VENOUS THROMBOEMBOLIC DISEASE

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Venous thromboembolism, which includes deep venous thrombosis (DVT) and pulmonary thromboembolism (PE), occurs for the first time in approximately 100 persons per 100,000 in the United States each year. **More than 80% of clinically significant PE occur from DVT in the lower extremities;** the remainder originate from pelvic and upper extremity veins. The estimated short-term mortality of untreated PE (30%) is markedly reduced (<5%) by successful diagnosis and appropriate therapy. Unfortunately, the diagnoses of DVT and PE are frequently missed and effective prophylactive treatment is underused.

DEEP VENOUS THROMBOSIS

Basic Information

- Virchow's triad
  - **Venous stasis**
    - Immobility
    - Elevated venous pressure
    - Elevated blood viscosity
  - **Vessel wall damage**
  - **Increased blood coagulability**
    - Activation of clotting
    - Inhibition of fibrinolytic system
    - Deficiencies of coagulation factors
- Mechanisms
  - **Most important clinical risk is venous stasis from immobility**

Clinical Risk Factors

- Lower extremity DVT
  - Recent surgery (**especially orthopedic leg surgery**)
  - Major trauma (**>50% develop DVT if nonprophylaxed**)
  - Previous DVT (**30% recurrence over 8 years after first DVT**)
  - Increasing age (exponential increase after age 50 years)
  - Pregnancy/puerperium (PE is second leading cause of death; 75% occur postpartum)
  - Oral contraception
  - Medical conditions with immobility/hypercoagulability
    - Common: Cancer, heart failure, myocardial infarction, obesity, myeloproliferative disorder, nephrotic syndrome
    - Uncommon: Systemic lupus erythematosis, antiphospholipid antibody, sickle cell anemia, homocystinuria, Behçet's syndrome
- Upper extremity DVT
  - Cancer
  - Central venous catheter

Familial Thrombophilic Disorders

- Common
  - Activated protein C resistance (factor V Leiden)
    - **Autosomal dominant defect of factor V: Prevents inactivation by protein C**
    - 5% normal white population; rare in African or Asian descent
    - **20% unselected DVT patients; 60% idiopathic, recurrent DVT**
  - Prothrombin 20210A
    - Gene defect causing increased prothrombin and thrombin
    - 2% normal white population; rare in African or Asian descent
    - 5% unselected DVT, problematic when coexisting with other defects
- Rare
  - Deficiencies of antithrombin III, protein C, protein S
    - Autosomal dominant

- **Proteins C and S deficiency associated with warfarin-induced skin necrosis**

Clinical Presentation

- **Symptoms and signs insensitive and nonspecific**
  - Only 35% of symptomatic patients have leg DVT
  - Leg pain or swelling may be present
  - Homans' sign (pain and tenderness with dorsiflexion of ankle) present in less than 40%
- Starts in calf (except leg trauma, orthopedic surgery); most self-limited
- 25% of calf DVT extend to thigh
- **Thigh DVT strongly associated with PE**
  - Untreated symptomatic proximal DVT: 20% mortality from acute PE
  - 40% to 50% of patients with symptomatic thigh DVT have silent PE
- DVT recurs in 30% by 8 years; 50% of recurrences in contralateral leg

