Pulmonary Arterial Hypertension and Scleroderma Treatment Options

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UC Health
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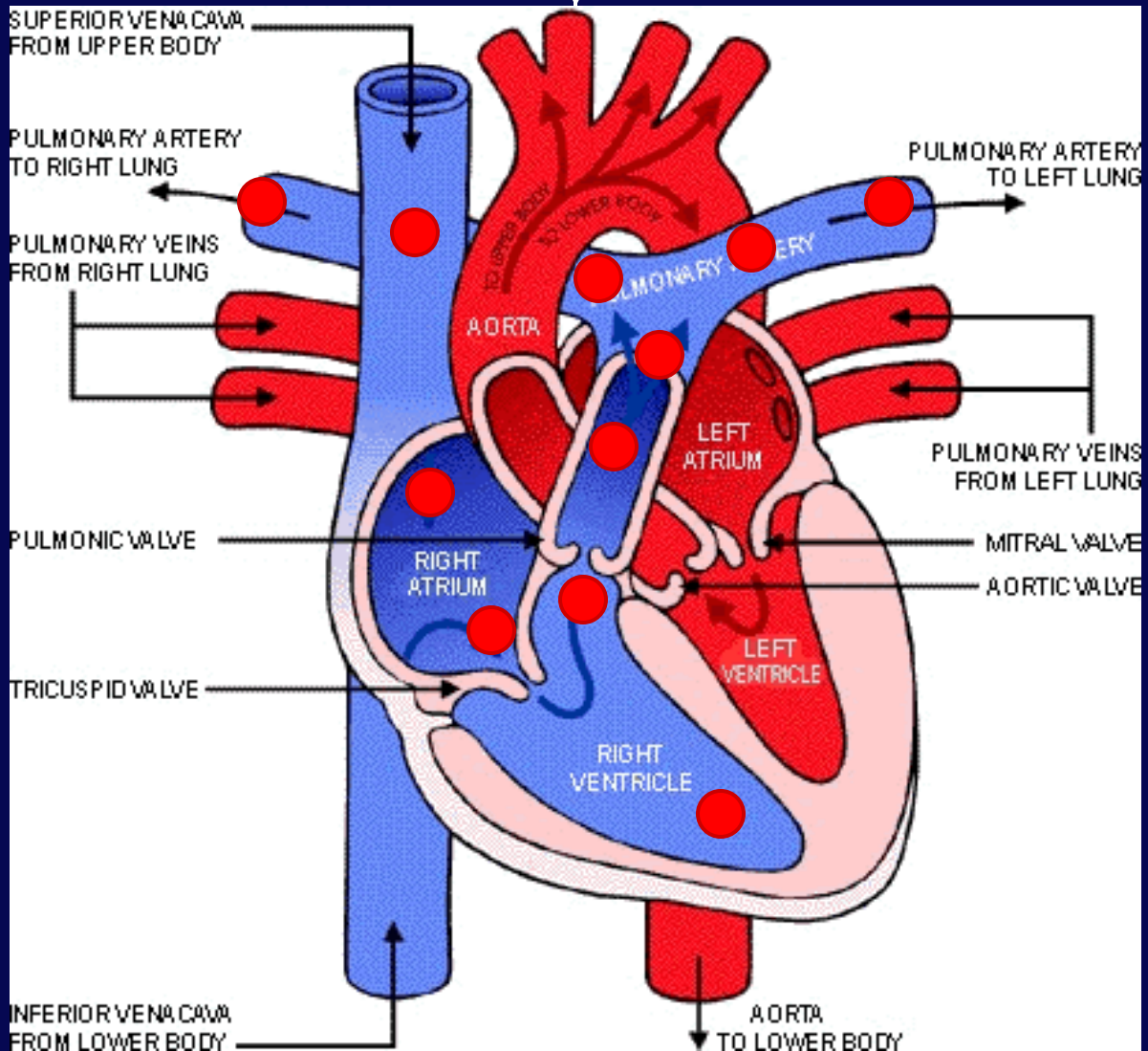
Is this a familiar feeling?

Normal Heart and Blood Vessels

4 Chambers

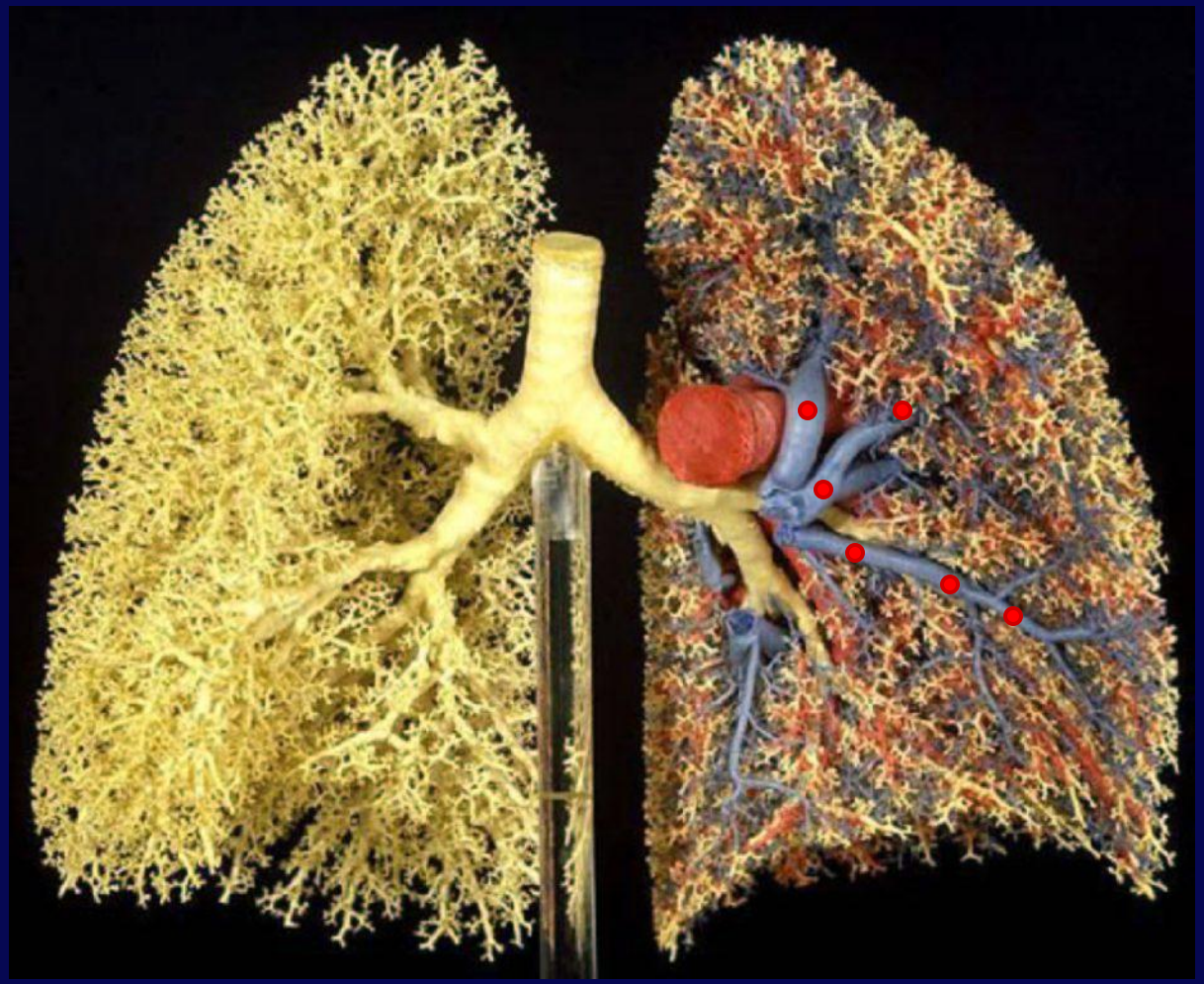
Right
Left

Atrium (top)
Ventricle (bottom)



