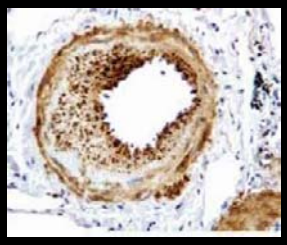
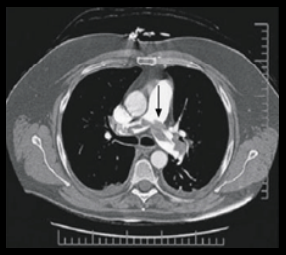
Pulmonary Vascular Disease: Pulmonary Hypertension and Pulmonary Embolism





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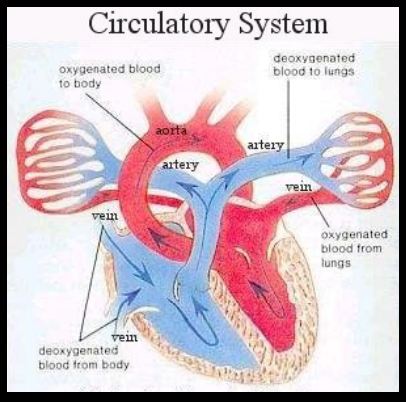
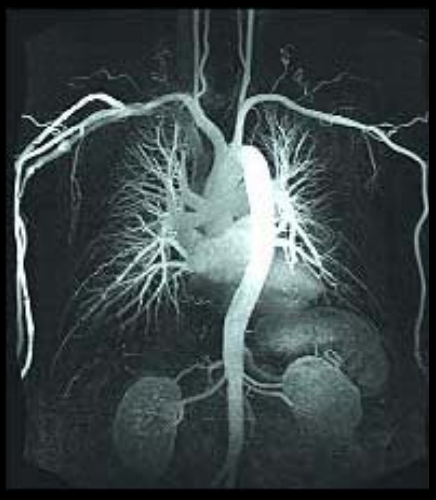




Pulmonary Vasculature

- 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

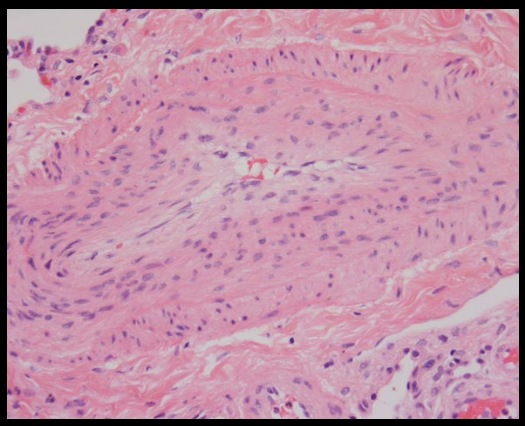
- Proximal
- Distal
- Other (tumor, parasite, foreign)

V. Miscellaneous

- Sarcoidosis, Langerhans-cell histiocytosis, vascular compression

Pulmonary Arterial Hypertension
Pathology (I)

