Pulmonary Hypertension in brief

Timothy J. Barreiro, DO, MPH, FCCP, FACOI, FACP
Section Chair, Professor of Medicine
Mercy Health Sciences, St. Elizabeth Hospital. Youngstown, Ohio
NIH Health Minority & Harvard Macy Scholar
Ohio University Heritage College of Osteopathic Medicine
Northeast Ohio Medical University
Director Pulmonary Health & Research Center
tbarreir@neomed.edu

Course Disclosures

I have no disclosures, conflicts of interest related to this subject or talk.

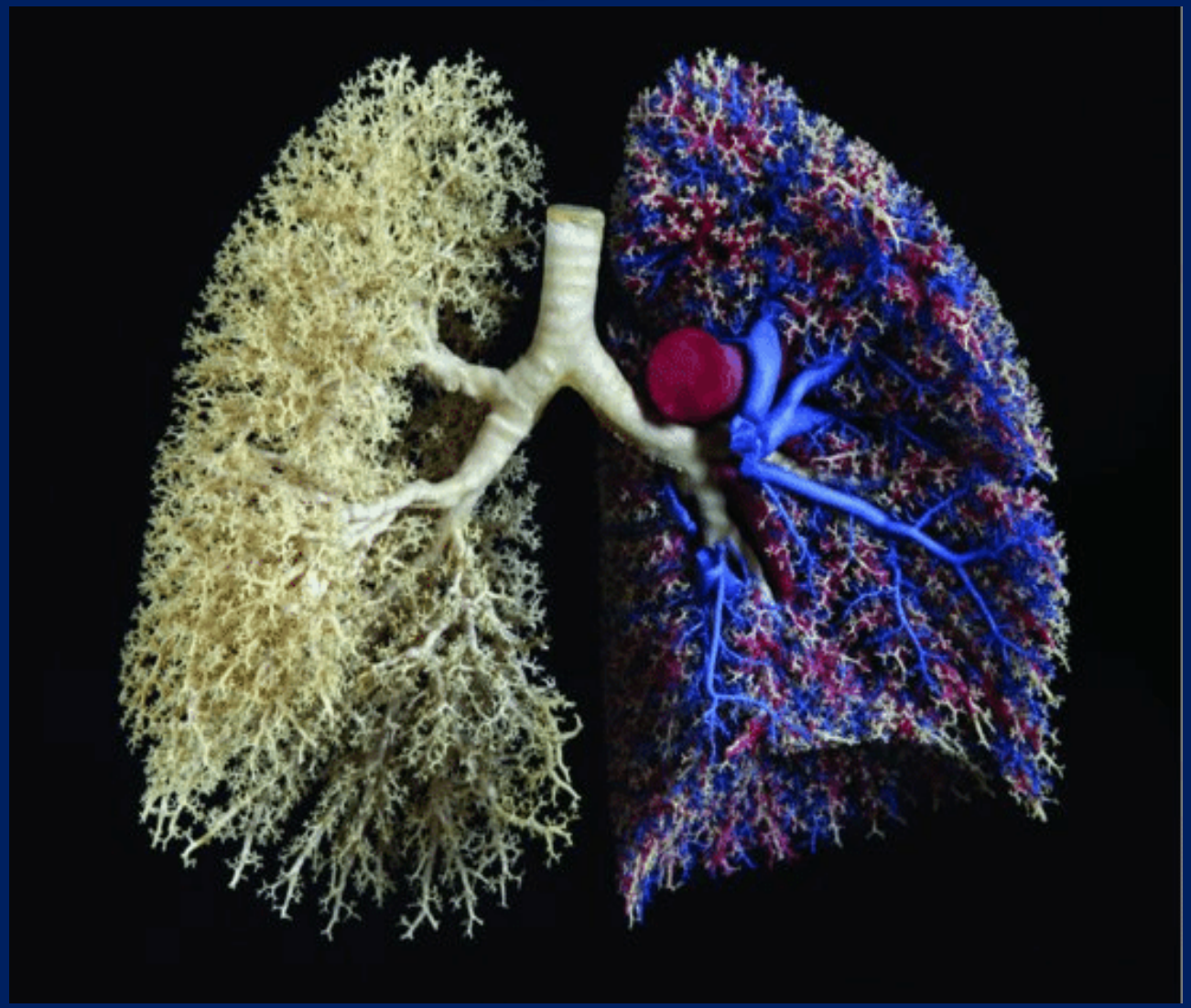
Learning Objectives

- Review pulmonary vascular anatomy
- Define pulmonary hypertension
- Discuss the pathophysiology and causes of PAH
- Become familiar with the diagnostic approach to PAH
- Summarize some key treatments concepts for prototypical PAH verse other from of pulmonary hypertension

Key Points to Consider

- **Pulmonary hypertension is not one disease but many**
  - *Appropriate treatment requires appropriate diagnosis*
- **Treatment for pulmonary arterial hypertension is focused on diuresis and afterload reduction**
  - *The current proliferation of drugs for PAH leaves many unanswered questions but a structured goal-directed approach is possible*
- **There has been progress in pulmonary arterial hypertension, but there is more work to be done**
  - *Novel targets and approaches are needed*

Pulmonary vascular anatomy



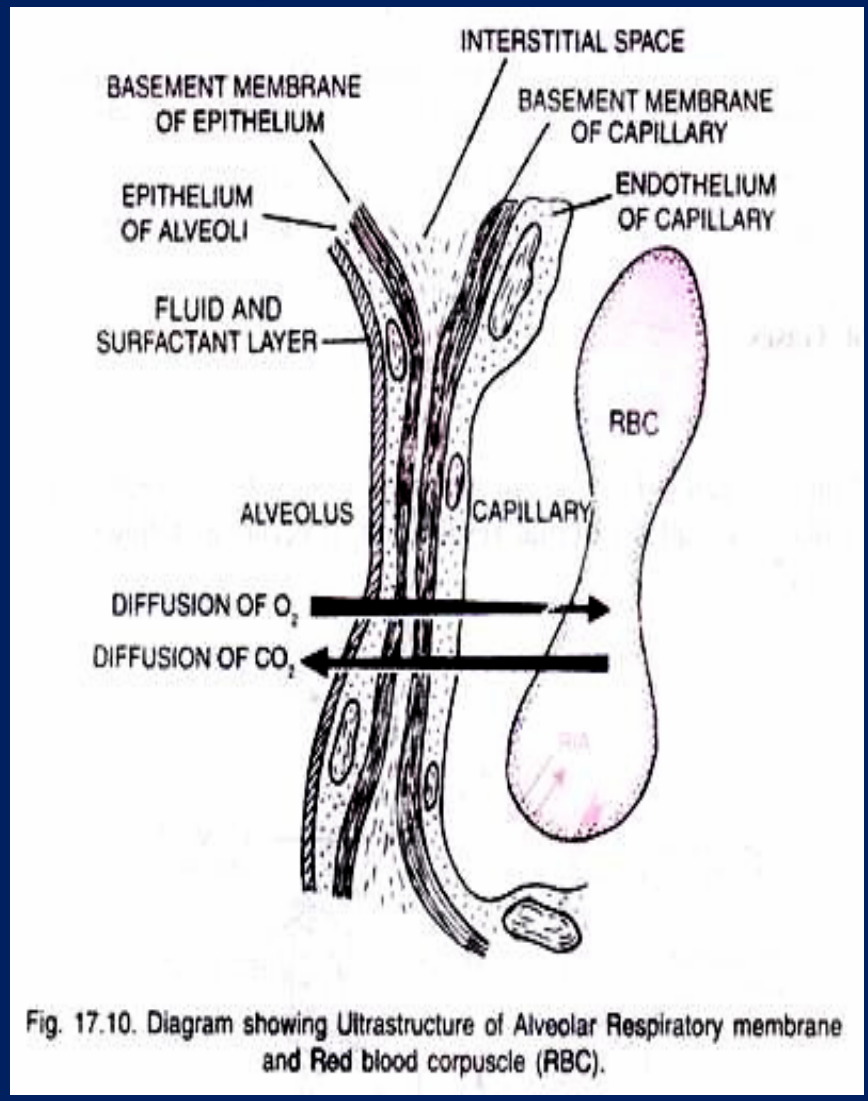


Fig. 17.10. Diagram showing Ultrastructure of Alveolar Respiratory membrane and Red blood corpuscle (RBC).

FISHMAN, A. P. (1963). 'Dynamics of the pulmonary circulation'. In *Handbook of physiology*. Section 2: Circulation. Vol. II (ed. W. F. Hamilton and P. Dow) American Physiological Society, Washington, D.C.
FISHMAN, A. P. and HECHT, H. H. (1969) (ed.). *The pulmonary circulation and interstitial space*. University of Chicago Press, Chicago and London.

Vascular Pressure in Systemic and Pulmonary Circulations (mm Hg)

Normal resting mean pulmonary arterial pressure (mPAP) = 14 ± 3 mm Hg

Upper limit of 20 mm Hg (including standard deviation of the study population)

Normal PVR is 100 – 200 dynes/sec/cm^{-5}

Silvestry, F. (2015). Pulmonary artery catheterization: interpretation of hemodynamic values and waveforms in adults. Uptodate.

What is pulmonary hypertension?

- Complex, progressive pathophysiologic and hemodynamic disease state hallmarked by:
  - Increases in pulmonary arterial pressures
  - Increased pulmonary vascular resistance (PVR)
  - Devastating end point: right ventricular failure

Hemodynamic Classification

- **Pulmonary hypertension**

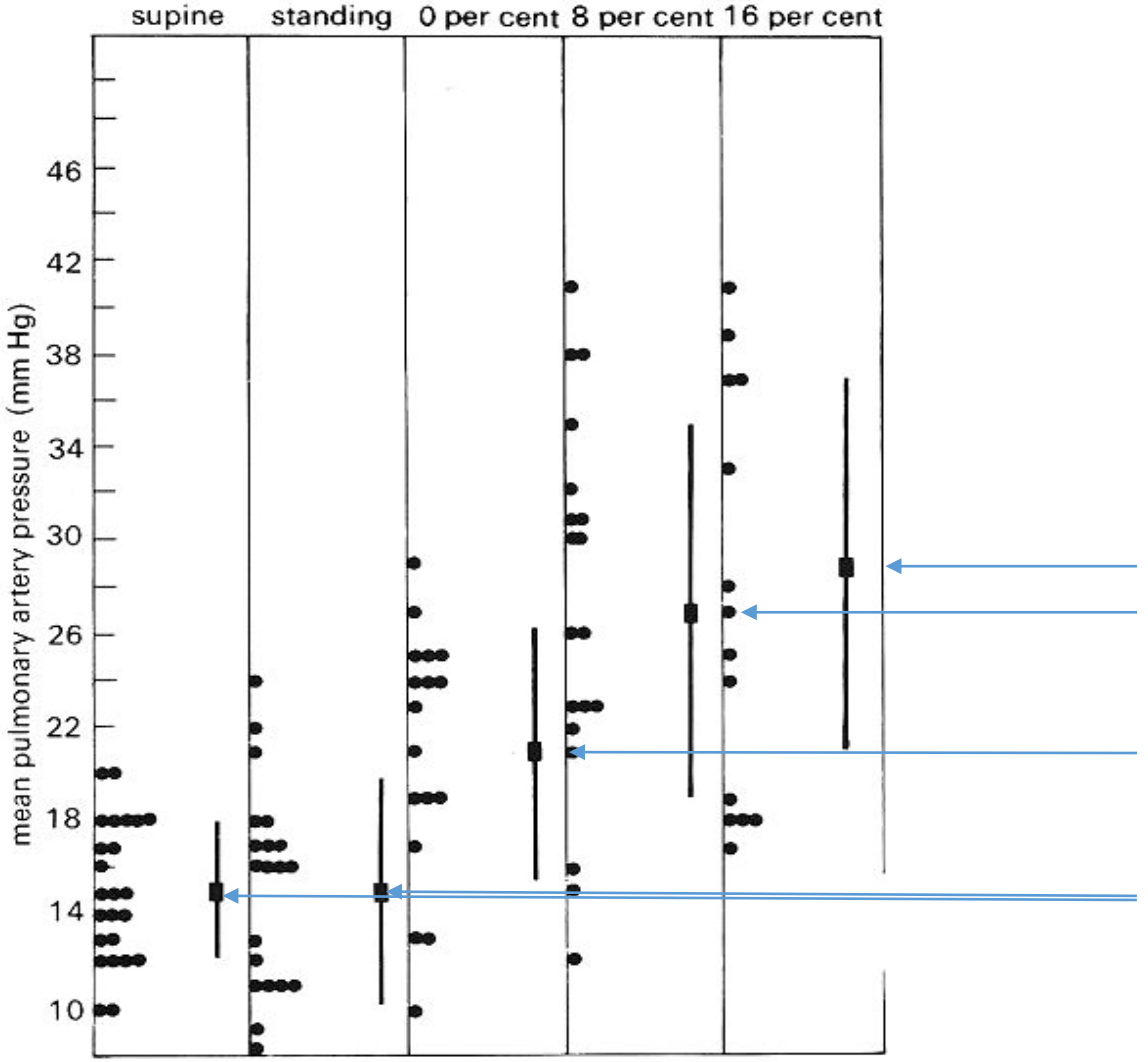
mPAP= PVR * CO + PAOP

mPAP	= mean pulmonary artery pressure;
PAOP	= pulmonary capillary wedge pressure;
PVR	=pulmonary vascular resistance
CO	= cardiac output

- **Gold standard diagnosis is assessed on right heart catheterization:**
  - **mPAP ≥ 25 mm Hg**
  - **PAOP < 15**
  - **Normal LVEF**
  - **No left-sided valular disease**

Simonneau, G, Gatzoulis, MA, Adatia, I et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013; 62: D34–D41.
George MG , Schieb LJ , Ayala C , Talwalkar A , Levant S . Pulmonary hypertension surveillance: United States, 2001 to 2010 . *Chest* . 2014 ; 146 (2): 476 - 495 .

Effects of exercise on pulmonary artery pressure

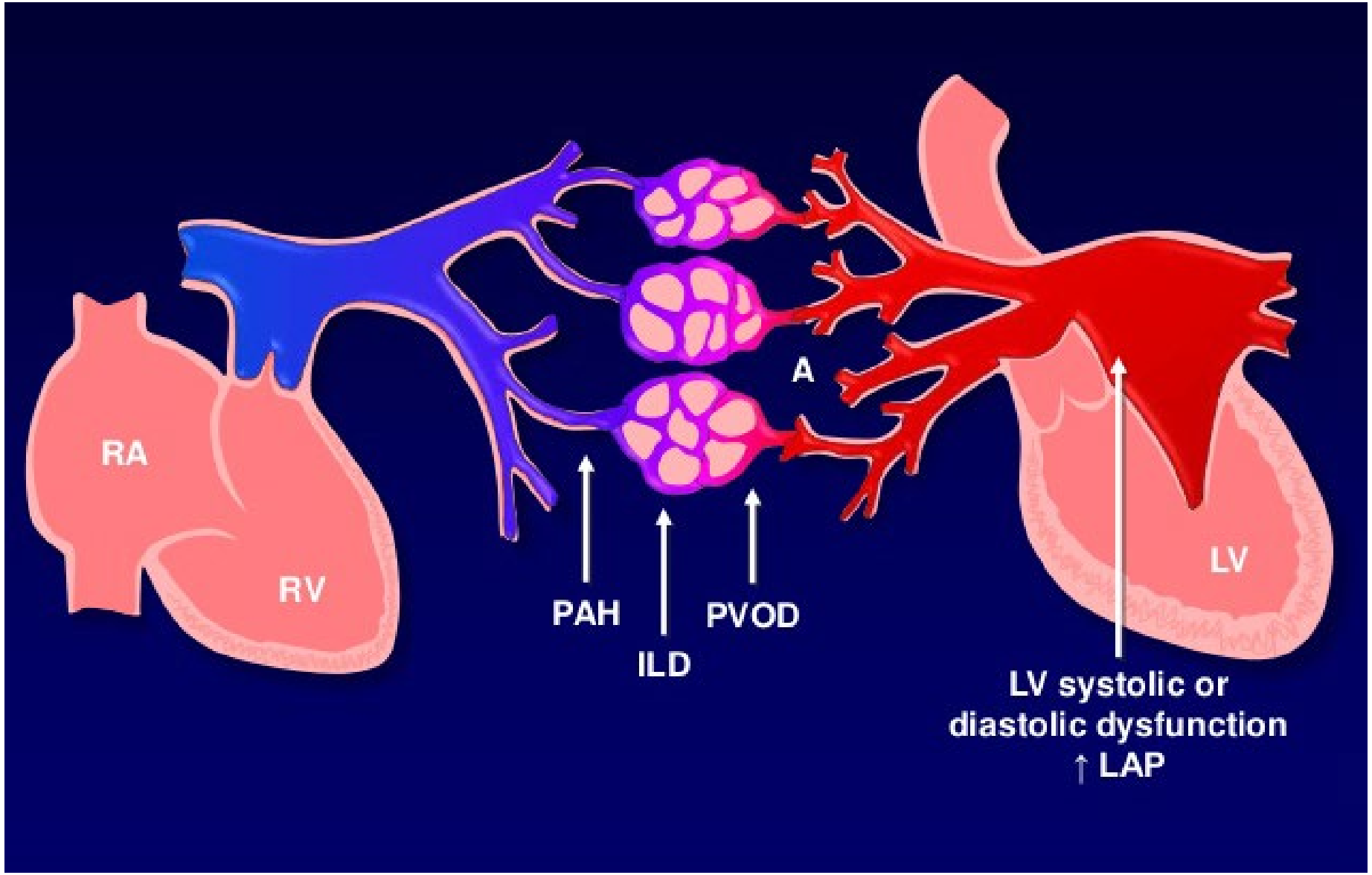


Mean pulmonary artery pressure (10 mm Hg = 1.36 x 10^3 N m^{-2}) in 24 normal subjects.
The columns show individual values and average values with 1 SD, when the subjects are supine, standing at rest, and walking at 4.8 km h^{-1} (2.8 miles/hr) on a treadmill which is horizontal; inclined at 8:100; and at 16:100.

Damato, Galante, and Smith (1965). 'Hemodynamic response to treadmill exercise in normal subjects'. *J. appl. Physiol.* **21**, 959-66.)