Normal Airways and Blood Vessels

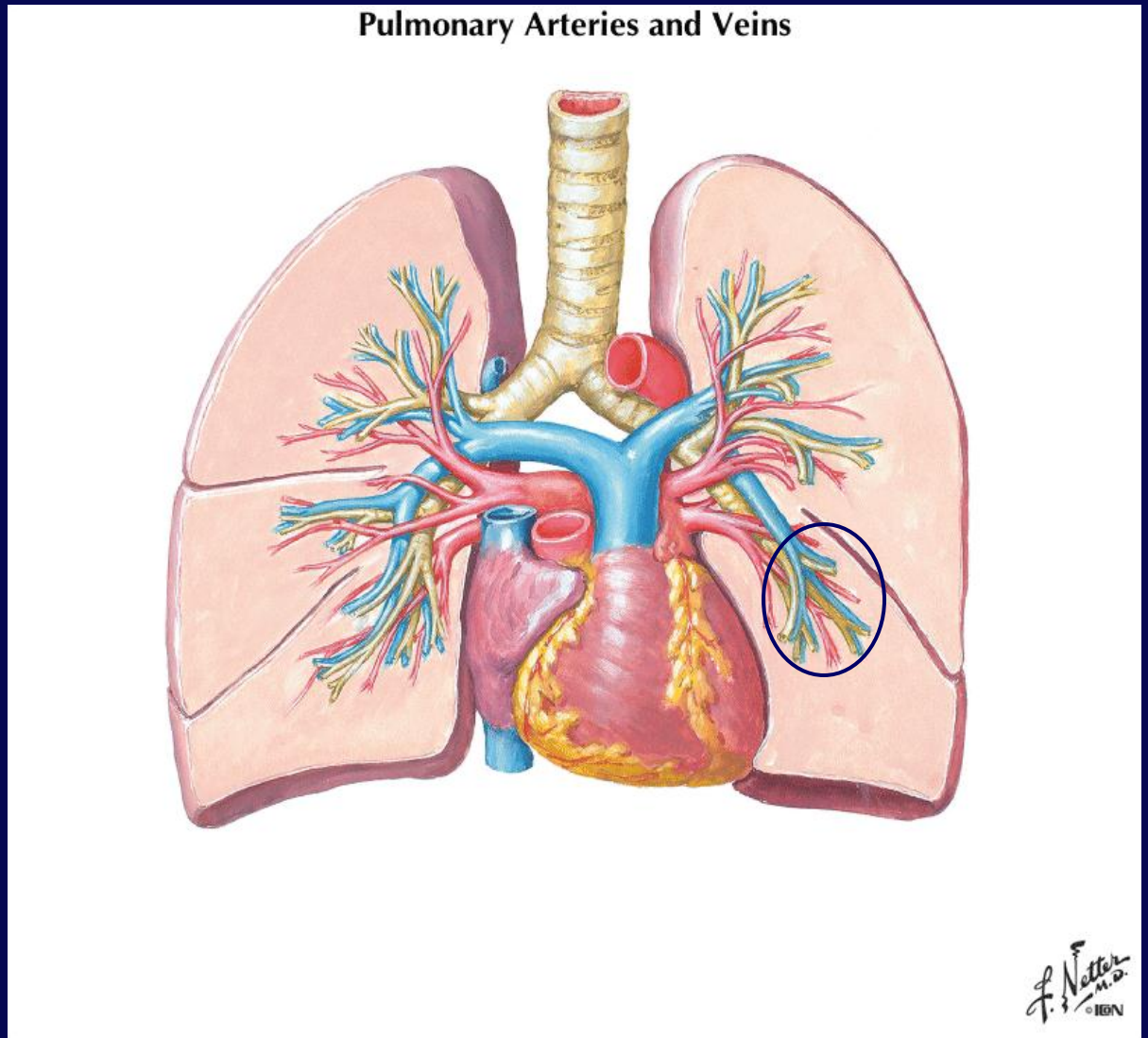
Airways



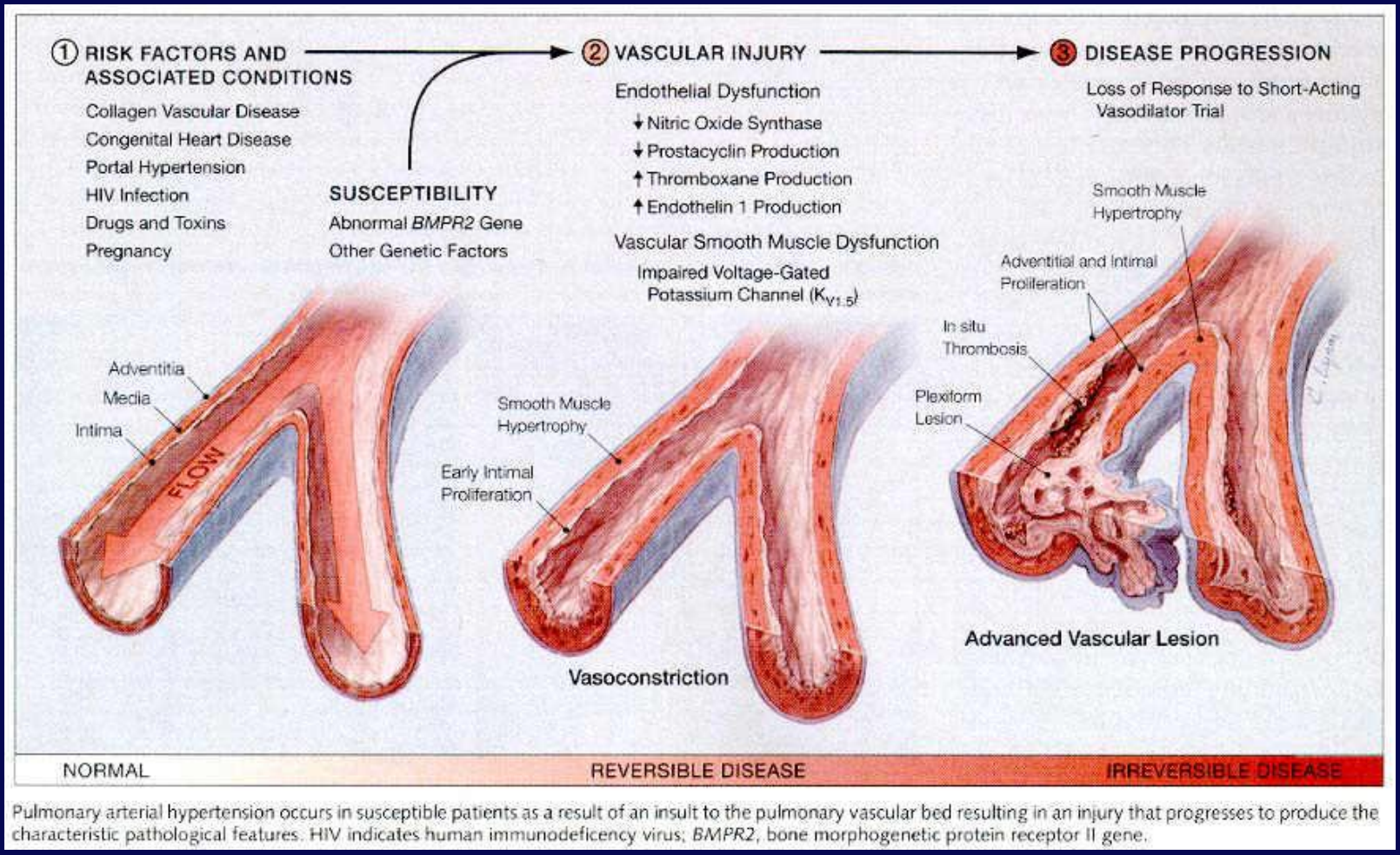
Airways

Vessels

Pulmonary Arteries and Veins



Lung Blood Vessels in Pulmonary Hypertension

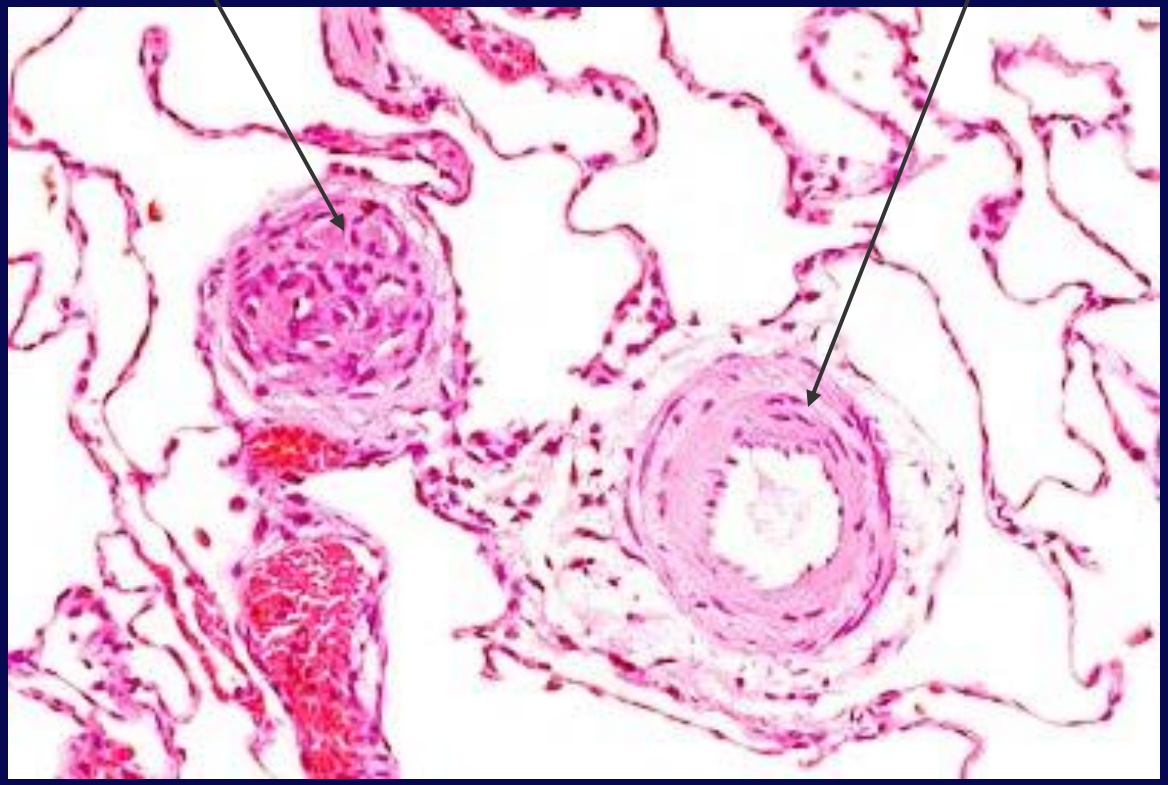


Pulmonary arterial hypertension occurs in susceptible patients as a result of an insult to the pulmonary vascular bed resulting in an injury that progresses to produce the characteristic pathological features. HIV indicates human immunodeficency virus; *BMPR2*, bone morphogenetic protein receptor II gene.

Lung Blood Vessels in Pulmonary Hypertension

Plexiform Lesion

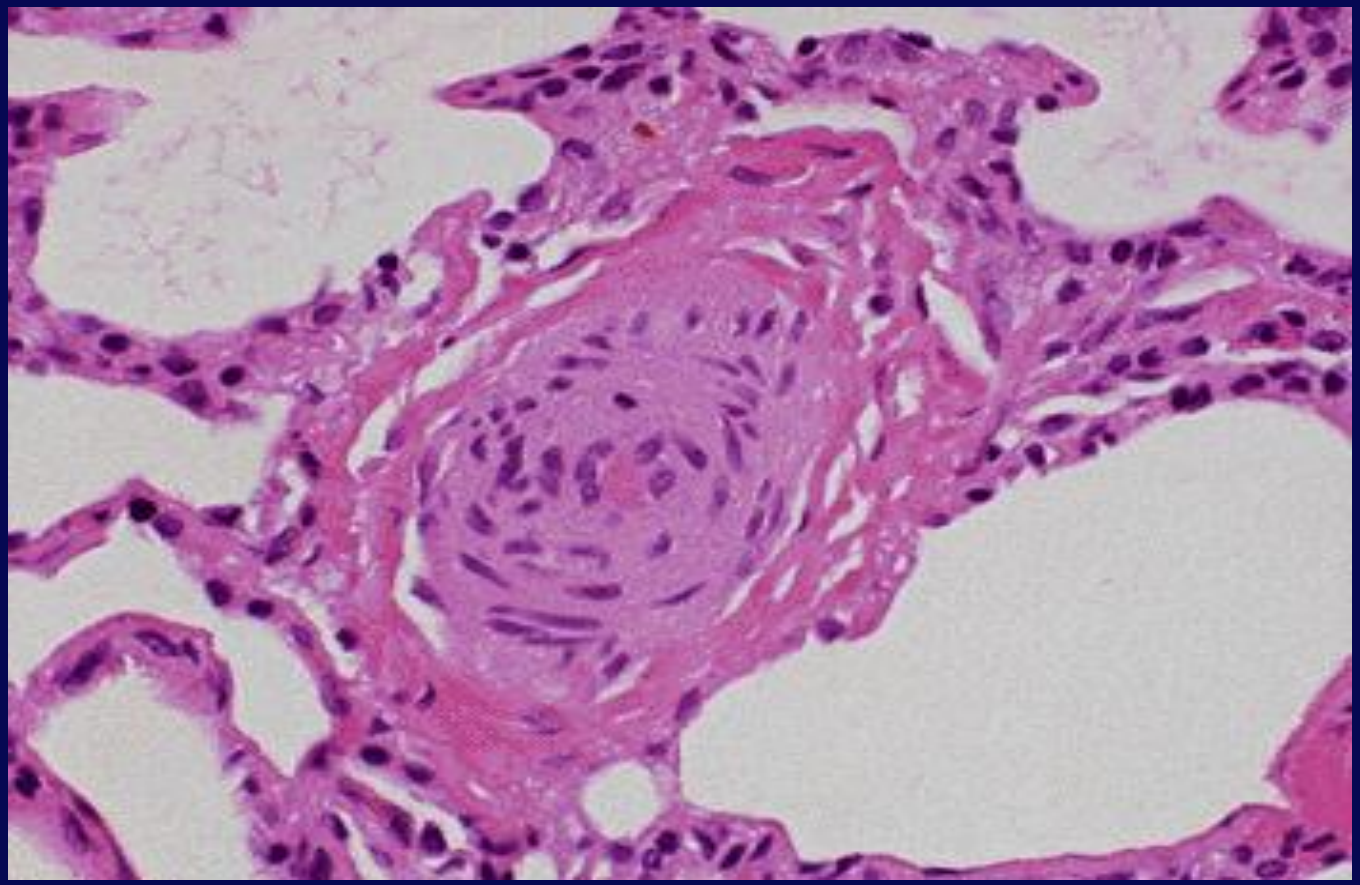
Thickening of the Wall



Small pulmonary arteries

http://pathhsw5m54.ucsf.edu/image63.html

Lung Blood Vessels in Pulmonary Hypertension



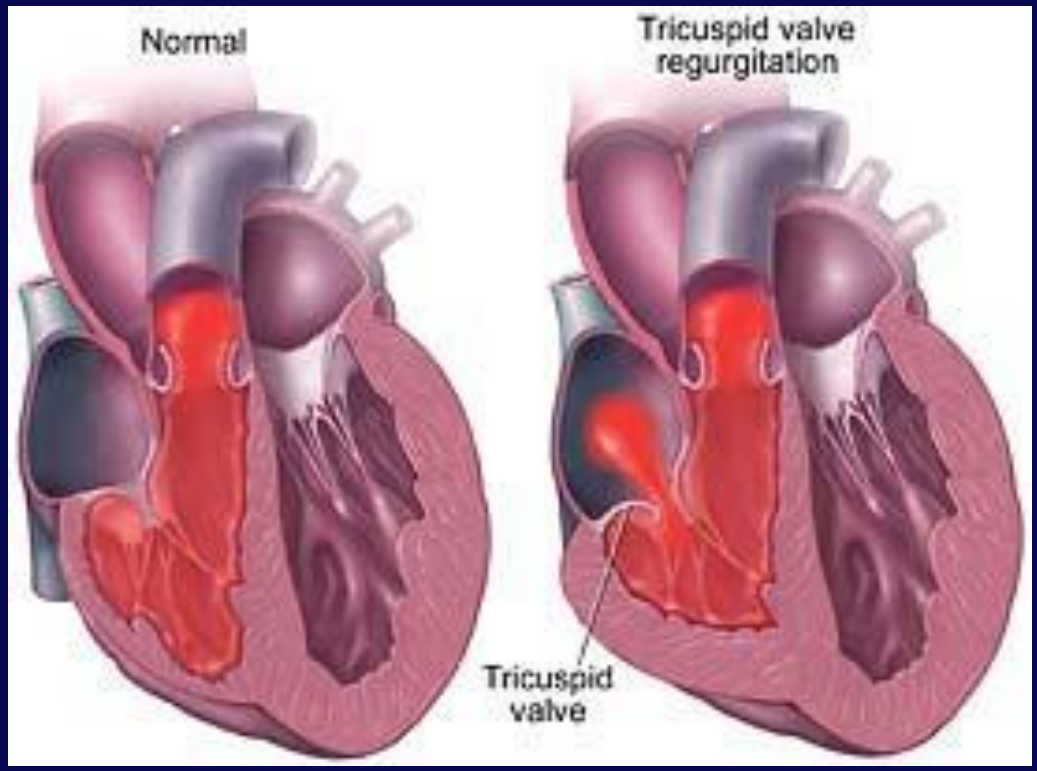
Symptoms

- Other symptoms
  - Fatigue
  - Chest pain or discomfort
  - Palpitations
  - Dizziness and light-headedness
  - Nearly fainting
  - Fainting

Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med 1987;107:216–223.

