Pulmonary Thromboembolism

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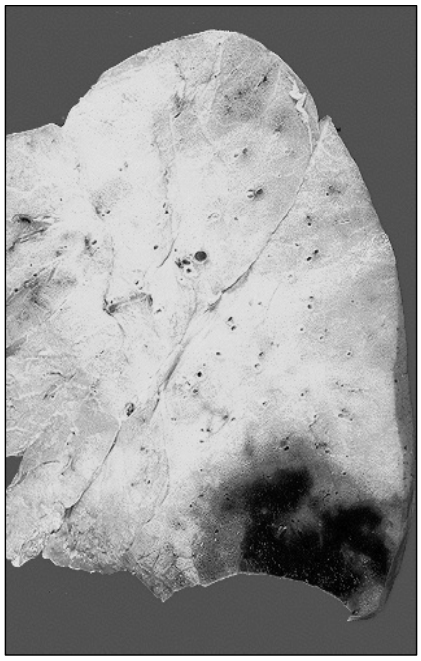
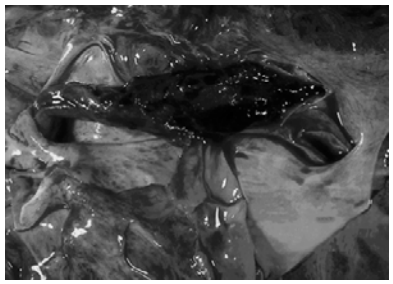
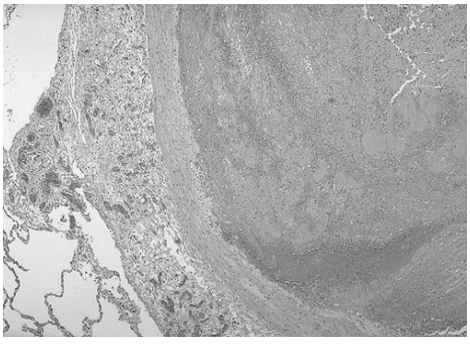
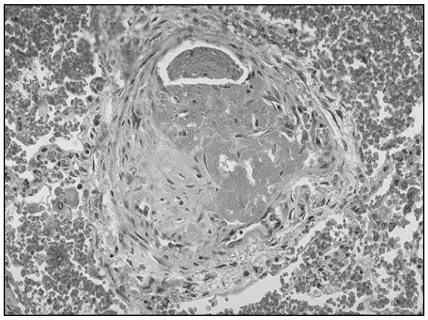
Epidemiology of Pulmonary Embolism

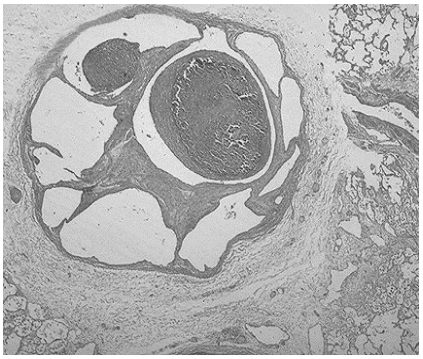
- **1,500,000 new cases per year**
- **Often asymptomatic**
- **300,000 deaths per year**
- **DVT or PE present in 10% of ICU patients**
- **Untreated mortality is 30%**











Clinical Case

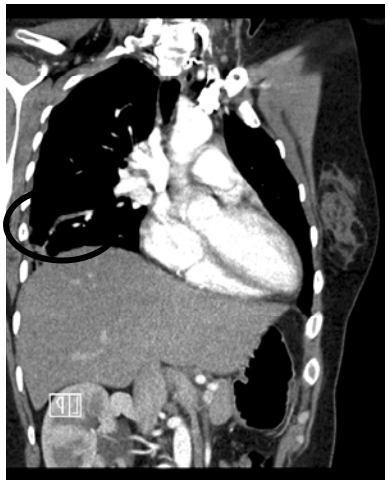
- 28 year old woman
- Three days previously: “charley horse” in the left calf
- Sudden onset right pleuritic chest pain and dyspnea
- Past medical history: negative
- Medications: birth control pills

Clinical Case

- Vital signs:
  - Temperature 97.6
  - BP 166/90
  - HR 92
  - RR 18
  - O2% = 94%
- Lungs clear to auscultation
- Leg exam normal
- CBC: normal
- Electrolytes: normal
- Brain natriuretic peptide (BNP): normal
- Troponin I: normal