History of Clinical Classification

- “Primary pulmonary hypertension”
  - 1973 – First World Symposium on Pulmonary Hypertension (WSPH)
  - Total of 6 between 1973 and 2018
  - World Health Organization (WHO) assembly on clinical classification


RA
RV
A
PAH
ILD
PVOD
LV
LV systolic or
diastolic dysfunction
↑ LAP

Pulmonary Hypertension Heterogeneity

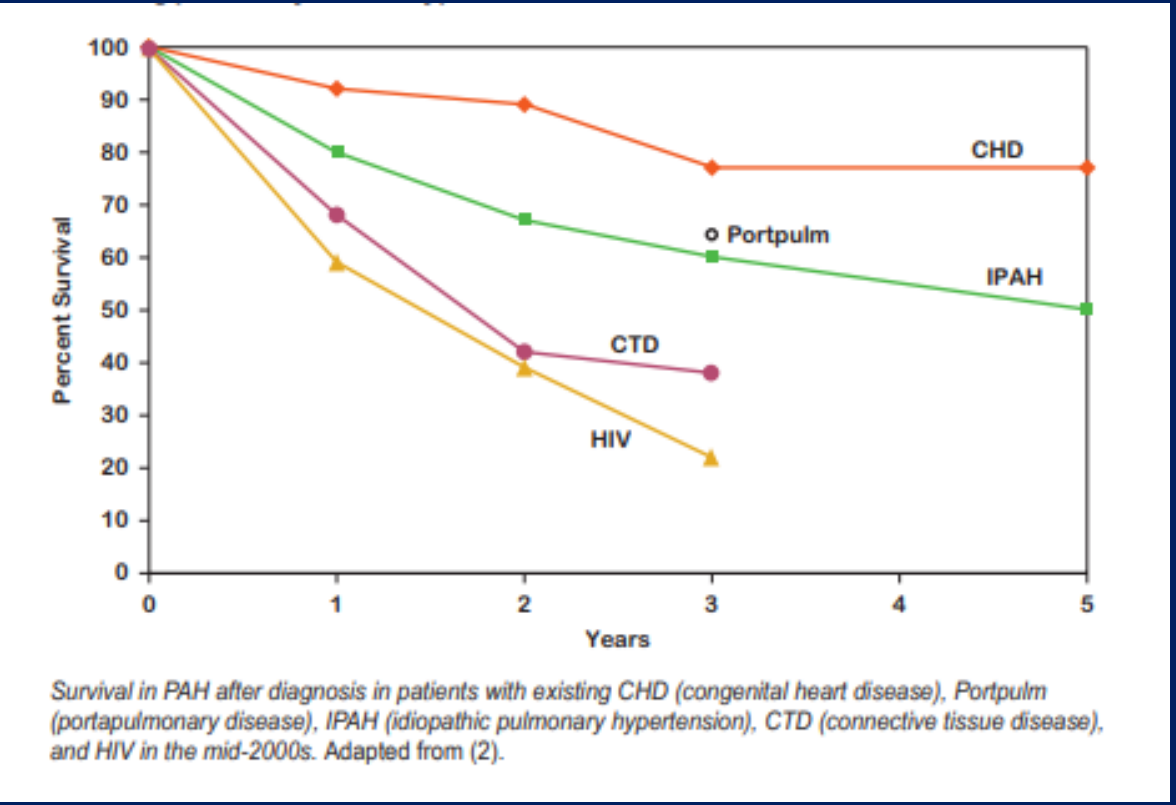
Group	Diseases
Group I - Pulmonary arterial hypertension	Idiopathic, heritable, toxic, associated (SSc, CREST, HIV)
Group II - Left heart disease	Systolic, diastolic, valvular heart disease
Group III - Alveolar hypoxemia, Lung dz	COPD, hypoxemia (OHVS, Sleep Apnea, Interstitial lung disease)
Group IV - Thromboembolic	CTEPH, tumor embolism
Group V - Miscellaneous	Sarcoid, LAM, vasculitis, metabolic disease

Galie N, JACC (2013), McLaughlin V, JACC (2015)

Clinical Classification

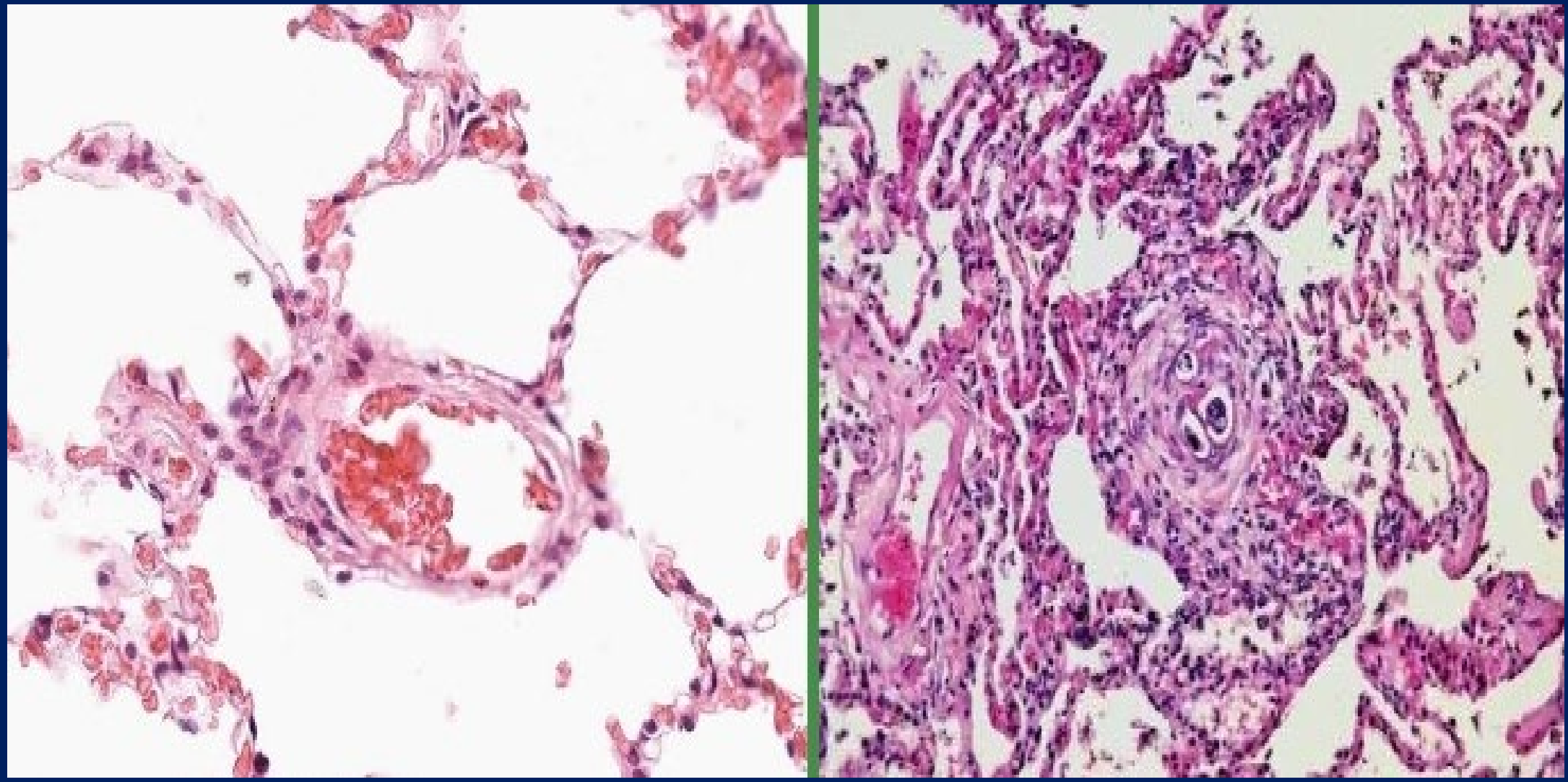
- WHO Group I:
  - Idiopathic
  - Heritable
  - Drugs and toxins
  - Associated with
    - Connective tissue disease
    - HIV
    - Portal hypertension
    - Congenital heart disease
    - Schistosomiasis
- WHO Group I’: veno-occlusive disease
- WHO Group I”: persistent PH of the newborn

Surviving pulmonary arterial hypertension



Survival in PAH after diagnosis in patients with existing CHD (congenital heart disease), Portpulm (portapulmonary disease), IPAH (idiopathic pulmonary hypertension), CTD (connective tissue disease), and HIV in the mid-2000s. Adapted from (2).

2. Hyduk A, Croft JB, Ayala C, Zheng K, Zheng ZJ, Mensah GA. Pulmonary hypertension surveillance—United States, 1980–2002. MMWR Surveill Summ 2005;54:1–28.

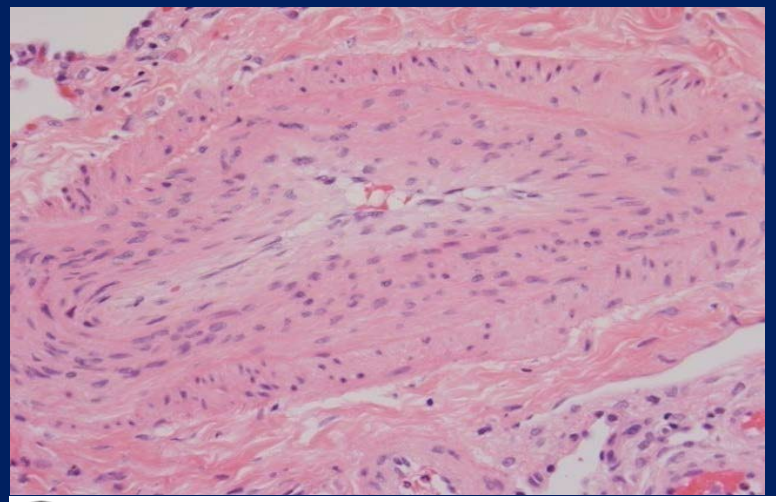


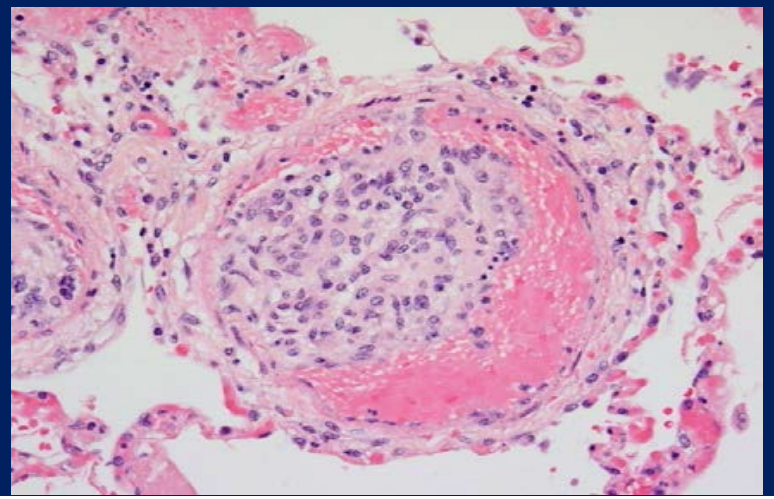
Normal Pulmonary Artery

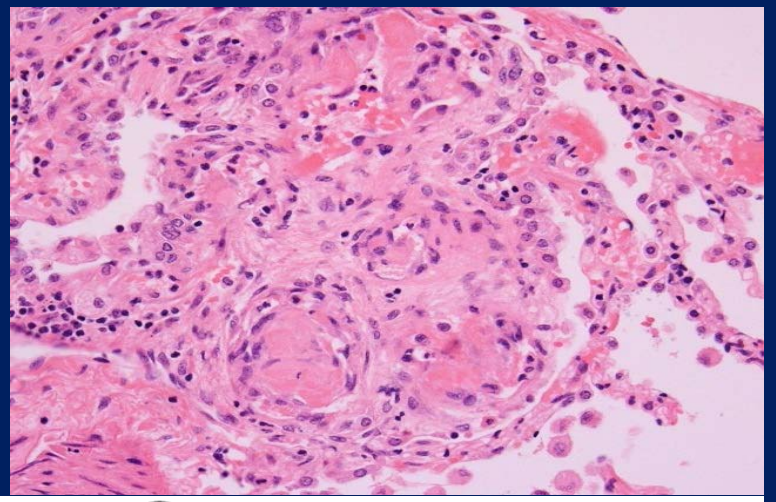
Pulmonary Arterial Hypertension

Endothelial thickening

In situ **thrombosis**





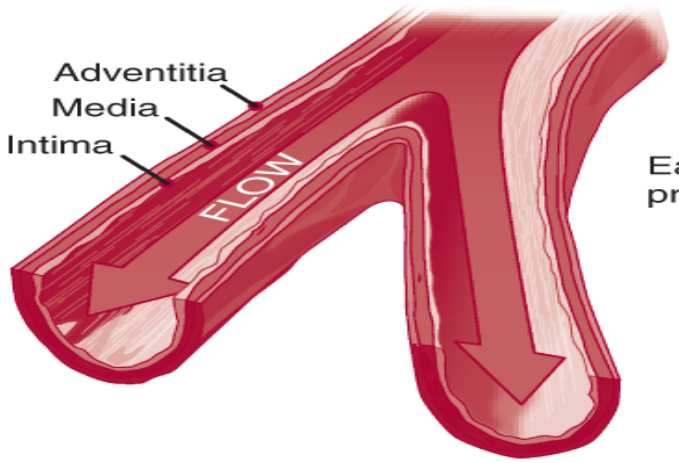


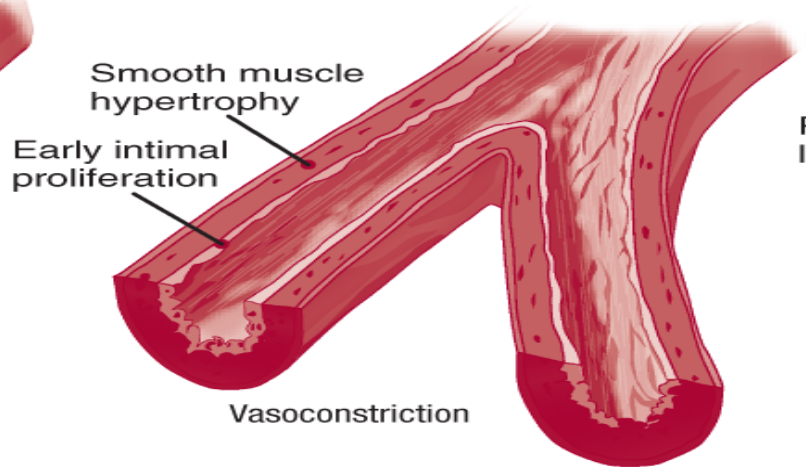
1 RISK FACTORS AND ASSOCIATED CONDITIONS
Collagen vascular disease
Congenital heart disease
Portal hypertension
HIV infection
Drugs and toxins
Pregnancy

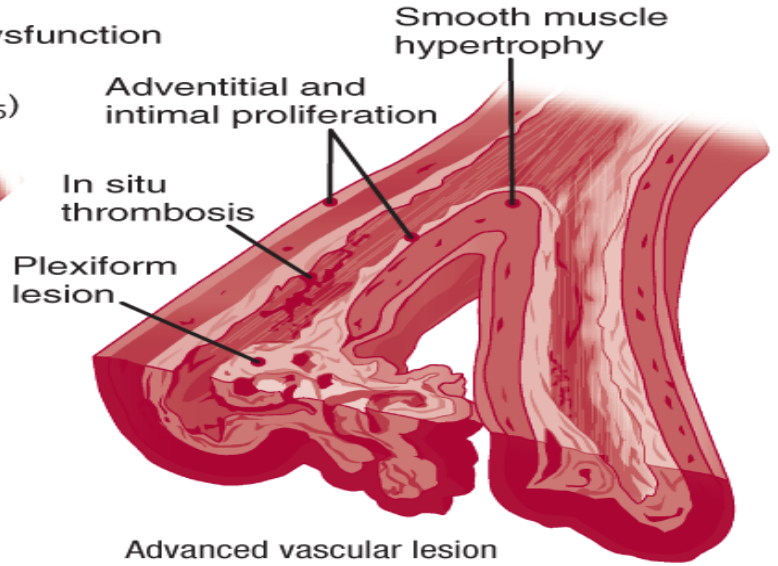
SUSCEPTIBILITY
Abnormal *BMPR*-2 gene
Other genetic factors

2 VASCULAR INJURY
Endothelial dysfunction
↓ Nitric oxide synthase
↓ Prostacyclin production
↑ Thromboxane production
↑ Endothelin-1 production
Vascular smooth muscle dysfunction
Impaired voltage-gated potassium channel ($K_{V1.5}$)

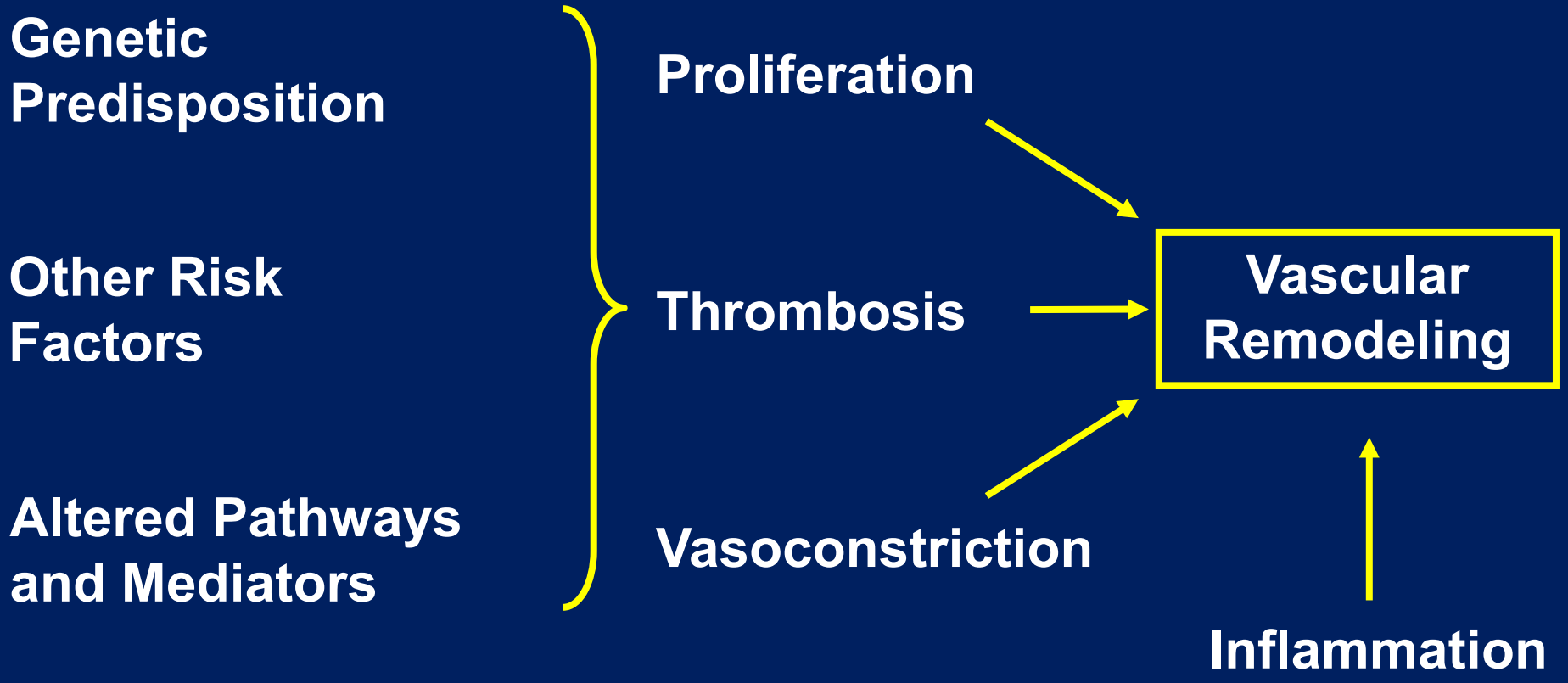
3 DISEASE PROGRESSION
Loss of response to short-acting vasodilator trial





