Pulmonary Arterial Hypertension

PRESENTED BY

DR. KHALED REFAAT, MD

Hemodynamic Definition of PH/PAH

PH	**Mean PAP ≥ 25 mm Hg**
PAH	**Mean PAP ≥ 25 mm Hg *plus* PCWP/LVEDP ≤ 15 mm Hg**

ACCF/AHA CECD includes PVR > 3 Wood units

PH = pulmonary hypertension; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; LVEDP = left ventricular end-diastolic pressure; ACCF = American College of Cardiology Foundation; AHA = American Heart Association; CECD = Clinical Expert Consensus Document; PVR = pulmonary vascular resistance

McLaughlin VV, et al. *J Am Coll Cardiol*. 2009;53:1573-1619.
Badesch D, et al. *J Am Coll Cardiol*. 2009;54:S55-S66.

Clinical Classification of PH

I. PAH

- Idiopathic PAH
- Heritable
- Drug- and toxin-induced
- Persistent PH of newborn
- Associated with:
  - Connective tissue disease
  - HIV infection
  - Portal hypertension
  - Congenital heart disease
  - Schistosomiasis
  - Chronic hemolytic anemia

1'. Pulmonary Veno-occlusive Disease and Pulmonary Capillary Hemangiomatosis

2. PH Due to Left Heart Disease

- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease

Simonneau G, et al. *J Am Coll Cardiol*. 2009;54:S43-S54.

Clinical Classification of PH (cont)

3. PH Due to Lung Diseases and/or Hypoxia

- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Other pulmonary diseases with mixed restrictive and obstructive pattern
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude

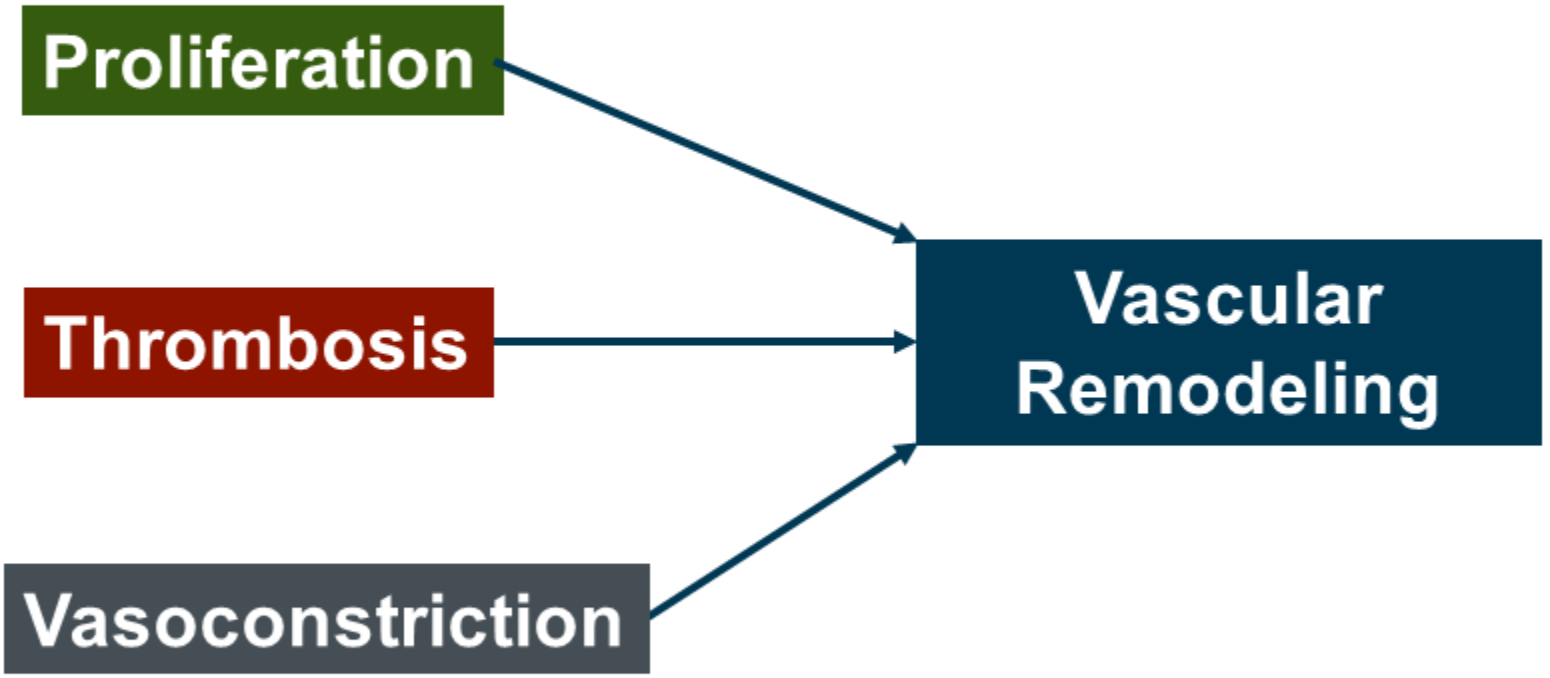
4. Chronic Thromboembolic PH

5. PH With Unclear or Multifactorial Mechanisms

- Hematologic disorders
- Systemic disorders
- Metabolic disorders
- Others

Simonneau G, et al. *J Am Coll Cardiol*. 2009;54:S43-S54.

Pathophysiology of PAH: Overview



Pathogenesis of PAH

① Risk Factors and Associated Conditions

Collagen Vascular Disease
Congenital Heart Disease
Portal Hypertension
HIV Infection
Drugs and Toxins
Pregnancy

Susceptibility

Abnormal *BMPR2* Gene
Other Genetic Factors

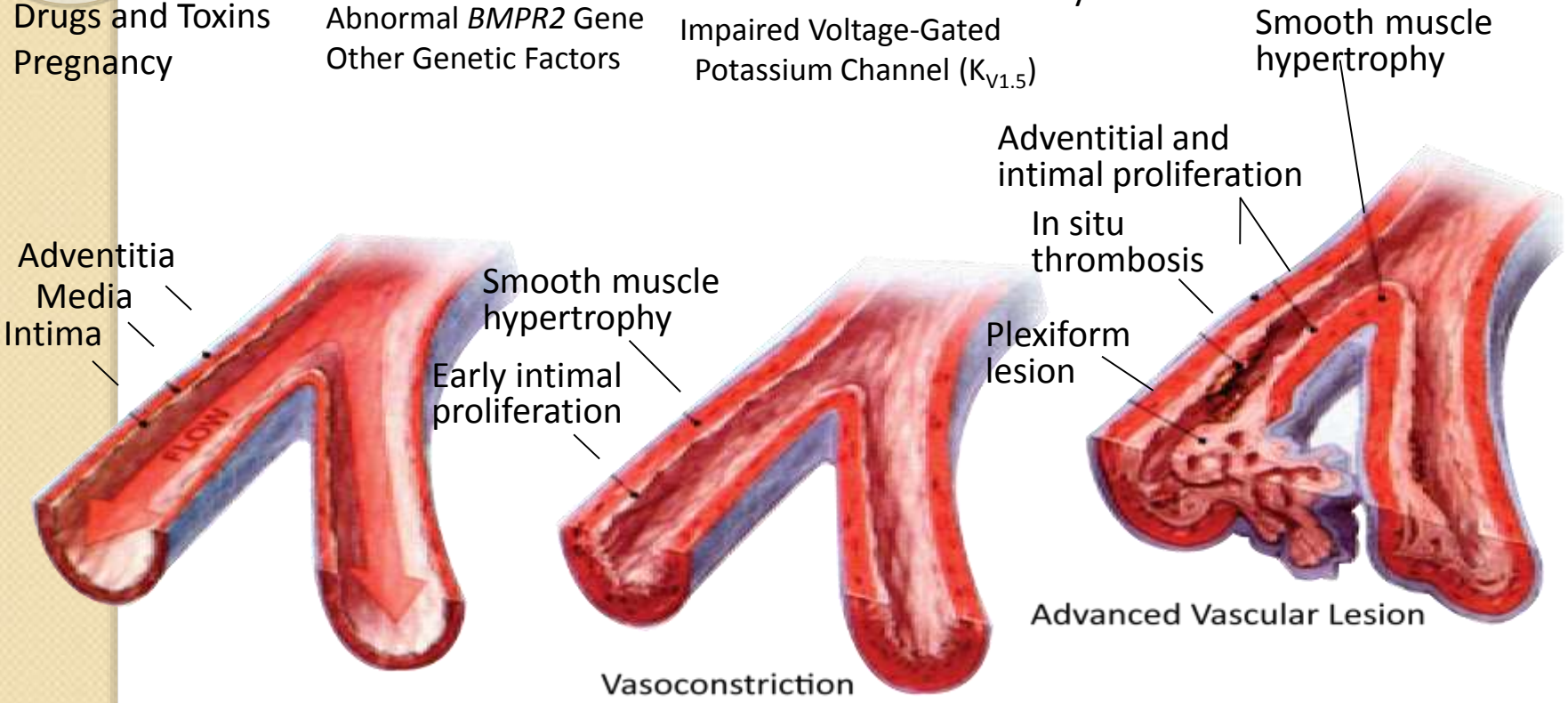
② Vascular Injury

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

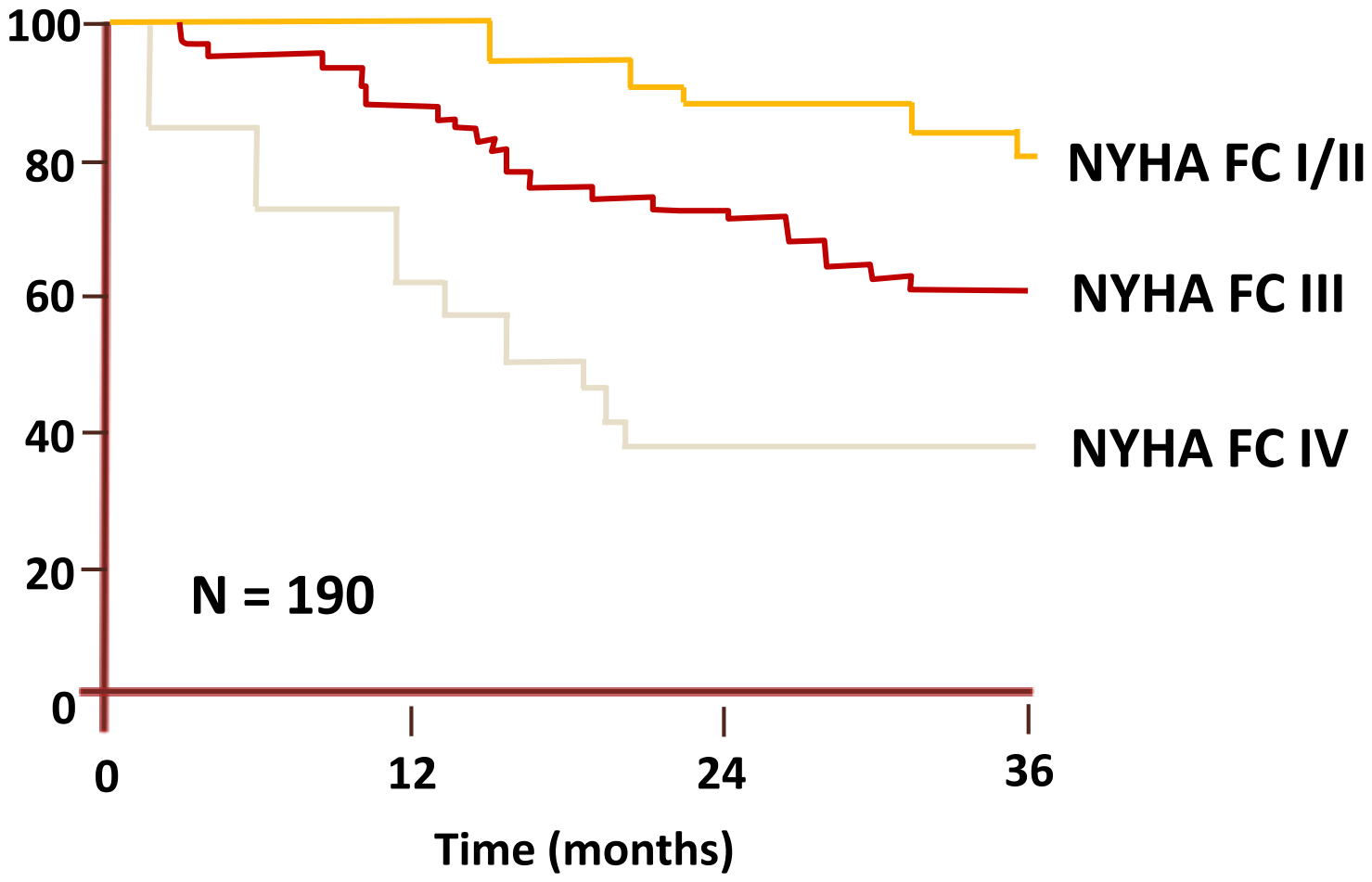
Loss of Response to Short-Acting Vasodilator Trial



Normal → **Reversible Disease** → **Irreversible Disease**

Gaine S. *JAMA*. 2000;284:3160-3168.