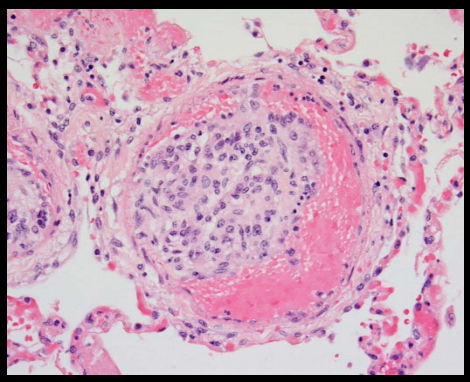
Endothelial thickening

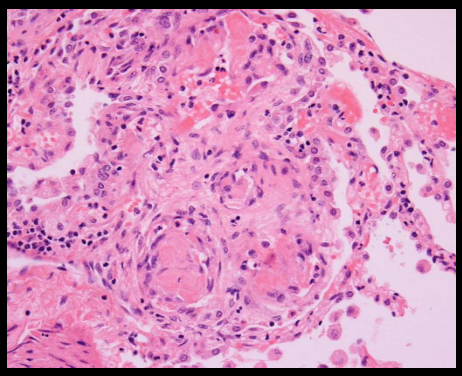


Smooth muscle hypertrophy

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

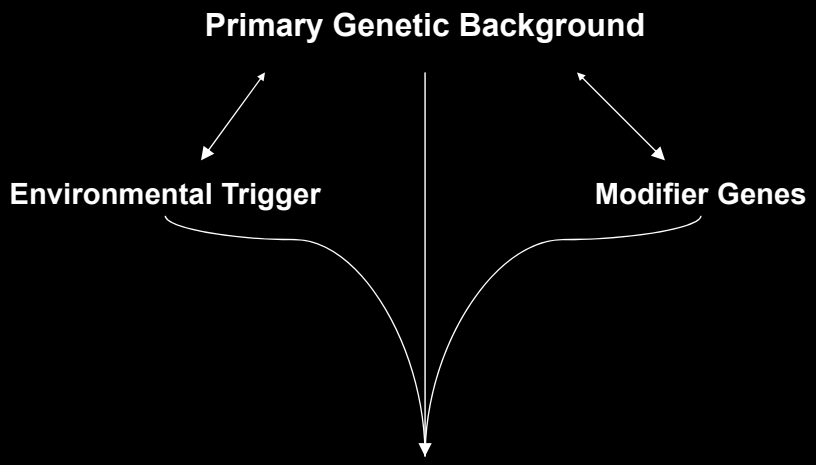
Genetics and Pathobiology of PAH

- 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

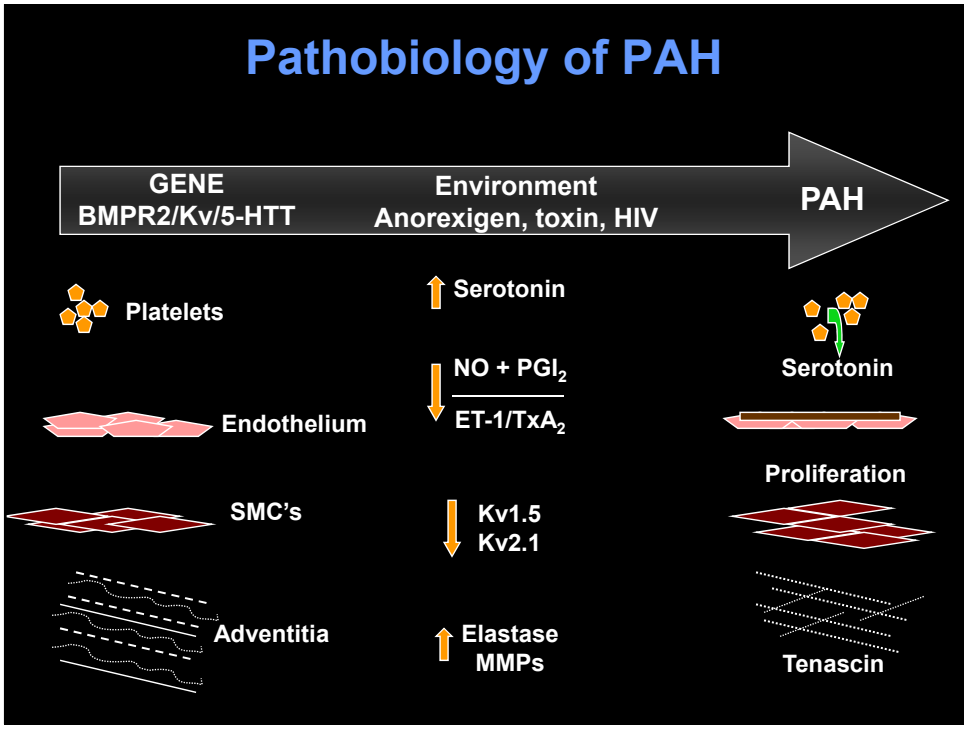
Pathogenesis of Pulmonary Arterial Hypertension