Physical Exam

- Clinical signs
  - Loud P2
  - Tricuspid regurgitation murmur
  - Right ventricular heave
  - Jugular venous distention
  - Signs of right heart failure

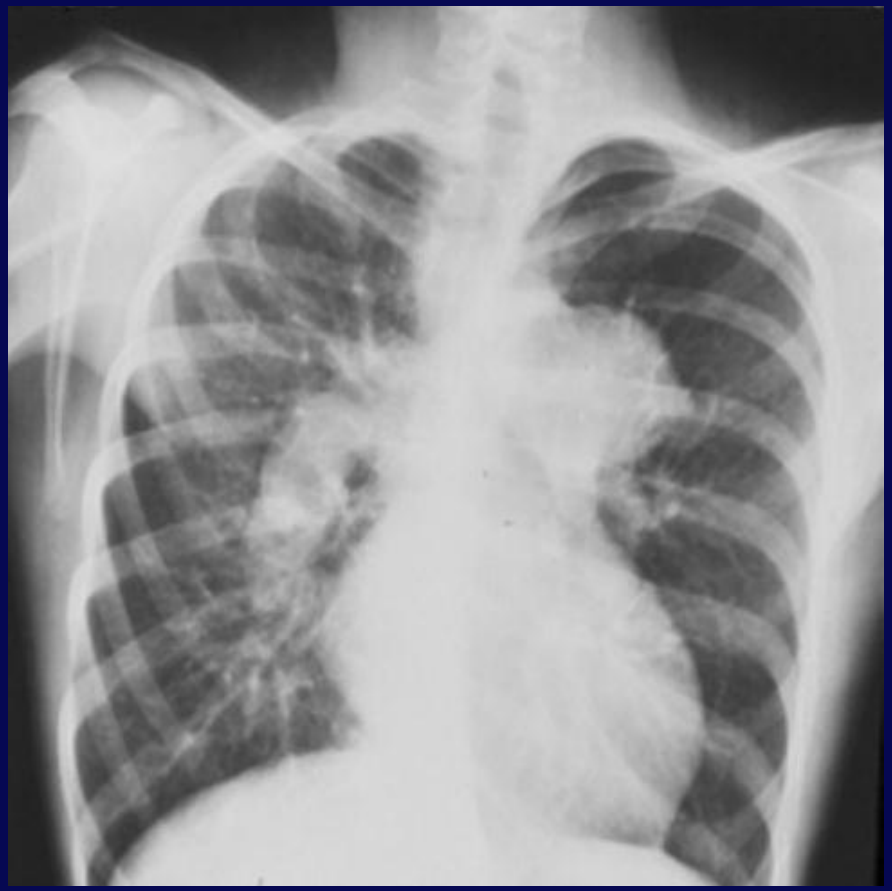


Testing

- Noninvasive Testing
  - Electrocardiogram (EKG)
  - Chest Radiograph (CXR)
  - Transthoracic Echocardiogram (TTE)
  - Possible future use of MRI
- Confirmatory Testing for PH
  - Right Heart Catheterization (RHC)

Chest radiograph (CXR)

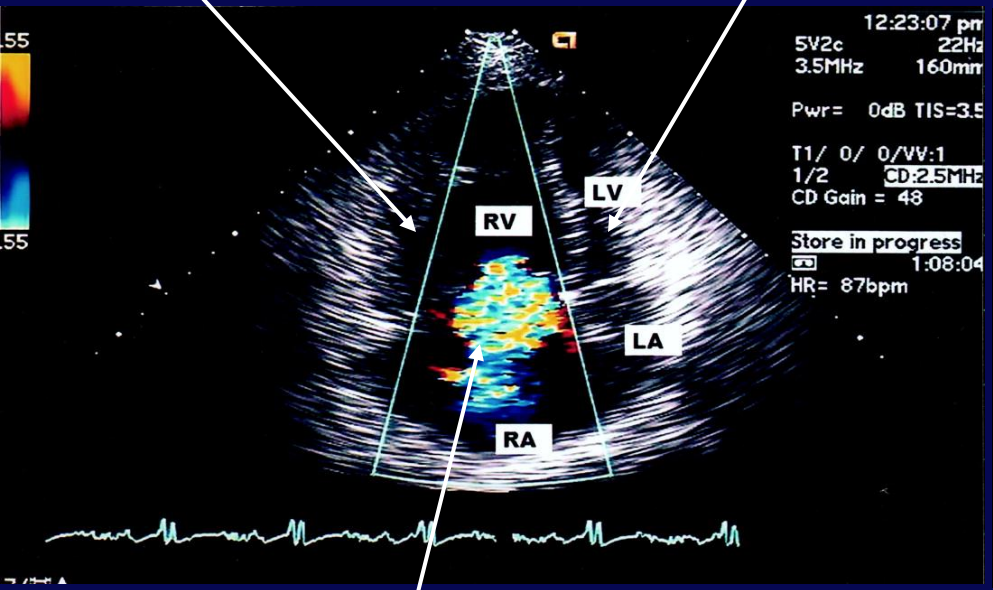
- Dilated central pulmonary arteries
- Attenuation of distal arteries
- Dilated right atrium and ventricle



Echocardiogram

Right sided chambers enlarged

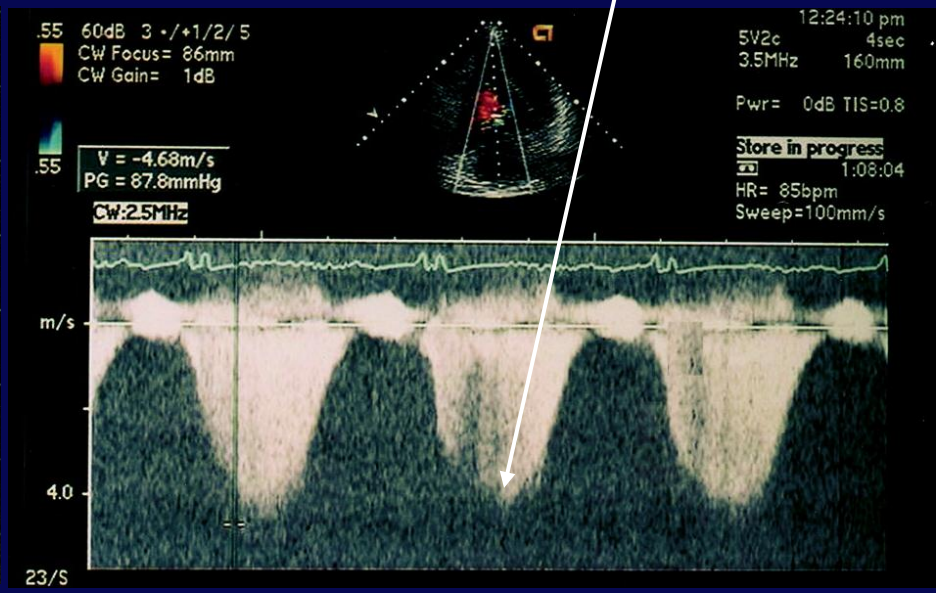
Left sided chambers compressed



Peak TR velocity of 4.68 m/s

$RVSP = RAP + 4v^2$

RVSP = 98 mmHg

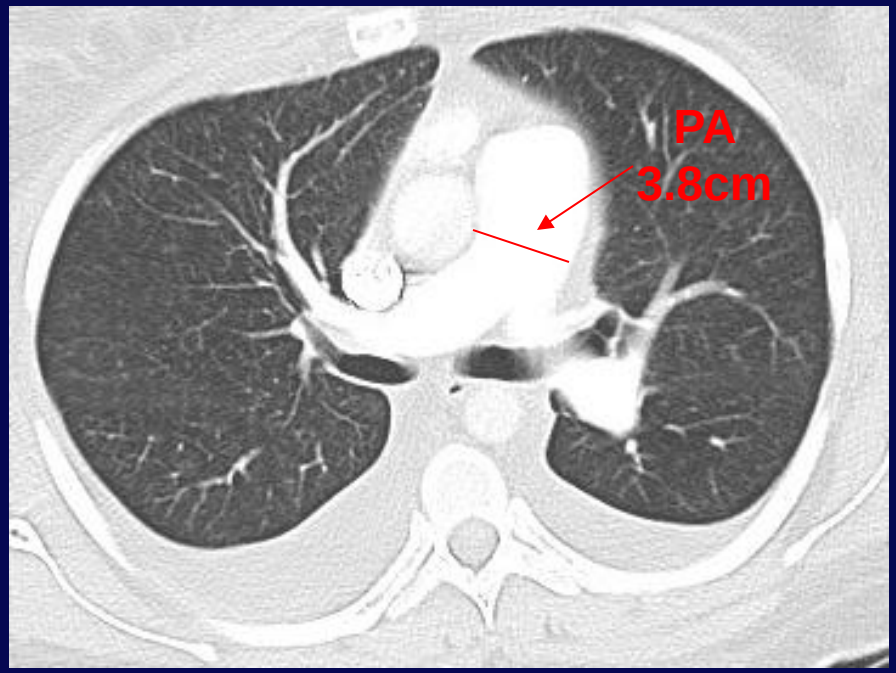


Severe Tricuspid Regurg

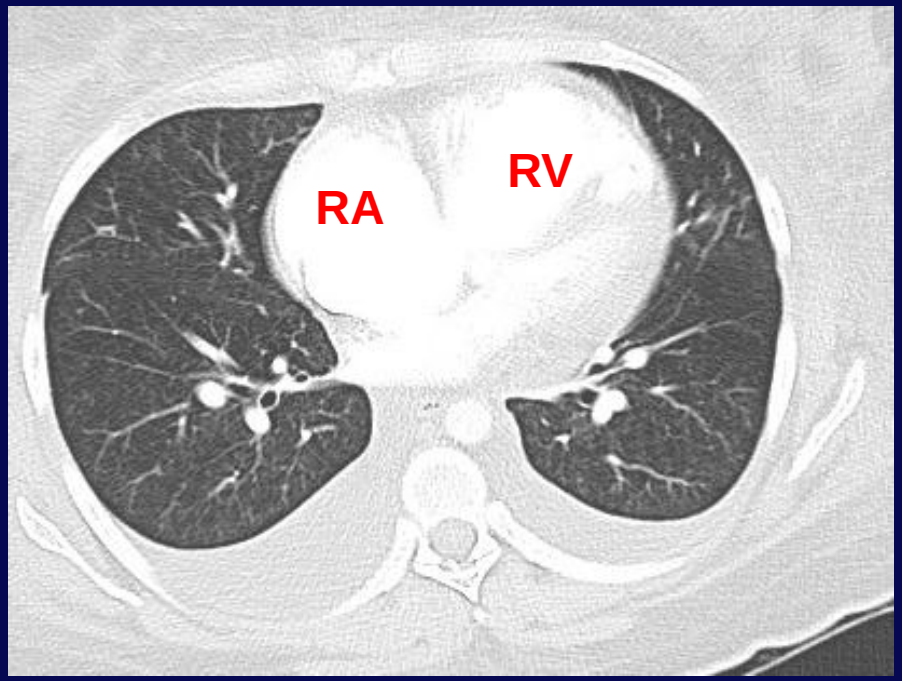
Apical Four Chamber View
Systole

Bossone ED, Bodini BD, Mazza A, et al. Pulmonary arterial hypertension: the key role of echocardiography. Chest 2005;127:1836-43.