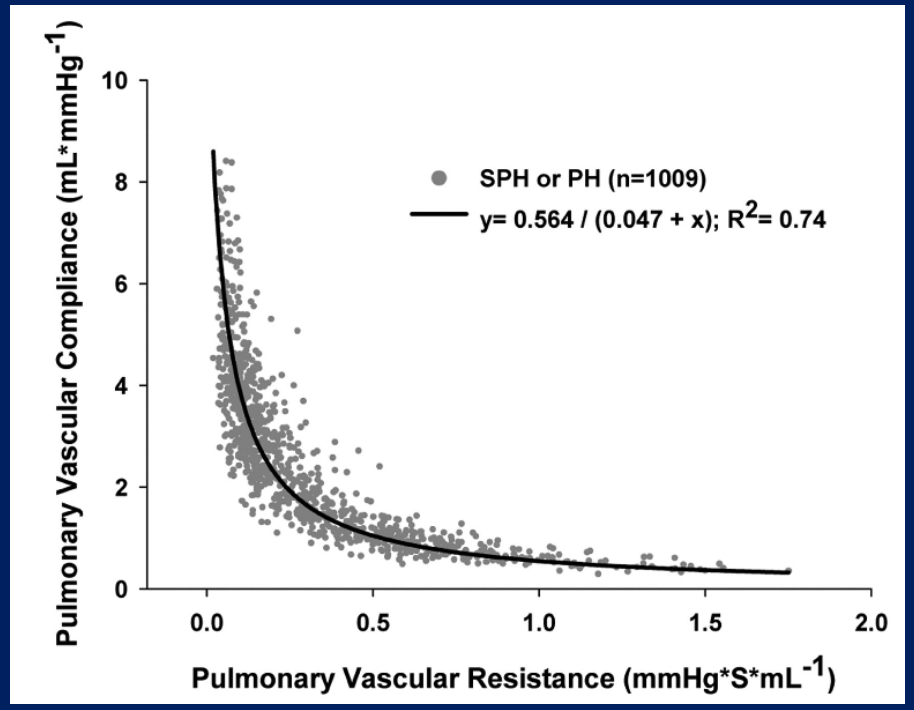


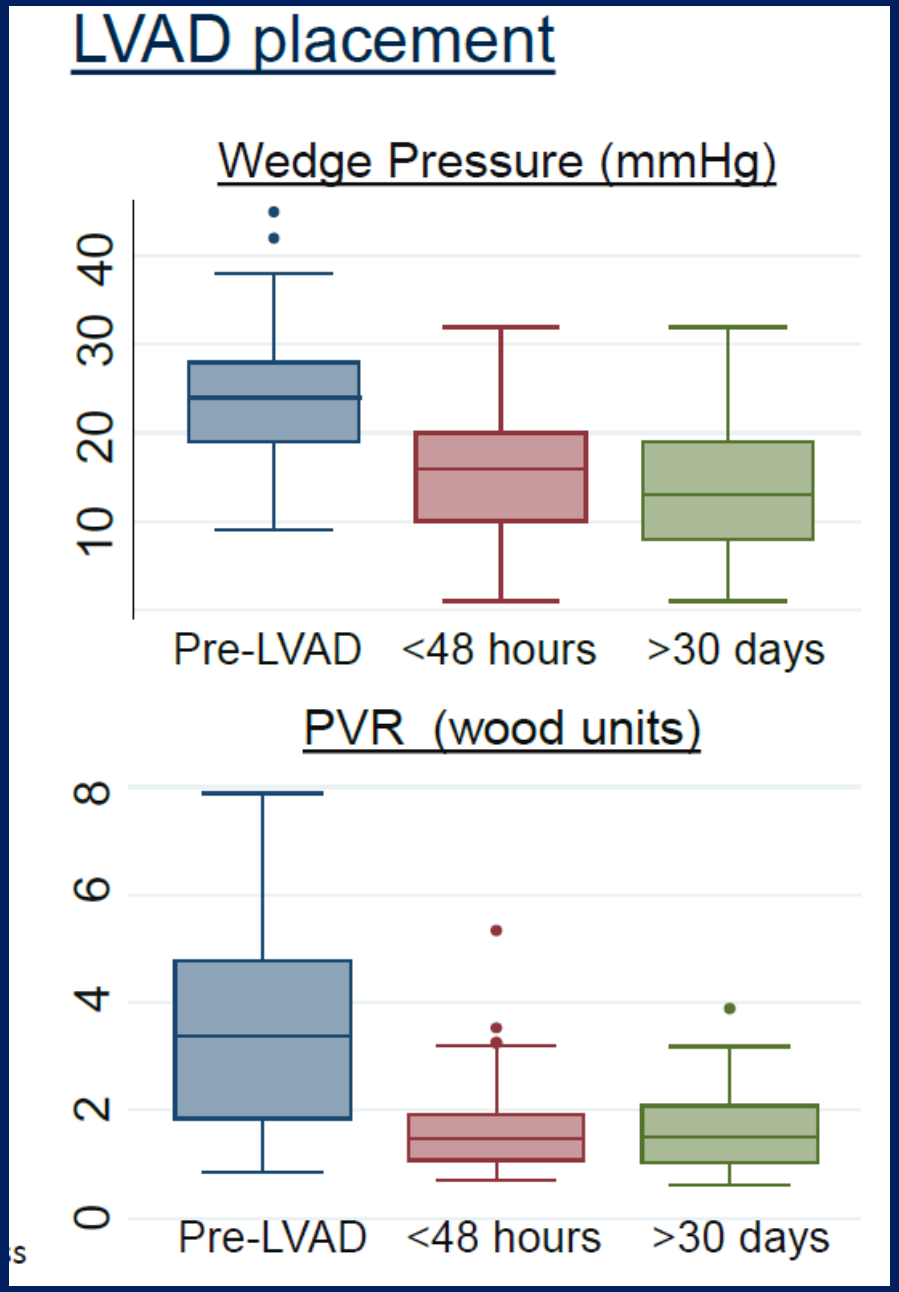
The Relentless Pathology



Clinical Classification

- **WHO Group 2**:
  - Increased wall stress
  - Activation of vascular stretch receptors



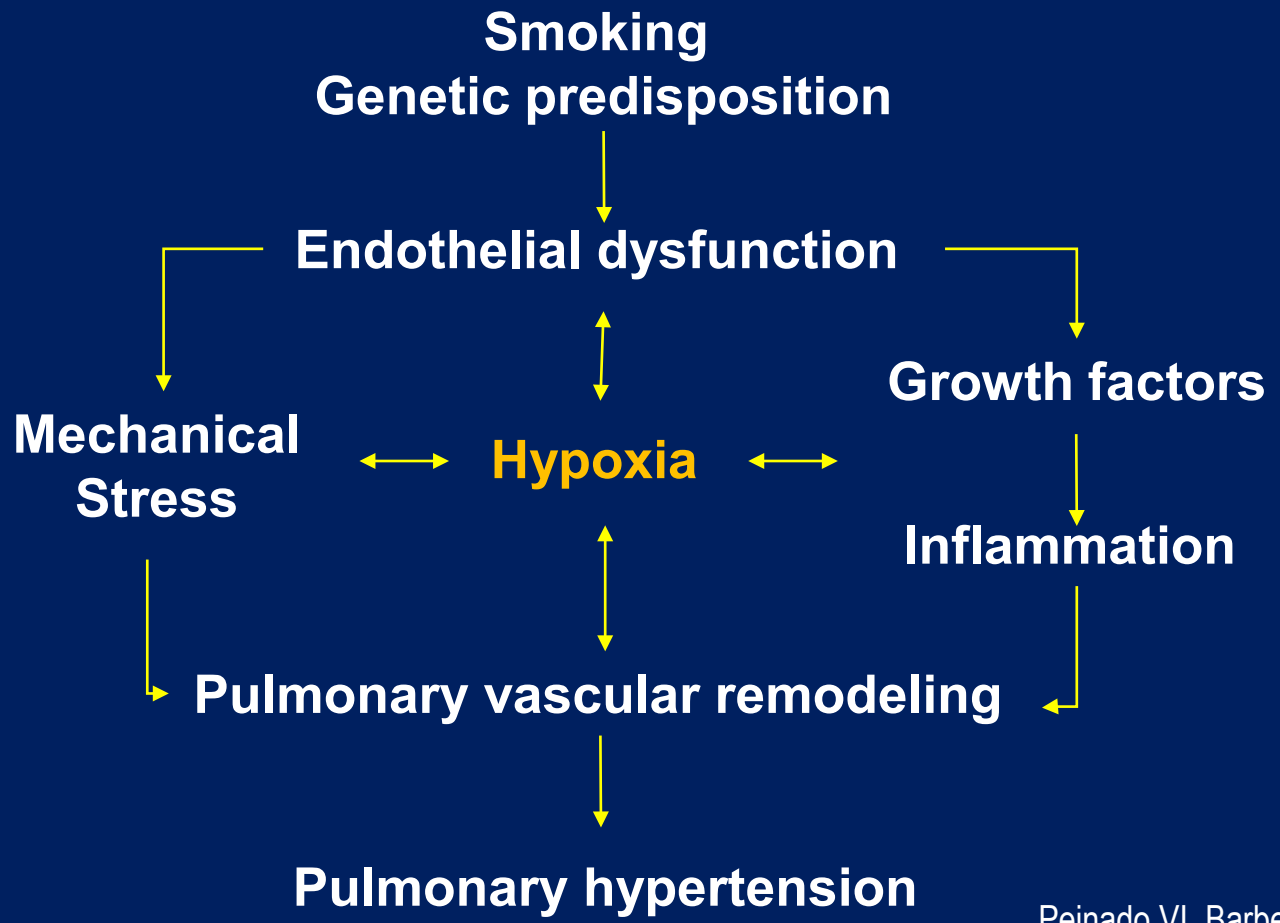


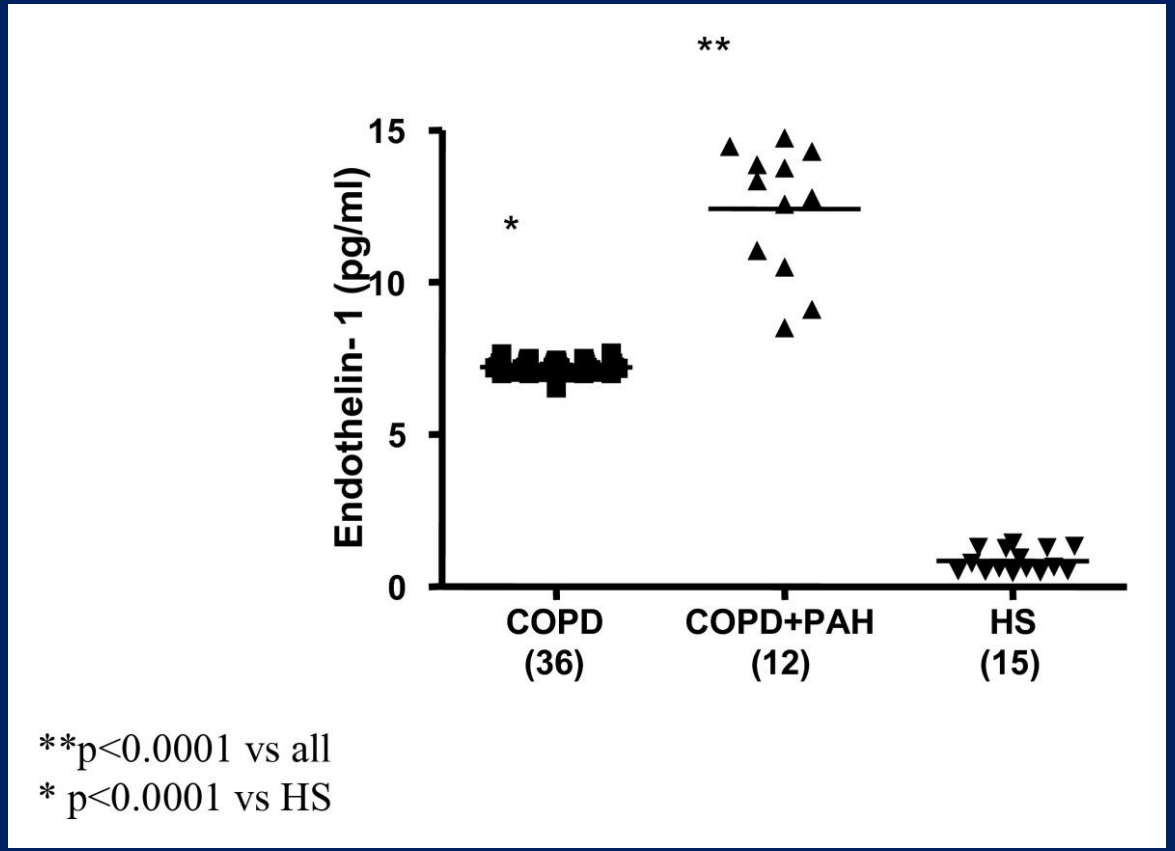
Kulik TJ. Pulm Circ (2014), Tedford RJ. Circulation (2012)

Clinical Classification

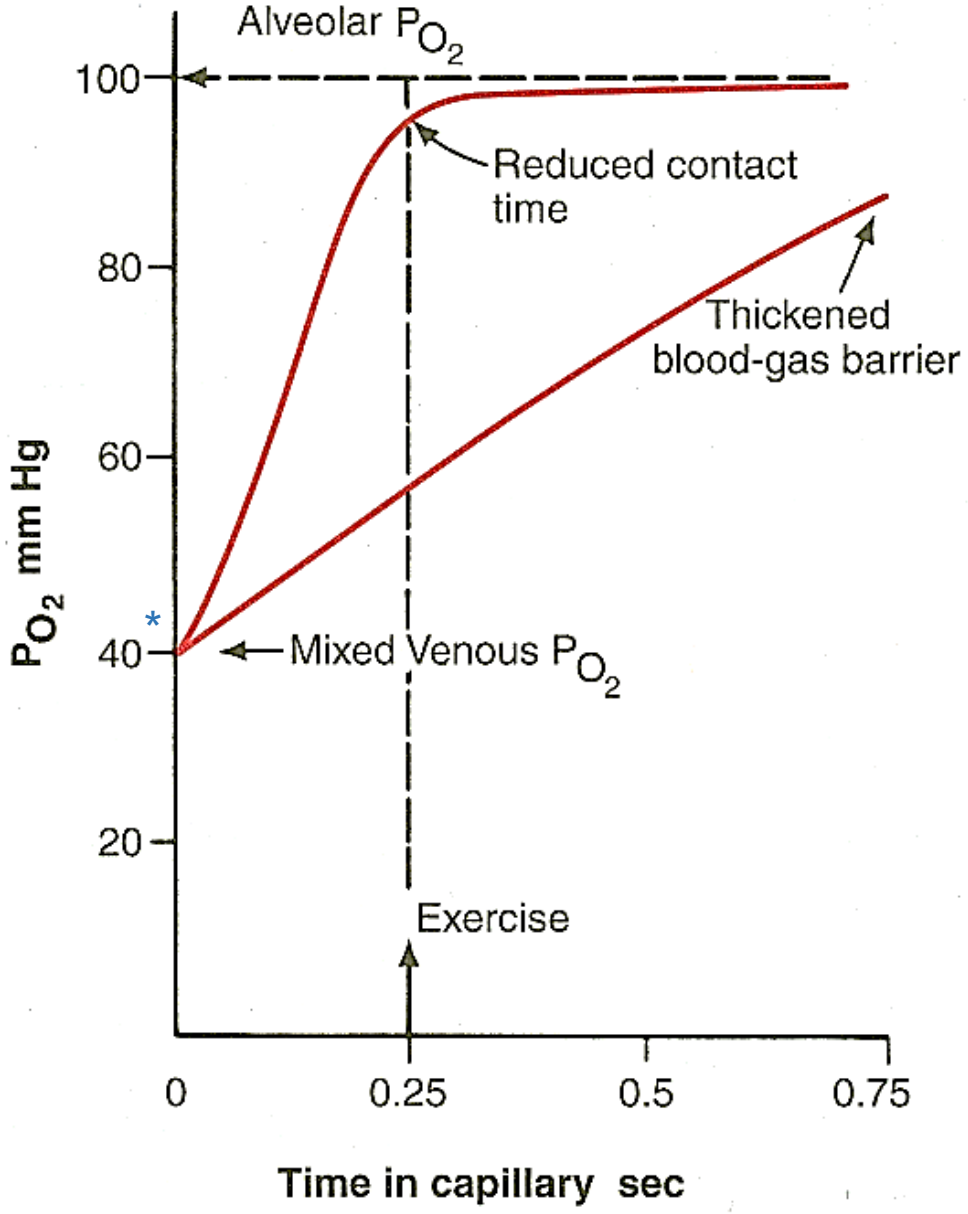
- WHO Group 3:
  - Chronic obstructive pulmonary disease
  - Interstitial lung disease
  - Pulmonary disease with mixed restrictive and obstructive pattern
  - Sleep-disordered breathing
  - Alveolar hypoventilation disorders
  - Chronic exposure to high altitude

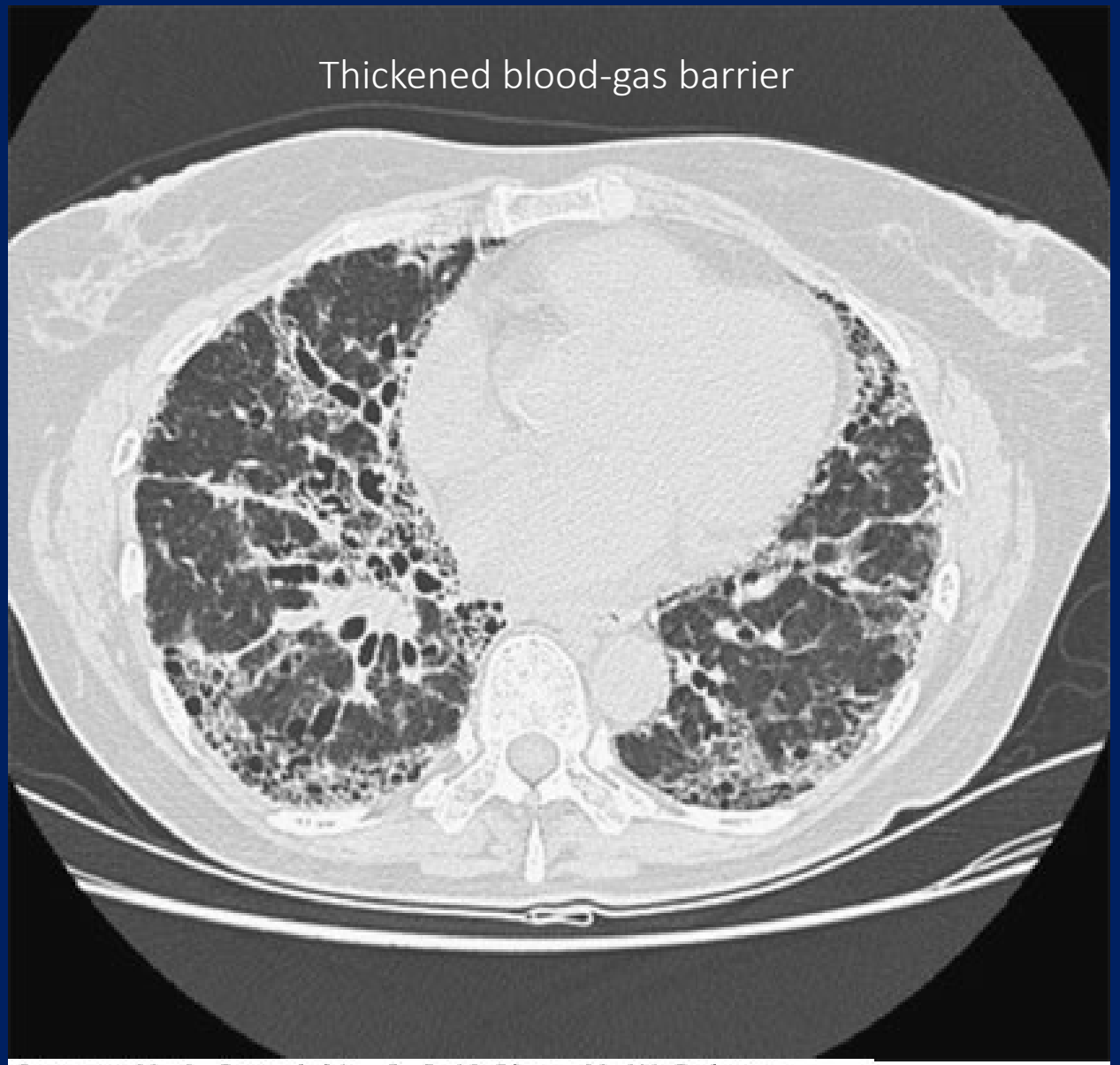
Pathophysiology of Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease





Peinado VI, Barbera JA, Ramirez J, et al. Endothelial dysfunction in pulmonary arteries of patients with mild COPD. Am J Physiol. 1998;274(6 Pt 1):L908-L913.
Castaldi PJ, Hersh CP, Reilly JJ, Silverman EK. Genetic associations with hypoxemia and pulmonary arterial pressure in COPD. Chest. 2009;135(3): 737-744.

