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Pulmonary Hypertension

Diagnosis and Therapy

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IT'S HOW MEDICINE SHOULD BE®

Pulmonary Hypertension

Definition

Updated Definition of PAH

Right Heart Catheterization Confirmed

Increased mean pulmonary arterial pressure (mPAP)*	**≥25 mm Hg at rest**
Normal pulmonary capillary wedge pressure (PCWP)	**≤15 mm Hg**
Increased pulmonary vascular resistance (PVR)†	**>3 Wood units**

Badesch DB, et al. *J Am Coll Cardiol.* 2009;54(suppl 1):S55–S66

Updated Hemodynamic Definitions of Pulmonary Hypertension

Definition	Characteristics	Clinical group
Pre-capillary PH	**Mean PAP ≥25 mm Hg** **PWP ≤15 mm Hg** **CO normal or reduced**	• **Pulmonary arterial hypertension** • **PH due to lung disease** • **CTEPH** • **PH with unclear or multifactorial mechanisms**
Post-capillary PH	**Mean PAP ≥25 mm Hg** **PWP >15 mm Hg** **CO normal or reduced** **Passive = TPG ≤12 mm Hg** **Reactive = TPG >12 mm Hg**	• **PH due to left heart disease**

CO = cardiac output.

TPG = transpulmonary pressure gradient.

Galie N, et al. *Eur Heart J.* 2009;30(20):2493-2537.