Multiple-Hit Hypothesis



Modified from Farber. NEJM 2004;351:1655

Pathobiology of PAH



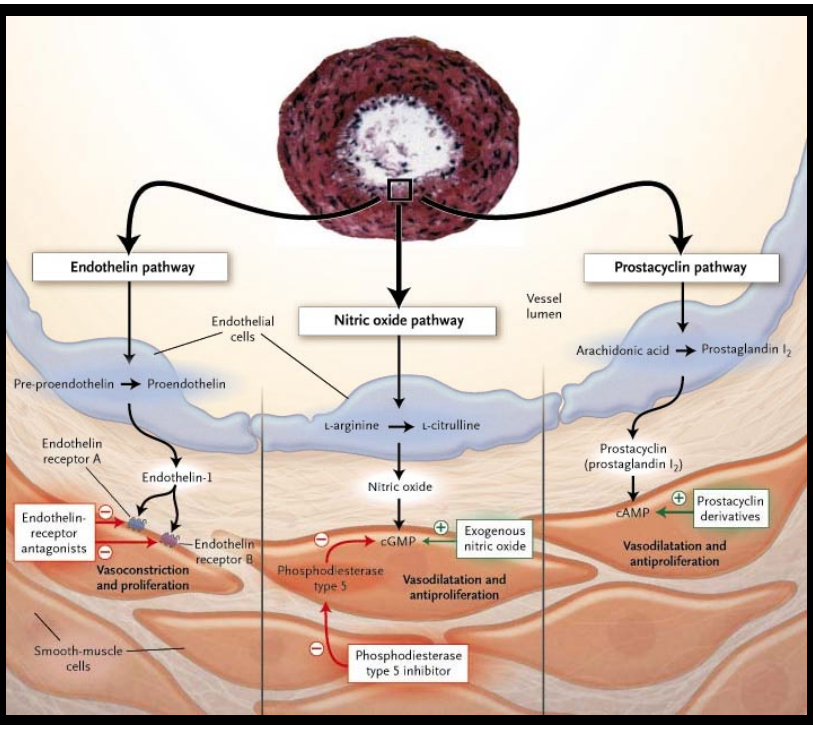
Imbalance of Vascular Effectors in PAH

- 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
Increased TxA2	Increased VEGF	Increased TxA2
Decreased PGI2	Decreased PGI2	Decreased PGI2
Decreased NO	Decreased NO	Decreased NO
Increased ET-1	Increased ET-1	---
Increased 5-HT	Increased 5-HT	Increased 5-HT
Decreased VIP	Decreased VIP	Decreased VIP

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

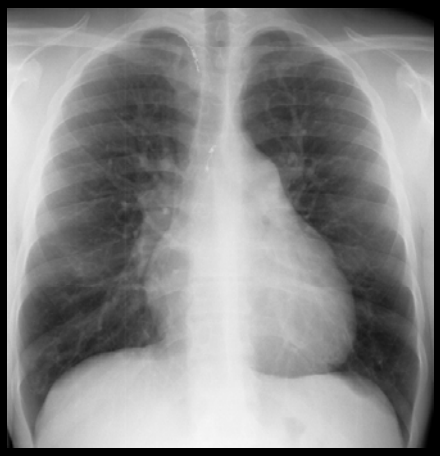
- **Signs**
  - Jugular venous distension with large a and v waves
  - Loud P_2
  - Early systolic click
  - TR murmur
  - Diastolic murmur
  - RV heave
  - S_4 and S_3 gallop
  - Hepatojugular reflux
  - Hepatomegaly
  - Pulsatile liver
  - Ascites
  - Edema
  - Hypoperfusion

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

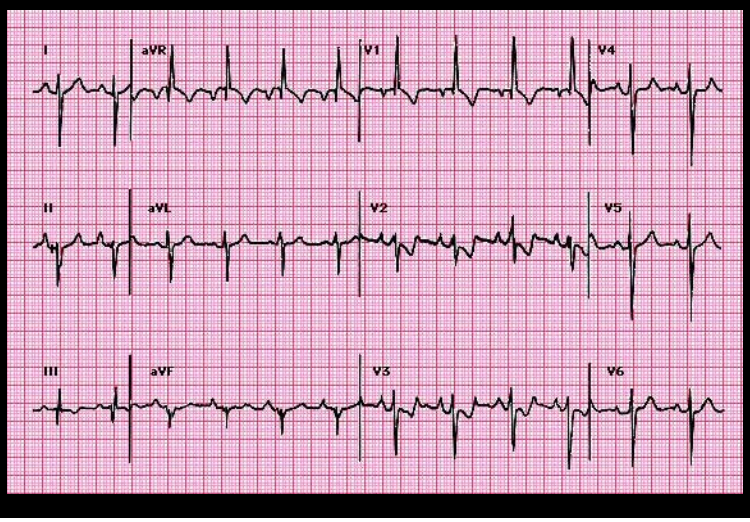
Chest Radiograph

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



Electrocardiography

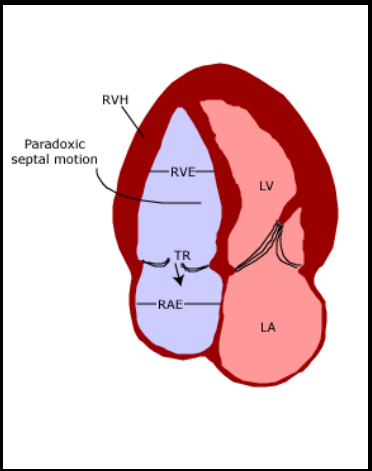
- Right ventricular hypertrophy, right axis deviation, right atrial enlargement