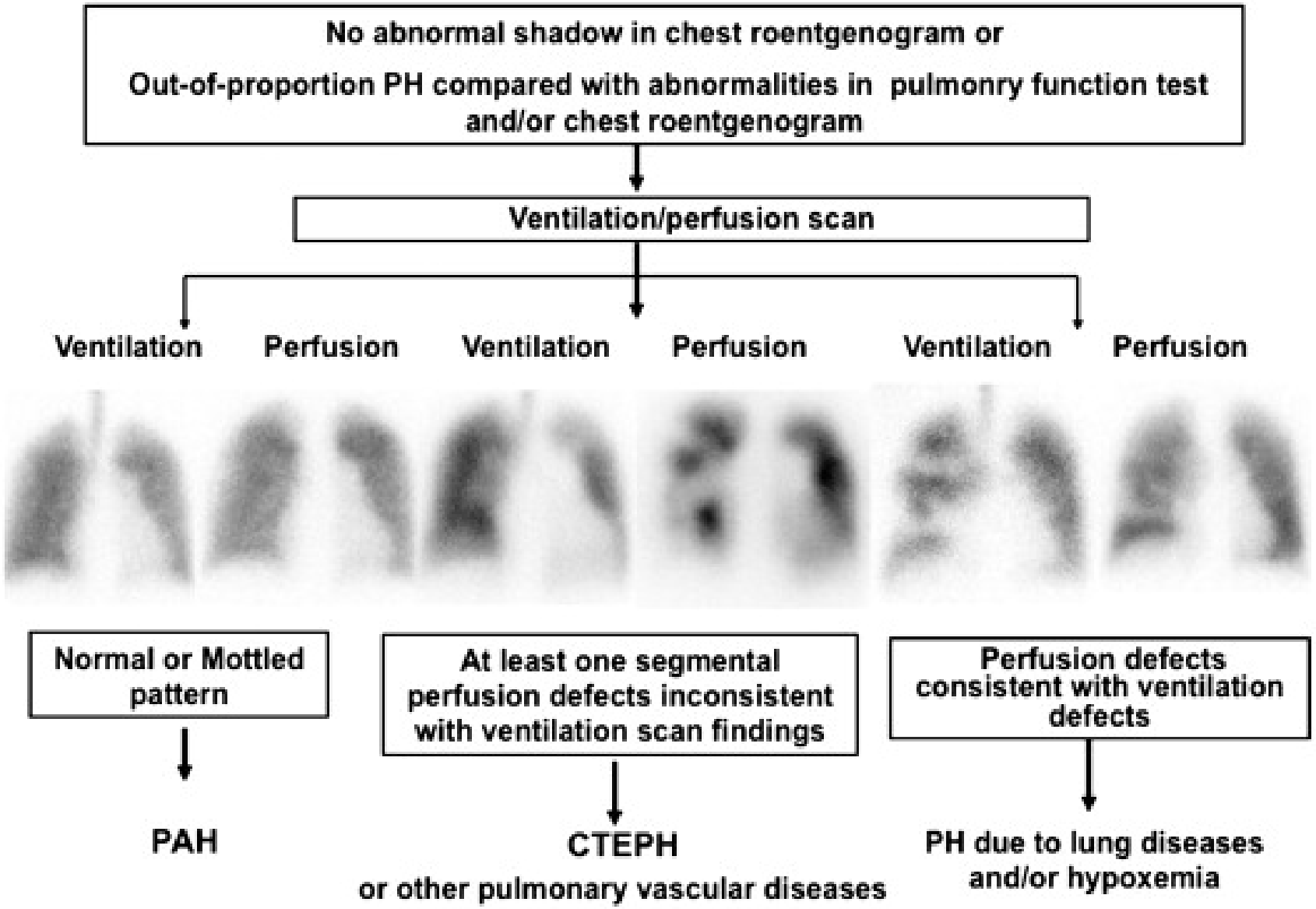




Source: M. A. Papadakis, S. J. McPhee, M. W. Rabow:
Current Medical Diagnosis & Treatment 2017, 56th Ed.
www.accessmedicine.com

Clinical Classification

- WHO Group 4:
  - Chronic thromboembolic pulmonary hypertension
  - Angiosarcoma
  - Arteritis
  - Congenital pulmonary artery stenosis
  - Parasites



Tanabe, N, Sugiura T and Tatsumi K. Respiratory Investigation. 51 (3): 2013; 134 – 146.

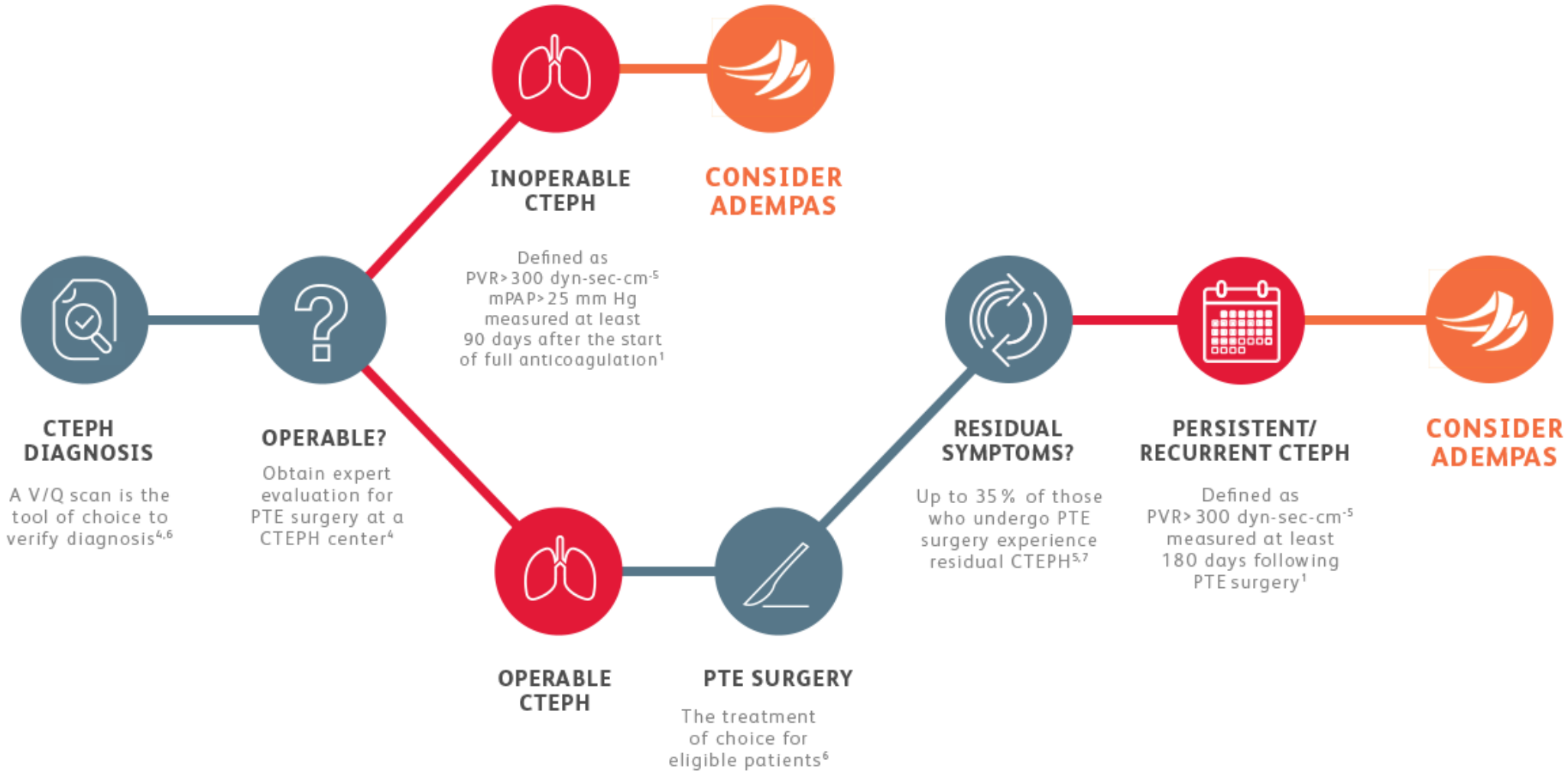
V/Q scan to rule out CTEPH

- Normal V/Q scan makes CTEPH unlikely
  - Sensitivity: 90 – 100%
  - Specificity: 94 – 100%

- > 1 segment-sized or larger mismatch perfusion defects seen in CTEPH

- CT angiography may miss and/or underestimate the degree of obstruction in chronic CTEPH
  - ~ 7% false negative rate

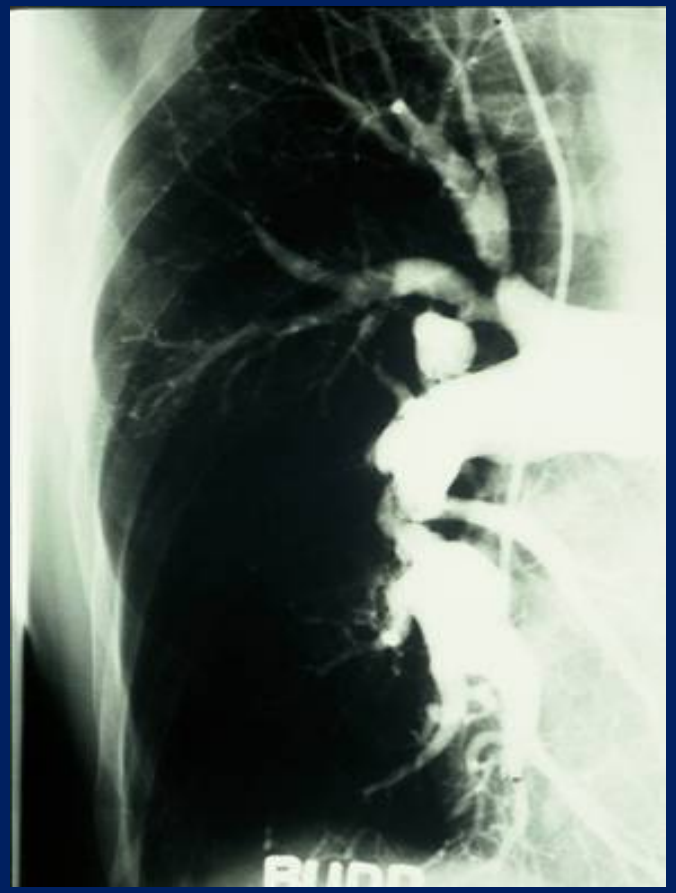
Freed DH, et al. Survival after pulmonary thromboendarterectomy: effect of residual pulmonary hypertension. *J Thorac Cardiovasc Surg*. 2011;141(2):383-387.
Kim NH, Delcroix M, Jenkins DP, et al. Chronic thromboembolic pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D92–D99.
Condliffe R, Kiely DG, Gibbs SR, et al. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. *Am J Respir Crit Care Med*. 2008;177(10):1122-1127.
Piazza G, Goldhaber SZ. Chronic thromboembolic pulmonary hypertension. *N Engl J Med*. 2011;364(4):351-360.
Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D34–D41

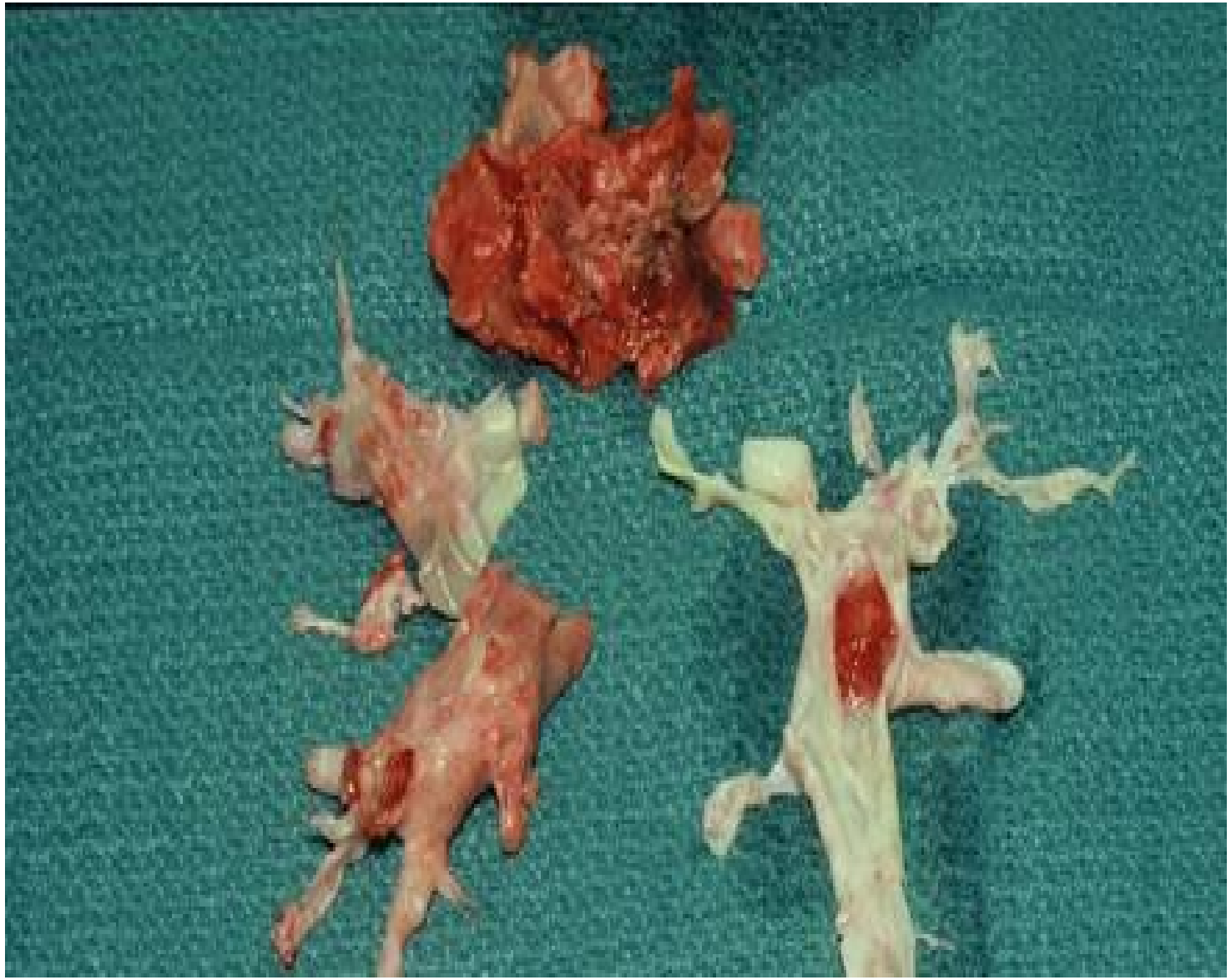


Ghofrani HA, D'Armini AM, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med*. 2013;369(4):319-329.
Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J.* 2016;37(1):67-119.

CTEPH: Pulmonary Angiography

- Confirms diagnosis of CTEPH in patients with PH
- Assess thrombus accessibility
- Distinct angiographic patterns
  - “Web” narrowing
  - Post-stenotic dilatation
  - Proximal occlusion
  - “Pouch” defects





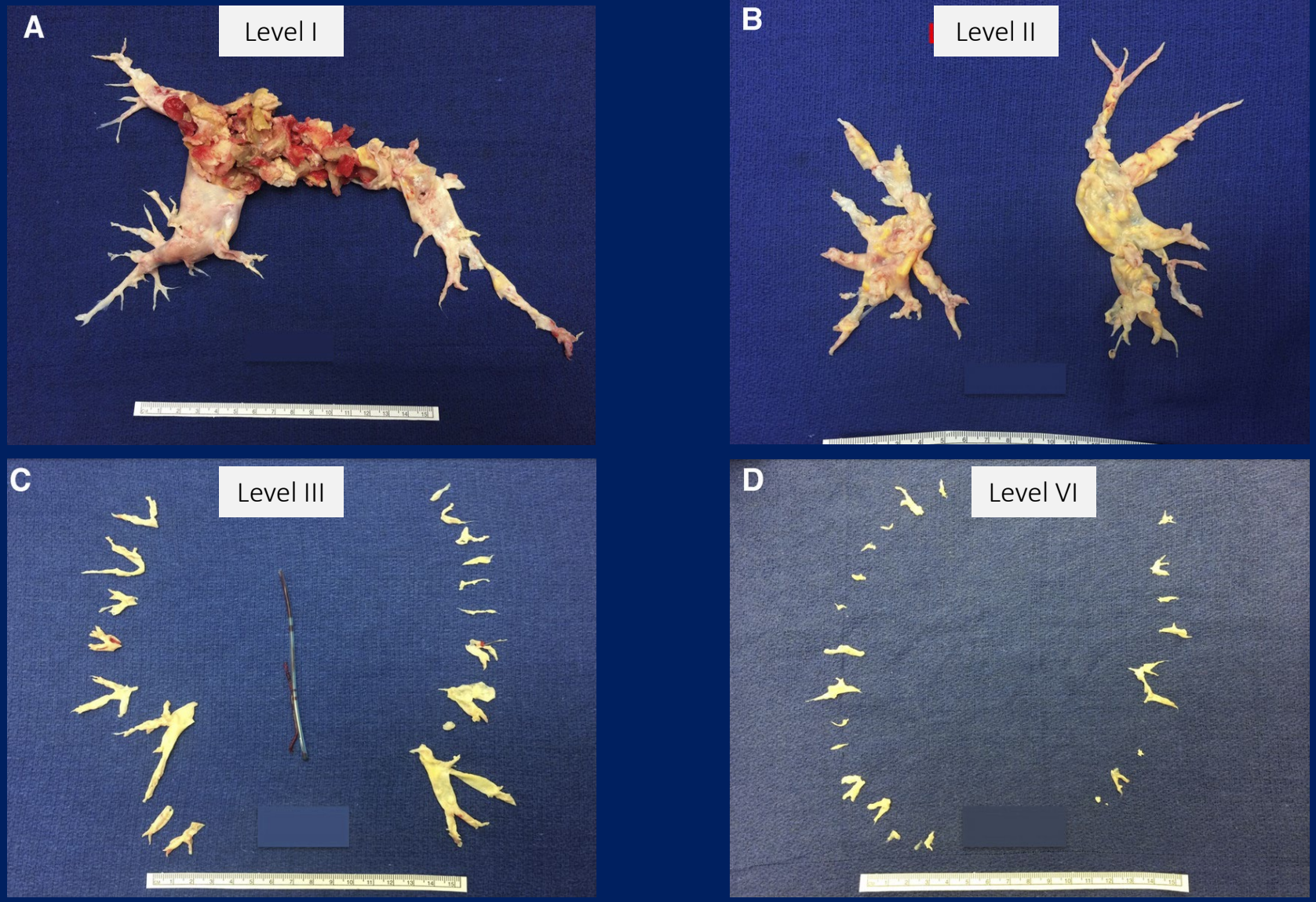


Figure. University of California, San Diego classification of pulmonary endarterectomy disease levels. This figure illustrates typical surgical specimens classified based on the most proximal level of obstruction, levels I to IV.
https://www.atsjournals.org/doi/abs/10.1513/AnnalsATS.201601-014AS
Published in: Michael Madani; Eckhard Mayer; Elie Fadel; David P. Jenkins; *Annals ATS* 13S240-S247. DOI: 10.1513/AnnalsATS.201601-014AS.

