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Pulmonary Vascular Disease

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Winter 2009

Goals

- To recognize the risk factors for pulmonary thromboembolic disease.
- To understand the physiologic consequences of pulmonary embolism.
- To understand the possible diagnostic approaches to the patient with possible pulmonary embolism.
- To understand the therapeutic approaches to the patient with pulmonary embolism.
- To understand the clinical presentation and physiologic consequences of pulmonary hypertension.

Review of Respiratory Circulation

Pulmonary Circulation:

- The pulmonary circulation consists of arteries, capillaries and veins.
- The major role of the pulmonary circulation is to bring blood in to close proximity to air, so that gas exchange can occur.
- The pulmonary vascular bed receives the entire cardiac output.
  -high volume/low pressure system.

Bronchial Circulation:

- The bronchial arteries typically originate off aorta and supply airways (2% of cardiac output).
  -low volume/high pressure.
- 1/3 of blood flow through the bronchial circulation empties into azygous vein.
- 2/3 of blood flow empties into pulmonary capillaries (broncho–pulmonary anastamoses).

Review of Respiratory Circulation

Pulmonary Circulation:

Please see:
http://academic.kellogg.cc.mi.us/herbrandsonc/bio201_McKinley/f22-1_cardiovascular_sy_c.jpg

- Infarction is an unusual problem

Bronchial Circulation:

Please see:
http://ak47boyz90.files.wordpress.com/2009/09/picture51.jpg

- Atherosclerosis does not occur

Problems with Pulmonary Vasculature: Case 1

- A 31 yo woman presents to the ER with abrupt onset of dyspnea.
  - Right pleuritic chest pain
  - previously healthy, but smokes (1/2 pack/day).
  - only medication is an oral contraceptive
  - recently traveled by car from California to Michigan
- On exam, she is uncomfortable, anxious and breathing rapidly.
  - pulse 105/min
  - BP 120/75
  - breathing 30/minute, lungs are clear except for a pleural rub on the right
- Laboratory studies are largely normal, except for arterial blood gases.
  - pH 7.48, pCO_2 30 mmHg, pO_2 75 mmHg (on 40% O_2)

What is the diagnosis?

Pulmonary Embolism-a Huge Problem

- Most Common Pulmonary Disorder Among Hospitalized Patients.
- Pulmonary Emboli Effect an Estimated 650,000 People Each Year in the US.
- Age Dependent Risk: Annual Rate of 5/100,000 in Children Rising to 400/100,000 Adults > 80 Years of Age.
- Pulmonary Emboli Account for 100,000 - 200,000 Deaths Each Year.

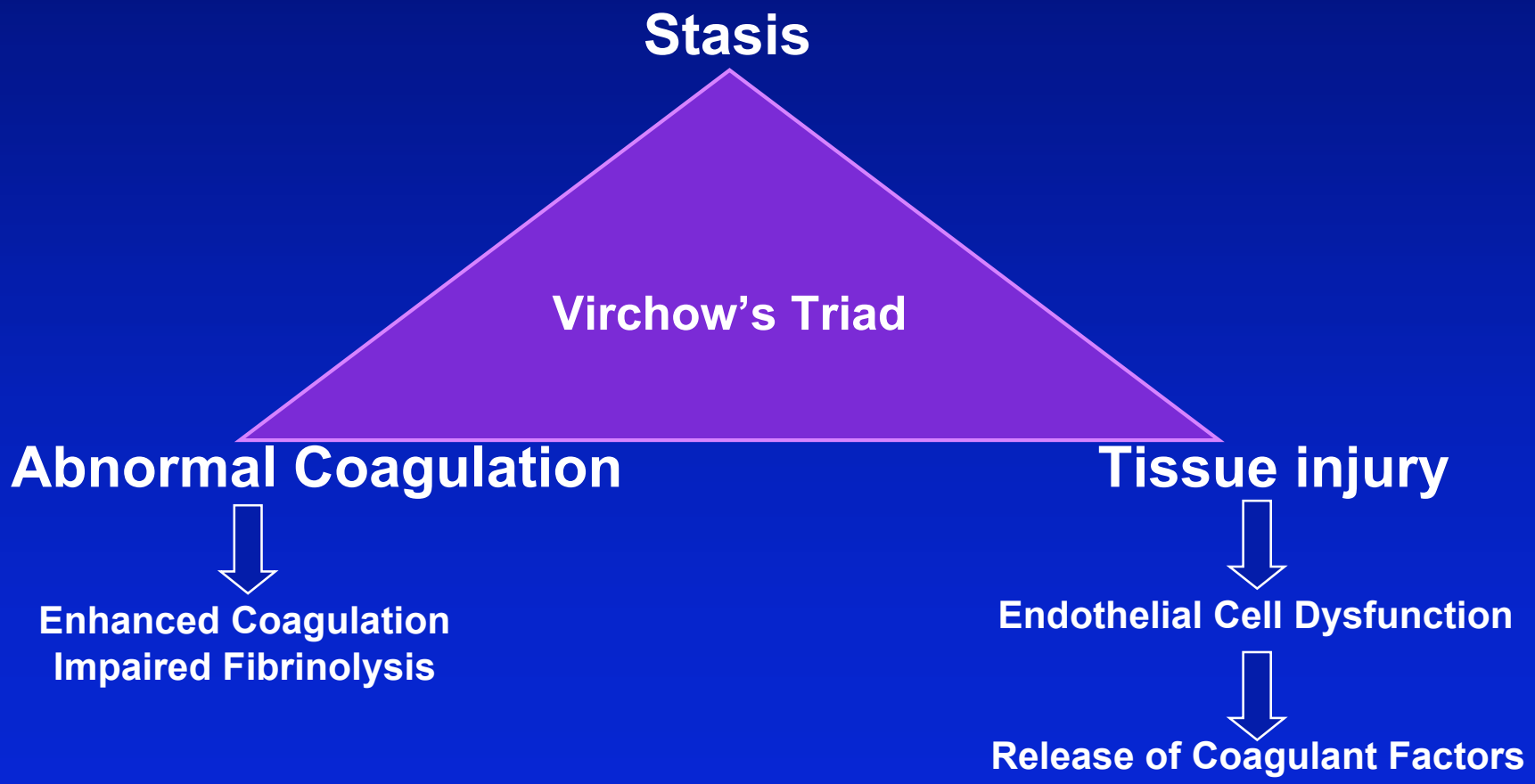
Sources of Pulmonary Emboli

- Thrombi that form in the venous circulation:
  - Propagate (grow).
  - Dislodge and travel through the central veins to the pulmonary arteries.
- Femoral, iliac and pelvic veins are the major sources for clinically important pulmonary emboli (>50% originate below the knee).
- Subclavian veins, right atrium/ventricle are less common sources (~10%).