Pathophysiology

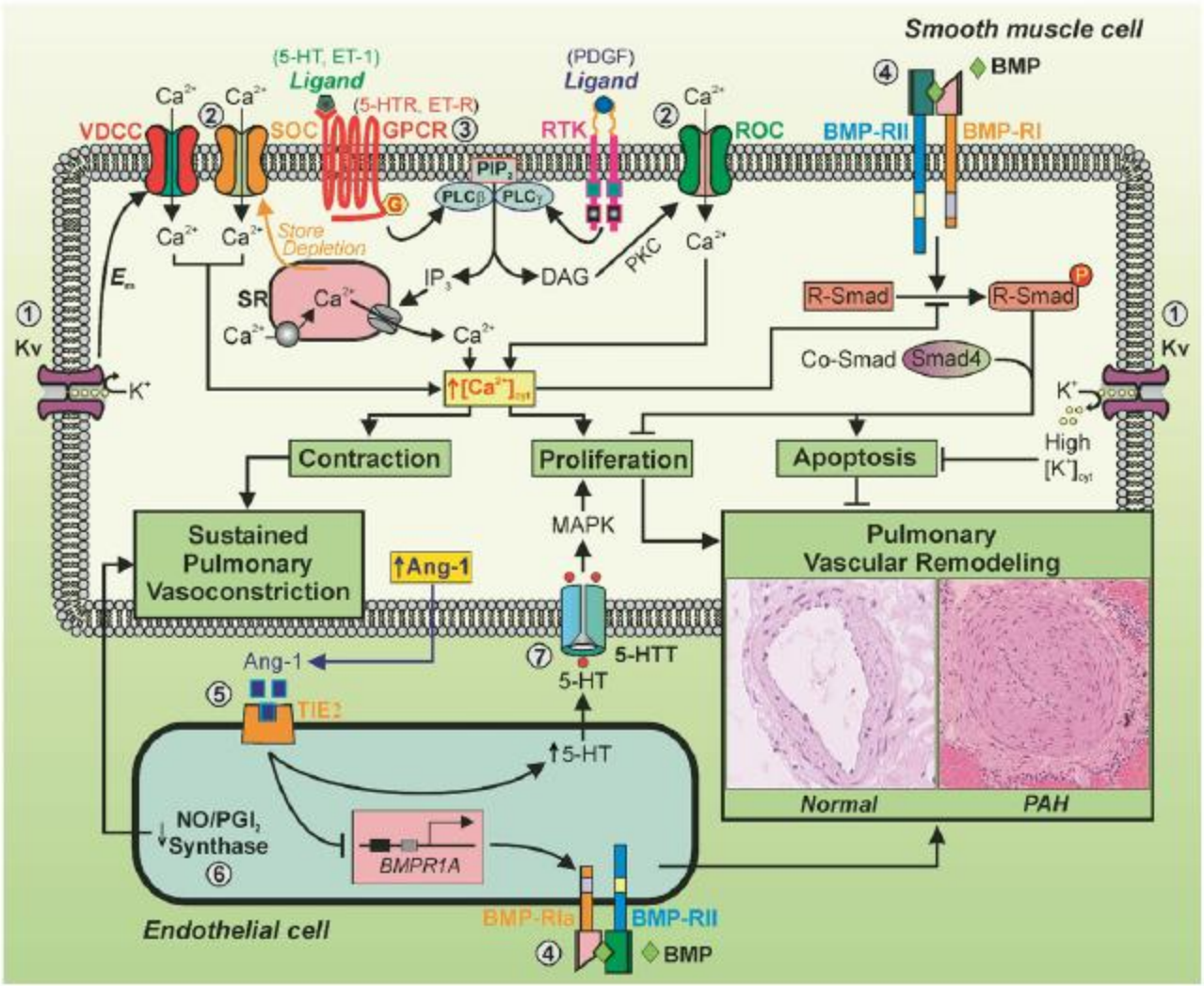


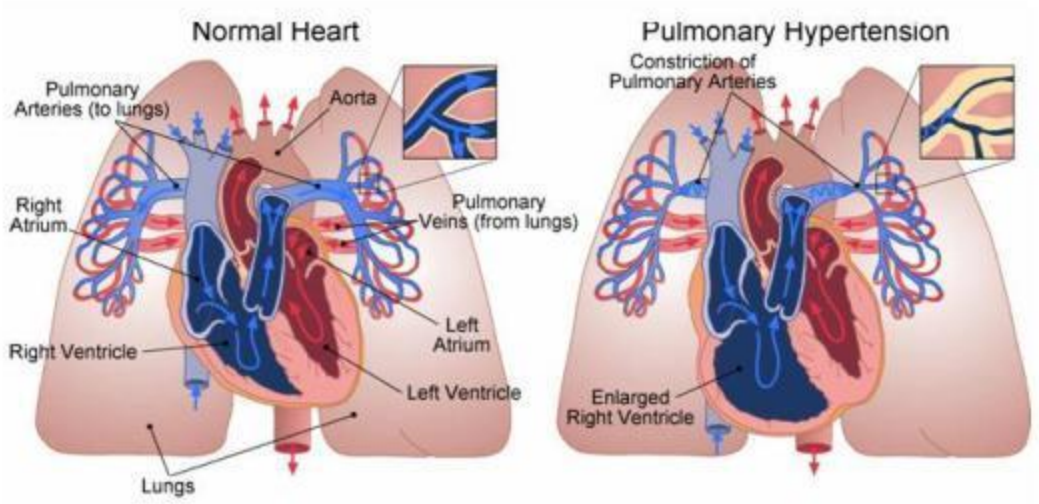
Figure 1. Relevant Pathways in the Pathogenesis of Pulmonary Arterial Hypertension

Causes

2009 Updated Clinical Classification of Pulmonary Hypertension

Group 1

- **Idiopathic (IPAH)**
- **Heritable (PAH)**
  - BMPR2
  - ALK1
  - Endoglin (with or without hereditary hemorrhagic telangiectasia)
  - Unknown
- **Drugs and Toxins induced**
- **Associated with**
  - Connective Tissue Diseases
  - HIV Infection
  - Portal Hypertension
  - Congenital Heart Diseases