Clinical Classification

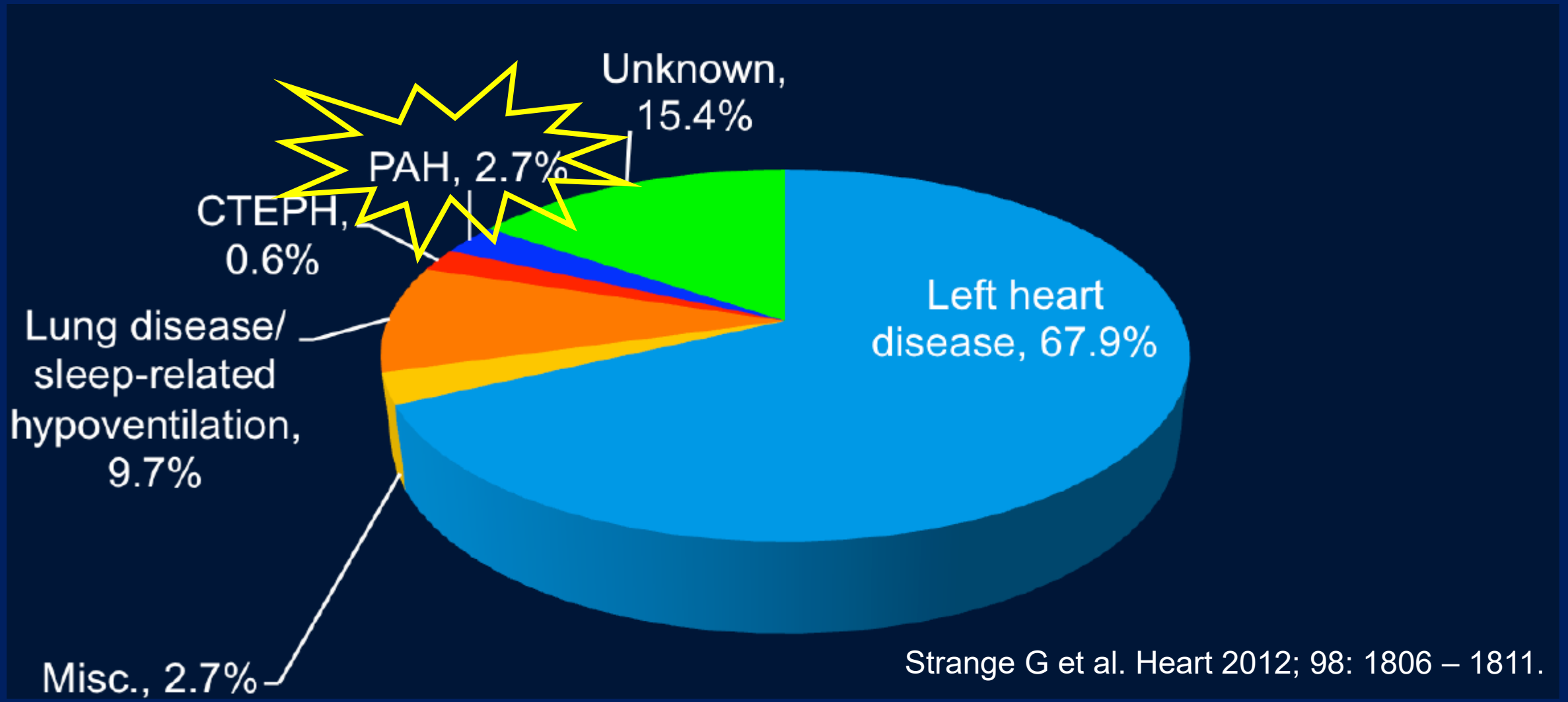
- WHO Group 5:

Pulmonary hypertension in ESRD

- Prevalence up 48% on echo reported in literature[1-4]
  - Only 10-14% had est. sPAP>45-50 mm Hg[1]
- Largest study: 500 pts, 68 (13%) on PD
  - Mean sPAP: 47± 9 mm Hg, range: 35-75 mm Hg
  - 5.9% incidence in PD patients
  - Longer duration of dialysis in PH pts, 51 vs 30 months
- Patients with PH had:
  - Higher CO[1-3]
  - Worse survival[1,3]

1. Yigla et al, Chest, 2003
2. Nakhoul, et al Nehrol Dial Transplant, 2005
3. Issa et al, Transplantation, 2008
4. Bozbas et al, Transplanat Proc, 2009
5. Hemnes et al, Nephrol Seminar, 2010

Epidemiology of pulmonary hypertension

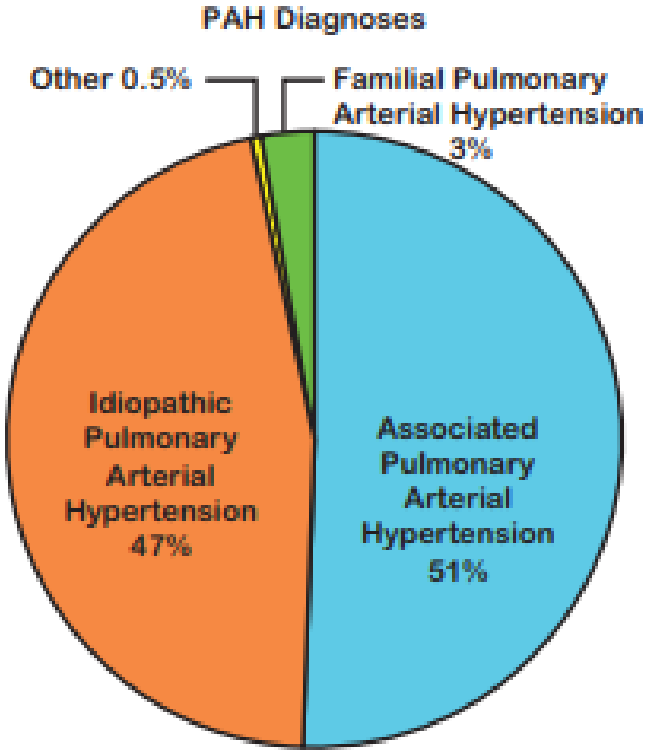


Strange G et al. Heart 2012; 98: 1806 – 1811.

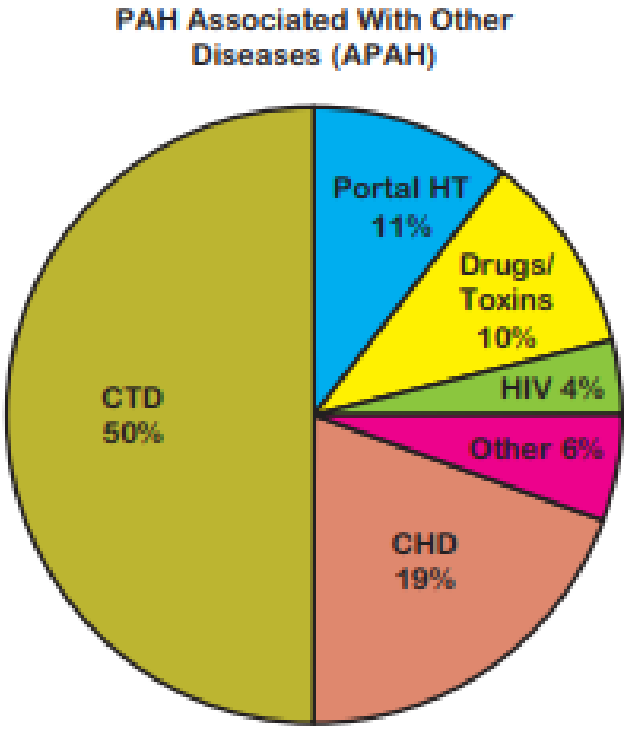
Epidemiology: PAH is rare in patients >65 years of age referred to our PH center

Diagnosis		Number (%) (n = 248)
Pulmonary Arterial Hypertension (PAH)		37 (15%)
	Idiopathic PAH	5
	CTD-associated PAH	28
	CHD-associated PAH	1
	Portopulmonary HTN	3
PH owing to left heart disease		70 (28%)
PH owing to lung disease and/or hypoxia		35 (14%)
Chronic thromboembolic PH		19 (8%)
Other or mixed causes of PH		42 (17%)
Unknown		24 (10%)
No PH		21 (8%)

Causes of pulmonary arterial hypertension



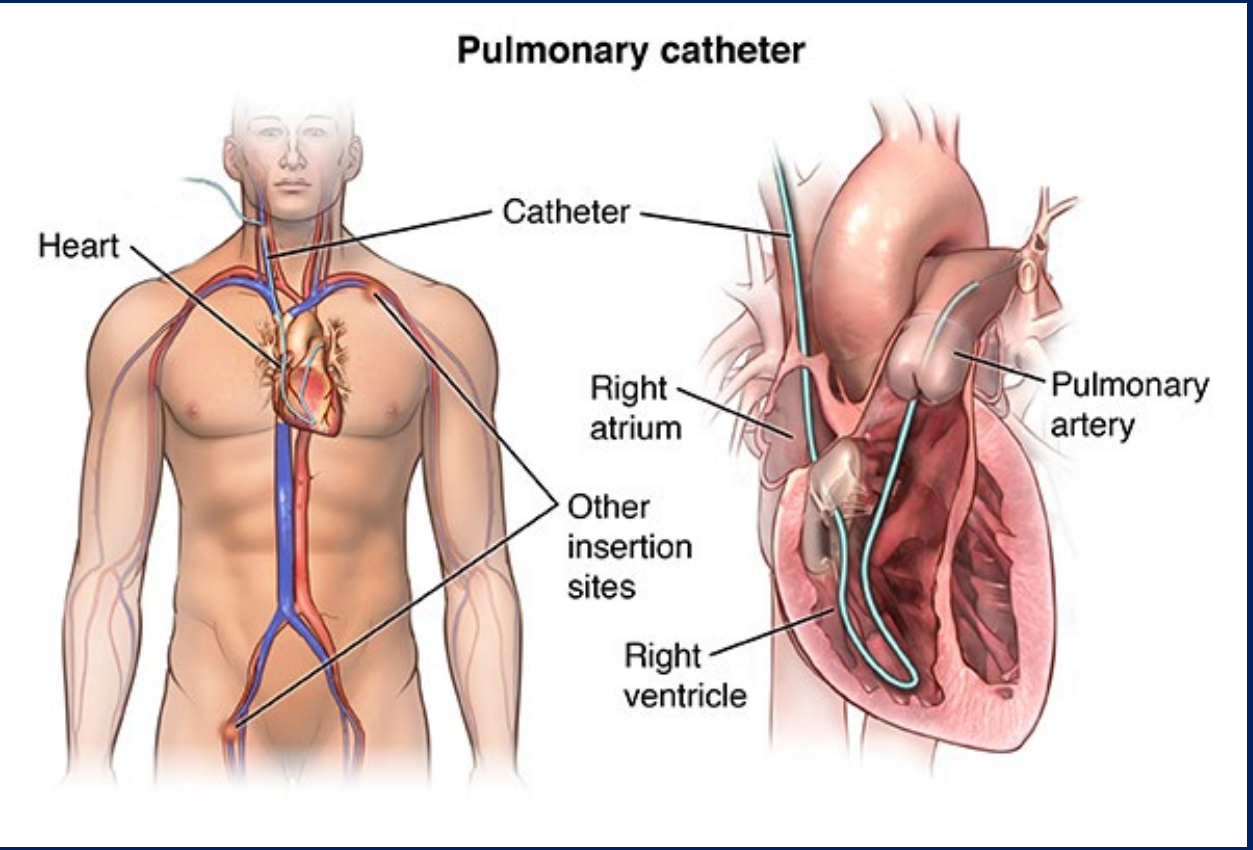
Diseases associated with pulmonary arterial hypertension

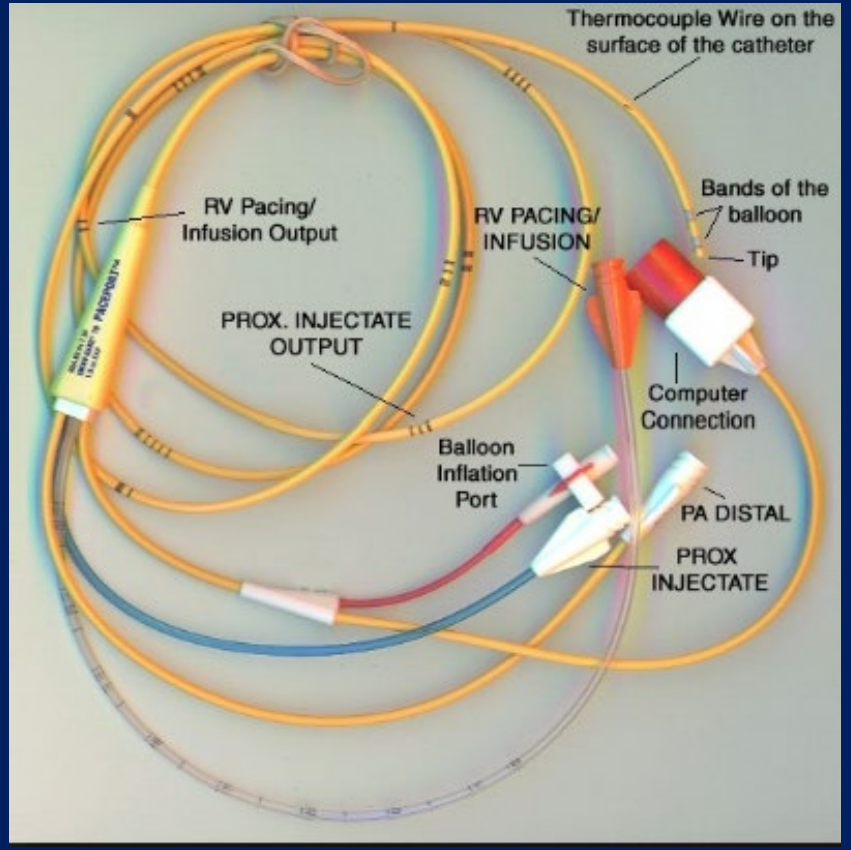


The pie chart on the left shows the causes of pulmonary arterial hypertension. The pie chart on the right breaks down the diseases associated with it. (Chronic thromboembolic pulmonary hypertension was not part of this registry.) Portal HT is pulmonary hypertension associated with liver disease. CTD is connective tissue disease; CHD is congenital heart disease. Reprinted from the *Journal of the American College of Cardiology,* Vol. 53. Issue 17, "ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension: A Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association," with permission from Elsevier.

Diagnosis

- **Right heart catheterization is gold standard**





Diagnosis

- Right heart catheterization is gold standard
- Absolutely needed before you make the diagnosis?
- Absolutely needed before you start therapy?
- Data to collect:
  - Chest CT, PFTs, Echocardiogram, VQ Scan, ANA, RF, anti-ccp, ANCA, anti-scl70, anti-Ro, anti-La, anti-ds dna, HIV, toxicology screen, a history, liver function tests, sleep study, stool ova and parasites, schistosomiasis serology

Screening for pulmonary hypertension

- History of present illness: (80%)
  - Dyspnea on exertion
  - Fatigue
- Delay in screening and diagnosis is 1.5 to 2 years

Historical Epoch	Time from 1st symptoms to diagnosis
Kennedy Era	~ 4.8 years
Regan Era	~ 2.3 years
Obama Era	~ 1.1 years

  - Other symptoms: (20%)
    - syncope / chest pain
    - palpitations
    - peripheral edema

Symptoms at diagnosis

Symptoms	Initial Symptoms (%)	At diagnosis
Dyspnea	60%	98%
Fatigue	19%	73%
Angina*	7%	47%
Near syncope	5%	41%
Syncope*	8%	36%
Leg edema*	3%	37%
Palpitations	5%	33%

* = symptoms of advanced disease, also includes dyspnea at rest

Hegewald MJ, Markewitz B, Elliott CG. Int J Clinic Practice Suppl. 2007; 156: 5 – 14.

Screening

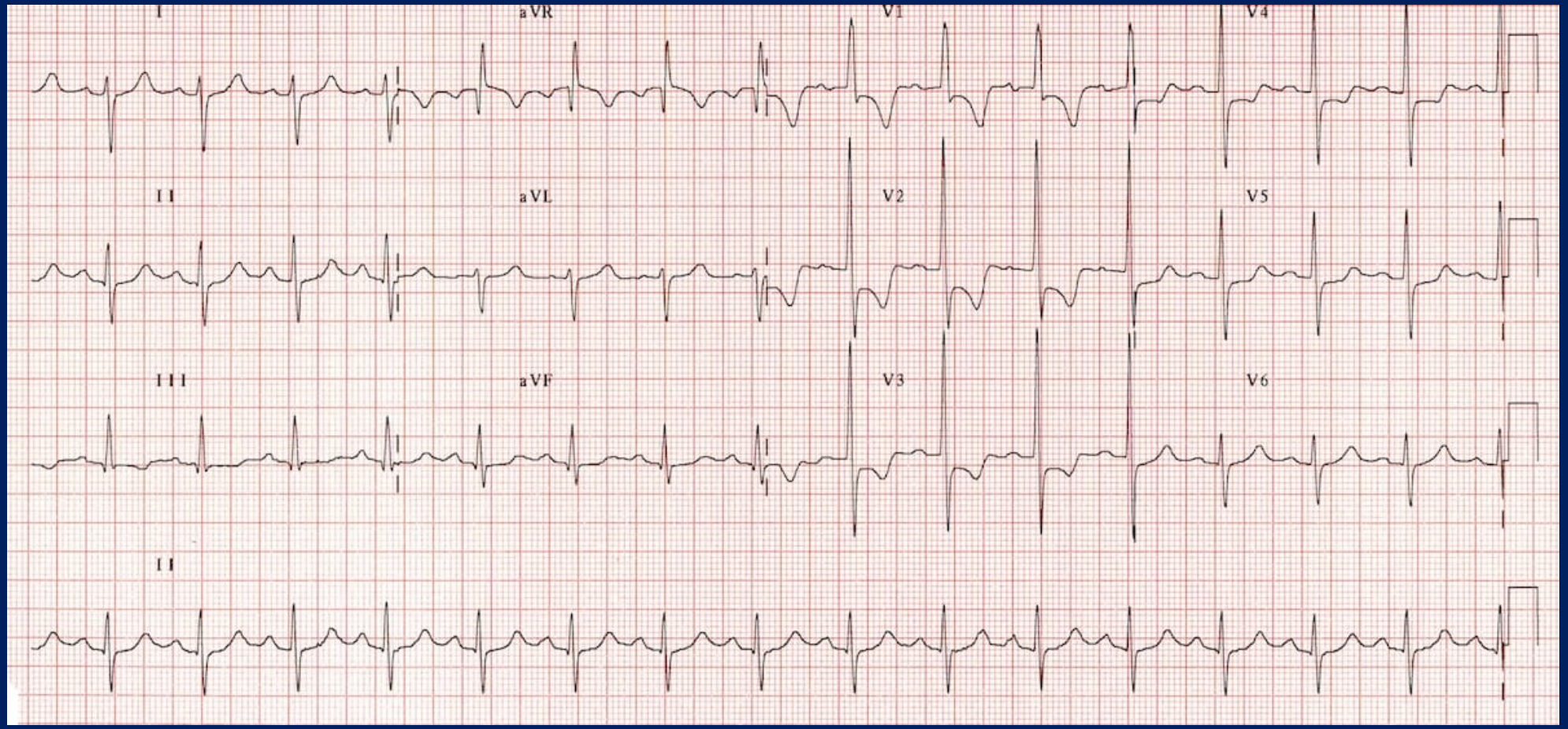
Definite	Likely	Possible
• Aminorex • Fenfluramine • Dexfenfluramine • Toxic rapeseed oil • Benfluorex • Selective serotonin reuptake inhibitors[a]	• Amphetamines • Dasatinib • L-tryptophan • Methamphetamines	• Cocaine • Phenylpropanolamine • St John's Wort • Amphetamine-like drugs • Interferon α and β • Some chemotherapeutic agents such as alkylating agents (mytomycine C, cyclophosphamide)[b]

- Past Medical History:
  - Connective tissue disease
    - 12% scleroderma-spectrum
  - Weight loss supplements/drugs
  - Deep venous thromboses, pulmonary emboli
    - 20 to 30% with no prior knowledge of above
  - Portal hypertension, cirrhosis
    - Portopulmonary hypertension is an indication for liver transplant evaluation
  - Congenital heart disease, especially ASD/VSD
    - 2.5% < 30 years, 35% > 30 years

Screening

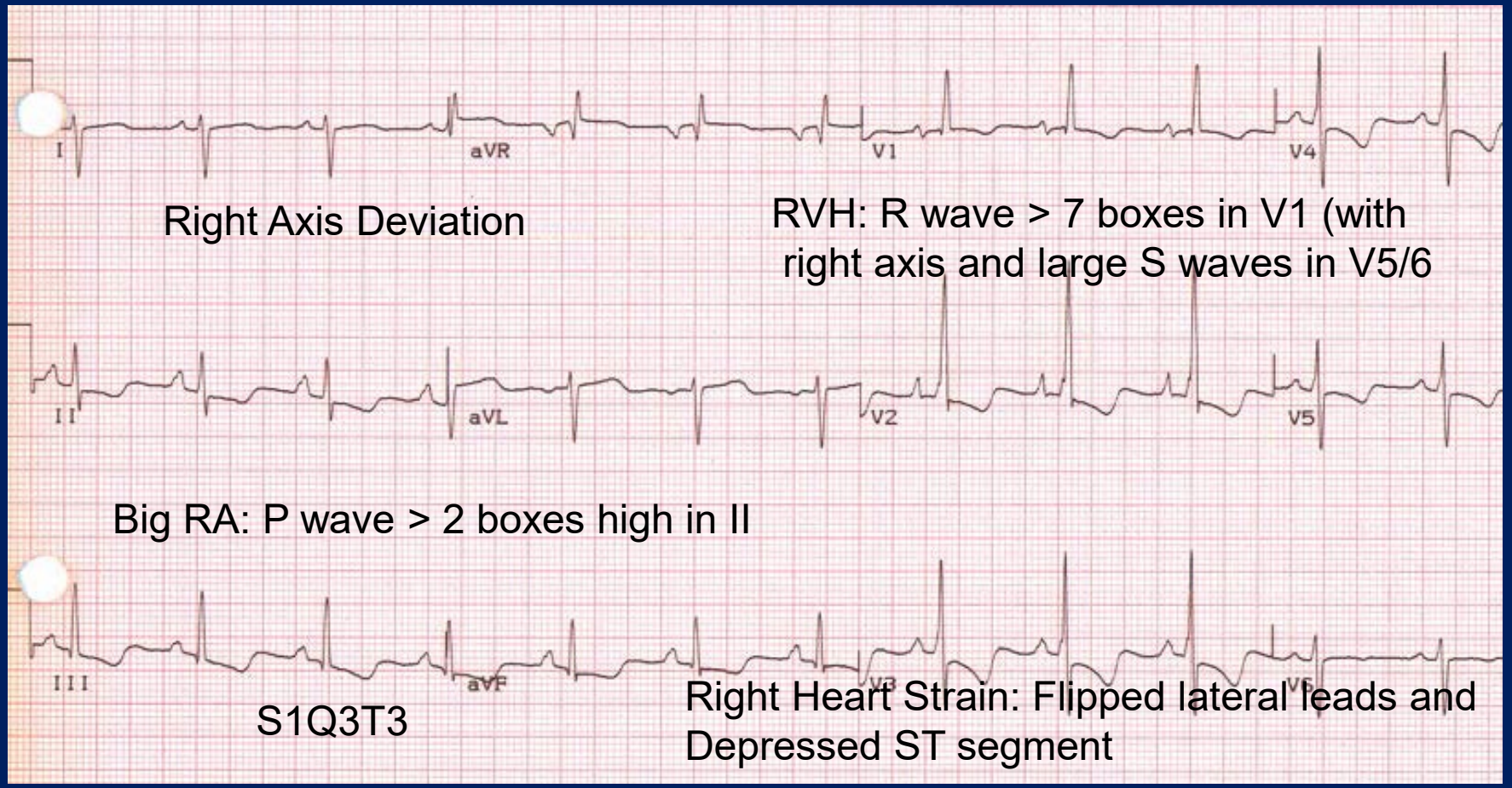
- Physical examination
  - Loud P2
  - Right ventricular lift/heave
  - Systolic or diastolic murmur/tricuspid, pulmonic insufficiency
  - Jugular venous distention, prominent V wave
  - Signs of RHF: abdominal distention/ascites/hepatomegaly/edema
  - Cool peripheral extremities
  - Sclerodactyly, Raynaud's, digital ulceration
  - Spider nevi, palmar erythema
  - Rales and cardiac wheezing are typically absent

