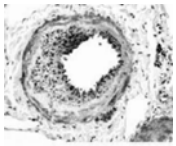
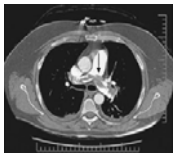
Pulmonary Vascular Disease: Pulmonary Hypertension and Pulmonary Embolism





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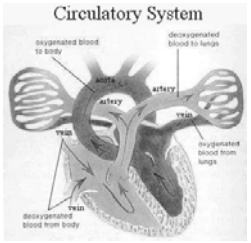


Pulmonary Vasculature

- Elastic pulmonary arteries (> 1-2 mm diameter)
- Muscular pulmonary arteries (100 µm-1 mm)
- Pulmonary arterioles (< 30-100 µm)--no muscle
- 7 times more compliant than systemic vasculature
  - Pulmonary VR is one tenth of systemic VR
  - Pulmonary VR stays low due to "recruitment" and/or "distention" of capillary network

Control of Pulmonary Circulation

- Hypoxia
  - To match regional perfusion/ventilation
- Nervous system
  - Parasympathetic, sympathetic, NANC fibers, neurohormones
- Passive mechanisms
  - Anatomy, gravity, lung volume, alveolar pressure

Hemodynamic Physiology of Pulmonary Hypertension

Back to Physics-Modified Ohm's Law

- Change in pressure = Flow x Resistance
  - Ppa - Ppv = Q x PVR
  - Ppa = (Q x PVR) + Ppv
  - PVR = (Ppa - Ppv)/ Q = 100 dynes/s/cm^{-5}
- Alterations in PVR, Q and Ppv raise Ppa
  - PVR: occlusive vasculopathy of small arteries / arterioles (PAH), decreased area of pulmonary vascular bed (PE, ILD), hypoxic vasoconstriction (COPD, high altitude)
  - Q: Left to right shunt due to congenital heart disease, liver cirrhosis
  - Ppv: Left heart and valvular disease, constrictive pericarditis
- Increase in PVR is the primary cause of PH

Pulmonary Hypertension

Hemodynamic Definition

- Increased pulmonary vascular pressure
  - Isolated increase in pulmonary arterial pressure or increase in both pulmonary arterial and venous pressures
- Pulmonary arterial hypertension
  - Mean PAP >25 mm Hg at rest or >30 mm Hg with exercise
  - Normal pulmonary capillary wedge pressure (< 15 mm Hg)
  - PVR > 3 Wood units (or >200 dynes/s/cm^{-5})

Pulmonary Hypertension
WHO Classification

- Five major categories based on pathophysiology, diagnostic findings and treatment response

I. Pulmonary arterial hypertension

II. Pulmonary hypertension with left heart disease

III. Pulmonary hypertension associated with lung diseases and/or hypoxemia

IV. Pulmonary hypertension due to chronic thrombotic and/or embolic disease

V. Miscellaneous

Simonneau. JACC 2004

WHO Classification
Simonneau. JACC 2004

I. Pulmonary arterial hypertension

- **Idiopathic**
- **Familial**
- **Associated with:**
  - **Drugs/Anorexigen use ("Fen-phen", cocaine, metham)**
  - **Collagen vascular disease**
  - **HIV infection**
  - **Portal hypertension**
  - **Congenital systemic-to-pulmonary cardiac shunts**
  - **Other (glycogen storage disease, HHT, splenectomy, hemoglobinopathy, myeloproliferative dis, thyroid)**
- **Associated with significant venous or capillary involvement (PVOD, PCH)**

WHO Classification
Simonneau. JACC 2004

II. Left Heart Disease
- **Atrial**
- **Ventricular**
- **Valvular**

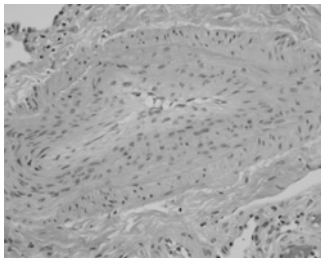
III. Lung Disease/Hypoxia
- **COPD**
- **ILD**
- **Sleep-disordered breathing**
- **Alveolar hypoventilation**
- **High altitude exposure**
- **Developmental abnormality**

