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 prophylactic 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
  - Performed 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)

- 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 PaCO₂ normal or low (from hyperventilation)

<table>
<thead>
<tr>
<th>TABLE 22-1</th>
<th>DVT Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Risks</td>
<td>Prophylaxis</td>
</tr>
<tr>
<td>Low risk (&lt;1% prox DVT)</td>
<td>Under 40 years old</td>
</tr>
<tr>
<td>Minor surgery (&lt;1 hour)</td>
<td>Compression stockings</td>
</tr>
<tr>
<td>Immobility</td>
<td></td>
</tr>
<tr>
<td>Moderate risk (8% DVT)</td>
<td>40 to 60 years old</td>
</tr>
<tr>
<td>General surgery</td>
<td>MICU or CCU</td>
</tr>
<tr>
<td>Moderate</td>
<td>Ortho leg surgery</td>
</tr>
<tr>
<td>High risk (20% DVT)</td>
<td>Hip fracture</td>
</tr>
<tr>
<td>Extensive trauma</td>
<td></td>
</tr>
</tbody>
</table>
**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 O₂ gradient
  - Respiratory alkalosis

- **Hypoxemia with the following caveats**
  - 12% to 25% of patients have a PaO₂ greater than 80 mm Hg
  - 20% have normal age-defined alveolar-to-arterial O₂ 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

- **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

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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)


**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.)
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

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


TABLE 22-2

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

TABLE 22-3

<table>
<thead>
<tr>
<th>Variables</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs and symptoms of DVT</td>
<td>3.0</td>
</tr>
<tr>
<td>Alternative diagnosis less likely than PE</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart rate &gt; 100/min</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization or surgery in preceding 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Assessment of Pretest Probability of Pulmonary Embolism

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.)
Treatment

- Thrombolytic therapy (TT)
- **PE/DVT:** Duration of therapy
- **Approved drugs:**
  - Effect on mortality (if any) unknown
  - TT indicated for
    - Twelve months to indefinite for idiopathic DVT/PE
    - Six months with reversible minor risk factors (estrogen therapy, partial immobilization)
    - Three months with reversible major risk factors
      - PE with severe hemodynamic/oxygenation compromise
      - Extensive iliofemoral DVT
    - Contraindications of TT
      - **Absolute:**
        - Intracranial or intraspinal disorders, surgery, trauma preceding two months
      - **Relative:**
        - Surgery, organ biopsy, large vessel puncture, CPR, within 10 days postpartum
      - Inferior vena caval filters
      - 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

**Venous Thromboembolic Disease**

- 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)

**Suggested Readings**