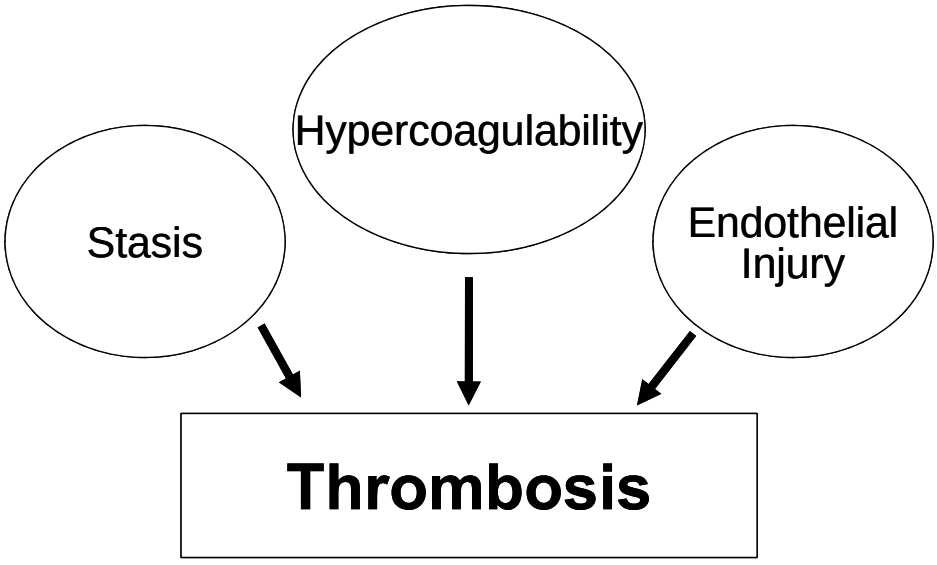
Clinical Case CT Angiogram

Clinical Case CT Angiogram



Why Did She Clot?

Virchow's Triad



Venous Stasis

- Immobility
- Bed rest
- Surgery
- Cor pulmonale
- Obesity

Endothelial Injury

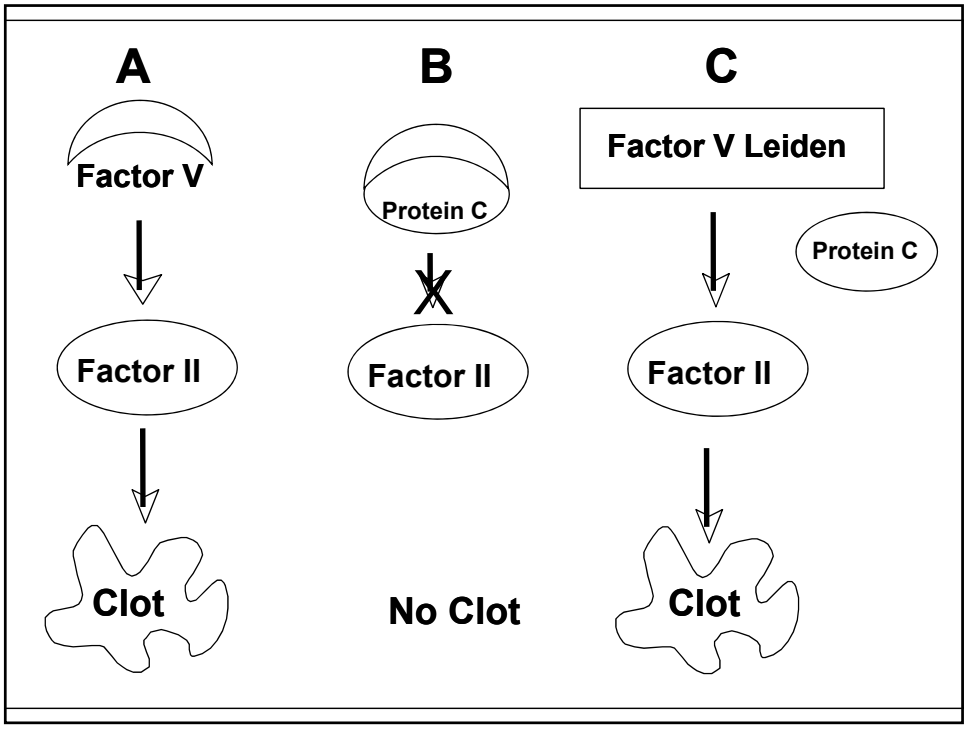
- Previous DVT
- Trauma
- Surgery
- Femoral venous catheters