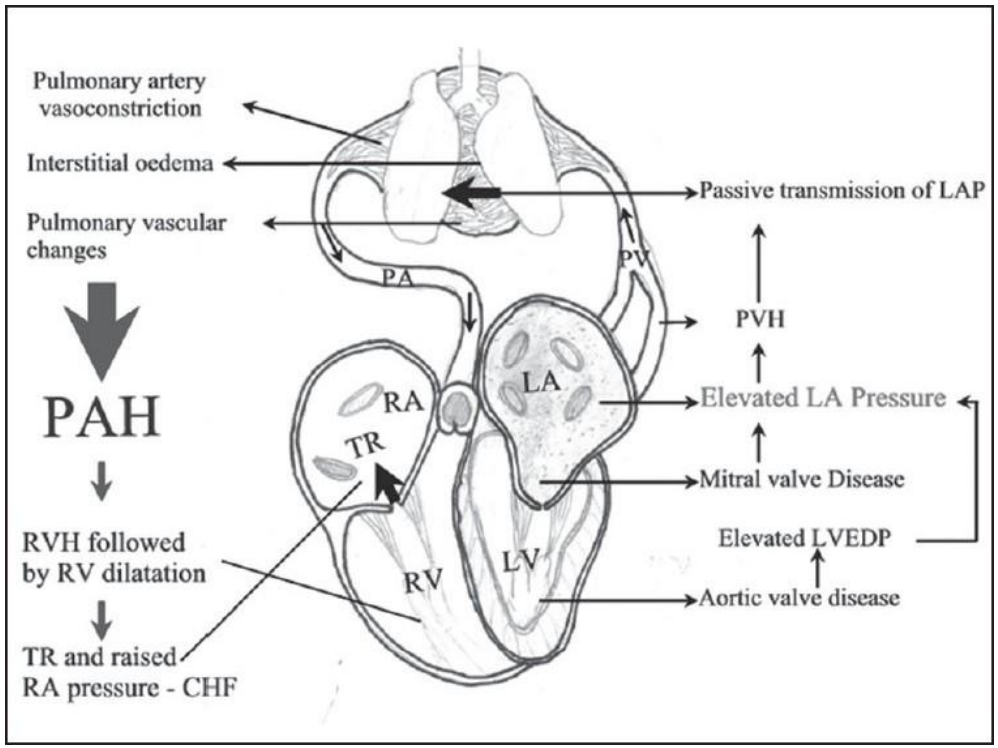


Simonneau G, et al. *J Am Coll Cardiol*. 2009;54(suppl 1):S43-S54.

2009 Updated Clinical Classification of Pulmonary Hypertension

Group 2

- **Pulmonary hypertension with left heart disease**
  - Systolic dysfunction
  - Diastolic dysfunction
  - Valvular disease



Simonneau G, et al. *J Am Coll Cardiol*. 2009;54(suppl 1):S43-S54.

2009 Updated Clinical Classification of Pulmonary Hypertension

Group 3

- **Pulmonary hypertension owing 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

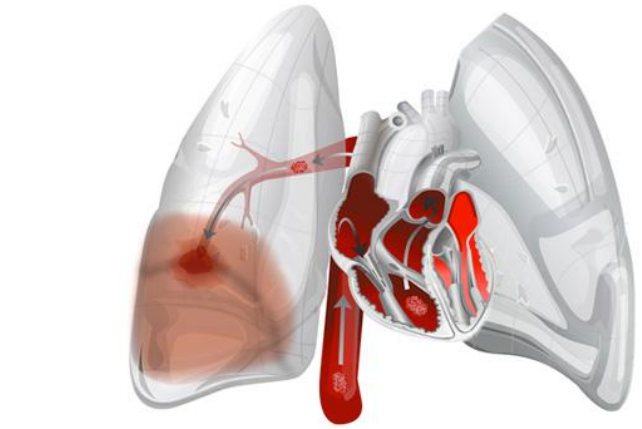
Simonneau G, et al. *J Am Coll Cardiol*. 2009;54(suppl 1):S43-S54.

2009 Updated Clinical Classification of Pulmonary Hypertension

Group 4

- **Chronic thromboembolic pulmonary hypertension (CTEPH)**

- Thromboembolic obstruction of the proximal pulmonary arteries
- Thromboembolic obstruction of the proximal pulmonary arteries
- Nontrombotic pulmonary embolism (tumour, parasites, foreign body)

