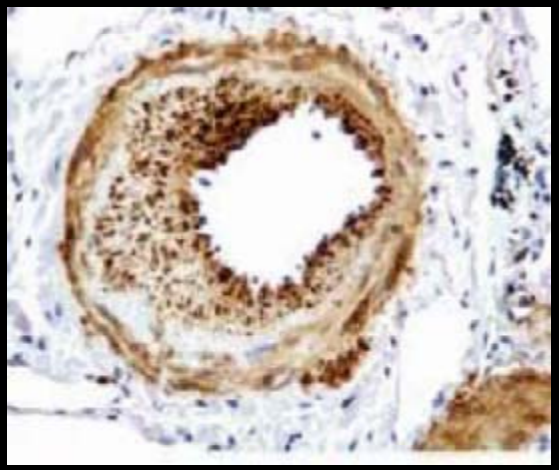
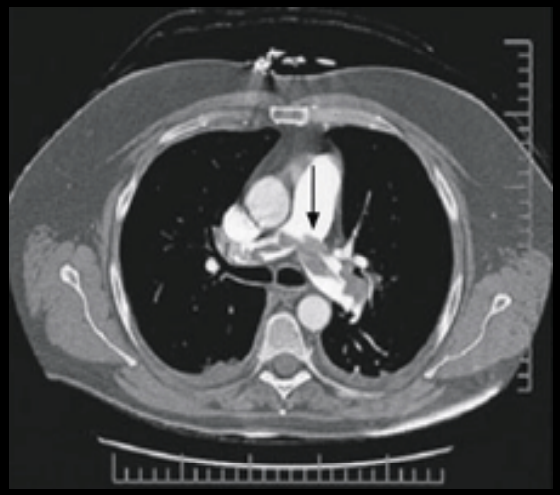
Pulmonary Vascular Disease:
Pulmonary Embolism &
Pulmonary Hypertension





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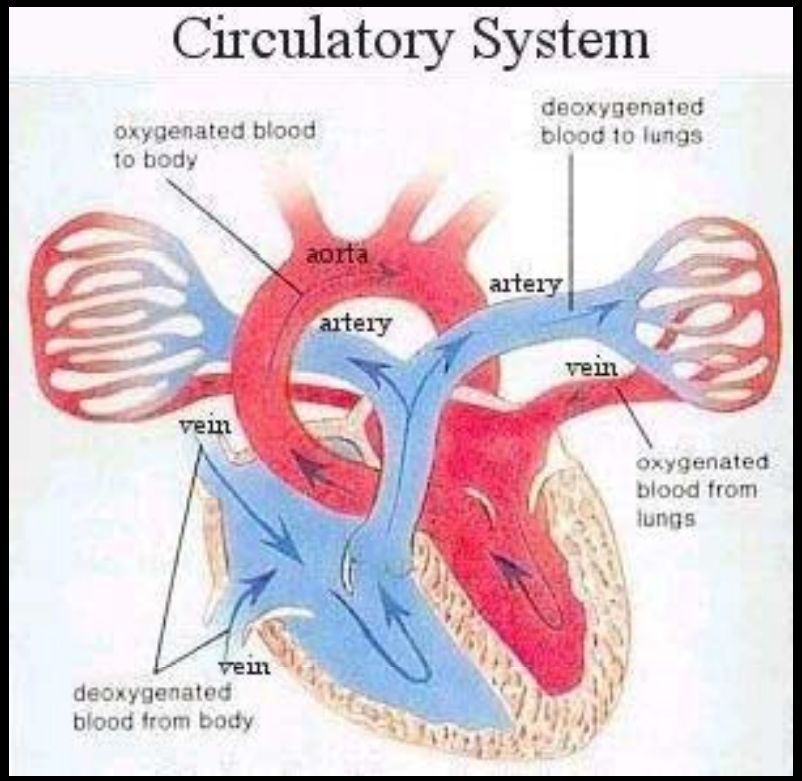
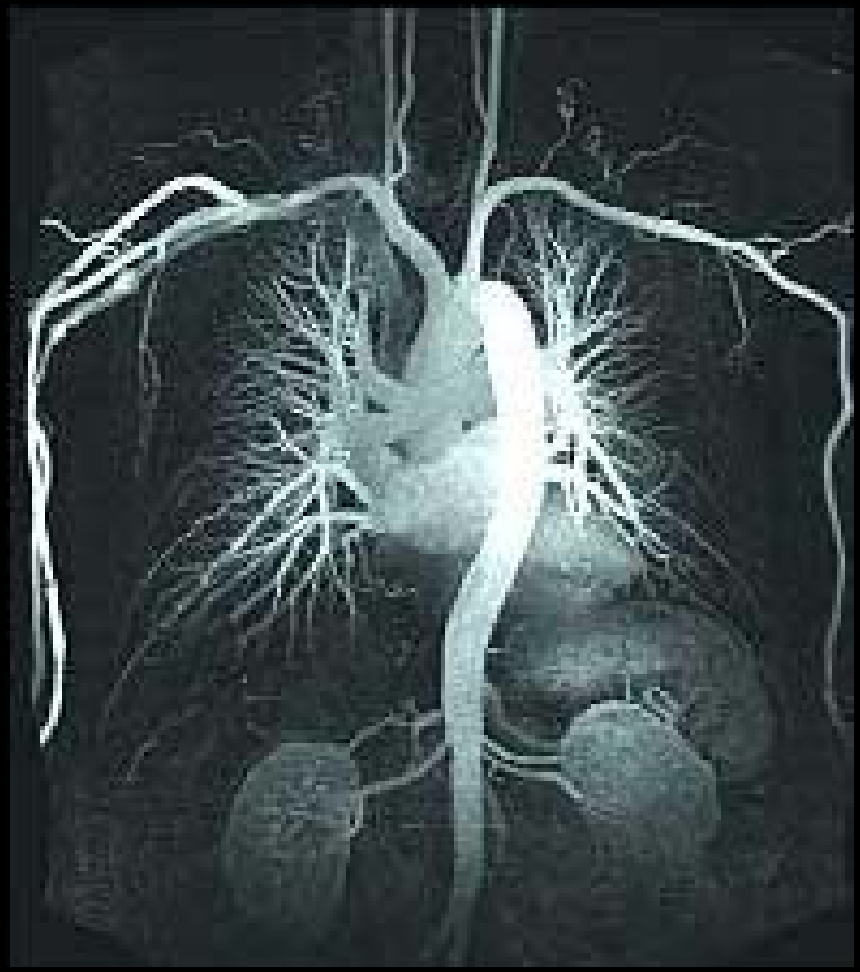
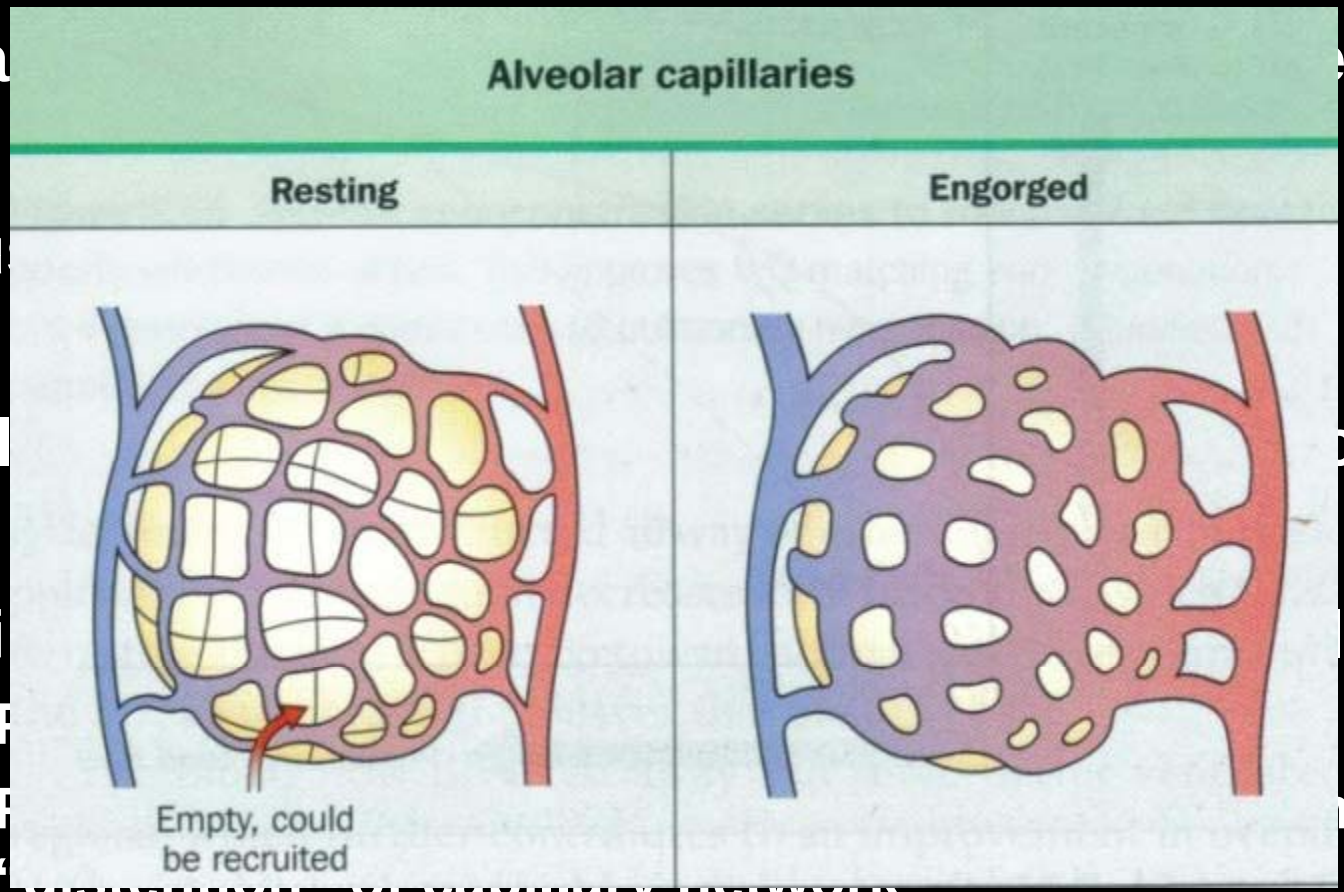