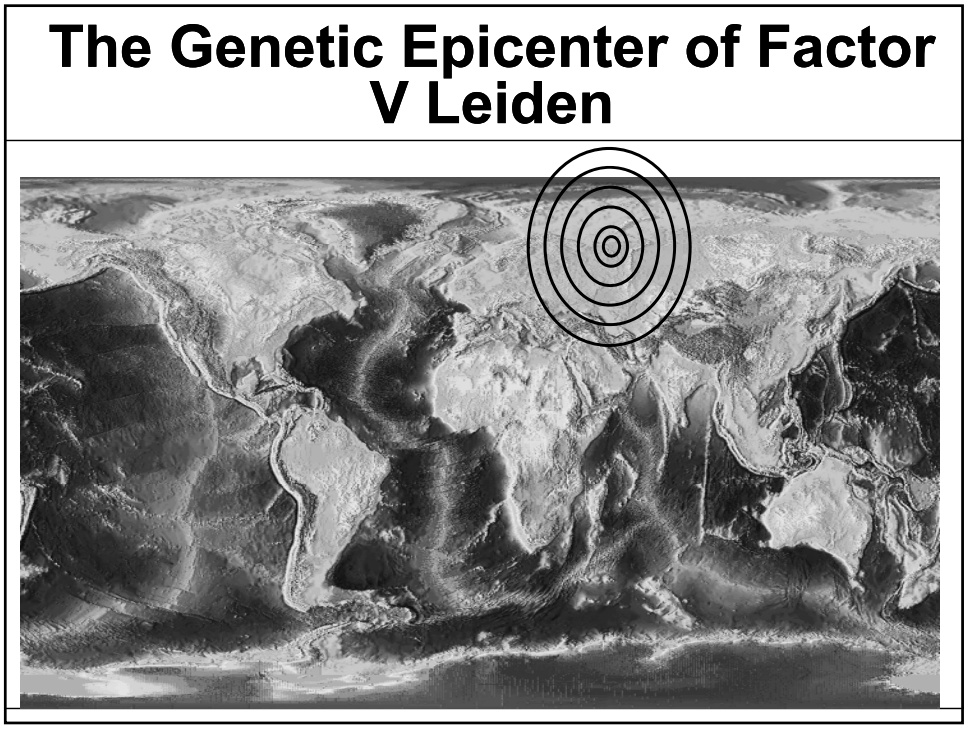
Heritable Hypercoaguability

- Factor V Leiden mutation
- Prothrombin G-A20210 mutation
- Hyperhomocysteinemia
- Protein C deficiency
- Protein S deficiency
- Anti-thrombin III deficiency
- Elevated factors VIII, IX, & XI

Factor V Leiden

- Causes resistance to activated protein C
- 4% of Americans are heterozygotes
- Contributes to about 10-26% of DVT/PE
- Heterozygotes = 7 fold increased risk
  - plus OCPs = 35 fold increased risk
- Homozygotes = 80 fold increased risk


A
B
C
Factor V
Protein C
Factor V Leiden
Protein C
Factor II
Factor II
Factor II
Clot
No Clot
Clot


The Genetic Epicenter of Factor V Leiden

United States Racial Distribution of Factor V Leiden

- 5.3% Caucasian Americans
- 2.2% Hispanic Americans
- 1.2% African Americans
- 1.2% Native Americans
- 0.4% Asian Americans

Prothrombin G-A20210 Mutation

- Causes increased prothrombin levels
- Contributes to about 6-8% of all DVT/PE
- Heterozygotes = 3 fold increased risk
  - heterozygote + factor V Leiden = 10 fold risk
- Homozygotes = very high risk

Hyperhomocysteinemia*

Causes

- Genetic
- Poor nutrition
- Renal insufficiency
- Malignancy
- Hypothyroidism
- High animal fat diet

Drug causes

- Methotrexate
- Phenytoin
- Carbamazepine
- Theophylline

*3-fold increased risk

Acquired Hypercoaguability

- Pregnancy
- Hyperhomo-cysteinemia
- Anti-phospholipid antibodies
- Malignancies
- Drugs:
  - Estrogens
  - Tamoxifen
  - Bevacizumab
  - Heparin-induced thrombocytopenia

Anti-Phospholipid Antibodies

IgG Antibodies

- Systemic lupus erythematosus
- Sjogren's
- Rheumatoid arthritis
- Scleroderma

IgM Antibodies

- Infections:
  - HIV
  - Hepatitis
  - Sepsis
- Medications:
  - Phenytoin
  - Hydralazine

Thrombocytopenia and Heparin

Non-Immune

- Platelets > 100,000
- Days 1-5 of heparin
- Not thrombogenic

Immune

- Platelets fall by > 50% (usually < 100,000)
- Between day 5-14 of heparin
- Highly thrombogenic
- 2.6% of patients treated > 4 days

Heparin-induced thrombocytopenia

- When suspected, discontinue all heparin pending HIT study
- Initial treatment = argatroban, lepirudin, or danaparoid
- Long-term (3-6 month) Coumadin

Beware of COPD "exacerbations"