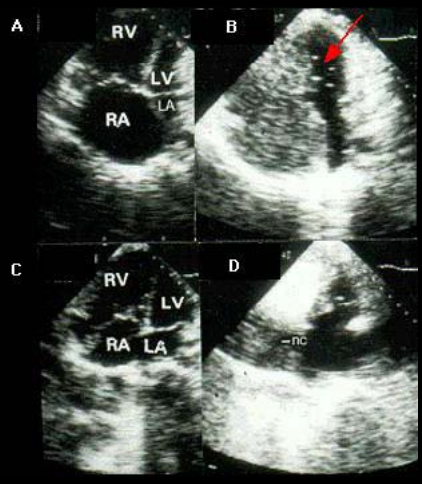


Doppler Echocardiography in PH

- 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

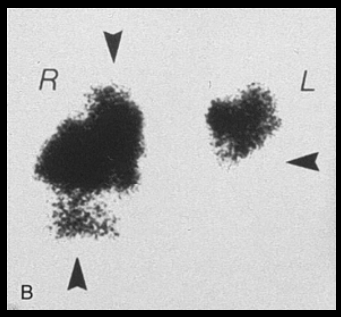
- Medical history
  - PMH: VTE, heart, lung, and blood disorders, HIV
  - Family history
  - Exposures: weight loss medications
  - Drugs: cocaine, methamphetamine
- Diagnostic tests
  - Serologic evaluation for autoimmune disease and HIV
  - Pulmonary function tests
  - Radiologic tests
    - Exclude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