Circulatory System
oxygenated blood to body
deoxygenated blood to lungs
aorta
artery
artery
vein
vein
oxygenated blood from lungs
vein
deoxygenated blood from body



Pulmonary Vasculature

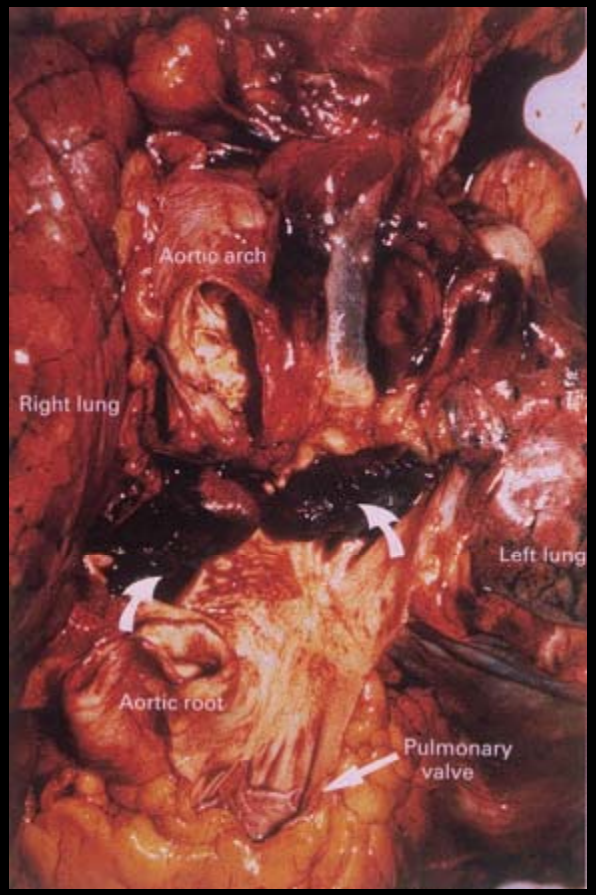
- Ela… …er)
- Mu…
- Pul… …cle
- 7 ti… …lature
  - R…
  - R… …nd/or
    “distention” of capillary network



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**

Pulmonary Embolism



Definition

- **Obstruction of pulmonary arterial branches by material originating from another location in the body**
  - **Thrombotic**
  - **Non-thrombotic: tumor, air, fat, foreign material, or parasitic**

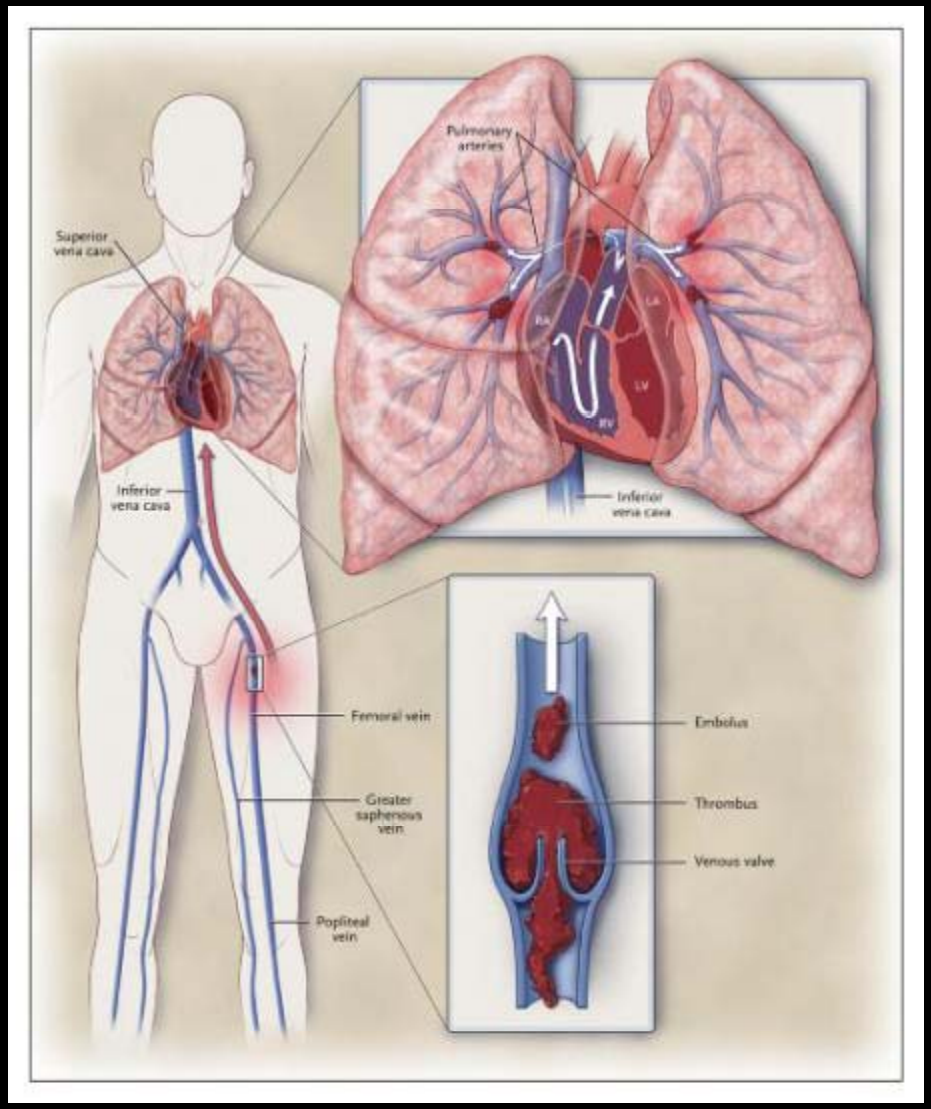
Epidemiology of Pulmonary Embolism

- **Estimated to occur in ~ 600,000 patients annually in the U.S.**
  - **Annual incidence ranges between 23 to 69 cases per 100,000 population**
- **Incidence of acute PE in hospitals ranges from 0.05 to 1%**
- **Causes or contributes to ~50,000 to 200,000 deaths**
  - **Accounts for 15% of in-hospital mortality**
- **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