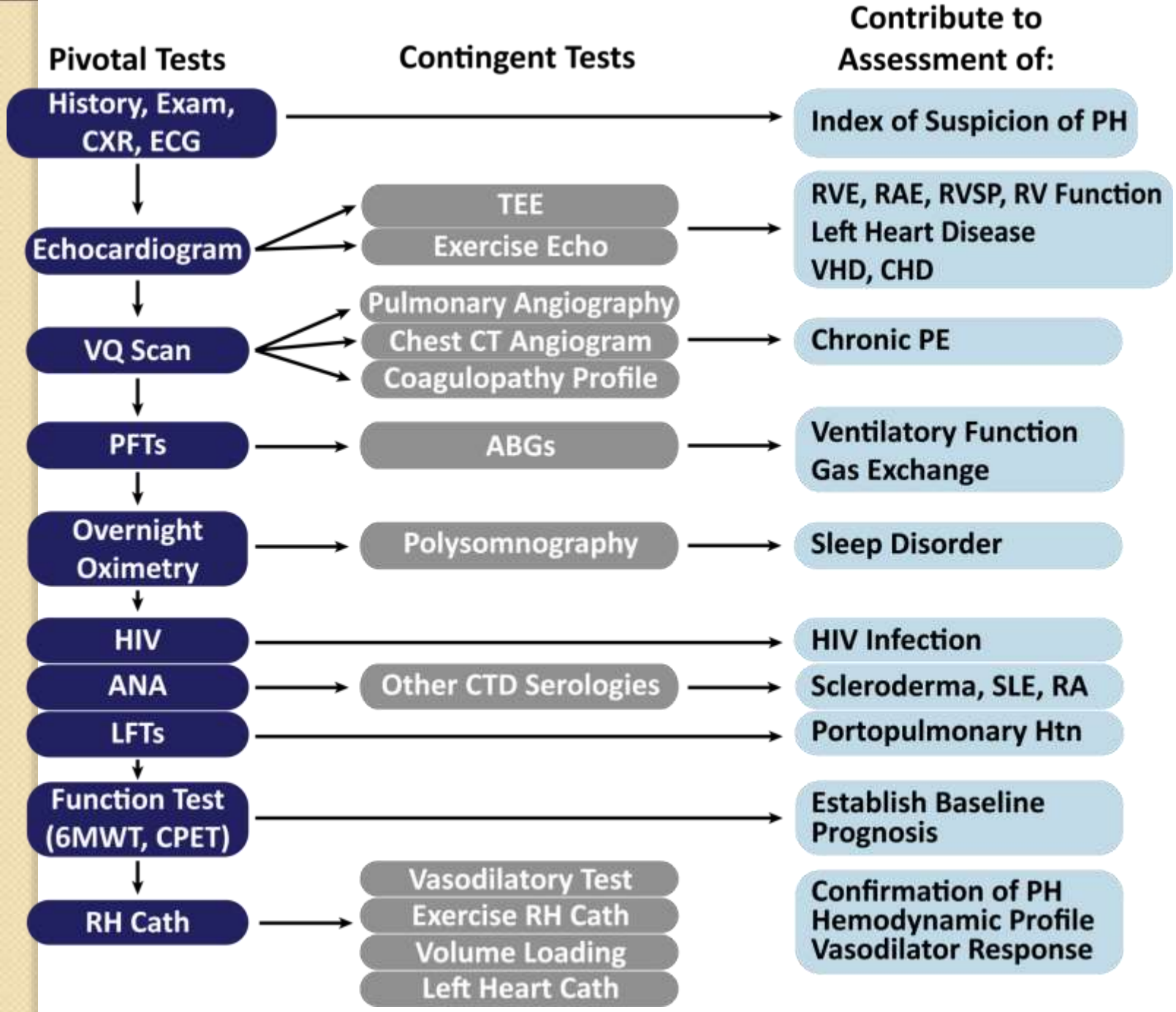
Survival of Patients with Idiopathic PAH According to NYHA FC at Diagnoses



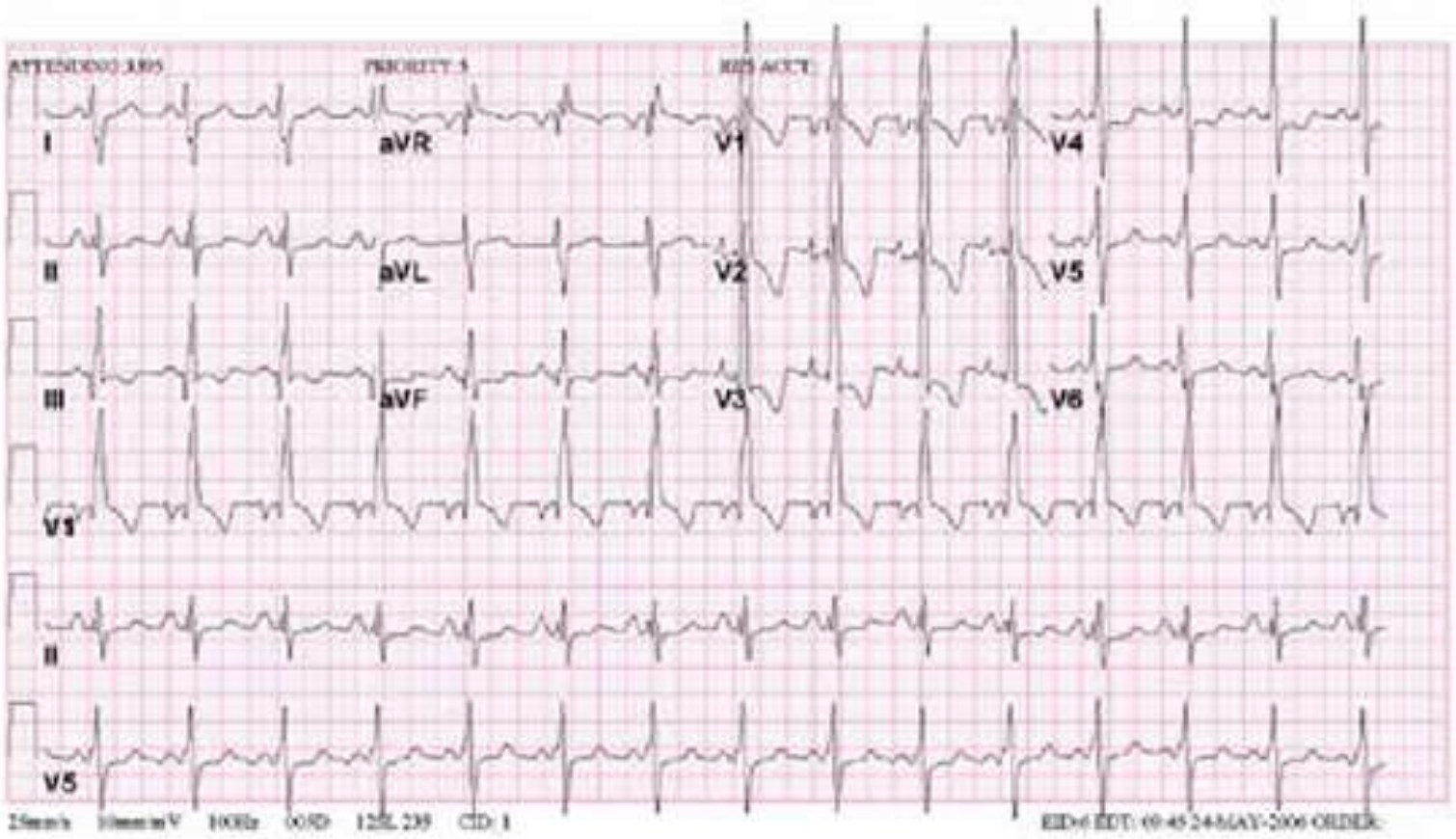
FC = functional class

Humbert M, et al. *Circulation*. 2010;122:156-163.

Diagnostic Approach for PAH



McLaughlin VV, et al. *J Am Coll Cardiol*. 2009;53:1573-1619.


I
aVR
V1
V4
II
aVL
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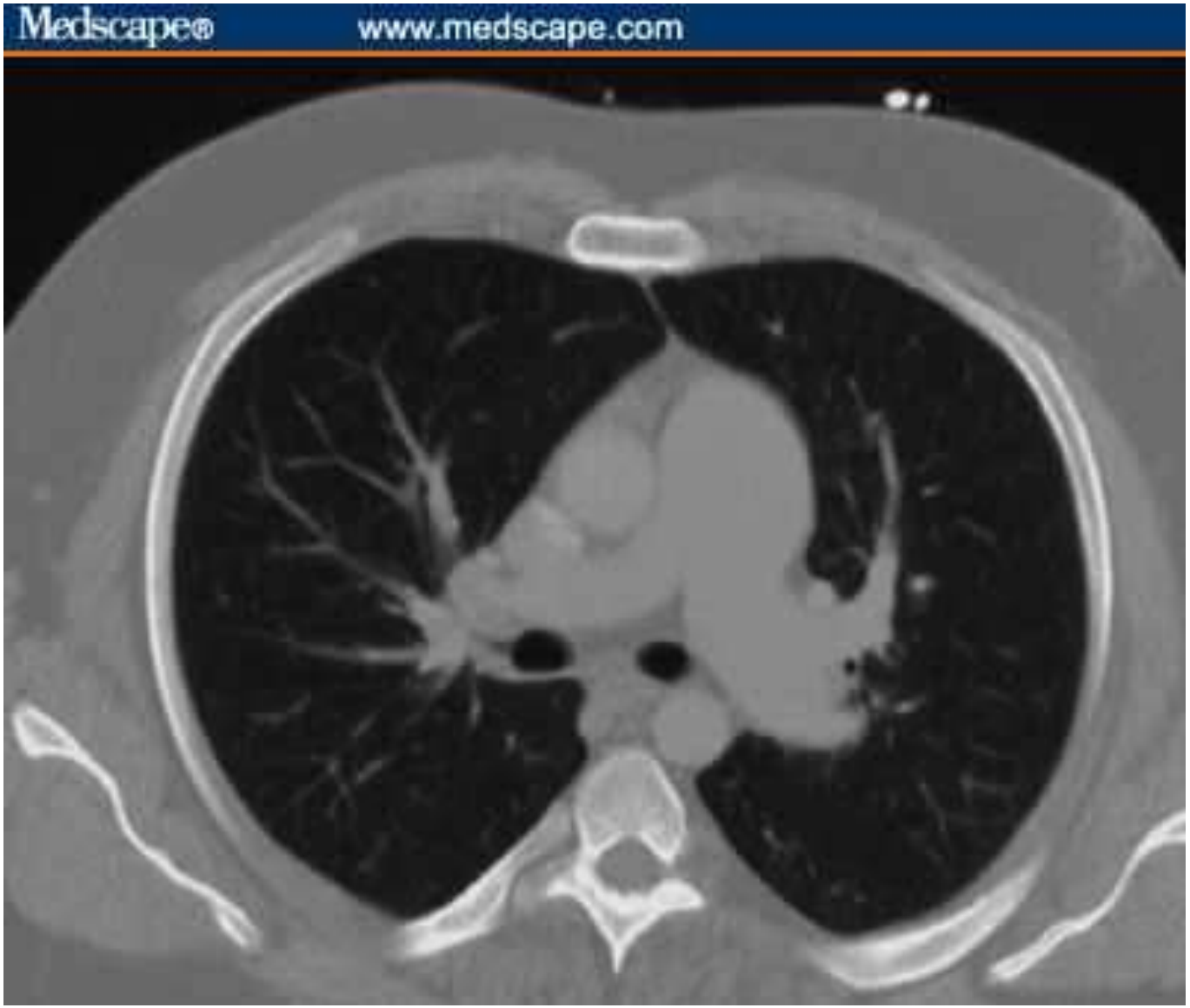
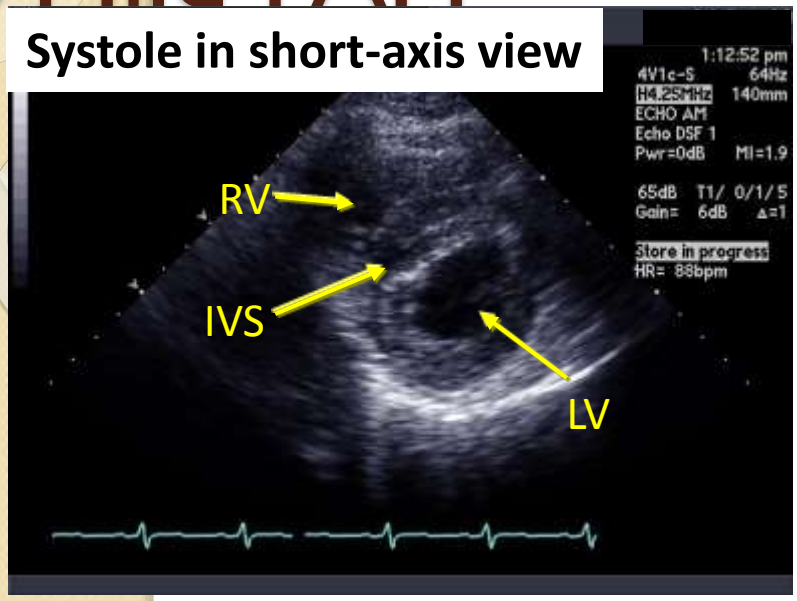
V5
III
aVF
V3
V6
V1
II
V5

