

## **Pathophysiology II**

### **Pulmonary Vascular Changes in Heart Disease**

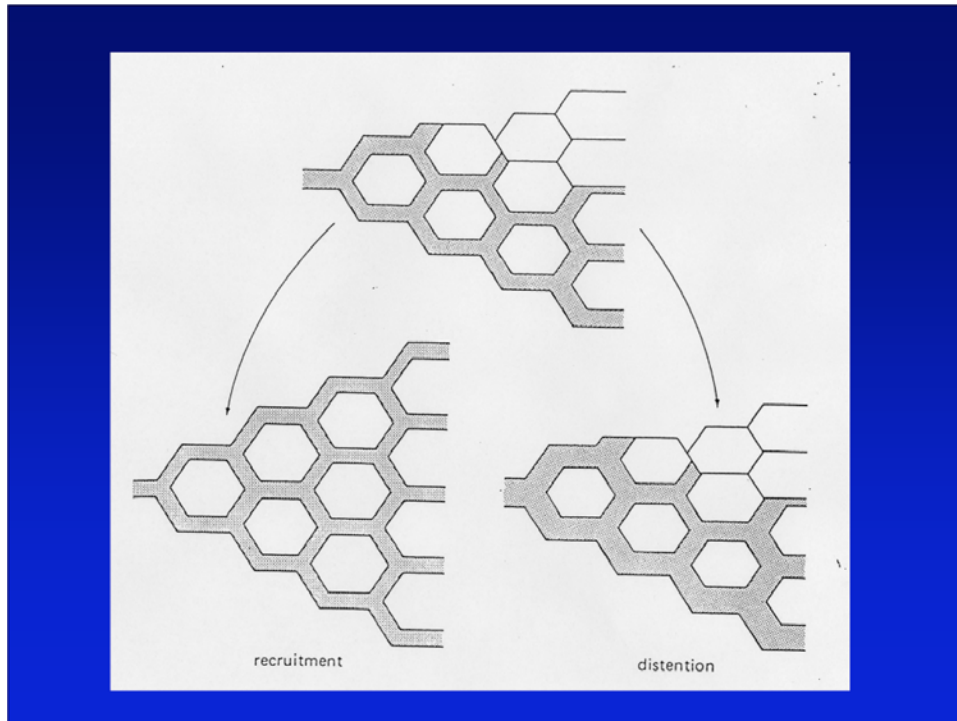
- **Normal Circulatory Dynamics  
Physiology**
- **Pulmonary Hypertension**
  - Definition**
  - Classification**
  - Pathology**
  - Pathophysiology**
  - Clinical Manifestations**
  - Diagnosis**
  - Treatment**

## **Pulmonary Circulation**

- **Low resistance, high compliance vascular bed**
- **Only organ to receive entire cardiac output (CO)**
- **Changes in CO as well as pleural/alveolar pressure affect pulmonary blood flow**
- **Different reactions compared to the systemic circulation**
- **Normally in a state of mild vasodilation**

## **Exercise**

- **Pulmonary blood flow increases up to 4-5x BL**
- **Increased flow accommodated by both recruitment and vasodilation**
- **Net effect is a decrease in pulmonary vascular resistance (PVR)**
- **No further decrease in PVR once all vessels fully recruited and dilated**



## Physiology: Circulatory Hemodynamics

### Pressure\* = Flow x Resistance

#### • Systemic Circulation

- Pressure = Pressure drop across systemic circulation (mmHg) = Systemic Arterial Pressure (SAPm) - Systemic Venous Pressure (RAPm)
- Flow = Systemic Blood Flow<sup>†</sup> = Cardiac Index (CI; l/m/M<sup>2</sup>)
- Resistance = Systemic Vascular Resistance (SVR; units • M<sup>2</sup>)

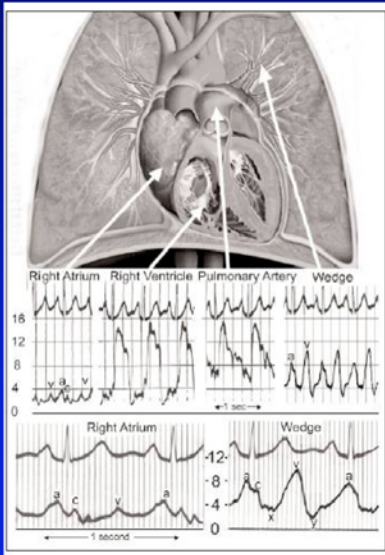
#### • Pulmonary Circulation

- Pressure = Pressure drop across pulmonary circulation (mmHg) = Pulmonary Artery Pressure (PAPm) - Pulmonary Venous Pressure (PCWPm)
- Flow = Pulmonary Blood Flow<sup>†</sup> = Cardiac Index (CI; l/m/M<sup>2</sup>)
- Resistance = Pulmonary Vascular Resistance (PVR; units • M<sup>2</sup>)

\*pressure drop across vascular bed

† without congenital systemic to pulmonary shunts

## Normal Hemodynamic Measurements During Right Heart Catheterization



Oudiz RJ, Langleben D. *Advances in Pulmonary Hypertension* 2005;4(3):15-25

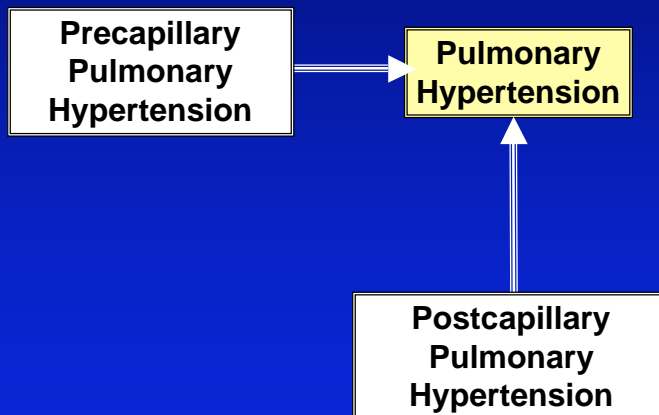
## Normal Pulmonary Hemodynamics at Sea Level (Rest and Mild Exercise) and at Elevated Altitude (Rest)

	Sea level Rest	Sea level Mild Exercise	Altitude (~15,000 ft) Rest
Pulmonary arterial pressure, (mean) mmHg	20/10(15)	30/13(20)	38/14(26)
Cardiac output, L/min	6.0	12.0	6.0
Left atrial pressure (mean), mmHg	5.0	9.0	5.0
Pulmonary vascular resistance, units	1.7	0.9	3.3

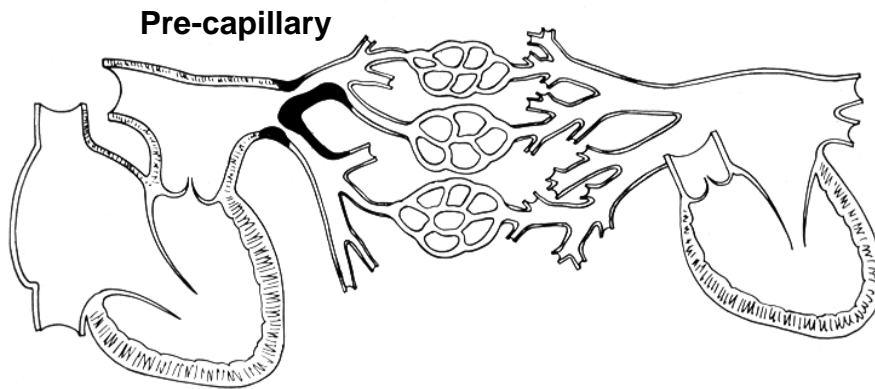
## **Pulmonary Hypertension: Definition**

**PAP mean  $\geq$  25 mm Hg at rest or  $\geq$  30 mmHg with exercise**

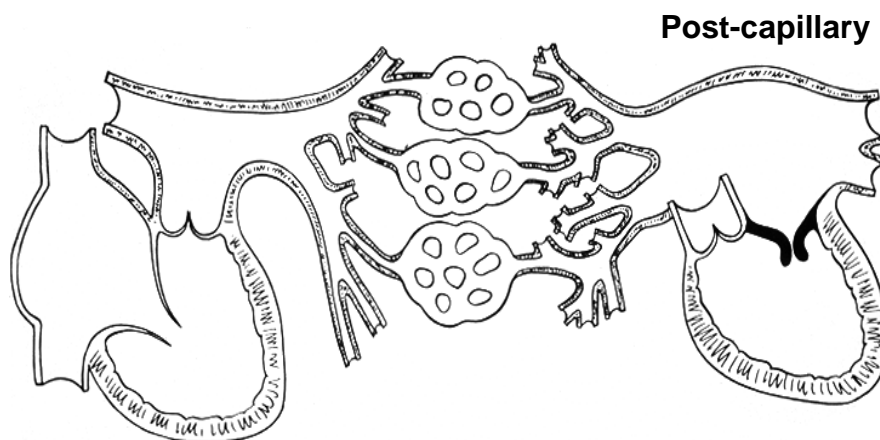
## **Pulmonary Hypertension: The Clinical Context**