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

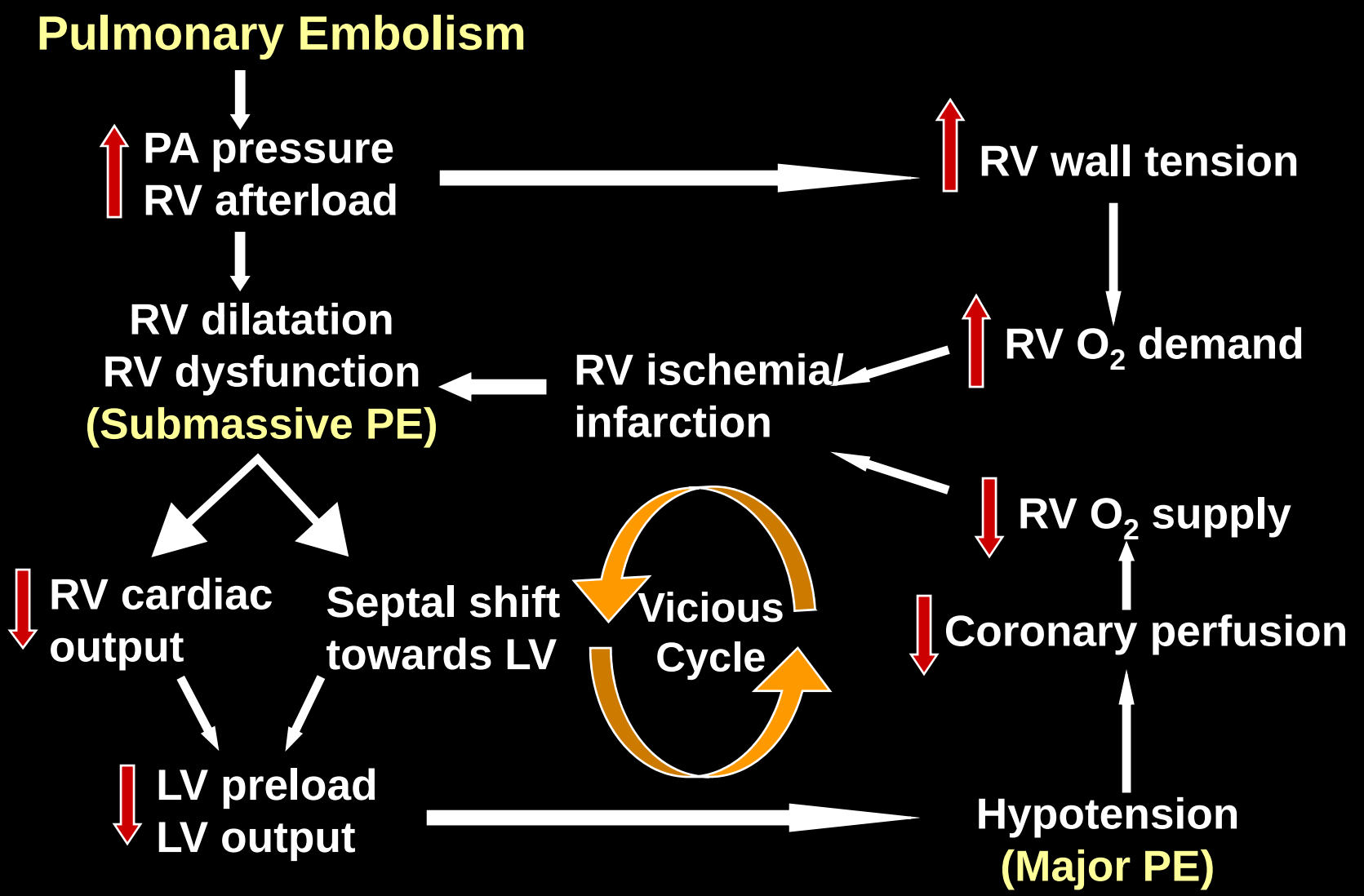


Tapson . N Engl J Med 2008;358:1037

Gas Exchange Physiology After PE

- Acute vascular obstruction and vasoconstriction
- Increased alveolar dead space
  - Reflex bronchoconstriction to minimize dead space
  - Hyperventilation
- Mechanisms of arterial hypoxemia
  - Shunt (flow through atelectatic regions, opening of latent pulmonary A-V anastomoses due high PAP or intracardiac)
  - V/Q mismatch (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

Pathophysiology of Hemodynamic Instability in 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 syndrome
  - Central venous catheter
  - Polycythemia vera
  - Obesity, hypertension
  - Heavy smoking
- **Hereditary factors**
  - Factor V Leiden
  - Activated protein C resistance without Factor V Leiden
  - 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

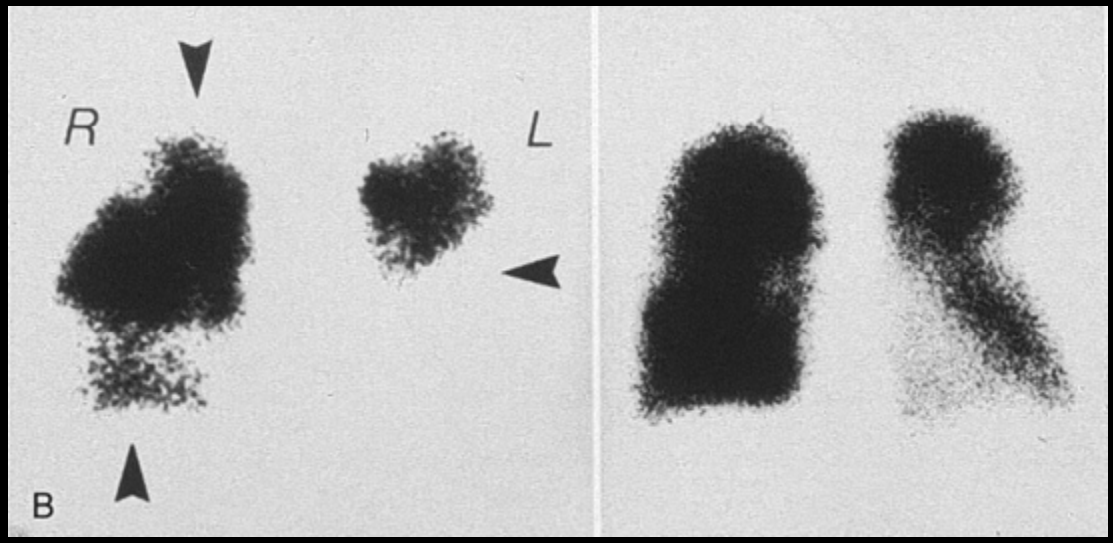
- **Develop an estimate of pretest clinical probability based on symptoms, signs and risk factors**
  - **High (very likely), low (unlikely) or intermediate (possible)**
  - **Clinical prediction scores (Wells or Geneva)**
- **Concomitant diagnosis, treatment, and resuscitation if needed**
  - **Start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

Diagnostic Tests For PE

- Ventilation-Perfusion (VQ) scan
- CT pulmonary angiography (CTPA or CTA)
- Duplex ultrasonography
- Laboratory markers
  - D-dimer, cardiac troponins, NT-pro-BNP and BNP
- Echocardiography
- Pulmonary angiography