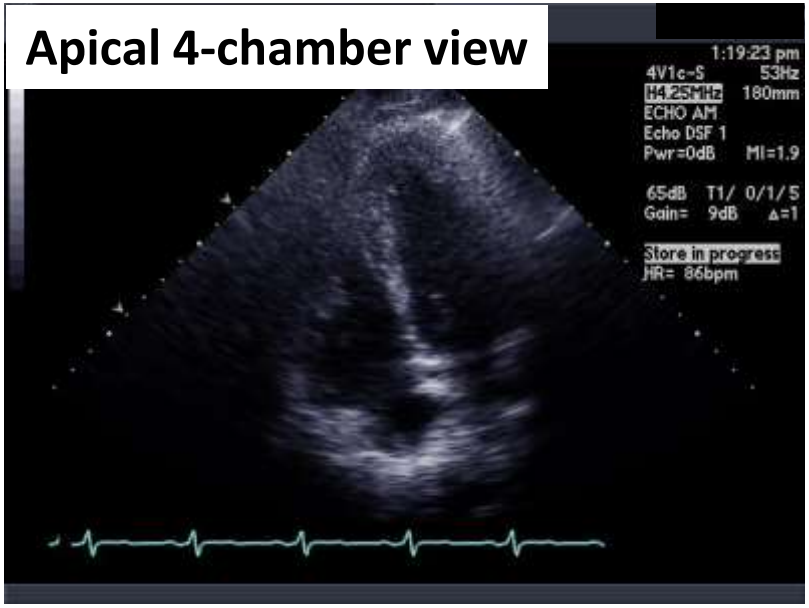

Medscape®
www.medscape.com

Mild PAH

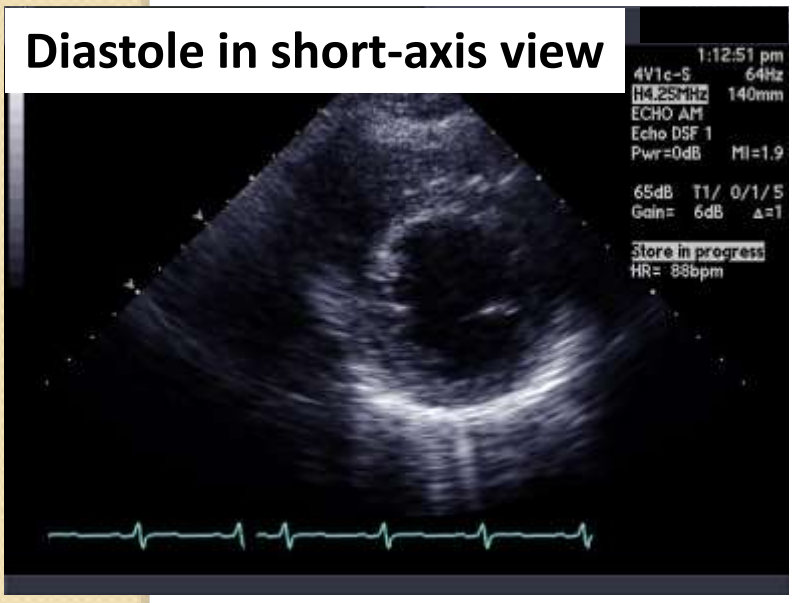
Systole in short-axis view



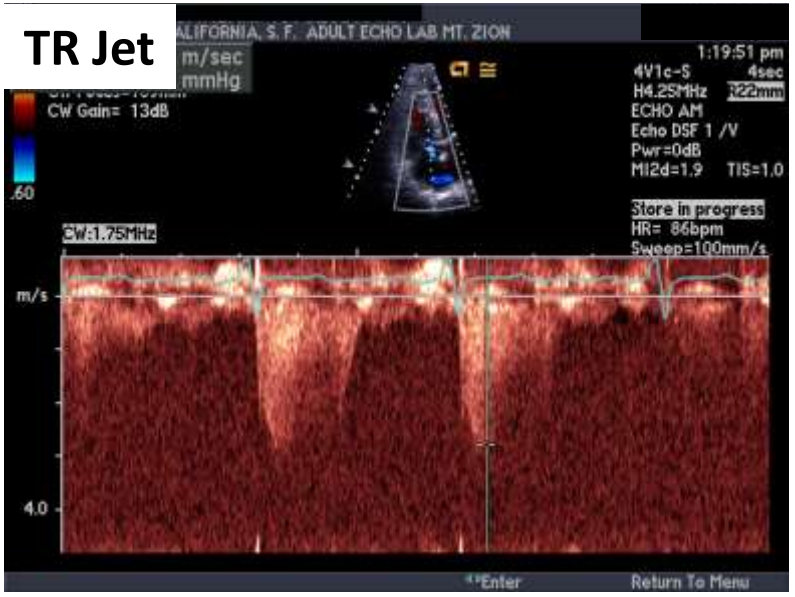
Apical 4-chamber view



Diastole in short-axis view

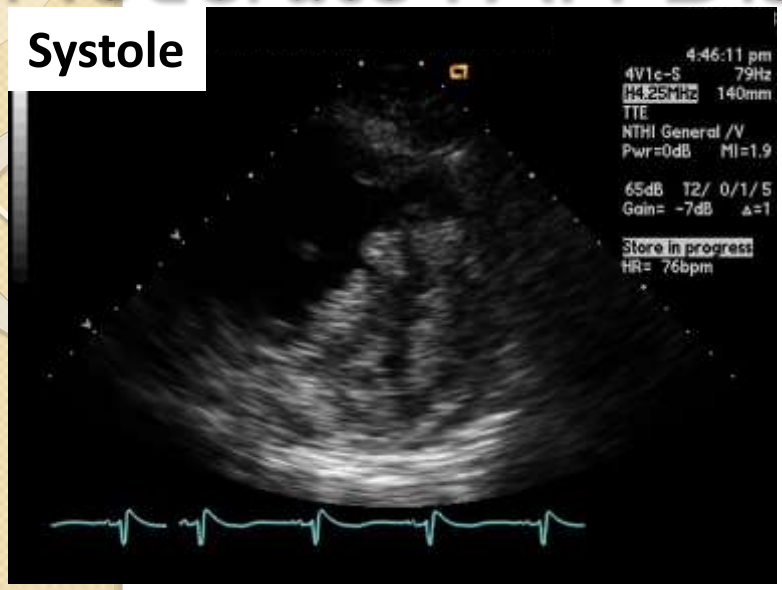


TR Jet

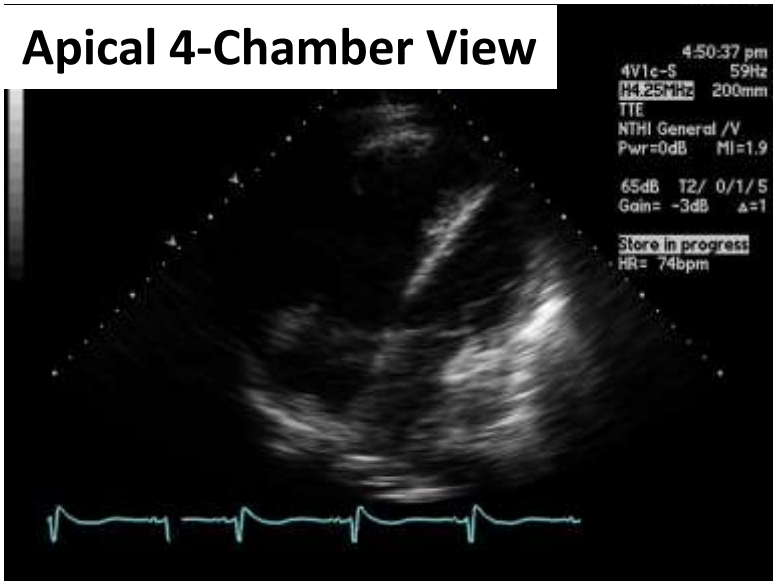


Moderate PAH Disease

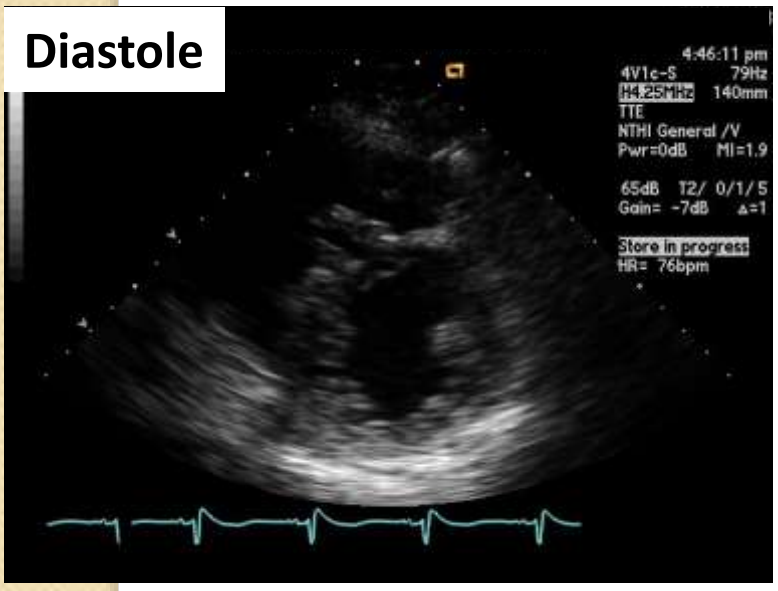
Systole



Apical 4-Chamber View



Diastole



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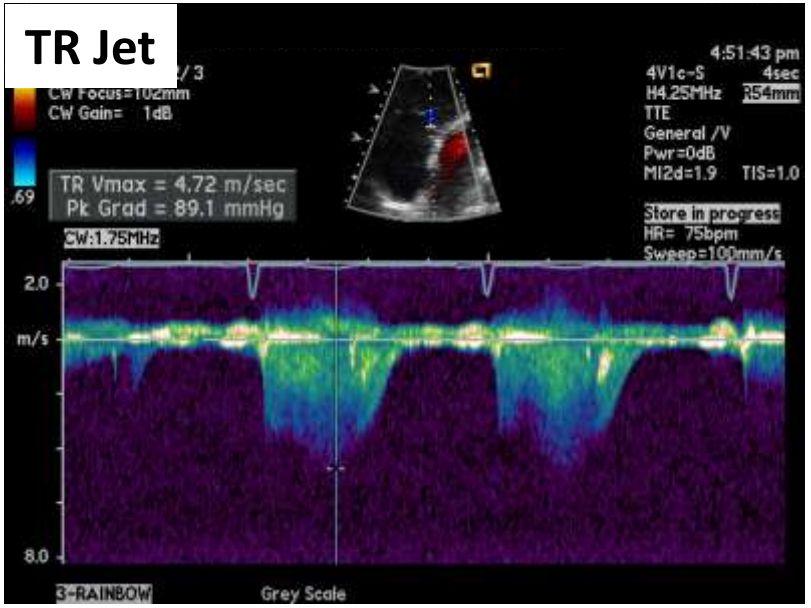
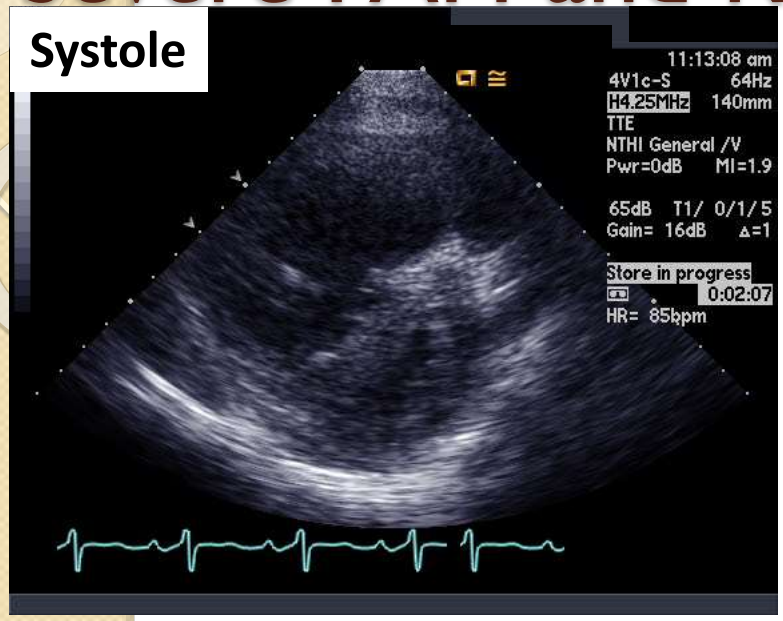
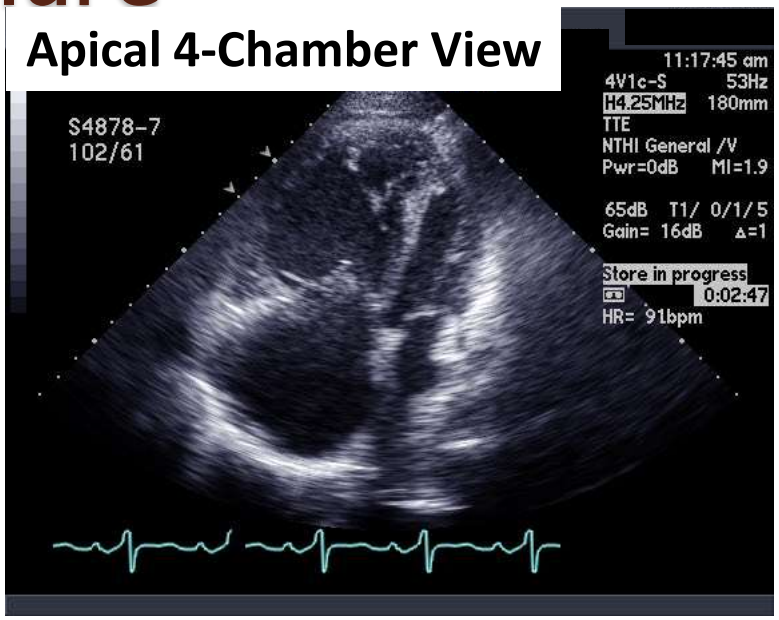


Severe PAH and RV Failure

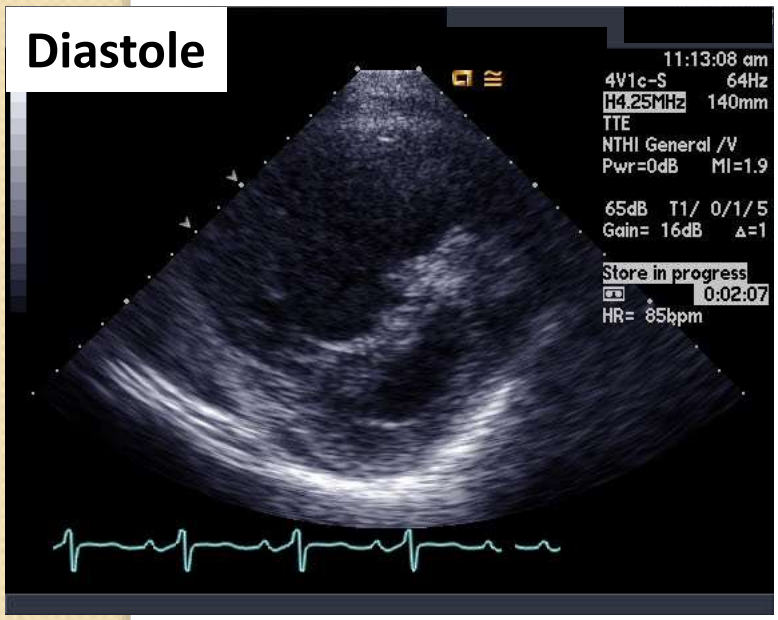
Systole



