Pulmonary Vascular Disease

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Definitions

- Thrombus- stationery blood clot; such as in deep veins of legs (DVT)
- Embolus- blockage of an artery by matter; such as, a blood clot- thromboembolism

Learning Objective

- Explain the etiologies, manifestations, diagnostic techniques and current management strategies for pulmonary thromboembolism and pulmonary hypertension.

Acute PE Epidemiology

- Incidence (US) - 650,000/yr.
- Mortality > 15% for first 3 mo. after diagnosis
- In 25% PE patients, first sign is sudden death
- Third most common cause of death
- Leading cause of maternal death

Pulmonary Thromboembolism

Acute PE Epidemiology

- Missed diagnosis of PE > 400,000/yr.
- About 100,000 patients die who would have survived with the proper diagnosis and treatment.
- Autopsies find much greater incidence of PE among patient deaths than are diagnosed
- PE among hospital patients considered a public health crisis in the UK.

Types of emboli

- Thromboemboli- blood clots
- Fat (lipid embolus) - fractured bones
- Air
  - decompression illness
  - parenteral injection

Risk factors

- Inherited predisposition - thrombophilia
  - younger patients
  - family members with history
- Deep venous thrombi (DVT)
  - stasis (immobility)
  - surgery
  - trauma
- Malignancy

Types of emboli

- Amniotic - significant cause of maternal death
- Septic
  - thrombophlebitis
  - IV drug abuse
- Foreign substances - IV drug abuse (fillers; e.g., talc)
- Worms; e.g., schistosomiasis

Click to see schistosoma mansoni in mesenteric veins (1.6)
http://www.youtube.com/watch?v=3FxaQabjYLE

Click to see schistosoma mansoni life cycle
http://www.dpd.cdc.gov/dpdx/images/ParasiteImages/S-Z/Schistosomiasis/Schistomes_LifeCycle.gif

Risk factors

- Obesity
- Myocardial infarction
- Pulmonary disease (smoking)
- Polycythemia
- Pregnancy
- Trauma
- Vascular catheters

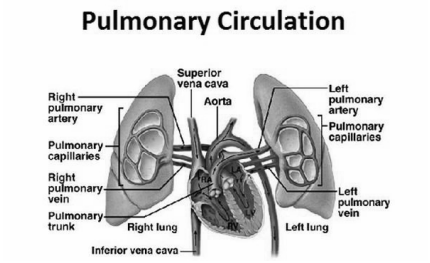
Sites for embolism

- Brain- cerebrovascular accident (CVA)
- Joints- sickle cell crisis
- Pulmonary arteries- pulmonary thromboembolism (our focus)

PE Pathophysiology

Perfusion of the lung

- Pulmonary circulation
- pulmonary arteries to alveolar capillaries
- perfuses alveoli for gas exchange



Perfusion of the lung

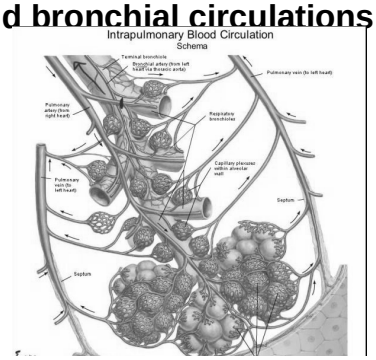
- Anastamoses between pulmonary and bronchial circulations
  - bronchioles to pulmonary capillary beds
  - bronchial circulation increases flow through anastamoses to compensate for pulmonary embolism

Perfusion of the lung

- Bronchial circulation
  - thoracic aorta to terminal bronchioles
  - perfuses
    - esophagus
    - trachea
    - visceral pleura
    - airways to terminal bronchioles