Electrocardiogram



Electrocardiogram

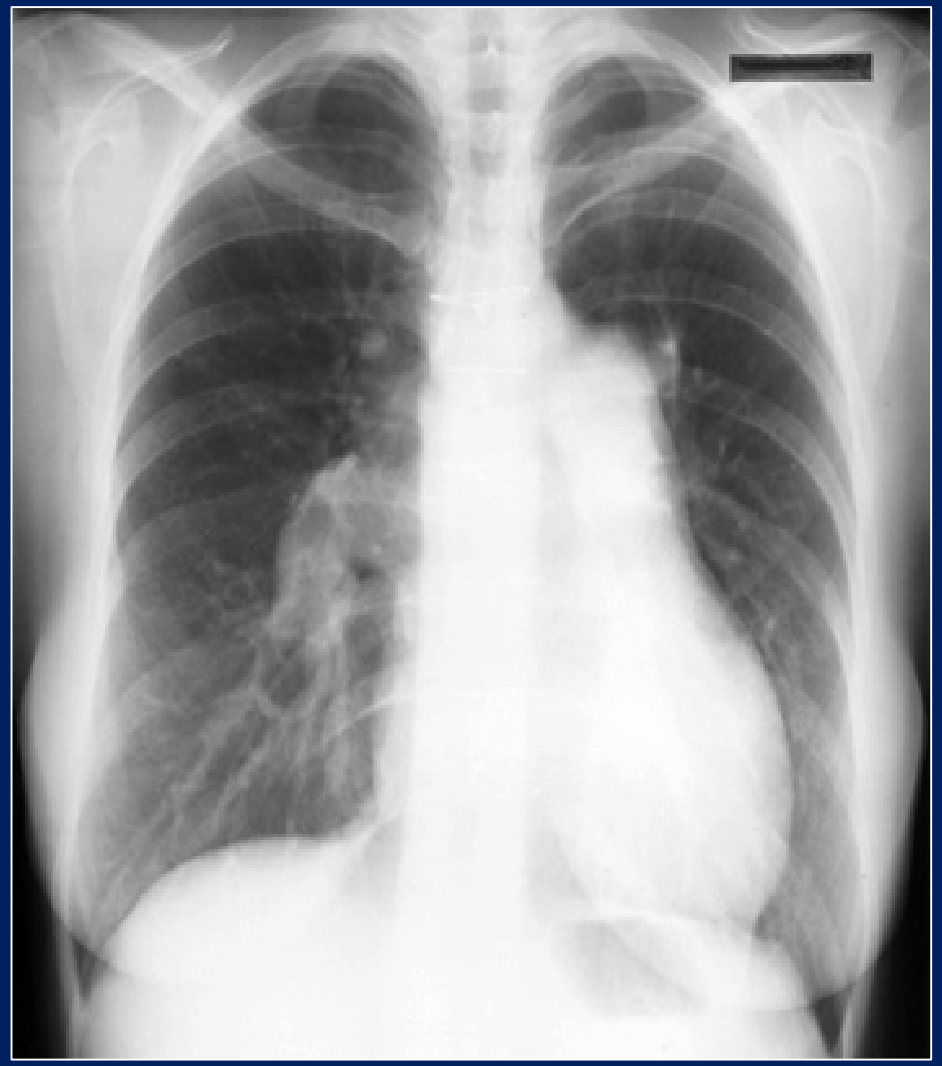
EKG is abnormal in ~ 80% of patients at dx



Chest radiograph

- Chest radiograph is abnormal in the majority of patients with pulmonary hypertension (PH);
  - No correlation between the severity of PH and the findings on chest X-ray.
  - Chest films allows the exclusion of disease.

- Findings of PH on chest X-ray include:
  - Hilar pulmonary arterial dilation
  - Loss of peripheral blood vessel markings
  - Enlarged right atrium and right ventricle in advanced diseases



Posteroanterior radiograph revealing enlarged pulmonary arteries in a patient with atrial septal defect

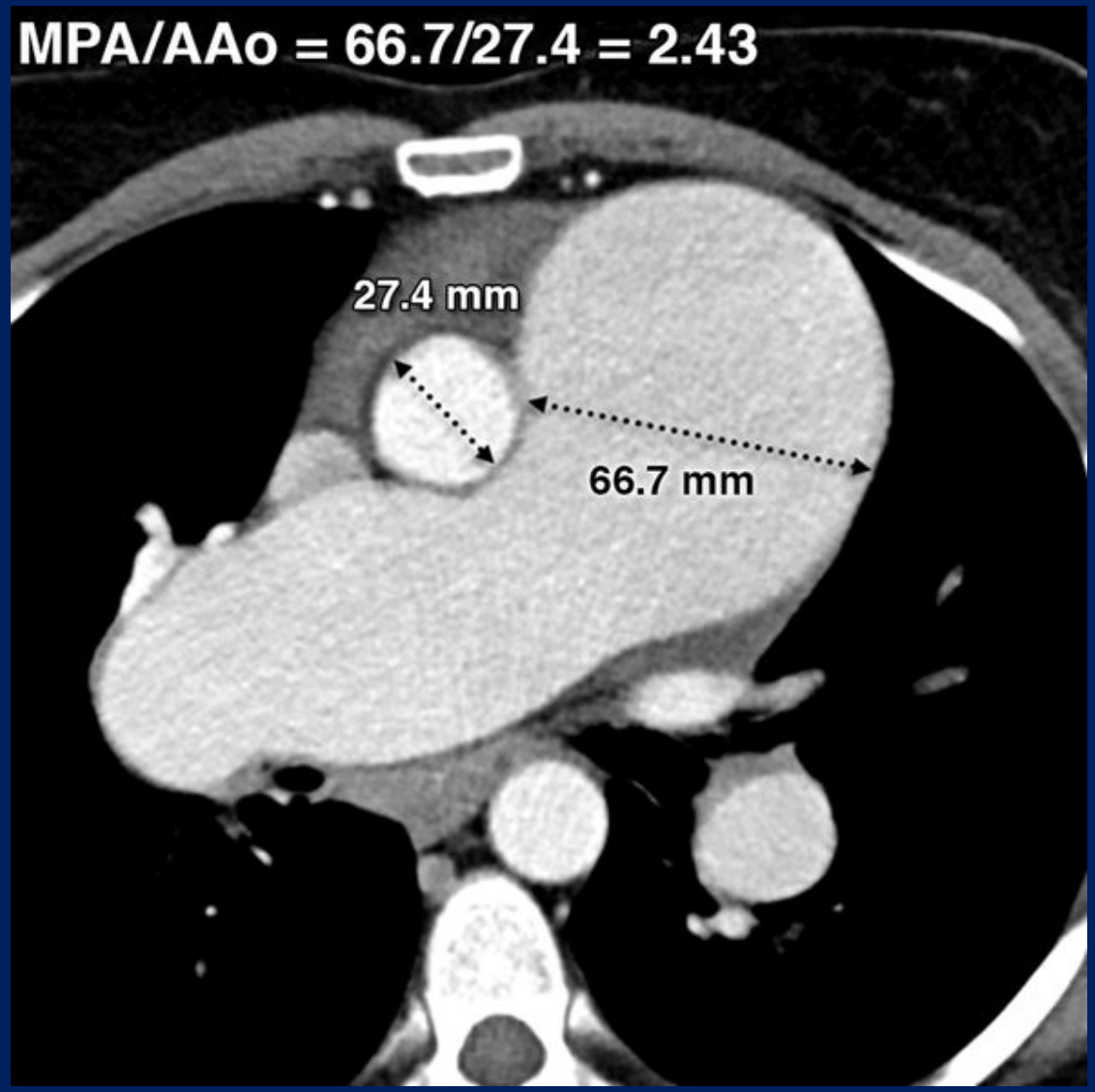
Korobkova IZ, Lazutkina VK, Nizovtsova LA, Riden TV (2015). "[Radiographic assessment of pulmonary hypertension: Methodical aspects]". Vestn Rentgenol Radiol (in Russian) (4): 45–53.

Pienn M, Kovacs G, Tscherner M, Avian A, Johnson TR, Kullnig P, Stollberger R, Olschewski A, Olschewski H, Bálint Z (March 2014). "Non-invasive determination of pulmonary hypertension with dynamic contrast-enhanced computed tomography: a pilot study". Eur Radiol. **24** (3): 668–76.

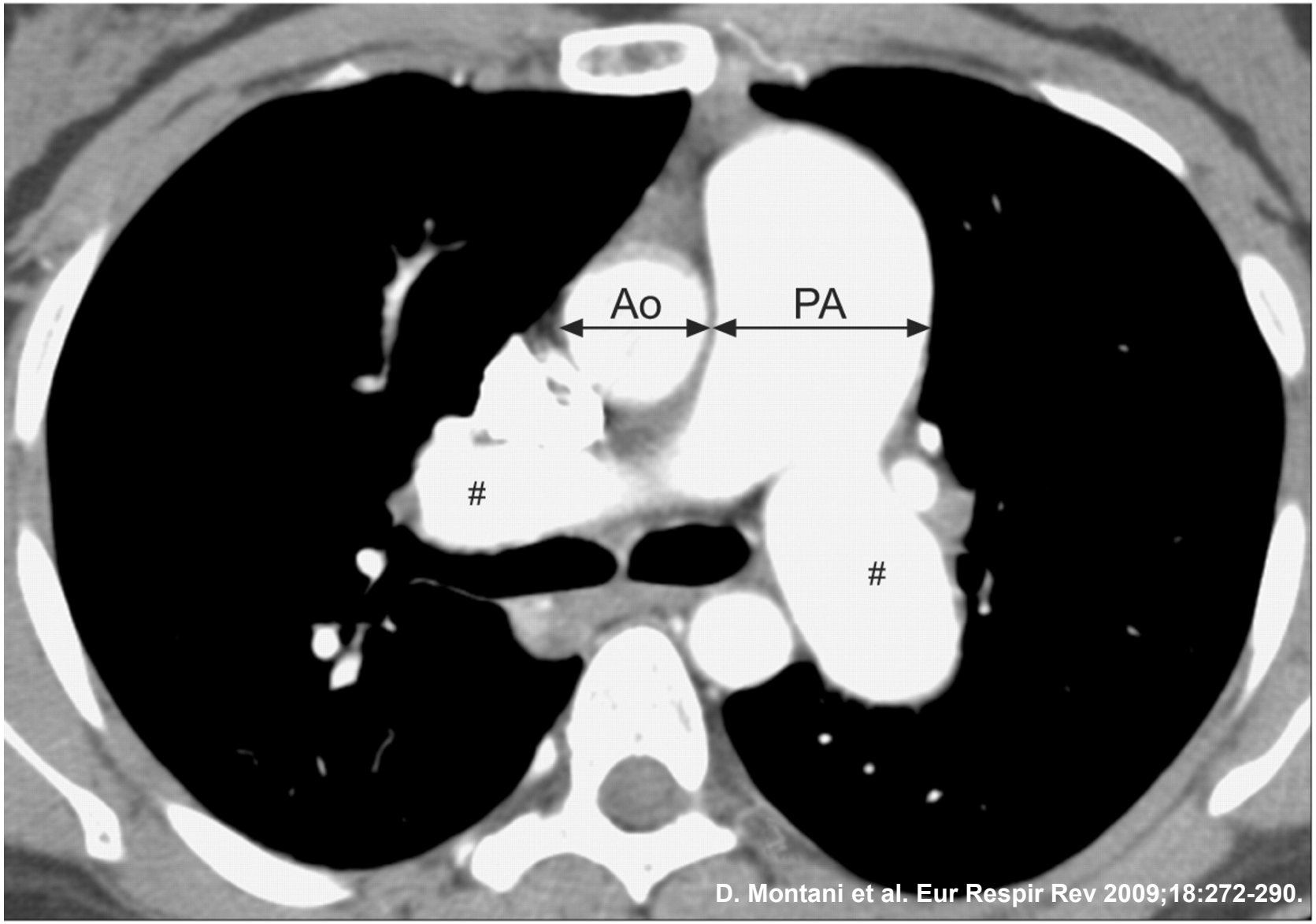
Cordova FC, D'Alonzo G (September 2013). "Sarcoidosis-associated pulmonary hypertension". Curr Opin Pulm Med. **19**(5): 531–7.

CT Scan findings

- Pulmonary artery /Ao diameter > 1 to identity pulmonary hypertension
  - Sensitivity 0.70
  - Specificity 0.92



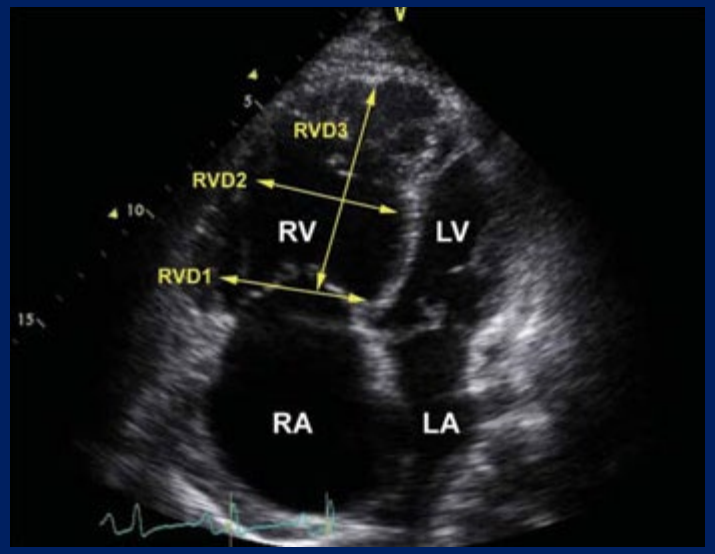
Benjamin H. Freed et al. JIMG 2016;9:715-732.

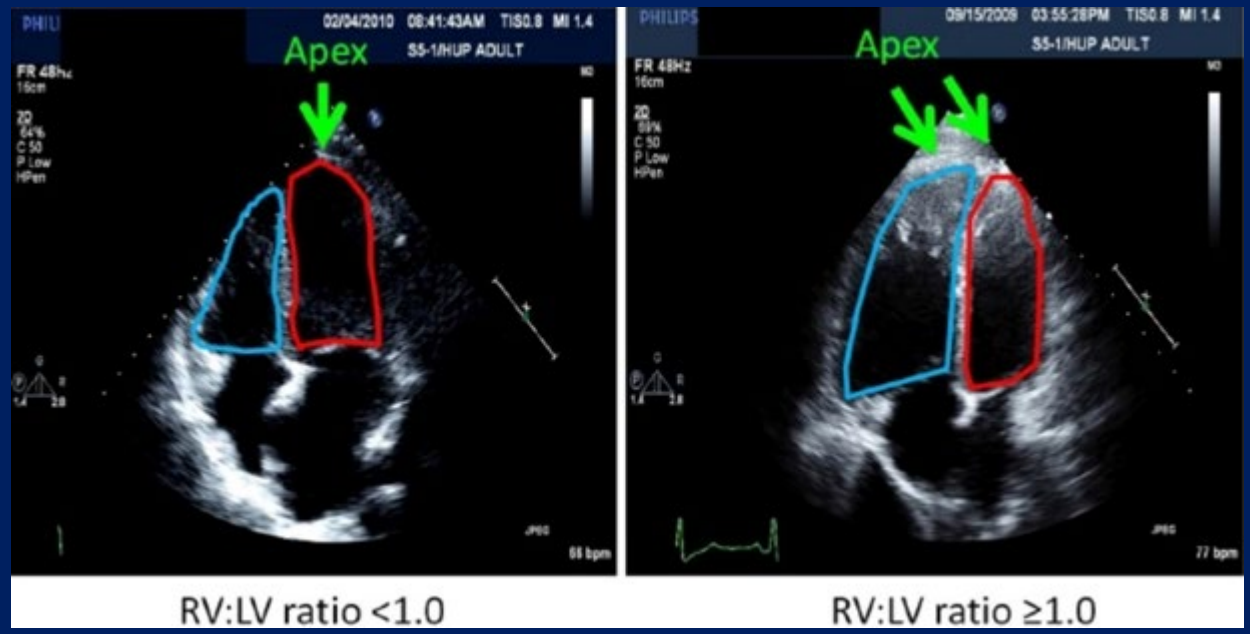


Contrast-enhanced computed tomography of the chest of a patient with pulmonary arterial hypertension associated with congenital heart disease (large atrial septal defect). Massive dilatation of the pulmonary arterial trunk and branches (#). The ratio of the diameter of aorta (Ao) to the diameter of main pulmonary artery (PA) is >1.5.