Risk Factors for the Development of Thrombus Formation

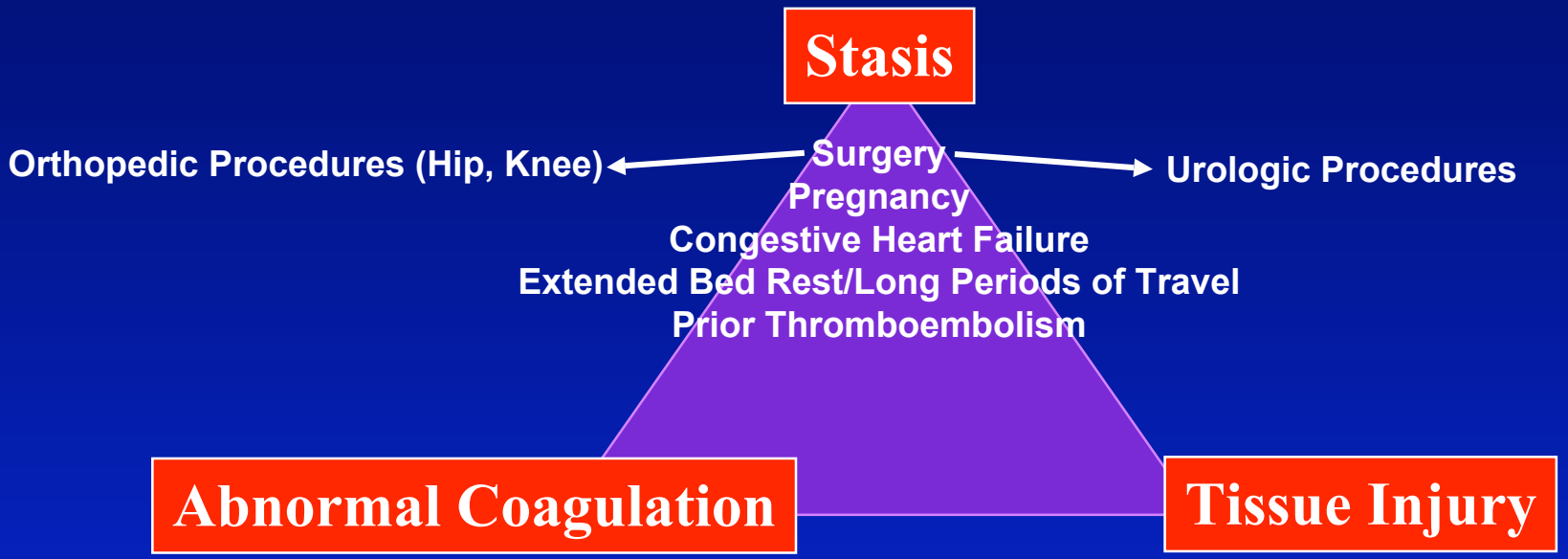
Rudolf Virchow ~1860

Risk Factors for the Development of Thrombus Formation



Risk Factor Identified in 80% of Patients

Specific Conditions Predisposing to Venous Thromboembolism



Oral Contraceptive
Hormone Replacement Therapy
Pregnancy
Malignancy
Anti-Phospholipid Antibody Syndrome
Nephrotic Syndrome
Hyperhomocysteine
Deficiency of Antithrombin III
Deficiency of Protein C
Deficiency of Protein S
Factor V Leiden Mutation (activated Protein C Resistance)

Surgery
Trauma
Intravenous Catheters
Prior Thromboembolism

Clinical Presentation of PE

Symptoms:

- Dyspnea
- Pleuritic chest pain
- Cough
- Hemoptysis
- Palpitations
- Syncope
- Leg pain/Swelling

Signs:

- Tachypnea (very frequent)
- Diaphoresis
- Rales (frequent)
- Wheezes
- Increased P2
- Pleural friction rub
- Low grade fever
- Hypotension
- Calf Swelling/Tenderness
- Homan's Sign (calf pain on dorsiflexion of foot)