Chest CT Scan



Enlargement Main Pulmonary Artery

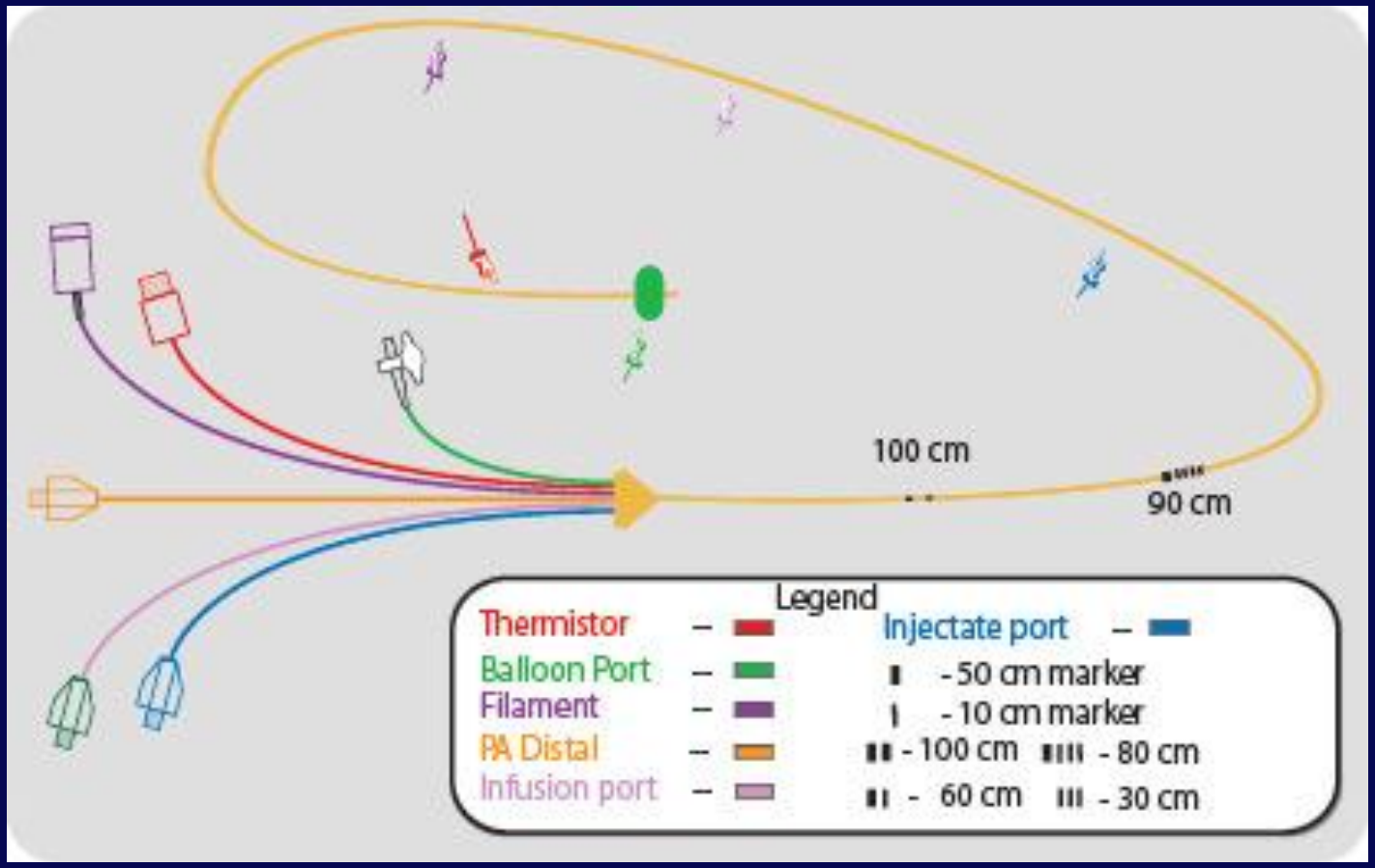


Right Atrial and Ventricular Enlargement

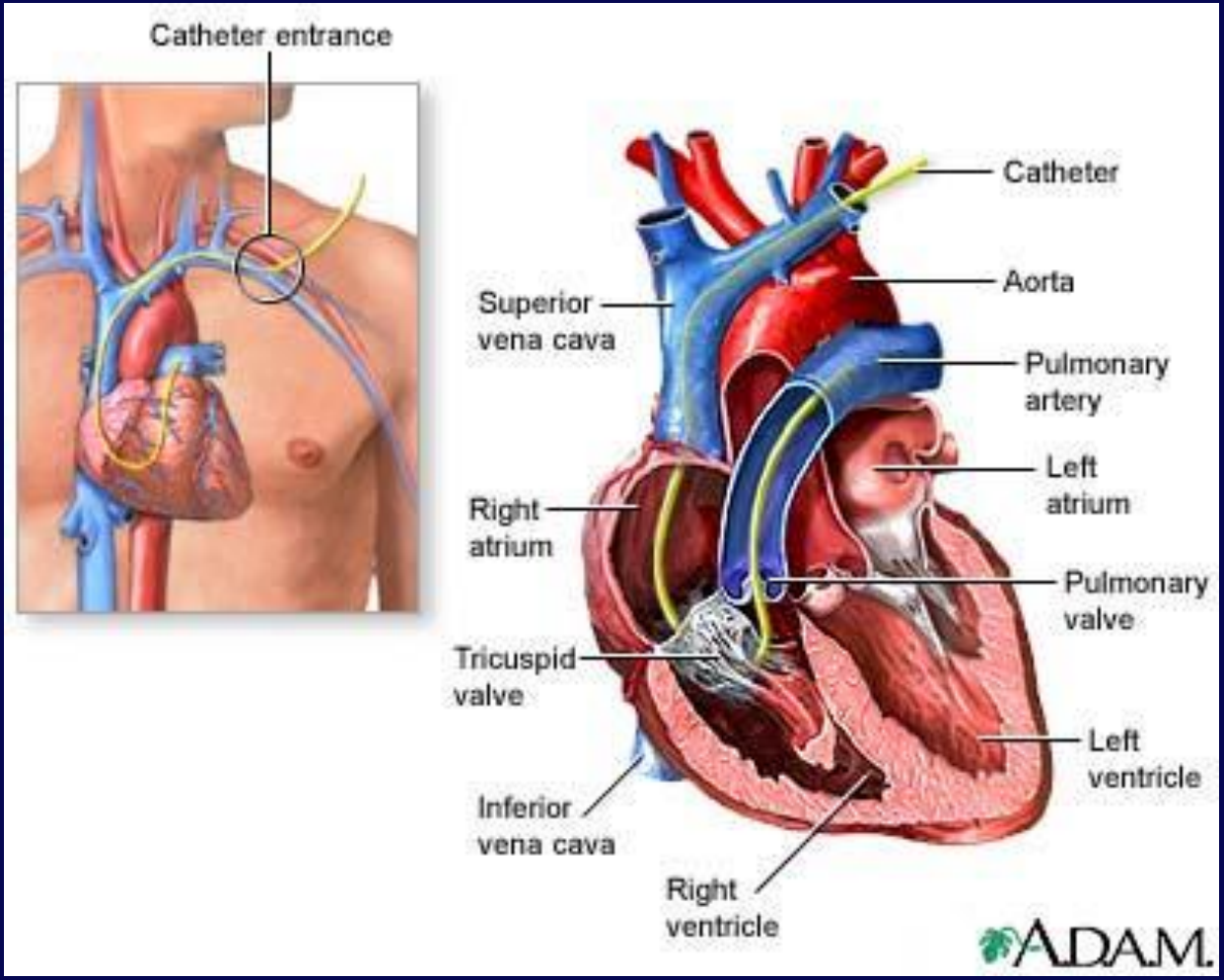
Right heart catheterization (RHC)

- Diagnosis
  - Noninvasive testing is part of the initial evaluation but is not confirmatory of PAH
  - RHC is necessary for a confirmed diagnosis of PAH
- Severity assessment
- Vasodilator challenges are performed in patients with PAH to assess for possible use of calcium channel blocker therapy