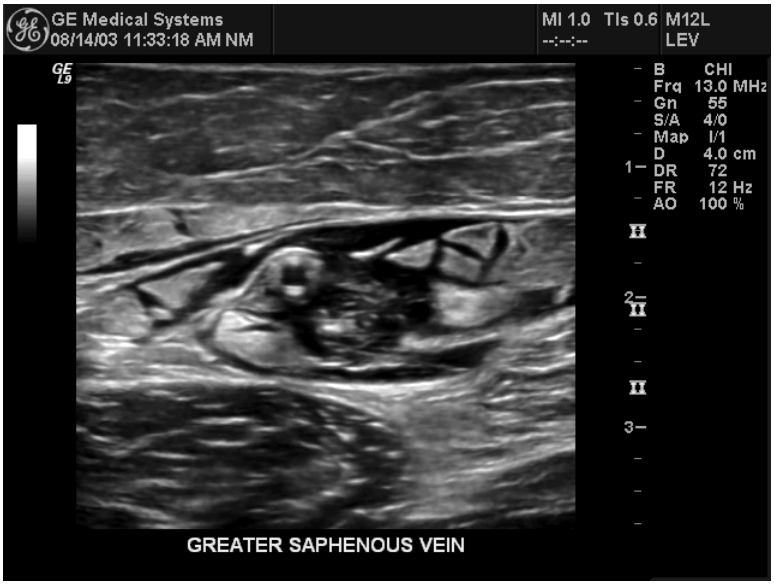
- One out of four patients hospitalized with COPD exacerbations have PE
- Signs and symptoms are often similar to usual COPD exacerbations
- The risk is higher for inpatients
- Be suspicious in patients lacking typical bronchitis symptoms

Chest 2009; 135:786-93

Deep Venous Thrombosis Diagnosis

- D-dimer – greatest value when negative in low/moderate risk patients
- Duplex ultrasound
  - Sensitivity & specificity = 99%
  - Accuracy best for femoral DVT
- Venography
- CT scanning
- MRI

Image courtesy of GE Healthcare; used with permission



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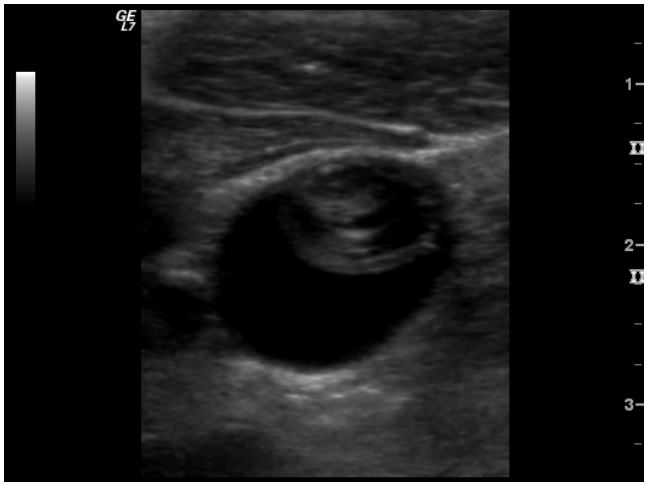

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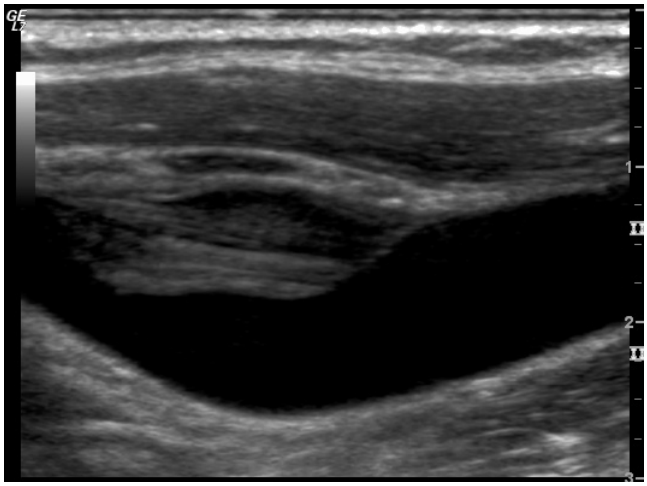

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Calf Vein Thrombosis

- **20% propagate into proximal veins**
- **Anticoagulation necessary if propagate**
- **Safest approach is to treat all cases for 3 months**
- **Serial duplex ultrasounds if anticoagulation is risky**

Pulmonary Embolism

Symptoms

- Dyspnea 80%
- Pleurisy 70%
- Cough 50%
- Hemoptysis 30%

Signs

- Increased A-a gradient 95%
- Tachypnea 92%
- Tachycardia 44%
- Fever 43%

Well's Criteria for PE

3.0 Signs of DVT
1.5 HR > 100
1.5 Immobilization for > 3 days or surgery in past 4 months
1.5 Previous PE
1.0 Hemoptysis
1.0 Malignancy
3.0 PE as or more likely than other diagnoses