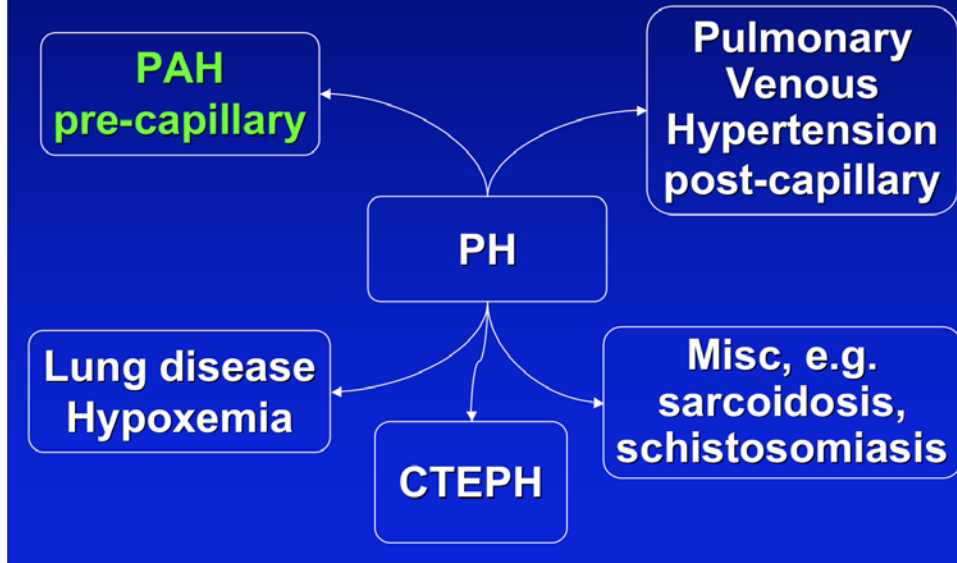
## Localizing the Problem



## Localizing the Problem



## Pulmonary Hypertension: Classification



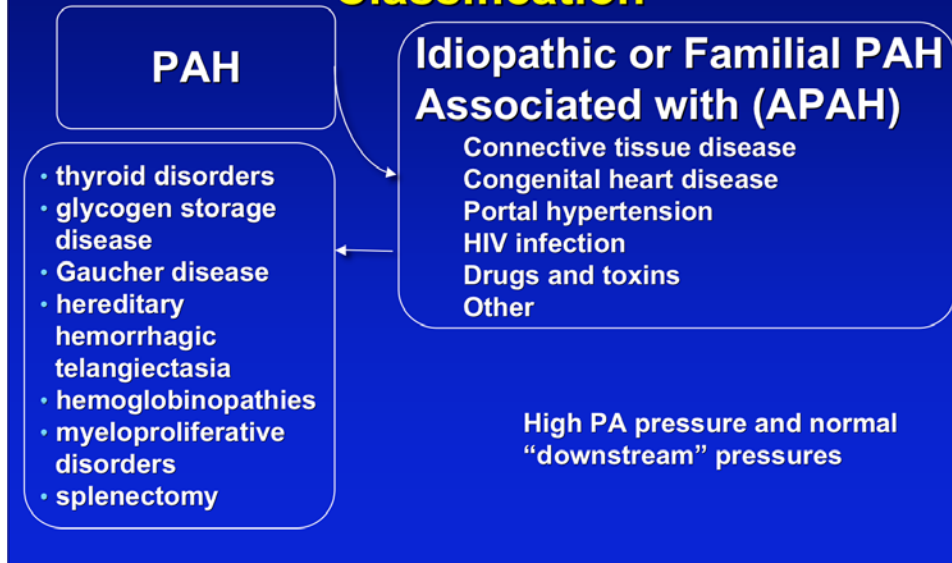
## Pre-capillary PH: Pulmonary Arterial Hypertension Definition

- PAP mean  $\geq 25$  mmHg at rest or  $\geq 30$  mmHg with exercise

AND

- PCWP or LVEDP  $\leq 15$  mmHg
- PVRI  $\geq 3$  units  $\cdot$  m<sup>2</sup>
- No left-sided heart disease

## Pre-capillary PH: Pulmonary Arterial Hypertension Classification



## Post-capillary PH: Pulmonary Venous Hypertension Definition

- PAP mean  $\geq 25$  mmHg at rest or  $\geq 30$  mmHg with exercise

AND

- PCWP or LVEDP  $>15$ mmHg

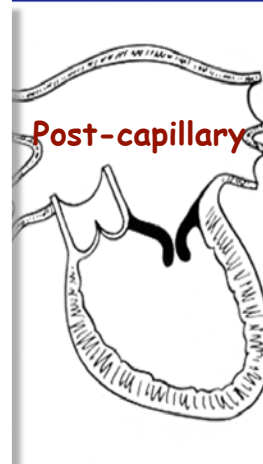


## Post-capillary PH: Pulmonary Venous Hypertension Classification



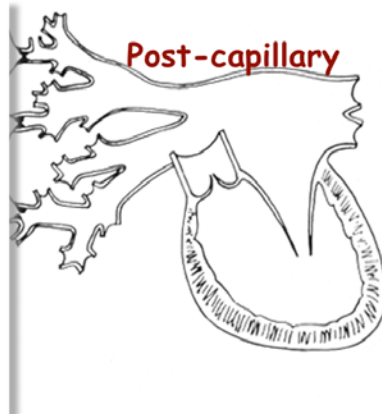
## Post-capillary PH: Pulmonary Venous Hypertension Localizing the Problem

- Left Heart Etiologies
  - Aorta - coarct, stenosis
  - LV - AS, AR, CM, constriction, myocardial disease, MS, MR, ischemic heart disease, congestive heart failure, diastolic dysfunction
  - LA - Ball-valve thrombus, myxoma, cor triatriatum



## Post-capillary PH: Pulmonary Venous Hypertension Localizing the Problem

- Venous Etiologies
  - Pulmonary Veins
    - stenosis
    - mediastinal fibrosis
    - neoplasm
    - pulmonary veno-occlusive disease



## Pulmonary Venous Hypertension Physiology

Pulmonary arterial → Lung → Pulmonary venous

PAP mean 35 mmHg → No obstruction → PCWP mean 25 mmHg

PAP mean 45-100 mmHg → Pulmonary arteriolar obstruction → PCWP mean 25 mmHg

## Mixed (Pulmonary Venous and Pulmonary Arterial Hypertension): Definition

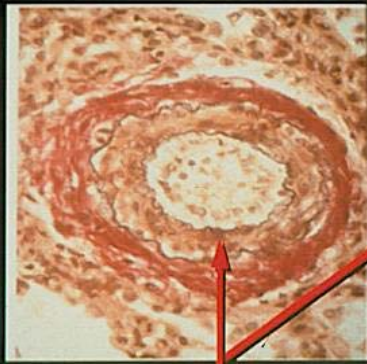
- PAP mean  $\geq 25$  mmHg at rest or  $\geq 30$  mmHg with exercise
- PCWP or LVEDP  $>15$  mmHg
- PVRI  $\geq 3$  units  $\cdot M^2$
- Increased Transpulmonary Gradient Across Pulmonary Vascular Bed

## Pathophysiology: Rest and Exercise Pulmonary Hemodynamics

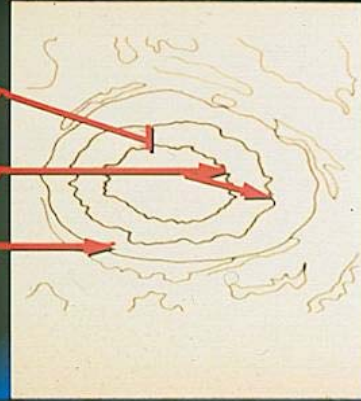
$$P = F \times R \quad \frac{\Delta P}{F} = R$$