IV. Thrombotic/embolic
- **Proximal**
- **Distal**
- **Other (tumor, parasite, foreign)**

V. Miscellaneous
- **Sarcoidosis, Langerhans-cell histiocytosis, vascular compression**

Pulmonary Arterial Hypertension
Pathology (I)

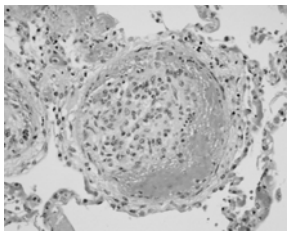
Endothelial thickening

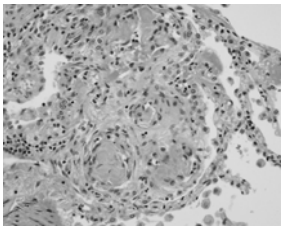


Smooth muscle hypertrophy

Pulmonary Arterial Hypertension
Pathology (II)

Plexiform lesions





In situ thrombosis

Pulmonary Arterial Hypertension

- Caused by an array of metabolic abnormalities that result in obliterative remodeling of pulmonary circulation
- Characterized by lumenal occlusion in medium-sized and small pulmonary arteries due to
  - Excessive cellular proliferation in vascular wall and in situ thrombosis
  - Loss of microvessels and capillaries
- Leads to increase in right ventricular afterload, right ventricular failure and death

Emerging Concepts in PAH

- Proliferative and antiapoptotic environment in vascular wall share common features with neoplasia
- Loss of endothelial cells and microvessels has features of a degenerative disease
- Circulating and vascular inflammatory cells and mediators suggest a systemic inflammatory disease

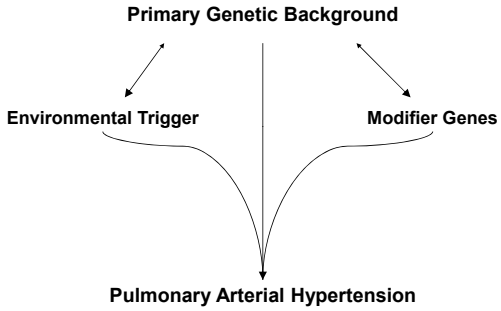
Genetics and Pathobiology of PAH

- Loss-of-function mutations in gene encoding bone morphogenetic protein receptor type 2 (BMPR2)
  - Detected in 70% of familial PAH and 10-40% of idiopathic PAH
  - Only 20% of BMPR2 mutation carriers develop PAH
- BMPR2 is TGF-β family receptor involved in regulation of apoptosis and growth
  - Decrease in BMPR2 signaling leads to PAH
- "Second hits"
  - Endogenous -other- genetic abnormalities (serotonin pathway), flow change or exogenous stimuli (drugs, viral)
  - Dysregulated inflammation (collagen vascular disease, HIV)

Deng, Am J Hum Gen, 2000
Lane, Nat Gen, 2000

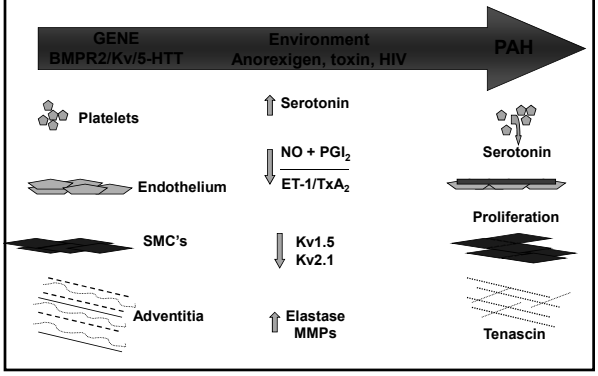
Pathogenesis of Pulmonary Arterial Hypertension