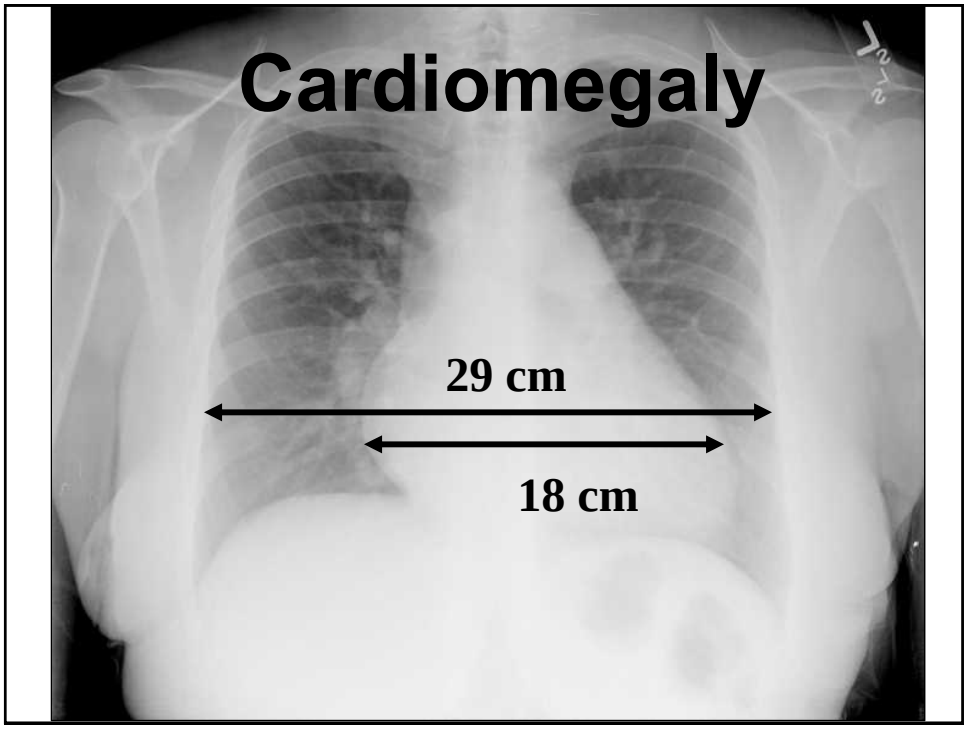
≤ 4 points – PE unlikely
≥ 5 points – PE likely

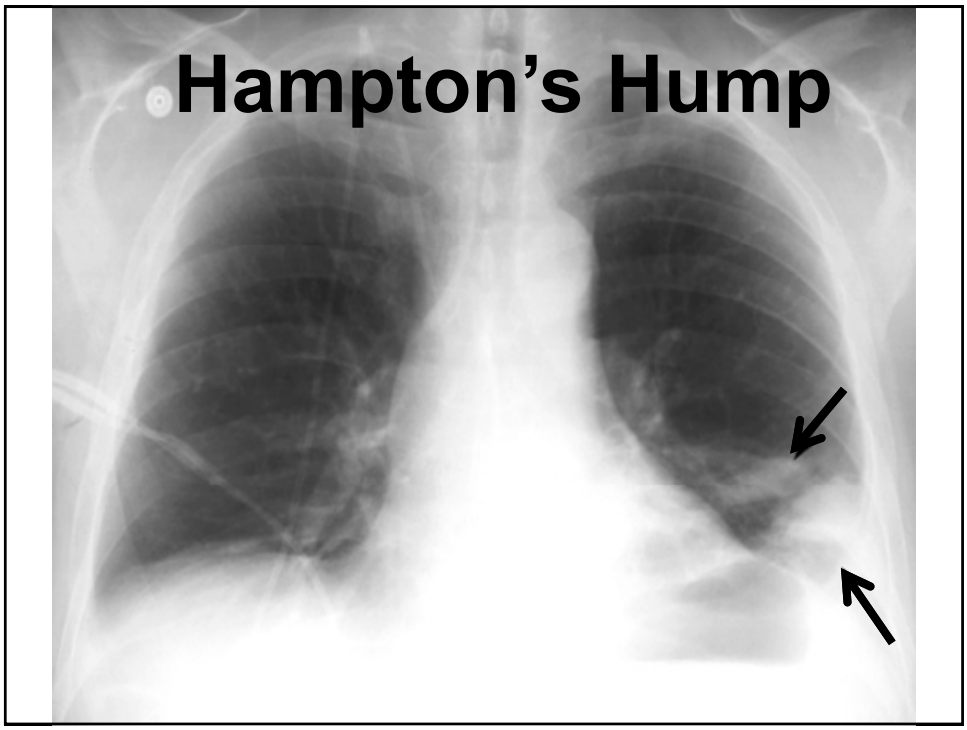
PERC (PE Rule out Criteria)