Screening Echocardiogram

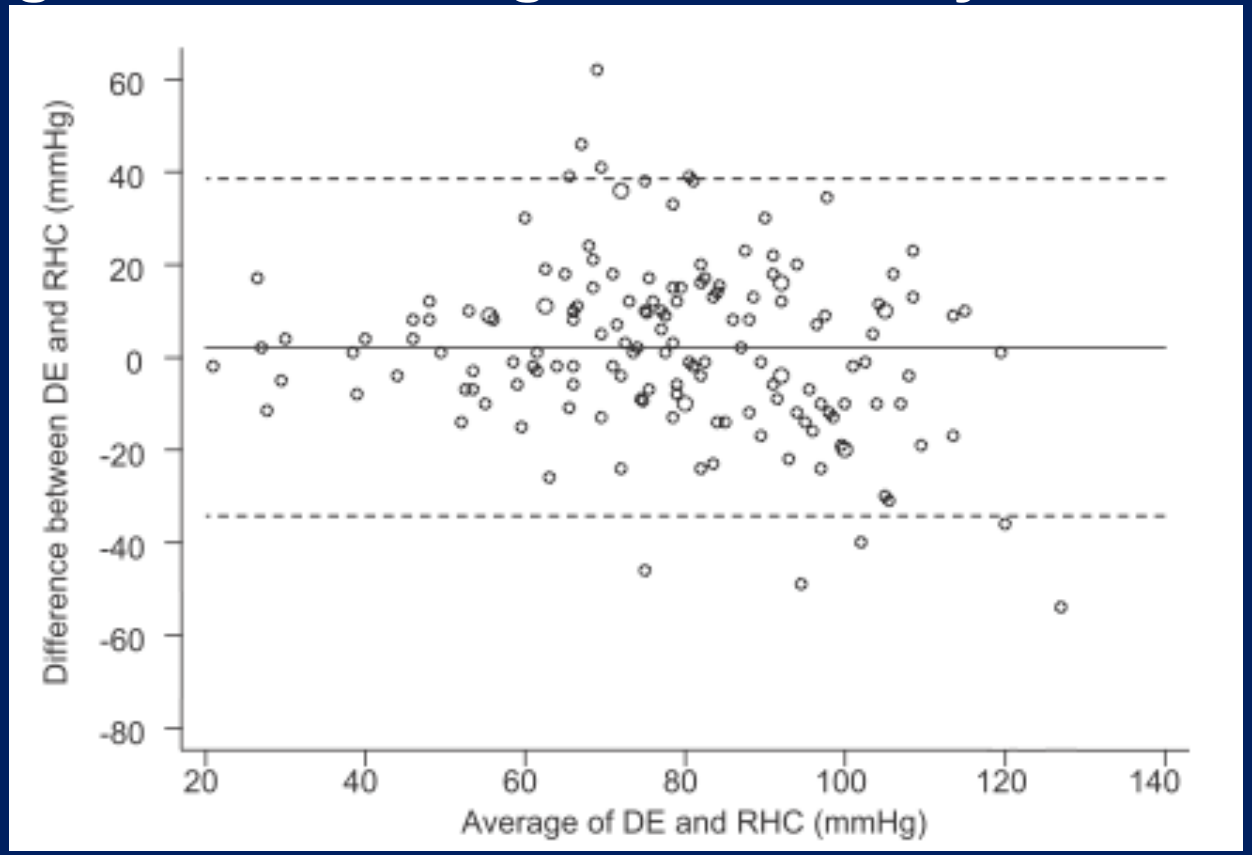
Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'[2]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	





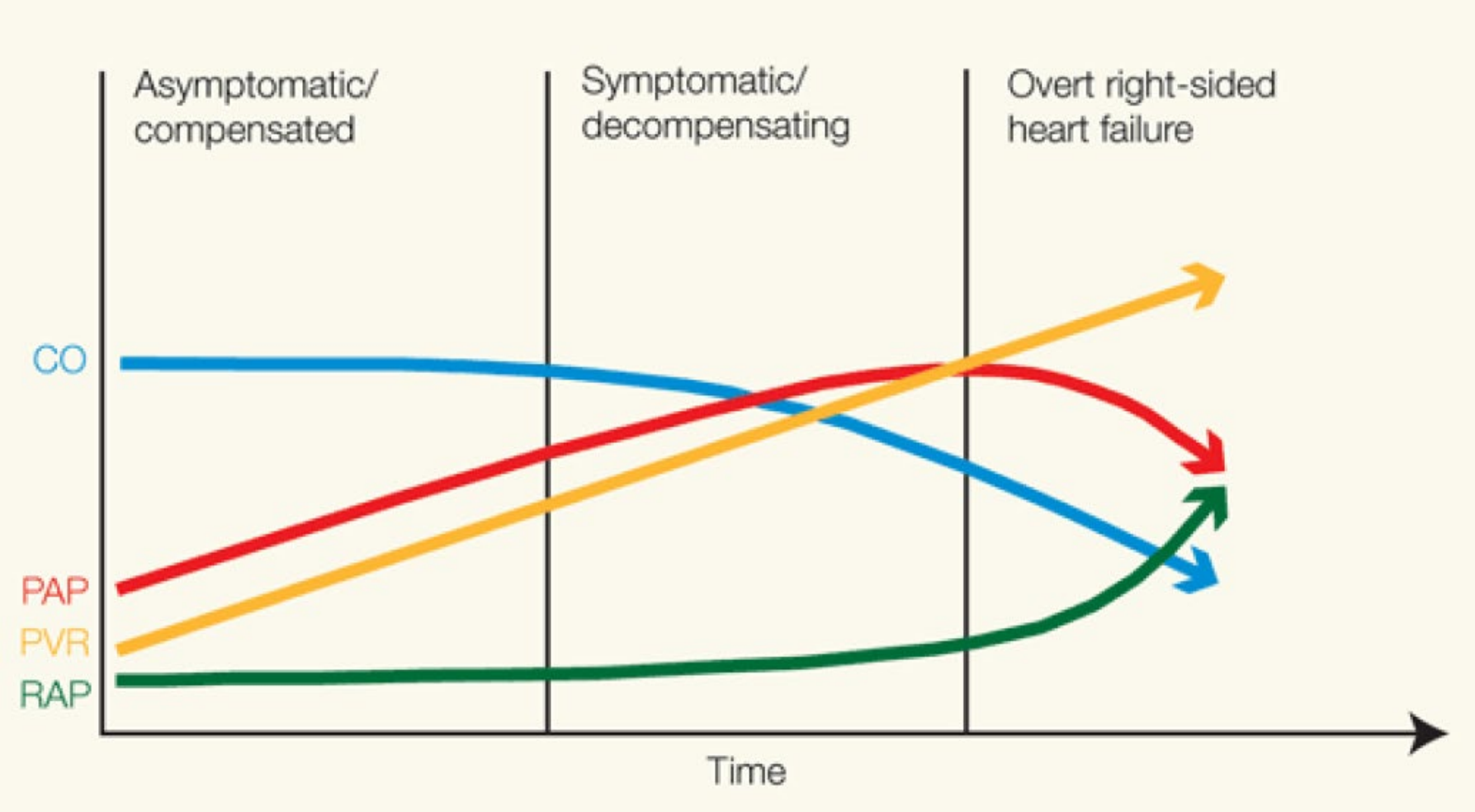
Echocardiogram

- Systolic pressures are recorded, not MAP
- Systolic PAP of 40 mmHg on echocardiogram to identify PAH
  - Sensitivity 0.76
  - Specificity 0.58



Janda S et al. Heart doi:10.1136/hrt.2010.212084
Rich J et al, Chest 139(5): 988-993, 2011.

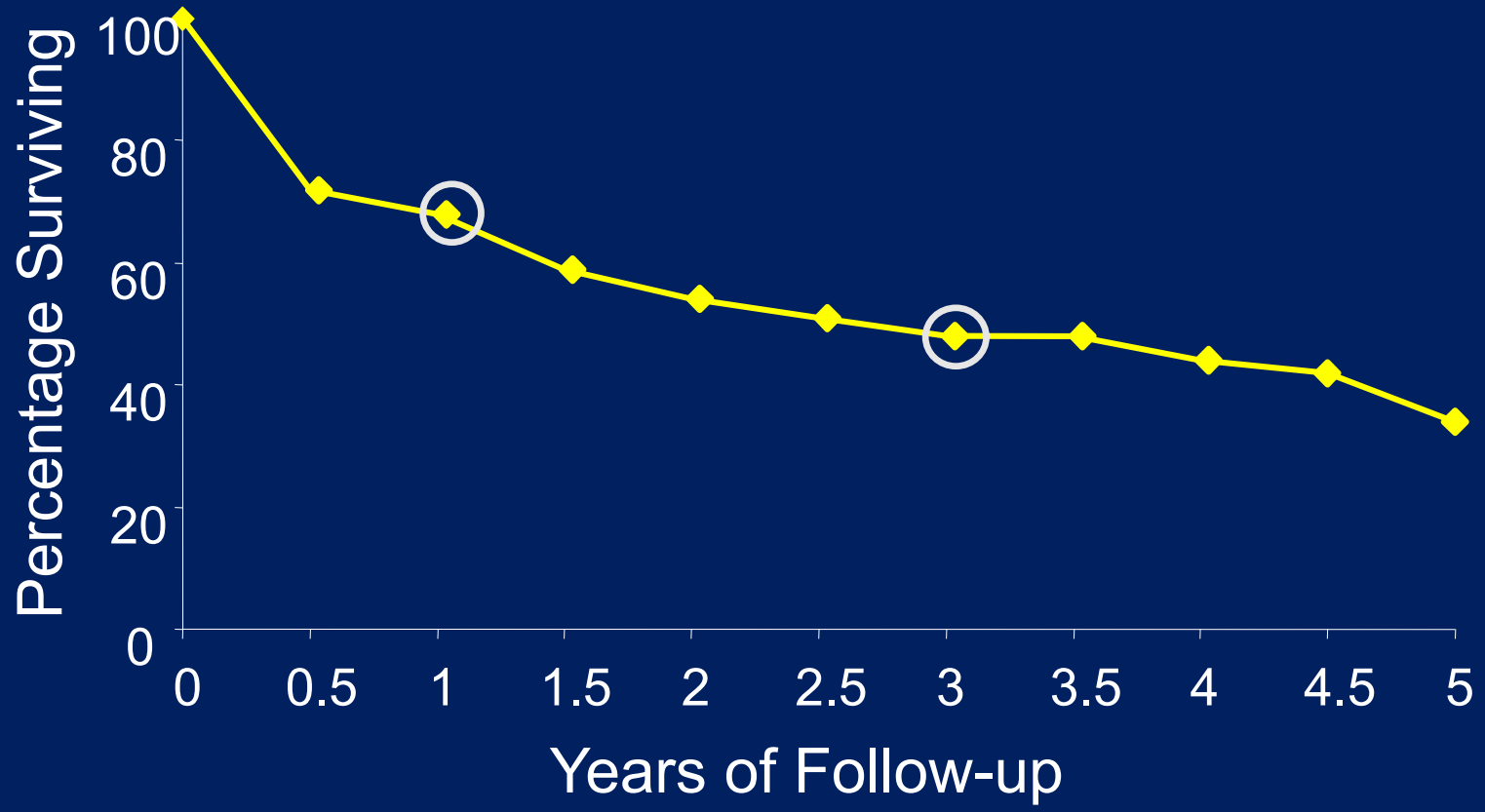
Natural history of pulmonary arterial hypertension



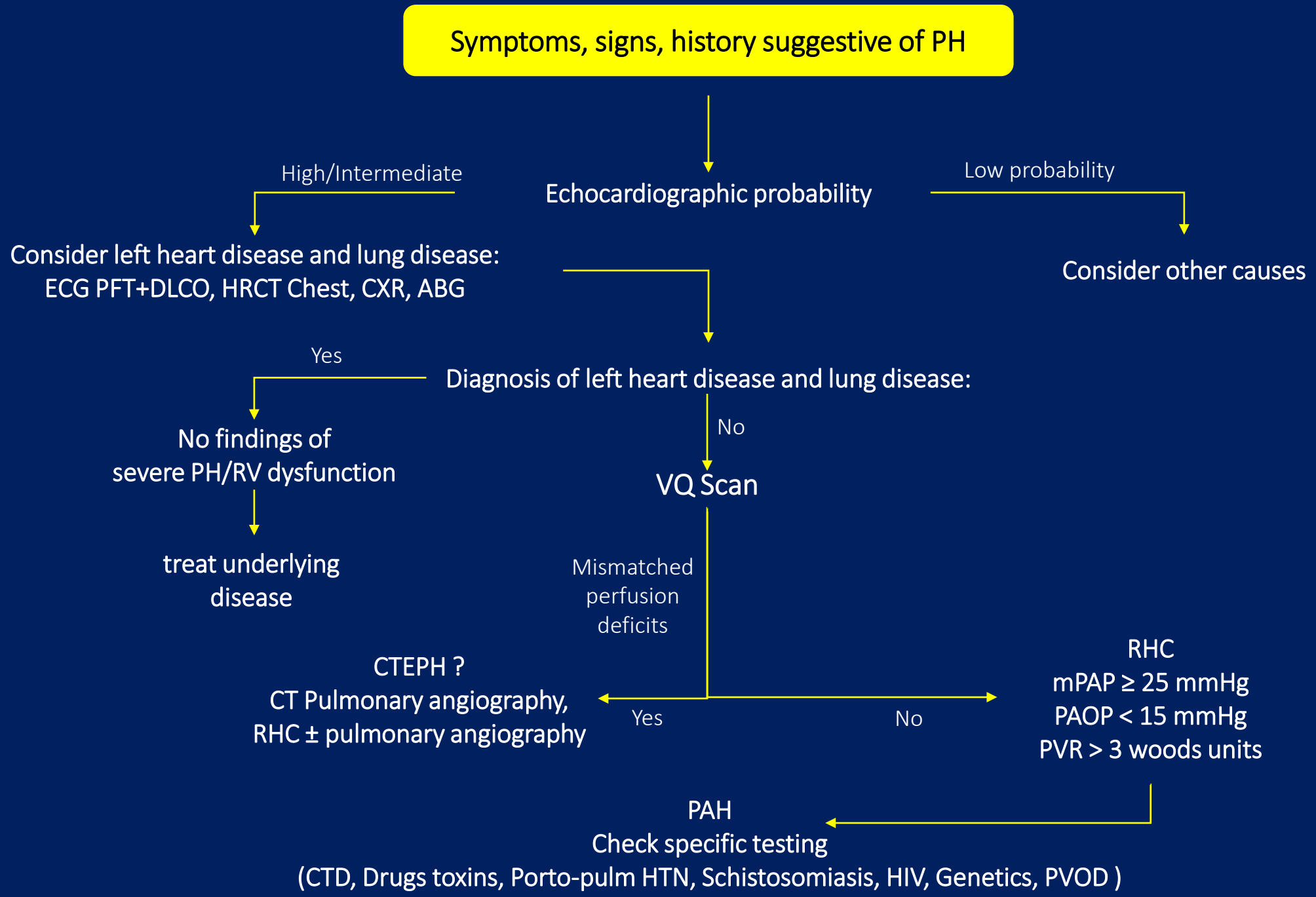
PAH: A Disease of Decline & Deterioration

- **Without treatment survival:**
  - **1 year – 68%**
  - **3 year – 48%**
  - **5 year – 35%**

IPAH NIH Registry



Adapted from: D'Alonzo GE, *Ann Int Med*, 1991


Symptoms, signs, history suggestive of PH
Echocardiographic probability
High/Intermediate
Low probability
Consider left heart disease and lung disease:
ECG PFT+DLCO, HRCT Chest, CXR, ABG
Consider other causes
Yes
Diagnosis of left heart disease and lung disease:
No
No findings of
severe PH/RV dysfunction
VQ Scan
treat underlying
disease
Mismatched
perfusion
deficits
CTEPH ?
CT Pulmonary angiography,
RHC ± pulmonary angiography
Yes
No
RHC
mPAP ≥ 25 mmHg
PAOP < 15 mmHg
PVR > 3 woods units
PAH
Check specific testing
(CTD, Drugs toxins, Porto-pulm HTN, Schistosomiasis, HIV, Genetics, PVOD)

Supportive therapy / General measures

"In most but not all cases RV failure (in PAH) is associated with fluid overload and a negative fluid balance is a key to successful therapy." –Marius Hoeper

- Approach chronic right heart failure conceptually like left heart failure (BNP, diuresis, salt avoidance, etc.)
- Oxygen for sitting or ambulatory saturation <88%
- Evaluate and treat for sleep apnea
- Evaluate and treat for thyroid dysfunction
- Don't get pregnant!
- Exercise
- Eat right (and treat iron deficiency aggressively – ferritin goal >100)

Hoeper et al, AJRCCM, 184: 1114-24, 2011.

A note on diuretics

- Meta-analyses of un-blinded but randomized evidence in 471 participants with torsemide relative to furosemide:

- RR for heart failure readmission: 0.41 ($p < 0.01$)
- RR for mortality: 0.86 ($p = 0.54$)

* non-randomized evidence is all over the place

** Loop diuretic is typically paired with spironolactone based on an observational re-analysis of the ambrisentan trials

DiNicolantonia et al, Future Cardiol, 8: 2012,
Maron BA et al, Am J Cardiol, 112: 2013.

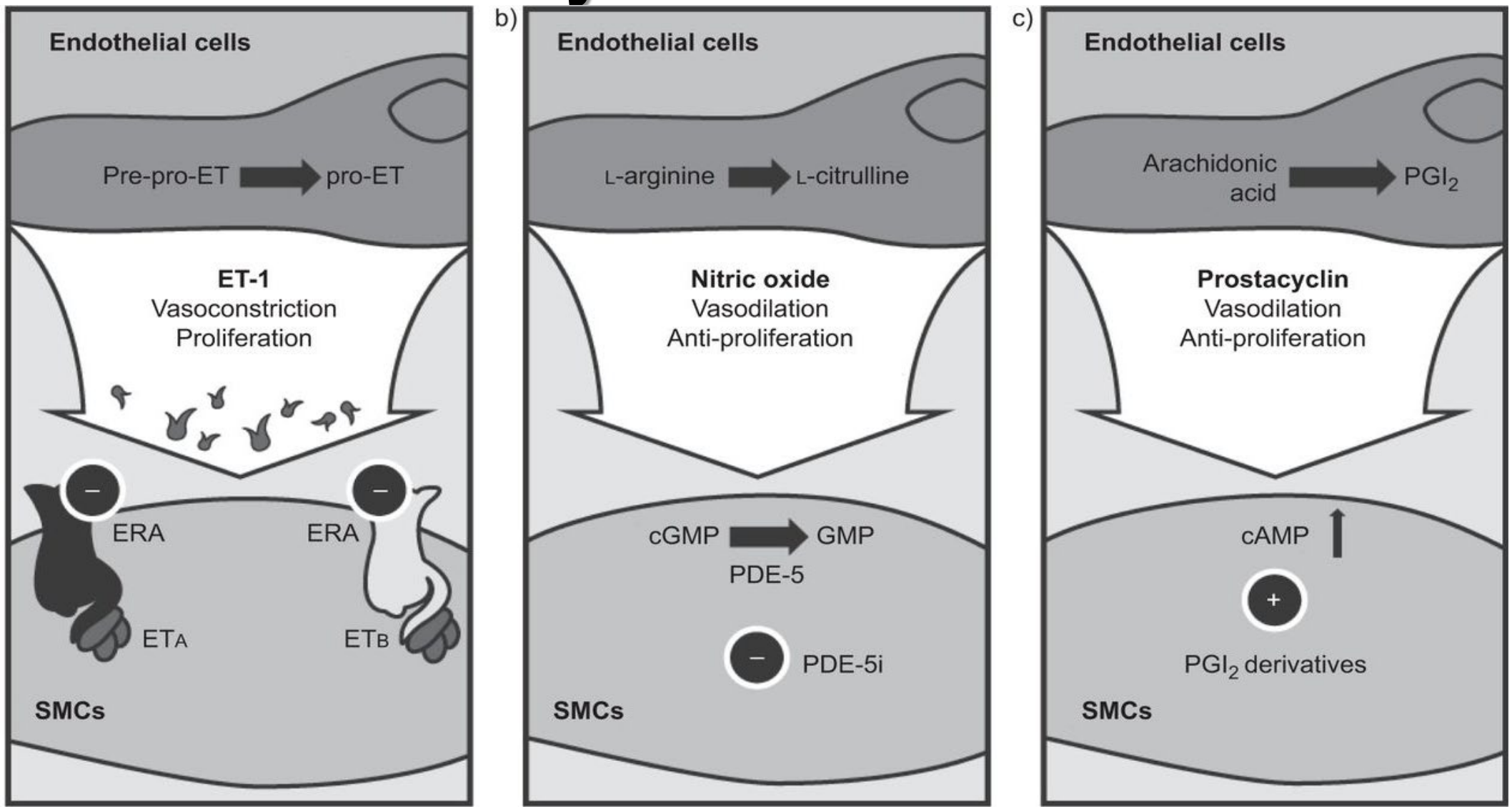
Exercise Is it safe? Effective?