Multiple-Hit Hypothesis



Modified from Farber. NEJM 2004;351:1655

Pathobiology of PAH



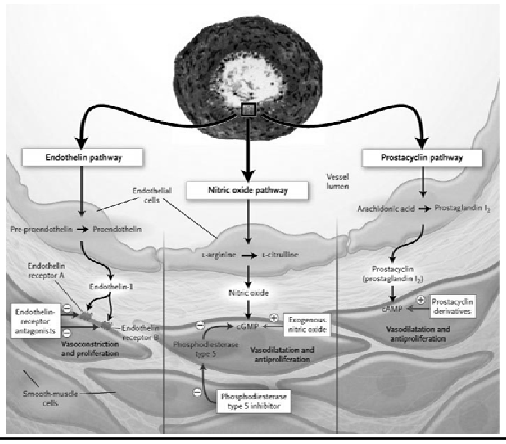
Imbalance of Vascular Effectors in PAH

- Likely exists because of endothelial-cell dysfunction or injury leading to
  - Vasoconstriction
  - Smooth-muscle cell and endothelial-cell proliferation
  - Thrombosis

Mediators of Pulmonary Vascular Responses in Pulmonary Arterial Hypertension

Vasoconstriction	Cell Proliferation	Thrombosis

Modified from Farber. NEJM 2004;351:1655



Epidemiology of PAH

- Prospective registries in the U.S., France and Scotland
- Prevalence of PAH 15 to 26 cases per 1 million adults
  - Half idiopathic and half associated with other conditions
- ~80% of patients referred to specialized centers are in NYHA class III or IV
- Mean age at diagnosis 36 to 50 years

Humbert. AJRCCM 2008;177:574

Pulmonary Hypertension
Clinical Presentation

- Symptoms
  - Dyspnea "out of shape"
  - Fatigue
  - Palpitations
  - Chest pain
  - Lightheadedness
  - Syncope
  - Edema
  - Abdominal fullness, anorexia
  - Cough, hemoptysis, hoarseness (Ortner's syndrome) less common
- Delay in diagnosis of >2 years

Pulmonary Hypertension
Clinical Presentation

- Signs
  - Jugular venous distension with large a and v waves
  - Loud P_2
  - Early systolic click
  - TR murmur
  - Diastolic murmur
  - RV heave
  - S_4 and S_3 gallop
  - Hepatojugular reflux
  - Hepatomegaly
  - Pulsatile liver
  - Ascites
  - Edema
  - Hypoperfusion

Diagnosis of Pulmonary Hypertension

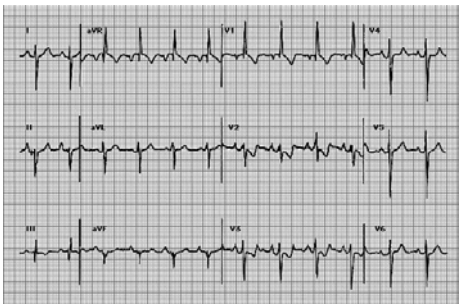
- Initial routine evaluation for dyspnea and other symptoms of PH
  - CXR, EKG, pulmonary function testing, arterial blood gas, cardiopulmonary exercise study
- Doppler echocardiography
- Right heart catheterization
  - To confirm diagnosis
  - To characterize hemodynamics

Chest Radiograph

- Enlarged main pulmonary arteries
  - Attenuation of peripheral pulmonary vascular markings (pruning)
- Right ventricular enlargement
- Exclusion of parenchymal lung disease

Electrocardiography

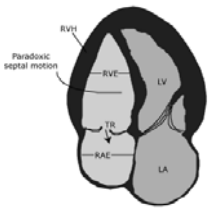
- Right ventricular hypertrophy, right axis deviation, right atrial enlargement

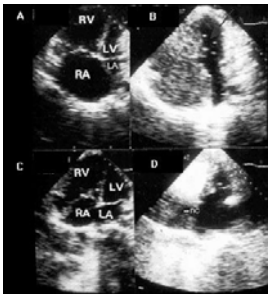


Doppler Echocardiography in PH

- Tricuspid regurgitation
- Right a/v dilatation
- Right ventricular hypertrophy
- Right ventricular dysfunction
- Pulmonic insufficiency
- Intracardiac shunt
- Congenital heart ds
- Left heart size/fx
- Valvular morphology
- Pericardial effusion