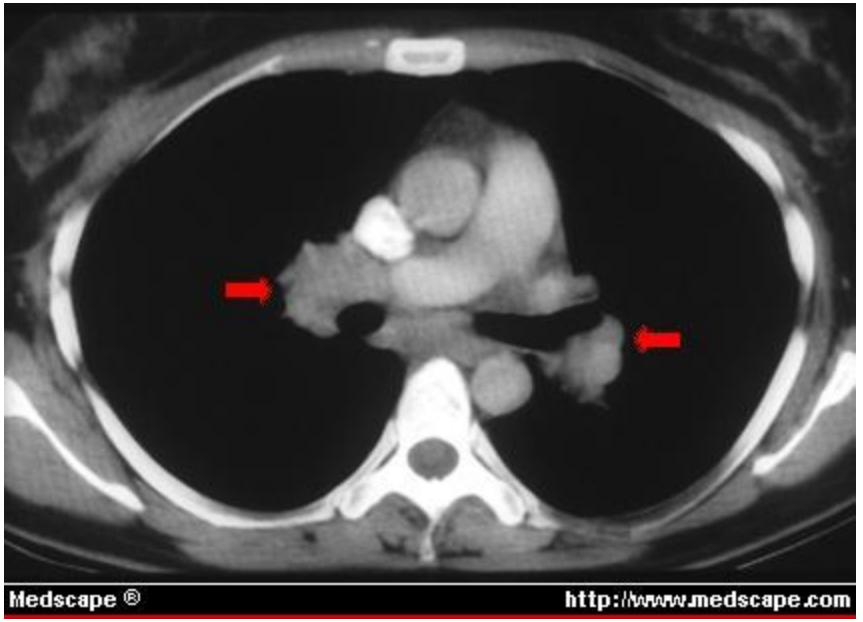


2009 Updated Clinical Classification of Pulmonary Hypertension

Group 5

- **Miscellaneous**

- Sarcoidosis
- histiocytosis X
- Compression of the pulmonary vessels



Simonneau G, et al. *J Am Coll Cardiol*. 2009;54(suppl 1):S43-S54.