Apical 4-Chamber View



Diastole



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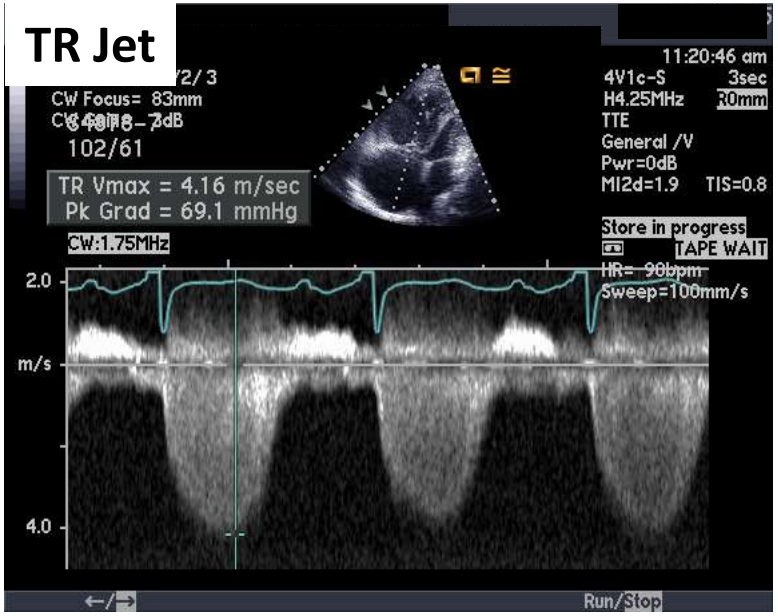
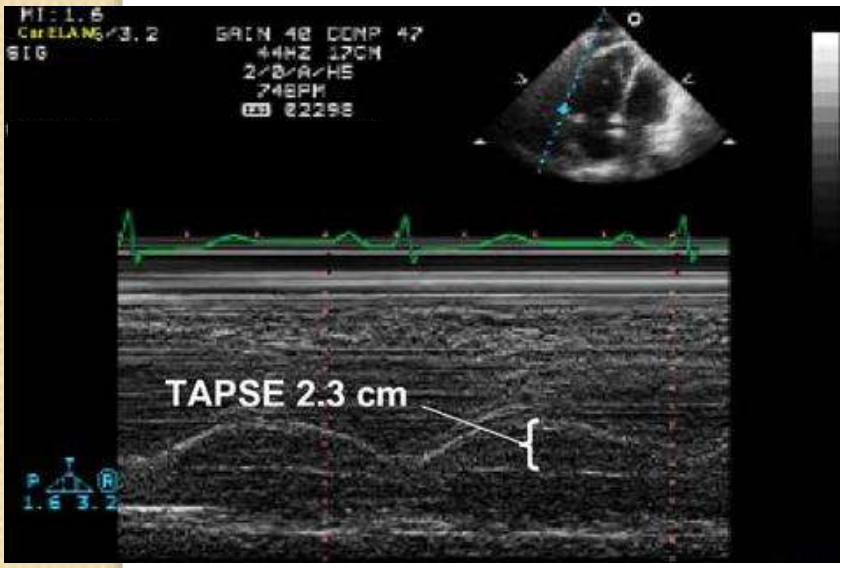
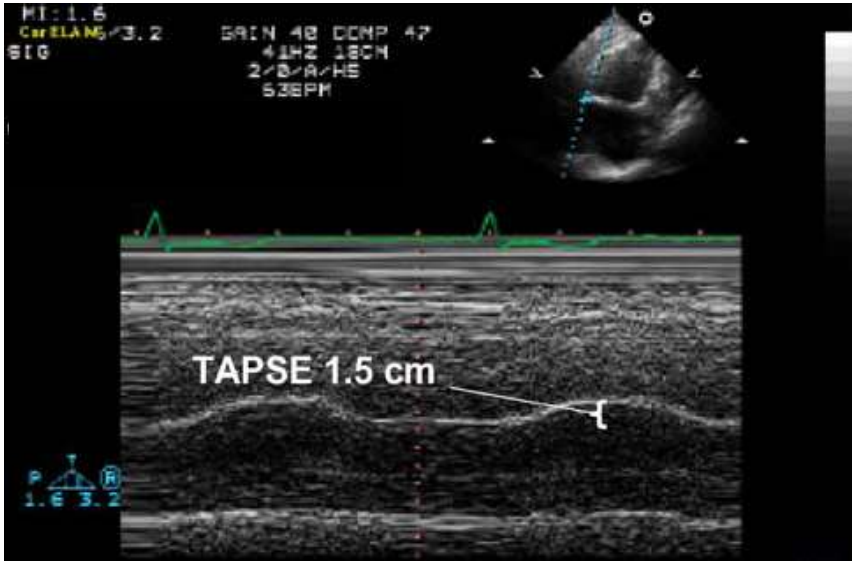


Tricuspid Annular Plane Systolic Excursion (TAPSE)

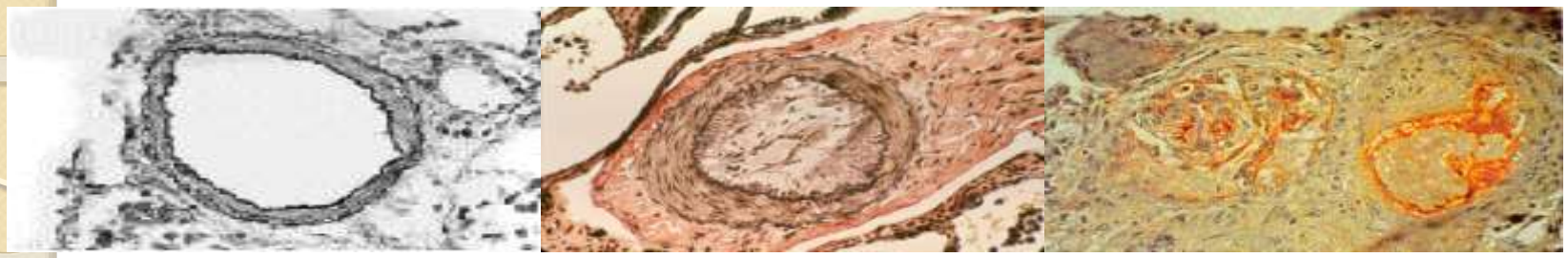
- Contraction of the RV is mainly longitudinal, and the tricuspid annulus displaces toward apex during systole
- Imaging through lateral RV free wall with M-mode assesses longitudinal displacement (excursion) of the tricuspid annulus
- Less TAPSE occurs when RV function declines
- Baseline TAPSE < 1.8 cm has negative prognostic implications





Forfia PR, et al. *Am J Respir Crit Care Med*. 2006;174:1034-1041.