Doppler Echocardiography





Right Heart Catheterization

- To diagnose/characterize pulmonary hypertension
  - Mean pulmonary artery pressure
  - Pulmonary capillary wedge pressure
  - Mean right atrial pressure
  - Cardiac index
  - PVR calculation
- To assess severity of pulmonary hypertension
- To evaluate acute vasoreactivity (vasodilator response)

Right Heart Catheterization

•RA-4 mm Hg	•RA-12 mm Hg
•PA- 90/60 mm Hg	•PA- 50/25 mm Hg
•PCWP- 8 mm Hg	•PCWP- 8 mm Hg
•CI- 2.4 L/m/m^2	•CI- 1.0 L/m/m2
•PVR ~ 2066 d•s•cm^{-5}	•PVR ~ 2000 d•s•cm-5

Detailed Evaluation After Diagnosis of PH

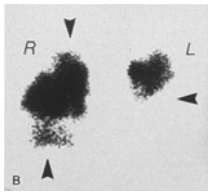
- Medical history
  - PMH: VTE, heart, lung, and blood disorders, HIV
  - Family history
  - Exposures: weight loss medications
  - Drugs: cocaine, methamphetamine
- Diagnostic tests
  - Serologic evaluation for autoimmune disease and HIV
  - Pulmonary function tests
  - Radiologic tests
    - Exclude thromboembolic disease, obstructive and restrictive pulmonary disease
  - Sleep study and nocturnal oxymetry

Radiologic Evaluation

- Ventilation perfusion scan***
  - Pulmonary angiography may be needed to diagnose and characterize CTEPH
- High resolution computed tomography
- Cardiac MRI

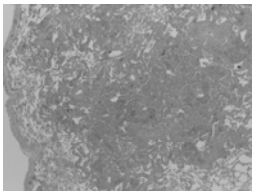
Ventilation Perfusion Scan

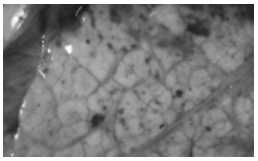
- To exclude chronic thromboembolic PH

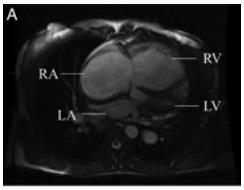


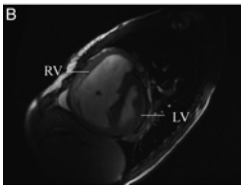
Chest Computed Tomography

Pulmonary Capillary Hemangiomatosis









Therapies for Pulmonary Arterial Hypertension

- Preventative care
- Anticoagulation
- Supplemental oxygen
- Diuretics
- Inotropes
- Calcium channel blockers
- Prostacyclin analogues
- Endothelin-1 receptor antagonists
- PDE-5 inhibitors
- Cardiopulmonary rehabilitation
- Atrial septostomy
- Lung transplantation

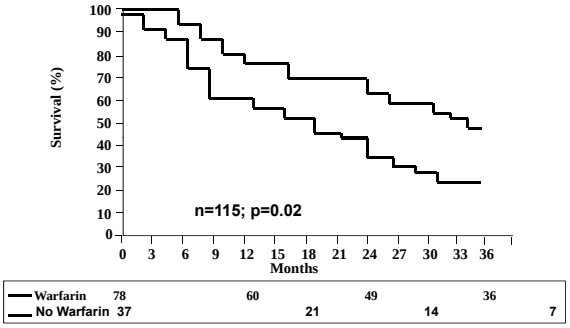
Preventive Measures
Do's and Don't's

- Cautious, graduated physical activity
- Supplemental oxygen to keep saturation ≥ 92%
- Avoid
  - Heavy physical activity
  - Bending over, rising quickly
  - Hot baths and showers
  - Excessive sodium intake
  - Air travel (use supplemental O2)
  - High altitude >1800 m above sea level (use supplemental O2)
  - Pregnancy
  - Concomitant medications, herbal preparations
  - Invasive procedures
- Immunization against influenza and pneumococcus