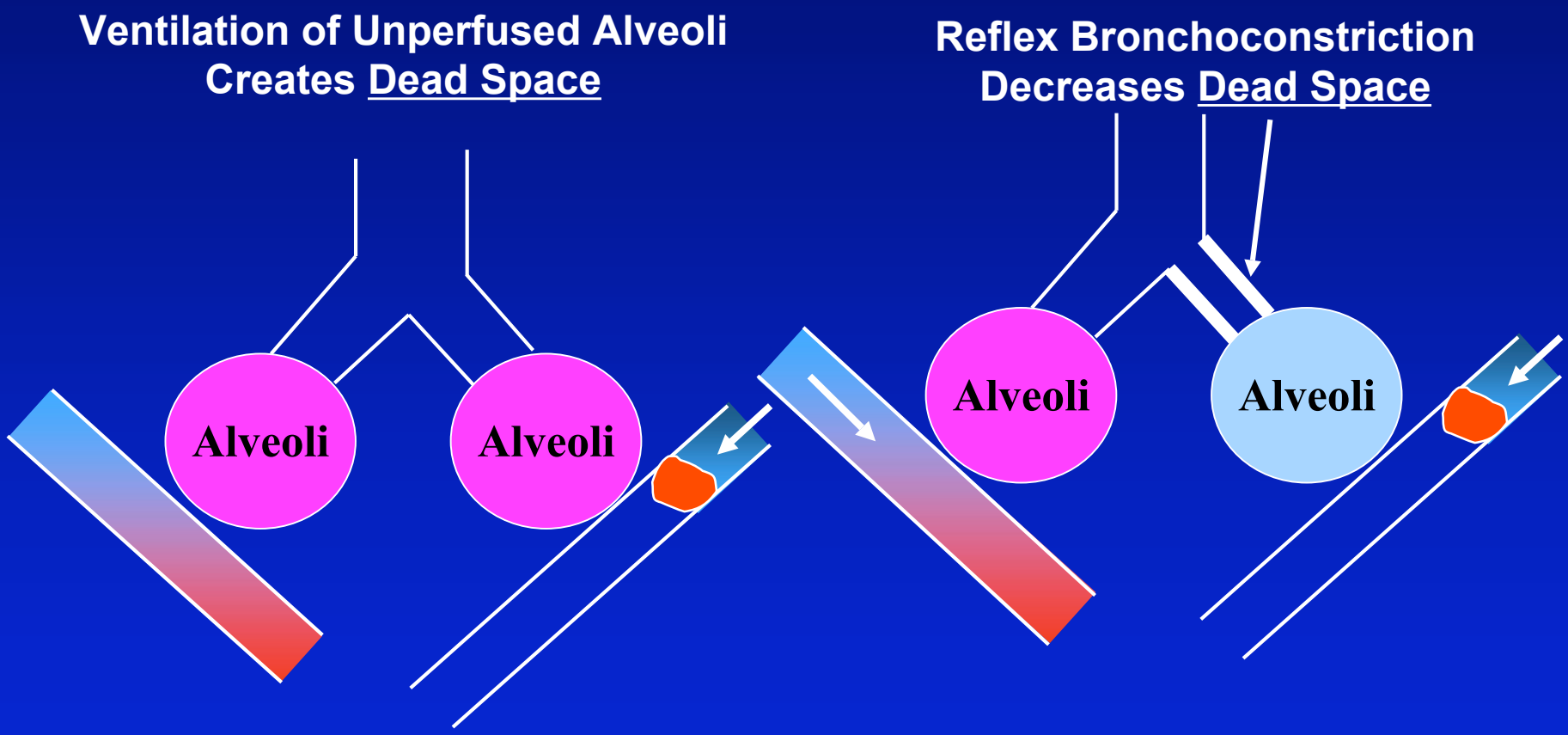
Signs and Symptoms Are Not Specific!!

Clinical Presentation of PE

Symptom	PE No CPD (%)	No PE No CPD (%)	PE All (%)	No PE All (%)
Dyspnea	73	68	79	73
Pleuritic Pain	44	57*	47	59*
Chest Pain	19	22	17	21
Cough	34	28	43	39
Wheezing	21	18	31	31
Calf or Thigh Swelling	41	17*	39	20*
Calf or Thigh Pain	44	23*	42	25*

 Stein et al. Am J Med 2007; 120:871

Physiologic Effects of PE: Ventilation



Remember $V_E = V_A + V_D$: What Are the Consequences of Increased V_D?

↑pCO2 unless patient increases minute ventilation

Arterial Blood Gases in PE

Remember: pH 7.48 PCO2 30 mmHg PO2 75 mmHg (on 40% O2)

- **Typical Blood Gas Demonstrates Increased Alveolar Ventilation; Not Deceased Alveolar Ventilation.**
  - **Increased ventilation due to increase in respiratory rate.**
  - **Results in ↓ PCO_2 and ↑ pH.**
  - **Exception in patients who can not increase minute ventilation (e.g. severe COPD).**
  - **Massive emboli may result in metabolic acidosis due to inadequate cardiac output.**
- **Hypoxemia with widened A-a O_2 gradient**
  - **Not universal.**

Physiologic Effects of PE: Hypoxemia

Why Hypoxemia with PE? Multifactorial:

- **Increased blood flow through regions of physiologic shunt or poor V/Q matching.**
- **Loss of pulmonary surfactant in areas of pulmonary inflammation/infarction.**

  creates areas of new V/Q mismatch.
- **Reduced mixed venous O_2 content due to reduced cardiac output.**

Other Physiologic Effects of PE: Case 2

- A 34 yo man presents with the abrupt onset of shock (low blood pressure).
  - Healthy athlete until 16 days previously.
  - Severe spinal cord injury playing football, resulting in paraplegia.
  - Now in rehabilitation center, making good progress overall.
- Physical Exam:
  - General: Ashen appearing with a clouded sensorium.
  - Pulse 120/min and weak.
  - BP 74/50
  - Breathing 28/minute, Lungs are clear.
- Laboratory Studies:
  - Normal
  - ABG: pH 7.19, PCO_2 28 mmHg, PO_2 52 mmHg (on 40% O_2)

Other Physiologic Effects of PE: Circulation

- Diagnosis: Massive Pulmonary Embolism with obstruction of > 1/2 pulmonary vascular circulation.

- The pulmonary capillary bed has enormous reserve:
  - With exercise, flow can increase 5-fold without increasing pulmonary artery pressure.
  - Surgical removal of 50% of the pulmonary circulation without increasing PA pressure.
  - When > 75% of circulation occluded: right heart failure.

- Loss of vascular bed due to emboli causes far greater circulatory disruption than expected from the fraction of circulation blocked.

Why?

