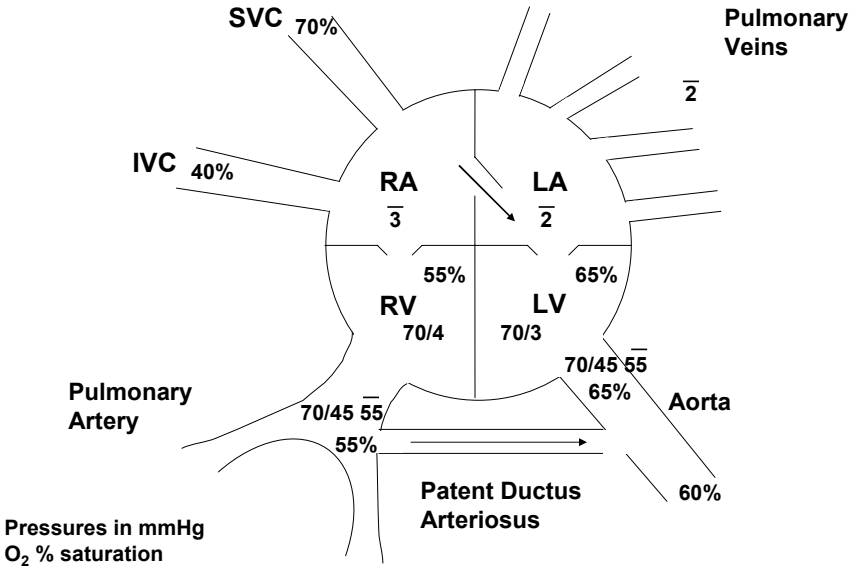
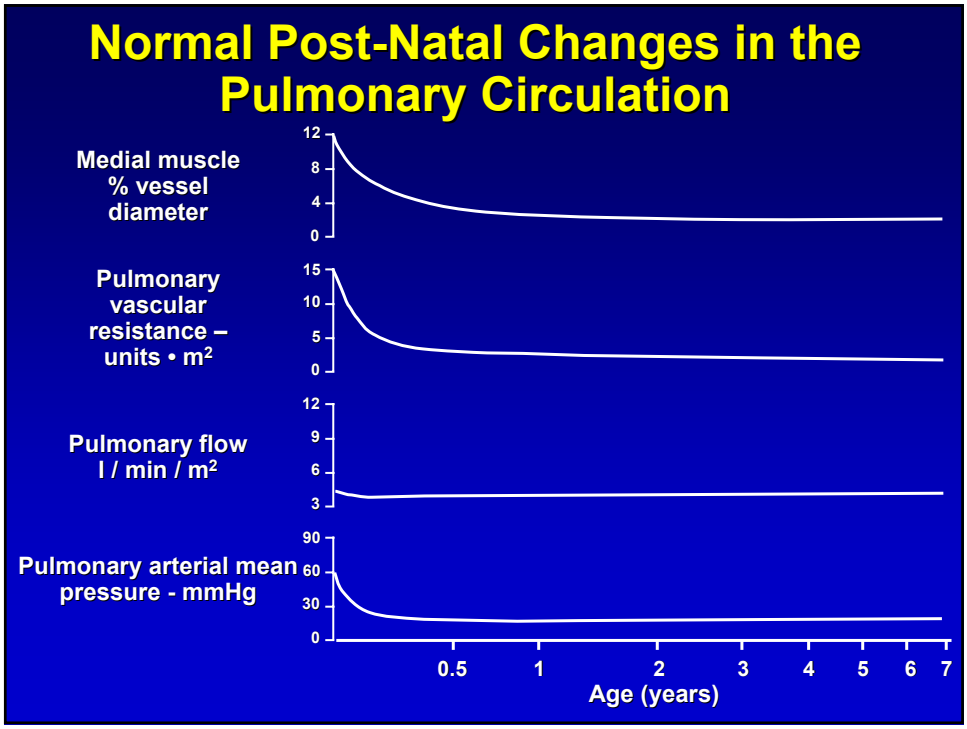
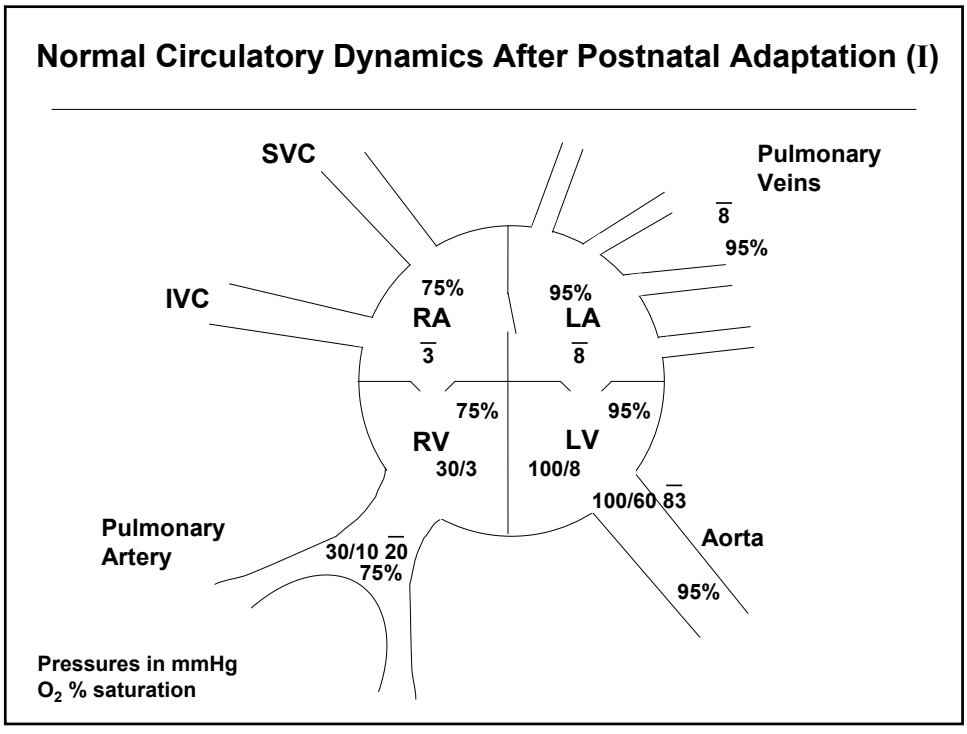
Pulmonary Vascular Changes in Heart Disease

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

Normal Circulatory Dynamics in Late-Gestation Fetus




Normal Post-Natal Changes in the Pulmonary Circulation
Medial muscle % vessel diameter
12
8
4
0
Pulmonary vascular resistance – units • m²
15
10
5
0
Pulmonary flow l / min / m²
12
9
6
3
Pulmonary arterial mean pressure - mmHg
90
60
30
0
0.5
1
2
3
4
5
6
7
Age (years)

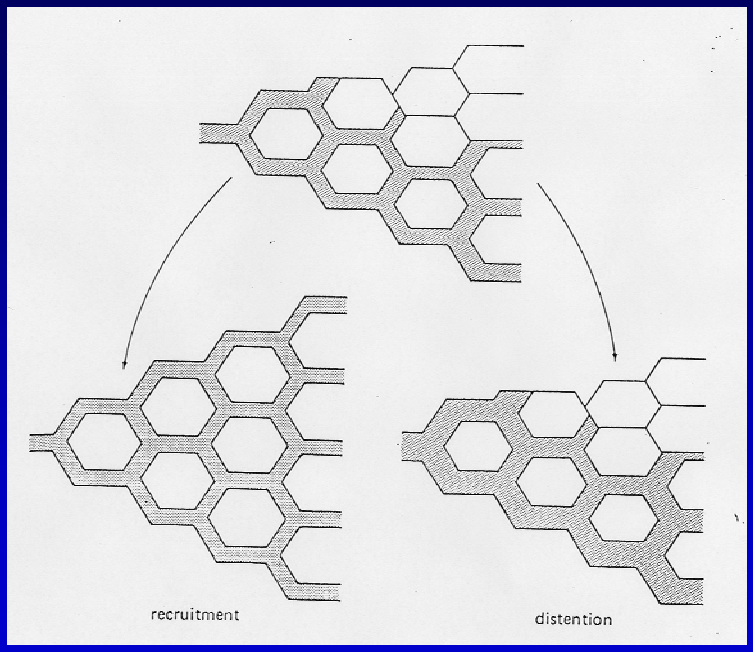

Normal Circulatory Dynamics After Postnatal Adaptation (I)
SVC
Pulmonary Veins
8
95%
IVC
75%
RA
3
95%
LA
8
75%
RV
30/3
95%
LV
100/8
100/60 83
Aorta
95%
Pulmonary Artery
30/10 20
75%
Pressures in mmHg
O2 % saturation

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

*pressure drop across vascular bed
† without congenital systemic to pulmonary shunts

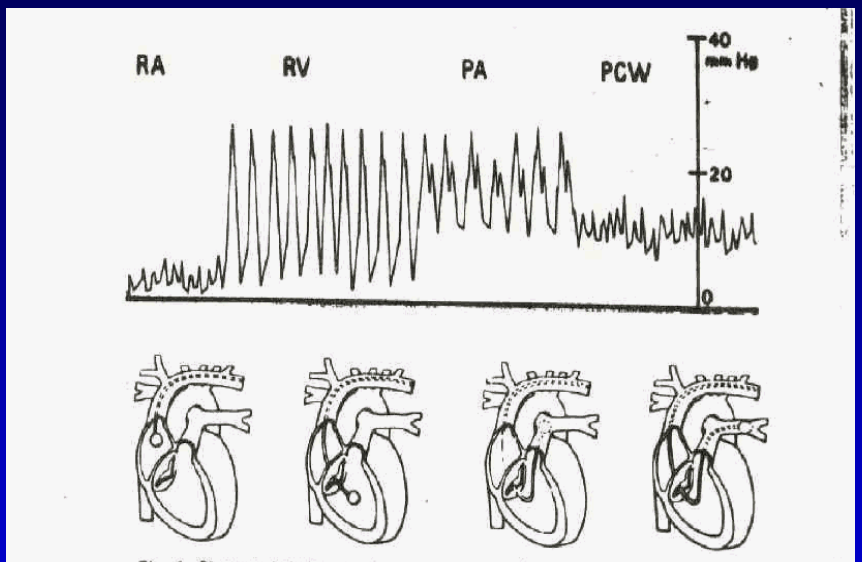
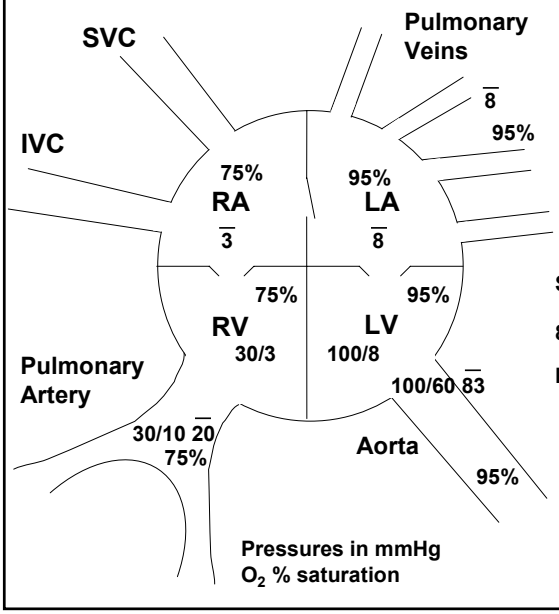


Fig. 1. Characteristic intracardiac pressure wave forms during passage through the heart

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

Normal Circulatory Dynamics (II)