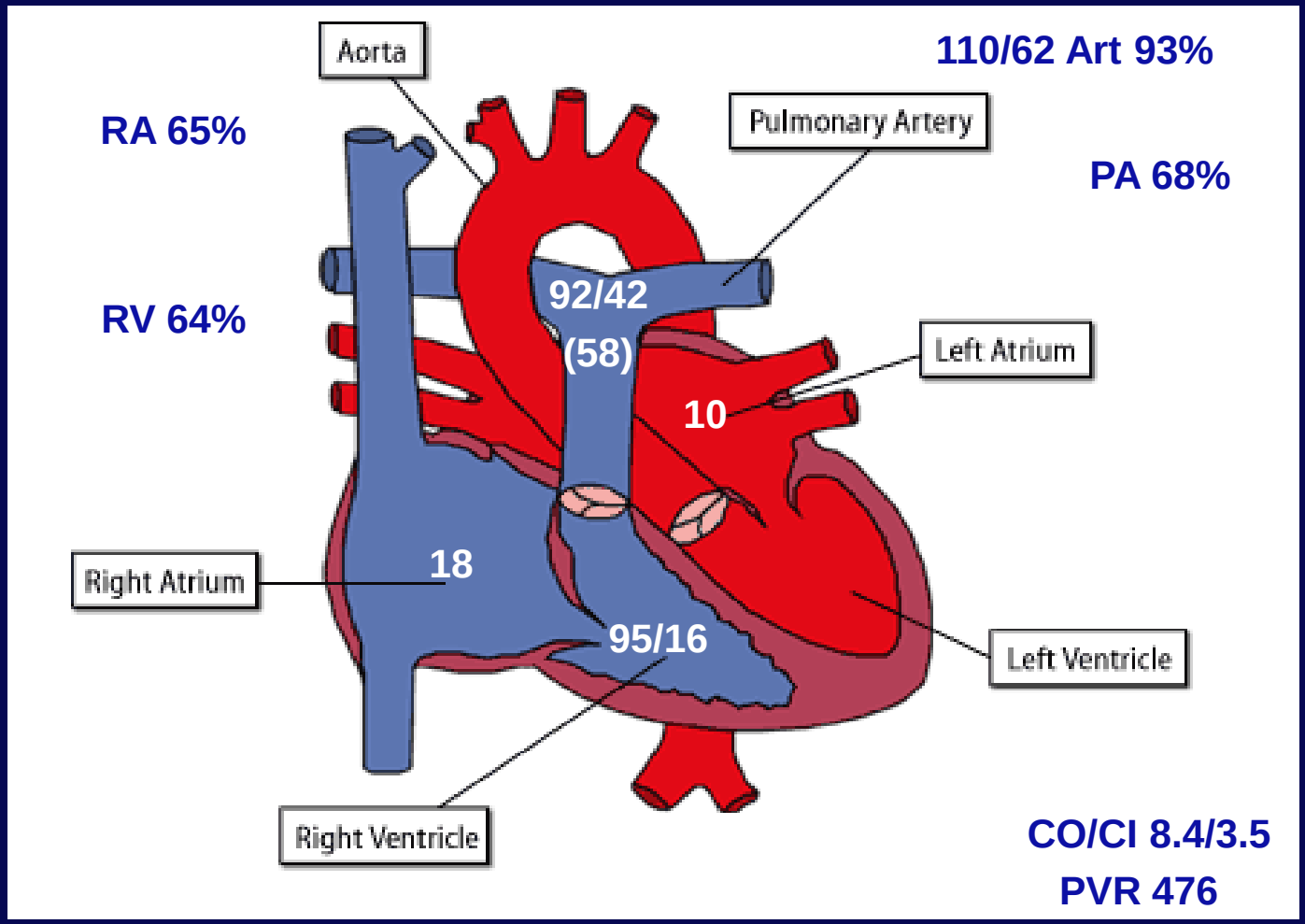
Right Heart Catheterization



Right Heart Catheterization

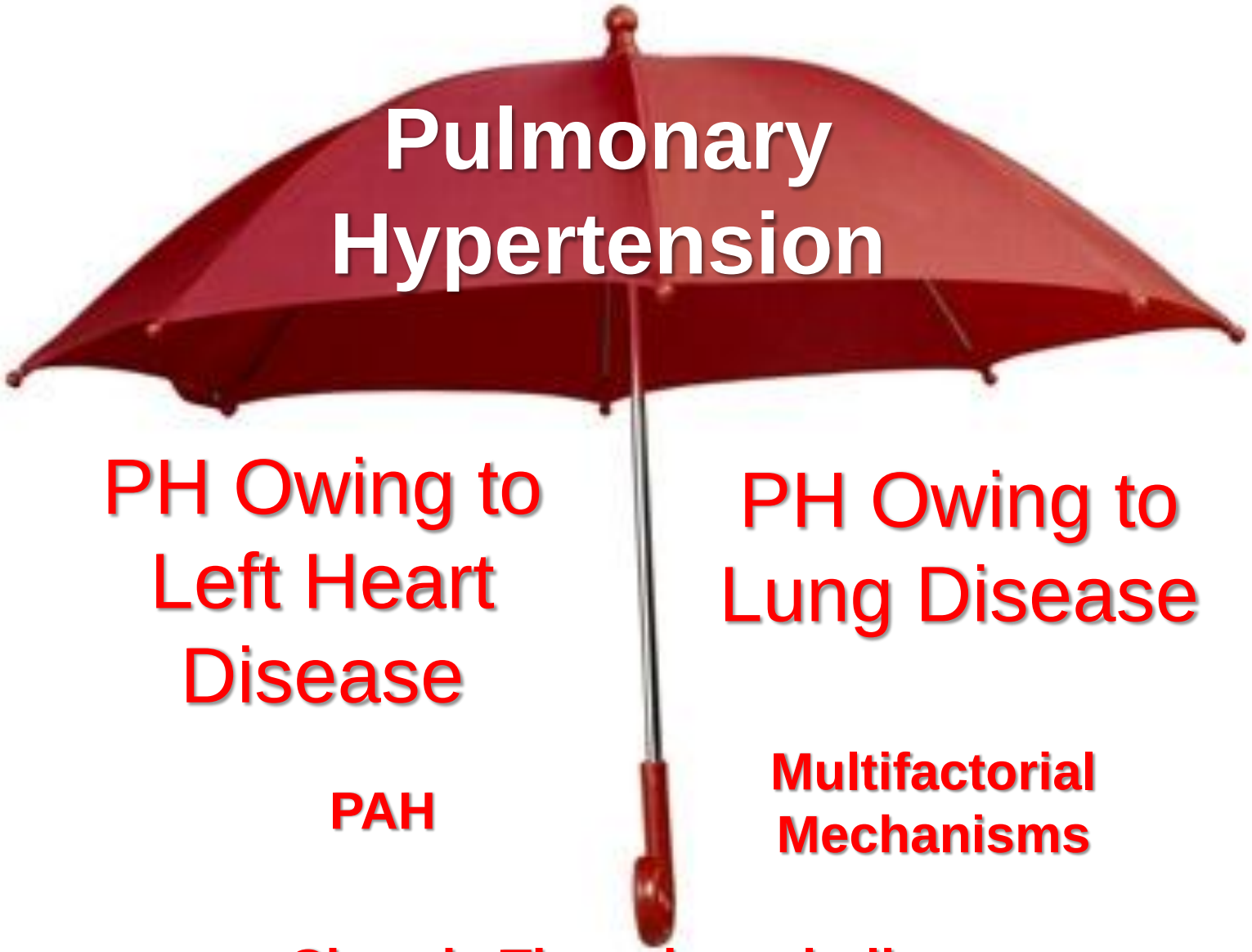


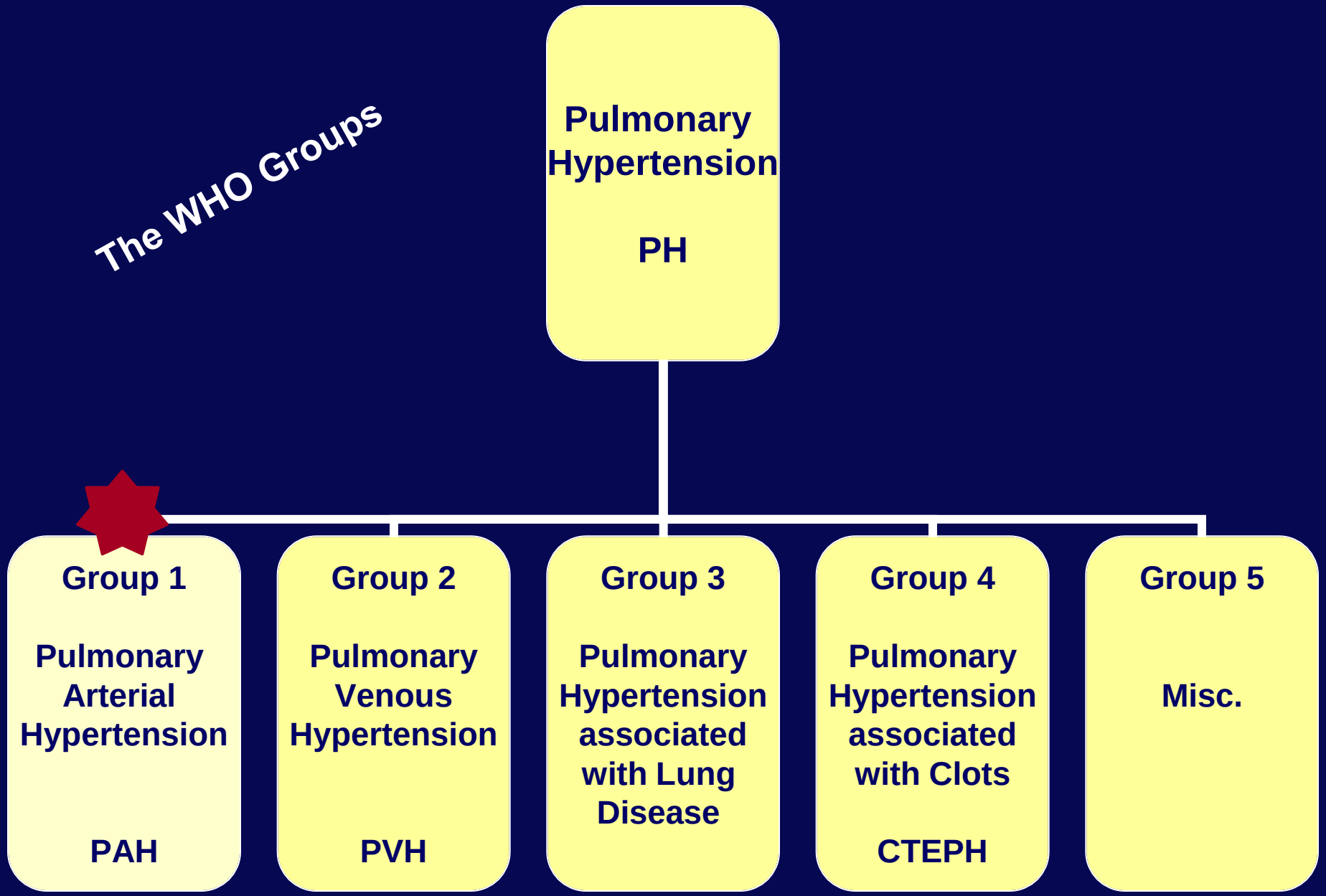
Detection of Pulmonary Hypertension



Definition of Pulmonary Hypertension

- Definition of Pulmonary Hypertension (PH)
  - Mean pulmonary artery pressure (mPAP) $\geq$25 mmHg at rest
- Hemodynamic Characteristics of Pulmonary Arterial Hypertension (PAH)
  - PH associated with pulmonary artery wedge pressure (PWP) $\leq$15 mmHg
  - Pulmonary vascular resistance (PVR) $\geq$3 mmHg/L/min (Wood units) or 240 dynes/sec/cm^{-5}

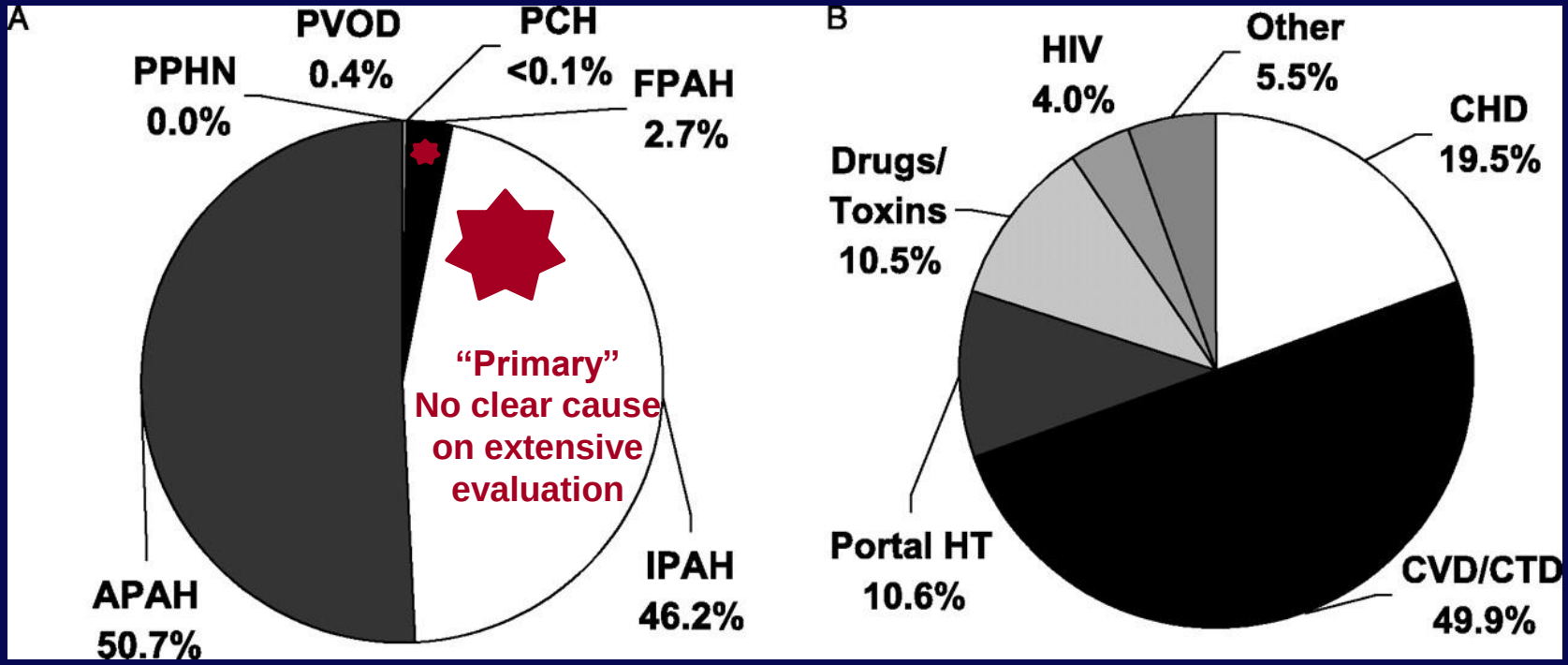

Pulmonary Hypertension
PH Owing to Left Heart Disease
PH Owing to Lung Disease
PAH
Multifactorial Mechanisms
Chronic Thromboembolic Disease


The WHO Groups
Pulmonary Hypertension
PH
Group 1
Pulmonary Arterial Hypertension
PAH
Group 2
Pulmonary Venous Hypertension
PVH
Group 3
Pulmonary Hypertension associated with Lung Disease
Group 4
Pulmonary Hypertension associated with Clots
CTEPH
Group 5
Misc.

Pulmonary Arterial Hypertension

WHO Group I

Reveal Registry Demographic

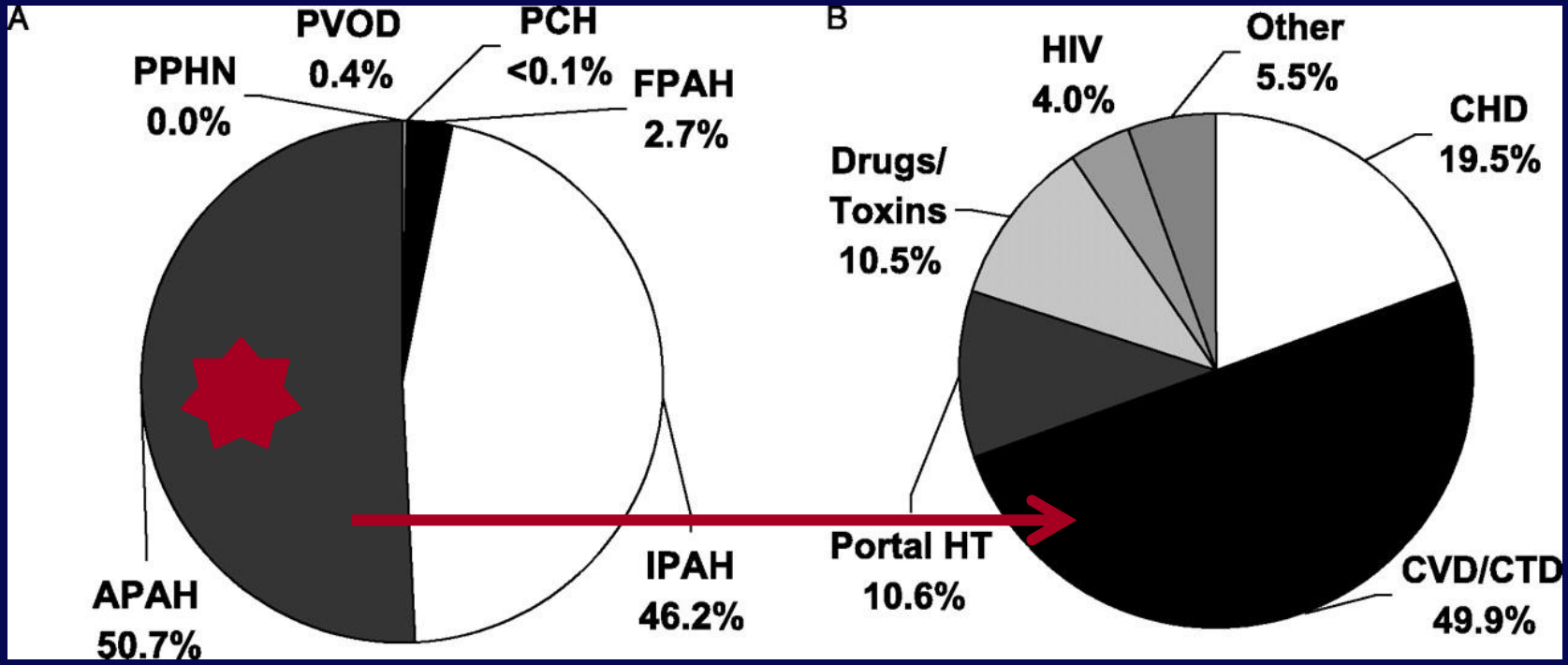


Badesch D, Raskob G, Elliott G, et al. Pulmonary Arterial Hypertension: Baseline Characteristics From the REVEAL Registry. *CHEST*. 2010,137(2):376-387.

Pulmonary Arterial Hypertension

WHO Group I

Reveal Registry Demographic

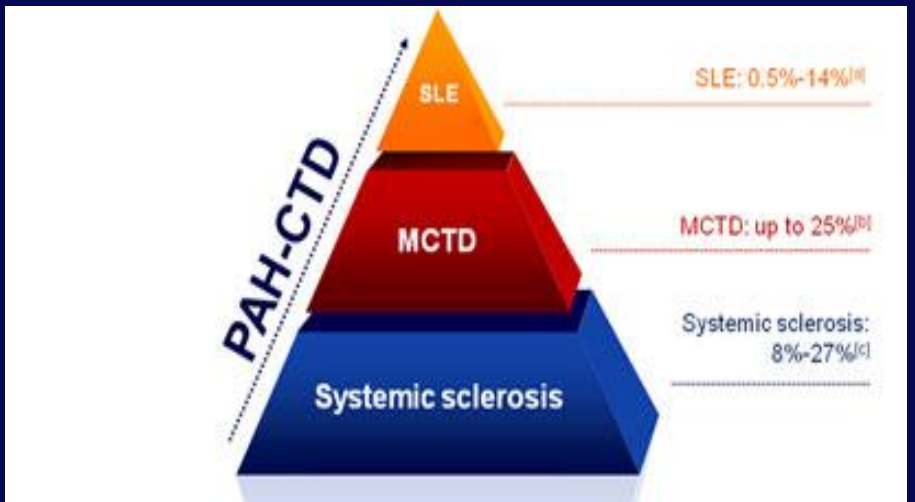


Badesch D, Raskob G, Elliott G, et al. Pulmonary Arterial Hypertension: Baseline Characteristics From the REVEAL Registry. *CHEST*. 2010,137(2):376-387.