Survival in Pulmonary Hypertension

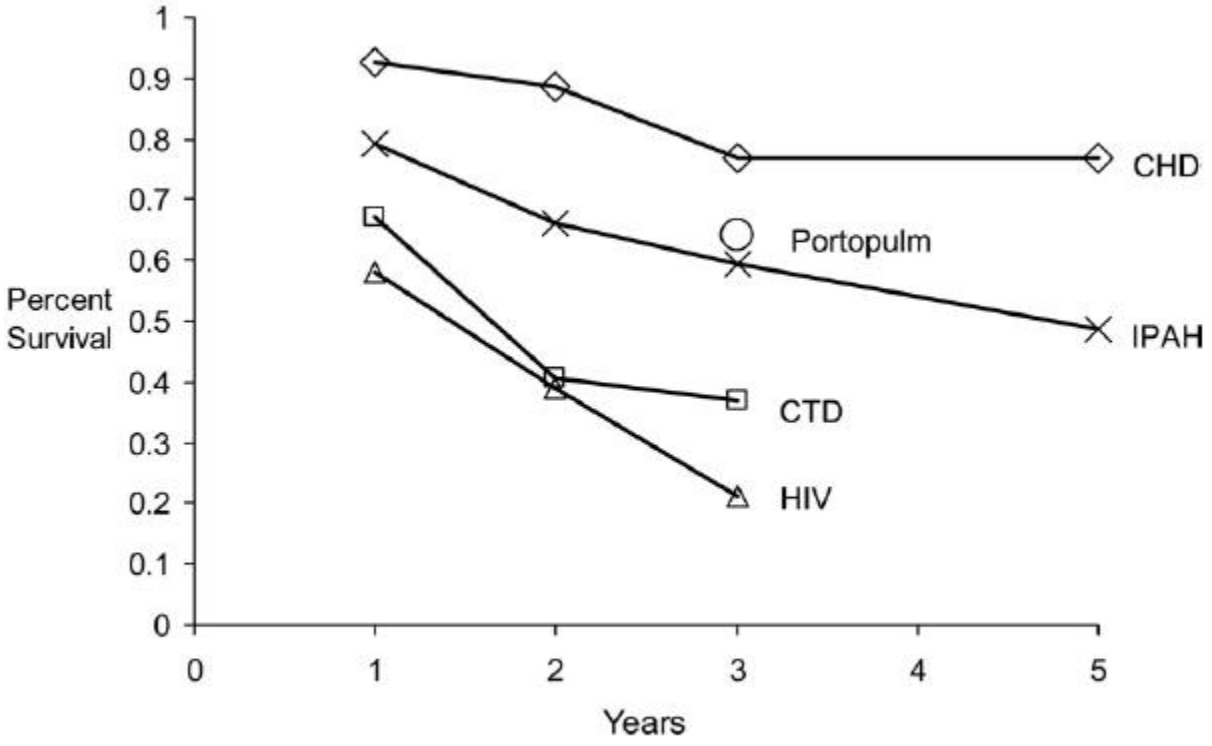


Figure 2. Mean Survival of Patients With PAH Based on Etiology

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Symptoms

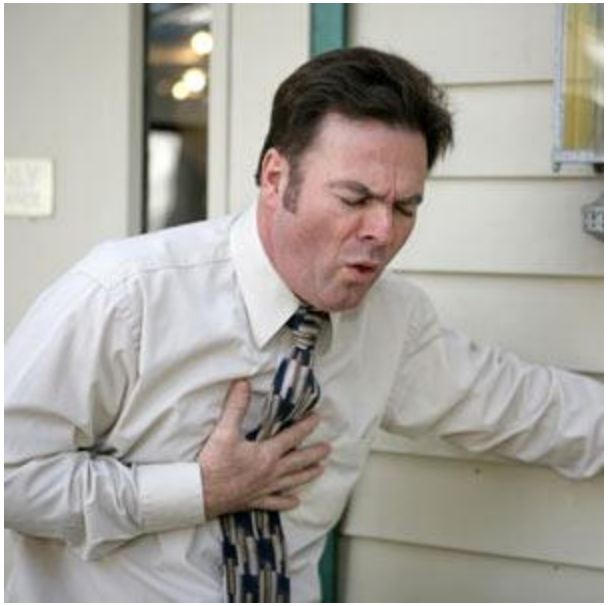
Dyspnea

- The most common symptoms of pulmonary hypertension is ***shortness of breath*** that worsens with activity – 83%

Elliott EG, et al. *Chest.* 2007;132(suppl 4):631S.

Chest pain/ chest discomfort

- ***Chest pain/ discomfort***
  – can occur in up to 23% of patients



Elliott EG, et al. *Chest.* 2007;132(suppl 4):631S.

Presyncope/ Syncope

- ***Syncope*** is a very severe symptom and can be the initial symptom of pulmonary hypertension in up to 20%

Elliott EG, et al. *Chest.* 2007;132(suppl 4):631S.

Other complains

- Other common complaints are:
- ***Cough***- 13%
- ***Fatigue*** -29%
- ***Dizziness/ lightheaded*** – 16%

Elliott EG, et al. *Chest.* 2007;132(suppl 4):631S.

Signs and Symptoms of PAH

No early symptoms of PAH

Annual screening in high-risk populations mandatory

Progressive dyspnea on exertion, fatigue, palpitations, chest pain, dizziness, syncope, coughing

Symptoms and signs of right heart failure, edema, ascites

Gaine SP, Rubin LJ. *Lancet*. 1998;352:719-725.
Erratum in: *Lancet*. 1999;353:74.

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Table 2. Functional Classification of Pulmonary Arterial Hypertension.*