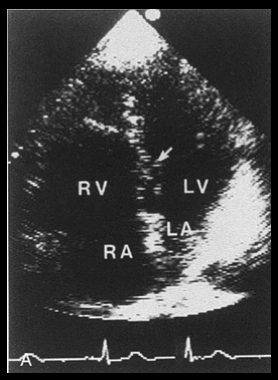
Radiologic Evaluation

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

Ventilation Perfusion Scan

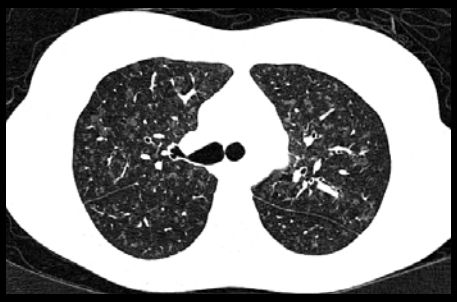
- To exclude chronic thromboembolic PH

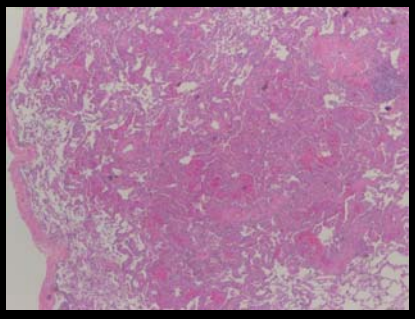


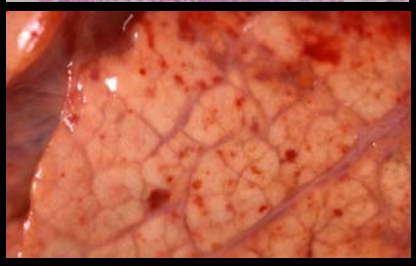


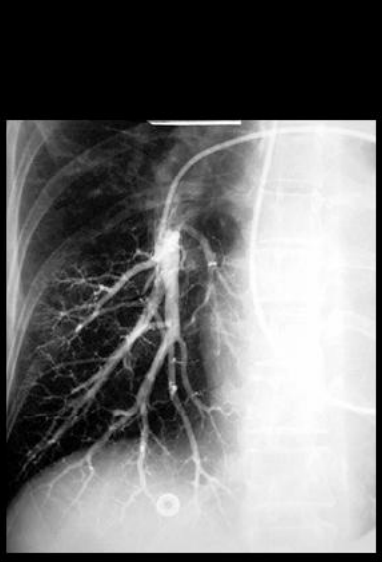
Chest Computed Tomography

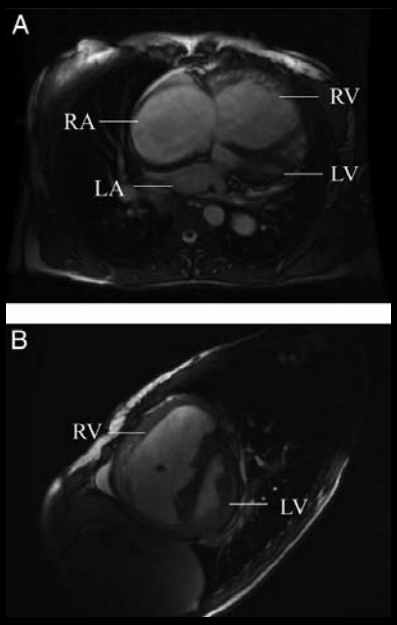
Pulmonary Capillary Hemangiomatosis











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

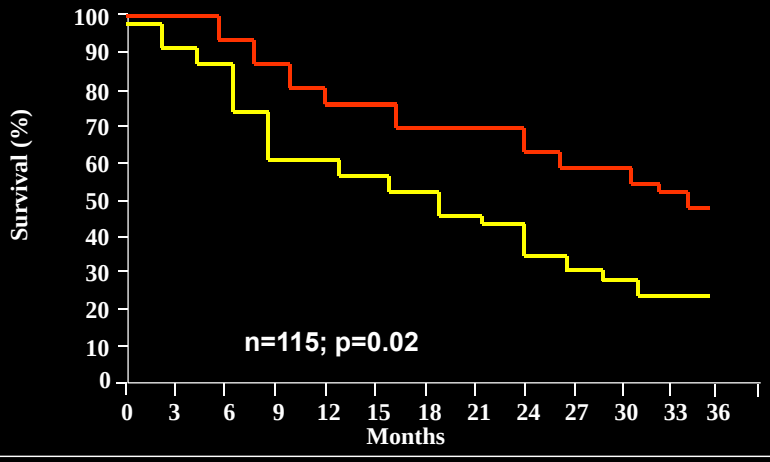
Preventive Measures
Do's and Don't's

- 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

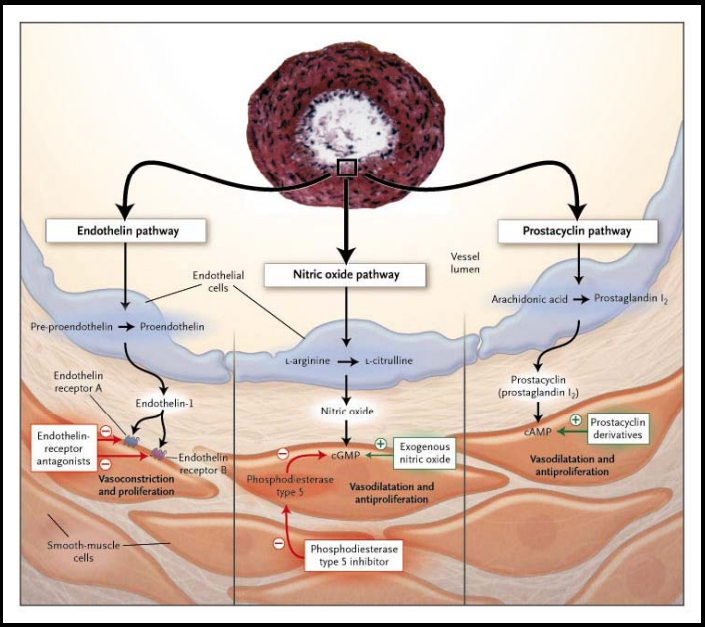


(Fuster, Circulation, 1984)