Diagnosis and Evaluation

- Noninvasive
  - B-mode compression ultrasonography (US)
    - Visualizes noncompressable clot in proximal veins; **poor for calf DVT**
    - 97% sensitive and specific for symptomatic proximal leg DVT
    - 30% to 60% sensitive, 98% specific for asymptomatic proximal leg DVT
    - **Initial test of choice for upper extremity DVT evaluation** but sensitivity and specificity 80%
    - Addition of Doppler flow or color adds little to sensitivity
  - Computerized tomographic (CT) venography
    - Performed with spiral chest CT; able to visualize clot in thigh, pelvic veins, IVC
    - **Perfomed with injured or casted leg** as US cannot be performed in this scenario
    - Contrast dye load
    - **Sensitivity and specificity less well defined**
  - Magnetic resonance imaging (MRI)
    - Able to visualize clot in calf, thigh, pelvic veins, IVC, upper extremities
    - Perfomed with injured or casted leg as US cannot be performed in this scenario
    - No contrast dye load
    - **Sensitivity and specificity greater than 90%**
- Invasive: Venography
  - **Gold standard**, detects thigh, calf, and upper extremity DVT regardless of symptoms
  - **Can distinguish between acute and recurrent clot**
  - Requires risks of contrast dye
  - Painful, can cause thrombosis
  - Decreasing availability
- DVT diagnosis in the **symptomatic** lower extremity
  - Low clinical suspicion (no risk factors or examination findings) and normal D-dimer
    - Further testing unnecessary, low incidence of DVT/PE if no therapy given
  - Low clinical suspicion and negative US (if D-dimer not available)
    - Further testing unnecessary, low incidence of DVT/PE if no therapy given
  - Moderate or high clinical suspicion: US necessary
    - **Negative initial US**: 15% of these patients have calf DVT; 20% to 30% will extend to thigh
      - US should be repeated at one week
    - Negative serial US: Acceptable 1% to 2% risk of thromboembolism if untreated
    - Immediate venogram is alternative to serial US

DVT Treatment/Prophylaxis

- Treatment of DVT—see PE treatment
- Prophylaxis choice is dependent upon the risk of thrombosis for an individual (Table 22-1)

PULMONARY EMBOLISM

Basic Information

- Effects of pulmonary emboli on gas exchange
  - Dead space increased but **$PaCO_2$ normal or low** (from hyperventilation)

TABLE 22-1

DVT Prophylaxis

	Clinical Risks	Prophylaxis
Low risk (<1% prox DVT)	Under 40 years old Minor surgery (<1 hour) minimal immobility	Early ambulation Compression stockings
Moderate risk (8% DVT)	40 to 60 years old General surgery MICU or CCU stroke	Unfractionated heparin 5000 U SQ q8–12 or LMWH (enoxaparin). (20–40 mg SQ qd) (Leg compression if CNS or eye surgery)
High risk (20% DVT)	>60 years with general surgery Extended surgery Ortho leg surgery Hip fracture Extensive trauma	LMWH (enoxaparin) 40 mg SQ qd or 30 mg q12 for trauma, fondaparinux (hip surgery or fracture), or moderate-dose warfarin (INR 2.5)

- **Hypoxemia variable** because it is epiphenomenon of clot (atelectasis, interatrial shunt)
- Effects of pulmonary emboli on pulmonary and systemic hemodynamics
  - In previously healthy patients
    - Peripheral vascular resistance (PVR) increase proportional to obstruction
    - Pulmonary artery pressure (Ppa) increases after 30% to 50% bed occluded
    - Normal right ventricle (RV): Maximal mean Ppa of 40 mm Hg
  - In patients with preexisting heart/lung disease
    - No correlation of clot burden with PVR or Ppa
  - Shock
    - Increased right atrial pressure decreases venous return
    - RV distension leads to shift interventricular septum, causing impaired left ventricular function

Clinical Presentation

- **PE presents as**
  - **Infarction-like syndrome: Chest pain, cough, hemoptysis (65%)**
  - **Dyspnea syndrome (22%)**
  - **Circulatory collapse (8%)**
- Major **symptoms: Dyspnea, chest pain, cough**
- Major **signs: Tachypnea, crackles, tachycardia**
  - Dyspnea, tachypnea, or pleuritic chest pain present in 97% PE

Diagnosis and Evaluation

See Figures 22-1 and 22-2.

- Chest x-ray and ECG
  - Abnormal 70% to 90% but nonspecific
    - Atelectasis, consolidation, diaphragm elevation on chest x-ray
    - Nonspecific ST changes on ECG
- Arterial blood gases
  - **Wide alveolar-to-arterial O_2 gradient**
  - **Respiratory alkalosis**
  - Hypoxemia with the following caveats
    - 12% to 25% of patients have a PaO_2 greater than 80 mm Hg
    - 20% have normal age-defined alveolar-to-arterial O_2 gradient
- D-dimer
  - Degradation product of cross-linked fibrin
  - Elevated in DVT/PE but also in
    - Surgery, trauma, malignancy, DIC, pregnancy, infection
  - Assay
    - ELISA more sensitive than latex agglutination
    - **Positive D-dimer not helpful; negative (i.e., normal) D-dimer more clinically useful as follows**
      - Normal sensitive D-dimer level has negative predictive value of 100% for DVT/PE
      - Normal less-sensitive value for D-dimer with low pretest probability for DVT or PE excludes thromboembolism