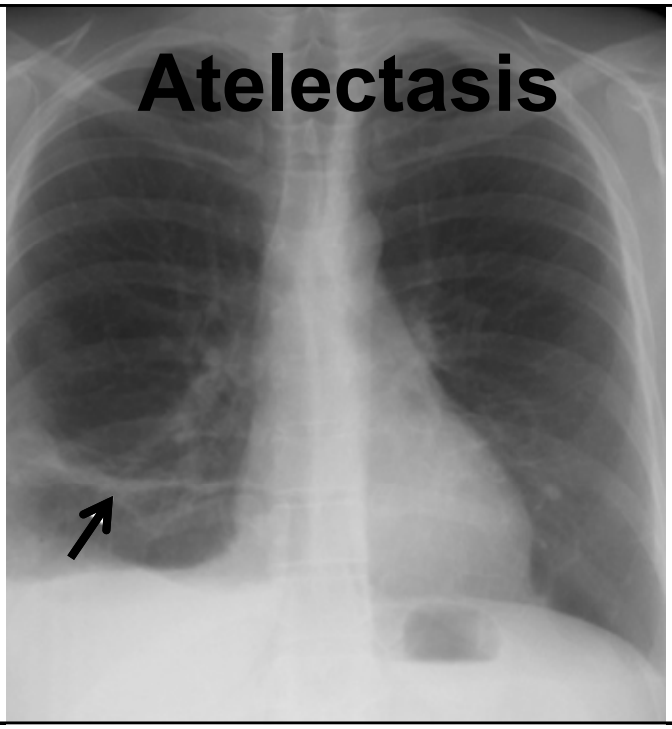
- Age < 50
- Heart rate < 100
- SaO2 > 95%
- No hemoptysis
- No estrogen use
- No prior DVT or PE
- No unilateral leg swelling
- No surgery/trauma in past 4 weeks

Chest X-Ray Findings

- Cardiomegaly
- Enlarged pulmonary artery
- Atelectasis
- Elevated hemidiaphragm
- Regional oligemia
- Pleural effusion
- Hampton's hump


Cardiomegaly
29 cm
18 cm


Hampton's Hump



D-Dimer In Pulmonary Embolism

- Sensitivity = 95%
- Specificity < 50%
- False positives are frequent after surgery and in hospitalized patients
- Negative test is strong evidence against DVT/PE in patients with low clinical suspicion
- Only validated for outpatients

Cardiac Enzymes

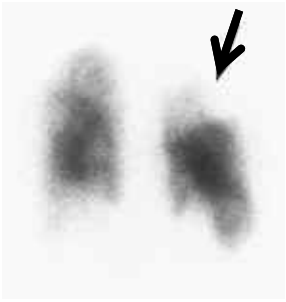
- Troponin I
  - Elevated in 30-50% of moderate to large PE
  - Correlates with embolism size and worse outcome
- BNP
  - Level > 90 predicts worse outcome, especially if the troponin I is elevated

Ventilation Perfusion Scan

- Still the best initial test for some patients
- Most valuable if normal
- Clinical decision making requires:
  - V/Q scan probability
  - Clinical probability

Ventilation/Perfusion Scan

Normal ventilation scan



Perfusion scan showing pulmonary embolus

Perfusion scan showing resolved pulmonary embolus

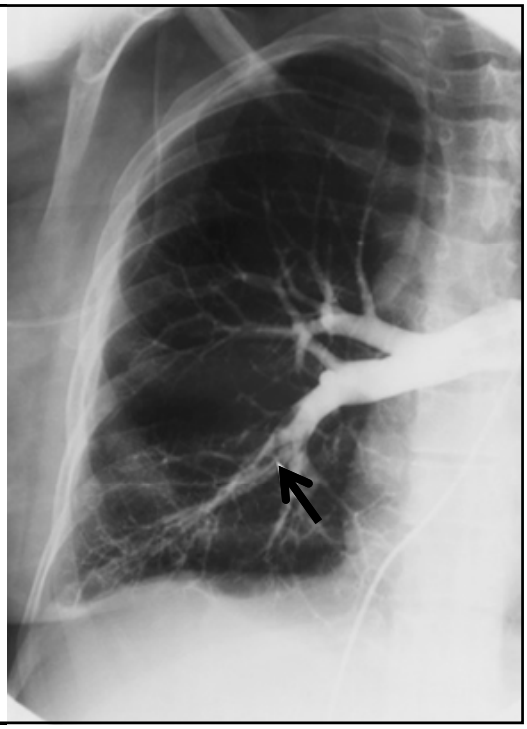
Probability of Pulmonary Embolus

V/Q Probability	Clinical Suspicion: High	Intermediate	Low
High	96%	88%	56%
Intermediate	66%	28%	16%
Low	40%	16%	4%