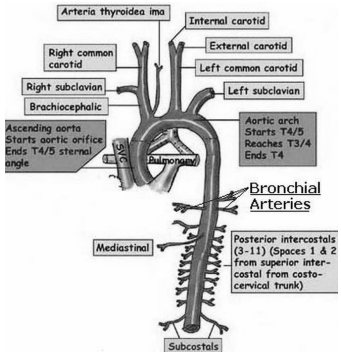
Perfusion of the lung

- Anastamoses between pulmonary and bronchial circulations



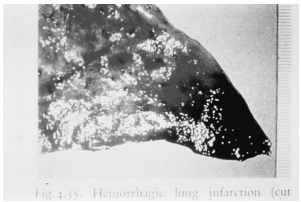
Perfusion of the lung

- Bronchial circulation



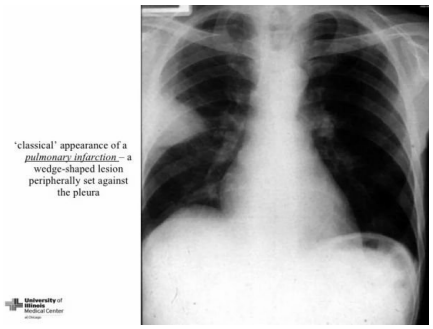
Perfusion of the lung

- Pulmonary infarction results from embolization of medium-size pulmonary artery; compensatory bronchial circulation causes reperfusion injury, hemorrhage



Perfusion of the lung

- Pulmonary infarction



PE pathophysiology

- Hemodynamics - severity depends on size of embolus
  - physical obstruction
  - release of vasoconstrictors
  - hypoxemia of distal lung causes vasoconstriction
  - acute pulmonary hypertension

Development of thrombi

- Blood clots in deep vein
  - calf
  - thigh
  - pelvis - frequently fatal
  - axillary, subclavian - frequently fatal

PE pathophysiology

- Hemodynamics
  - acute pulmonary hypertension
  - increased right ventricular afterload
    - ventricular dilatation
    - interseptal bulging to left
    - left ventricular impairment
    - right ventricular infarction - release of troponin, brain natriuretic peptide (BNP)

Development of thrombi

- Blood clots in deep vein
  - calf
  - thigh
  - pelvis - frequently fatal
  - axillary, subclavian - frequently fatal
- Clotting predisposed by:
  - hemostasis
  - coagulopathy
- Clot breaks off, flows to lung

Click to see video of DVT & pulmonary embolism
http://www.youtube.com/watch?v=gGrDAGN5pC0

PE Pathophysiology

- Gas exchange O2
  - non-perfused lung - increased VQ (dead space units)
  - blood directed to other units decreases their VQ (shunt)
  - overall, mixed VQ defects
  - alveolar hemorrhage and atelectasis may contribute to hypoxemia
  - if patent foramen ovale, then right-to-left shunt (severe hypoxemia)

PE Pathophysiology

- Gas exchange - CO_2
  - tachypnea - arterial hypocapnea
  - alveolar dead space - alveolar hypocapnea, with increased $P(a - E)CO_2$
  - if hypercapnea ==>
    - massive embolus
    - comorbidity; e.g., emphysema

Physical signs

- Tachypnea
- New onset wheezes
- Crackles (usually with infarction)
- Tachycardia
- Fever
- Diaphoresis
- Cyanosis
- Hemoptysis
- Thrombophlebitis

PE Manifestations

Massive PE

- Dyspnea
- Cyanosis
- Altered mental status
- Cardiogenic shock
- Cardiac arrest

Symptoms

- Anxiety
- Chest pain
- Chest wall tenderness (important)
- Syncope
- Shortness of breath
- Back pain
- Wheezing

Chest radiograph

- May be normal
- Used to rule out alternatives
- Reduced distal vascular markings
- Dilated pulmonary arteries
- Atelectasis - common with infarction
- Wedge-shaped density - infarction
- Pleural effusion - 1/3 of PE patients
  - small
  - unilateral
  - likely to loculate

Electrocardiograph

- May be unchanged from baseline
- May suggest alternatives; e.g., MI
- Most common with PE
  - sinus tachycardia
  - right axis deviation
  - right bundle branch block

Goals for diagnostic techniques

- Rule in/out PE
- Risk stratification to select treatment
  - risk-benefits for drugs, interventions
  - avoid costly procedures; e.g., imaging

Blood gases

- Nonspecific for PE
  - hypocapnia
  - mild-severe hypoxemia
- Severe hypoxemia with patent foramen ovale - worsens with PEEP
- End-tidal CO2 & ABG used to measure V_D/V_T

Bases for diagnosis

- History
- Physical findings
- Laboratory tests
- Imaging

PE Diagnosis

Clinical probability for PE

- Wells score - parameters
  - clinically suspected DVT
  - alternative diagnosis is less likely than PE
  - tachycardia
  - immobilization/surgery in previous four weeks