Other Physiologic Effects of PE: Circulation

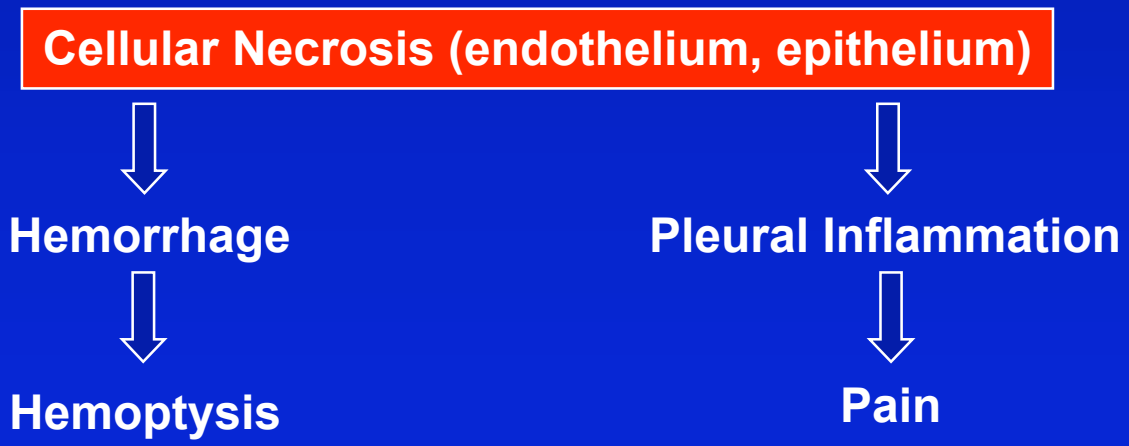
- Emboli lead to pulmonary vasoconstriction and disproportionate increase in pulmonary vascular resistance.
  - Soluble vasoconstricting mediators released from platelets.
  - Autonomic reflexes from hypoxemia.

- <u>Large Embolism</u> ⇒ ↑↑ Pulmonary Vascular Resistance ⇒ Right Ventricular Failure ⇒ Inadequate Left Ventricular Filling ⇒ ↓↓ Cardiac Output ⇒ Hypotension and Shock.

- The first clinical presentation of massive emboli (>50% of the vascular bed obstructed) may be circulatory collapse or sudden death.

Other Physiologic Effects of PE:

- The lung receives blood supply from both bronchial and pulmonary circulations decreasing risk of infarction.
- Bronchial vessel supply to the gas exchange units is marginal.
- Therefore: smaller, peripheral emboli may result in pulmonary infarction.



Diagnosis of PE:

- PE is a very common and potentially life threatening problem.
- The presenting symptoms and signs are nonspecific.
- The clinician needs a high index of suspicion.
- Diagnostic studies for PE must be interpreted in conjunction with clinical suspicion .
  - V/Q scan.
  - CT Angiography.
  - Pulmonary Angiography.

EKG and Chest X-ray Not Very Helpful

EKG

- Sinus tachycardia.
- Atrial arrhythmias.
- Right bundle branch block.
- "Classic" S1 Q3 T3 pattern.

Chest X-ray

- Normal.
- Low lung volumes.
- Small pleural effusion.
- Atelectasis.
- Decreased vascular markings in an area of lung (Westermark's sign).
- Wedge-shaped infiltrate extending to the pleural surface (Hampton's hump)

EKG and Chest X-ray Are Not Sensitive or Specific!!

Criteria to Help Determine Clinical Likelihood of PE

Table 1. **Model for Determining the Clinical Probability of Pulmonary Embolism, According to the Wells Score.***

Clinical Feature	Score
Clinical signs and symptoms of DVT (objectively measured leg swelling and pain with palpation in the deep-vein system)	3.0
Heart rate >100 beats/min	1.5
Immobilization for ≥3 consecutive days (bed rest except to go to bathroom) or surgery in previous 4 weeks	1.5
Previous objectively diagnosed pulmonary embolism or DVT	1.5
Hemoptysis	1.0
Cancer (with treatment within past 6 mo or palliative treatment)	1.0
Pulmonary embolism likely or more likely than alternative diagnoses (on the basis of history, physical examination, chest radiography, ECG, and blood tests)	3.0

* Data are from Wells et al.[24] The condition of patients is scored according to the following criteria: less than 2.0, low probability; 2.0 to 6.0, moderate probability; and more than 6.0, high probability. DVT denotes deep venous thrombosis, and ECG electrocardiography.

 Stein et al. NEJM 354: 2317, 2006

Diagnostic Tests: Pulmonary Angiography

- Advantages:
  - The “gold standard”; directly images pulmonary artery very effectively.
  - Allows measurement of pulmonary artery pressures.
- Disadvantages:
  - Invasive
  - Administration of intravenous radiocontrast.
  - Expensive.
  - Operator time/availability/skill.

Because of Disadvantages: Used as Last Resort in Difficult Cases

Diagnostic Tests: Radionucleotide V/Q Scan

- **Perfusion Scanning**: Venous injection with radiolabeled-macroaggregated albumin (technetium 99)
  - Labeled aggregates are trapped in pulmonary arterioles; retained thoracic radioactivity is imaged with a camera.
  - Sensitive for decreased flow to areas of the pulmonary vascular bed - not specific.
  - Areas of parenchymal abnormality may lead to reflex vasoconstriction.

- **Ventilation Scanning**: Inhalation of a gas mixture containing a different radiotracer (xenon 133)
  - In PE- areas of vascular obstruction should have loss of perfusion but preservation of ventilation
  - Processes such as pneumonia, COPD, obstructed large airway present as matched ventilation and perfusion defects