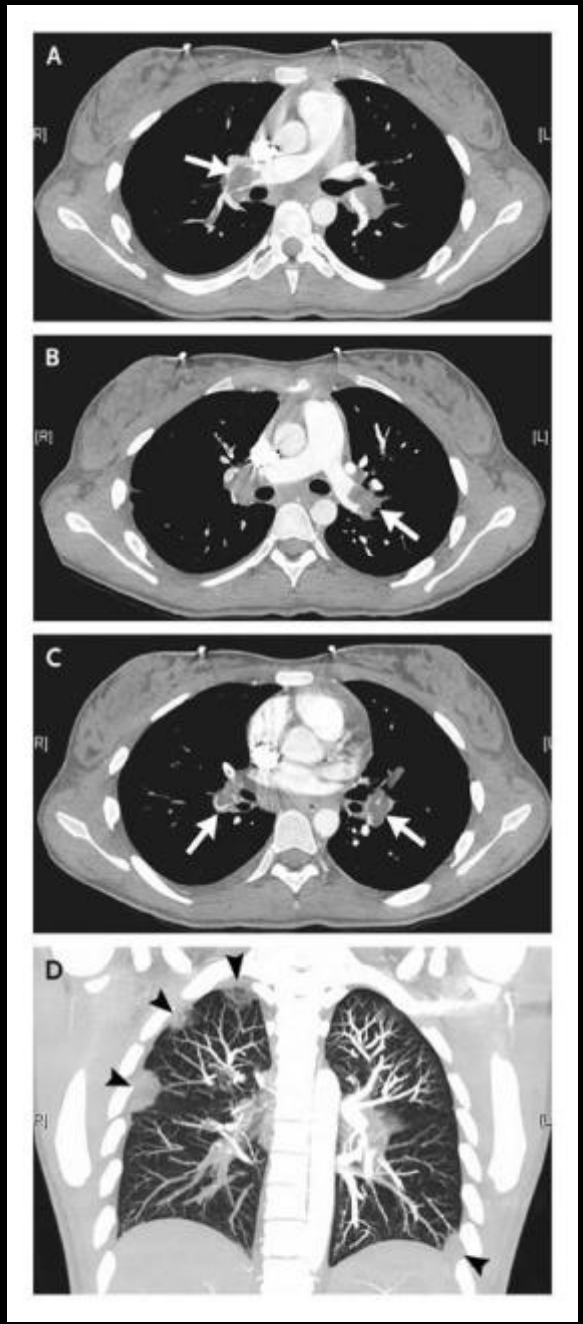
Perfusion Defects on VQ scan

Before Treatment After Treatment

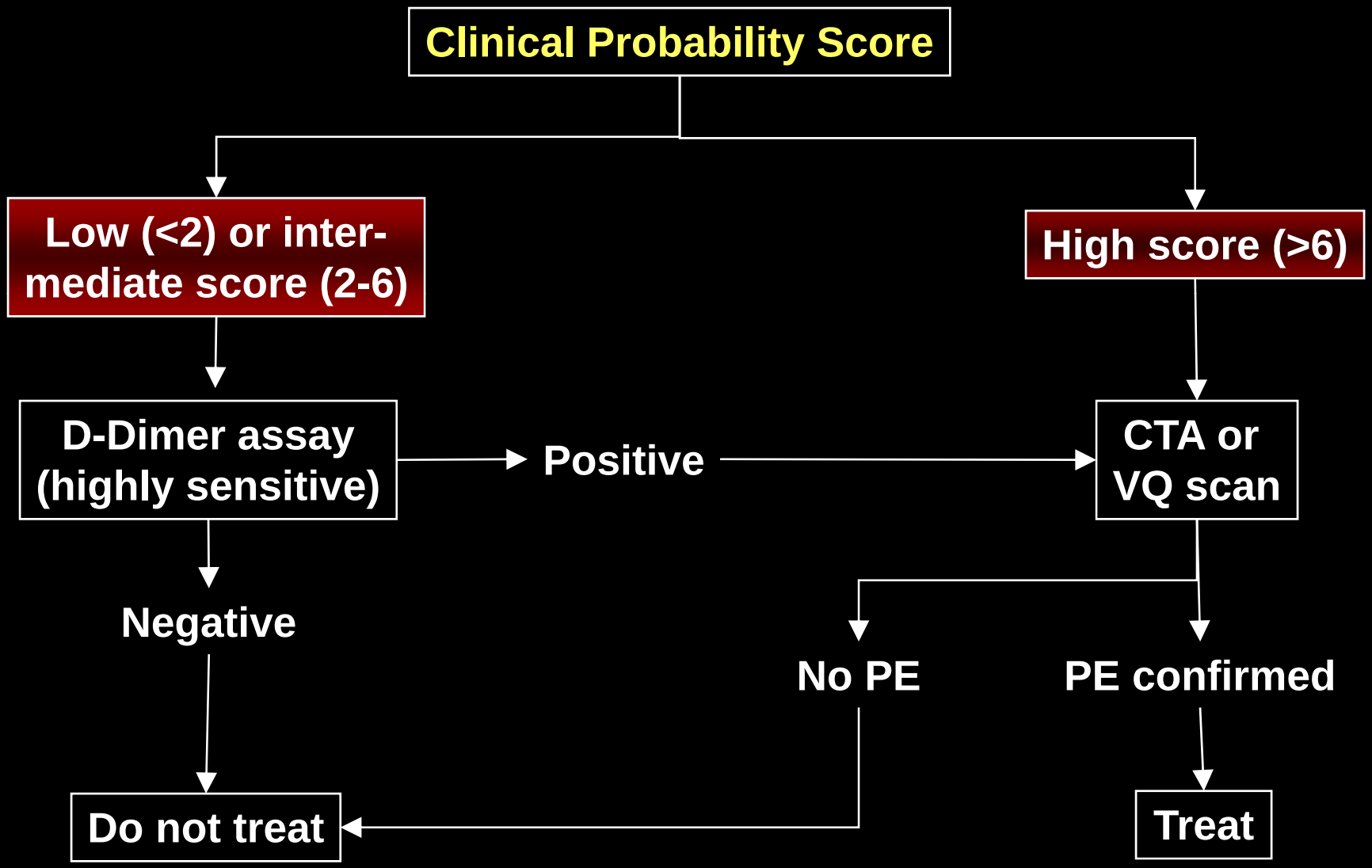


Pulmonary Embolism
CT Findings

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



Diagnostic Algorithm Using Wells Criteria for Suspected Pulmonary Embolism

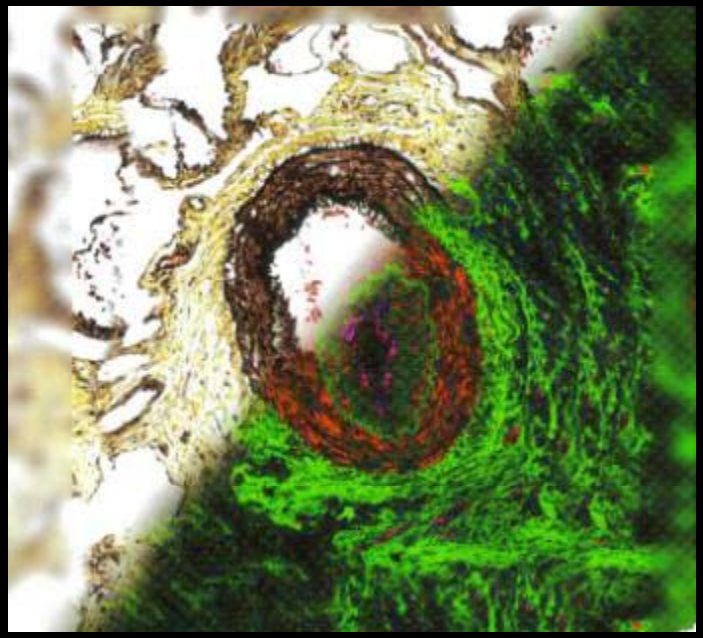


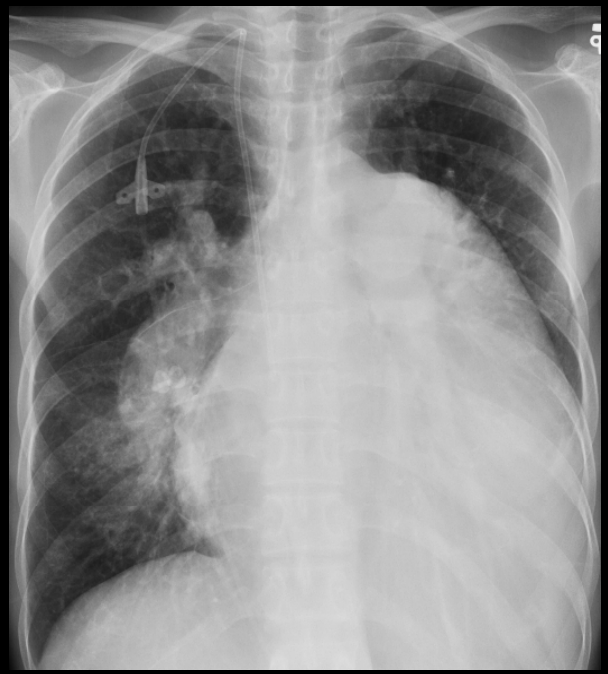
Konstantinides. NEJM 2008;359:2804

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 or catheter embolectomy
  - Major PE unresponsive to anticoagulation, thrombolysis or contraindications to medical Rx

Pulmonary Hypertension





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

- **A disorder characterized by increase in pulmonary vascular pressure**
  - **Isolated increase in pulmonary arterial pressure or increase in both pulmonary arterial and venous pressures**
- **Pulmonary arterial hypertension**
  - **Mean PAP >25 mmHg at rest**
  - **Normal pulmonary capillary wedge pressure (< 15 mmHg)**
    - **Elevated PCWP indicates PH due to left heart disease**
  - **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 thromboembolic disease (CTEPH)

V. PH with multifactorial and/or unclear mechanisms

Simonneau. JACC 2009

WHO Classification

Simonneau. JACC 2009

I. Pulmonary arterial hypertension

- **Idiopathic**
- **Heritable (BMPR2, ALK-1, endoglin)**
- **Associated with (APAH):**
  - **Drugs/Anorexigen use (“Fen-phen”, cocaine, metham)**
  - **Collagen vascular disease**
  - **HIV infection**
  - **Portal hypertension**
  - **Congenital systemic-to-pulmonary cardiac shunts**
  - **Other (schistosomiasis, chronic hemolytic anemia)**
- **Persistent pulmonary hypertension of newborn**
- **(1`) Associated with significant venous or capillary involvement (PVOD, PCH)**

WHO Classification

Simonneau. JACC 2009

II. Left Heart Disease

- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease

III. Lung Disease/Hypoxia

- COPD
- ILD
- Sleep-disordered breathing
- Alveolar hypoventilation
- High altitude exposure
- Developmental abnormality

IV. Chronic Thromboembolic Pulmonary Hypertension

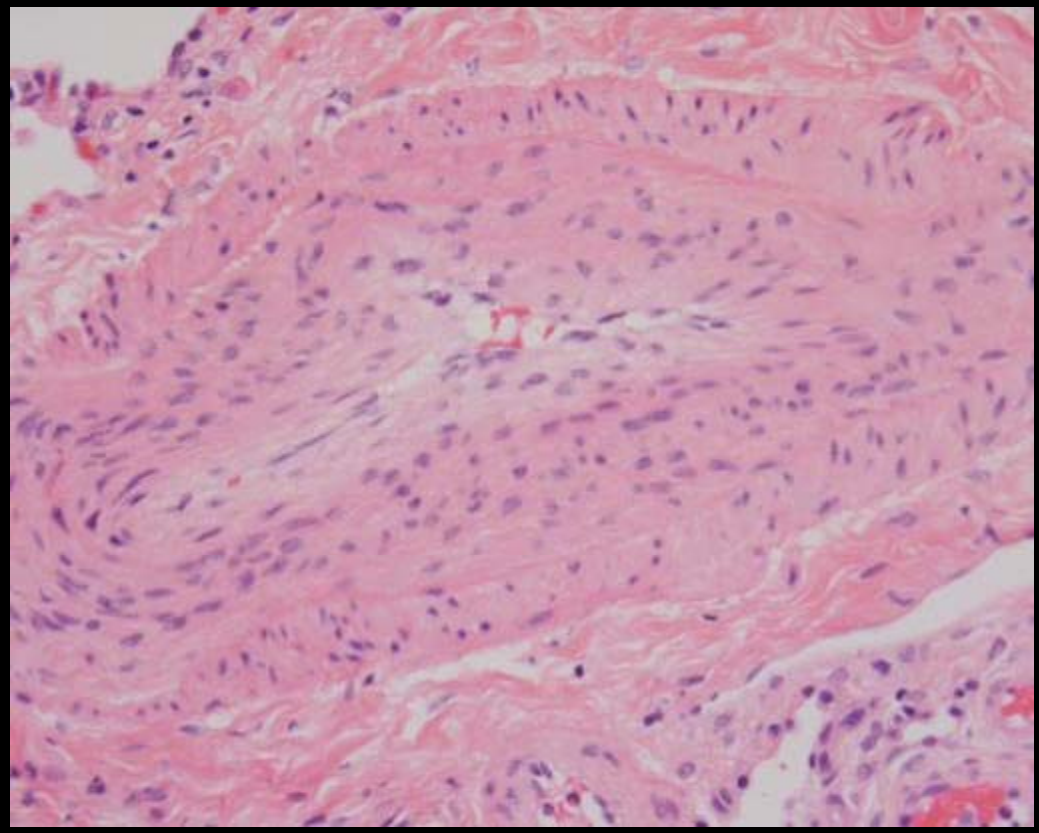
V. Unclear/Multifactorial

- Hematological (splenectomy, myeloproliferative), systemic (Sarcoidosis, Langerhans-cell histiocytosis, vasculitis), metabolic (glycogen storage, Gaucher's, thyroid), others (vascular compression, chronic renal failure on hemodialysis)