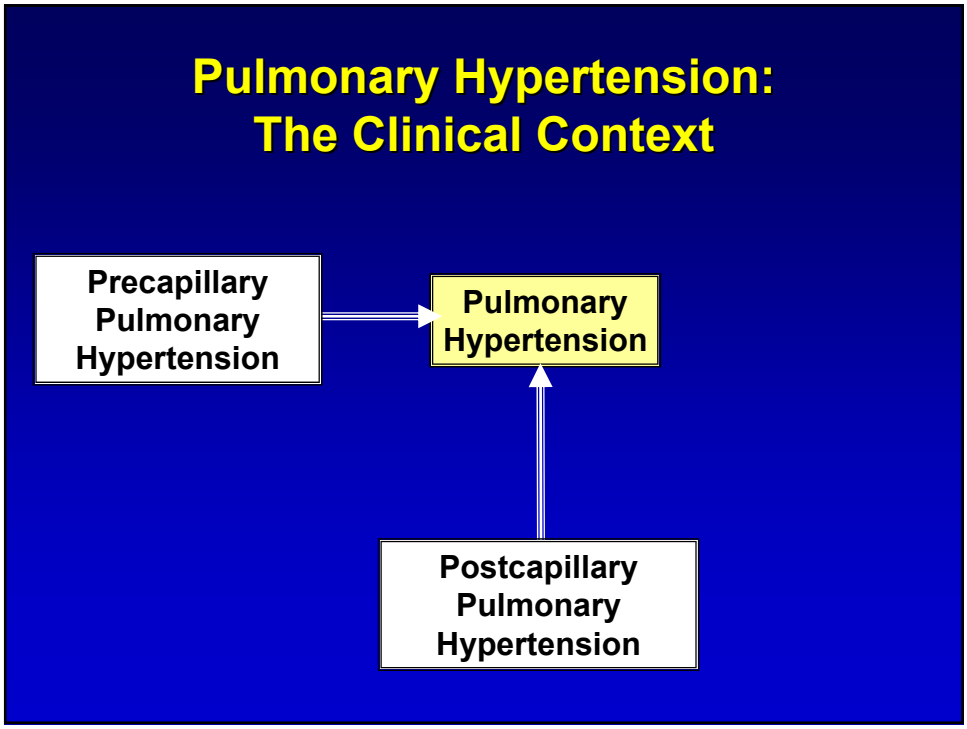
Pressure = Flow x Resistance

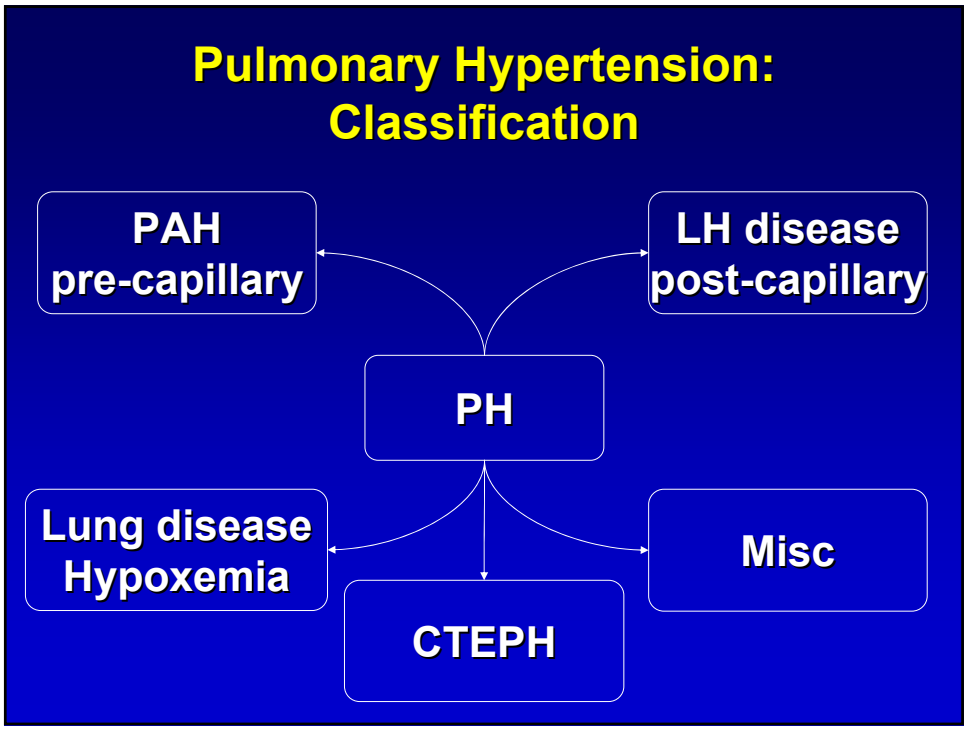
Systemic Circulation
SAPm - RAPm = CI x SVR
83mmHg-3mmHg=5 l/min/M^2x16 U•M^2

Pulmonary Circulation
PAPm - PCWPm = CI x PVR
20mmHg-8mmHg=5 l/min/M^2x2 U•M^2

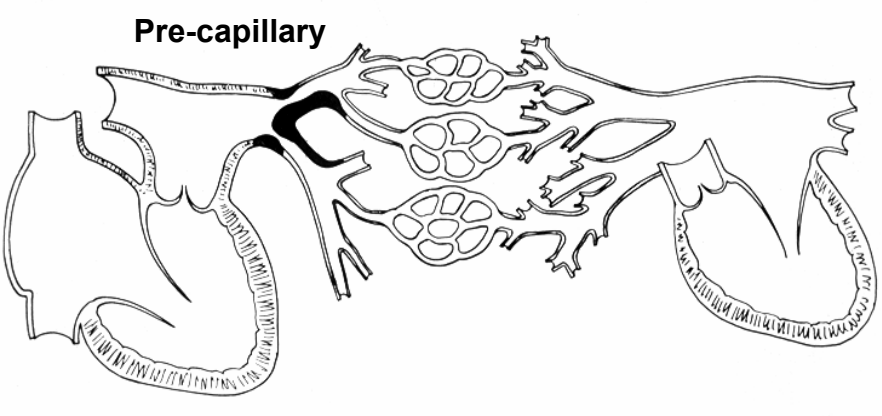
Pulmonary Hypertension: Definition

PAP mean ≥ 25 mm Hg at rest or ≥ 30 mmHg with exercise

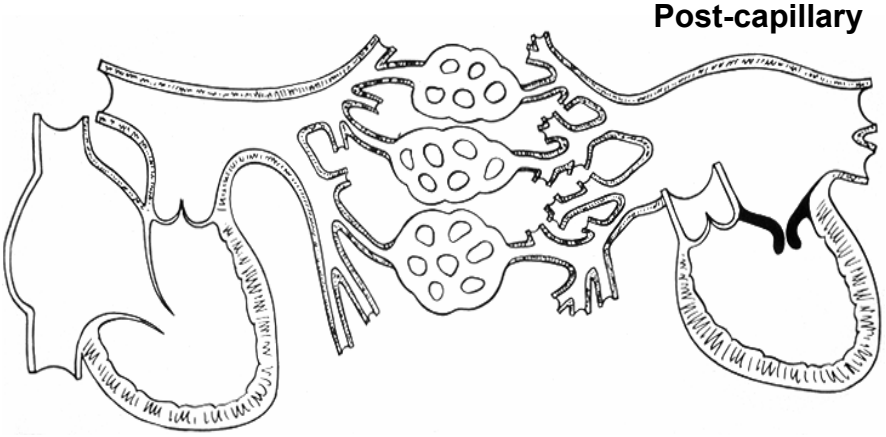

Pulmonary Hypertension:
The Clinical Context
Precapillary Pulmonary Hypertension
Pulmonary Hypertension
Postcapillary Pulmonary Hypertension


Pulmonary Hypertension:
Classification
PAH pre-capillary
LH disease post-capillary
PH
Lung disease Hypoxemia
Misc
CTEPH

Localizing the Problem



Localizing the Problem



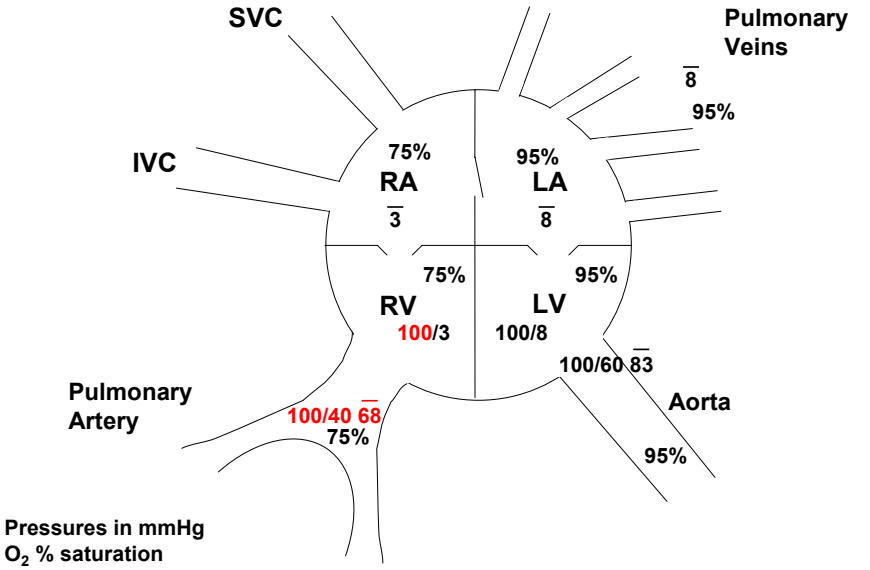
Pre-capillary PH: Pulmonary Arterial Hypertension Definition

- PAP mean ≥ 25 mmHg at rest or ≥ 30 mmHg with exercise

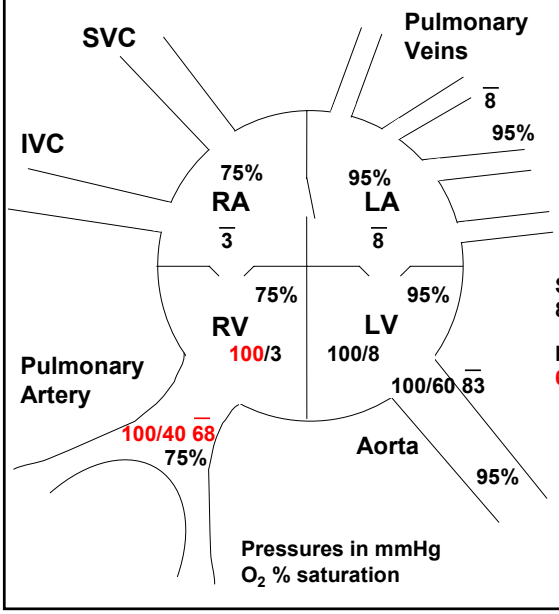
AND

- PCWP or LVEDP ≤ 15 mmHg
- PVRI ≥ 3 units • m^2
- Normal LVEF
- No left-sided valvular disease

Pulmonary Hypertension - Pre-Capillary (I)
(Pulmonary Arterial Hypertension)



Pulmonary Hypertension - Pre-Capillary (II)
(Pulmonary Arterial Hypertension)



Pressure = Flow x Resistance

Systemic Circulation
83mmHg-3mmHg=5 l/min/M^2x16 U•M^2

Pulmonary Circulation
68mmHg-8mmHg=5 l/min/M^2x12 U•M^2

Pre-capillary PH: Classification

PAH

Idiopathic or Familial PAH
Associated with (APAH)
- Connective tissue disease
- Congenital syst-pulm shunts
- Portal hypertension
- HIV infection
- Drugs and toxins
- Other

- thyroid disorders
- glycogen storage disease
- Gaucher disease
- hereditary hemorrhagic telangiectasia
- hemoglobinopathies
- myeloproliferative disorders
- splenectomy

High PA pressure and normal "downstream" pressures

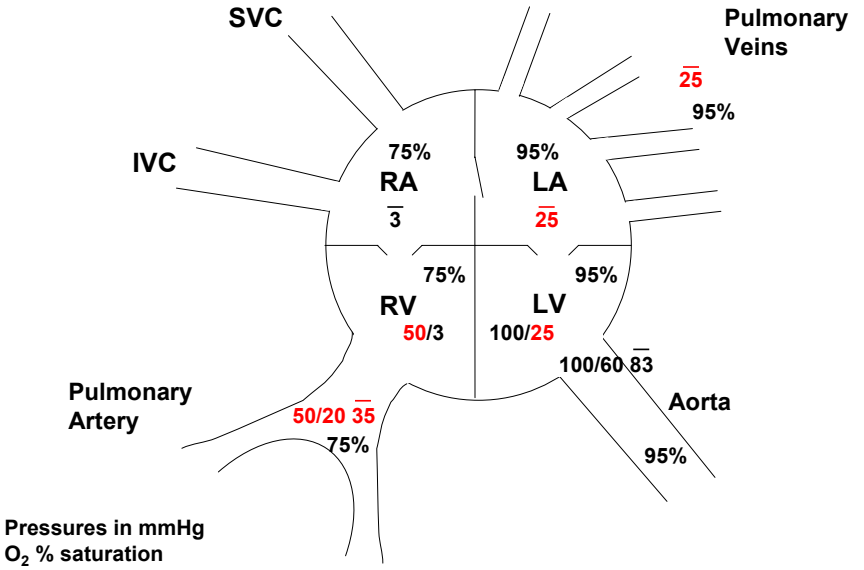
Post-capillary PH: Definition

- PAP mean ≥ 25 mmHg at rest or ≥ 30 mmHg with exercise

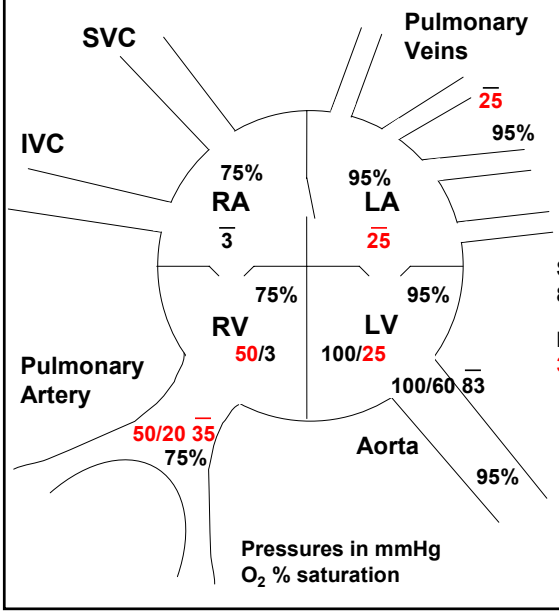
AND

- PCWP or LVEDP >15mmHg

Pulmonary Hypertension - Post-Capillary (I)
(Pulmonary Venous Pulmonary Hypertension)