General Measures

- Anticoagulation
  - INR goal 1.5 to 2.5
  - Controversial in diseases other than iPAH
- Supplemental oxygen
- Diuretics and inotropic medications
  - Right ventricular failure
  - Monitor electrolytes and renal function
- Digitalis
  - Right ventricular failure and arrhythmia

Survival by Use of Chronic Anticoagulation

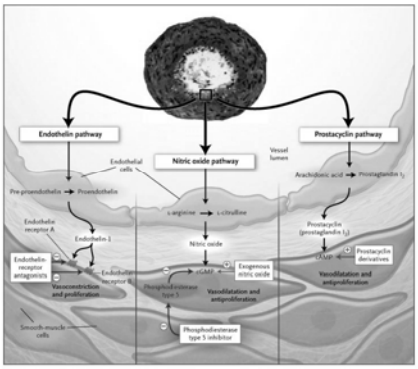


(Fuster, Circulation, 1984)

Vasodilator Testing and Calcium Channel Blockers

- Vasodilator testing during RHC
  - IV adenosine, epoprostenol or inhaled nitric oxide
- Definition of vasodilator responsiveness
  - Decrease of > 10 mm Hg in mean PAP to ≤ 40 mm Hg with an increase in or no change in cardiac output
  - Uncommon, occurring in 10% of patients with iPAH, less common with other subtypes
- iPAH with acute response to vasodilators may have improved survival with long-term use of CCB's
  - Close follow-up for continued benefit essential as only 50% of patients maintain long-term benefit

Targets for Therapies in PAH



Humbert, N Engl J Med 2004;351:1425

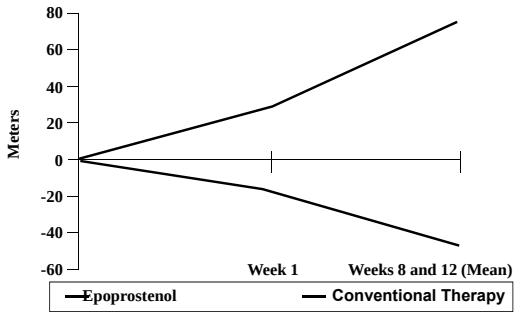
Targets for Therapy in PH

- Downregulation of prostacyclin axis
  - Reversed by exogenous prostacyclin analogues
- Downregulation of NO/cGMP axis
  - Reversed by inhaled NO and PDE5 inhibition
- Upregulation of endothelin axis
  - Reversed by endothelin receptor antagonists

Prostanoids

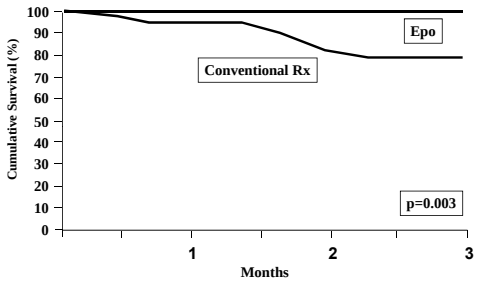
- Underproduction of prostacycline in PAH
  - Prostacycline promotes vasodilatation, inhibits vascular proliferation and platelet aggregation
- Epoprostenol (IV)
- Beraprost (PO)
- Treprostinil (SC or IV)
- Iloprost (inhalation)
- Improvement in hemodynamics, exercise capacity and symptoms and survival (with epoprostenol)

Change from Baseline in 6-Minute Walk Test with Epoprostenol Therapy



(Barst, NEJM, 1996)

Survival With Epoprostenol Therapy



(Barst, NEJM, 1996)

Endothelin-Receptor Antagonists

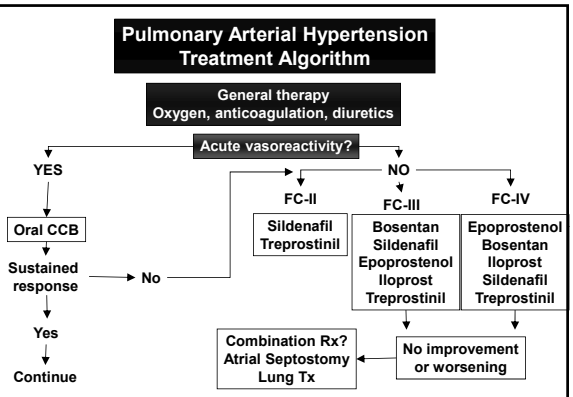
- 2 endothelin-receptor isoforms
  - ETA: vasoconstriction, proliferation of VSMC
  - ETB: Endothelin clearance and vasodilatation
- Dual ETA and ETB-receptor antagonist
  - Bosentan
- Selective ETA-receptor antagonists
  - Ambrisentan
  - Sitaxsentan
- Improvement in exercise capacity and hemodynamics in 12- to 16-wk clinical trials