Pulmonary Arterial Hypertension

Pathology (I)

Endothelial thickening

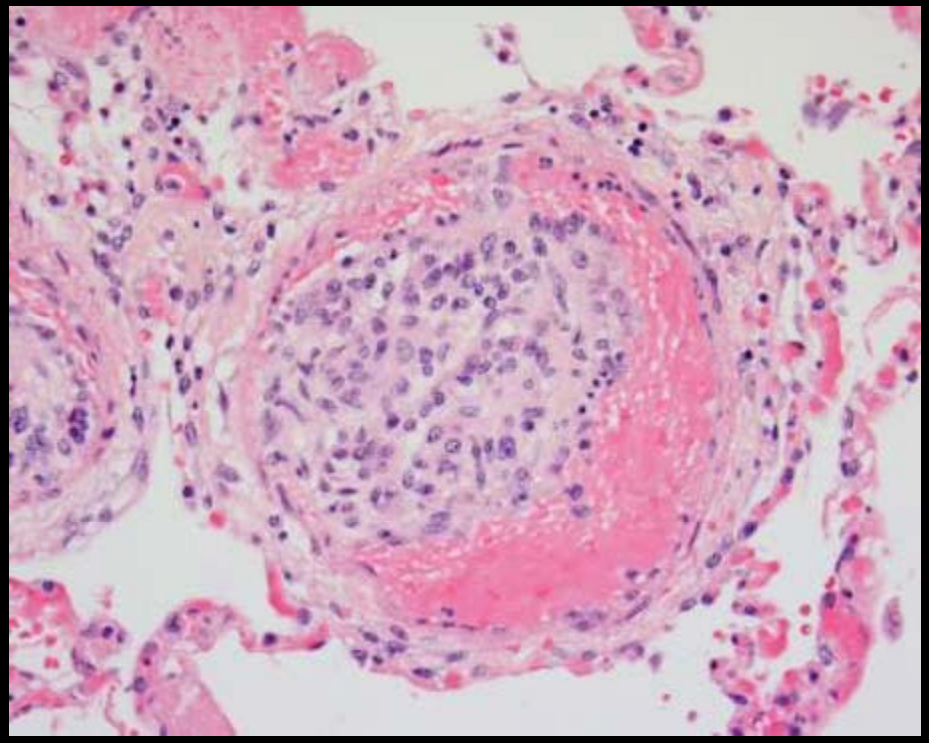


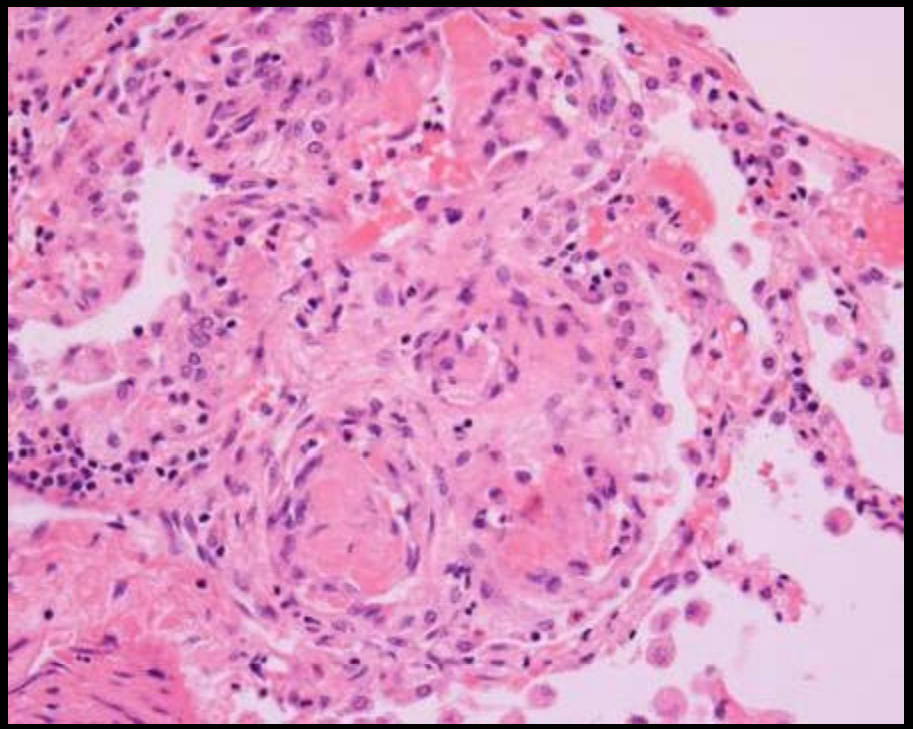
Smooth muscle hypertrophy

Pulmonary Arterial Hypertension

Pathology (II)

Plexiform lesions

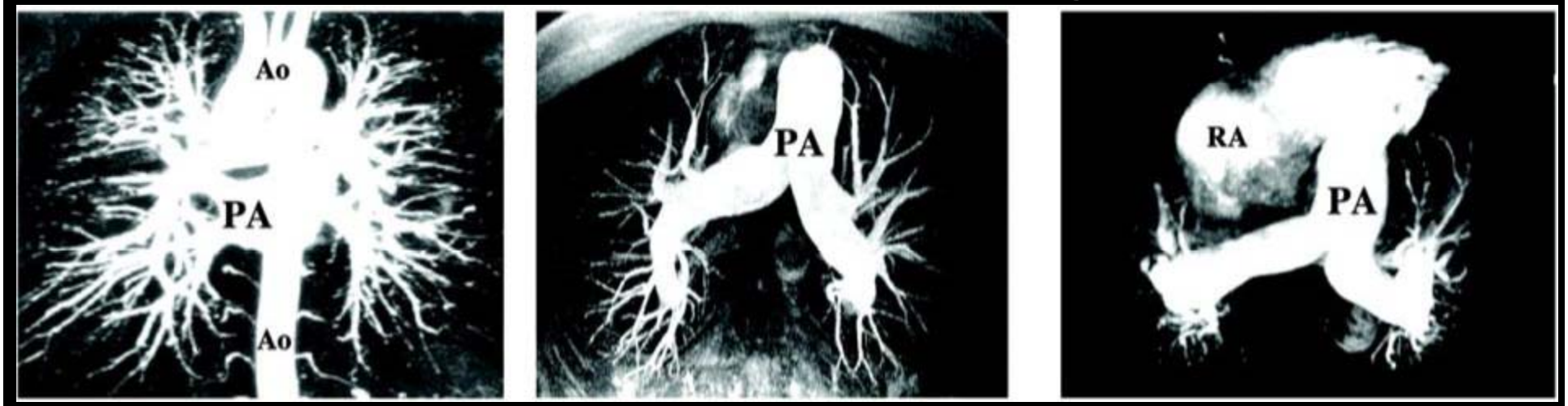




In situ
thrombosis

Pulmonary Arterial Hypertension

- Caused by an array of metabolic abnormalities that result in obliterative remodeling of



  - Loss of microvessels and capillaries

- Leads to increase in right ventricular afterload, right ventricular failure and death

Emerging Pathophysiologic 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"**
  - **Other endogenous genetic abnormalities (serotonin pathway), changes in blood flow or exogenous stimuli (drugs, viral)**
  - **Dysregulated inflammation (collagen vascular disease, HIV)**

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

Pathobiology of PAH

Platelets

Serotonin

Serotonin

$NO + PGI_2$

$ET\text{-}1/TxA_2$

Endothelium

Proliferation

SMC's

Kv1.5
Kv2.1

Adventitia

Elastase
MMPs

Tenascin

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

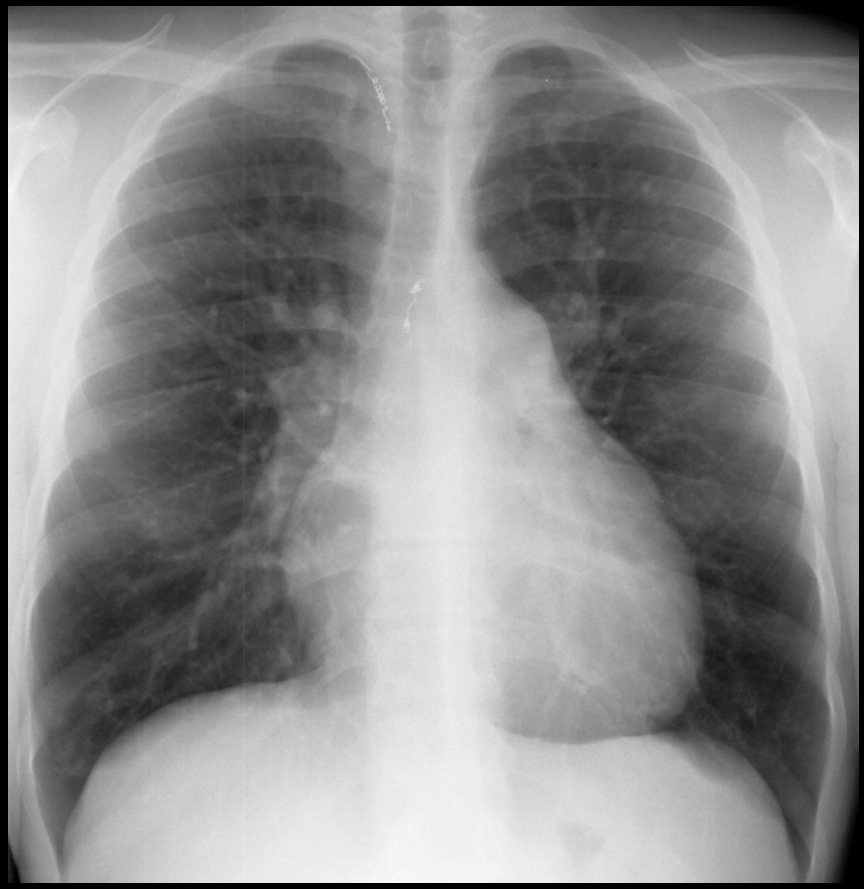
- **Signs**
  - **Jugular venous distension with large a and v waves**
  - **Loud P_2**
  - **Early systolic click**
  - **TR murmur**
  - **Diastolic murmur**
  - **RV heave**
  - **S_4 and S_3 gallop**
  - **Hepatojugular reflux**
  - **Hepatomegaly**
  - **Pulsatile liver**
  - **Ascites**
  - **Edema**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