JAMA 1990; 263:2753-9

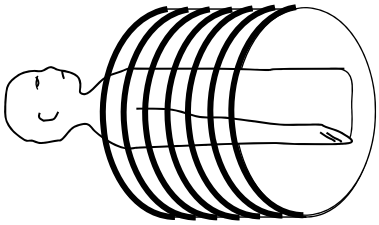
Pulmonary Angiogram

- "Gold standard"
- Negative study excludes PE
- Relatively low complication rate
- False positives rare

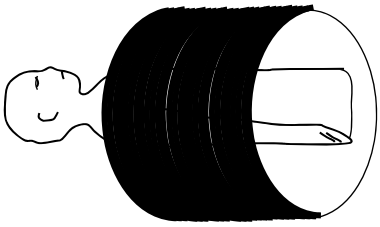


CT Pulmonary Angiogram

- Specificity about 95%
- Sensitivity about 85%
- Optimal study requires:
  - Recent generation CT scanner
  - Technician experience
  - Radiologist experience



One channel CT:
Fewer image slices per scan
Less sensitive for PE



Multi channel CT:
More image slices per scan
More sensitive for PE

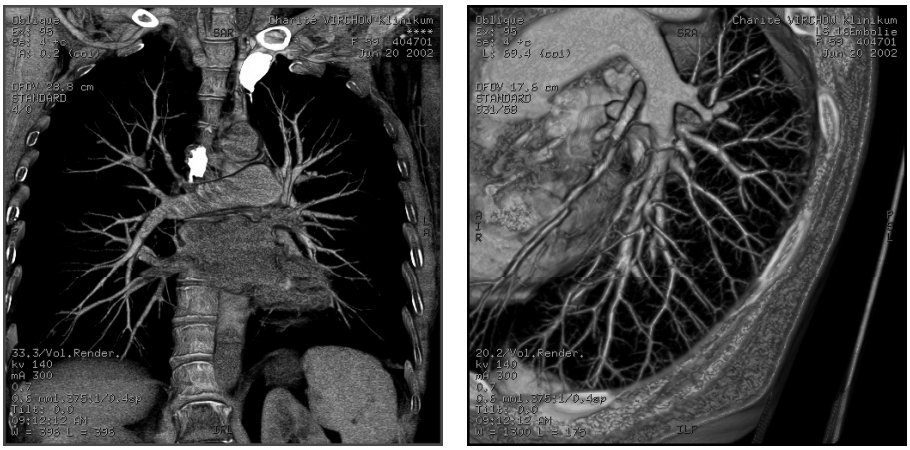
CT Pulmonary Angiogram

Normal

Pulmonary emboli

Inadequate technique

Reconstructed high speed multi-channel CT angiogram



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Probability Of True PE

	High Clinical Suspicion	Medium Clinical Suspicion	Low Clinical Suspicion
CTPA/CTV Positive	**96%**	**90%**	**57%**
CTPA/CTV Negative	**18%**	**8%**	**3%**

N Engl J Med 2006; 354:2317-27

PIOPED II Conclusions

- **CTPA should not be used alone**
- **CTPA positive in main or lobar arteries more accurate than CTPA positive in segmental arteries**

Practical Use of CT-PA

In the ED:

- **If clearly positive = PE present**
- **If negative:**
  - **Negative D-dimer = no PE**
  - **Positive D-dimer = clinical judgment**

In the ICU:

- **If clearly positive = PE present**
- **If negative:**
  - **Low clinical suspicion = no PE**
  - **Intermediate or high clinical suspicion = additional testing**

What Rules Out PE?

- Normal V/Q scan
- Low clinical suspicion and D-dimer less than 500 ng/ml
- Normal angiogram
- Low probability V/Q and normal D-dimer
- Negative CT-PA plus normal D-dimer

In other situations, clinical judgment is required

What does NOT rule out PE? If the clinical suspicion is *high*:

- Low probability V/Q scan alone
- Negative CT-PA alone
- Normal D-dimer test alone
- Negative MRI

So, what is the best initial test?

- CT scan:
  - Previous PE
  - Significant underlying lung disease
- V/Q scan:
  - Dye allergy
  - Renal insufficiency
  - ?Patients with normal CXR
- Duplex ultrasound:
  - Pregnancy
  - ICU patients with transportation risks
- D-dimer
  - Low risk outpatients

Predictors of worse outcome

- Shock
- Severe hypoxemia
- Elevated troponin I
- BNP > 90
- RV dysfunction by echo

Initial Resuscitation

- Oxygen
- Maintain blood pressure:
  - IV fluids
  - Vasopressors
- Telemetry monitoring
- ICU care for patients with severe hypoxemia or with hypotension

"Shoot first, ask questions later"