Clinical probability for PE

- Wells score - parameters
  - clinically suspected DVT
  - alternative diagnosis is less likely than PE
  - tachycardia
  - immobilization/surgery in previous four weeks
  - history of DVT or PE
  - hemoptysis
  - malignancy (palliative treatment within 6 months)

Laboratory studies

- Potential markers for PE - need additional study
  - C-reactive protein
  - Myeloperoxidase

Clinical probability for PE

- Wells score interpretations
  - Traditional interpretation
  - Score >6.0 - High
  - Score 2.0 to 6.0 - Moderate
  - Score <2.0 - Low
- Alternate interpretation
  - Score > 4 - PE likely ==> diagnostic imaging
  - Score 4 or less - PE unlikely ==> D-dimer to rule out PE

Laboratory studies

- Troponin I - prognostic indicator
  - marker for myocardial injury
  - elevation suggest right ventricular overload
  - peaks 4 hours after suspected PE
  - may predict adverse outcome for PE
  - may be used to select aggressive treatment

Laboratory studies

- D-dimer - formed by lysis of fibrin (clot)
- increased by:
  - aging
  - inflammation
  - malignancy
  - embolism
- negative predictive value
- combined with Wells score - strong negative predictive value

Laboratory studies

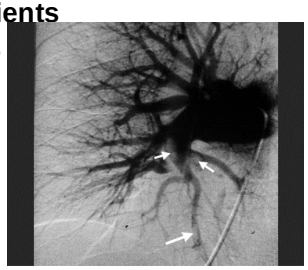
- Brain natriuretic peptide (BNP) - prognostic marker
  - elevated with right ventricular dysfunction
  - elevation is proportional to severity of embolism

Pulmonary testing

- Dead space measurement
  - PE increases alveolar dead space and V_D/V_T
  - measurement requires ETCO2 and PaCO2
  - combined with negative D-dimer has strong negative predictive value
  - research needed to standardize techniques and parameters for PE evaluation

Imaging

- Pulmonary angiography
  - criterion standard for PE
  - adverse effects - cannot be done on sickest patients
  - expensive



Imaging

- Computed tomographic pulmonary angiography (helical, spiral)
  - agrees with VQ scan for exclusion
  - detects PE not found by VQ scan
  - useful in detecting alternative diagnoses

Imaging

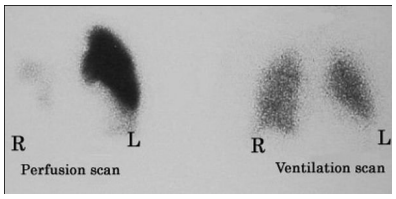
- Ventilation-perfusion (VQ) scan
  - former, usual test for PE
  - if normal, excludes PE
  - significant number of abnormal scans do not have PE
  - high probability scan - confirms PE

Imaging

- Magnetic resonance imaging (MRI)
  - similar accuracy to CT scanning
  - also detects alternative diagnoses
  - no ionizing radiation - safer for pregnant patients, esp. females
  - technology is advancing

Imaging

- Ventilation-perfusion (VQ) scan



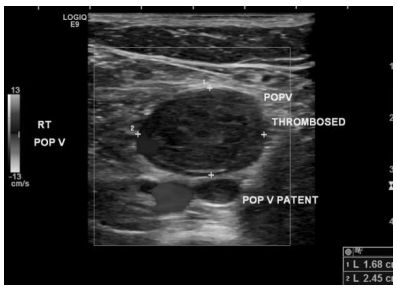
Imaging

- Ultrasonography
  - detection of DVT
  - positive test ==> evidence of PE
  - negative result suggests decreased risk for recurrence of PE
  - safe- no ionizing radiation

PE Management & Prevention

Imaging

- Ultrasonography



Respiratory Care

- Oxygen - all PE patients
- Ventilation - PEEP may open foramen ovale by increasing pulmonary vascular resistance
- ETCO2 particularly useful - observe for changes in P(a - E)CO2

Imaging

- Echocardiography
  - not a routine test for PE
  - may visualize central emboli
  - identifies cardiac dysfunction and alternative causes of hemodynamic compromise
  - detects shunting through patent foramen ovale