Diagnostic Tests: Radionucleotide V/Q Scan

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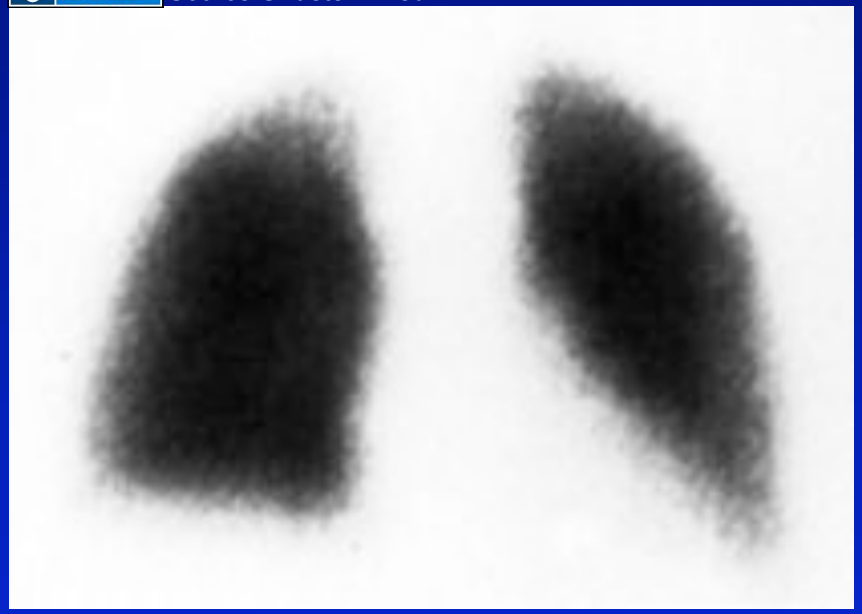


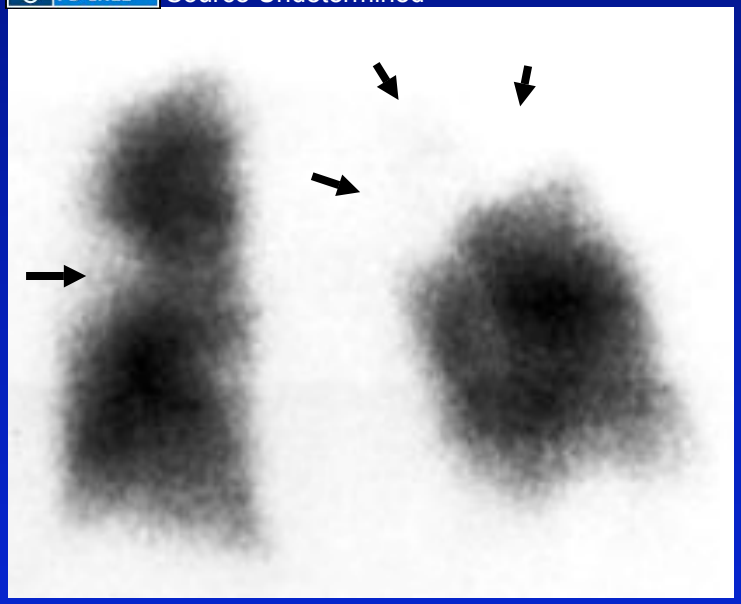
Normal Anterior Perfusion

PD-INEL Source Undetermined

Normal Anterior Ventilation

Diagnostic Tests: Radionucleotide V/Q Scan

PD-INEL Source Undetermined



Abnormal Posterior Perfusion

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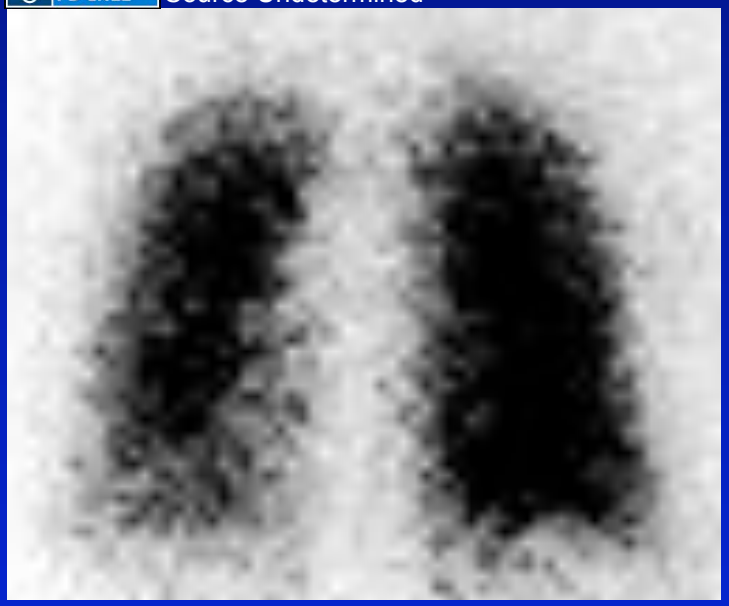


Normal Posterior Ventilation

Diagnostic Tests: Radionucleotide V/Q Scan

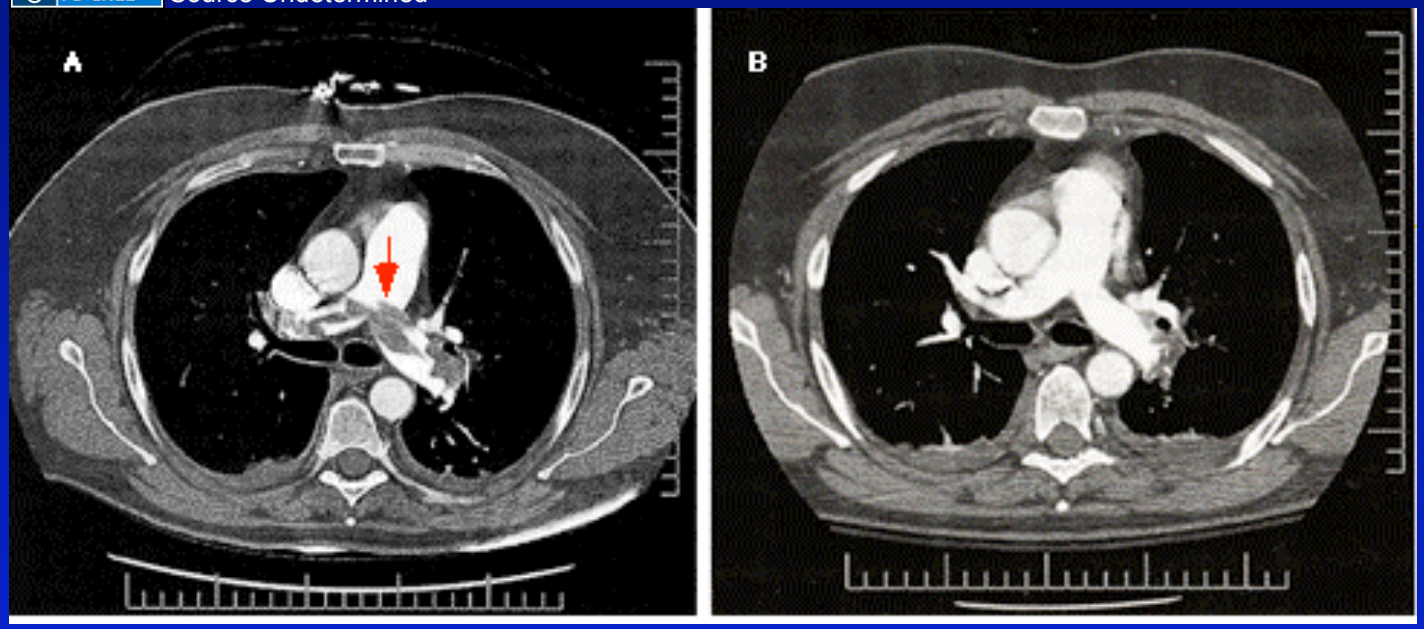
- **Interpretation:**
  - V/Q scans provide estimates of the probability that a patient has a PE.
  - The level of clinical suspicion for PE must be taken into account.
  - Normal perfusion scan excludes the diagnosis of PE.
  - High probability scan: multiple segmental unmatched perfusion defects. With *high clinical suspicion* gives >95% likelihood of PE.
  - Intermediate or Low probability scans are much less helpful.