Pulmonary Hypertension - Post-Capillary (II)
(Pulmonary Venous Pulmonary Hypertension)



Pressure = Flow x Resistance

Systemic Circulation
83mmHg-3mmHg=5 l/min/M^2x16 U•M^2

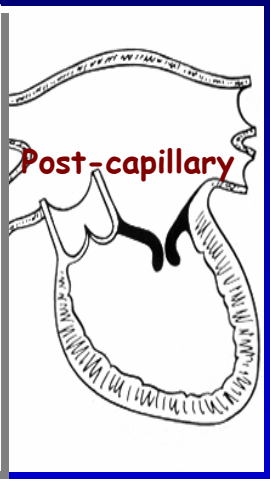
Pulmonary Circulation
35mmHg-25mmHg = 5 l/min/M^2x2 U•M^2

Post-capillary PH: Classification

- LH disease
- Left-sided atrial or ventricular heart disease
- Left-sided valvular heart disease

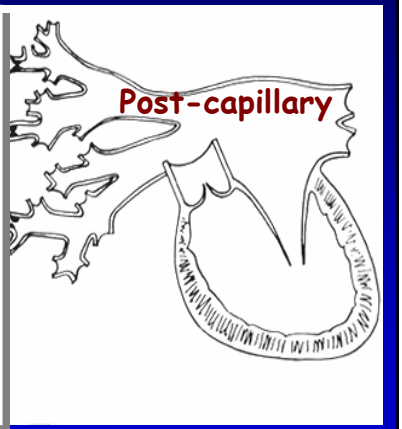
Post-capillary PH : Localizing the Problem

- 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 : Localizing the Problem

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



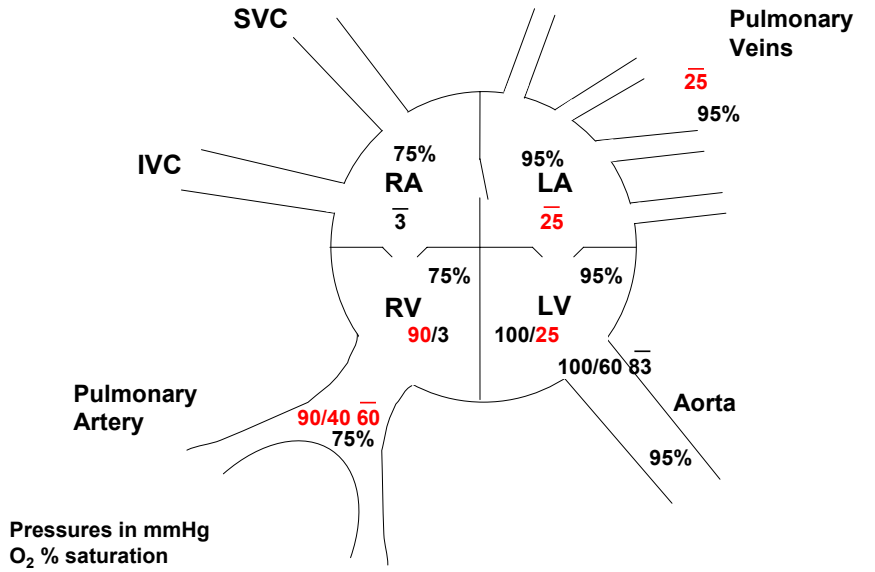
Pulmonary Venous Hypertension Physiology

Pulmonary arterial	→	Lung	→	Pulmonary venous
35 mmHg	→	No obstruction	→	25 mmHg
45-100 mmHg	→	Pulmonary arteriolar obstruction	→	25 mmHg

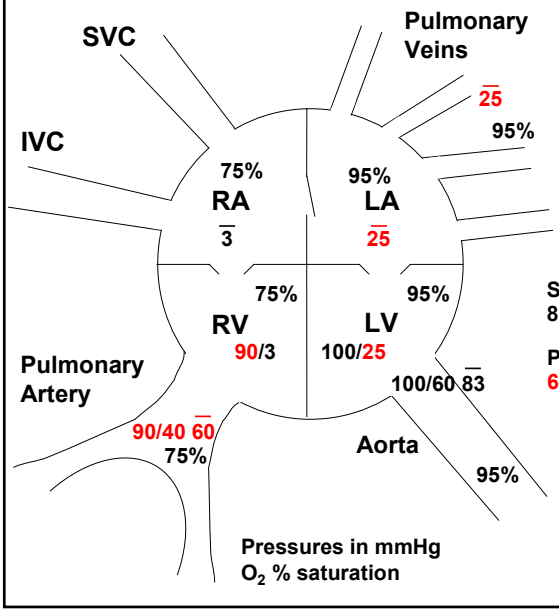
Mixed (Pulmonary Venous and Pulmonary Arterial Hypertension): Definition

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

Pulmonary Hypertension - Mixed (Pulmonary Venous and Pulmonary Arteriolar Hypertension) (I)



Pulmonary Hypertension - Mixed (Pulmonary Venous and Pulmonary Arteriolar Hypertension) (II)



Pressure = Flow x Resistance

Systemic Circulation
83mmHg-3mmHg=5 l/min/M²x16 U•M²

Pulmonary Circulation
60mmHg-25mmHg=5 l/min/M²x7 U•M²

Pathophysiology: Rest and Exercise Pulmonary Hemodynamics

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

	Rest	Exercise
Normal	15mmHg-10mmHg = 1 unit•M² 5 L/min/M²	30mmHg-12mmHg = <1unit•M² 20 L/min/M²
PAH (Pre-Cap)	50mmHg-10mmHg = 8 units•M² 5 L/min/M²	90mmHg-10mmHg = 10 units•M² 8 L/min/M²
Pulm Venous PH (post-cap)	35mmHg-25mmHg = 2 units•M² 5 L/min/M²	55mmHg-35mmHg = 2 units•M² 10 L/min/M²
Mixed PH (Pre-cap & Post-cap)	50mmHg-25mmHg = 5 units•M² 5 L/min/M²	75mmHg-35mmHg = 5 units•M² 8 L/min/M²

Pathology: Pulmonary Vascular Disease Heath Edwards Classification

Grade 1 - Medial hypertrophy in the small pulmonary arteries.

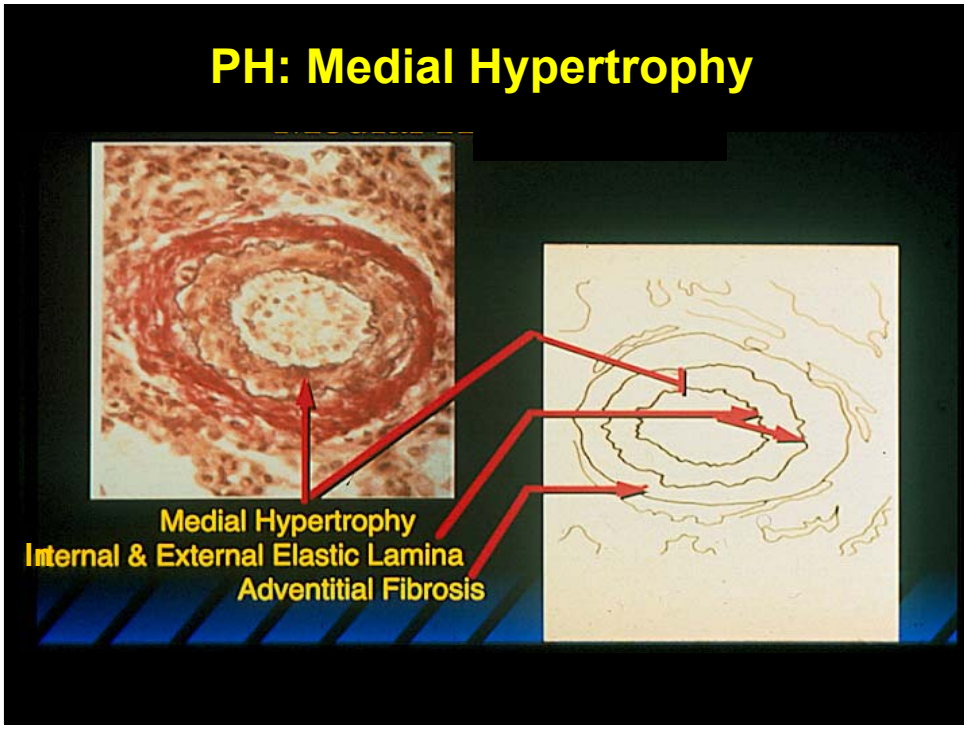
Grade 2 - Concentric or eccentric cellular intimal proliferation and thickening within the smaller pulmonary arteries and arterioles.

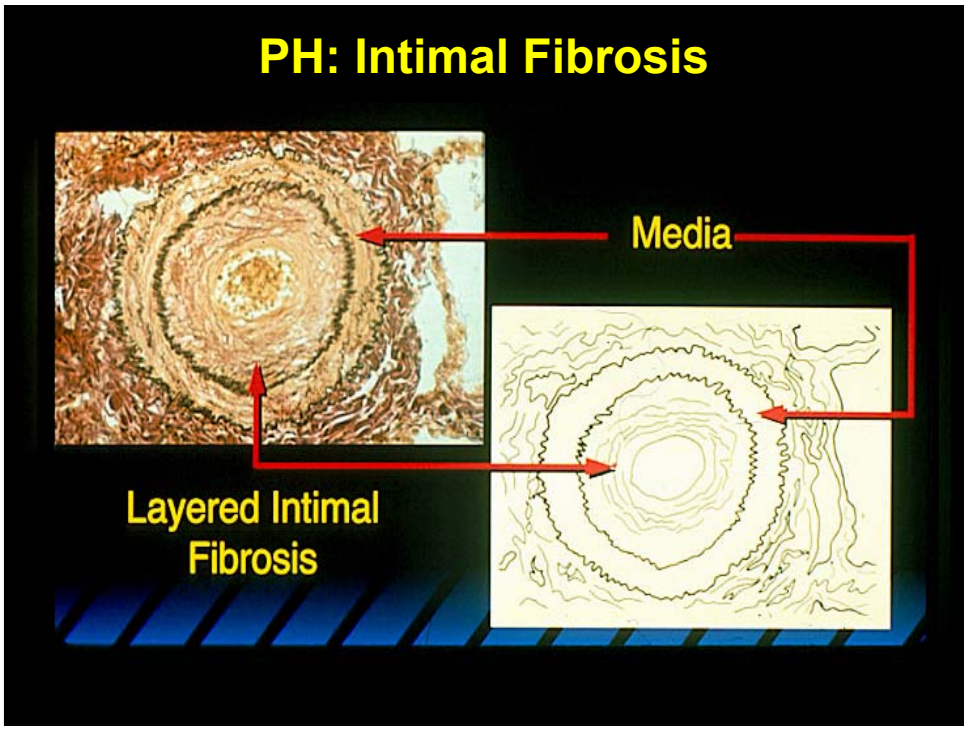
Grade 3 - Relatively acellular intimal fibrosis with accumulation of concentric or eccentric masses of fibrous tissue leading to wide spread occlusion of the smaller pulmonary arteries and arterioles.

Grade 4 - Progressive, generalized dilatation of the muscular arteries and the appearance of plexiform lesions, complex vascular structures composed of a network or plexus of proliferating endothelial tissue, frequently accompanied by thrombus, within a dilated thin-walled sac.

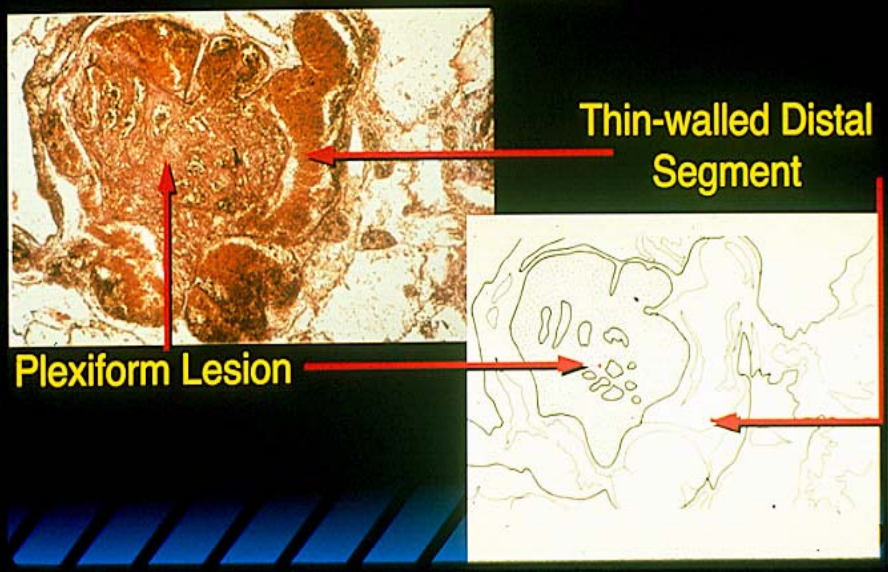
Grade 5 –Thinning and fibrosis of the media superimposed upon the formation of numerous complex dilatation lesions.