	Rest	Exercise
Normal	$\frac{15\text{mmHg}-10\text{mmHg}}{5 \text{ L/min/M}^2} = 1 \text{ unit}\cdot\text{M}^2$	$\frac{30\text{mmHg}-12\text{mmHg}}{20 \text{ L/min/M}^2} = <1 \text{ unit}\cdot\text{M}^2$
PAH (Pre-Cap)	$\frac{50\text{mmHg}-10\text{mmHg}}{5 \text{ L/min/M}^2} = 8 \text{ units}\cdot\text{M}^2$	$\frac{90\text{mmHg}-10\text{mmHg}}{8 \text{ L/min/M}^2} = 10 \text{ units}\cdot\text{M}^2$
Pulm Venous PH (post-cap)	$\frac{35\text{mmHg}-25\text{mmHg}}{5 \text{ L/min/M}^2} = 2 \text{ units}\cdot\text{M}^2$	$\frac{55\text{mmHg}-35\text{mmHg}}{10 \text{ L/min/M}^2} = 2 \text{ units}\cdot\text{M}^2$
Mixed PH (Pre-cap & Post-cap)	$\frac{50\text{mmHg}-25\text{mmHg}}{5 \text{ L/min/M}^2} = 5 \text{ units}\cdot\text{M}^2$	$\frac{75\text{mmHg}-35\text{mmHg}}{8 \text{ L/min/M}^2} = 5 \text{ units}\cdot\text{M}^2$

## PH: Medial Hypertrophy



Medial Hypertrophy  
Internal & External Elastic Lamina  
Adventitial Fibrosis

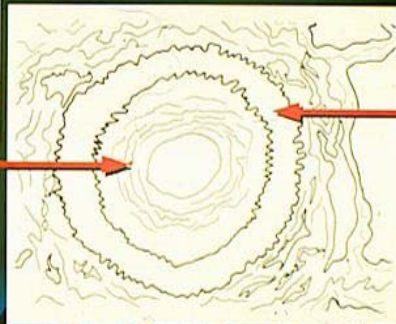


## PH: Intimal Fibrosis

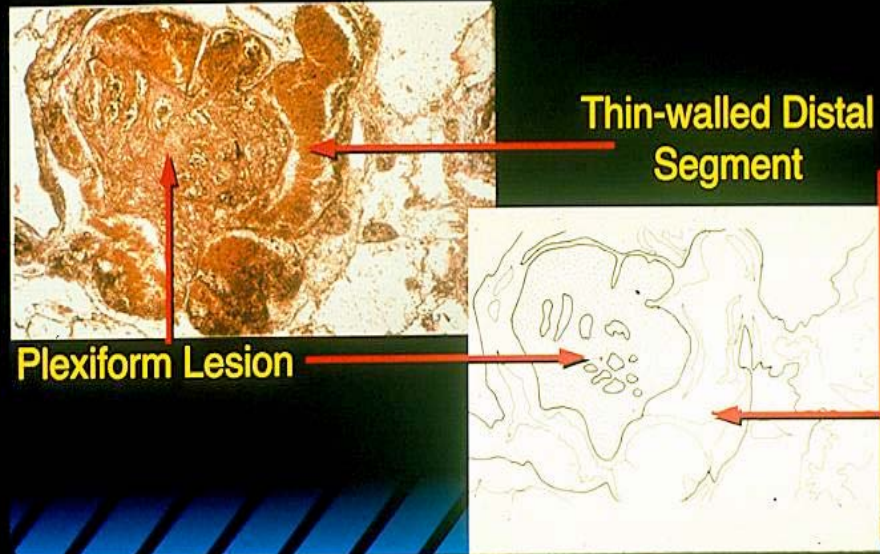


Layered Intimal  
Fibrosis

Media



## PAH: Plexiform Lesions



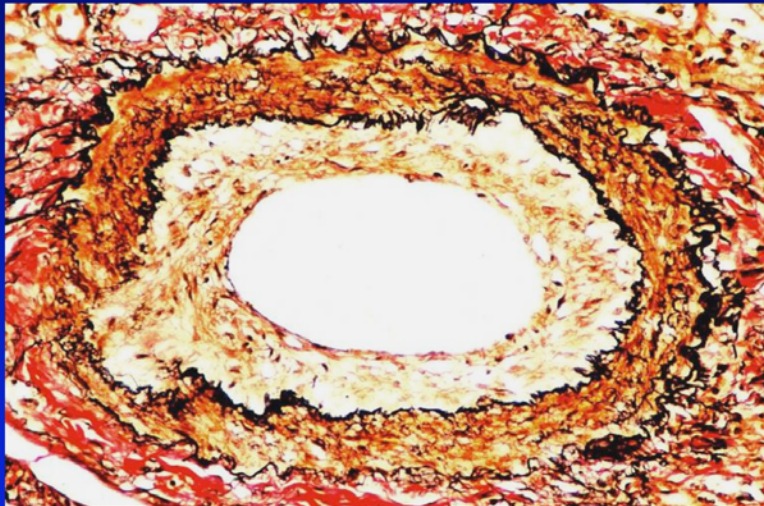
## Pulmonary Venous Hypertension Microscopic Features



Thickened Pulmonary Vein (VVG Stain)

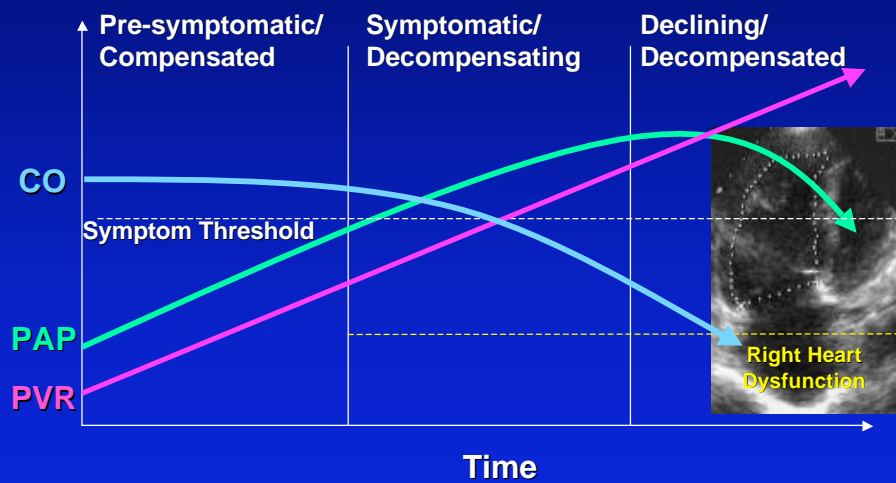


## Pulmonary Venous Hypertension Microscopic Features



Thickened Muscular Pulm Art (VVG Stain)

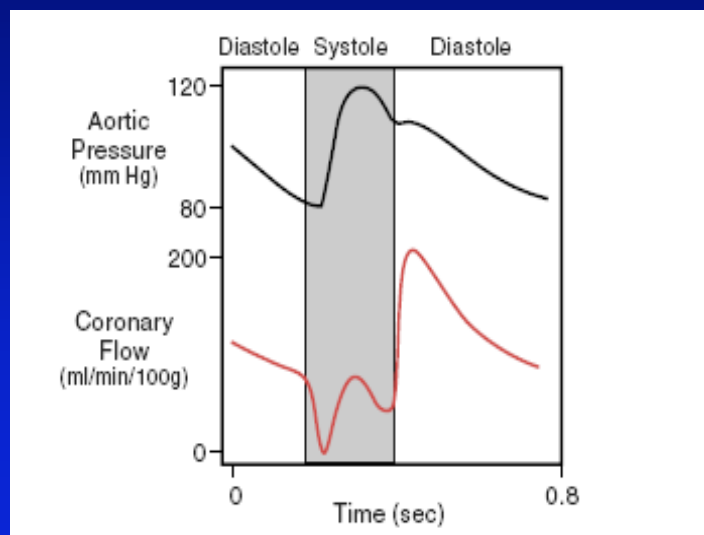
## Pathophysiology: Hemodynamic Progression of PH