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

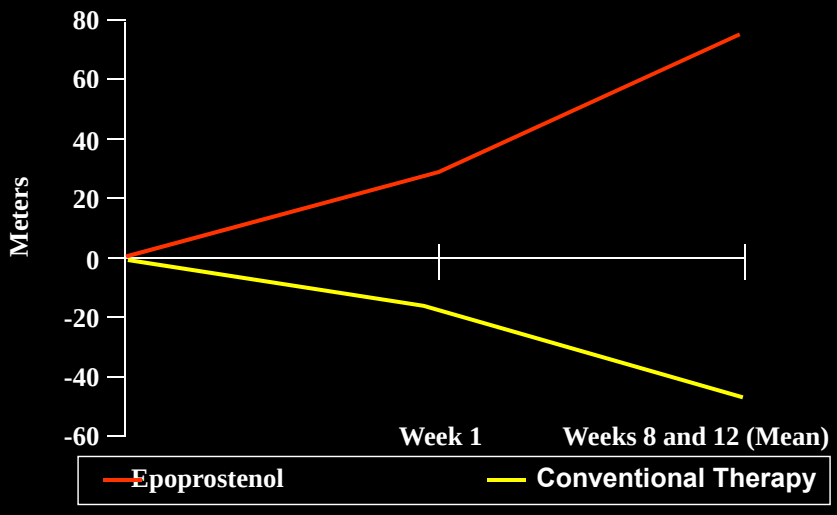
Targets for Therapy in PH

- **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

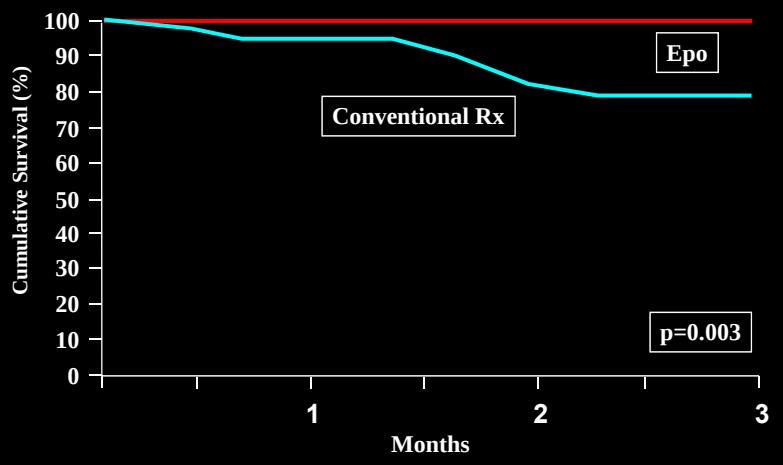
- Underproduction of prostacycline in PAH
  - Prostacycline promotes vasodilatation, inhibits vascular proliferation and platelet aggregation
- Epoprostenol (IV)
- Beraprost (PO)
- Treprostinil (SC or IV)
- Iloprost (inhalation)
- Improvement in hemodynamics, exercise capacity and symptoms and survival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

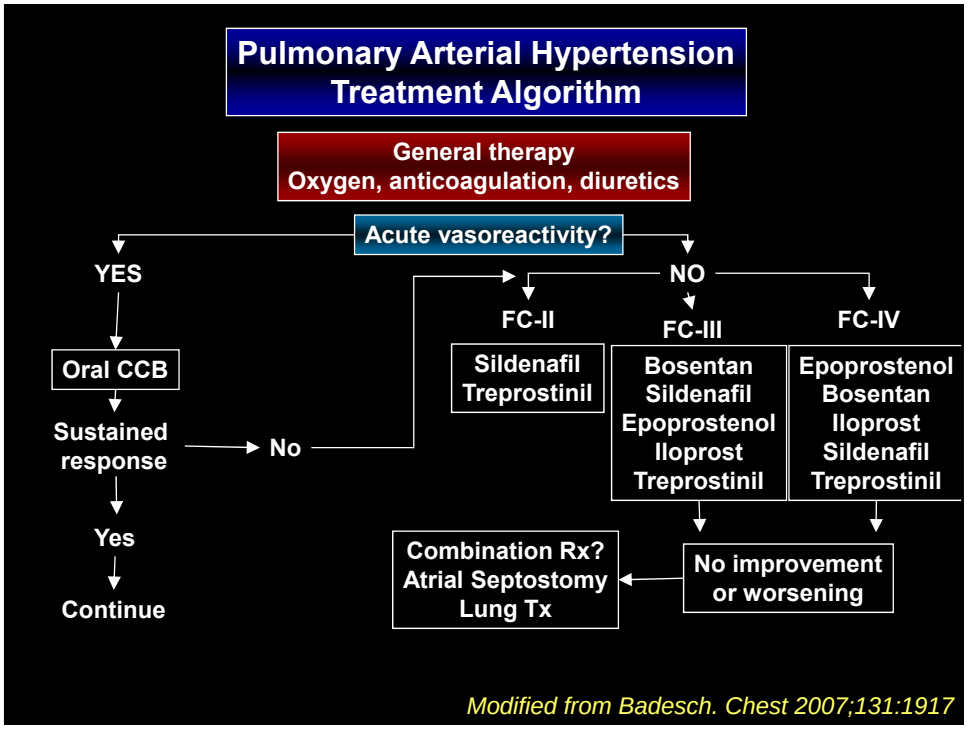
- 2 endothelin-receptor isoforms
  - ETA: vasoconstriction, proliferation of VSMC
  - ETB: Endothelin clearance and vasodilatation
- Dual ETA and ETB-receptor antagonist
  - Bosentan
- Selective ETA-receptor antagonists
  - Ambrisentan
  - Sitaxsentan
- Improvement in exercise capacity and hemodynamics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