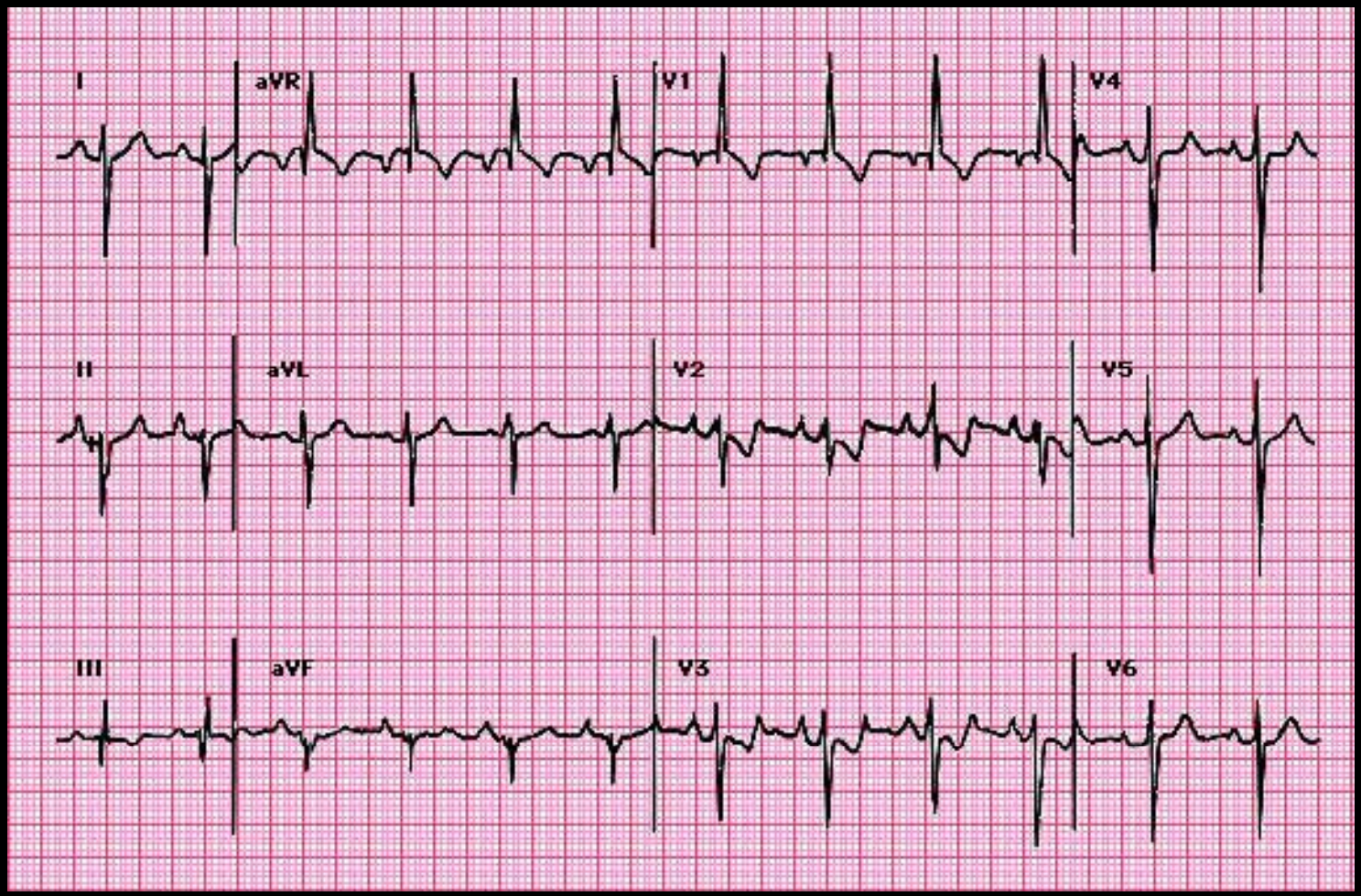
Chest Radiograph

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

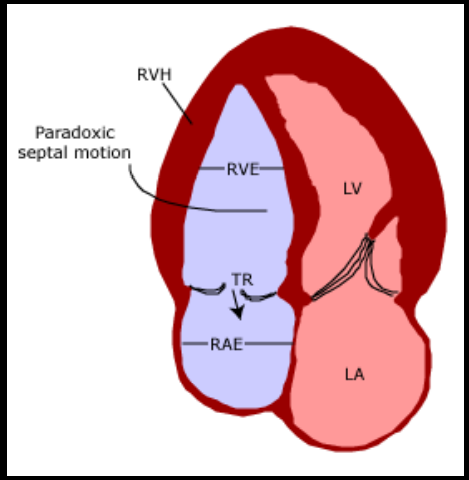


Electrocardiography

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



Doppler Echocardiography in Pulmonary Hypertension



- 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

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

- **Patient 1**
  - RA-4 mm Hg
  - PA- 90/60 mm Hg
  - PCWP- 8 mm Hg
  - CI- 2.4 $L/m/m^2$
  - PVR ~ 2066 $d \cdot s \cdot cm^{-5}$

Patient 2

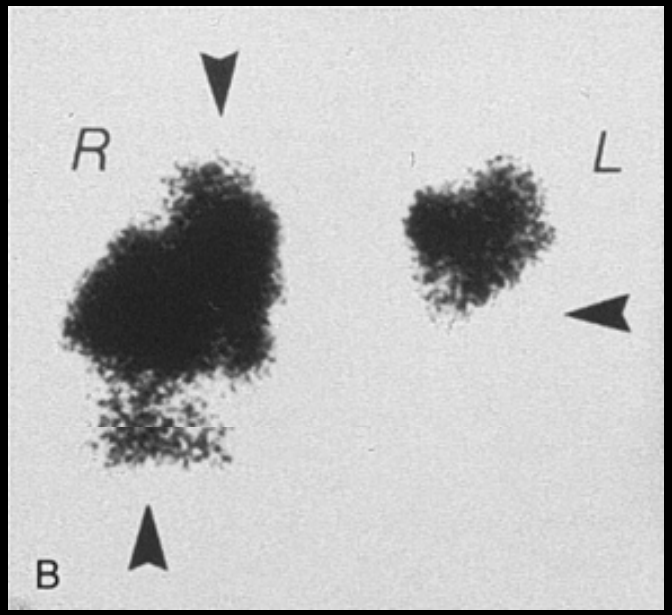
- RA-12 mm Hg
- PA- 50/25 mm Hg
- PCWP- 8 mm Hg
- CI- 1.0 L/m/m2
- PVR ~ 2000 d•s•cm-5

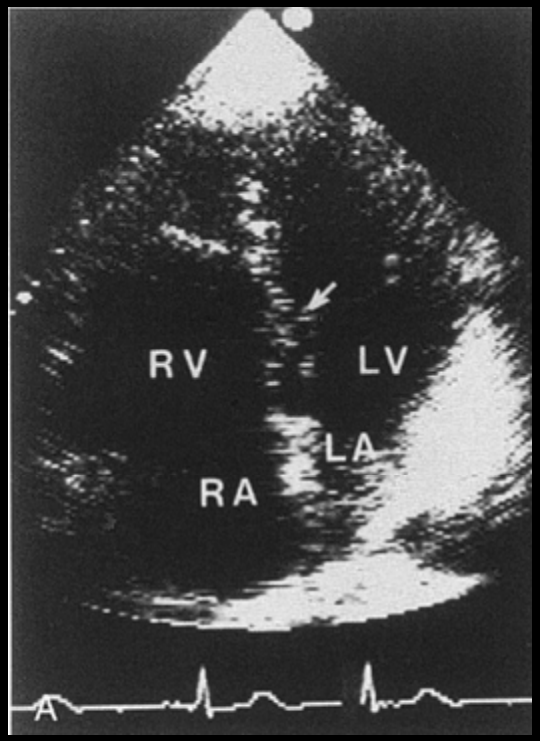
Detailed Evaluation During Diagnosis of PH

- **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: VQ scan, chest HRCT, cardiac MRI**
    - **Exclude thromboembolic disease, parenchymal pulmonary disease and aid in differential diagnosis of PH**
  - **Sleep study and nocturnal oxymetry**