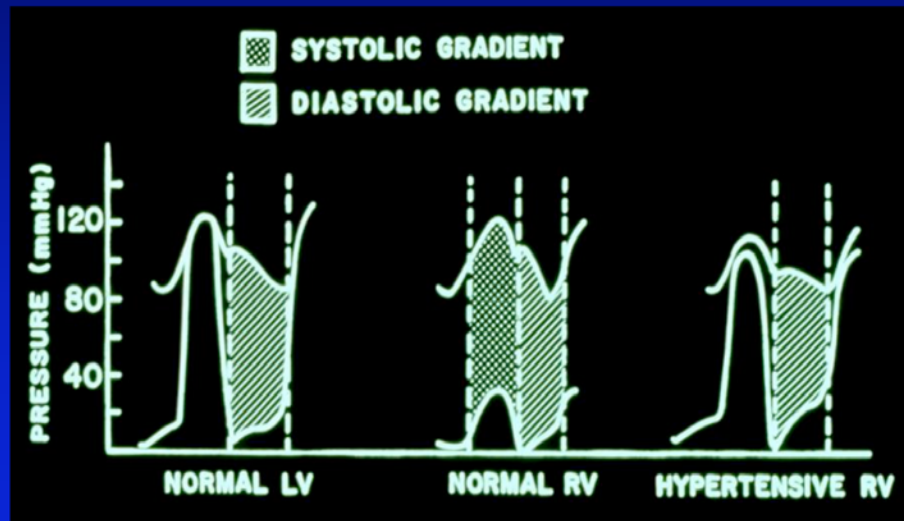
## Right Ventricular Dysfunction in Pulmonary Hypertension

Right ventricular failure is a consequence of chronic ischemia on a hypertrophied pressure overloaded ventricle

## Normal Aortic Pressure and LV Coronary Flow



## Coronary Driving Pressure Gradient and the Effect of Pulmonary Hypertension

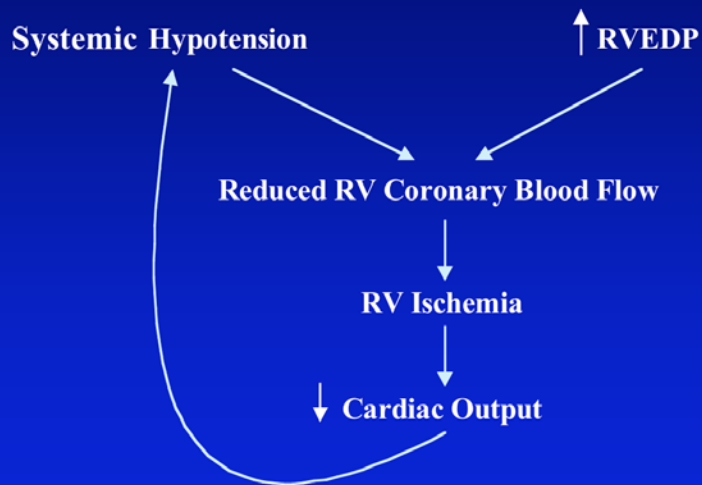


### Effects of pulmonary hypertension on RV myocardial perfusion

- Myocardial perfusion goes from being both systolic and diastolic to mostly diastolic
- The RV hypertrophies, but coronary blood supply remains unchanged
- RV work is dramatically increased without a compensatory increase in coronary blood flow
- Tachycardia makes everything worse



## PH: Progressive Right Heart Failure



## Pulmonary Arterial Hypertension: Clinical Manifestations - Symptoms

- Dyspnea on Exertion/Rest
- Fatigue
- Chest Discomfort/Pain
- Cough
- Syncope/Presyncope
- Hemoptysis
- Edema
- Hoarseness

## PAH: Clinical Manifestations

- **Dyspnea**
  - Reduced O<sub>2</sub> diffusion
  - Ventilation-perfusion mismatching
  - Low O<sub>2</sub> transport
- **Angina**
  - RV ischemia
  - Left main coronary compression
- **Syncope**
  - Hypotension due to systemic vasodilation and fixed pulmonary resistance
  - Arrhythmia
- **Edema, hepatic congestion, ascites**
  - RV failure

## PAH: Findings on Physical Examination

- Tachypnea
- Jugular venous distention
- Right ventricular heave
- Right-sided fourth heart sound
- Loud pulmonic valve closure (P<sub>2</sub>)
- Tricuspid regurgitation murmur
- Pulmonary insufficiency murmur
- Hepatomegaly (pulsatile)
- Peripheral edema, ascites, pleural effusions
- Decreased peripheral perfusion
- Cyanosis

## Pulmonary Venous PH: Symptoms

- Angina
- Syncope
- Congestive heart failure
- Dyspnea
- Hemoptysis
- Hoarseness
- Edema
- Ascites
- Paroxysmal nocturnal dyspnea
- Orthopnea
- Central and peripheral cyanosis



## Pulmonary Venous PH: Findings on Physical Examination

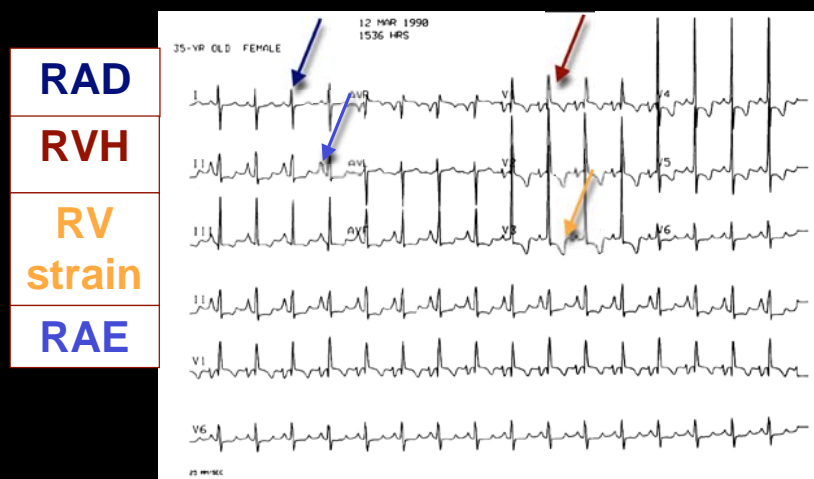
- Tachypnea, cough, wheezing
- Basilar crackles
- Central and peripheral cyanosis
- Specific signs Re: Left Heart or Pulmonary Venous Hypertension Etiology
- Signs of PH



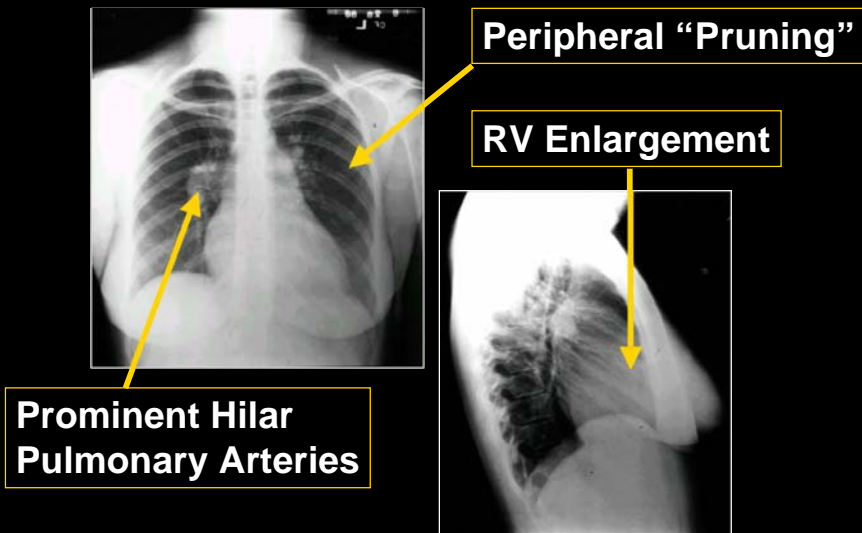
## Diagnosis of PH: Procedures

- Electrocardiogram
- Chest radiography
- Echocardiogram
- Ventilation perfusion scan (V/Q scan)
- Serologic studies, HIV
- Pulmonary function tests (PFT)
- Sleep study (if indicated)
- Arterial blood gases (ABG) (if indicated)
- Right-heart catheterization (with acute vasodilator testing if PAH)