Pulmonary Embolism Treatment

- Heparin
- Low molecular weight heparin
- Fondaparinux
- Coumadin
- Thrombolytics
- IVC filters
- Catheter extracation/fragmentation
- Surgical embolectomy

Initial Treatment

- DVT:
  - Outpatients: LMW heparin
  - Inpatients:
    - LMW heparin*
    - Unfractionated heparin
- PE:
  - Outpatients: no FDA-approved treatments!
  - Inpatients:
    - LMW heparin*
    - Unfractionated heparin

*Avoid LMW heparin in

1. obese (weight > 150 kg)
2. renal failure (creatinine clearance <25)

Heparin Dosing

- Bolus with 80 u/kg
- IV infusion of 16-18 u/kg
- Check PTT Q6 hrs until stable, then QD
- Keep PTT 60-105 seconds*
- Check platelets every other day
- Minimum 5 day infusion

* Appropriate therapeutic range may vary by hospital lab

Low Molecular Weight Heparins

- Equally or more effective than heparin
- Equal or less bleeding than heparin
- Lower incidence of thrombocytopenia
- Longer half life
- Monitoring PTT unnecessary
- Dose once or twice daily
- Problems: renal insufficiency & obesity

Coumadin

- Start on day #1 of heparin
- Initial dose = 5 mg
- Keep INR 2.0 - 3.0
- Genetic testing may help guide dosing in the future

Duration of treatment

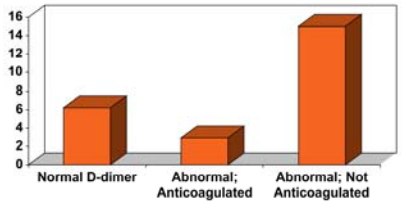
- Reversible factor: minimum of 3 months
- First idiopathic: minimum of 3 months and consider extended therapy
- Second DVT/PE: extended anticoagulation if bleeding risk is low

Thromboembolism in patients with cancer

- Patients can clot through Coumadin
- Use <u>minimum</u> of 6 months heparin or low molecular weight heparin
- Patients remain hypercoaguable as long as they still have cancer

D-dimer predicts recurrence

- 608 patients with venous thromboembolism treated > 3 months
- 233 had elevated D-dimer after treatment
- Patients randomly assigned to anti-coagulation or no treatment



N Engl J Med 2006; 355:1780

Anticoagulants on the horizon:

- Idrabiotaparinux – SQ anticoagulant not requiring INR monitoring
- Rivaroxaban – oral anticoagulant not requiring INR monitoring – only FDA approved for atrial fibrillation and DVT prophylaxis
- Apixaban – oral anticoagulant not requiring INR monitoring
- Dabigatran – oral anticoagulant not requiring INR monitoring – only FDA approved for atrial fibrillation

*None are currently approved for PE by the FDA

Inferior Vena Cava Filters

- Indications:
  - Contraindication to anticoagulation
  - Failure of anticoagulation
  - Complications of anticoagulation
- Varieties:
  - Permanent
  - Retrievable

Upper extremity DVT

- Initial therapy: heparin (low molecular weight or unfractionated)
- Long term treatment with Coumadin as per DVT

Mortality of Pulmonary Embolus

- Untreated: 30%
- Heparin Treated: 2%

Complications of Thrombolytics in Pulmonary Embolus

- Cerebral hemorrhage 3%
- Major bleeding 9%

Heparin vs. Thrombolytics in PE

	Heparin Alone	Thrombolytics
Uncomplicated	X	
Shock		X
Resp. Failure		X
RV Dysfunction	?	?
High Troponin	?	?

Other Treatments

Surgical embolectomy

- **Mainly if thrombolysis is contraindicated or fails**
- **Best outcomes at experienced centers**

Catheter techniques

- **Mainly if thrombolysis is contraindicated or fails**
- **Best outcomes at experienced centers**

Bottom Line: Pulmonary embolism is a medical disease in most patients

The Key to Improving Mortality from PE is to Prevent PE

DVT/PE Prevention Strategies

Medical/Surgical Patients

- SQ heparin
- Low molecular weight heparin
- Adjusted dose Coumadin
- Pneumatic compression devices
- Fondaparinux

Orthopedic patients

- Low molecular weight heparin
- Fondaparinux
- Dabigatran
- Rivaroxaban
- SQ heparin
- Coumadin
- Aspirin
- Pneumatic compression devices

Watch for new anticoagulants!

The new world of pay for performance

1. Your prophylaxis record will be publicly reported
2. Failure to prevent = failure to get paid

Clinical Case Outcome

- Factor V Leiden heterozygous
- Treatment
  - Low molecular weight heparin
  - Coumadin x 6 months
  - stop oral contraceptives
- Now pregnant and on prophylactic low molecular weight heparin

Key Points:

- No imaging test is perfect
- Your clinical assessment is critical
- Treatment decisions need to be individualized for individual patients