Phosphodiesterase-5 Inhibitors

- Inhibition of cGMP-specific phosphodiesterase
  - Pulmonary arterial vasodilatation and inhibition of smooth muscle cell growth by enhancing effects of locally produced NO via its second messenger cGMP
- Sildenafil
- Improvement in symptoms, exercise capacity and hemodynamics in short-term studies

Atrial Septostomy and Lung Transplantation

- Atrial septostomy
  - Creation of right-to-left interatrial shunt for right ventricular decompression
  - Palliative or as bridge to lung transplantation
- Lung transplantation
  - Early referral
  - Close monitoring for response to therapy
  - Perform lung transplantation before advanced right heart failure and poor performance status



Modified from Badesch. Chest 2007;131:1917

Survival in Idiopathic Pulmonary Arterial Hypertension

NIH[1] (1981-1985)	68%	~58%	48%
New York[2] (1994-2002)	87%	77%	75%
Chicago[3] (1991-2001)	88%	76%	63%
Nashville[4] (1995-2001)	85%	76%	65%
Philadelphia[5] (1997-2001)	84%	71%	71%
Clamart[6] (1992-2001)	85%	70%	63%
Germany[7] (1996-2001)	68%	--	--

[1]*D'Alonzo, Ann Int Med, 1991*
[2]*Kawut, AJC, 2005*
[3]*McLaughlin, Circ, 2002*
[4]*Kuhn, AJRCCM, 2003*
[5]*Kawut, Chest, 2003*
[6]*Sitbon, JACC, 2002*
[7]*Wensel, Circ, 2002*

Prognosis

- Median survival in untreated PAH < 3 yrs
- Contemporary registries reveal improved survival
  - 65-75% survival at 3 years
  - 47-55% at 5 years in epoprostenol treated patients
- Right heart failure = lower survival rates
  - Elevated RAP, low CI, low MVO_2, poor exercise capacity, pericardial effusion, high BNP
- Close monitoring to evaluate treatment response, plan additional therapy and for lung transplantation

Future Directions

- Discovery of novel mechanistic pathways and translational application into clinical practice
- Stem cell replacement/transplant with endothelial progenitor cells

Pulmonary Embolism

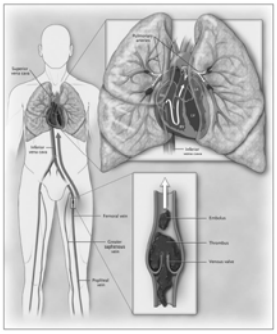
Epidemiology of Pulmonary Embolism

- Estimated to occur in ~ 600,000 patients annually in the U.S.
- Causes or contributes to ~50,000 to 200,000 deaths
  - Accounts for 15% of in-hospital mortality
- Incidence of acute PE in hospitals ranges from 0.05 to 1%
- Diagnosis is missed in 50-70% of patients antemortem
- Wide spectrum of severity with short-term mortality figures between 2.5% and >50%

Dalen JE. Prog Cardiovasc Dis 1975;17:259
Goldhaber SZ. Am J Med 1982;73:822
Pineda. Chest 2001;120:791

Pathophysiology of Pulmonary Embolism

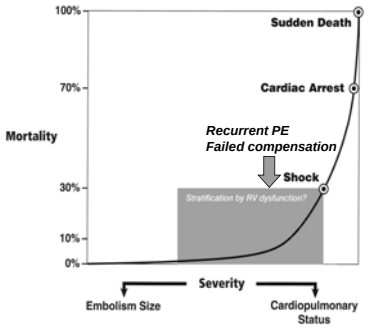
- Sources of PE
  - Iliofemoral veins***
  - Pelvic, upper extremity, renal, right heart
- ~50% of iliofemoral DVT result in PE
  - 50-80% of iliofemoral DVT originate in calf veins
- Virchow's triad
  - Endothelial injury, stasis, hypercoagulability