Pulmonary Arterial Hypertension

WHO Group I

- Connective tissue disease associated PAH
  - Systemic sclerosis
    - ~ 10%
  - Mixed connective tissue disease
  - Systemic lupus erythematosus



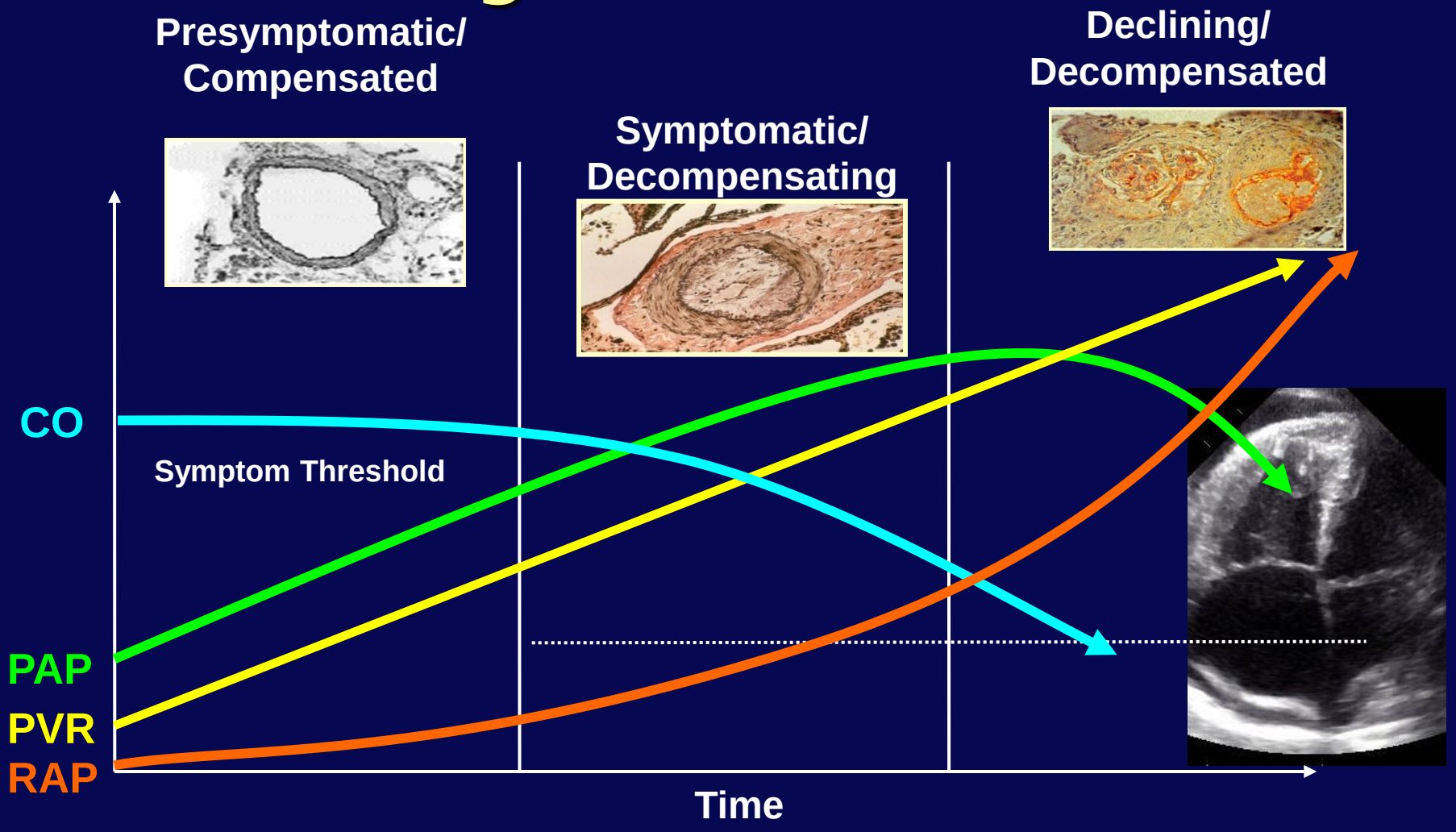
McLaughlin V. theheart.org

McLaughlin V. Archer S, Badesch D, et al. ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension. J Am Coll Cardiol. 2009;53(17):1573-1619.

Imbalance in Pulmonary Blood Vessels

- Excessive of vasoconstriction
- Lack of vasodilation

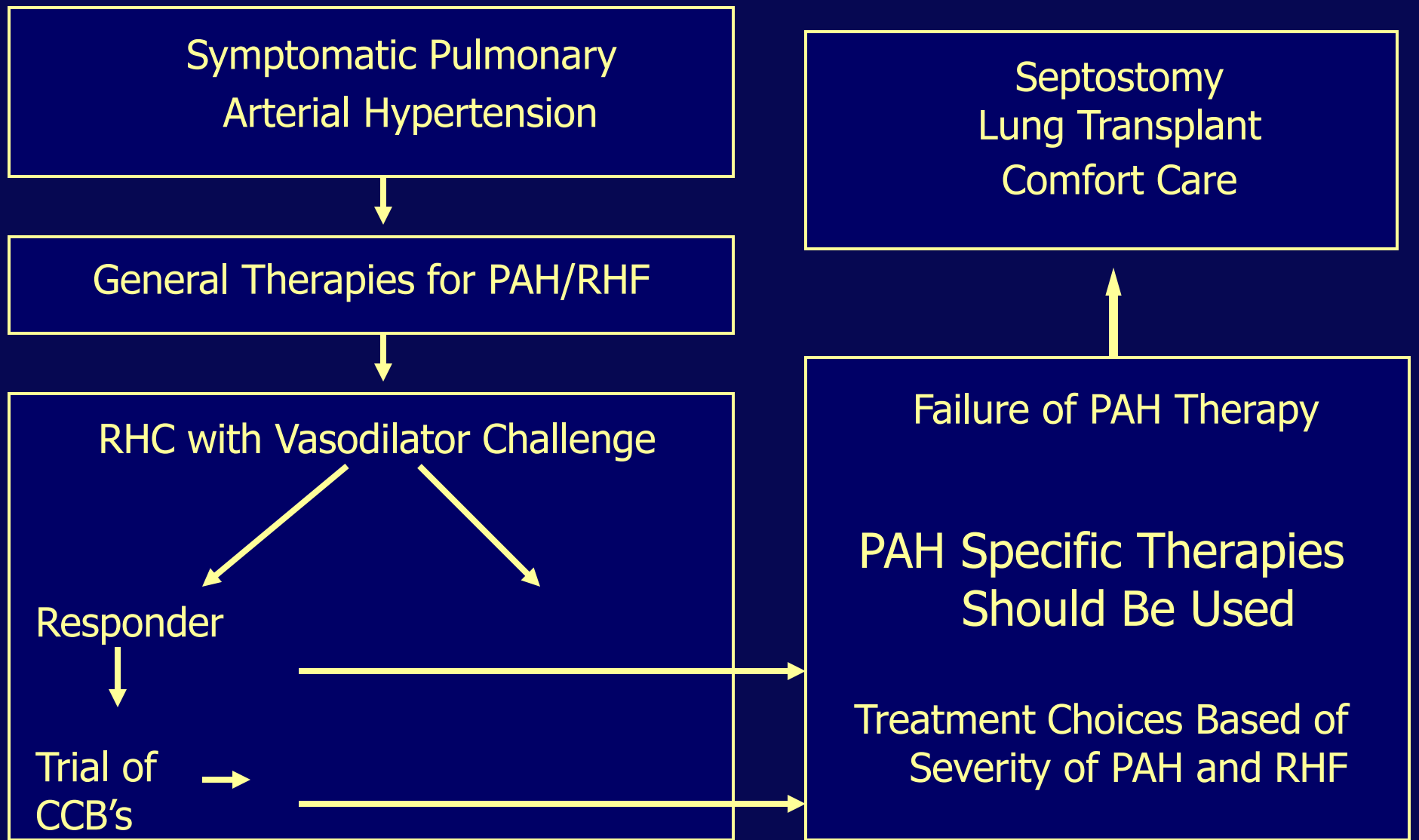
Progression of PAH



CO=cardiac output; PAP=pulmonary arterial pressure; PVR=pulmonary vascular resistance; RAP=right atrial pressure.

Adapted from Minai OA, Budev MM. *Cleveland Clin J.* 2007;74:737-747.

Treatment Algorithm for Pulmonary Arterial Hypertension



Treatment – General Measures

- Physical activity
  - In general, encourage physical activity
  - Limit if chest pain, severe dyspnea, syncope results
- Travel/altitude
  - Avoid air travel if possible
  - Air travel may increase pulmonary hypoxic vasoconstriction
  - Recommend the use of supplemental oxygen if air travel

Treatment – General Measures

- Infectious Disease
  - Vaccinate for Influenza and Strep Pneumonia
  - Promptly treat pulmonary infections
- Pregnancy
  - American Heart Association recommends avoidance or termination of pregnancy in patients with PH
- Contraception
  - Recommended
  - No consensus on safest form

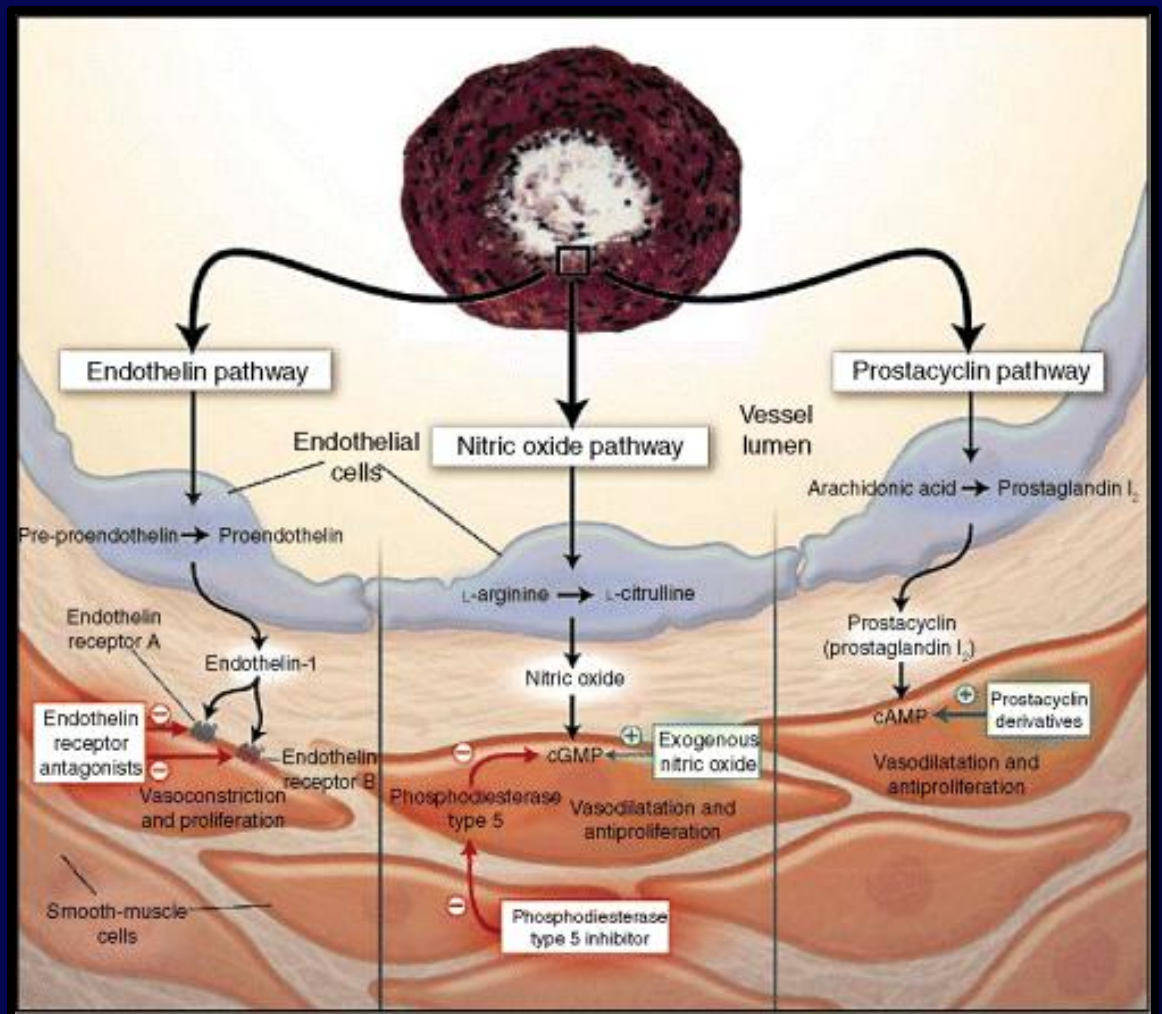
General Pharmacological Therapy in PH

- Oral Anticoagulant Treatment
  - Goal International Normalized Ratio (INR) 1.5-2.0
- Diuretics
  - Institute in patients with right heart failure (RHF)
  - Use with caution due to pre-load dependence
- Oxygen
  - Supplement oxygen to keep saturations > 90%
- Inotropic Agents
  - Consider digoxin for RHF and/or tachyarrhythmias