Survival in Idiopathic Pulmonary Arterial Hypertension

Cohort	Years 1	2	3
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

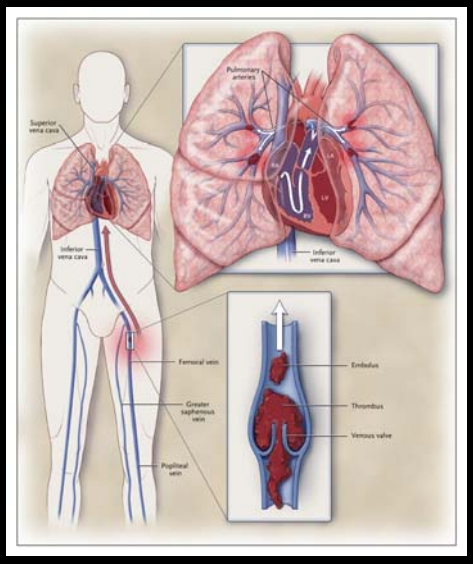
Epidemiology of Pulmonary Embolism

- 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

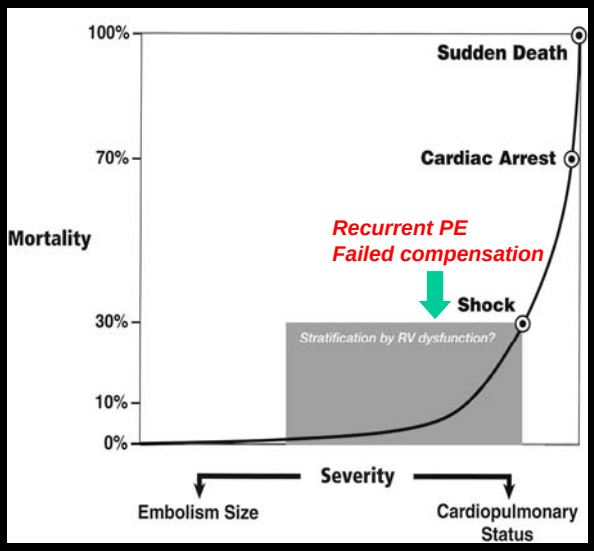
- Sources of PE
  - Iliofemoral veins***
  - Pelvic, upper extremity, renal, right heart
- ~50% of iliofemoral DVT result in PE
  - 50-80% of iliofemoral DVT originate in calf veins
- Virchow's triad
  - Endothelial injury, stasis, hypercoagulability



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

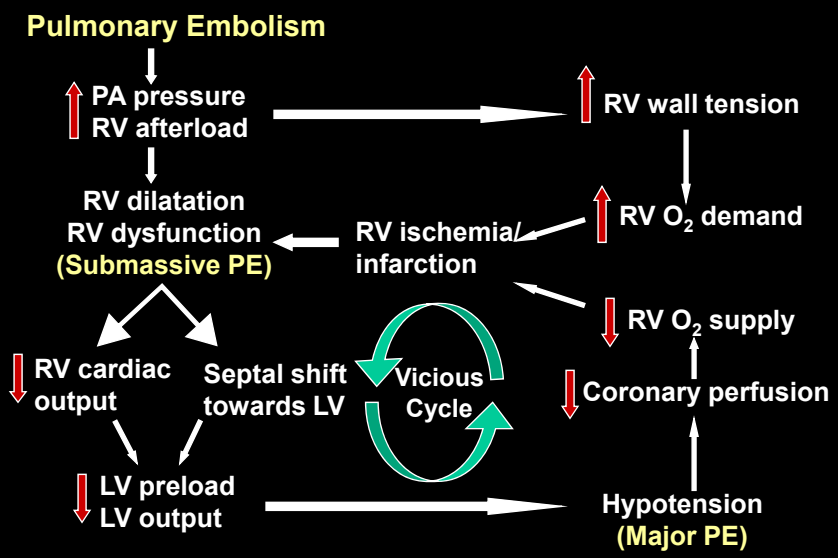
Pathophysiologic Response to PE (I)

- ***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 ≥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

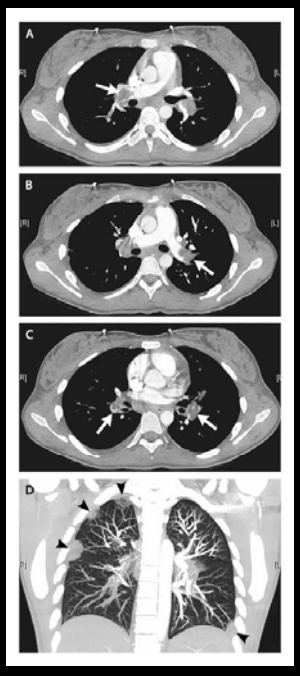
Modified Wells Criteria	
Clinical symptoms of DVT (leg swelling, pain)	3.0
Other diagnosis less likely than PE	3.0
Heart rate >100	1.5
Immobilization (≥3 days) or surgery within last 4 weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy	1.0
Probability	**Score**
Traditional clinical probability assessment	
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