Anticoagulants

- Reduce risk of additional clots
- Slow clot progression
- Do not dissolve clots
- Low molecular weight heparin
  - Enoxaparin (Lovenox)
  - Ardeparin (Normiflo)
  - Dalteparin (Fragmin)

Thrombolytics

- Dissolve clots
- Definite for massive PE
  - clinical ventricular dysfunction
  - hypotension
  - severe hypoxemia
- Controversial for submassive PE

Invasive Interventions

- Percutaneous methods
  - catheter-directed thrombolysis
  - embolectomy
- Pulmonary endarterectomy
  - circulatory arrest
  - hypothermia
  - serious postoperative complications
- Embolectomy via thoracotomy

Thrombolytics

- Considered for all patients with PE & without contraindications; e.g.:
  - previous hemorrhagic stroke at any time
  - active internal bleeding
  - suspected aortic dissection
  - acute pericarditis
- Decrease mortality, morbidity, recurrence

Prevention

- Anticoagulants
  - heparin
  - warfarin (Coumadin)
- Compression stockings
- Pneumatic compression
- Physical activity

Thrombolytics

- Agents
  - Tissue plasminogen activators (TPA)
    - Alteplase (Activase®)
    - Retaplase (Retavase®)
    - Tenecteplase (TNK-tPA)
  - Streptokinase (Eminase®)
  - Urokinase (Abbokinase®)

Prevention

- Air travel - longer flights, greater risk for PE
- Prevention
  - fluids
  - avoidance of alcohol and smoking
  - loose clothing
  - elastic support stockings
  - avoidance of leg crossing
  - physical activity

Prevention

- Vena cava (Greenfield) filter
  - especially for patients with contraindications to anticoagulation
  - percutaneous insertion
  - outpatient procedure
  - temporary, retrievable filters are available

PAH WHO Classifications

- Group I - Pulmonary arterial hypertension (PAH)
  - idiopathic- unknown etiology
  - familial
  - persistent pulmonary hypertension of newborns (PPHN)
  - associated with
    - portal hypertension
    - collagen dx
    - HIV
    - toxins; e.g., Fen-Phen (litigation)

Pulmonary Hypertension

PAH WHO Classifications

- Group II - Pulmonary hypertension associated with left heart disease
  - left-sided atrial or ventricular disease
  - left-sided valvular disease

Pulmonary Arterial Hypertension (PAH)

- Elevated pulmonary artery pressure
- Normal = 13 mm Hg (mean)
- Hypertension = 25 mm Hg (mean) at rest

PAH WHO Classifications

- Group III - Pulmonary hypertension associated with lung diseases and/or hypoxemia
  - COPD
  - interstitial lung disease
  - sleep-disordered breathing
  - chronic high-altitude exposure

PAH WHO Classifications

- Group IV - Pulmonary hypertension due to chronic thrombotic and/or embolic disease
- Group V - Miscellaneous
  - sarcoidosis
  - histiocytosis
  - compression of pulmonary vessels (neoplasms)

NYHA Functional Classifications

- Class I – no limitation of physical activity. Ordinary physical activity
- Class II – slight limitation of physical activity.
  - comfortable at rest.
  - ordinary physical activity- undue dyspnea or fatigue, chest pain, etc.

Acute PAH and Cardiac Interventions

- reperfusion injury- return of blood flow to ischemic myocardium- 'stunned myocardium'
- definition- prolonged post-ischemic dysfunction of viable tissue salvaged by reperfusion.

NYHA Functional Classifications

- Class III – marked limitation of physical activity.
  - comfortable at rest.
  - minimal activity causes dyspnea, fatigue, chest pain
- Class IV – inability for physical activity without symptoms.
  - right heart failure.
  - dyspnea and/or fatigue at rest.
  - discomfort with any physical activity.

Acute PAH and Cardiac Interventions

- reperfusion injury
- occurs after:
  - coronary thrombolysis
  - percutaneous coronary interventions
  - coronary artery bypass
  - heart transplantation

PAH Manifestations

Manifestations

- Increased pulmonary artery pressure
  - echocardiography - noninvasive
  - right heart catheterization (definitive)
- RV hypertrophy
- severe hypoxemia, esp. in presence of anatomic shunt (cyanosis)

PAH General Management (first line)

- Oxygen- reverses hypoxemic vasoconstriction
- Anticoagulants
- Diuretics
- Potassium
- Inotropic agents
- see management algorithm at web address below.