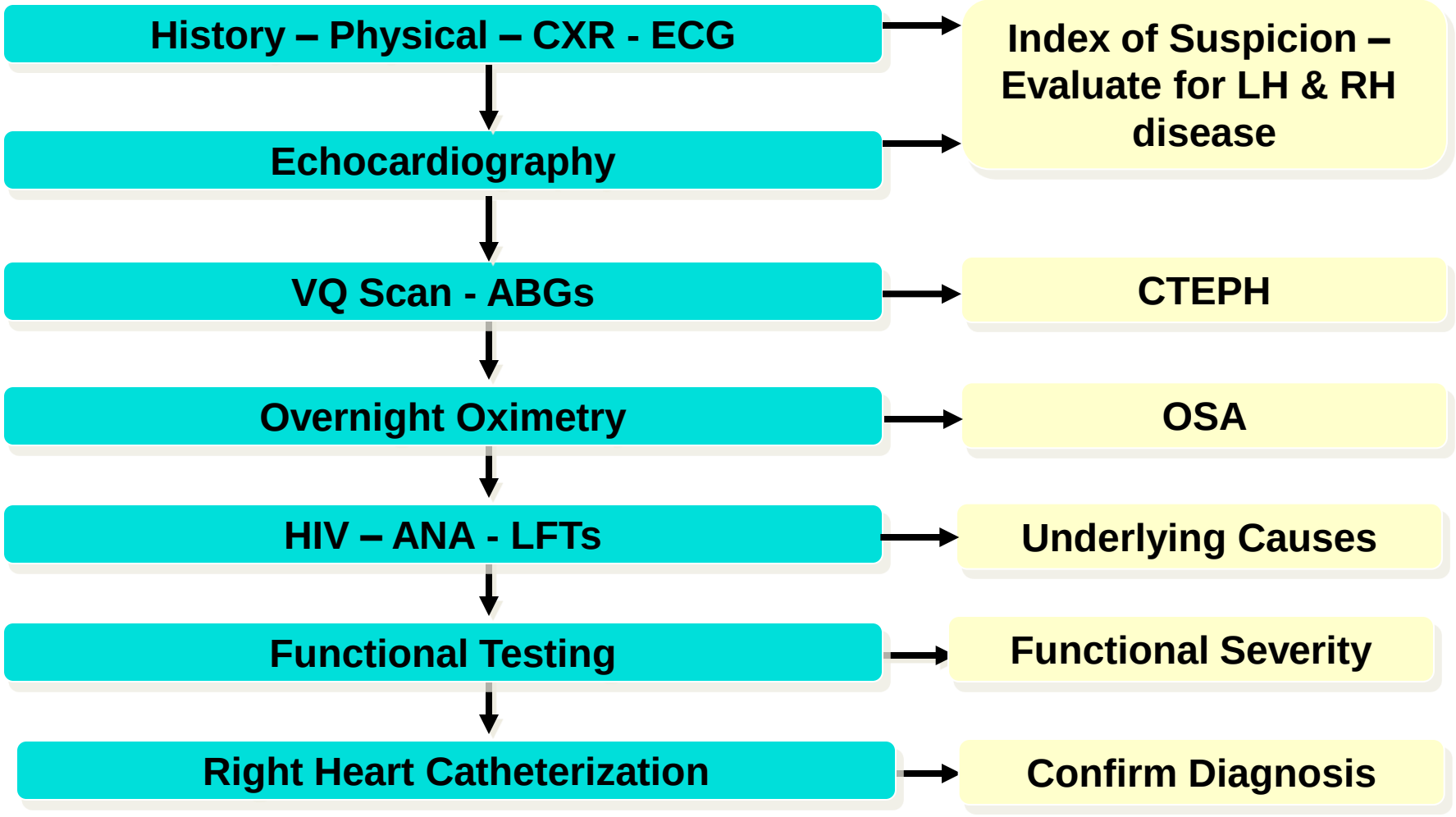
Class	Description
Class I	Pulmonary arterial hypertension without a resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II	Pulmonary arterial hypertension resulting in a slight limitation of physical activity. The patient is comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near-syncope.
Class III	Pulmonary arterial hypertension resulting in a marked limitation of physical activity. The patient is comfortable at rest, but less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near-syncope.
Class IV	Pulmonary arterial hypertension resulting in an inability to carry out any physical activity without symptoms. The patient has signs of right heart failure. Dyspnea, fatigue, or both may be present even at rest, and discomfort is increased by any physical activity.

* This classification was modified from the New York Heart Association classification of patients with cardiac disease. It is adapted from the executive summary of the World Symposium on Primary Pulmonary Hypertension in Evian, France, in 1998.[31]