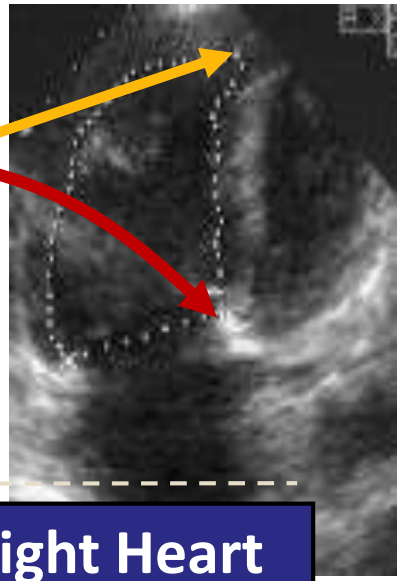
Progression of PAH



Presymptomatic/ Compensated

Symptomatic/ Decompensating

Declining/ Decompensated



CO

Symptom Threshold

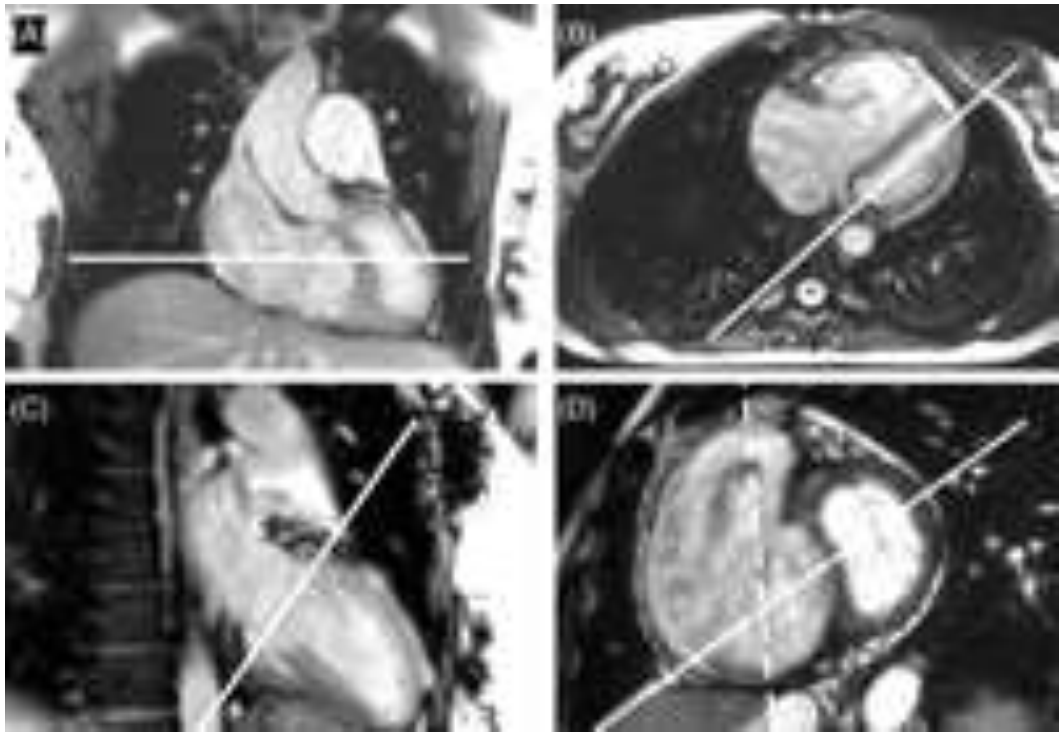
PAP

PVR

Right Heart Dysfunction

Time

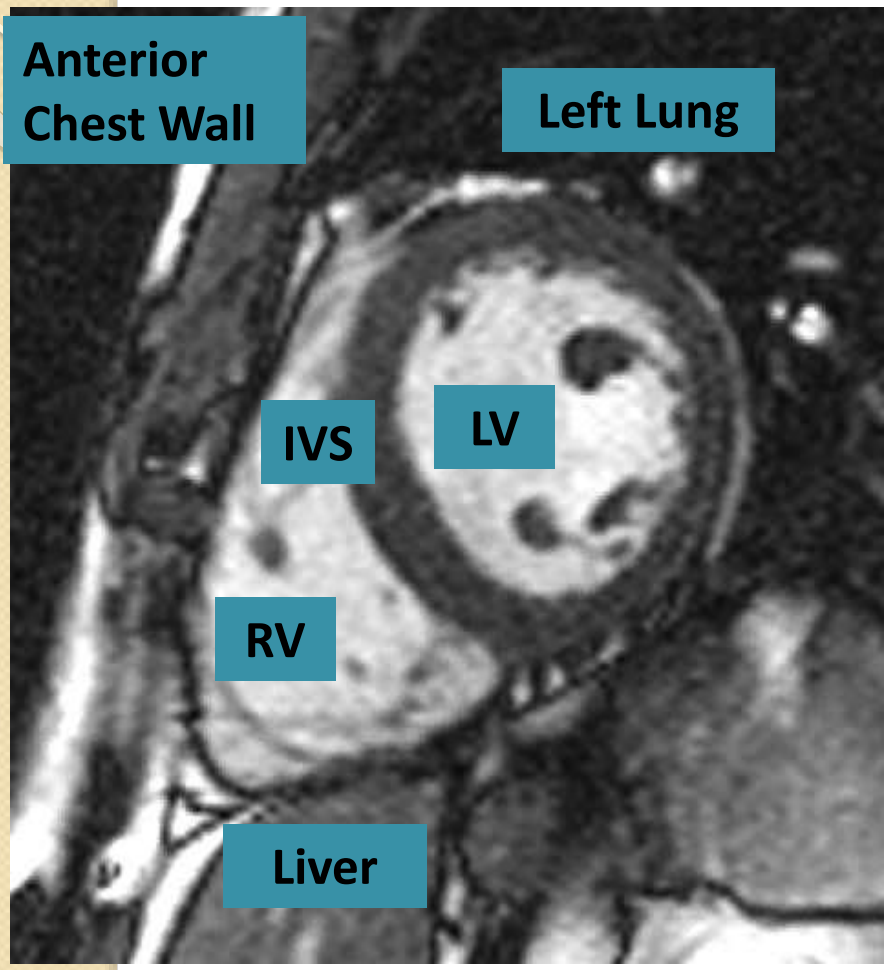
Role of MRI in PAH Assessment



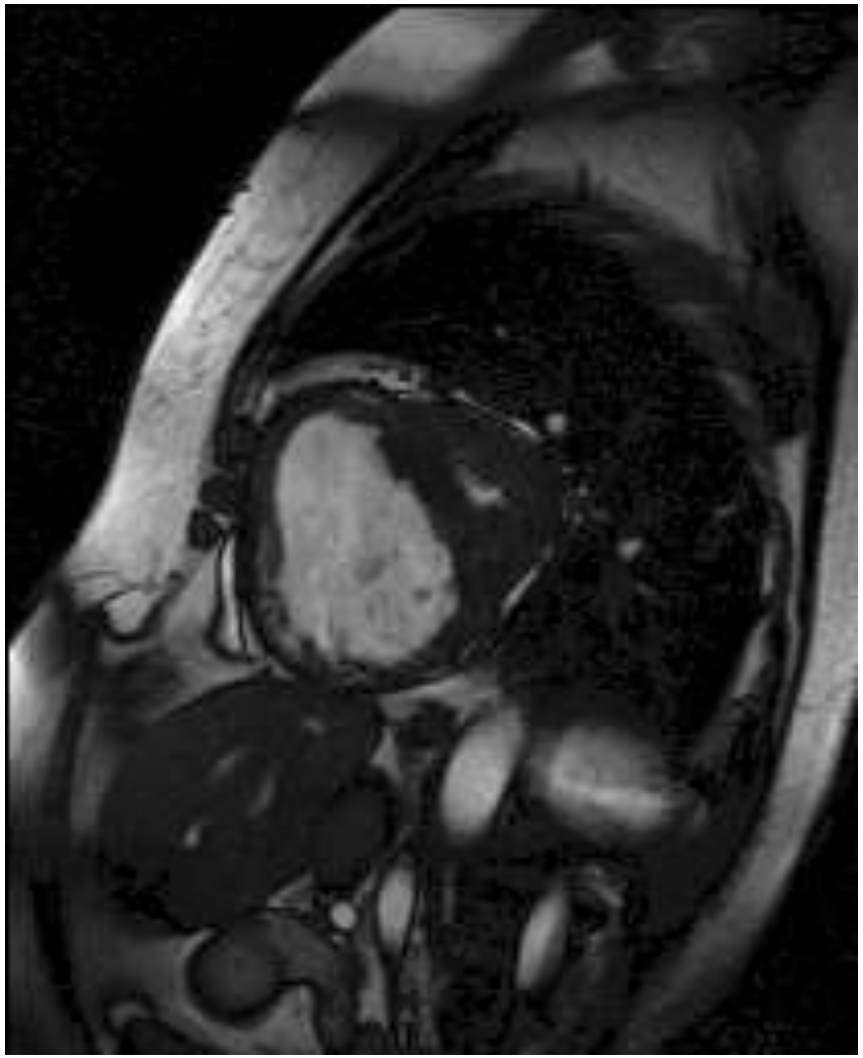
- Quantify RV size, function, viability, and interaction with LV
- Evaluate pulmonary vascular structure and function

Vonk-Noordegraaf A, et al. *Eur Heart J*. 2007; 9(suppl H):H29-34.

Cardiac MRI in PH



Normal short-axis cine MRI



Short-axis cine in severe PH

PAH Determinants of Risk

Lower Risk	Determinant of Risk	Higher Risk
No	Clinical evidence of RV failure	Yes
Gradual	Progression of symptoms	Rapid
II, III	WHO class	IV
Longer (> 400 m)	6-minute walk distance	Shorter (< 300 m)

McLaughlin V, et al. *J Am Coll Cardiol*. 2009;53:1573-1619.

PAH Determinants of Risk (cont)

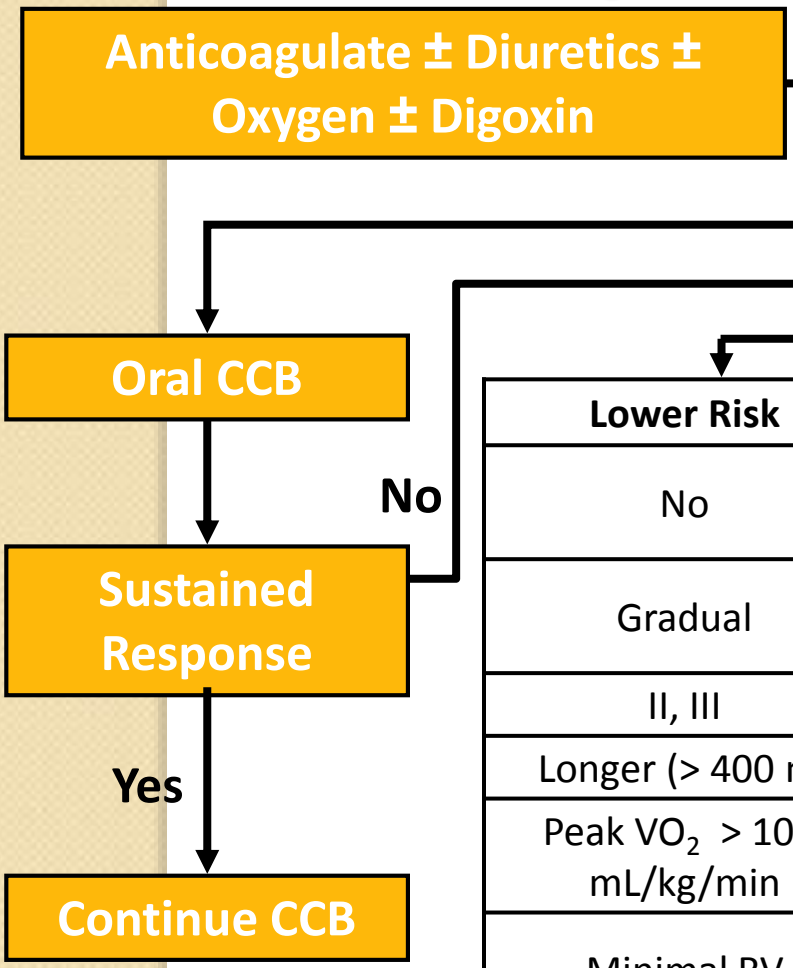
Lower Risk	Determinant of Risk	Higher Risk
Peak VO_2 > 10.4 mL/kg/min	CPET	Peak VO_2 < 10.4 mL/kg/min
Minimal RV dysfunction	Echocardiography	Pericardial effusion, significant RV enlargement/ dysfunction; RA enlargement
RAP < 10 mm Hg; CI > 2.5 L/min/m^2	Hemodynamics	RAP > 20 mm Hg; CI < 2.0 L/min/m^2
Minimally elevated	BNP	Significantly elevated

McLaughlin V, et al. *J Am Coll Cardiol*. 2009;53:1573-1619.