Grade 6 - Necrotizing arteritis within the media with surrounding areas of inflammatory reaction and granulation tissue.


PH: Medial Hypertrophy
Medial Hypertrophy
Internal & External Elastic Lamina
Adventitial Fibrosis

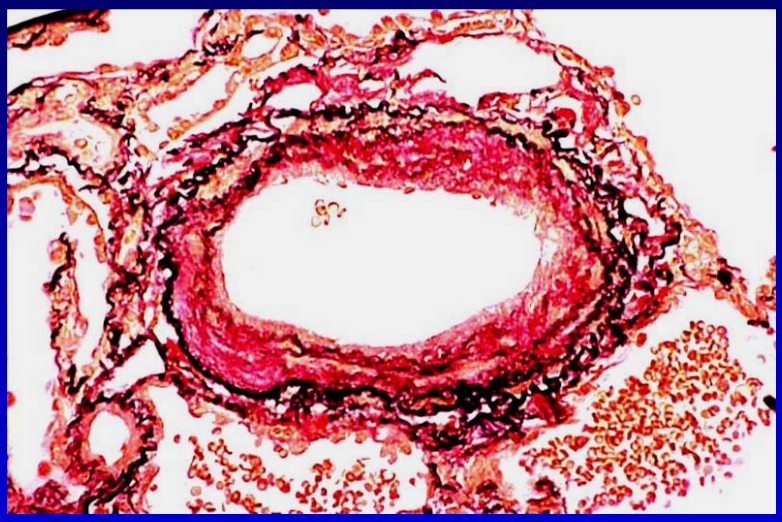

PH: Intimal Fibrosis
Media
Layered Intimal
Fibrosis

PAH: Plexiform Lesions



Pulmonary Venous Hypertension

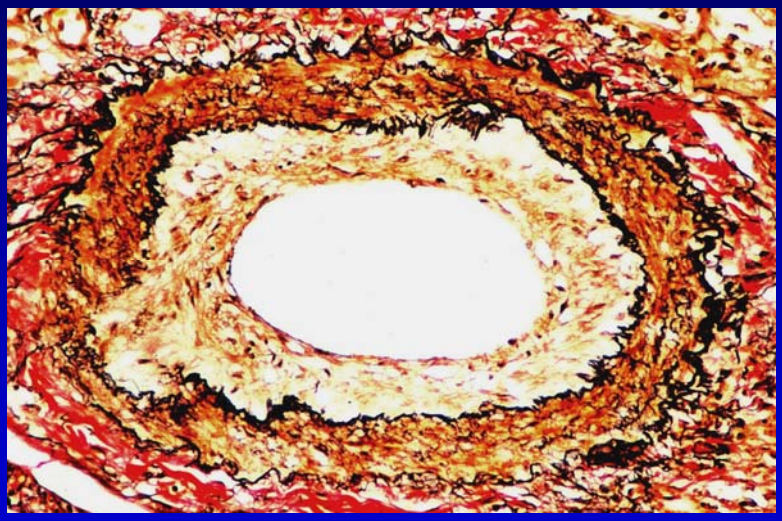
Microscopic Features



Thickened Pulmonary Vein (VVG Stain)

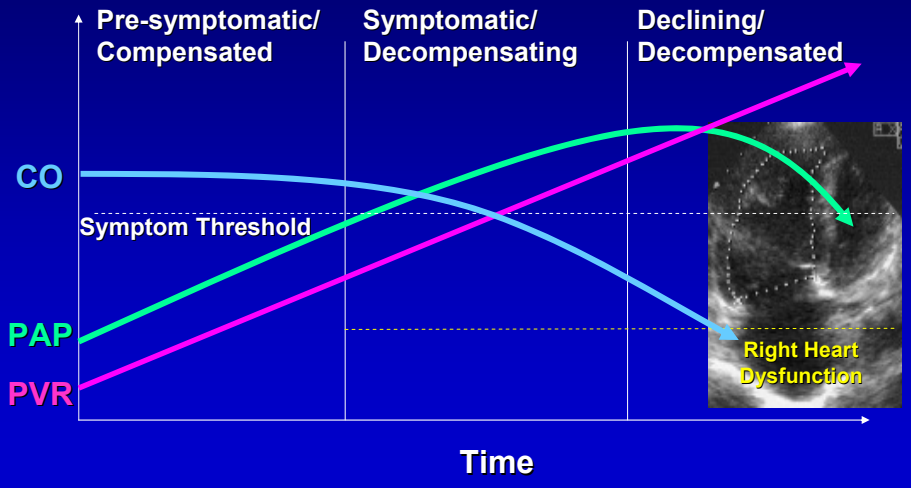
Pulmonary Venous Hypertension

Microscopic Features



Thickened Muscular Pulm Art (VVG Stain)

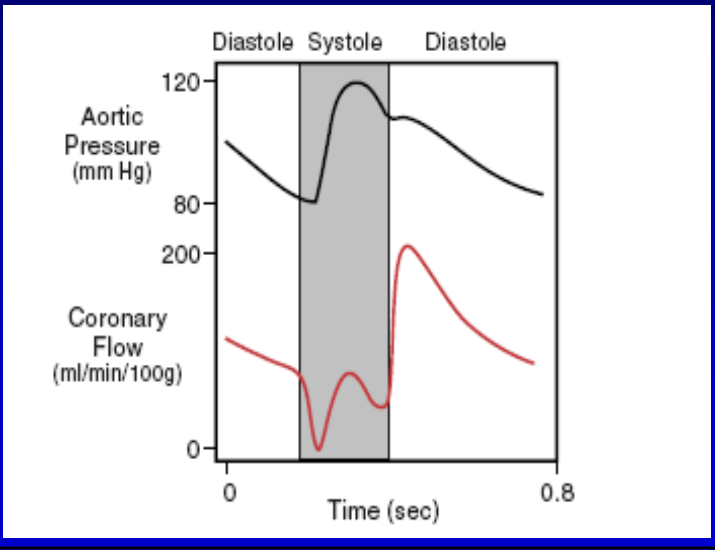
Pathophysiology: Hemodynamic Progression of PAH



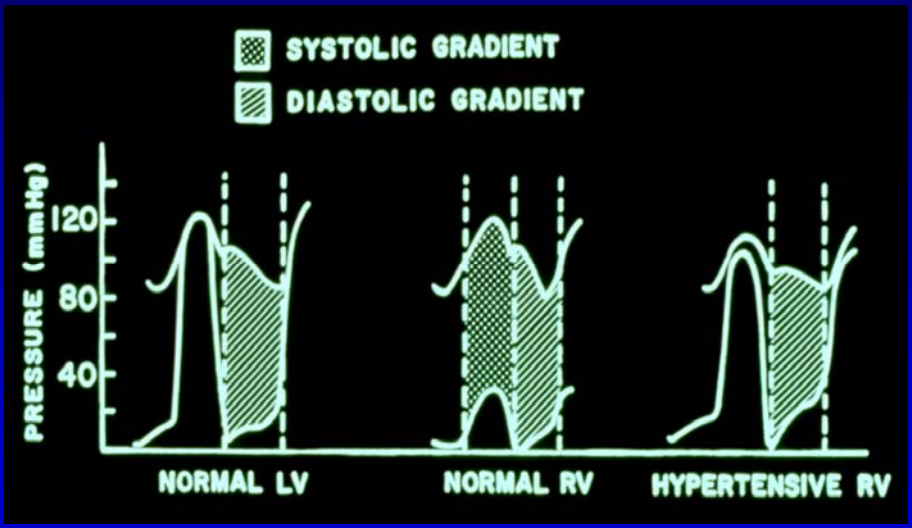
Right Ventricular Dysfunction in Pulmonary Hypertension

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

Normal Aortic Pressure and LV Coronary Flow



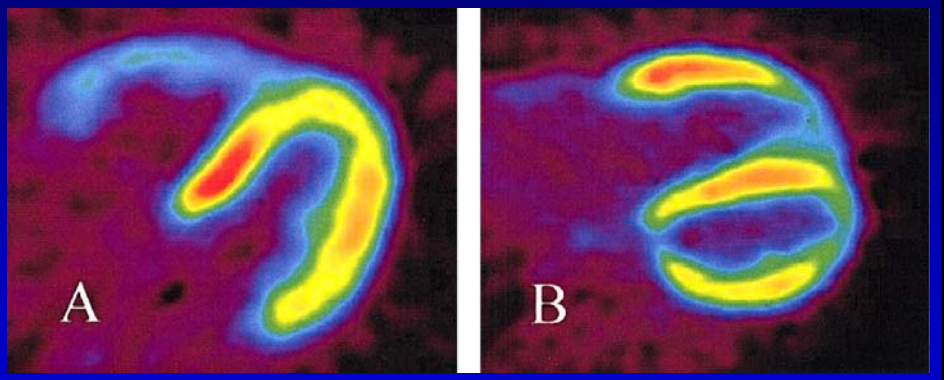
Coronary Driving Pressure Gradient and the Effect of Pulmonary Hypertension



Effects of pulmonary hypertension on RV myocardial perfusion

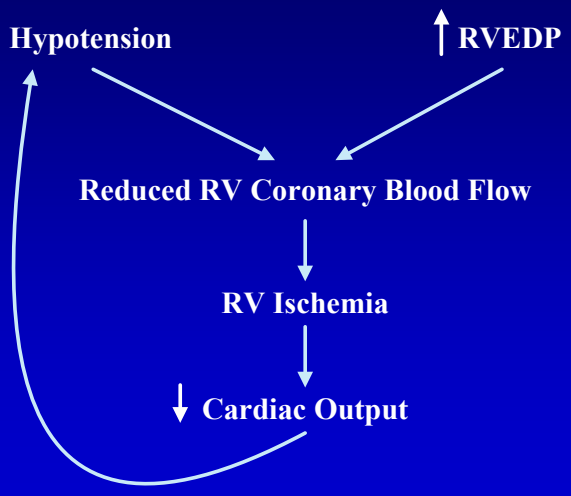
- Myocardial perfusion goes from being both systolic and diastolic to mostly diastolic.
- The RV hypertrophies, but coronary blood supply remains unchanged.
- RV work is dramatically increased without a compensatory increase in coronary blood flow.
- Tachycardia makes everything worse.

Fluorodeoxyglucose PET images of a patient with mild (A, mean pulmonary artery pressure, 33 mm Hg) and severe pulmonary hypertension (B, mean pulmonary artery pressure, 81 mm Hg)

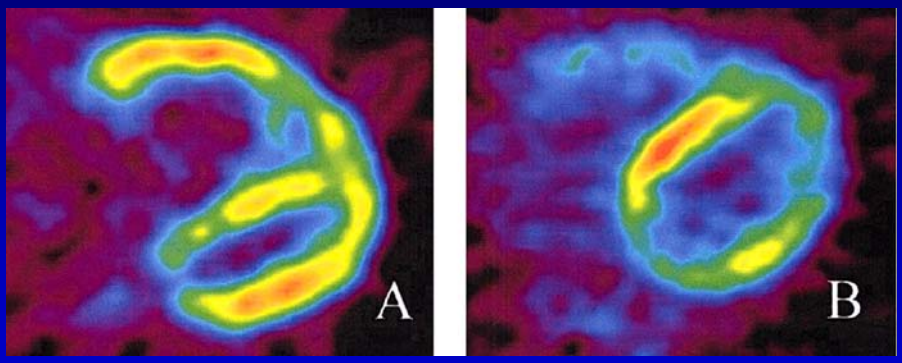


Oikawa, M. et al. J Am Coll Cardiol 2005;45:1849-1855

PH: Progressive Right Heart Failure



FDG PET images of a patient with pulmonary arterial hypertension before and after therapy



Oikawa, M. et al. J Am Coll Cardiol 2005;45:1849-1855

Pulmonary Arterial Hypertension: Clinical Manifestations - Symptoms

- Dyspnea on Exertion/Rest
- Fatigue
- Chest Discomfort/Pain
- Cough
- Syncope/Presyncope
- Cerebral Vascular Accidents
- Seizures
- Hemoptysis
- Poor Appetite
- Nausea/Vomiting
- Edema
- Hoarseness
- Gout
- Heart Failure