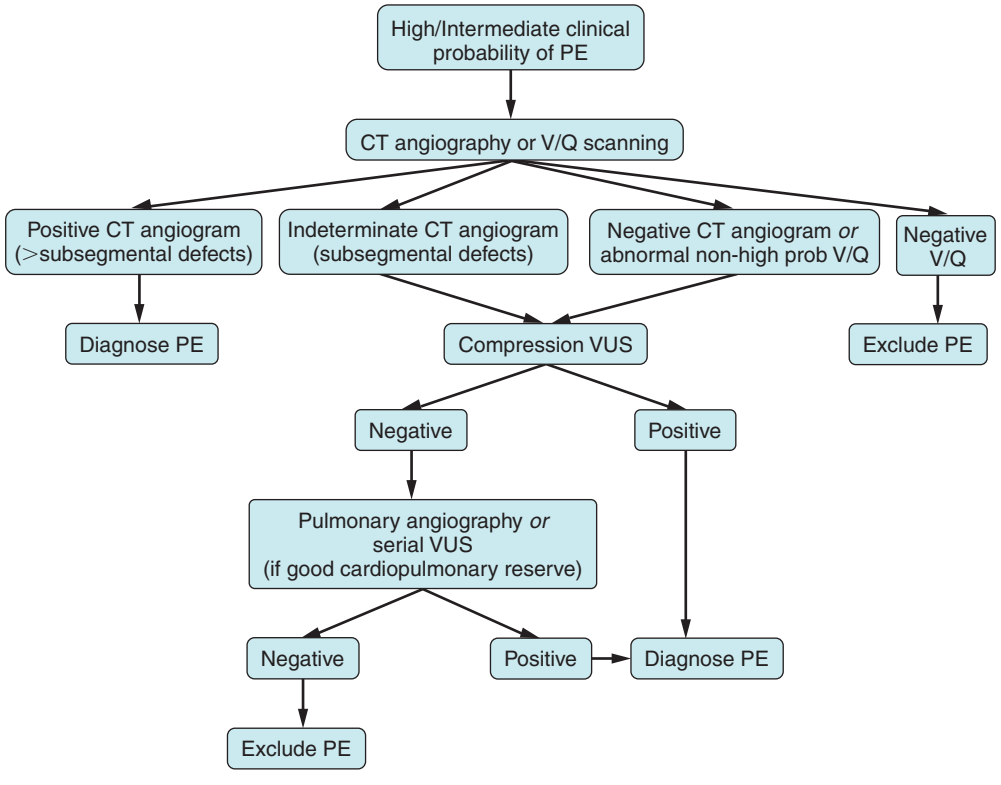


FIGURE 22-1. Proposed diagnostic algorithm for PE in patients with high or intermediate pretest probability using either V/Q scan or CT angiography as initial test. V/Q, ventilation perfusion scan; VUS, venous ultrasound. (*Modified from Fedullo PF, Tapson VF: Clinical practice. The evaluation of suspected pulmonary embolism. N Engl J Med 349:1247, 2003.*)