Ventilation Perfusion Scan

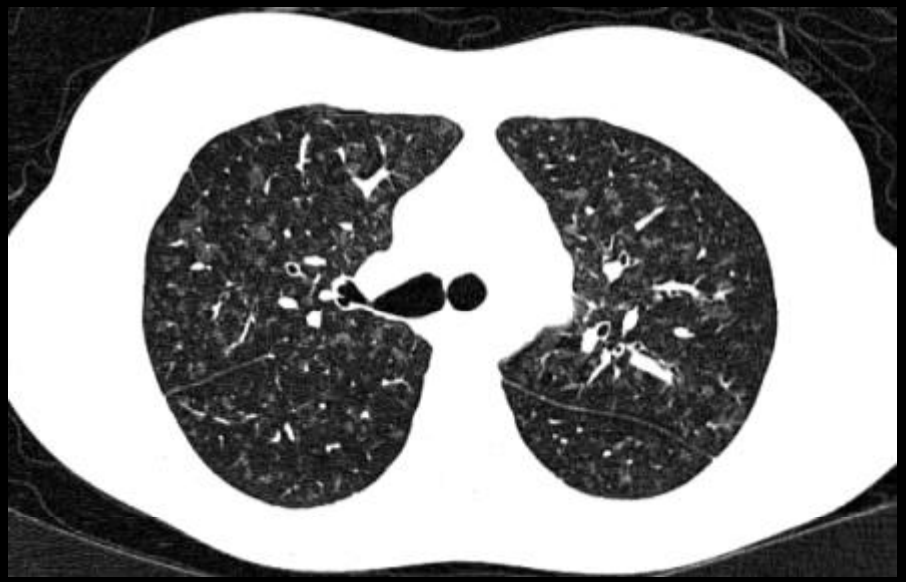
- **To exclude chronic thromboembolic PH**