## PAH: Screening - ECG

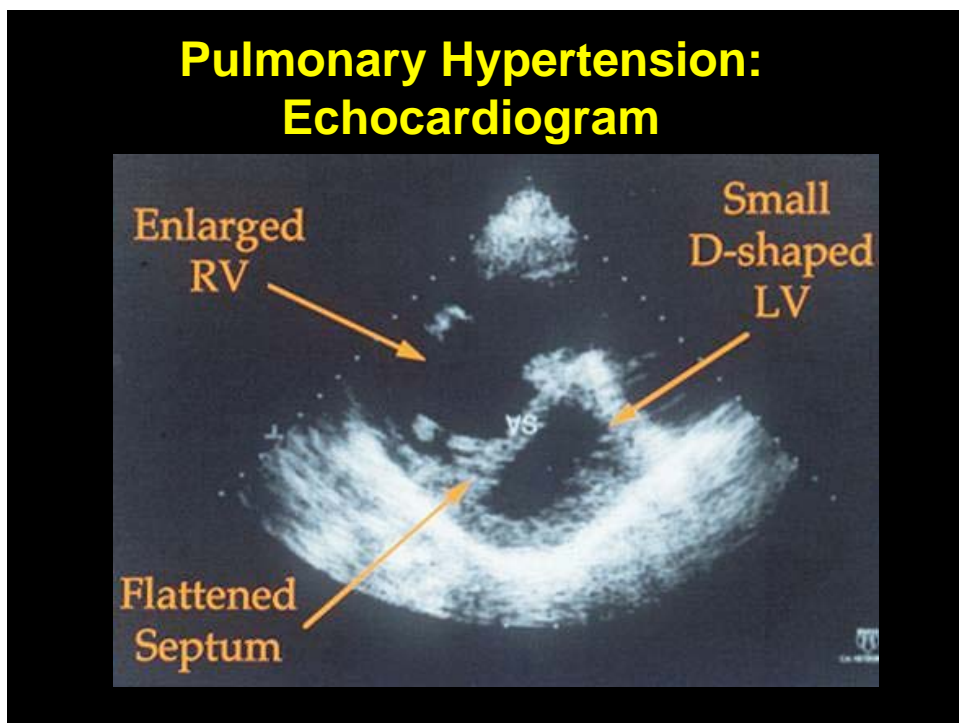
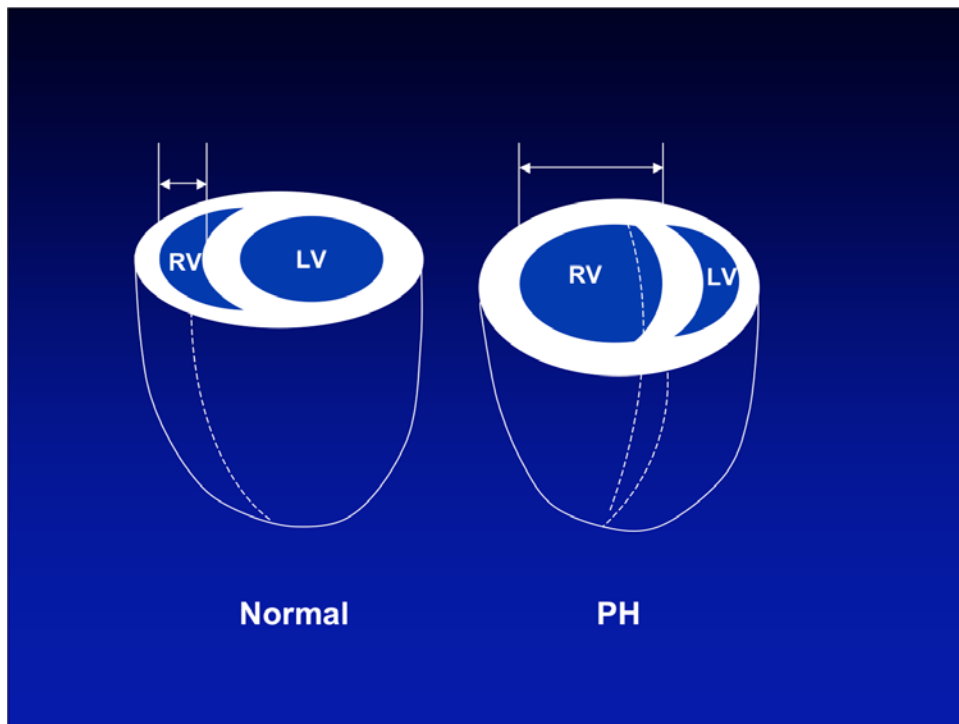


## PAH: Screening - CXR

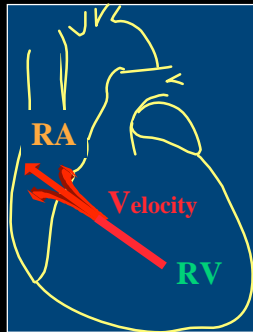


## PAH: Findings on the Echocardiogram

- TR (tricuspid regurgitation)
- RVE (right ventricular enlargement)
- RAE (right atrial enlargement)
- RVH (right ventricular hypertrophy)
- Flattening of IVS (interventricular septum)
- Dilated IVC/Hepatic veins



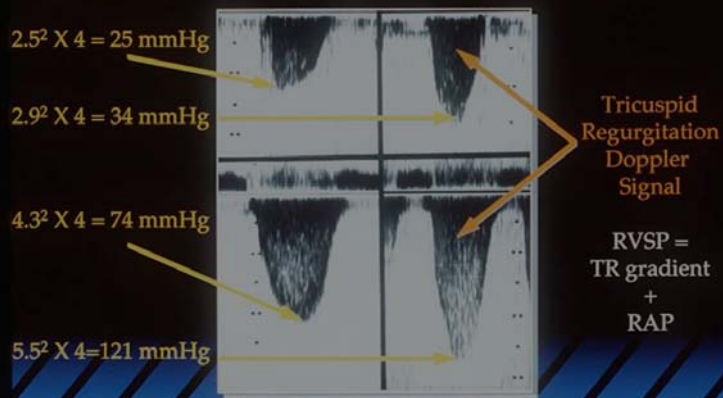
## Echocardiogram Estimate of RVSP



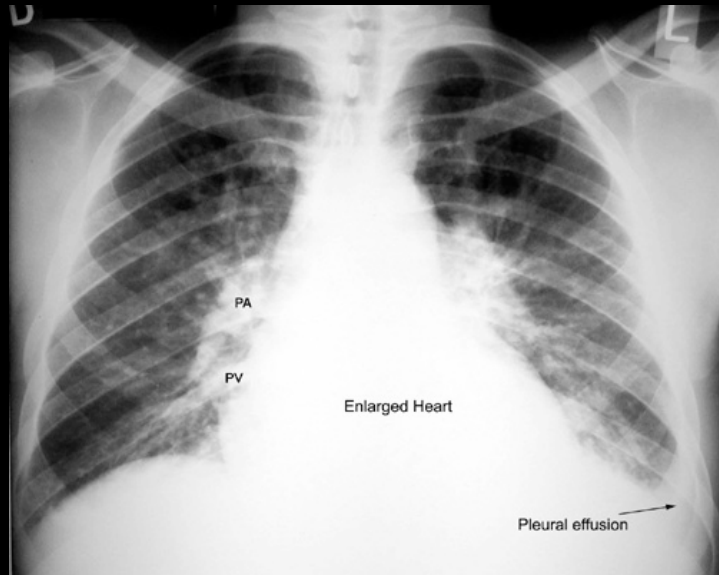
- $4V^2 = \text{Pressure Gradient } (\Delta P)$  (Modified Bernoulli Equation)
- $\text{RVSP} - \text{RAP mean} = \Delta P$
- $\text{RVSP} = \text{RAP mean} + \Delta P$

## Echocardiogram

### Doppler Estimation of RV Systolic Pressure



## PH: Congestive Heart Failure - CXR hilar fullness and haziness



### Diagnosis of PH: ECHO May Suggest an Underlying Etiology

- LV diastolic dysfunction
  - MS or MR
  - LV systolic dysfunction
- } Post-capillary pulmonary venous hypertension
- Congenital heart disease, e.g. ASD, VSD, PDA