NEJM, 351;14 September 30, 2004

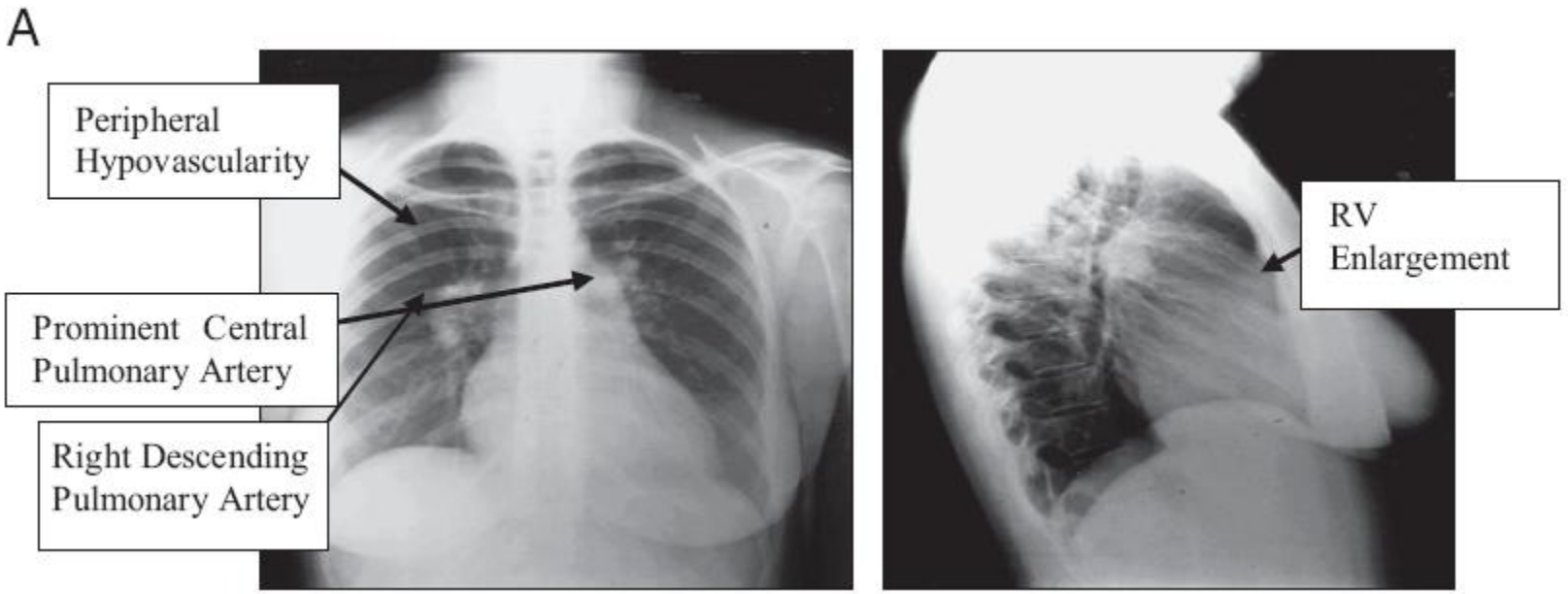
Diagnostic Tests

Algorithm for Diagnosing and Rating Severity of PH



Adapted from McLaughlin VV, et al. *Circulation.* 2009;119(16):2250-2294

CXR in Pulmonary Hypertension



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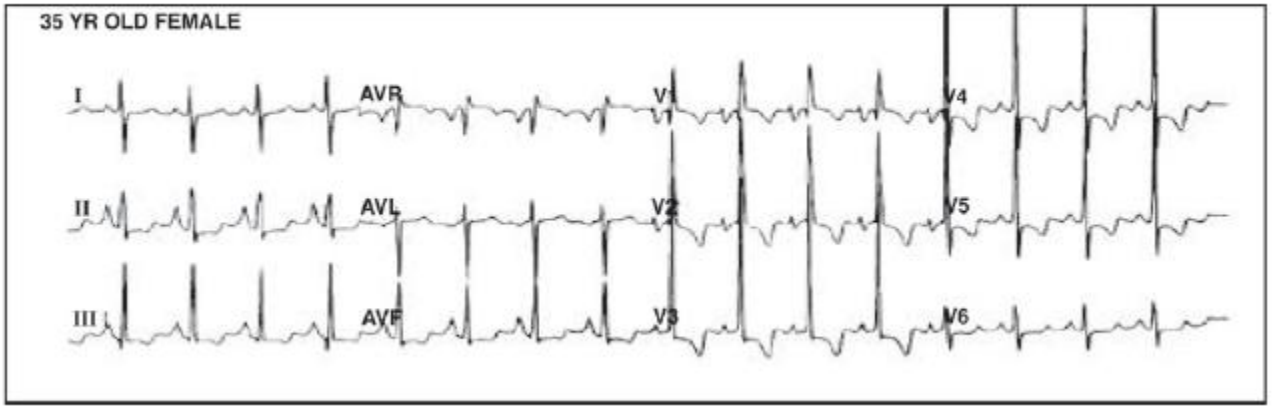
ECG in Pulmonary Hypertension