PAH Treatment Goals

- Improves symptoms
- Improves exercise capacity
- Improves hemodynamics
- Improves quality of life
- Improves survival

What Is the Optimal Treatment Strategy?



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Gradual	Progression of symptoms	Rapid
II, III	WHO class	IV
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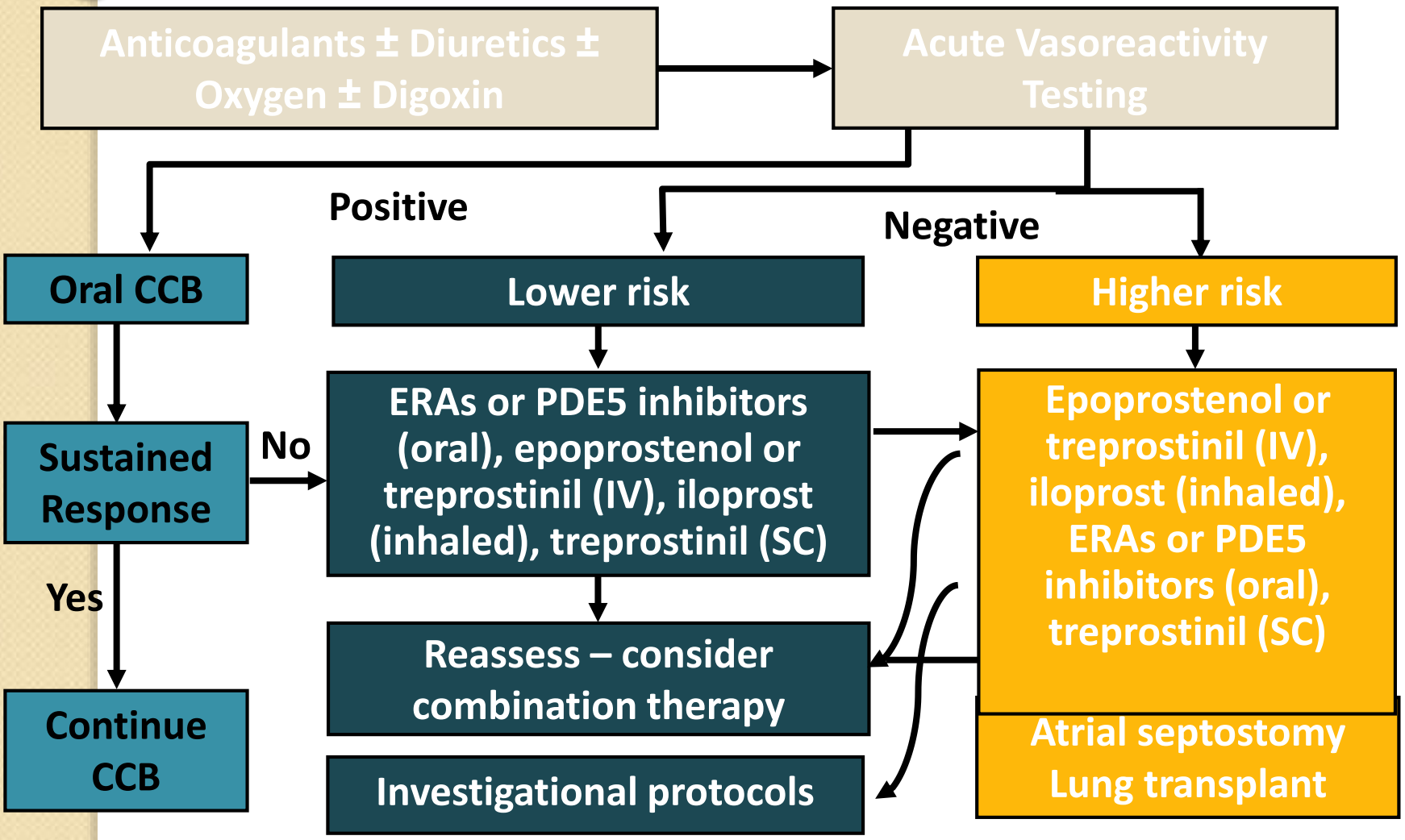
McLaughlin V, et al. *J Am Coll Cardiol*. 2009;53:1573-1619.

ACCF/AHA Consensus PAH Treatment Algorithm



McLaughlin VV, et al. *J Am Coll Cardiol*. 2009;53:1573-1619.

Longitudinal Evaluation of the Patient

Stable; no increase in symptoms and/or decompensation	Clinical course	Unstable; increase in symptoms and/or decompensation
No evidence of right heart failure	Physical exam	Signs of right heart failure
I/II	WHO functional class	IV
> 400 m	6MW distance	< 300 m
RV size/function normal	Echocardiography	RV enlargement/dysfunction
RAP normal; CI normal	Hemodynamics	RAP high; CI low
Near normal, remaining stable, or decreasing	BNP	Elevated or increasing
Oral therapy	Treatment	IV prostacyclin and/or combination treatment

McLaughlin V et al. *J Am Coll Cardiol*. 2009;53:1573-1619.

Longitudinal Evaluation (cont)

Stable; no increase in symptoms and/or decompensation	**Clinical course**	**Unstable; increase in symptoms and/or decompensation**
Every 3-6 months	Frequency of evaluation	Every 1-3 months
Every clinic visit	Functional class assessment	Every clinic visit
Every clinic visit	6MW distance	Every clinic visit
Every 12 months or center dependent	Echocardiography	Every 6-12 months or center dependent
Center dependent	BNP	Center dependent
Clinical deterioration and center dependent	Right heart catheterization	Every 6-12 months or clinical deterioration

McLaughlin V, et al. *J Am Coll Cardiol*. 2009;53:1573-1619.

Important Prognostic Variables

- **French Registry**
  - Functional class
  - 6-minute walk
  - RAP
  - Cardiac index
  - Age
  - Gender
  - Etiology
- **REVEAL Registry**
  - Functional class
  - 6-minute walk
  - PVR, RAP
  - Vitals
  - BNP
  - Pericardial effusion
  - DLCO
  - Age
  - Gender
  - Etiology

DLCO = carbon-monoxide diffusing capacity

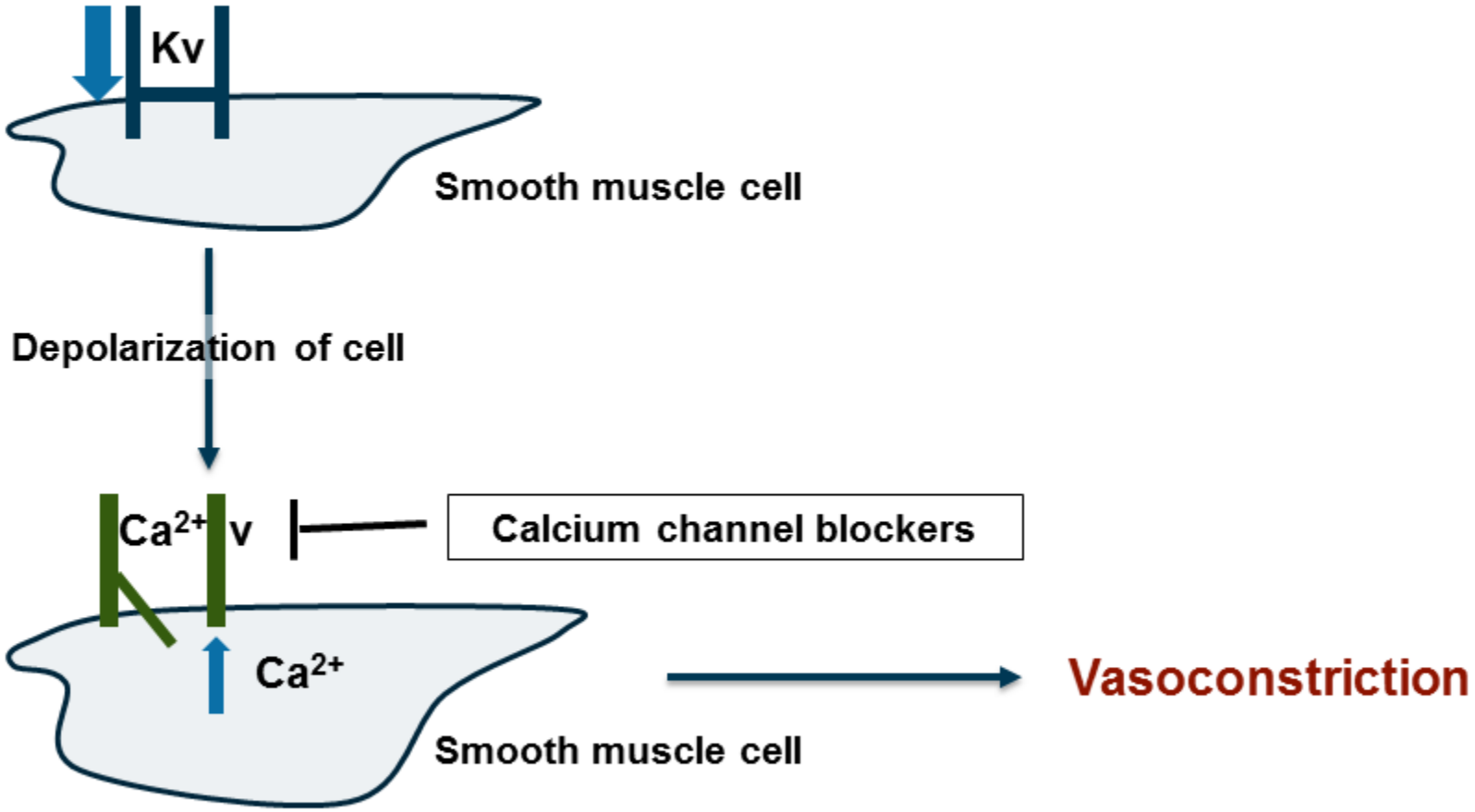
Humbert M, et al. *Circulation*. 2010;122:156-163.
Benza RL, et al. *Circulation*. 2010;122:164-172.

Candidate "Goals of Therapy"

- Functional class I/II
- 6-minute walk distance
- Hemodynamics
  - RAP
  - Cardiac output/cardiac index
- BNP
- ? Echocardiography