## **Cardiac Catheterization**

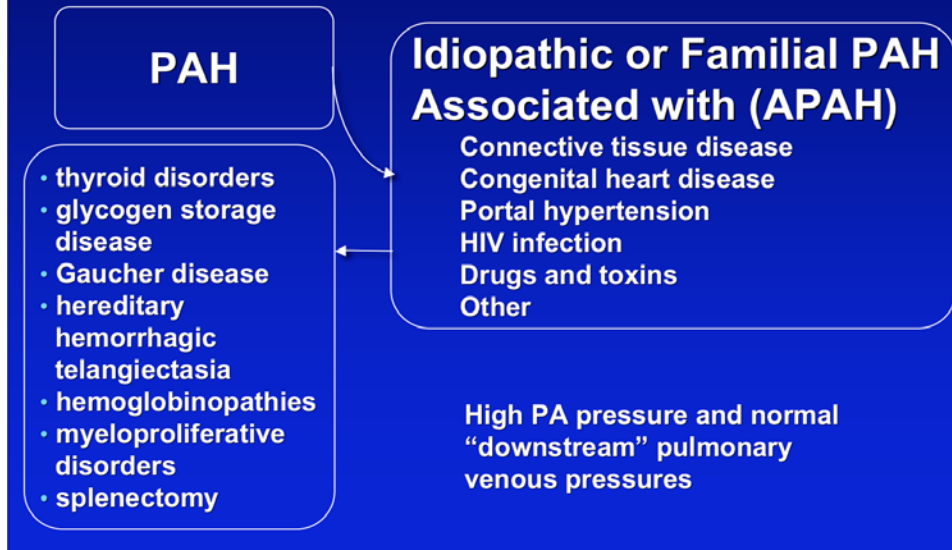
- To exclude congenital heart disease
- To measure PCWP or LVEDP
- To establish severity and prognosis
- Acute vasodilator drug testing

Cardiac catheterization should be performed in patients with suspected pulmonary hypertension

## **Diagnosis of Pulmonary Hypertension**

- High index of suspicion
- Thorough and complete evaluation

## Pre-capillary PH: Pulmonary Arterial Hypertension Classification



## Treatment: Pre-capillary PH - Pulmonary Arterial Hypertension

- Treat associated conditions, e.g. thyroid disease
- Early surgery to repair congenital heart disease, e.g. VSD, PDA
  - However, if no longer “operable” due to progressive pulmonary vascular obstructive disease, “corrective” surgery is contra-indicated
    - Medical PAH Therapy
    - Lung or Heart-Lung Transplantation

## Post-capillary PH: Pulmonary Venous Hypertension Classification

LH disease

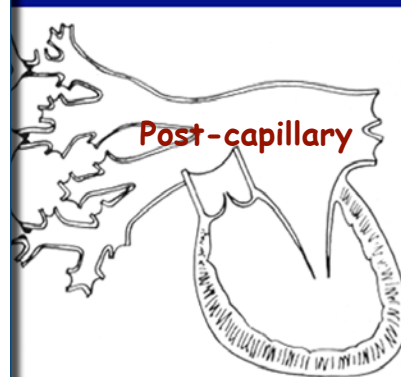
Left-sided atrial or  
ventricular heart disease

Left-sided valvular heart  
disease

## Pulmonary Venous Hypertension

### Acute Pulmonary Edema Treatment

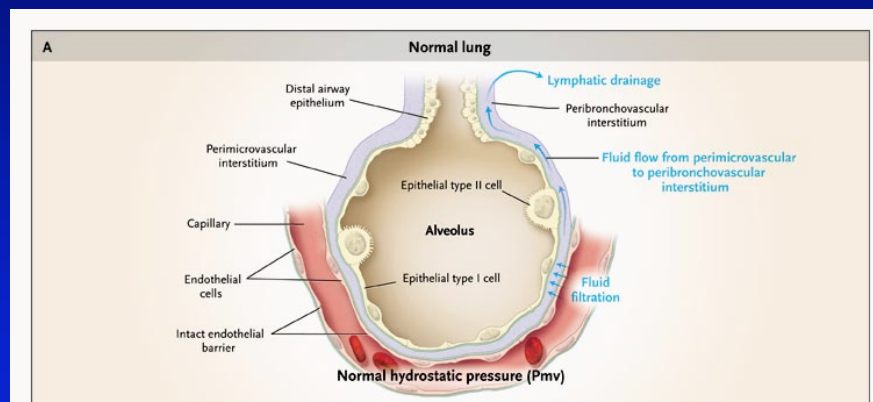
- Upright posture
- Increase FiO<sub>2</sub>
- Intravenous diuretic, e.g. furosemide
- Vasodilator therapy, e.g. nitroprusside
- Intubation and mechanical ventilation
- Hemodynamic monitoring
- Narcotics, e.g. morphine
- Inotropic support, e.g. dopamine



## Acute Pulmonary Edema

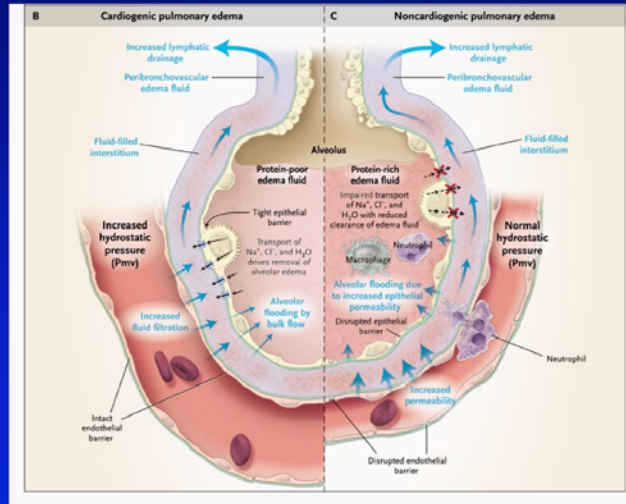
- Cardiogenic Pulmonary Edema
- Noncardiogenic Pulmonary Edema

## Physiology of Microvascular Fluid Exchange in the Lung



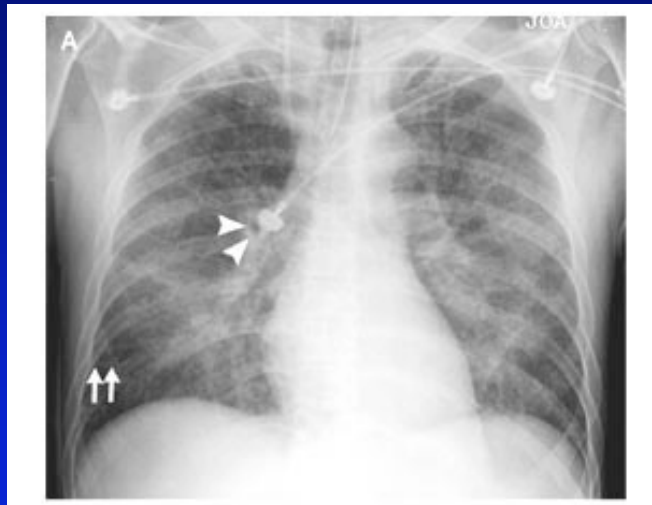
Ware L and Matthay M. N Engl J Med 2005;353:2788-2796

# Physiology of Microvascular Fluid Exchange in the Lung



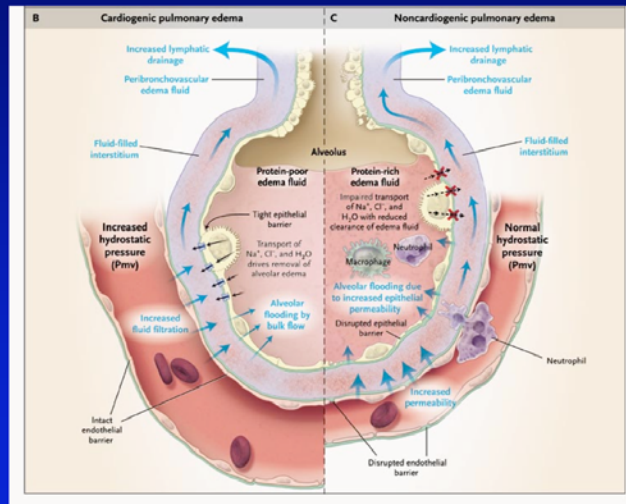
Ware L and Matthay M. N Engl J Med 2005;353:2788-2796