- **Safety:**
  - **In over 700 participants the only significant side effects in cardiac rehabilitation were dizziness**

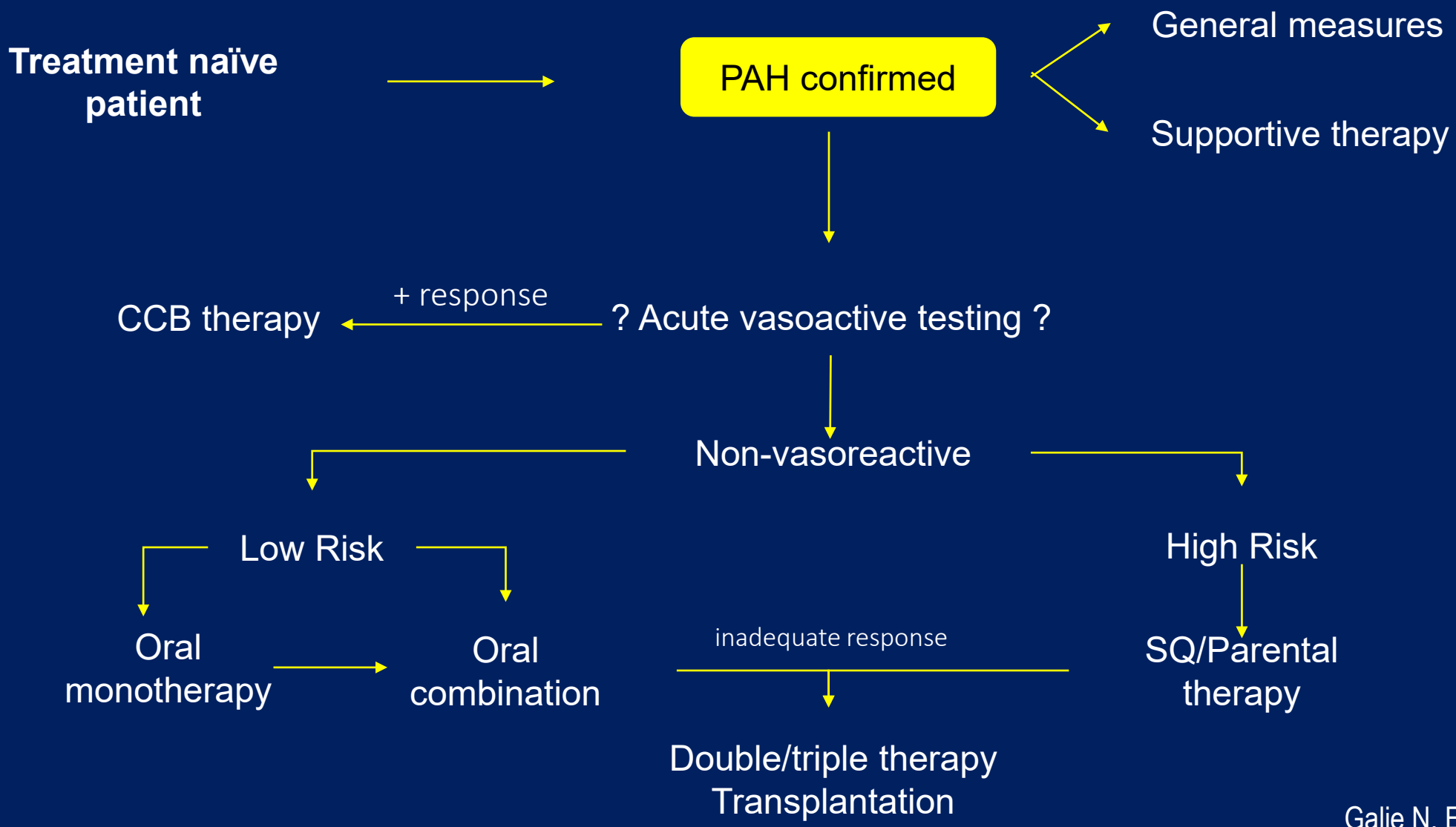
- **Efficacy:**
  - **Six Minute Walk Distance: Mean improvement 72m**
  - **Peak VO_2: mean improvement 1.1 – 2.1 ml/kg/min**
  - **NYHA Functional Class: ~1 NYHA class improvement**
  - **Even evidence that exercise decreases resting PVR (~2 wood units)**

J Skalski et al. Circulation (2012); R Buys et al. BMC Pulm Med (2015);
AS Babu et al. Heart Lung Circ (in press),
Ehlken et al. Eur Heart J (2016)

Treatment Pathways



How and when to treat



Galie N, ESC/ERS 2015 Guidelines

Risk Strata

Estimated 1 year mortality	Low risk (<5%)	Intermediate risk (5 – 10%)	High risk (>10%)
Right heart failure	No	No	Yes
Progression	No	Slow	Rapid
Syncope	No	Occasional	Repeated
WHO/NYHA Functional Class	I or II	III	IV
CPET	VO_2 mas > 15 Ve/VCO_2 <36	VO_2 mas 11 – 15 Ve/VCO_2 36 – 45	VO_2 mas < 10 Ve/VCO_2 > 45
BNP	< 50	50 – 300	> 300
Hemodynamics	RA < 8 mmHg CI > 2.5 SvO_2 >65%	RA - 8 - 14 mmHg CI - 2.0 – 2.4 SvO_2 - 60 - 65%	RA > 14 mmHg CI < 2 SvO_2 <60%

Galie N, ESC/ERS 2015 Guidelines

PAH Drugs

- **Epoprostenol (generic and Flolan®)**
- **Treprostinil (Remodulin®)**
- **Iloprost (Ventavis®)**

} Prostaglandins

- **Bosentan (Tracleer®)**
- **Ambrisentan (Letairis®)**

} Endothelin receptor antagonists (ERAs)

- **Tadalifil (Adcirca®)**
- **Sildenafil (Revatio®)**

} Phosphodiesterase 5 inhibitors (PDE5 inhibitors)

Nitric Oxide Targeted Therapy

Sildenafil, tadalafil, and riociguat

- Quickest action of the pulmonary vasodilators (hours to days)
- Side effects (headaches, myalgias, etc.) are common, but typically subside in a few weeks
- Should NOT be used together or alongside nitrates
- *May* have some benefit in WHO Group II Pulmonary hypertension
- Biggest impact on systemic vascular resistance (especially riociguat) and should be used cautiously in Eisenmenger's, Cirrhosis, etc.
- Riociguat is the only approved medical therapy for CTEPH

Endothelin Receptor Antagonist

Bosentan, Ambrisentan, Macitentan

- Differ in dosing frequency and side effects
- Can take several weeks to begin seeing an effect
- No data on comparative efficacy, but some combinations may interact (e.g. bosentan + sildenafil may interact and ambrisentan + tadalafil have been studied together directly)
- Bosentan is rarely used because of the need for monthly LFT testing and the risk for idiosyncratic liver injury

Prostacyclin-targeted therapy

Treprostinil (SQ, IV, inhaled, PO), Epoprostenol (IV), Selexipag (PO)

- Continuous parenteral NOT equivalent to oral or inhaled and not appropriate for all patients
- Can take several weeks to begin seeing an effect and are weak negative inotropes (e.g. rough for salvage therapy in a decompensated ICU patient)
- Be attentive for stigmata of overdosing (hypotension, flushing, jaw pain, myalgia, low back pain, diarrhea) or under dosing (dyspnea, tachycardia, lightheadedness, cardiorenal syndromes, etc) "Weight-based" parenteral dosing, but fixed at the initial weight when the med was started.

Adapted from Hoeper et al, AJRCCM, 184: 1114-24, 2011.

Non-Group I: Therapy doesn't work

- WHO Group II – HFrEF
  - Endothlin–receptor antagonist
    - REACH-1, EARTH, ENABLE: = no benefit
  - Prostacyclin analogues (epoprostenol)
    - FIRST: = stopped early for excess heart failure

- WHO Group II – HFpEF
  - Endothlin-receptor antagonist
    - Setaxsentan: 90 s longer on the treadmill but no difference in LV mass, diastology or NYHC FC at 24 weeks

Zile et al. JACC-HF 2014; 2: 123-30.

Acute management in PAH patients

- 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

Acute management in PAH patients

Step 1 — **Assess severity:**

- Clinical evaluation (BP, mental status, diuresis)
- Biochemical evaluation (lactate, liver function, BNP, troponins)
- Imaging (echocardiography, CT scan)
- Invasive evaluation (CVP, PAOP catheters)

Step 2 — **Identify and treat triggering factor(s):**

- Sepsis, arrhythmias, drug withdraw
- PCI for RV infarction, reperfusion for acute pulmonary embolism

Step 3 — **Optimize fluid status:**

- IV diuretic if volume overload
- RRT if situation insufficiently managed with diuretics
- Cautions fluid filling if low CVP; avoid overfilling

Gaine S, Naeije R, Peacock A, eds. The Right Heart. Springer Verlag, London, 2013, pages 261–275.

Acute management in PAH patients

Step 4

Maintain arterial pressure:

- **Norepinephrine**

Step 5

Consider inotropes reduction cardiac filling pressures:

- **Dopamine**
- **Phosphodiesterase III inhibitors**

Step 6

Further measures for afterload reduction:

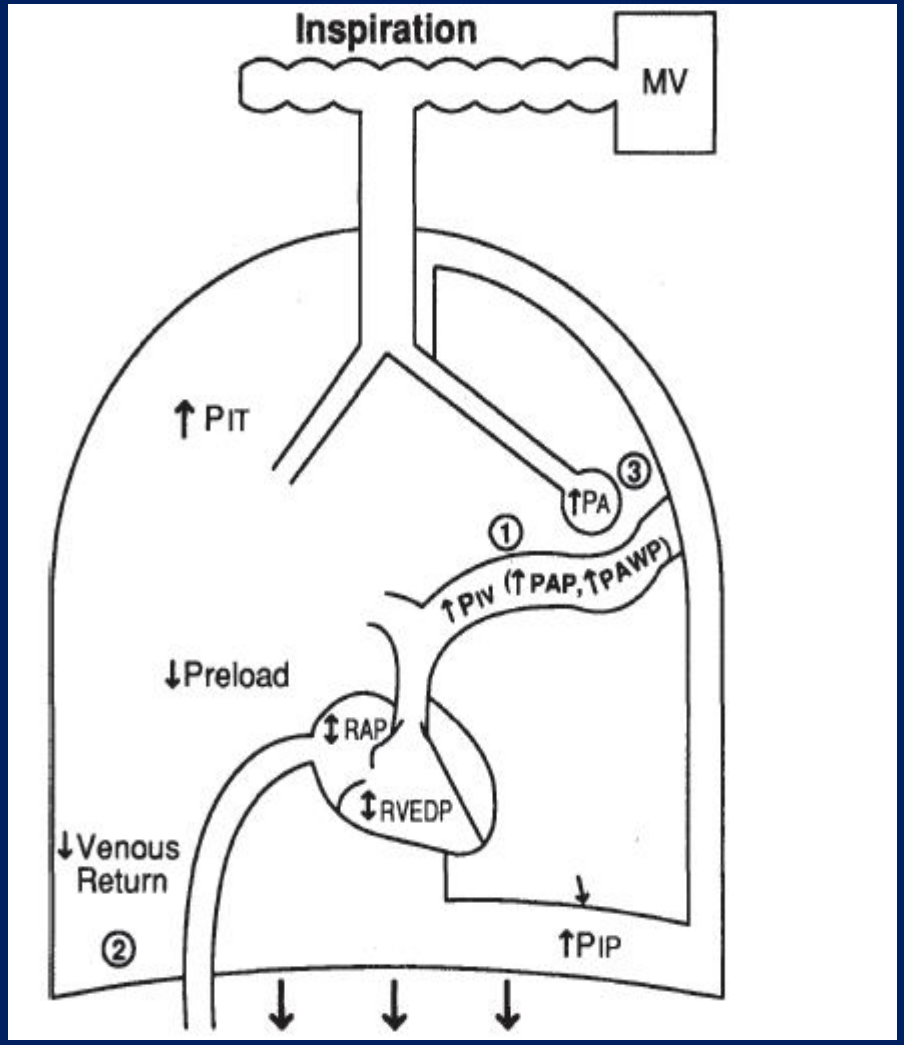
- **Inhaled NO**
- **Inhaled prostacyclins**
- **Consider transfer to hospital for ECMO circulatory support**

Gaine S, Naeije R, Peacock A, eds. The Right Heart. Springer Verlag, London, 2013, pages 261–275.
Nieminen MS, Fruhwald S, Heunks LM, et al. Levosimendan: current data, clinical use and future development. *Heart Lung Vessel*. 2013;5(4):227–245.

Comorbidity management - Ventilation

- Try not to intubate
- If you do:
  - PVR may be lowest at functional residual capacity
    - Therefore, low tidal volume ventilation may be appropriated for all patients with PAH

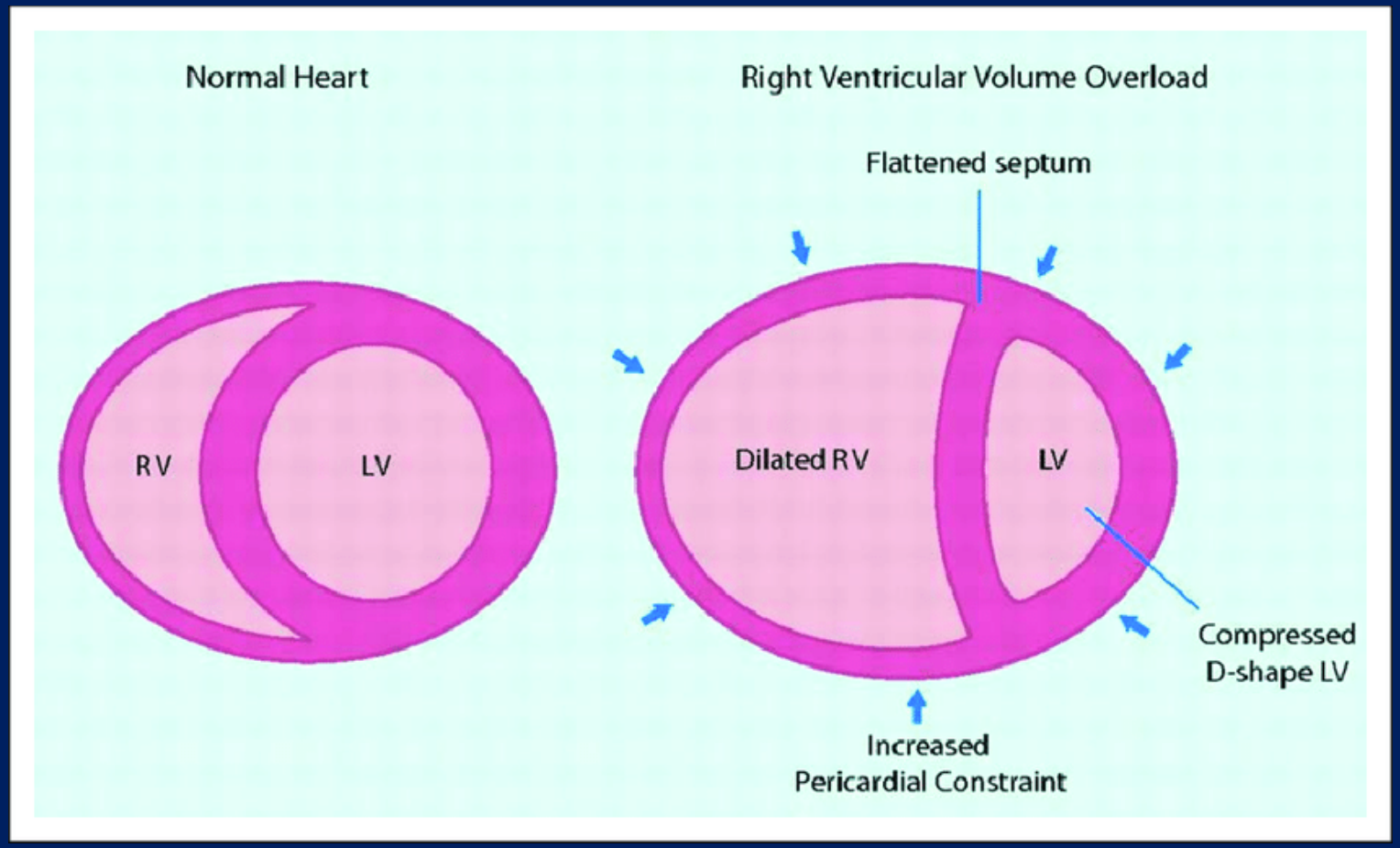
- However, be cautious of PEEP
    - PEEP increases PVR and should be minimized
    - Permissive hypercapnia can increase PVR by > 50% and mPAP by > than 30%



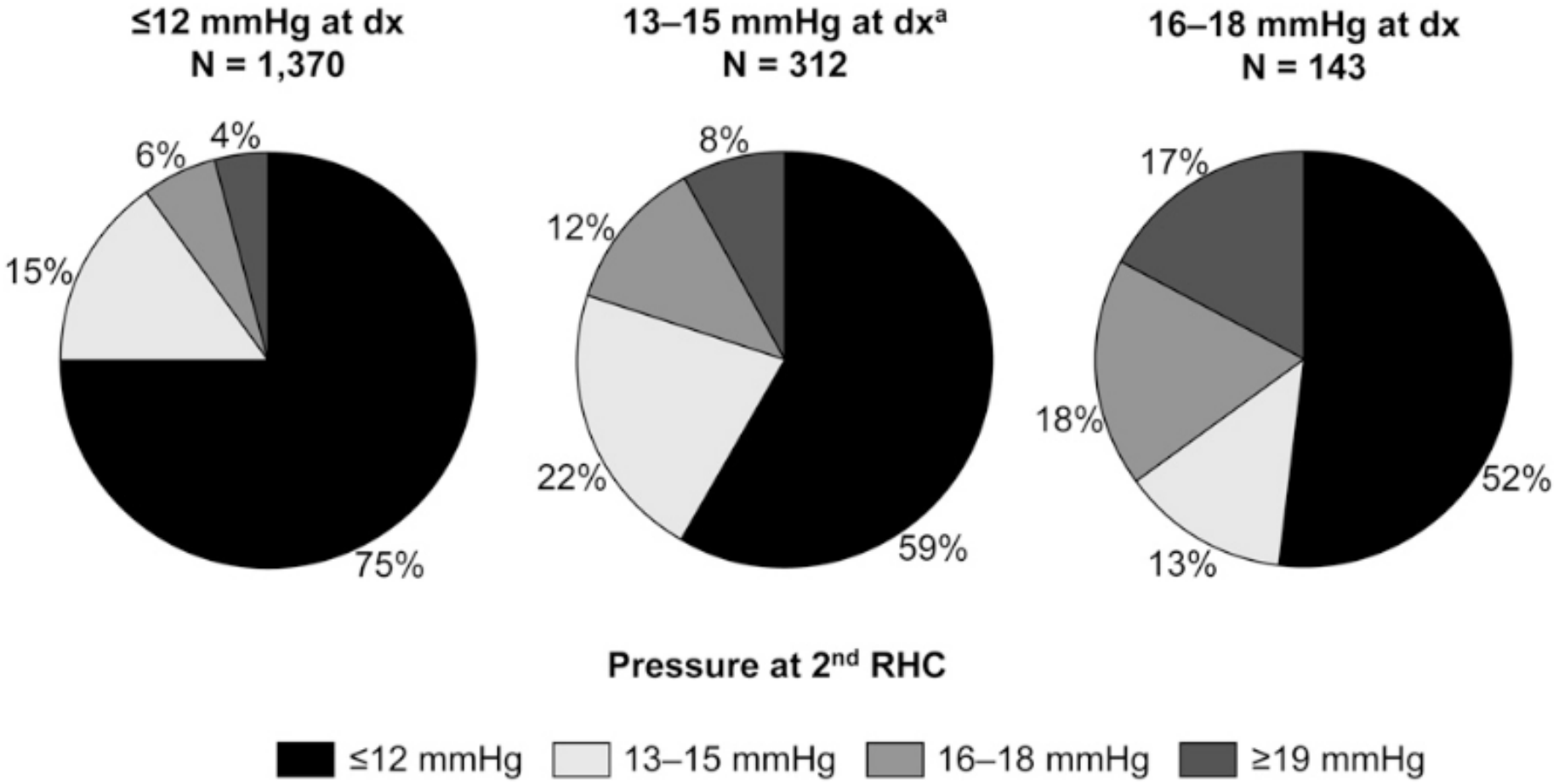
Ventricular Interdependence
The reverse "Bernheim effect"

Anatomical shared
- Ventricular septum
- Pericardium
- Myocardial fibers

One ventricle affects the size, shape and pressure to volume relations



Circulation 2008;117:1717–1731



Pressure is typically less than 25 mmHg and PVR >8 wu in the rare case of ventricular interdependence

"PAH" patients with high wedge on subsequent catheterizations have less treatment response to pulmonary vasodilators and may not be PAH but unmasked HFpEF

Frost A, Chest (2013); & Wain Hobson, IJC Heart & Vessels (2014)

Conclusions

- Pulmonary hypertension is classified anatomically, hemodynamically and clinically
- If it is untreated then it can lead to progressive right ventricular dysfunction and failure
- Usually you treat the underlying cause
  - > 15% of the time (at least) there is treatment
    - WHO groups 1 and 4
- There may be treatment options for other WHO groups
- Right heart catheterization is gold standard
- Pulmonary hypertension specialist is helpful if available