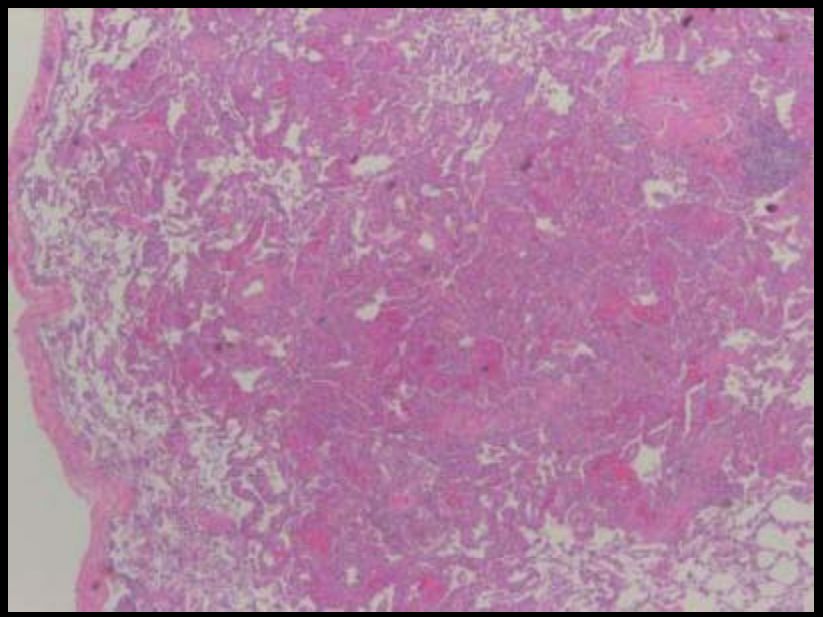


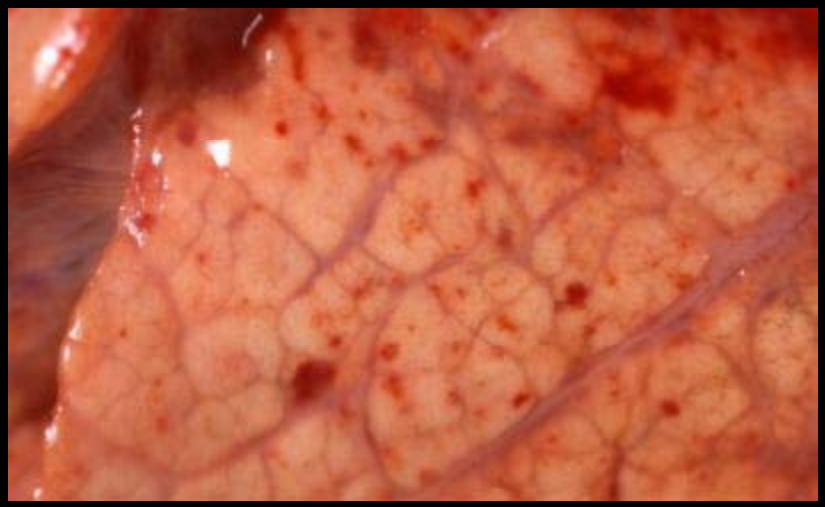


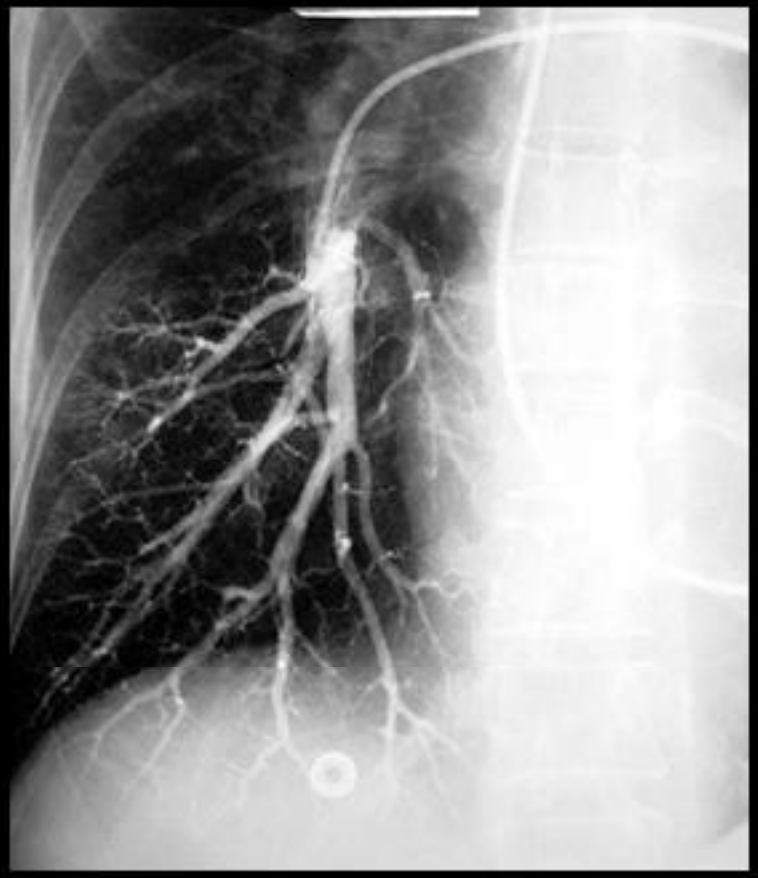
Chest Computed Tomography

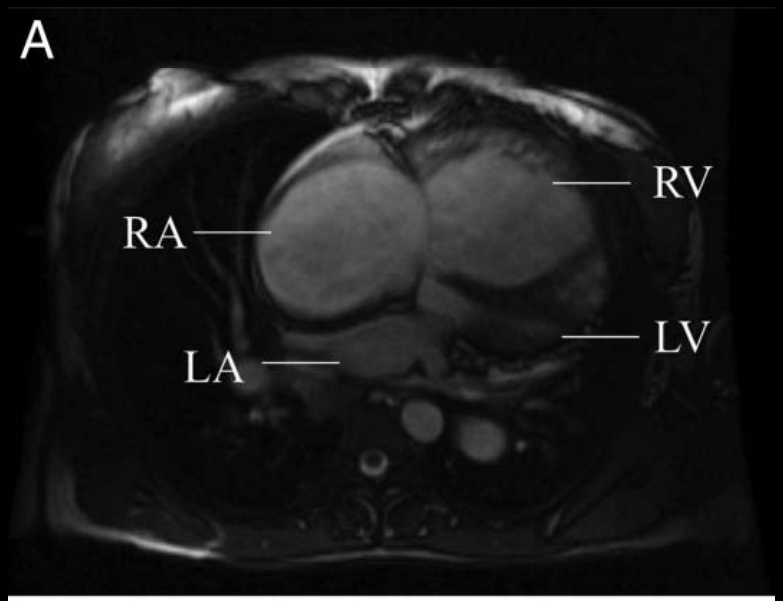
Pulmonary Capillary Hemangiomatosis

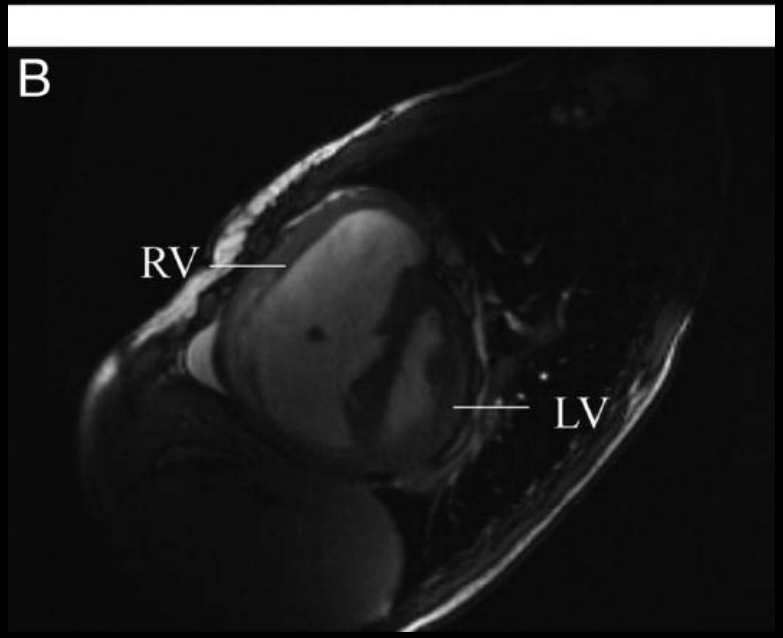









A
RV
RA
LV
LA


B
RV
LV

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

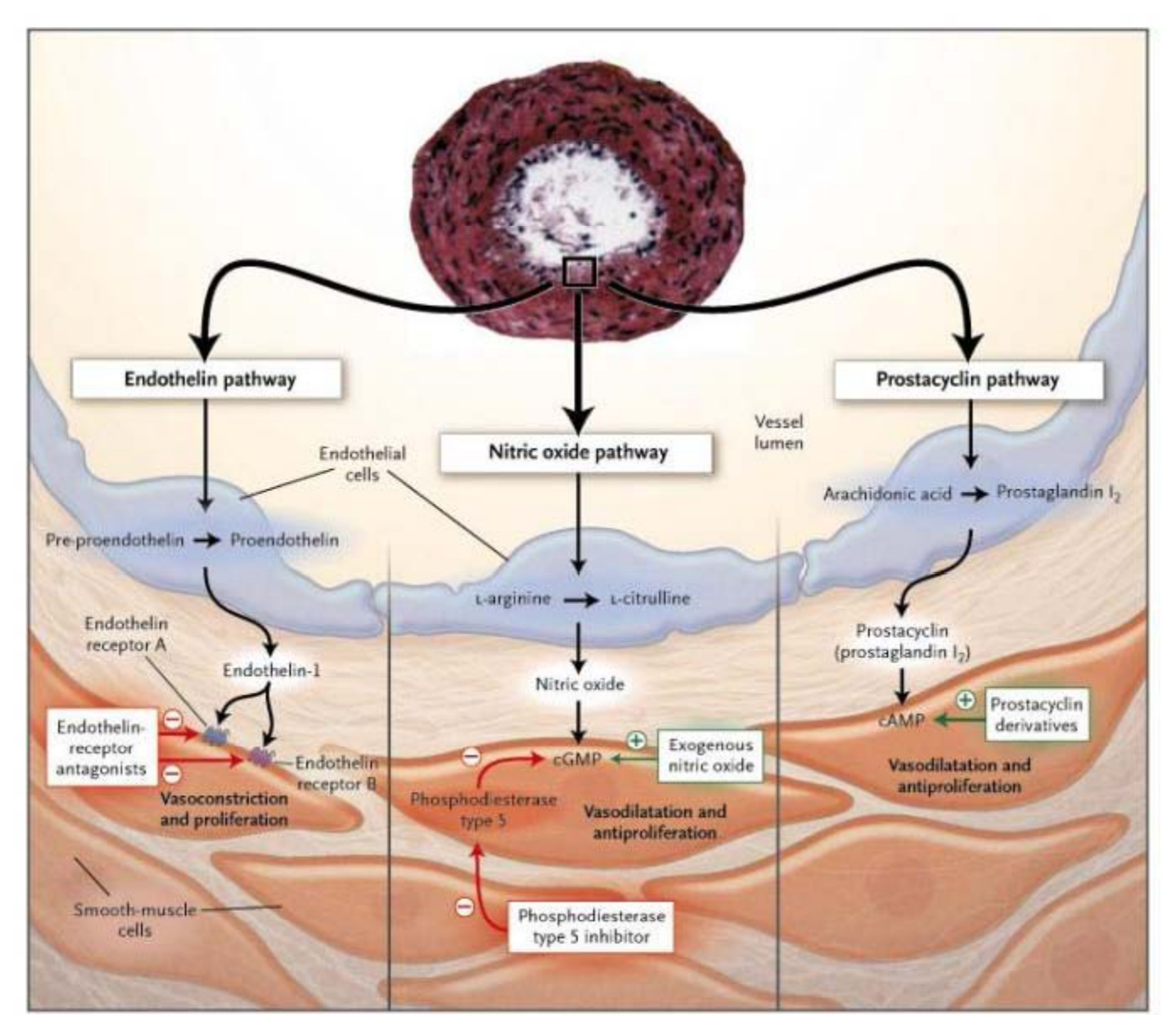
General Measures

- 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

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 PAH

- **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, symptoms and survival (with epoprostenol)

Endothelin-Receptor Antagonists

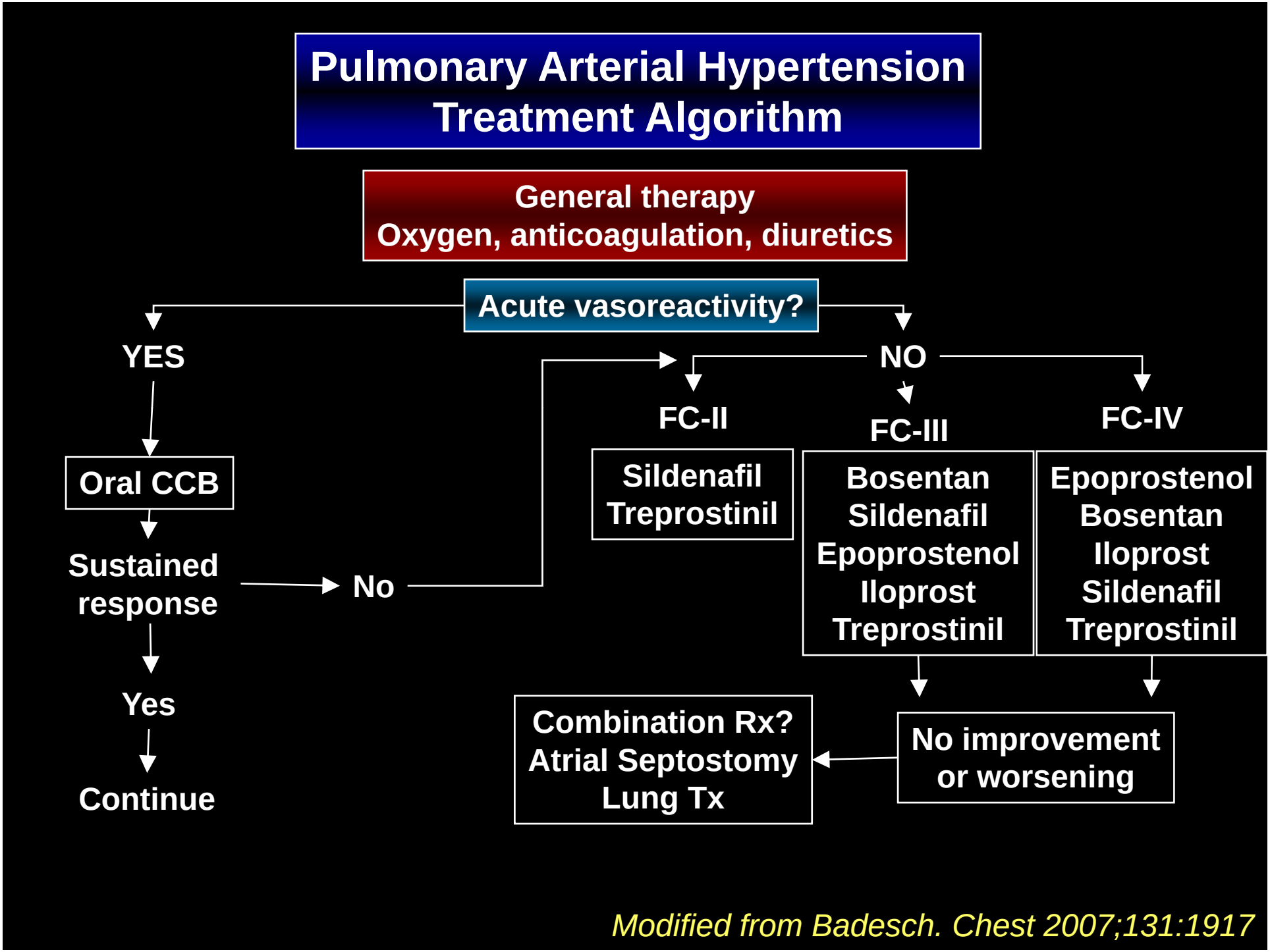
- 2 endothelin-receptor isoforms
  - ETA: vasoconstriction, proliferation of VSMC
  - ETB: Endothelin clearance and vasodilatation
- Dual ETA and ETB-receptor antagonist
  - Bosentan
- Selective ETA-receptor antagonists
  - Ambrisentan
  - Sitaxsentan
- Improvement in exercise capacity and hemodynamics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

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**