Tapson . N Engl J Med 2008;358:1037

Severity and Outcomes in Pulmonary Embolism

Modified from Wood. Chest 2002;121:877-905



Gas Exchange Physiology After PE

- Acute vascular obstruction and vasoconstriction
- Increased alveolar dead space
  - Reflex bronchoconstriction to minimize dead space--**Trivial
  - Hyperventilation due to dead space
- Mechanisms of arterial hypoxemia
  - Shunt (flow through atelectatic regions, opening of latent pulmonary A-V anastomoses due high PAP or intracardiac)
  - VQ inequality (increased flow to low V areas without emboli due to increased PA pressure)
  - Diffusion impairment (high flow with reduced transit time)
  - Increased A-V O_2 difference from RV strain and decreased CO

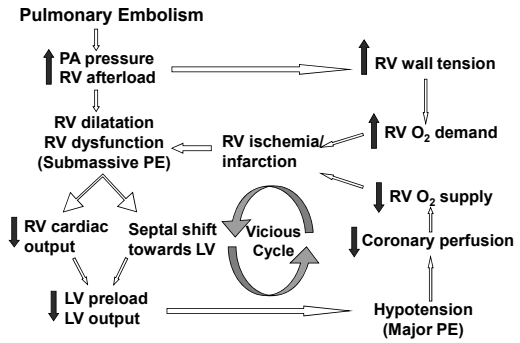
Pathophysiologic Response to PE (I)

- *Without pre-existing cardiopulmonary disease*
  - Clinical and physiologic findings are related to embolism size
  - mPAP increases with 25-30% obstruction of vascular bed
  - RAP rises with 35-40% obstruction of vascular bed
  - mPAP remains under 40 mm Hg even if there is $\geq$50% obstruction (maximal pressure that a normal right ventricle can generate)
  - Cardiac output decreases when obstruction exceeds 50%

Pathophysiologic Response to PE (II)

- *With pre-existing cardiopulmonary disease*
  - Significant hemodynamic instability is common with lesser degree of pulmonary vascular obstruction
  - mPAP is much more elevated and cardiac output decreased with no consistent relationship between cardiovascular instability and magnitude of obstruction

Pathophysiology of Major PE



Risk Factors for Venous Thromboembolism

- **Acquired Factors**
  - Reduced mobility
  - Advanced age
  - Cancer and chemotherapy
  - Acute medical illness
  - Major surgery and trauma
  - Spinal cord injury
  - Pregnancy/postpartum
  - Oral contraceptives
  - Hormone replacement Rx
  - Antiphospholipid ab synd
  - Central venous catheter
  - Polycythemia vera
- **Hereditary factors**
  - Factor V Leiden
  - Activated protein C resistance without F V L
  - Antithrombin deficiency
  - Protein C and S deficiency
  - Prothrombin gene mutation
  - Dysfibrinogenemia
  - Plasminogen deficiency
- **Probable factors**
  - Elevated lipoprotein(a)
  - Elevated homocysteine, factors VIII, IX, XI, fibrinogen

Tapson. N Engl J Med 2008;358:1037

Clinical Findings of PE

- **Symptoms and signs**
  - Dyspnea, chest pain, wheezing, cough, apprehension, leg pain and swelling, syncope, hemoptysis, fever
  - Tachycardia, tachypnea, accentuated P2, rales, JVD, DVT
- **Chest radiograph**
  Atelectasis, pleural effusion, pleural-based opacity, cardiomegaly, diaphragmatic elevation, prominent central PA, Westermark sign
- **ECG**
  Anterior T-wave inversions, ST-T segment changes, RBBB, $S_1Q_3T_3$
- **Arterial blood gas**
  Hypoxemia and hypocapnia