Scan Interpret.	Clinical Probablility		
	High	Inter.	Low
High	95	86	56
Inter.	66	28	15
Low	40	15	4
Normal	0	6	2

Diagnostic Tests: CT Angiography

- Bolus radiocontrast injection given intravenously.
- High speed, multi-slice CT scanner takes thin section images.
- Excellent definition of main, lobar, and even segmental pulmonary arteries.
- May provide bonus information about the lungs and mediastinal structures.

Diagnostic Tests: CT Angiography



Saddle Embolus → **Resolution**

Thrombolysis

Diagnostic Tests: CT Angiography

- A major modality in current practice at U of M.
- A recent multi-center trial found that CT scanning had excellent positive and negative predictive values.
- Like V/Q scanning, results still should be interpreted in light of the clinical context.

Table 5. Positive and Negative Predictive Values of CTA, as Compared with Previous Clinical Assessment.*

Variable	High Clinical Probability		Intermediate Clinical Probability		Low Clinical Probability	
	No./Total No.	Value (95% CI)	No./Total No.	Value (95% CI)	No./Total No.	Value (95% CI)
Positive predictive value of CTA	22/23	96 (78–99)	93/101	92 (84–96)	22/38	58 (40–73)
Positive predictive value of CTA or CTV	27/28	96 (81–99)	100/111	90 (82–94)	24/42	57 (40–72)
Negative predictive value of CTA	9/15	60 (32–83)	121/136	89 (82–93)	158/164†	96 (92–98)
Negative predictive value of both CTA and CTV	9/11	82 (48–97)	114/124	92 (85–96)	146/151†	97 (92–98)

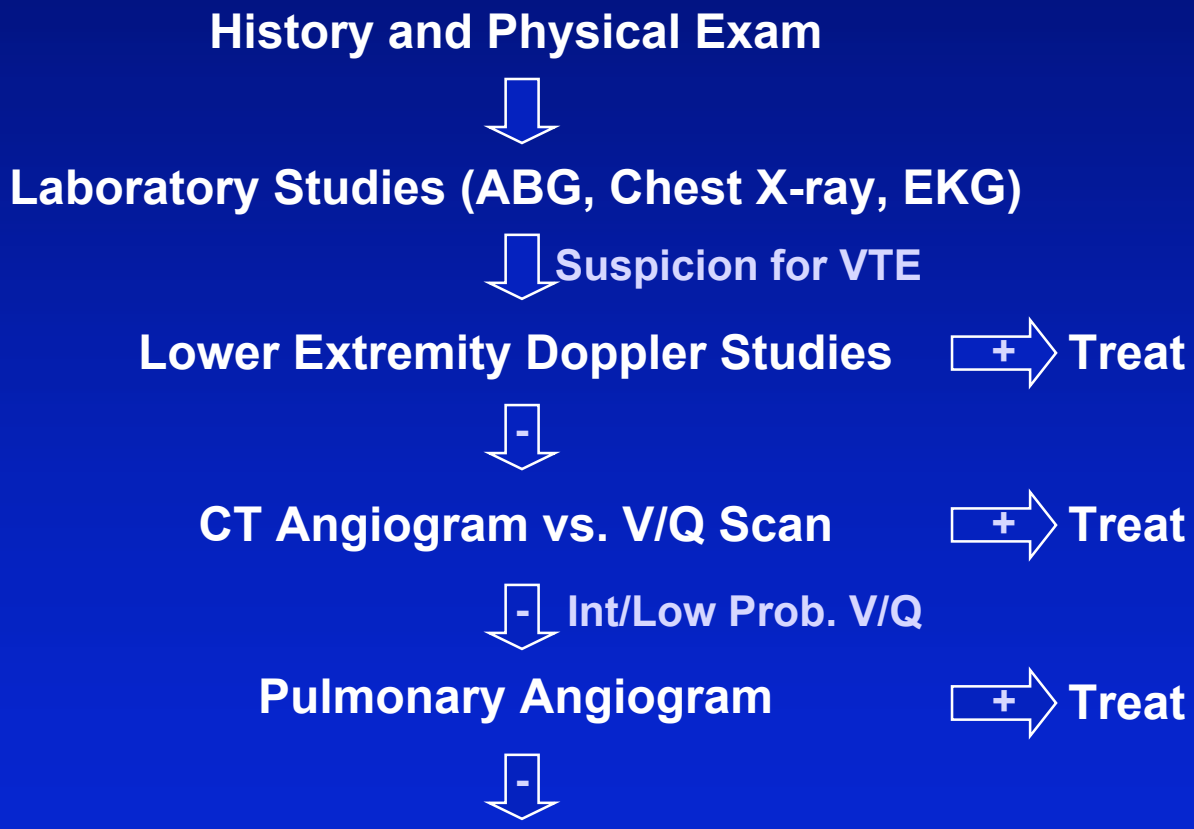
* The clinical probability of pulmonary embolism was based on the Wells score: less than 2.0, low probability; 2.0 to 6.0, moderate probability; and more than 6.0, high probability. CI denotes confidence interval.
† To avoid bias for the calculation of the negative predictive value in patients deemed to have a low probability of pulmonary embolism on previous clinical assessment, only patients with a reference test diagnosis by ventilation–perfusion scanning or conventional pulmonary DSA were included.