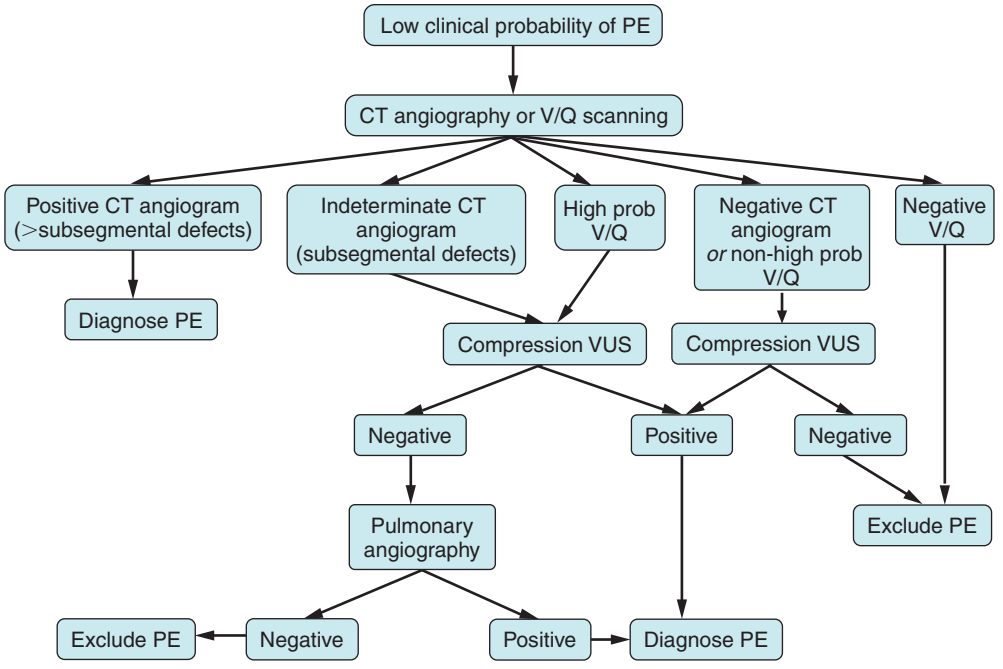
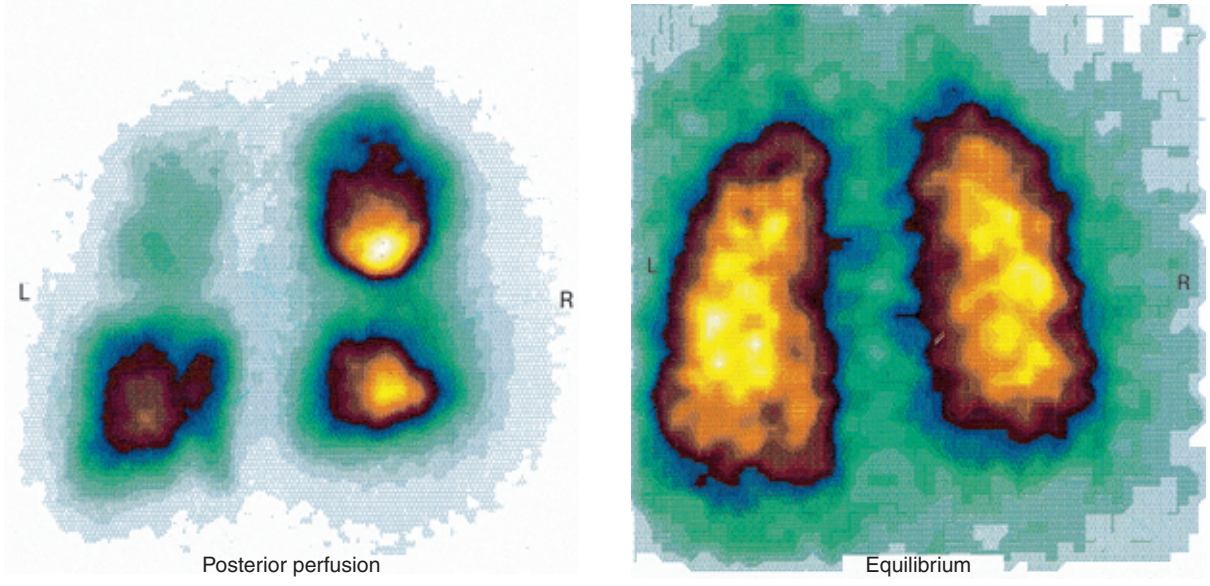


FIGURE 22-2. Proposed diagnostic algorithm for PE in patients with low pretest probability using either V/Q scan or CT angiography as initial test. V/Q, ventilation perfusion scan; VUS, venous ultrasound. (*Modified from Fedullo PF, Tapson VF: Clinical practice. The evaluation of suspected pulmonary embolism. N Engl J Med 349:1247, 2003.*)