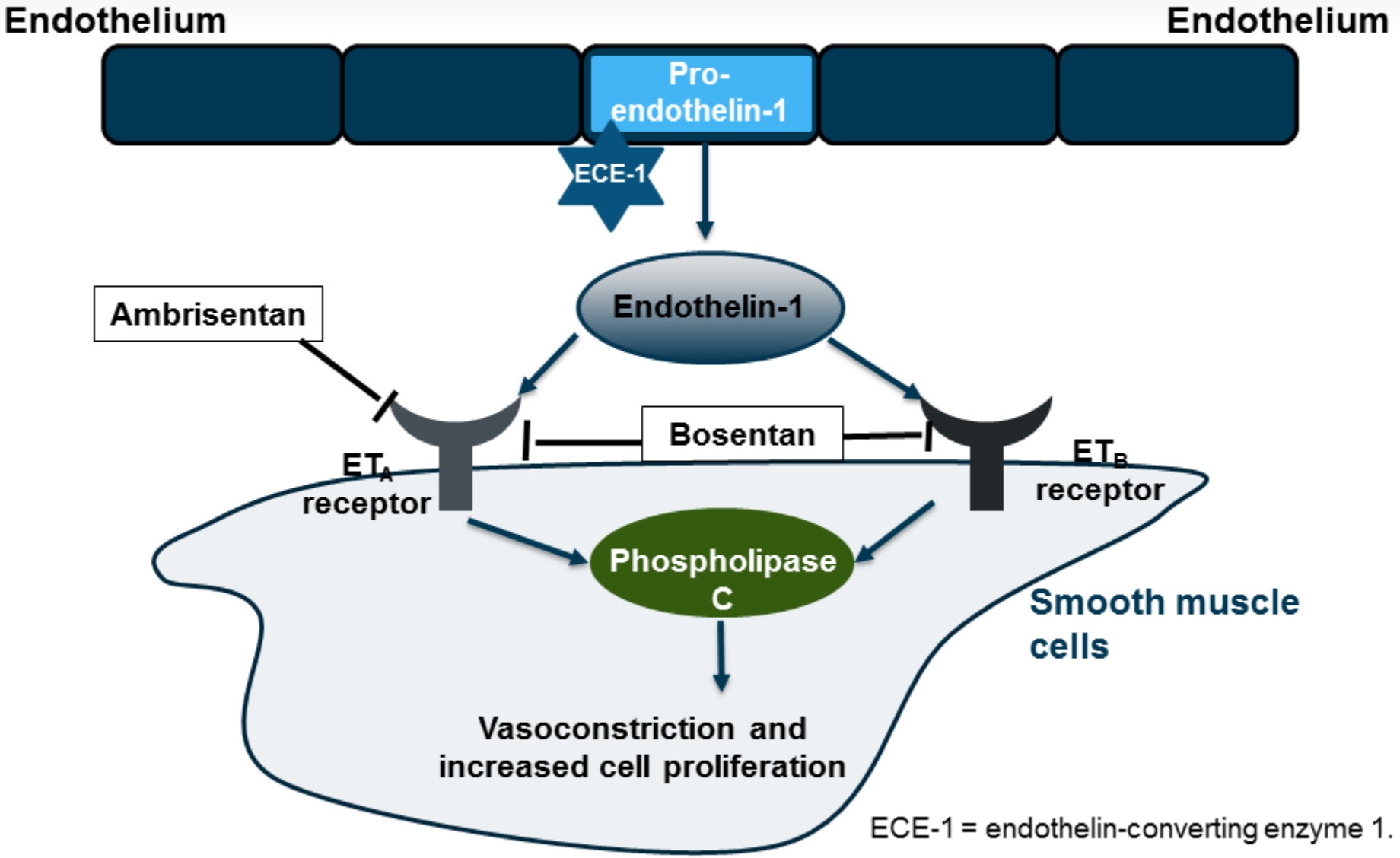
Guided by the Rationale; Therapeutic Strategies in PAH

Link Between Potassium and Calcium Channels



Ca^{2+} v = voltage-gated calcium channel.

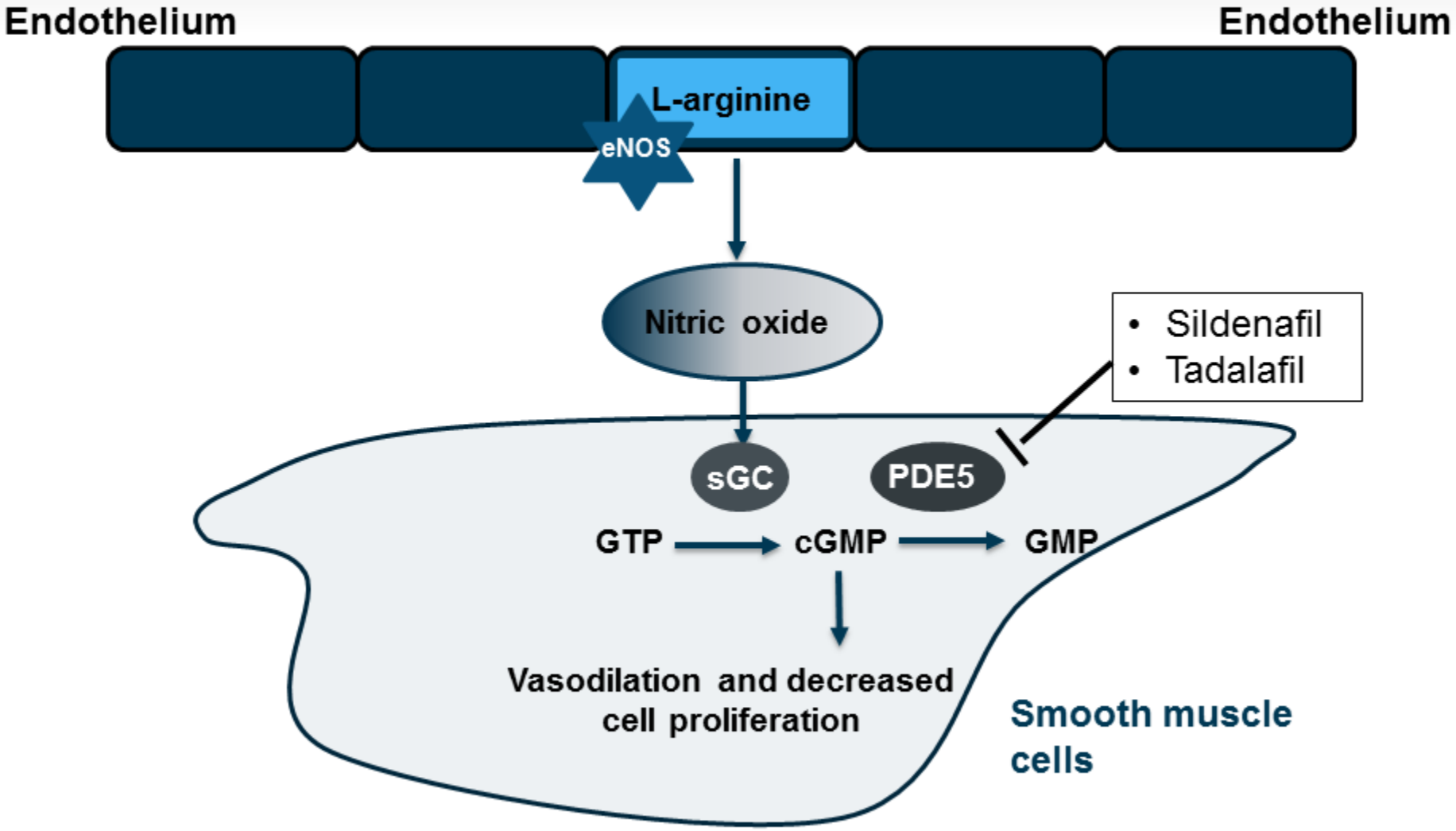
Endothelin-1 Pathway: Modulation by Available Agents



ECE-1 = endothelin-converting enzyme 1.

O'Callaghan DS, et al. *Nat Rev Cardiol.* 2011;8:526-538.

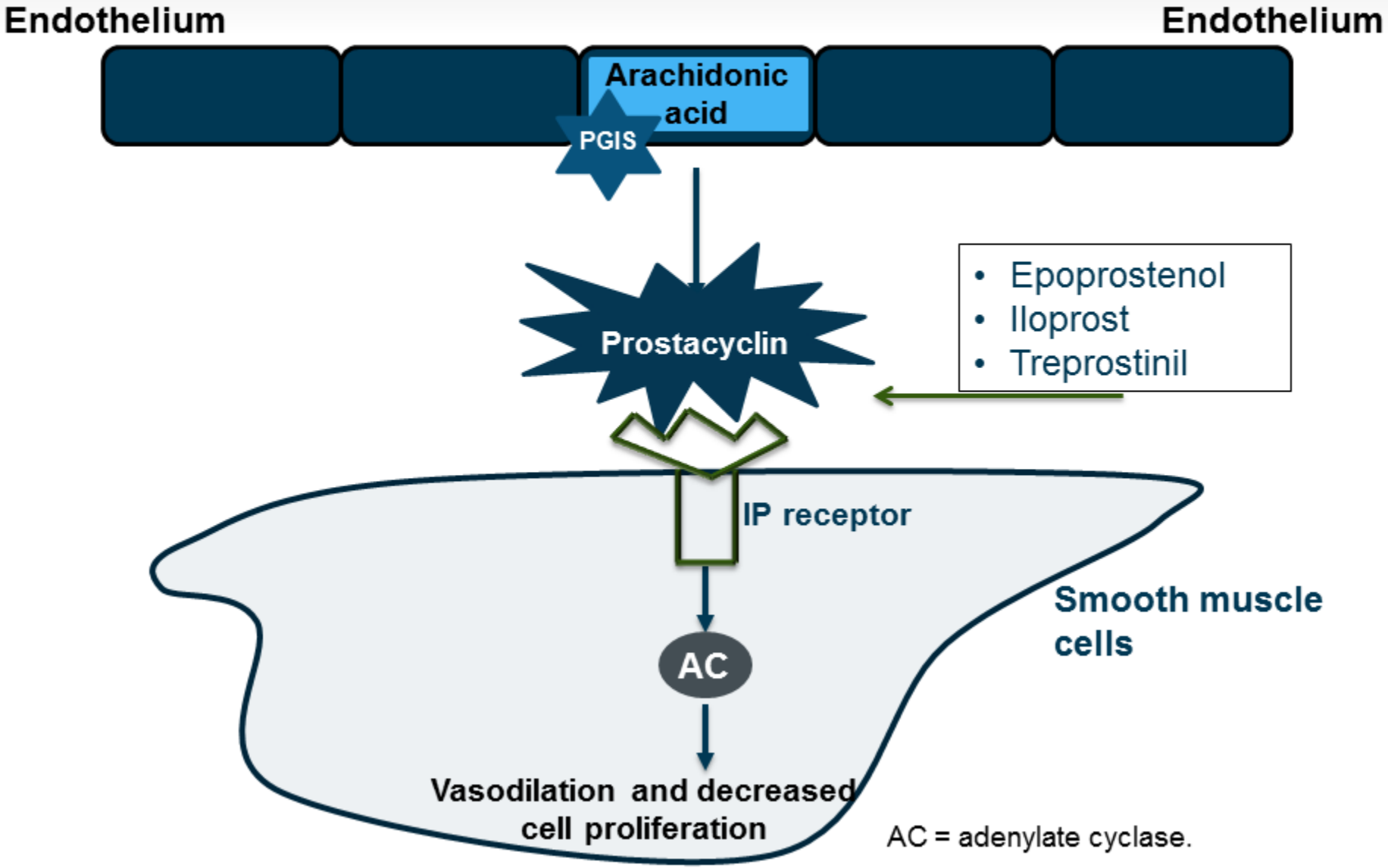
Nitric Oxide Pathway: Modulation by Available Agents



GMP = guanosine monophosphate.

O'Callaghan DS, et al. *Nat Rev Cardiol.* 2011;8:526-538.

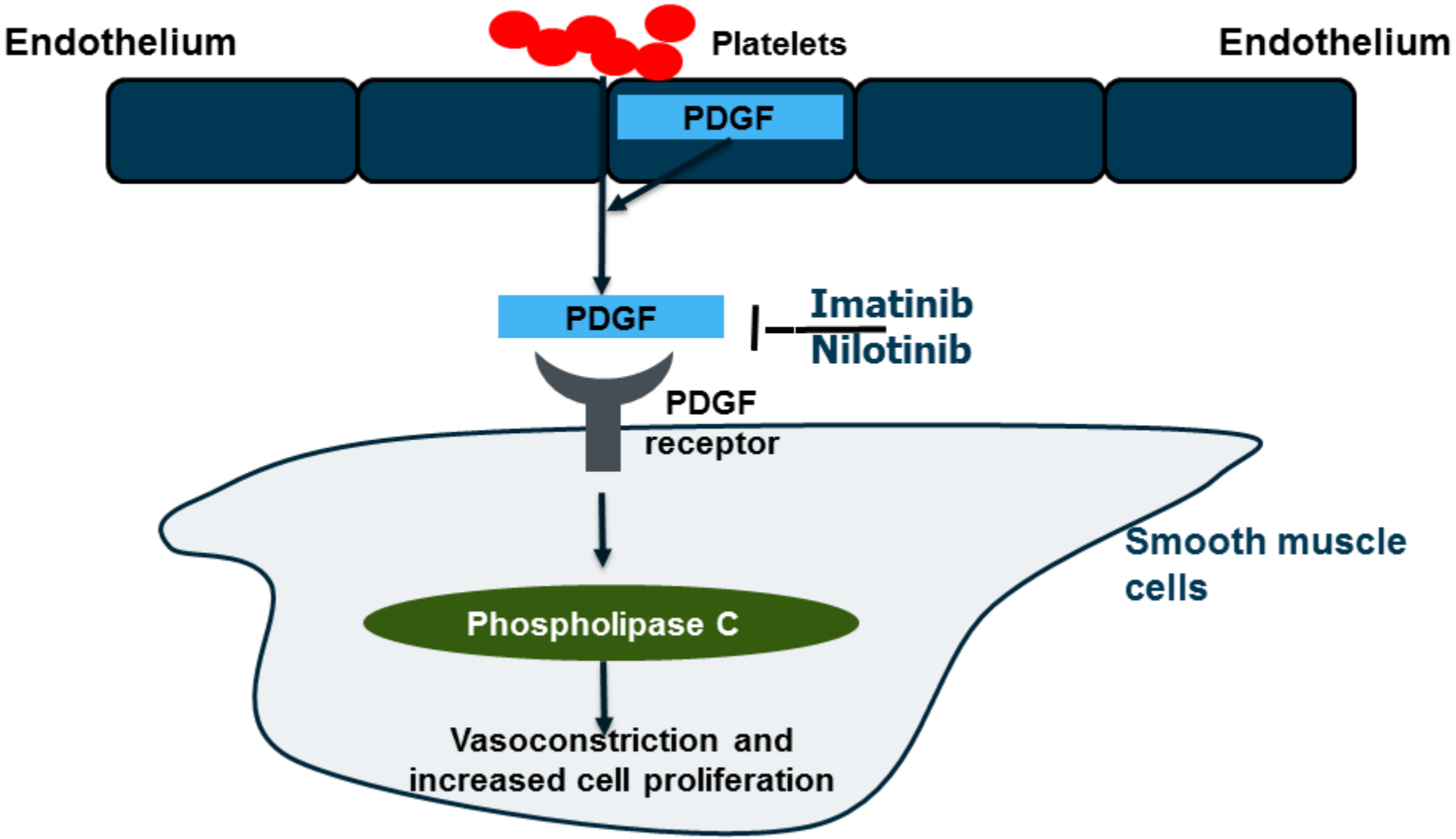
Prostacyclin Pathway: Modulation by Available Agents