# Representative Chest Radiograph from Patient with Cardiogenic Pulmonary Edema



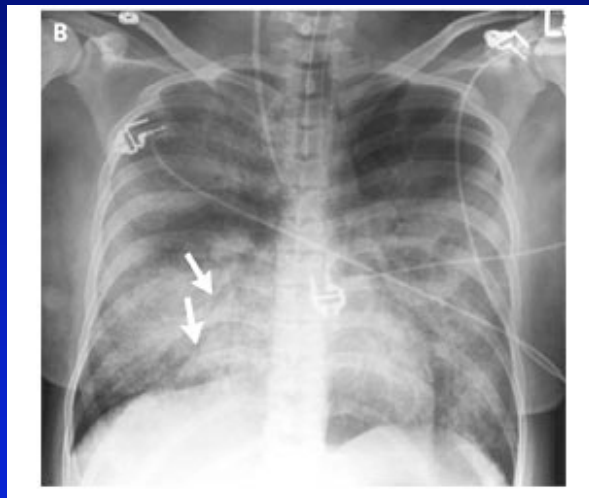
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## Physiology of Microvascular Fluid Exchange in the Lung



Ware L and Matthay M. N Engl J Med 2005;353:2788-2796

## Representative Chest Radiograph from Patient with Noncardiogenic Pulmonary Edema



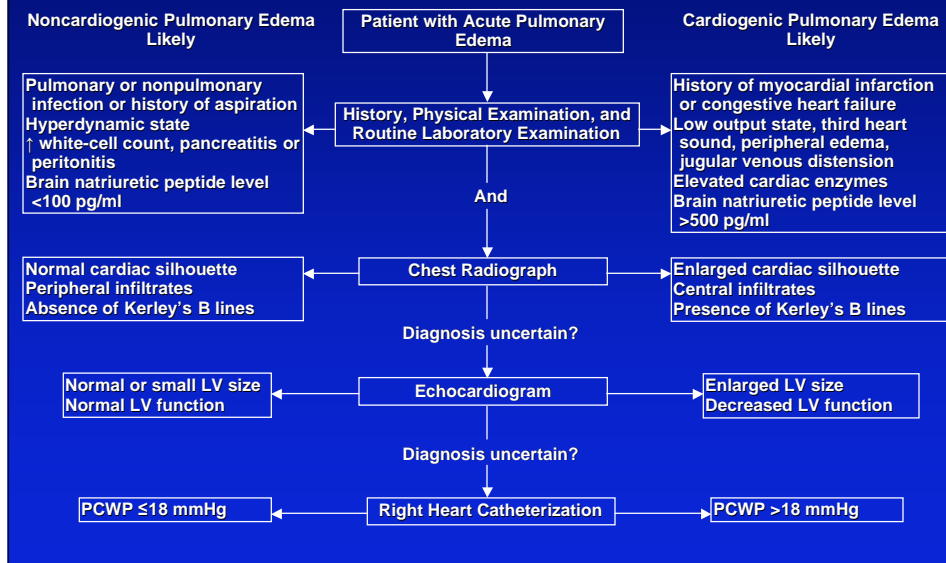
Ware L and Matthay M. N Engl J Med 2005;353:2788-2796

## Radiographic Features That May Help to Differentiate Cardiogenic from Noncardiogenic Pulmonary Edema

Radiographic Feature	Cardiogenic Edema	Noncardiogenic Edema
Heart size	Normal or greater than normal	Usually normal
Vascular distribution	Balanced or inverted	Normal or balanced
Distribution of edema	Even or central	Patchy or peripheral
Pleural effusions	Present	Not usually present
Peribronchial cuffing	Present	Not usually present
Septal lines, i.e. Kerley's B lines	Present	Not usually present
Air bronchograms	Not usually present	Usually present

Adapted from:  
Ware L and Matthay M. N Engl J Med 2005;353:2788-2796

## Algorithm for the Clinical Differentiation between Cardiogenic and Noncardiogenic Pulmonary Edema



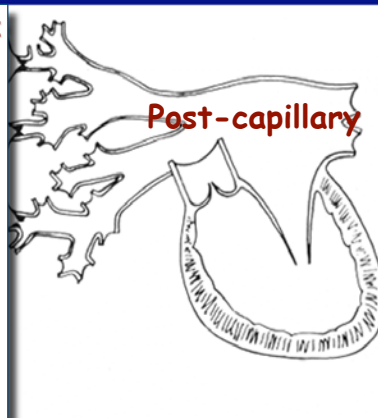
## Treatment: Post-capillary PH - Pulmonary Venous Hypertension

- Surgery to eliminate left-sided cardiac obstruction
- Heart transplantation for left ventricular failure
- Additional medical and/or surgical treatment as needed
  - Specific re: left heart or pulmonary venous hypertension etiology
  - PAH treatment

## Pulmonary Venous Hypertension

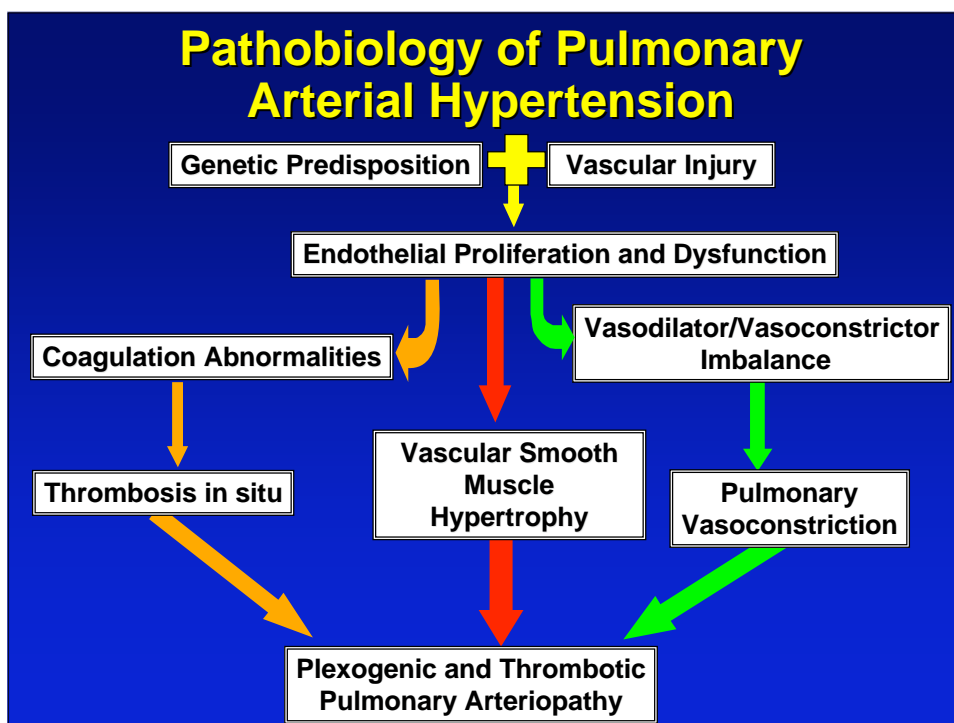
### Chronic Heart Failure Treatment

- Sodium restriction
- Afterload reduction, e.g. ACE inhibitors
- Inotropic support, e.g. digitalis
- Diuretics
- Beta-blockers
- Identification and treatment of underlying cause(s)





## Targeted Pulmonary Arterial Hypertension Medical Treatment



# Pathobiology of Pulmonary Arterial Hypertension

Genetic Predisposition



Vascular Injury

Endothelial Proliferation and Dysfunction

**Vasodilator-antiproliferative/  
vasoconstrictor-proliferative  
Imbalance**

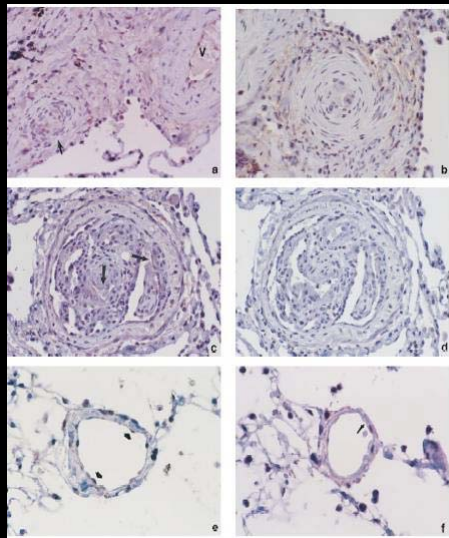
- Deficient prostacyclin
- Excess thromboxane
- Excess endothelin
- Deficient nitric oxide