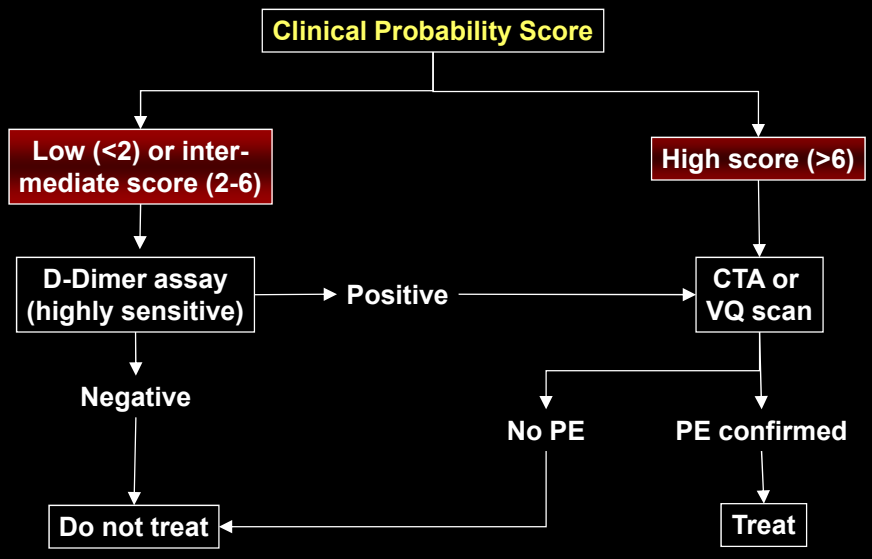
- Chest radiograph and EKG
- VQ scan
- CT pulmonary angiography (CTPA)
- Duplex ultrasonography
- Laboratory markers
  - D-dimer, cardiac troponins, NT-pro-BNP and BNP
- Echocardiography
  - Findings compatible with or diagnostic of PE
  - Excludes alternative diagnoses in major PE
    - Acute MI, pericardial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

Pulmonary Embolism *CT Findings*

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



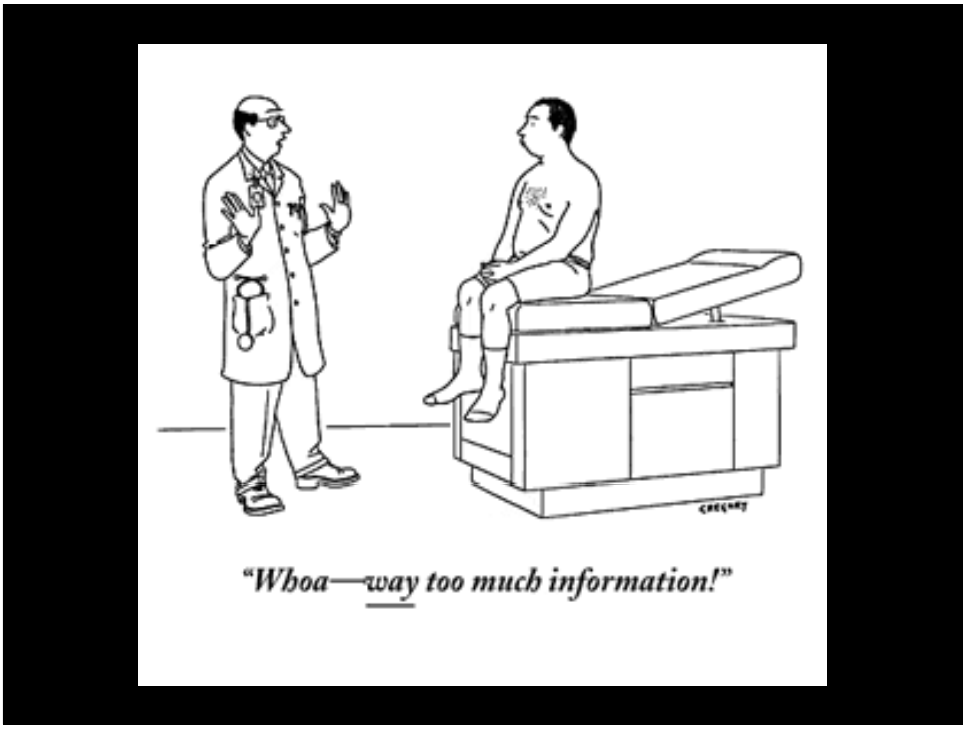
Diagnostic Algorithm Using Wells Criteria for Suspected Pulmonary Embolism



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!"