of pulmonary hemorrhage due to arterial dissection or rupture, especially in smaller caliber pulmonary arteries • Associated with vascular access site complications • Data are lacking in patients with hemodynamically stable PE • Hemolysis
Inferior vena cava filter insertion	• Effective for the prevention of recurrent PE • Useful in patients with contraindications to fibrinolysis and surgical or catheter-assisted embolectomy • Retrievable filters offer temporary protection from recurrent PE	• Associated with an increased incidence of deep vein thrombosis • Does not address the initial PE or its hemodynamic effects • May be associated with vascular access site complications

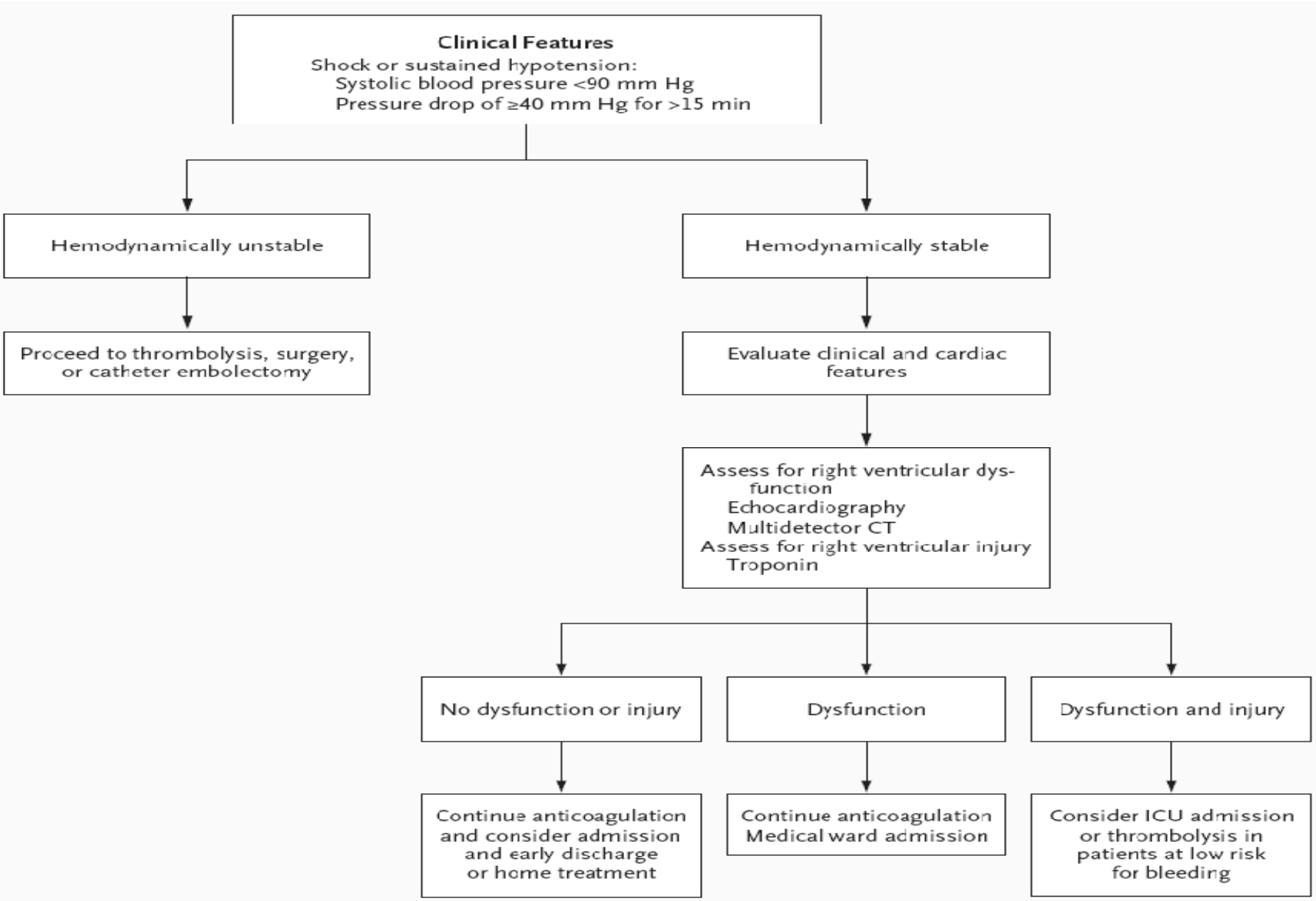
Ambulation

- Bed rest is not recommended unless there is substantial pain and swelling
- When PE is diagnosed, initial bed rest for 24 to 48 hours is often recommended
- early ambulation on day 2 after initiation of outpatient anticoagulant therapy
- Early ambulation without compression stockings is not recommended