Diagnostic Evaluation

- **Develop an estimate of pretest clinical probability based on symptoms, signs and risk factors**
  - High (very likely), low (unlikely) or intermediate (possible/probable)
  - Clinical prediction scores (Wells or Geneva)
- **Evaluation must be RAPID since majority of deaths occur within 6 hours of presentation**
- **Concomitant diagnosis, treatment, and resuscitation if needed**
  - Start anticoagulation if PE is highly suspected and there are no contraindications

Estimation of Pretest Clinical Probability

- **High (very likely)**
  - Symptoms compatible with PE, not explained otherwise
    Sudden-onset dyspnea, tachypnea, pleuritic pain, syncope
  - CXR, ECG, ABG findings compatible with PE, not explained otherwise
  - Presence of risk factors for venous thromboembolism
- **Low (unlikely)**
  - Symptoms incompatible with PE or compatible symptoms explained by alternative diagnoses (eg. pneumothorax, pneumonia)
  - No CXR, ECG findings of PE or findings that can be explained otherwise
  - Absence of risk factors for venous thromboembolism
- **Intermediate (possible/probable)**

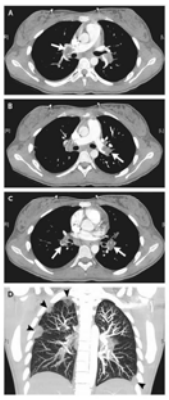
Quantitative Clinical Assessment for PE

Modified Wells Criteria	
Clinical symptoms of DVT (leg swelling, pain)	3.0
Other diagnosis less likely than PE	3.0
Heart rate >100	1.5
Immobilization (≥3 days) or surgery within last 4 weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy	1.0
Probability	Score
Traditional clinical probability assessment	
High	>6.0
Moderate	2.0 to 6.0
Low	<2.0
Simplified clinical probability assessment	
PE likely	>4.0
PE unlikely	≤4.0

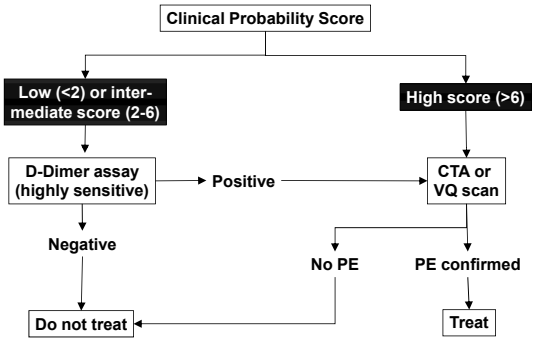
Diagnostic Tests For Major PE

- Chest radiograph and EKG
- VQ scan
- CT pulmonary angiography (CTPA)
- Duplex ultrasonography
- Laboratory markers
  - D-dimer, cardiac troponins, NT-pro-BNP and BNP
- Echocardiography
  - Findings compatible with or diagnostic of PE
  - Excludes alternative diagnoses in major PE
    - Acute MI, pericardial tamponade, aortic dissection
- Pulmonary angiography

Pulmonary Embolism
CT Findings
Kinane T et al. N Engl J Med 2008;358:941-52



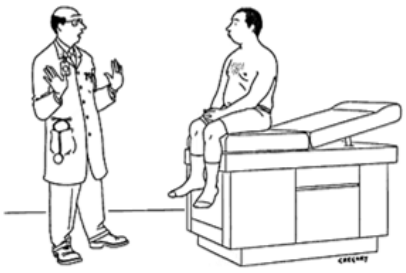
Diagnostic Algorithm Using Wells Criteria for Suspected Pulmonary Embolism



Konstantinides. NEJM 2008;359:2804

Treatment of Acute Pulmonary Embolism

- Anticoagulation with heparin products
  - Reach therapeutic levels quickly
  - Transition to oral anticoagulation
- Inferior vena cava filter placement
  - Anticoagulation contraindicated
  - DVT present along with severe PE
- Thrombolytic therapy
  - Hemodynamic instability
- Surgical embolectomy
  - Major PE unresponsive to anticoagulation, thrombolysis or contraindications to medical Rx



"Whoa—way too much information!"