AC = adenylate cyclase.

O'Callaghan DS, et al. *Nat Rev Cardiol.* 2011;8:526-538.

Angiogenesis and PDGF: Modulation by Investigational Agents



PDGF = platelet derived growth factor.

Vasoactive Intestinal Peptide (VIP)

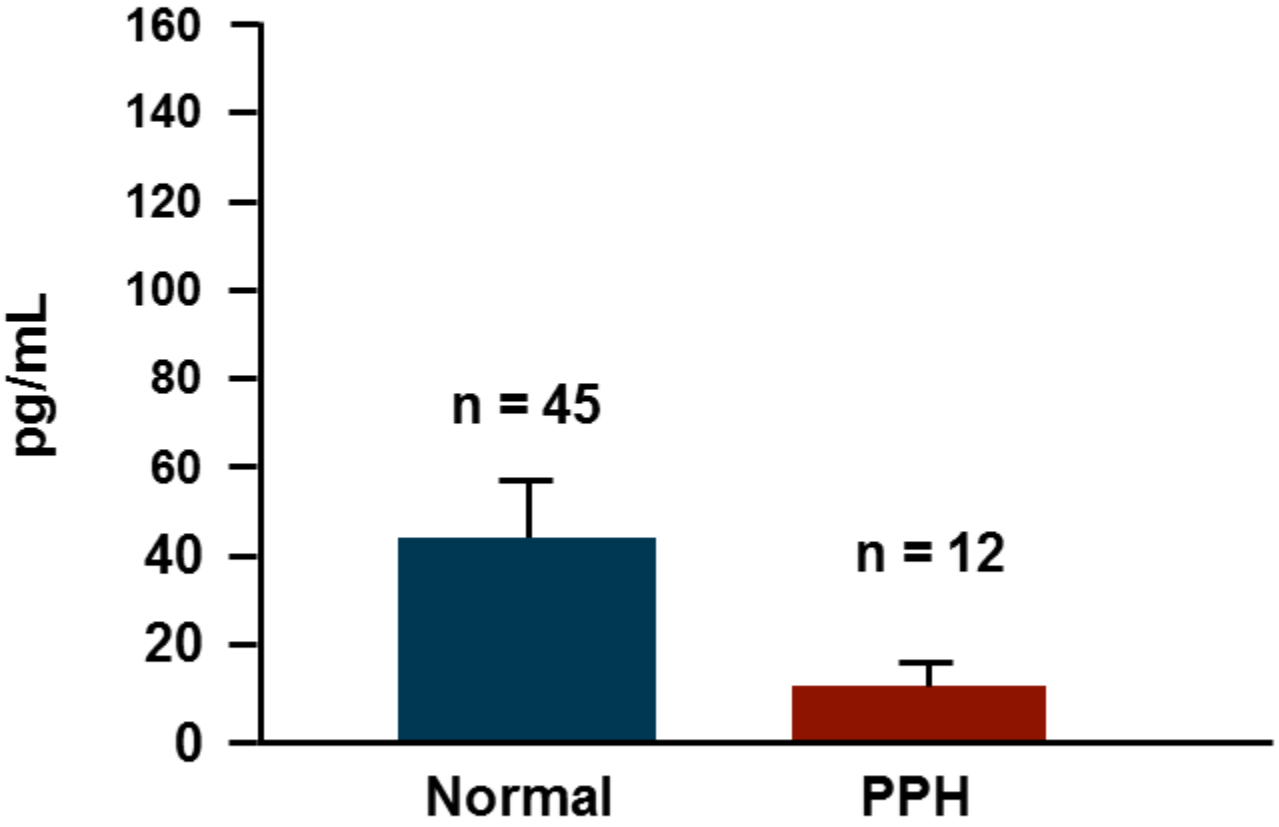
Member of the glucagon growth-hormone releasing superfamily

Pharmacologic profile similar to epoprostenol:

- Endogenous vasodilator
- Inhibitor of smooth muscle cell proliferation
- Inhibitor of platelet aggregation

Said SI, et al. *Circulation*. 2007;115:1260-1268; Petkov V, et al. *J Clin Invest.* 2003;111:1339-1346.

Reduced Serum Levels of VIP in PPH



PPH = primary pulmonary hypertension.

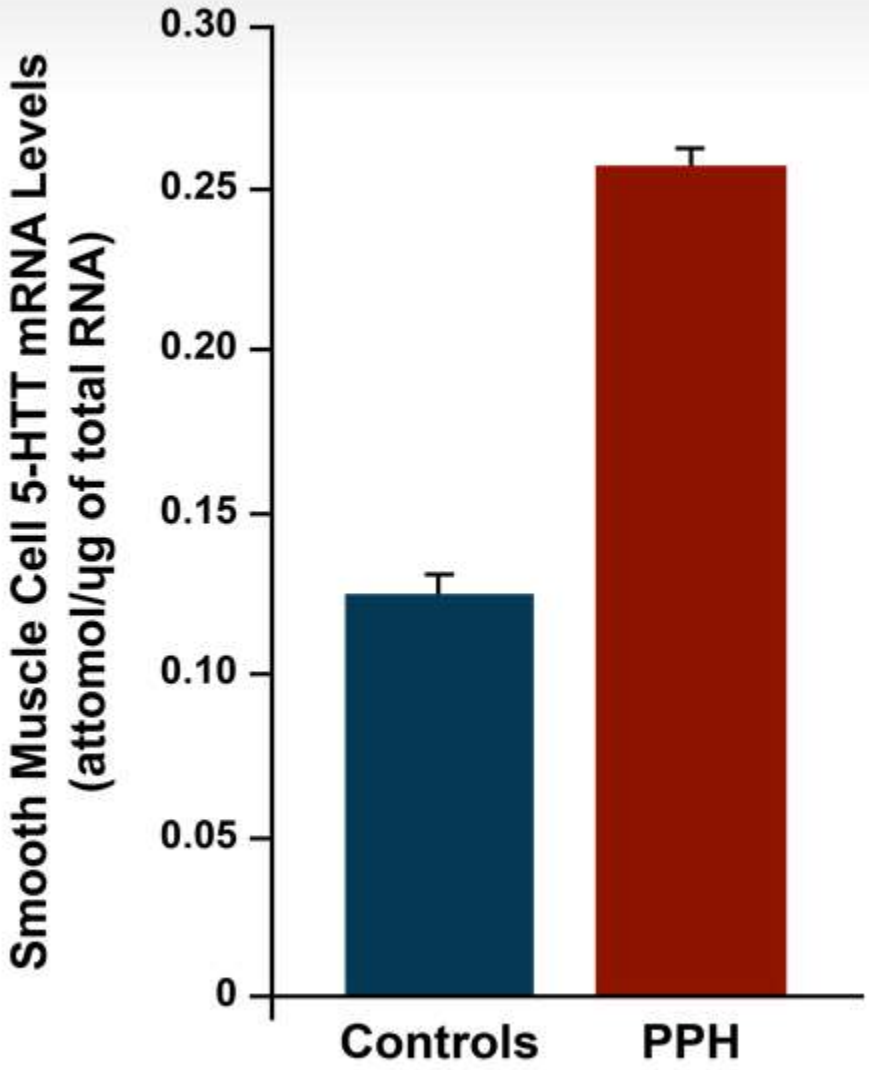
Petkov V, et al. *J Clin Invest.* 2003;111:1339-1346.

Serotonin Pathway

- Serotonin is a smooth muscle mitogen
- Transported into cells primarily via the serotonin transporter (SERT) and to a lesser extent, via the receptors
- Transgenic mice lacking SERT or pharmacologic inhibition of SERT prevents hypoxic vasoconstriction

Eddahibi S, et al. *J Clin Invest*. 2001;108:1141-1150; Morecroft I, et al. *Cardiovasc Res*. 2010;85:593-603.

Serotonin and PAH

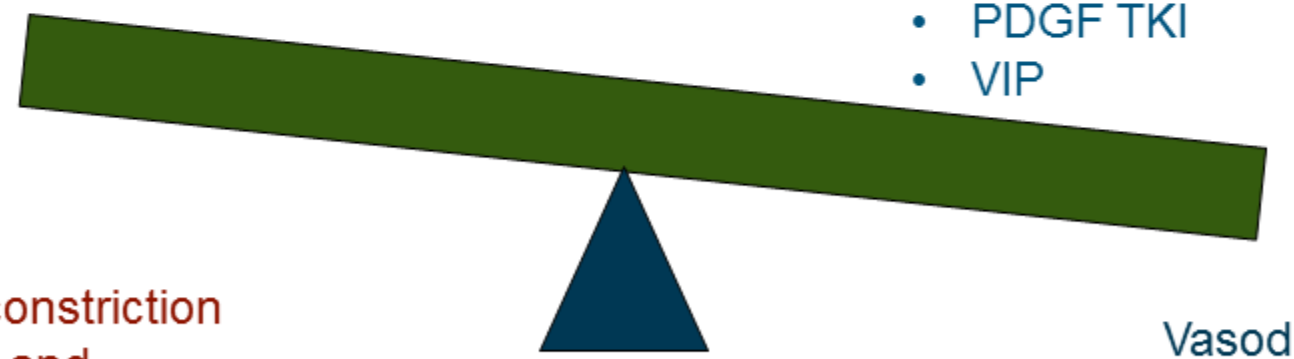


5-HTT = 5-hydroxytryptamine transporter.

Restoring the Balance in PAH: Combining Synergistic Pathways

- ET-1 levels
- PDE5
- PDGF
- Serotonin

- ERAs
- Oral sGC stimulators
- PDE5 inhibitors
- Prostacyclin receptor agonists
- Prostanoids
- PDGF TKI
- VIP



Vasoconstriction
and
Increased proliferation

Vasodilation
and
Decreased proliferation

TKI = tyrosine kinase inhibitor.

PAH: Predictors of Mortality

Characteristic	Hazard Ratio
PVR > 32 Wood units	4.08
Portopulmonary hypertension	3.60
WHO functional class: III/IV	1.41-3.13
Familial PAH	2.17
BNP > 180 pg/mL	1.97
Renal insufficiency	1.90
mRAP > 20 mm Hg	1.79
6MWD < 165 m	1.68
Systolic BP < 110 mm Hg	1.67
PAH associated with connective tissue disease	1.59
DLCO ≤ 32%	1.46
HR > 92 BPM	1.39
Presence of pericardial effusion	1.35

Benza RL, et al. *Circulation*. 2010;122:164-172.

Thanks for Attention