

Pulmonary Vascular Disease

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<http://www.geocities.com/jonesapjr/index.html>

Learning Objective

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

Pulmonary Thromboembolism

Definitions

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

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

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

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. Mansonii

http://biology.nebrwesleyan.edu/courses/Labs/Biology_of_Animals/ZooLab10/Schistosoma_wm_25X.jpg

Sites for embolism

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

Risk factors

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

Risk factors

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

PE Pathophysiology

Perfusion of the lung

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

Click to see pulmonary circulation

http://www.bg.ic.ac.uk/Staff/khparker/homepage/BSc_lectures/2002/Pulmonary_anatomy.jpg

Perfusion of the lung

- ^ **Bronchial circulation**
 - ◆ thoracic aorta to terminal bronchioles
 - ◆ perfuses
 - f*esophagus
 - f*trachea
 - f*visceral pleura
 - f*airways to terminal bronchioles

Click to see bronchial circulation

http://www.lib.mcg.edu/edu/eshuphysio/program/section4/4ch4/s4ch4_3.htm

Perfusion of the lung

- ^ **Anastomoses between pulmonary and bronchial circulations**
 - ◆ bronchioles to pulmonary capillary beds
 - ◆ bronchial circulation increases flow through anastomoses to compensate for pulmonary embolism

Click to see peripheral bronchial and pulmonary circulation

http://commons.wikimedia.org/wiki/Image:Bronchial_anatomy_with_description.png

Perfusion of the lung

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

Click to see pulmonary infarction

<http://library.med.utah.edu/WebPath/ATHHTML/ATH033.html>

Development of thrombi

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

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://video.google.ca/VideoPlayer?docid=919332128287113683&v#f4h1-en>

PE pathophysiology

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

Click to download excellent article on pulmonary vascular pathophysiology
<http://radiographics.rsnajnl.org/cgi/reprint/20/2/491>

PE pathophysiology

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

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 - CO₂
 - ◆ tachypnea - arterial hypocapnea
 - ◆ alveolar dead space - alveolar hypocapnea, with increased P(a - E)CO₂
 - ◆ if hypercapnea ==>
 - f* massive embolus
 - f* comorbidity; e.g., emphysema

Click to download article on acute PE
<http://circ.ahajournals.org/cgi/content/full/108/22/2726>

PE Manifestations**Symptoms**

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

Physical signs

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

Massive PE

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

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

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

PE Diagnosis

Goals for diagnostic techniques

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

Bases for diagnosis

- ^ History
- ^ Physical findings
- ^ Laboratory tests
- ^ Imaging

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)

Clinical probability for PE

- ^ Wells score interpretations
 - ◆ Traditional interpretation
 - f*Score >6.0 - High
 - f*Score 2.0 to 6.0 - Moderate
 - f*Score <2.0 - Low
 - ◆ Alternate interpretation
 - f*Score > 4 - PE likely ==> diagnostic imaging
 - f*Score 4 or less - PE unlikely ==>

D-dimer to rule out PE

Click for Wells score calculator

http://www.icumedicus.com/clinical_criteria/pe_wells_score.php

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

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

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

- ▲ 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

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

Click for algorithm of PE diagnosis with CT angiography
http://www.acponline.org/acp_press/essentials/cdim_ch80_wes03.pdf

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

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

Click to see PE on angiography
<http://video.google.ca/videoplay?docid=5891944428513598217&hl=en>

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

Click to see VQ scan with PE

http://www.med.yale.edu/intmed/cardio/imaging/cases/pulmonary_embolus1/perfusion.html

Imaging

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

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

PE Management & Prevention

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

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

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

Thrombolytics

- ^ Agents
 - ◆ Tissue plasminogen activators (TPA)
 - f Alteplase (Activase®)
 - f Retaplast (Retavase®)
 - f Tenecteplase (TNK-tPA)
 - ◆ Streptokinase (Eminase®)
 - ◆ Urokinase (Abbokinase®)

Invasive Interventions

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

Link to article on invasive interventions for PE
http://circ.ahajournals.org/cgi/reprint/110/9_suppl_1/1-27

Prevention

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

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

Link to article on air travel and PE
<http://content.nejm.org/cgi/reprint/345/11/779.pdf>

Prevention

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

Click to see vena cava filter (need to scroll down)
http://www.gsirichmond.com/vasc_proc.htm

Pulmonary Hypertension**Pulmonary Arterial Hypertension (PAH)**

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

PAH WHO Classifications

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

PAH WHO Classifications

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

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)

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.

Link to AHA article on reperfusion injury
<http://circ.ahajournals.org/cgi/reprint/105/20/233>

Acute PAH and Cardiac Interventions

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

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.

Link to NYHA Functional Classifications
<http://www.cochranfoundation.com/docs/nyha-class.htm>

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.

PAH Manifestations

Manifestations

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

Manifestations

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

PAH Management

PAH General Management (first line)

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

Link to page with treatment algorithm for PHA (slide 7 on the page)
<http://www.cardiosource.com/ExpertOpinions/hottopics/article.asp?paperID=54>

Calcium channel blockers

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

Endothelin antagonist

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

Link to information on endothelin antagonists
http://www.medscape.com/viewarticle/423213_3

Phosphodiesterase inhibitors

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

Link to information on phosphodiesterase inhibitors
<http://cvpharmacology.com/vasodilator/PDEI.htm>

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

Nitric oxide gas delivery

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

Link to nitric oxide and PAH
<http://cvpharmacology.com/vasodilator/PDEI.htm>

Prostacyclins

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

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

Click to see nebulizers for Ventavis
http://ineb.respirionics.com/aad_products.asp

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

Link to Flolan information
http://www.flolan-center.com/pages/flolan_effective.html

Epoprostenol (Flolan)

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

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

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

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

Links to treprostinil (Remodulin)
<http://jap.physiology.org/cgi/reprint/99/6/2363>
http://www.rxlist.com/cgi/generic/remodulin_cp.htm

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