PAH: Clinical Manifestations

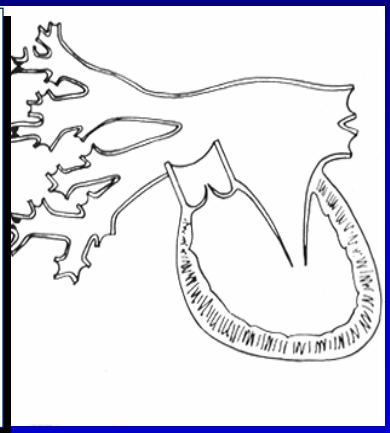
- Dyspnea
  - Reduced O2 diffusion
  - Ventilation-perfusion mismatching
  - R-L shunting
  - Low O2 transport
- Angina
  - RV ischemia
  - Left main coronary compression
- Syncope
  - Hypotension due to systemic vasodilation and fixed pulmonary resistance
  - Arrhythmia
- Edema, hepatic congestion, ascites
  - RV failure
  - Tricuspid regurgitation

PAH: Findings on Physical Examination

- Tachypnea, cough, wheezing
- Jugular venous distention
- Right ventricular heave
- Right-sided fourth heart sound
- Loud pulmonic valve closure (P_2)
- Tricuspid regurgitation murmur
- Pulmonary insufficiency murmur
- Hepatomegaly (pulsatile)
- Peripheral edema, ascites, pleural effusions
- Decreased peripheral perfusion
- Cyanosis

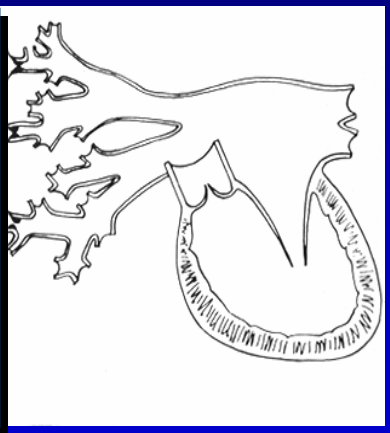
Pulmonary Venous PH: Symptoms

- 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
- Initial respiratory alkalosis, then combined acidosis (lactic acidosis)
- Central and peripheral cyanosis
- Specific signs Re: Left Heart or Venous Etiology
- Signs of PAH



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)

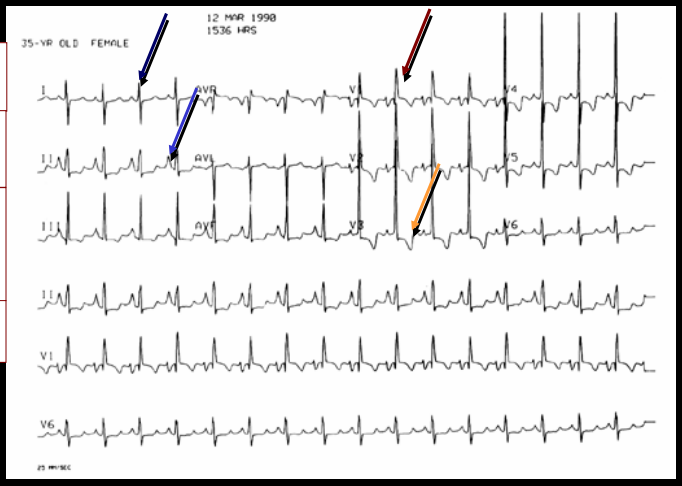
PAH: Screening - ECG

RAD

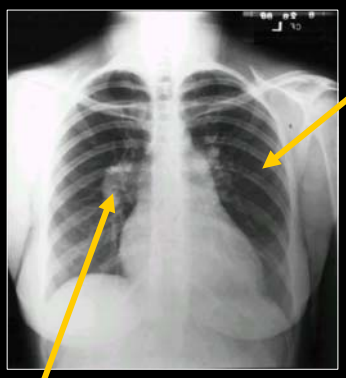
RVH

RV strain

RAE

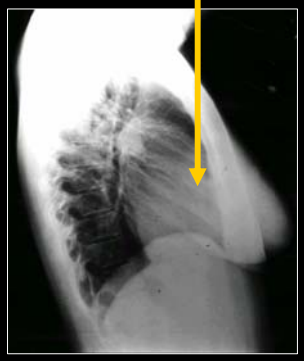


PAH: Screening - CXR



Peripheral "Pruning"

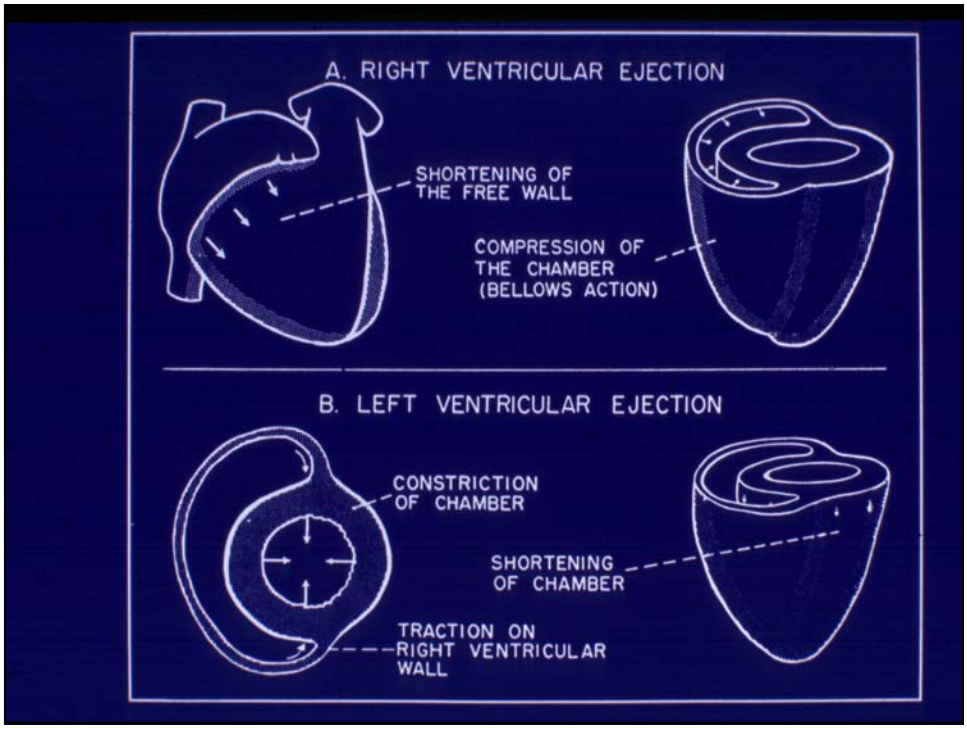
RV Enlargement

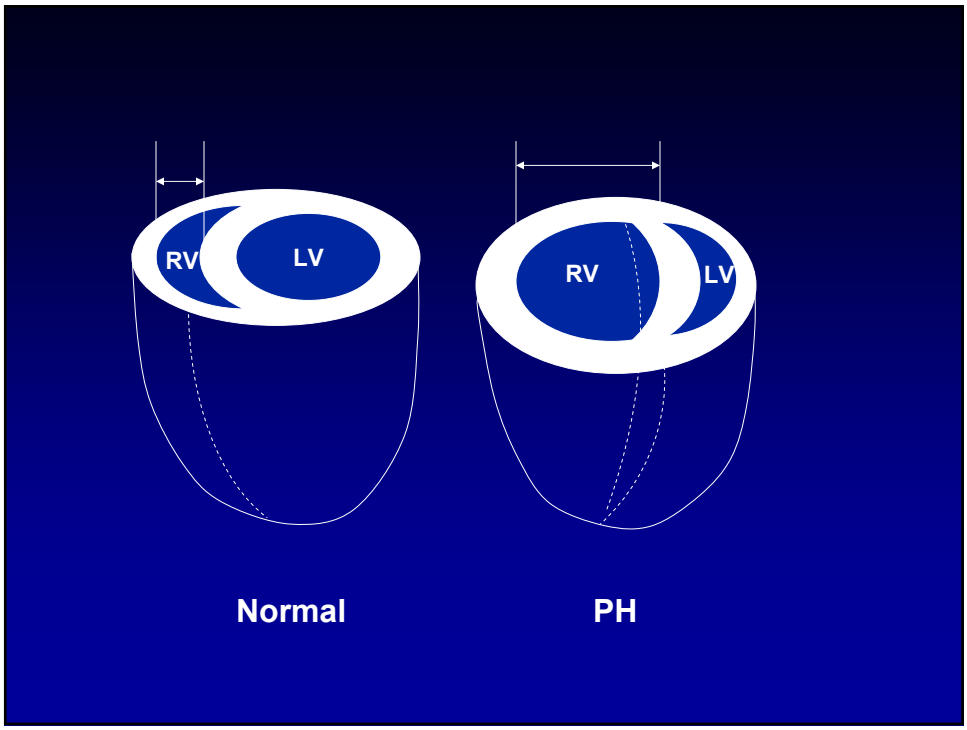


Prominent Hilar Pulmonary Arteries

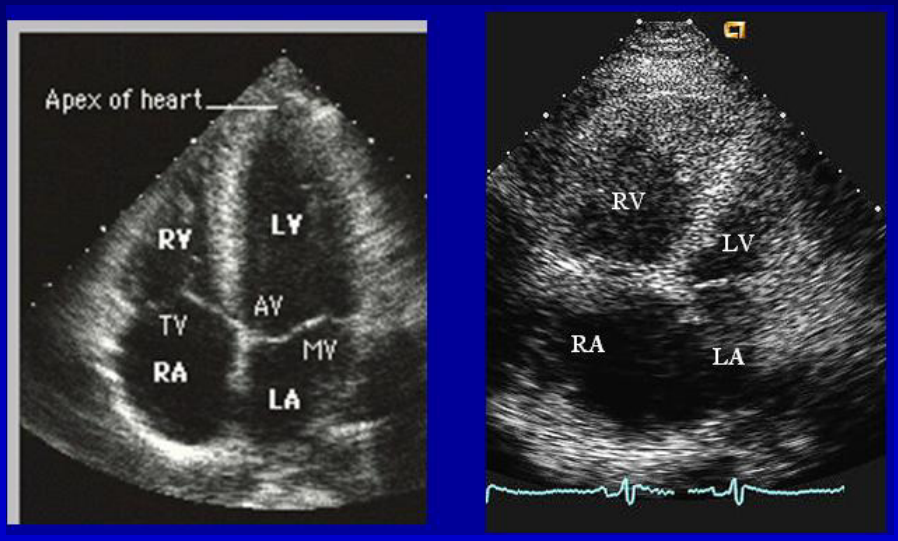
PAH: Findings on the Echocardiogram

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

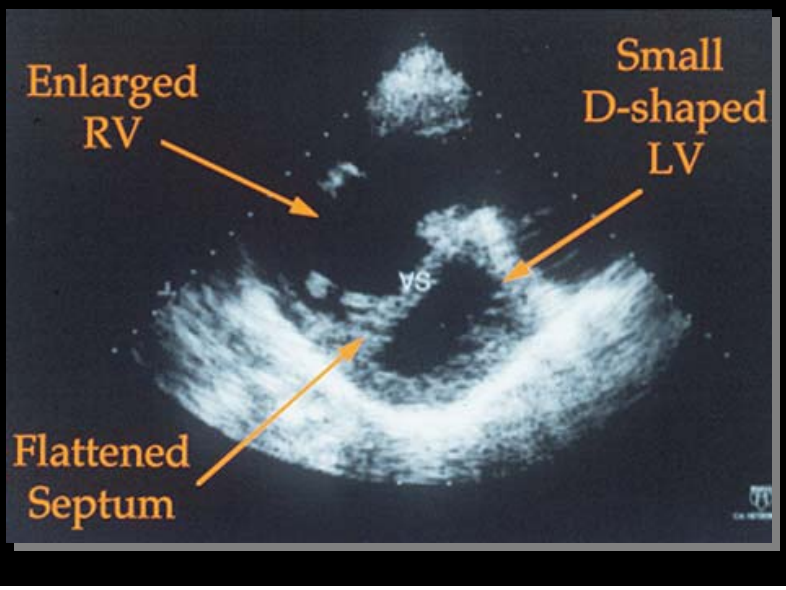

A. RIGHT VENTRICULAR EJECTION
SHORTENING OF THE FREE WALL
COMPRESSION OF THE CHAMBER (BELLOWS ACTION)
B. LEFT VENTRICULAR EJECTION
CONSTRICTION OF CHAMBER
SHORTENING OF CHAMBER
TRACTION ON RIGHT VENTRICULAR WALL


RV
LV
RV
LV
Normal
PH

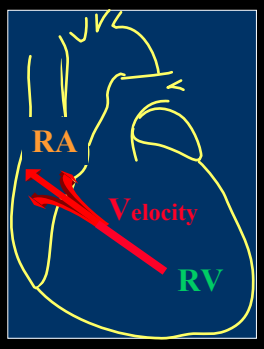
PAH: RV, RA Enlargement on Echocardiogram