- Normal less-sensitive value for D-dimer with nondiagnostic V/Q scan excludes PE
- Usefulness limited in inpatients
  - Normal values for D-dimer in only 5% of all inpatients
  - Normal values for latex assay occur in documented PE
  - ELISA assay better but slow turnaround
- The ventilation perfusion (V/Q) lung scan (Fig. 22-3)
  - PIOPED study used to interpret results (Table 22-2)
    - Normal perfusion scan rules out PE regardless of clinical suspicion or ventilation scan findings
  - Assigning pretest probability improves scan interpretation (Table 22-3)



A B

FIGURE 22-3. Lung ventilation and perfusion scintigraphy. **A,** Multiple perfusion defects in left upper lobe and right midzone on perfusion scan. **B,** Normal ventilation scan. This combination is consistent with high probability of pulmonary embolism. (*From Haslett C, Chilvers ER, Boon NA, et al:* Davidson's Principles and Practice of Medicine*, 19th ed., New York, Churchill Livingstone, 2002, figure 13.6.*)

TABLE 22-2

Ventilation Perfusion Lung Scanning: The Pioped Study Criteria

Scan Pattern (Prevalence)	Original Definition	Revised Definition
High probability (13%)	Segmental mismatches ≥2 large 1 large + 2 moderate ≥4 moderate	≥2 moderate/large segmental mismatch
Intermediate (39%)	Not high or low	1 moderate/large segmental mismatch or match Not high or low
Low (34%)	1 moderate/large segmental mismatch ≤4 moderate/large segmental match	>3 small subsegmental defects Nonsegmental perfusion defects
Very low/normal (14%)	Normal perfusion ≤3 small subsegmental perfusion defects	Normal perfusion ≤3 small subsegmental perfusion defects

- High probability V/Q and moderate/high clinical probability: 88% to 96% positive predictive value
- High probability V/Q and low clinical probability: 50% positive predictive value
- All other abnormal scan/clinical probability combinations: PE risk unpredictable but substantial (20% to 40%)
- Specificity of high probability pattern not altered by underlying lung disease such as COPD

- Management with the V/Q is nondiagnostic
  - **Pulmonary angiography is next step and is the gold standard**
    - Low morbidity (<2%) and mortality (<0.01%)
    - Clinically proven 98% to 100% negative predictive value
    - Expensive and not widely available
  - **Alternative second step after V/Q: Leg studies for DVT**
    - Patients with abnormal non–high probability V/Q with PE (angiogram confirmed): Only 24% have proximal DVT by US
- Role for serial leg studies
  - Intermediate or low probability V/Q, negative leg US, low/intermediate clinical probability, and good cardiopulmonary reserve
    - Two additional leg studies at 7 and 14 days off anticoagulant; if negative, no treatment
  - Poor cardiopulmonary reserve (shock, syncope, RV dysfunction, respiratory failure) or severe symptoms
    - Immediate pulmonary angiogram
  - This strategy results in
    - Less than 10% overall need for pulmonary angiography in PE workup
    - Less than 3% subsequent thromboembolism at three months if anticoagulant withheld
- Spiral CT (Fig. 22-4)
  - Compared with pulmonary angiogram
    - **Sensitivity adequate for lobar or larger emboli** (>95%)
    - **Sensitivity poor for more distal emboli** (<20%; many false negatives)
    - Specificity varies from 78% to 97% (**significant false positives, especially in subsegmental vessels**)
  - **Can be used as initial study in place of V/Q**
    - Intraluminal filling defects in segmental to main pulmonary arteries diagnostic for PE

TABLE 22-3

Assessment of Pretest Probability of Pulmonary Embolism

Variables	Points
Clinical signs and symptoms of DVT	3.0
Alternative diagnosis less likely than PE	3.0
Heart rate > 100/min	1.5
Immobilization or surgery in preceding 4 weeks	1.5
Previous DVT or PE	1.5
Hemoptysis	1.0
Cancer	1.0

Clinical pretest probability for PE: Low, <2.0; Intermediate, 2.0–6.0; High, >6.0.Data from Wells PS, Anderson DR, Rodger M, et al: Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: Increasing the models utility with the SimpliRED D-dimer. Thromb Haemost 83:416–420; 2000.