Treatment Algorithm for Pulmonary Arterial Hypertension

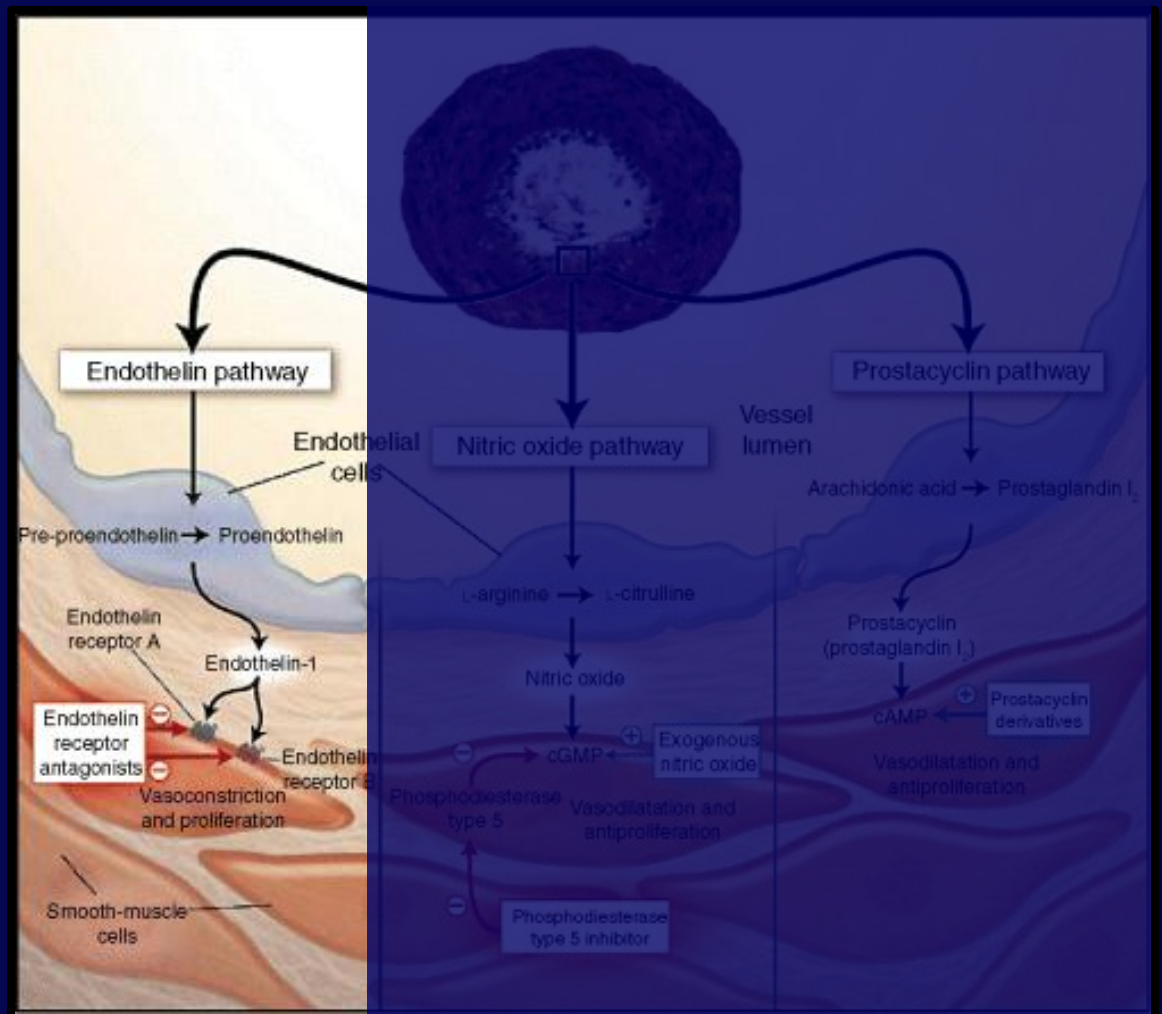
Determinant	Higher Risk	Lower Risk
Evidence of RV failure	Yes	No
Progression	Rapid	Gradual
WHO class	IV	II, III
6-minute walk distance	<325 m	>380 m
Brain natriuretic peptide	>180 pg/mL	<180 pg/mL
Echo findings	Pericardial effusion; significant RV dysfunction	Minimal RV dysfunction
Hemodynamics	High RAP, low CI	Normal/near normal RAP and CI

Vasodilator Therapy in PAH for Patients with Negative Vasoreactivity Trials



Humbert M, Sitbon O, Simonneau G, Treatment of Pulmonary Arterial Hypertension. NEJM. 2004; 351:1425-39.

Vasodilator Therapy in PAH for Patients with Negative Vasoreactivity Trials



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Endothelin-1 (ET-)1 Receptor Antagonists

- Bostentan (Tracleer)
- Ambrisentan (Letairis)
- Macitentan (Opsumit)

Endothelin-1 (ET-)1 Receptor Antagonists

- Bosentan
  - Oral Endothelin-1 Blocking Agent
  - Improved exercise capacity, functional class, hemodynamics, echocardiographic measurements and time to clinical worsening
  - Elevated hepatic aminotransferases occurred in 10%
  - Bosentan has been approved in 2001 for NYHA class III and IV PAH; NYHA class II 2009

Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan Therapy for Pulmonary Arterial Hypertension. NEJM 2002; 346:896-903.

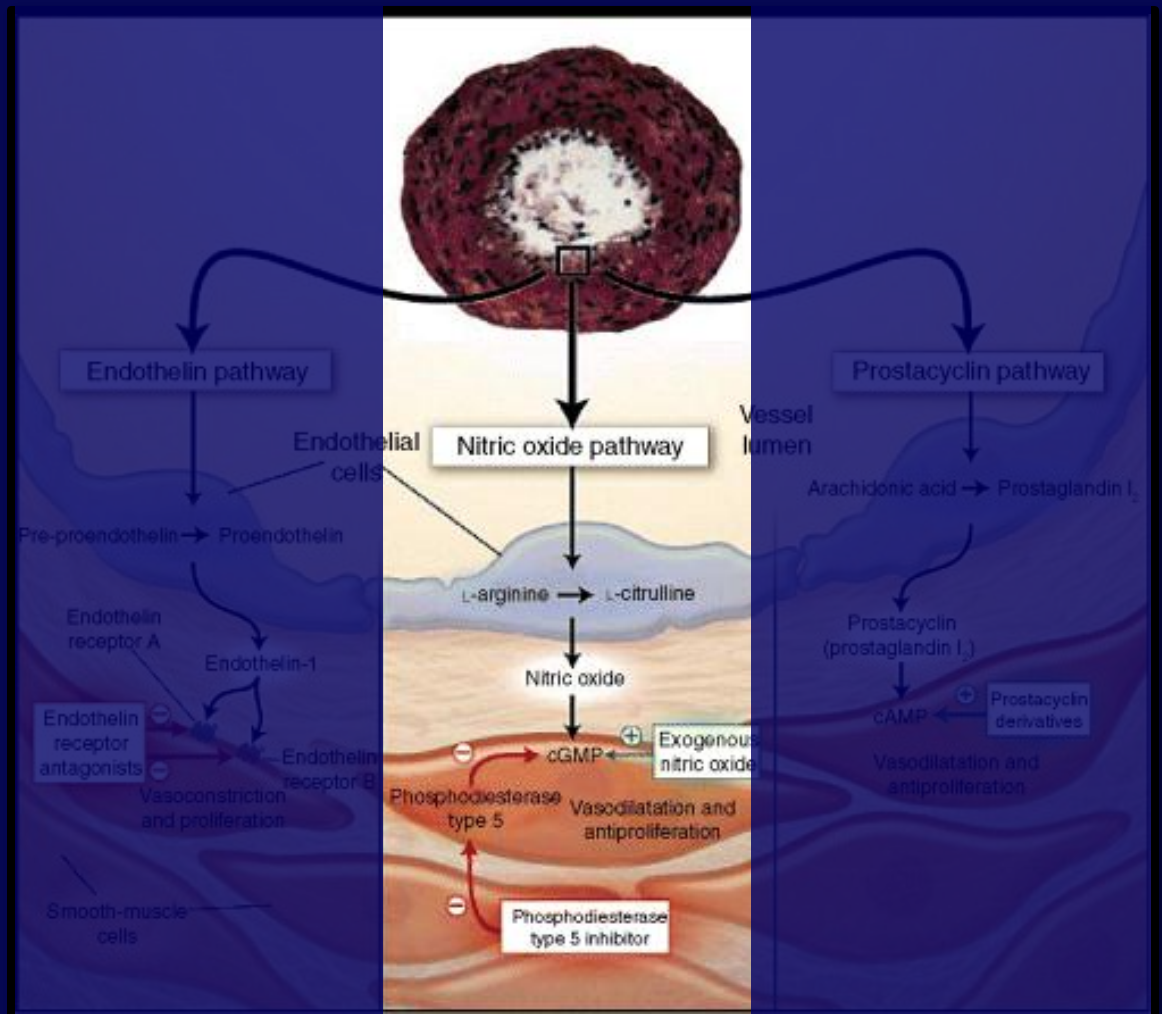
Endothelin-1 (ET-)1 Receptor Antagonists

- Ambrisentan
  - Oral Endothelin-1 Blocking Agent
  - Improved exercise capacity,hemodynamics, and time to clinical worsening
  - Elevated hepatic aminotransferases occurred in 3%
  - Ambrisentan has been approved in 2007 for NYHA class II and III PAH

Endothelin-1 (ET-)1 Receptor Antagonists

- Macitentan
  - Oral Endothelin-1 Blocking Agent
  - Delay in progression of disease
  - Improved morbidity / mortality, exercise capacity, hemodynamics
  - Anemia 13%
  - Macitentan was been approved in 2013 for NYHA functional class II-IV PAH

Vasodilator Therapy in PAH for Patients with Negative Vasoreactivity Trials



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Nitric Oxide
Type 5 Phosphodiesterase (PDE) Inhibitors
Soluble Guanylate Cyclase Stimulators

- Inhaled Nitric Oxide
- Sildenafil (Revatio)
- Tadalafil (Adcirca)
- Riociquat (Adempas)

Type 5 Phosphodiesterase (PDE) Inhibitors

- Sildenafil
  - Orally-active medication and intravenous (IV)
  - Selective inhibitor of cyclic guanosine monophosphate (cGMP)-PDE type 5
  - Induces smooth muscle relaxation
  - Antiproliferative effects on vascular smooth muscle cells
  - Improvement in 6MWT and hemodynamics
  - FDA approved in 2005 for NYHA II-IV PAH

Galie N, et al. Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension. *NEJM* 2005; 353:2148-2157.

Type 5 Phosphodiesterase (PDE) Inhibitors

- Tadalafil
  - Orally-active medication
  - Selective inhibitor of cyclic guanosine monophosphate (cGMP)-PDE type 5
  - Induces smooth muscle relaxation
  - Antiproliferative effects on vascular smooth muscle cells
  - Improvement in 6MWT
  - Improved time to clinical worsening
  - FDA approved in 2009 for PAH

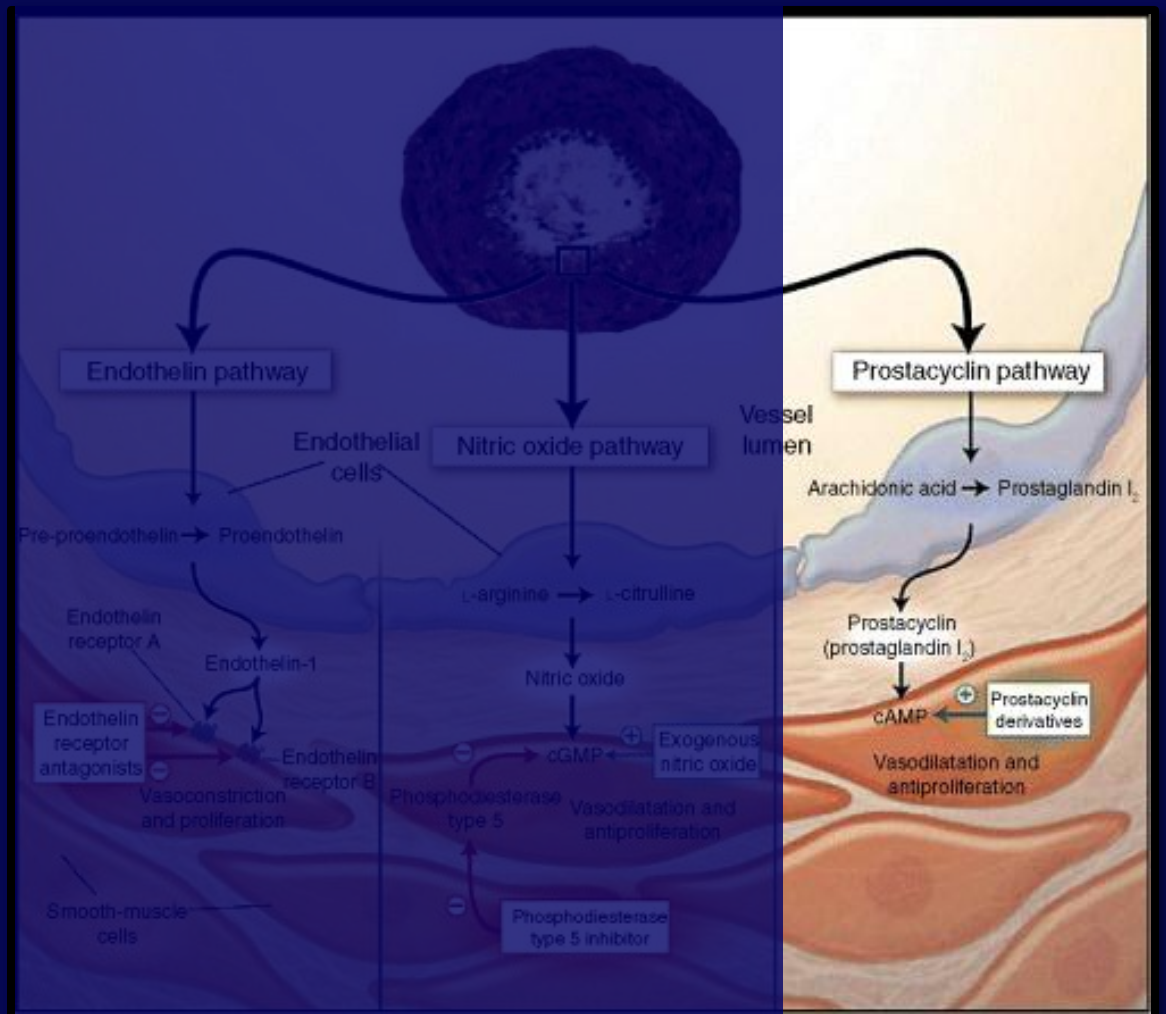
Galie N, et al. Tadalafil Therapy for Pulmonary Arterial Hypertension. *Circulation;* 2009 119: 2861-2862.