Manifestations

- dyspnea, fatigue
- syncope
- chest pressure or pain.
- edema- pedaledema, ascites
- tachycardia, palpitations
- can mimic asthma, especially in young persons

Calcium channel blockers

- amlodipine (Norvasc)
- nifedipine (Procardia)
- diltiazem (Cardizem)
- verapamil (Isoptan)

PAH Management

Endothelin antagonist

- bosentan (Tracleer)
  - oral administration
  - likely to cause birth defects
  - potential for hepatotoxicity

Phosphodiesterase inhibitors

- sildenafil (Viagra)
- vardenafil (Levitra)
- tadalafil (Cialis)
- milrinone (Primacor)- nebulized for PAH from reperfusion injury

Prostacyclins

- endogenous vasodilators
- prostaglandin i2 analogs (synthetic)
- non-acute indications
  - WHO Group I
  - NYHA Class III- IV severity
  - failure of other medications

Nitric oxide gas

- selectively dilates pulmonary vessels, because it is rapidly taken up by hemoglobin and neutralized
- Effects:
  - decreases pulmonary vascular resistance
  - improves V/Q matching by increasing blood flow to ventilated alveoli

Prostacyclins

- iloprost (Ventavis) - prostaglandin i2 analog
  - potency $\geq$ nitric oxide
  - effect duration = 120 min
  - aerosol 2.5 or 5.0 mcg 6-9 times daily
  - unit doses 2.5 or 5.0 mcg
  - specific nebulizers required

Nitric oxide gas delivery

- Disadvantages of NO
  - additional equipment- iNOvent, monitors
  - additional training
  - rebound PAH with cessation of delivery
  - bottom line- very costly

Epoprostenol (Flolan)

- Short-acting PGi-2
- Less expensive than iNO
- Duration of action 3-5 min.
- Delivery
  - continuous infusion- acute or non-acute care
  - continuous aerosol- acute care alternative to nitric oxide

Epoprostenol (Flolan)

- Delivery by infusion
  - same indications as Ventavis for non-acute setting
  - cost > $100,000/year
  - home care setting- patient has infusion pumps

Treprostinil (Remodulin)

- formulated for IV of SC injection
- four hour duration of action
- pilot studies of aerosolized treprostinil found sustained vasodilation (>3 H) with dosage delivered in a single breath
- additional study required for aerosol route

Flolan acute care aerosol delivery

- Indications - severe PAH, refractory to standard therapy
  - reperfusion injury; e.g., post-cardiopulmonary bypass
  - portal-pulmonary hypertension
  - independent or single-lung ventilation
  - ARDS
  - PPHN
  - RV failure
  - septic shock

Summary & Review

Flolan acute care aerosol delivery

- precautions/contraindications
  - interruption of delivery can result in rebound, death
  - may cause systemic hypotension (unlikely)
  - may cause hemorrhage
  - Flolan is photosensitive, so must be shielded from light

Summary and Review

- Pulmonary embolism epidemiology and importance
- Types & sites for embolism
- Risk factors for thromboembolism
- PE Pathophysiology
  - hemodynamics
  - gas exchange

Summary and Review

- PE manifestations
  - symptoms & signs
  - radiograph
  - ECG
  - Blood gases
- PE diagnosis
  - Clinical probability - Wells score
  - Laboratory studies - PE markers, vs. prognostic indicators
  - Imaging

Summary and Review

- General management- O2, etc.
- Calcium channel blockers
- Endothelin antagonist
- Phosphodiesterase inhibitors
- Nitric oxide gas
- Prostacyclins
  - Flolan
  - Ventavis
  - Remodulin

Summary and Review

- PE management
  - respiratory care
  - anticoagulants
  - thrombolytics
  - invasive interventions
- PE prevention
  - anticoagulants
  - thromboembolic deterrent (TED) stockings
  - vena cava filters

END

Summary and Review

- PAH classifications (WHO groups)
- PAH functional classifications (NYHA classes)
- Manifestations

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