PAH: Echocardiogram

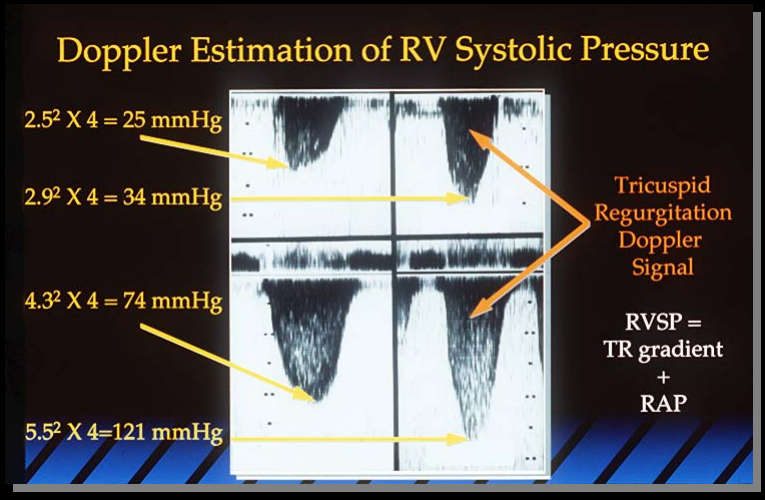


Echocardiogram

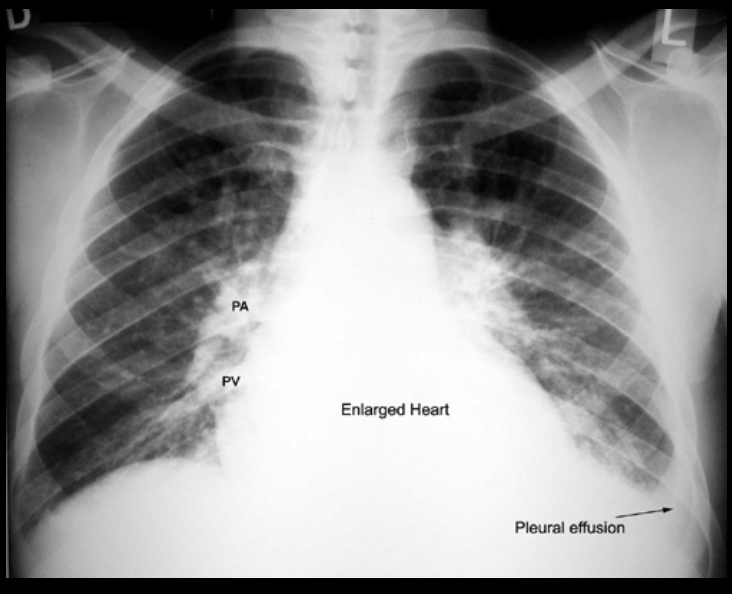


- $4V^2$ = Pressure Gradient (Δ P) (Modified Bernoulli Equation)
- RVSP - RAP = Δ P
- RVSP = RAP + Δ P

Echocardiogram



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 systemic to pulmonary shunt lesion (ASD, VSD, PDA, etc)

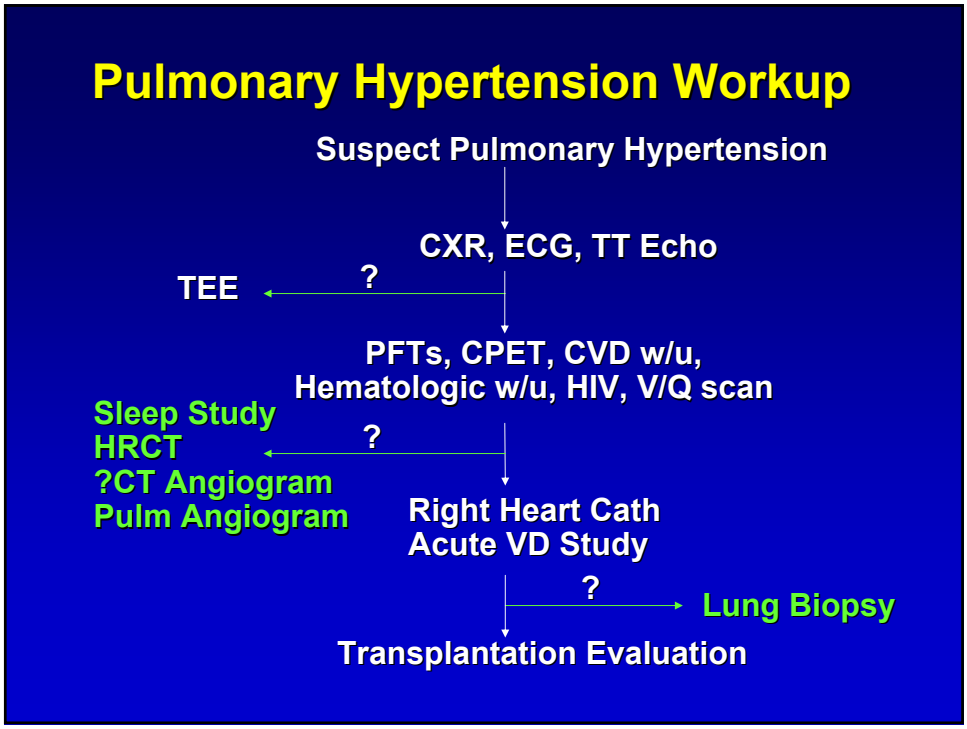
Cardiac Catheterization

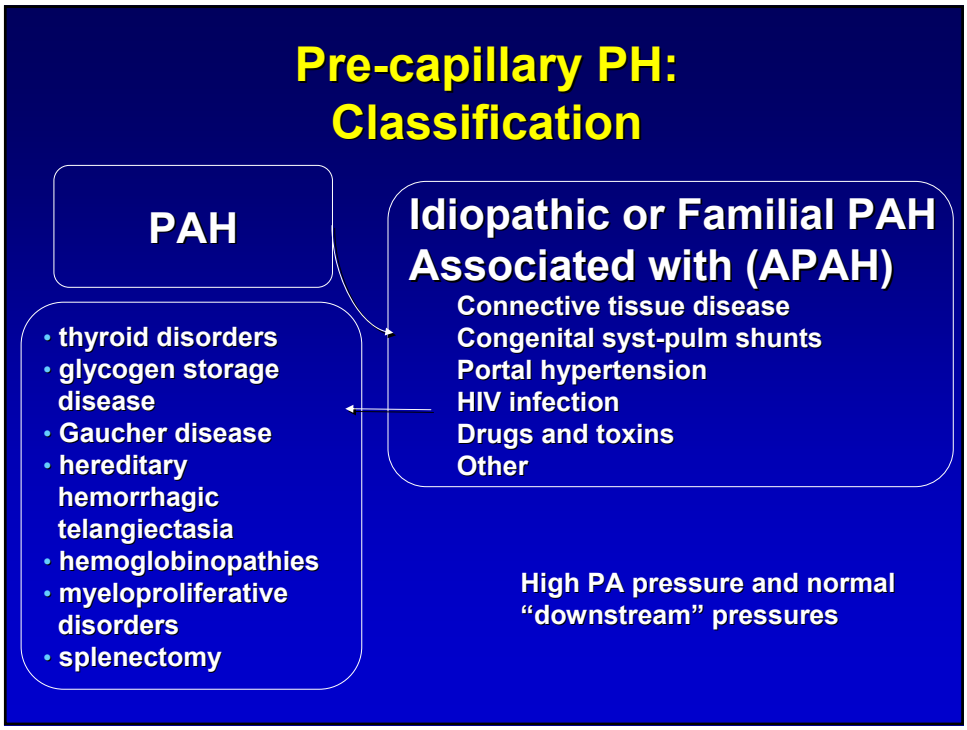
- To exclude congenital heart disease
- To measure wedge pressure or LVEDP
- To establish severity and prognosis
- Acute vasodilator drug testing

Cardiac catheterization should be performed in patients with suspected pulmonary hypertension

Diagnosis of Pulmonary Hypertension

- High index of suspicion
- Thorough and complete evaluation


Pulmonary Hypertension Workup
Suspect Pulmonary Hypertension
CXR, ECG, TT Echo
?
TEE
PFTs, CPET, CVD w/u,
Hematologic w/u, HIV, V/Q scan
Sleep Study
HRCT
?CT Angiogram
Pulm Angiogram
?
Right Heart Cath
Acute VD Study
?
Lung Biopsy
Transplantation Evaluation


Pre-capillary PH:
Classification
PAH
Idiopathic or Familial PAH
Associated with (APAH)
Connective tissue disease
Congenital syst-pulm shunts
Portal hypertension
HIV infection
Drugs and toxins
Other
• thyroid disorders
• glycogen storage disease
• Gaucher disease
• hereditary hemorrhagic telangiectasia
• hemoglobinopathies
• myeloproliferative disorders
• splenectomy
High PA pressure and normal
“downstream” pressures

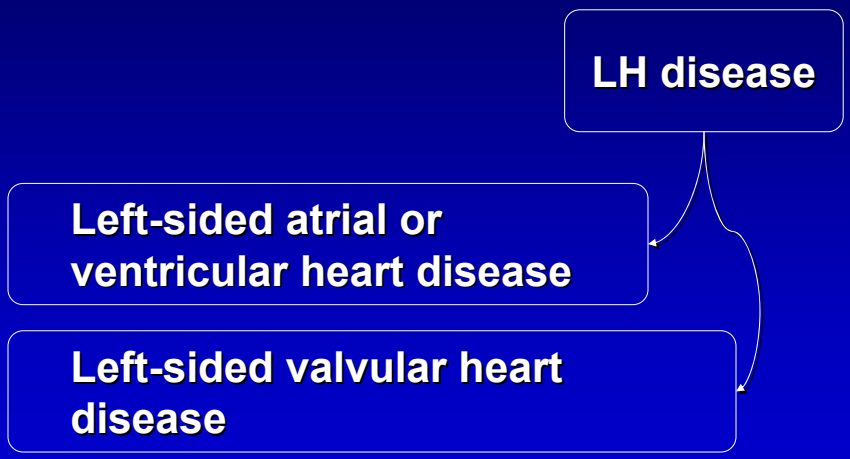
Treatment: Pre-capillary PH - Pulmonary Arterial Hypertension

- Early surgery to repair congenital systemic to pulmonary shunts, e.g. VSD, PDA

However, if no longer "operable" due to progressive pulmonary vascular obstructive disease

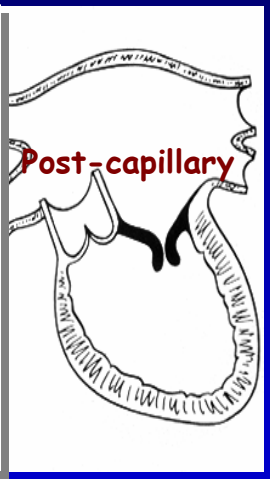
- Anticoagulation
- Vasodilator/Antiproliferative Therapy
- Lung or Heart-Lung Transplantation

Post-capillary PH: Classification



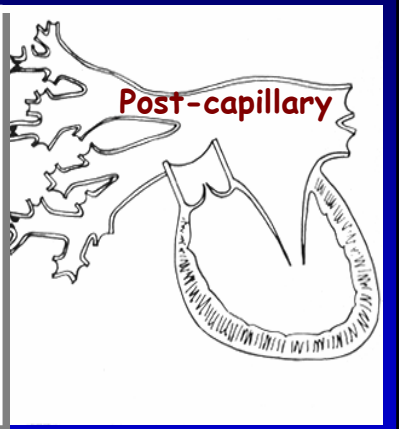
Post-capillary PH : Localizing the Problem

- 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 : Localizing the Problem

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



Treatment: Post-capillary PH - Pulmonary Venous Hypertension

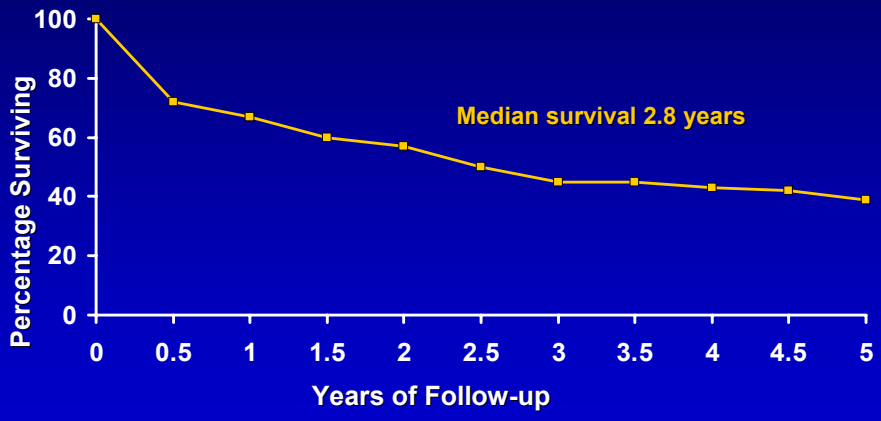
- Surgery to eliminate obstruction
- Heart transplantation for left ventricular failure
- Treatment - Medical and/or Interventional
  - Specific Re: Left Heart or Venous Etiology
  - PAH treatment

Why Diagnose Pulmonary Arterial Hypertension?

Why Treat Pulmonary Arterial Hypertension?