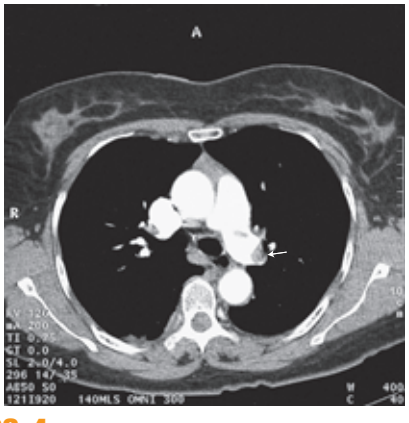


FIGURE 22-4. CT scan demonstrating filling defect in proximal left pulmonary artery *(arrow)* from thrombus. Distal branches of artery are occluded. (*From Souhami R:* Textbook of Medicine*, New York, Churchill Livingstone, 2002, figure 13.6.2A.*)

- Isolated subsegmental filling defects inconclusive
- Low or intermediate clinical probability with negative spiral CT and lower extremity US rules out PE
- **High clinical probability and negative spiral CT and US require additional testing (V/Q or angiogram)**

Treatment

- Acceptable forms of therapy
  - Unfractionated heparin (UH) 80 U/kg IV bolus, 18 U/kg/hour, APTT 1.5 to 2.5 continuous *or*
  - UH 17,500 U SQ every 12 hours, APTT 1.5 to 2.5 continuous, *or*
  - Low-molecular-weight heparin (LMWH) 100 U/kg every 12 hours or 200 U/kg once per day (no monitoring, contraindicated if renal failure), *then*
  - Warfarin 5 mg/day started day 1 overlapped with heparin 4 to 7 days INR 2.0 to 3.0
    - Protein C and S decline when warfarin started during active thrombotic state. This decline causes an increase in thrombogenic potential. Heparin can counteract this temporary procoagulant effect
- PE/DVT: Duration of therapy
  - **Three months with reversible major risk factors**
  - **Six months with reversible minor risk factors** (estrogen therapy, partial immobilization)
  - **Six months to indefinite for idiopathic DVT/PE**
    - Indefinite if low bleeding risk and patient agrees
    - Six months if significant bleeding risk or patient refuses indefinite treatment
  - **Twelve months to indefinite for**
    - **First DVT/PE with cancer, antiphospholipid antibody, deficiency of ATIII**, *or*
    - **Second DVT/PE, which is idiopathic or associated with thrombophilic disorder**
    - Indefinite if low bleeding risk and patient agrees
    - Twelve months if significant bleeding risk or patient refuses indefinite treatment
- Thrombolytic therapy (TT)
  - TT indicated for
    - **PE with severe hemodynamic/oxygenation compromise**
      - In PE, TT accelerates resolution of physiological abnormalities and scan defects
      - However, no difference at 48 hours compared with heparin
    - **Extensive iliofemoral DVT**
      - In DVT: Decreases postphlebitic syndrome
  - Effect on mortality (if any) unknown
  - Risk of TT
    - Serious bleeding 6% to 45% (three-fold >heparin)
    - Fatal bleeding 2% (ten-fold >heparin)
  - Approved drugs
    - Streptokinase infusion over 24 hours
    - Urokinase infusion over 12 to 24 hours
    - rt-PA infusion over two hours
  - Contraindications of TT
    - **Absolute**
      - **Intracranial or intraspinal disorders, surgery, trauma preceding two months**
      - **Active bleeding**
    - Relative
      - Surgery, organ biopsy, large vessel puncture, CPR, within 10 days postpartum
- Inferior vena caval filters
  - Indications
    - Contraindication to anticoagulation
    - Recurrence of DVT/PE on therapeutic anticoagulation
  - Effects
    - Decrease early recurrent PE after anticoagulation without mortality effect
    - Increase incidence of later DVT

SUGGESTED READINGS

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