 Stein et al. NEJM 354: 2317, 2006

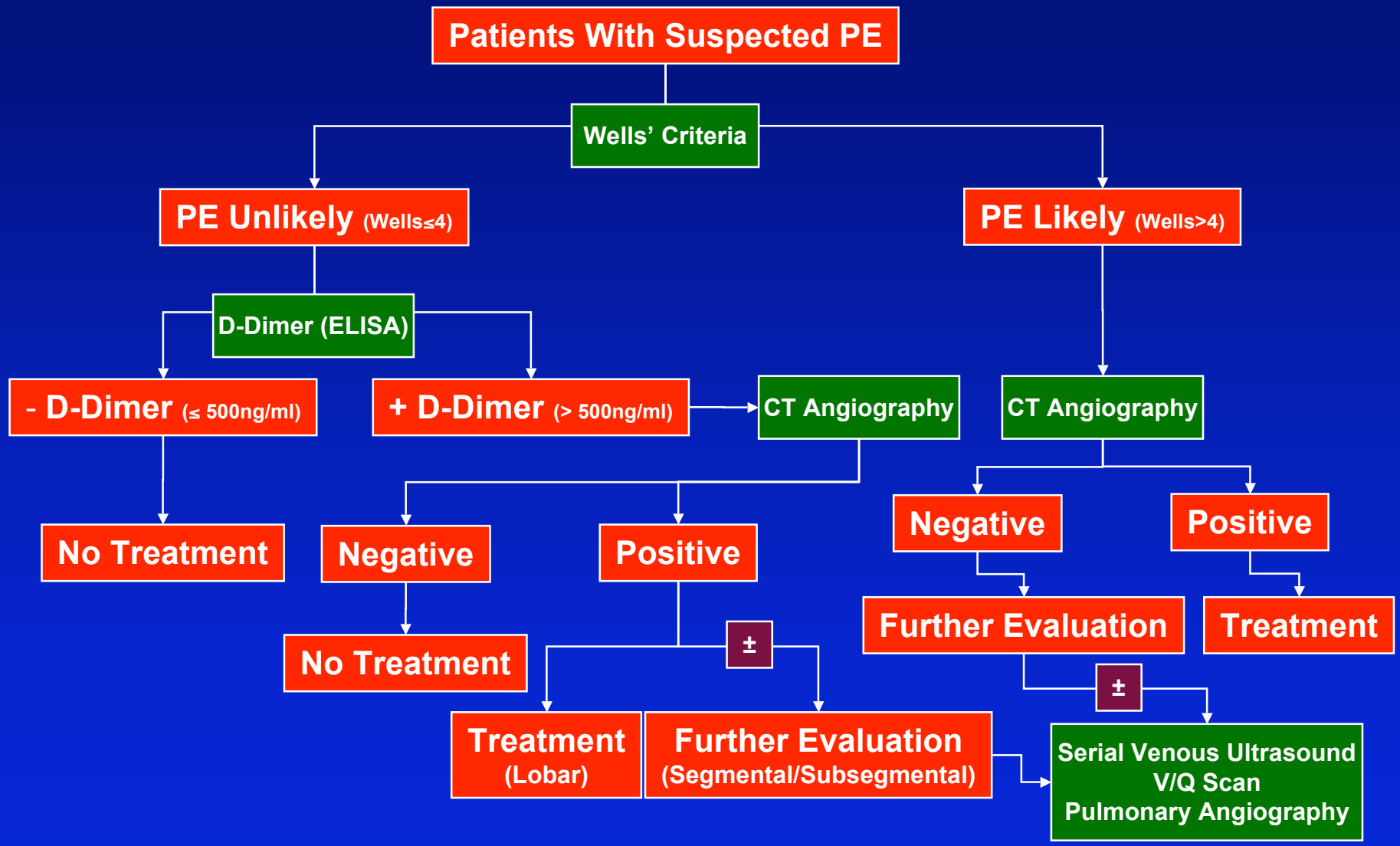
Diagnostic Tests: Non-Invasives

- **Doppler ultrasound:**
  - **Most PE originate as lower extremity DVT.**
  - **Tests for lower extremity DVT are useful *if positive* - may support anticoagulant therapy without invasive studies.**
- **D-Dimer:**
  - **Tests for enhanced clot degradation.**
  - **A negative test (i.e. normal value) may greatly decrease the likelihood of thromboembolism.**
  - **In conjunction with low (intermediate?) clinical probability, normal D-dimer can be used to rule out DVT.**

Diagnostic Algorithm for PE



Diagnostic Algorithm for Pulmonary Embolism



 Stein et al. Am J Med 2006 119: 1048

Treatment of PE

- **Prevention:**
  - **Ambulation.**
  - **Pneumatic compression stockings.**
  - **Prophylactic anticoagulants in patients at high risk.**
- **Supportive therapy with oxygen and fluids.**
- **Prompt Anticoagulation with heparin.**
  - **heparin prevents clot formation; does not lyse clot.**
- **Mortality of untreated pulmonary embolism >30%.**
- **Mortality after initiation of heparin <5%.**

Treatment of PE

- **Heparin:**
  - Prevents clot formation by potentiating anti-thrombin III and inhibiting thrombin activity.
  - Unfractionated heparin
    - short half-life: continuous infusion required.
    - variability requiring frequent laboratory studies.
  - Low molecular weight heparin-(enoxaparin, dalteparin)
    - longer half-life: twice daily subcutaneous injections.
    - standard dosing; no requirement for frequent lab monitoring.
    - stable patients without great physiologic compromise may be managed at home.