Why Treat Pulmonary Arterial Hypertension?

Idiopathic PAH: PPH NIH Registry Data



NIH = National Institutes of Health

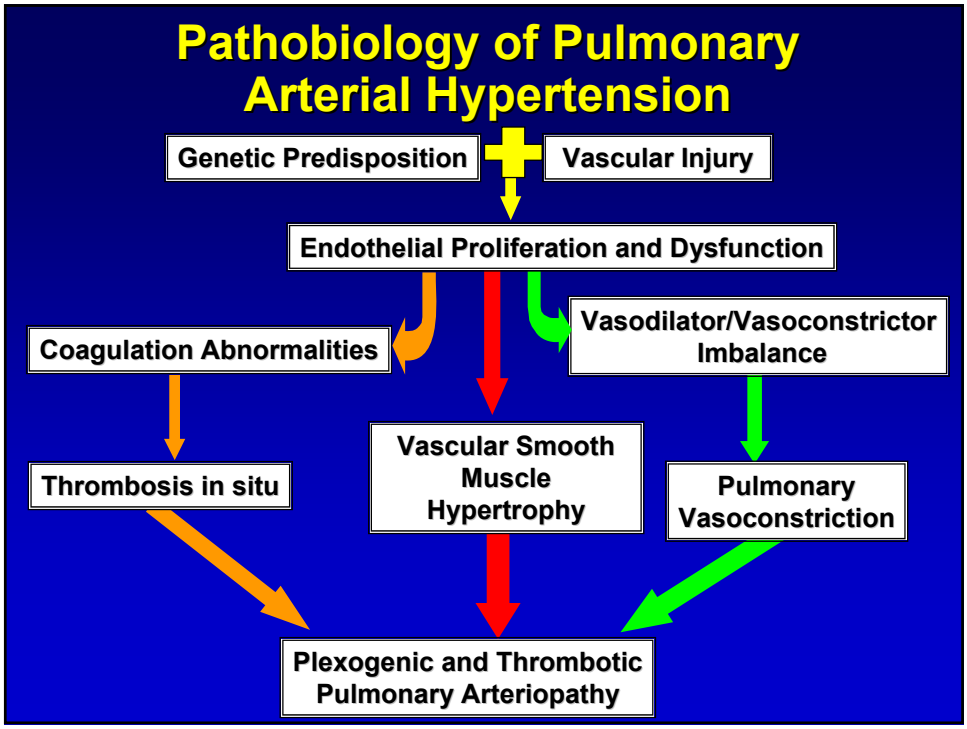
D'Alonzo et al. Ann Int Med 1991

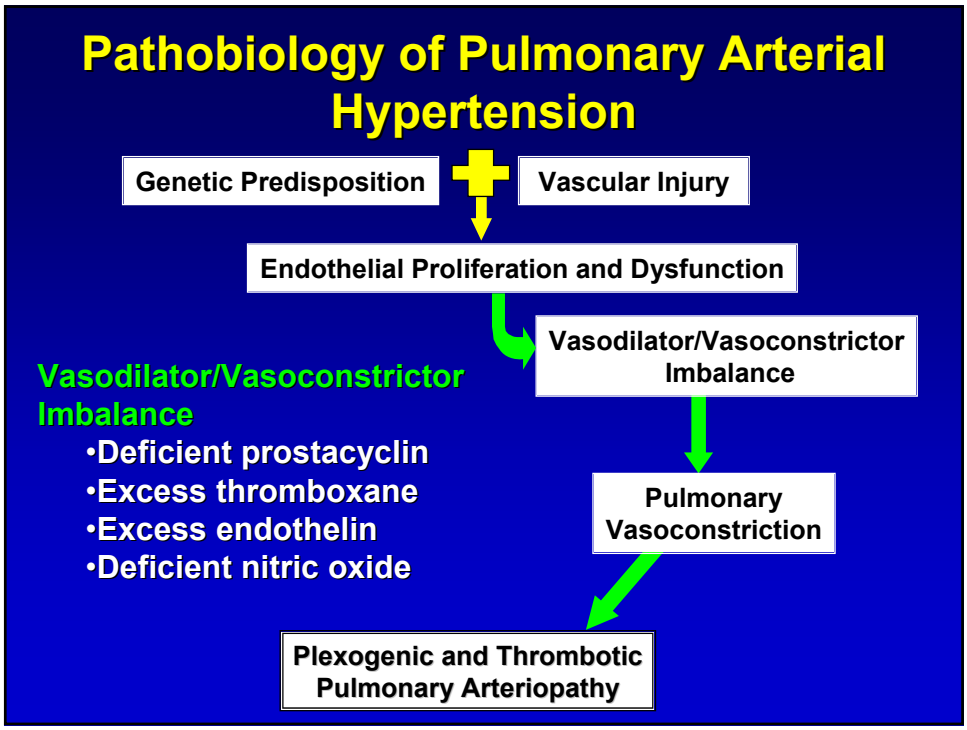
Pathobiology of Pulmonary Arterial Hypertension

Genetic Predisposition + **Vascular Injury**

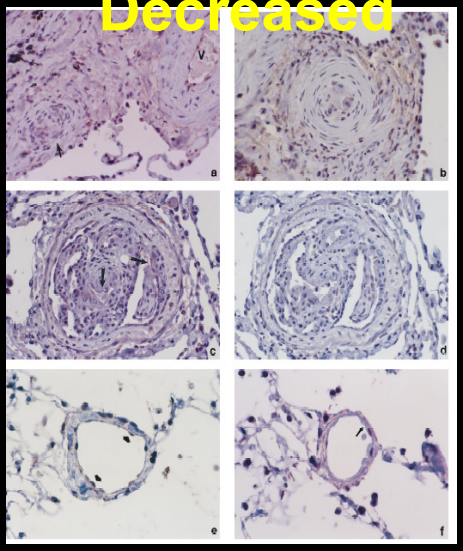
- ~15% prevalence of positive family history
  - Autosomal dominant
- Co-ancestry in sporadic cases
- PPH1 locus on chromosome 2q31-q32
- BMPR2 mutations

- Appetite suppressants
- Other exogenous toxins
- Hepatic toxins
- HIV
- Autoimmune Dysfunction
- Shear Stress


Pathobiology of Pulmonary Arterial Hypertension
Genetic Predisposition
Vascular Injury
Endothelial Proliferation and Dysfunction
Coagulation Abnormalities
Vasodilator/Vasoconstrictor Imbalance
Thrombosis in situ
Vascular Smooth Muscle Hypertrophy
Pulmonary Vasoconstriction
Plexogenic and Thrombotic Pulmonary Arteriopathy

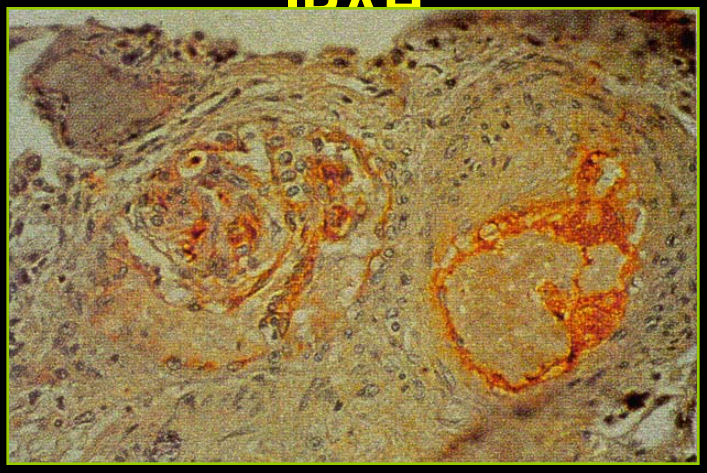

Pathobiology of Pulmonary Arterial Hypertension
Genetic Predisposition
Vascular Injury
Endothelial Proliferation and Dysfunction
Vasodilator/Vasoconstrictor Imbalance
Vasodilator/Vasoconstrictor Imbalance
•Deficient prostacyclin
•Excess thromboxane
•Excess endothelin
•Deficient nitric oxide
Pulmonary Vasoconstriction
Plexogenic and Thrombotic Pulmonary Arteriopathy

In IPAH, Prostacyclin Synthase Expression in the Lung is Decreased



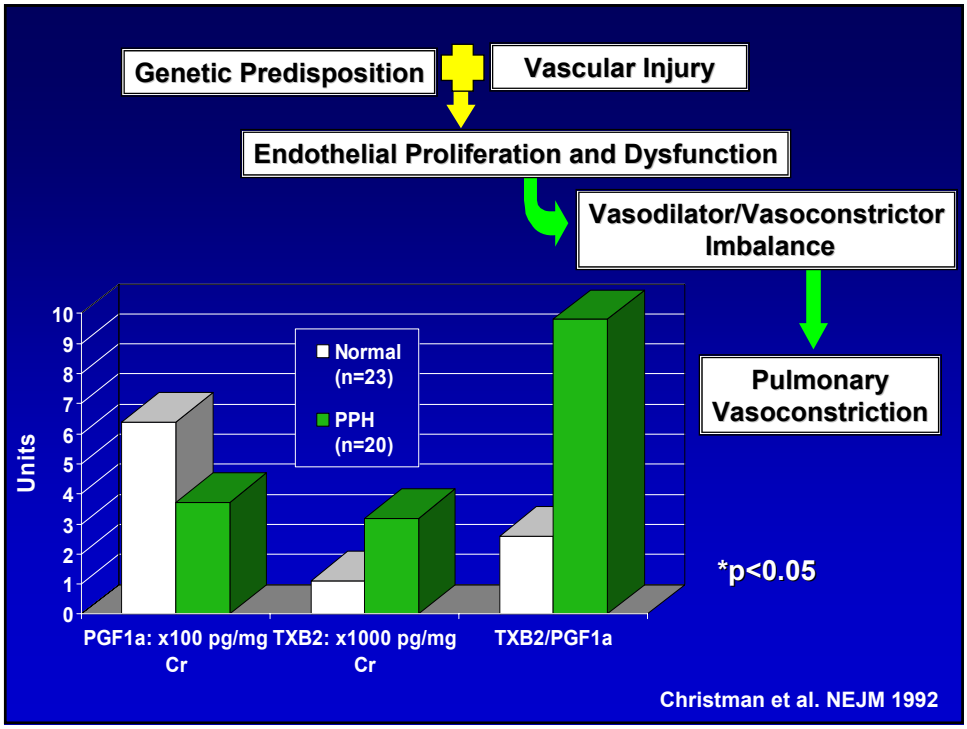
Tuder et al. AJRCCM 1999

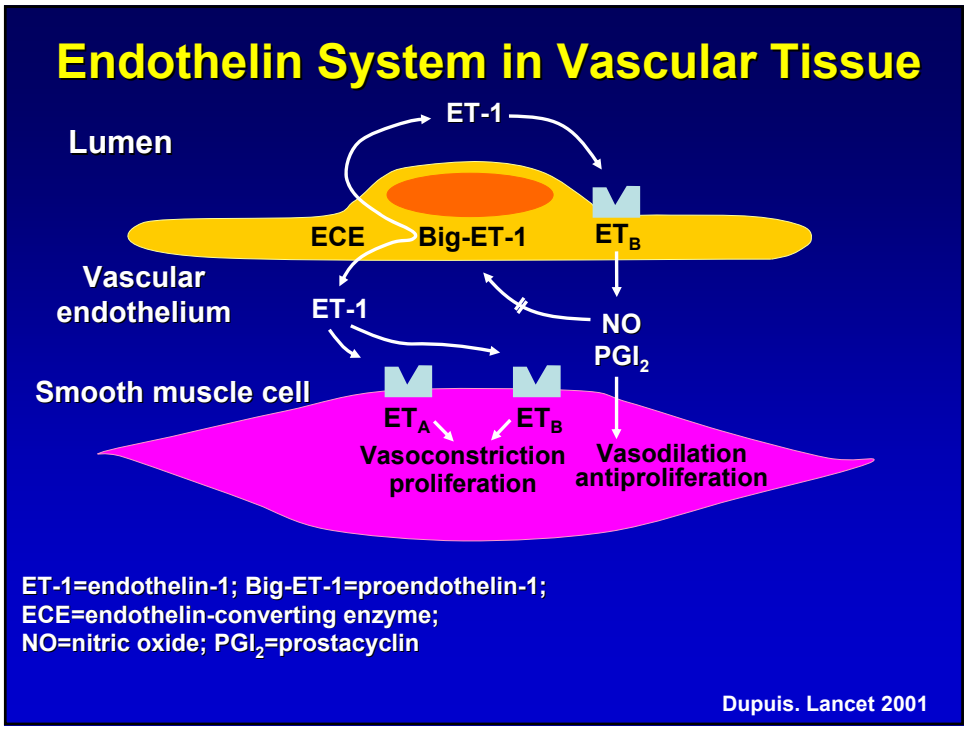
Expression of Endothelin in the Lungs of Patients with IPAH