Recommended duration of anticoagulant

Type of event	Recommended treatment duration
First DVT or PE secondary to a transient (reversible) risk factor ('provoked' event)	3 – 6 months
First idiopathic ('unprovoked') DVT or PE	At least 6 months
Recurrent VTE, malignancy, immobilization, morbid obesity	>?6 months, ?Long-term treatment
Patients of PE and preexisting irreversible risk factors (deficiency of AT III, protein S and C)	Long-term treatment
Recurrent DVT or PE or strong thrombophilia	Long-term treatment

Management of PE



Pregnancy

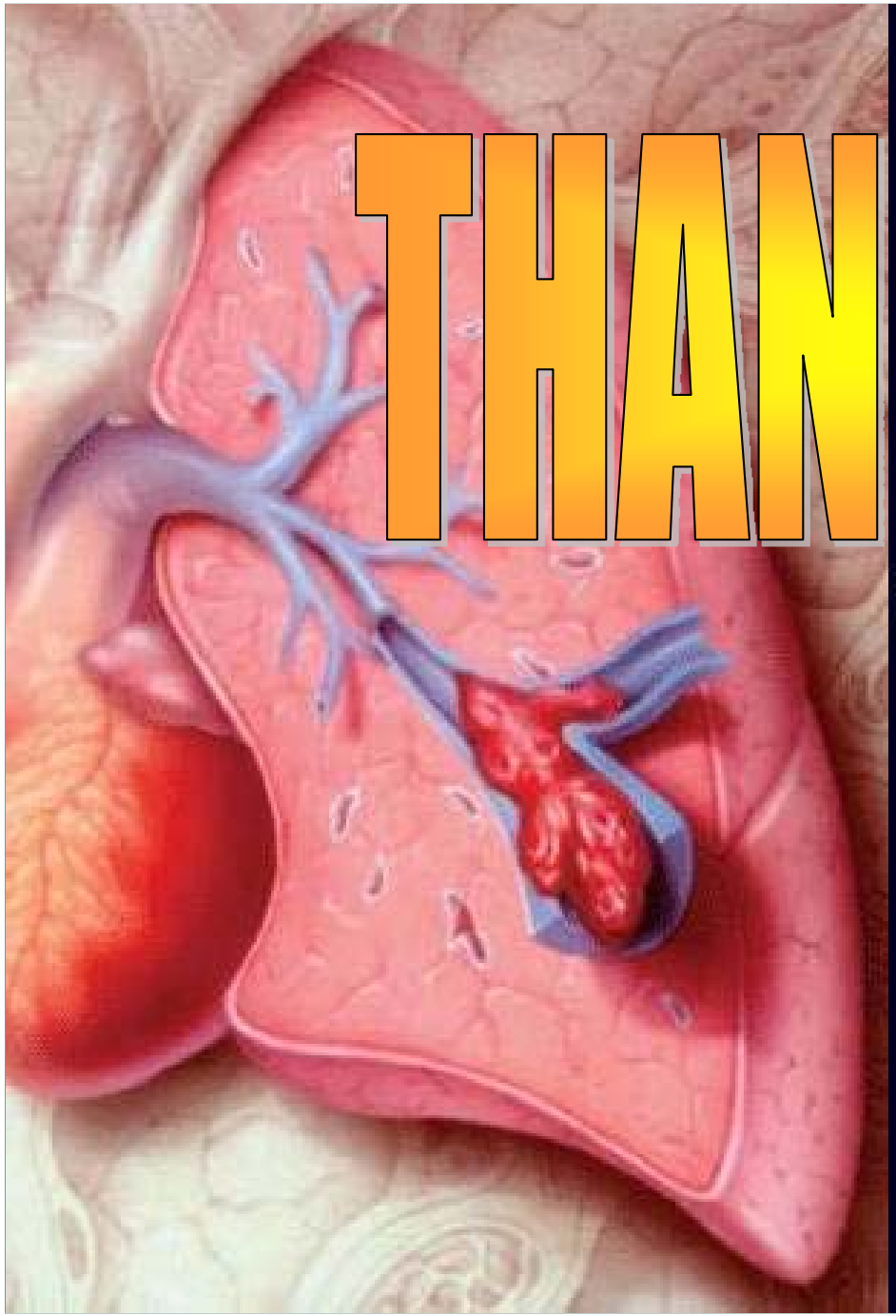
- VTE are common during all trimesters of pregnancy and 6-12 weeks after delivery
- Diagnostic approach exactly same in a pregnant patient as in a non pregnant one
- If PE is suspected in pregnancy and leg symptoms are present, compression ultrasonography is should be done
- If positive, diagnosis of PTE is confirmed
- VQ scan, CT chest, Heparin, Fibrinolysis is safe in pregnancy

Rosuvastatin in the Prevention of Venous Thromboembolism

- One recent study concluded that rosuvastatin was a/w significant ↓ in the risk of VTE
- This risk reduction was an independent benefit of statin use, beyond the reduction in the risk of arterial thrombosis

Prevention

- Heparin, LMWH, fondaparinux, warfarin, newer anti coagulants, mechanical prophylaxis (Intermittent pneumatic compression)
- Inferior vena caval filters not advised
- Extended prophylaxis with enoxaparin (for 38 days) as compared with 7 -10 days



THANK YOU