Additional Treatment Modalities for PE

- Treatments for the Patient with a Hemodynamically Significant PE.

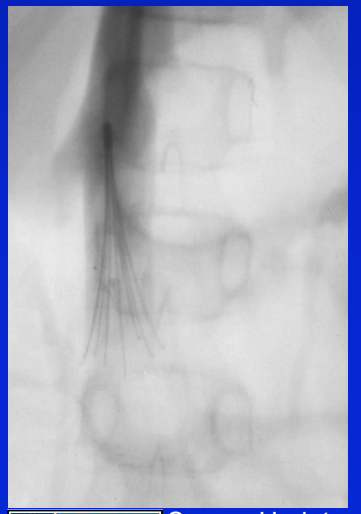
  Thrombolytic agents - “Drano”
  - Streptokinase
  - Urokinase
  - Tissue plasminogen activator

  Embolectomy - “plumber’s helper”

- Treatment for the Patient who Cannot Tolerate Anticoagulation (risk of bleeding).

  - Inferior Vena Cava Filter-Prevent lower extremity clots from reaching the lung.

  - Increased risk of lower extremity thrombosis.



Long-term Treatment of PE

Inhibits Vitamin K-dependent Clotting Factors

Duration May Be Extended to Life Long if Persistent Risk Factors

Pulmonary Vascular Disease

Thomas Sisson, M.D.

Case 3

- A 32 yo woman comes to your office complaining of progressive fatigue and shortness of breath for several months.
  - Previously healthy and quite active.
  - She now is quite limited in her exercise tolerance.
  - She denies cough, wheezing, chest pain, but has intermittent palpatations and light-headedness.
  - She has seen several doctors who considered depression, asthma, hypothyroidism, pregnancy, mitral valve disease.
- Physical Exam: resting tachycardia and mild tachypnea.
  - Her lungs are clear.
  - Cardiac exam reveals prominent P2 and right ventricular lift.
  - Extremity exam reveals 2+ pitting edema.

What is the diagnosis?

Pulmonary Hypertension

Normal Pulmonary Hemodynamics

- The normal pulmonary circulation is a low resistance circuit.
- Enormous capacity to recruit and distend vessels.
- Large increase in blood flow with exercise does not increase the resistance across the pulmonary vascular bed.

Etiology of Pulmonary Hypertension

Mean PA pressure = (Flow x pulmonary vascular resistance) + mean pulmonary venous pressure

Pulmonary Hypertension results from:

- Elevated pulmonary venous pressure (CHF)
- Increased pulmonary blood flow
- Increased pulmonary vascular resistance

Causes of Pulmonary Hypertension

Increased Pulmonary Blood Flow

- Left-to-right shunt
- With chronically increased flow there is remodeling of the arteriolar wall.

Causes of Pulmonary Hypertension

Increased Pulmonary Vascular Resistance

- **Vasoconstriction from Chronic Hypoxemia:**
  - Chronic High altitude.
  - COPD.
  - Pulmonary Fibrosis.
  - Obstructive Sleep Apnea.

  } Loss of vasculature

- **Vascular Obstruction**
  - Recurrent/unresolved pulmonary emboli
  - Schistosomiasis

Causes of Pulmonary Hypertension

Increased Pulmonary Vascular Resistance

- **Idiopathic Disorder: Primary Pulmonary HTN**
  - Women 20-45 years old.
  - Pathological changes in the pulmonary arteriolar wall
    - medial hypertrophy
    - intimal proliferation and fibrosis
  - Similar pattern in pulmonary hypertension due to specific causes.
    - Fenfluamine/dexfenfluramine use for weight loss
    - chronic cocaine use
    - HIV
    - liver disease with portal hypertension

Symptoms of Pulmonary Hypertension

- Dyspnea on exertion.
- Fatigue.
- Chest pain (due to right ventricular strain).
- Peripheral edema.
- Syncope – due to severe disease with impaired LV filling.
- In secondary pulmonary hypertension, symptoms of an underlying disease process can predominate.

Signs of Pulmonary Hypertension

- Increased pulmonic component of the second heart sound (P2).
- Right ventricular lift/heave.
- Elevated jugular venous pressure.
- Distended liver.
- Peripheral edema.
- Right ventricular S3 gallop.

Studies in Pulmonary Hypertension

- ECG: Right Ventricular Hypertrophy.
- CXR: Dilated main pulmonary arteries/pruning of peripheral vascular markings.
- ABG: Hypoxemia with exertion.
- PFT's: Findings c/w underlying disease; Decreased DLCO.
- Echocardiogram:
- Right heart catheterization:

} Pulmonary Pressure Measurement

Diagnostic Approach to Pulmonary Hypertension

- History and Physical Exam often suggestive.
- ECG and echocardiogram: elevated pulmonary pressures.
- Right heart catheterization ± pulmonary angiography.
- Identify treatable causes of secondary pulmonary hypertension.
  - Hypoxemia (at rest or at night, with sleep apnea).
  - Chronic Thromboembolic Disease.

Treatment of Pulmonary Hypertension

- Treat underlying disease.
- Oxygen supplementation- minimize hypoxic vasoconstriction.
- Long term anticoagulation (even when not due to chronic PE).
- Vasodilators especially for primary pulmonary hypertension:
  - Calcium channel blockers.
  - Prostacyclin.
  - Endothelin receptor blockers (Bosentan).
- Transplantation

Questions?

Additional Source Information

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Slide 10: Department of Health and Human Services, Centers for Disease Control and Prevention, http://www.cdc.gov/eid/content/13/5/732-G1.htm
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