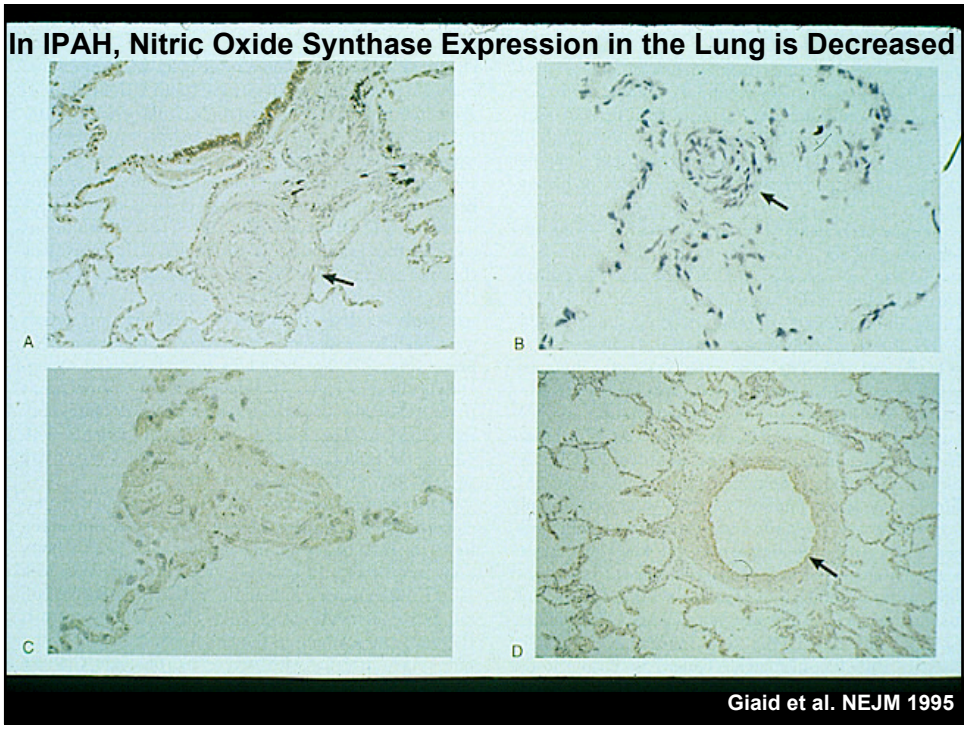


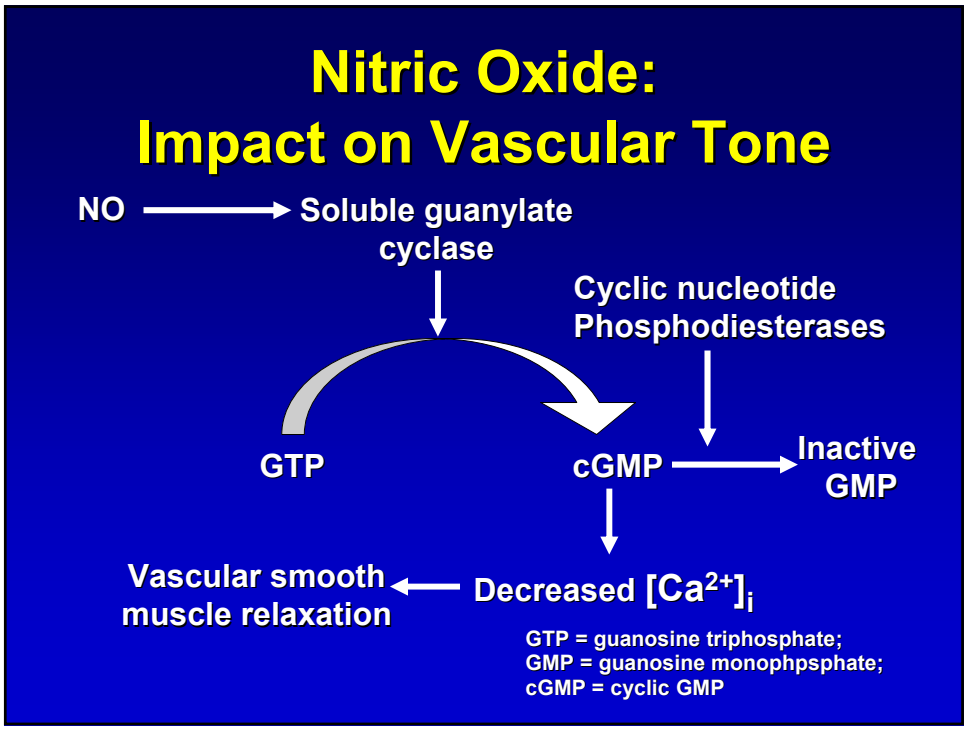
Plexiform Lesions in IPAH

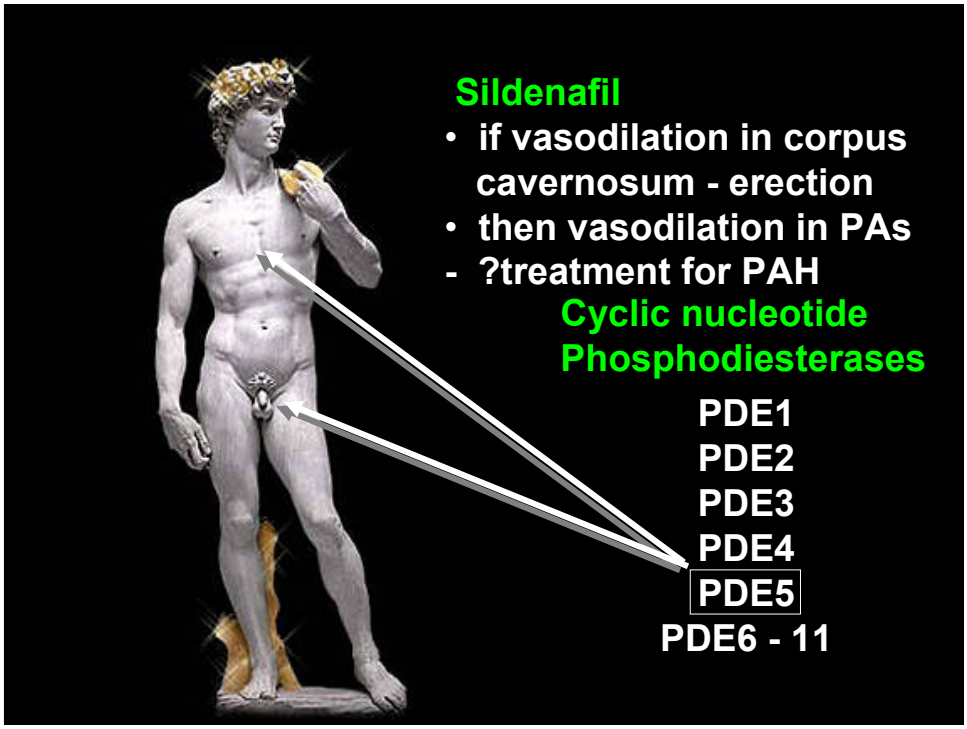
Giaid A et al. NEJM 1993

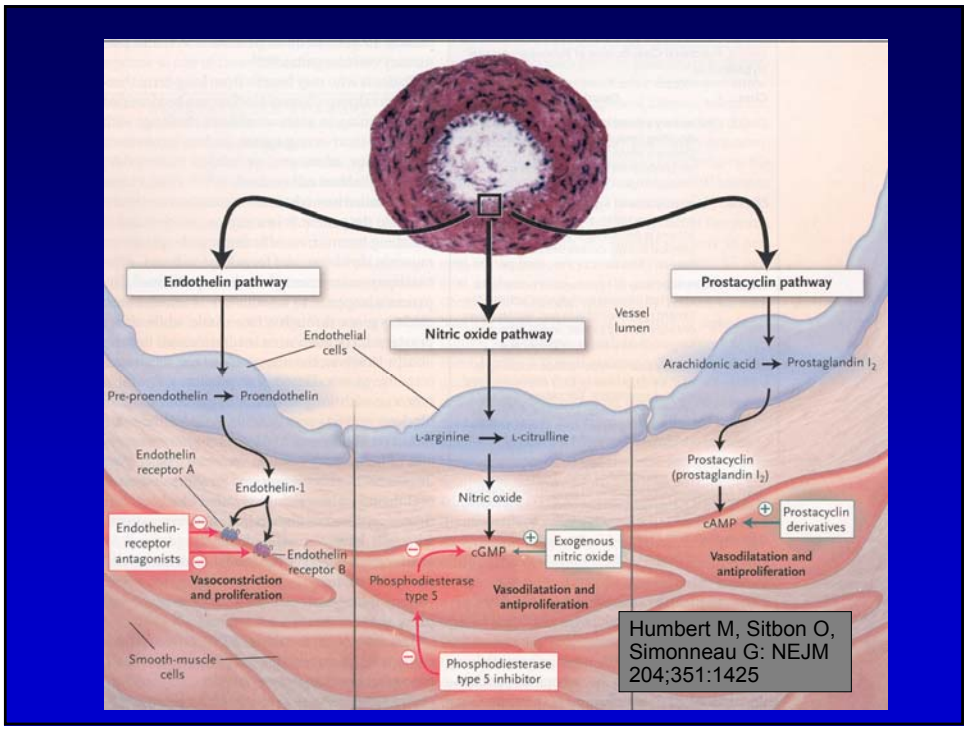

Genetic Predisposition
Vascular Injury
Endothelial Proliferation and Dysfunction
Vasodilator/Vasoconstrictor Imbalance
Pulmonary Vasoconstriction
Units
10
9
8
7
6
5
4
3
2
1
0
Normal (n=23)
PPH (n=20)
PGF1a: x100 pg/mg Cr
TXB2: x1000 pg/mg Cr
TXB2/PGF1a
*p<0.05
Christman et al. NEJM 1992


Endothelin System in Vascular Tissue
Lumen
ET-1
ECE
Big-ET-1
ET$_B$
Vascular endothelium
ET-1
NO
PGI$_2$
Smooth muscle cell
ET$_A$
ET$_B$
Vasoconstriction proliferation
Vasodilation antiproliferation
ET-1=endothelin-1; Big-ET-1=proendothelin-1;
ECE=endothelin-converting enzyme;
NO=nitric oxide; PGI$_2$=prostacyclin
Dupuis. Lancet 2001

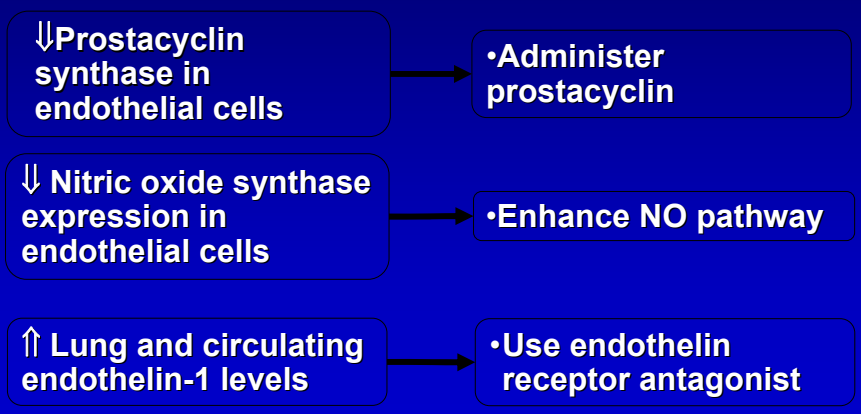

In IPAH, Nitric Oxide Synthase Expression in the Lung is Decreased
A
B
C
D
Giaid et al. NEJM 1995


Nitric Oxide:
Impact on Vascular Tone
NO
Soluble guanylate cyclase
Cyclic nucleotide Phosphodiesterases
GTP
cGMP
Inactive GMP
Vascular smooth muscle relaxation
Decreased [Ca2+]i
GTP = guanosine triphosphate;
GMP = guanosine monophpsphate;
cGMP = cyclic GMP


Sildenafil
• if vasodilation in corpus cavernosum - erection
• then vasodilation in PAs
- ?treatment for PAH
Cyclic nucleotide Phosphodiesterases
PDE1
PDE2
PDE3
PDE4
PDE5
PDE6 - 11


Endothelin pathway
Nitric oxide pathway
Prostacyclin pathway
Vessel lumen
Endothelial cells
Arachidonic acid
Prostaglandin I2
Pre-proendothelin
Proendothelin
L-arginine
L-citrulline
Endothelin receptor A
Endothelin-1
Nitric oxide
Prostacyclin (prostaglandin I2)
Endothelin-receptor antagonists
Endothelin receptor B
cGMP
Exogenous nitric oxide
cAMP
Prostacyclin derivatives
Vasoconstriction and proliferation
Phosphodiesterase type 5
Vasodilatation and antiproliferation
Vasodilatation and antiproliferation
Smooth-muscle cells
Phosphodiesterase type 5 inhibitor
Humbert M, Sitbon O, Simonneau G: NEJM 204;351:1425

Mechanisms Behind Current Therapeutic Options



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*