Vasodilator/Vasoconstrictor  
Imbalance

Pulmonary  
Vasoconstriction

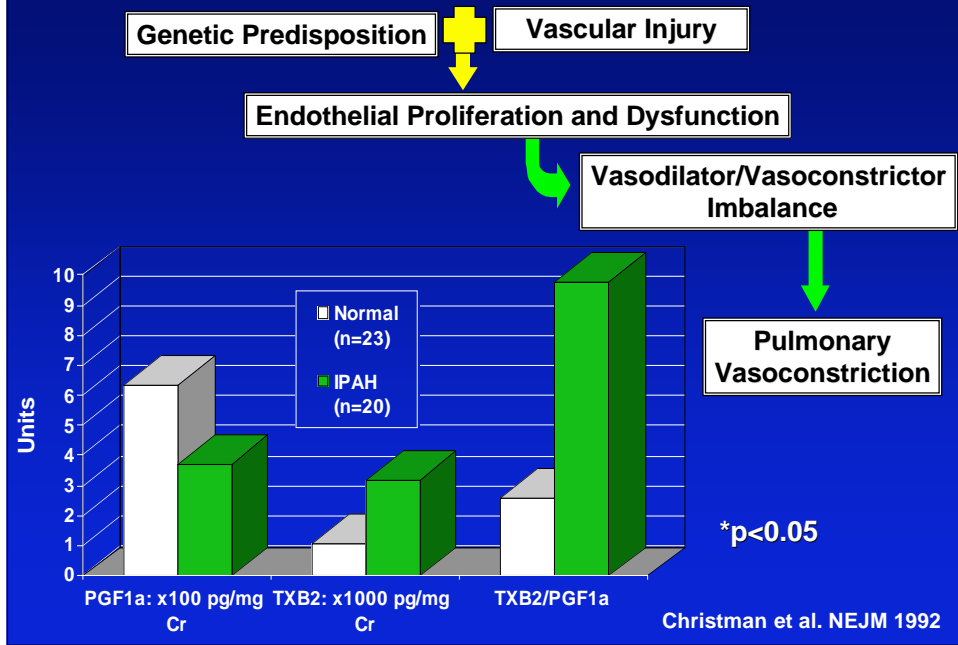
Plexogenic and Thrombotic  
Pulmonary Arteriopathy

## PAH: Decreased Expression of Prostacyclin Synthase in the Lung

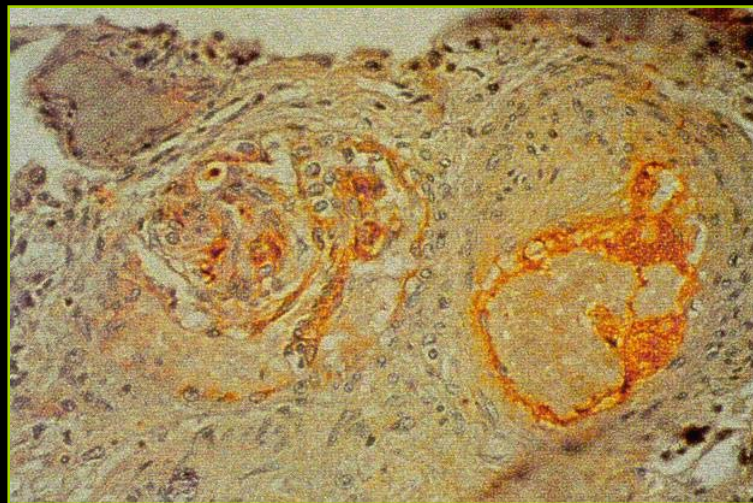


Tuder et al. AJRCCM 1999

## PAH: Increased Thromboxane A<sub>2</sub> Production

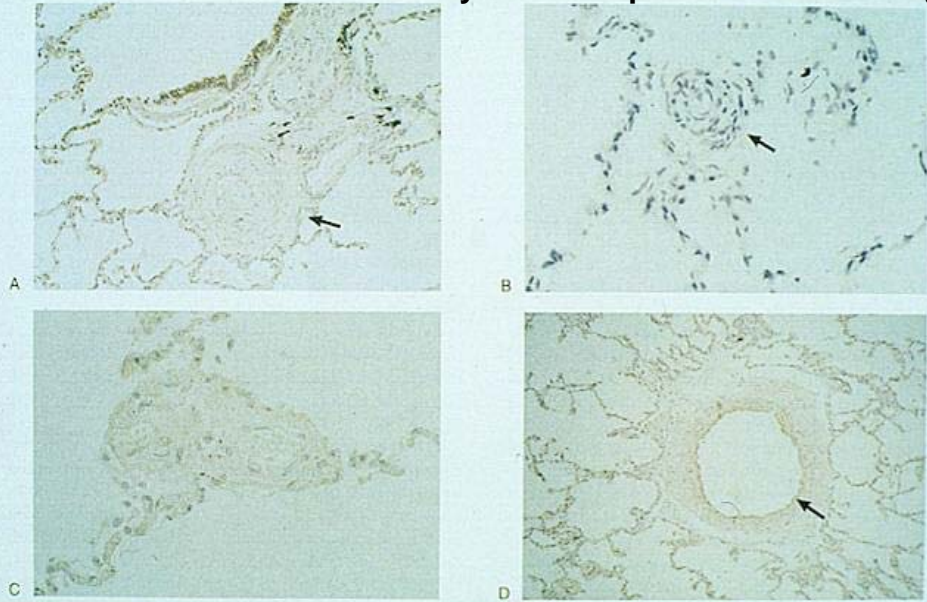


## PAH: Increased Expression of Endothelin in the Lung

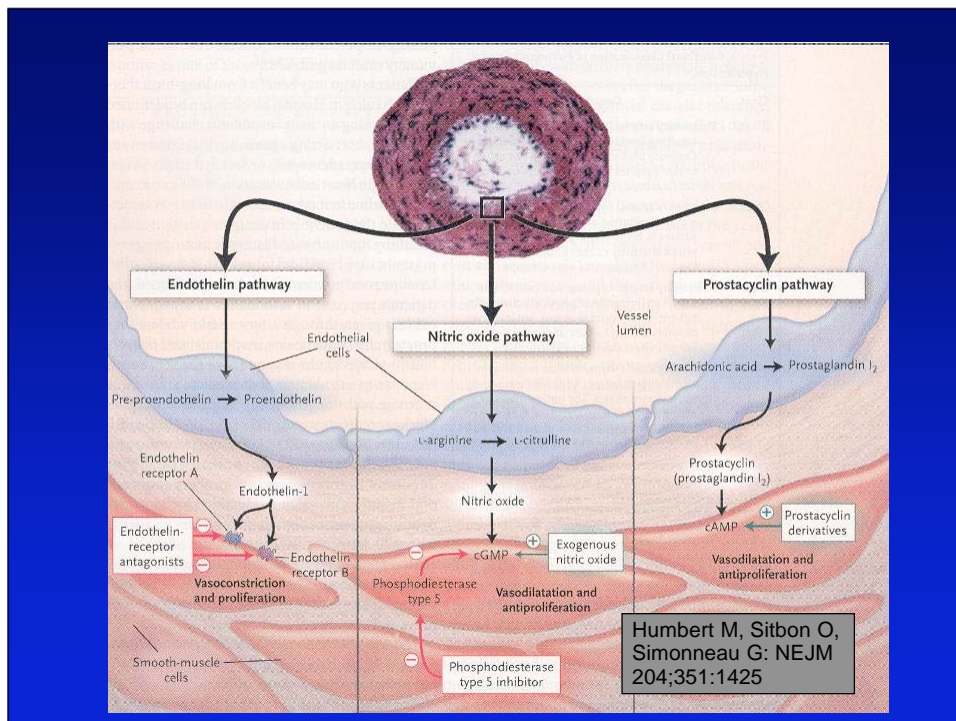


Giaid A et al. NEJM 1993

**PAH: Decreased Nitric Oxide Synthase Expression in the Lung**



Giaid et al. NEJM 1995



## Mechanisms Behind Current Targeted PAH Medical Therapeutic Options

### Abnormality in PAH

### Therapeutic Implication

↓ Prostacyclin synthase in endothelial cells

• Administer prostacyclin

↓ Nitric oxide synthase expression in endothelial cells

• Enhance NO pathway

↑ Lung and circulating endothelin-1 levels

• Use endothelin receptor antagonist

## Experience and Reason

“In Medicine one must pay attention not to plausible theorizing but to experience and reason together . . . I agree that theorizing is to be approved, provided that it is based on facts, and systematically makes its deductions from what is observed . . . But conclusions drawn from unaided reason can hardly be serviceable; only those drawn from observed fact.”

Hippocrates (460-377 BC): *Precepts*