Soluble Guanylate Cyclase Stimulator

- Riociguat
  - Stimulator of the NO receptor soluble guanylate cyclase
  - Orally active medication
  - Indicated for the treatment of adults WHO Group 1 PAH
  - Improve exercise capacity, WHO functional class and to delay clinical worsening

Ghofrani H, et al. PATENT-1 - Riociguat for the Treatment of Pulmonary Arterial Hypertension N Engl J Med 2013; 369:330-340July 25, 2013.

Vasodilator Therapy in PAH for Patients with Negative Vasoreactivity Trials



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Prostacyclin Therapy

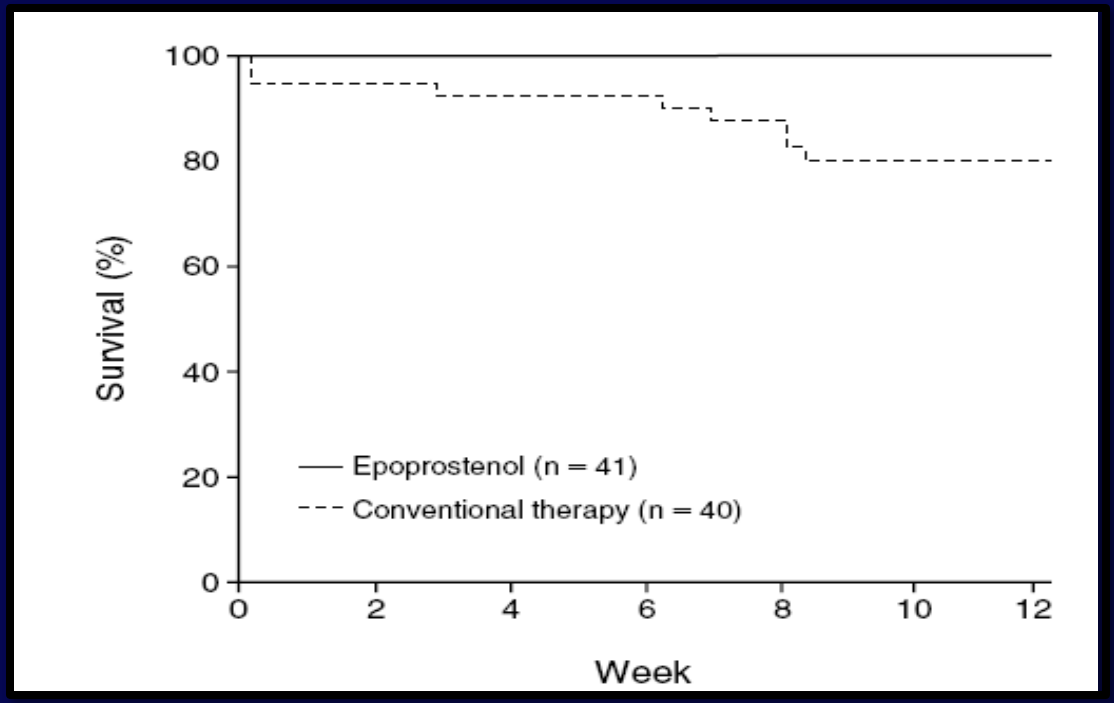
- Epoprostenol
  - RTS Option
  - Continuous IV Infusion
- Treprostinil
  - SQ or IV
  - Inhaled
  - Oral
- Iloprost
  - Inhaled

Epoprostenol Continuous IV Infusion

- Used frequently in advanced disease
  - Delivered by continuous intravenous infusion
  - Half life 3-5 minutes
  - Epoprostenol (Flolan) must be maintained at 2-8^{o}C
  - Epoprostenol for Injection (Veletri) is stable at room temperature
  - Interruption may cause serious deterioration or fatal
- FDA approved in 1995 for NYHA class III and IV IPAH
- FDA approved in 2000 for PAH associated with scleroderma
- FDA approved room temperature stable epoprostenol in 2010.

Epoprostenol Continuous IV Infusion Improves Survival in IPAH

- Prospective, randomized, multi-center, open trial
  - 12 weeks
  - 81 IPAH patients
  - NYHA FC III - IV
  - Epoprostenol vs. conventional therapy



Improvement in symptoms, hemodymanics and survival

Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol with conventional therapy for PPH. NEJM. 1996;334:296-302.

Treprostinil
Continuous SQ or IV Infusion

- Half-life 3-4 hrs
- Absorbed completely with subcutaneous administration
- Stable at room temperature
- Stable at a neutral pH
- FDA approved in 2002 for NYHA II-IV PAH patients

Simonneau G, Barst R, Galie Nazzareno, et al. Continuous Subcutaneous Infusion of Treprostinil, a Prostacyclin Analogue, in patients with Pulmonary Arterial Hypertension. AJRCCM 2002; 165:800-805.

Iloprost
Intermittent Inhaled Prostanoid

- Stable analogue of prostacyclin
  - Delivered via a I-neb AAD specialized nebulizer
  - 5mcg inhaled 6-9 times daily
  - 60 to 90 minutes duration of action
- Improved a composite endpoint consisting of exercise tolerance, symptoms and lack of deterioration
- Studied as monotherapy
- FDA approved in 2005 for NYHA III-IV PAH

Olschewski H, et al. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002; 347:322.

Inhaled Treprostinil Intermittent Inhaled Prostanoid

- Stable analogue of prostacyclin
  - Delivered via the Optineb device
  - Goal of 9 breaths 54mcg inhaled 4 times daily
  - Approximately 4 hour duration of action
- Improves exercise tolerance
- Studied as combination therapy with an oral PAH therapy
- FDA approved in 2009 for NYHA III PAH

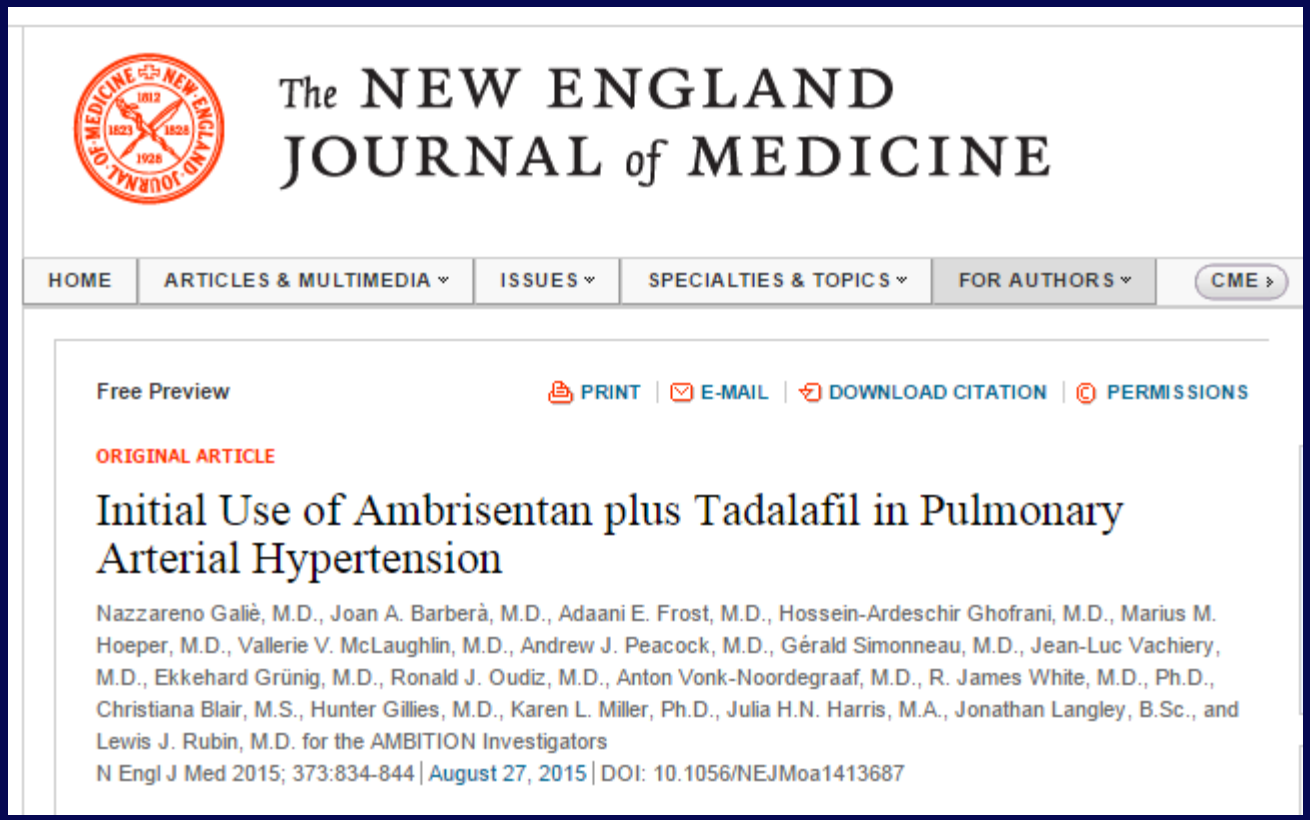
McLaughlin V, et al. Addition of Inhaled Treprostinil to Oral Therapy for Pulmonary Arterial Hypertension. *J Am Coll Cardiol.* 2010; 55: 1915-1922.

Oral Treprostinil Extended-Release Tablets

- Oral treprostinil
  - Improve exercise capacity.
  - Functional class II-III symptoms
  - Etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%)
  - As the sole vasodilator, the effect on exercise is small. Oral treprostinil has not been shown to add to other vasodilator therapy.

Jing C. et al, Efficacy and Safety of Oral Treprostinil Monotherapy for the Treatment of Pulmonary Arterial Hypertension: A Randomized Controlled TrialCirculation. 2013;127:624-633.

Combination Therapy



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ORIGINAL ARTICLE

Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension

Nazzareno Galiè, M.D., Joan A. Barberà, M.D., Adaani E. Frost, M.D., Hossein-Ardeschir Ghofrani, M.D., Marius M. Hoeper, M.D., Vallerie V. McLaughlin, M.D., Andrew J. Peacock, M.D., Gérald Simonneau, M.D., Jean-Luc Vachiery, M.D., Ekkehard Grünig, M.D., Ronald J. Oudiz, M.D., Anton Vonk-Noordegraaf, M.D., R. James White, M.D., Ph.D., Christiana Blair, M.S., Hunter Gillies, M.D., Karen L. Miller, Ph.D., Julia H.N. Harris, M.A., Jonathan Langley, B.Sc., and Lewis J. Rubin, M.D. for the AMBITION Investigators

N Engl J Med 2015; 373:834-844 | August 27, 2015 | DOI: 10.1056/NEJMoa1413687

Drug Name	Class	Indication (PI)	Route	FC	Goal of Therapy (PI)
Bosentan (Tracleer)	ERA (non-select)	WHO Group 1	PO	II-IV	*EC and decrease rate of clinical worsening
Macitentan (Opsumit)	ERS	WHO Group 1	PO	II-IV	Improve morbidity
Ambrisentan (Letairis)	ERA (selective)	WHO Group 1	PO	II-III	*EC and delay clinical worsening
Sildenafil (Revatio)	PDE-I 5	WHO Group1	PO / IV	II-IV	*EC
Tadalafil (Adcirca)	PDE-I 5	WHO Group1	PO	II-IV	*EC, delay clinical worsening
Riociquat (Adempas)	GC	WHO Group 1, 4	PO	II-IV	EC
Epoprostenol (Flolan, Veletri)	Prostacyclin	IPAH and PAH w/ Scleroderma	IV	III-IV	*EC and Survival IPAH *EC Scleroderma
Treprostinil (Remodulin)	Prostacyclin	WHO Group 1	IV, SQ, PO	II-IV	Decrease PAH symptoms related Exercise
Iloprost (Ventavis)	Prostacyclin	WHO Group 1	Inhaled	III-IV	*EC, Improve *FC, delay deterioration
Inhaled Treprostinil (Tyvaso)	Prostacyclin	WHO Group 1	Inhaled	III	*EC

*EC = Exercise Capacity, FC = Functional Class

PAH Treatment Goals

Variable	Recommended Goal
WHO functional class (FC)	I or II
Echocardiography/CMRI	Normal/near-normal RV size and function
Hemodynamics	Normalization of RV function • RAP <8 mm Hg and • CI > 2.5 to 3.0 L/min/m^2
Cardiopulmonary exercise testing	Peak VO_2 >15 mL/min/kg and $EqCO_2$ <45 L/min/L/min
B-type natriuretic peptide	Normal

McLaughlin VV, et al. *J Am Coll Cardiol.* 2013;62:D73-D81.

Extremely Important

- Avoid any interruption in PAH therapy
  - May result in significant worsening and RHF
- PAH therapy should be continued pre, intra and postoperatively
- Patient may be unable to continue a specific PAH therapy
    - Critical illness
    - Surgery
    - Malabsorption
    - Mental status changes
  - An alternative therapy must be considered immediately
- Contact the prescribing physician to discuss situation

Finding the Right Plan of Care for YOU

- Many factors are considered
  - Symptoms, examination and test rests
  - Your goals for therapy
  - Your response to medications for PAH
  - Side effects
- Collaborative effort with your PAH team with you as the MVP

Thank You

Questions?