B



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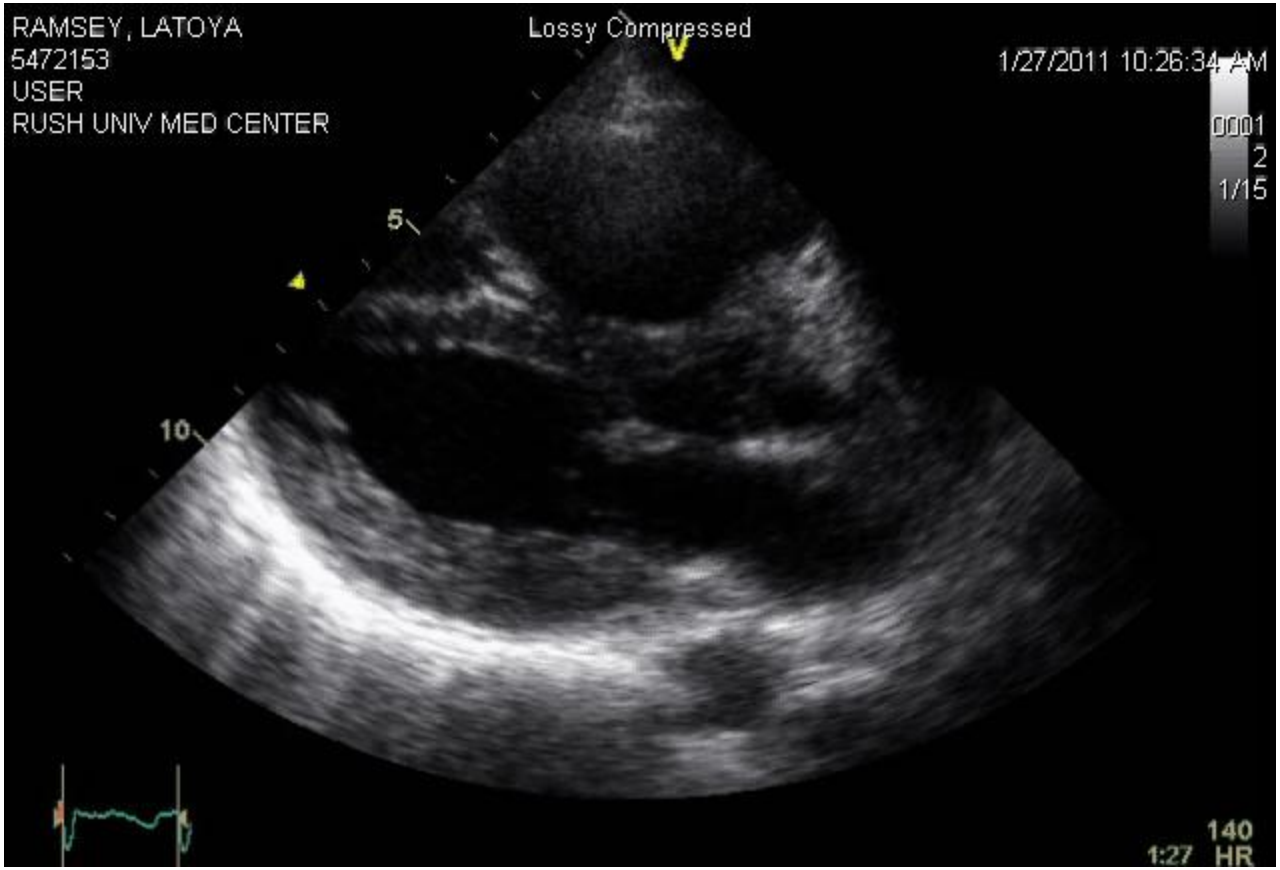
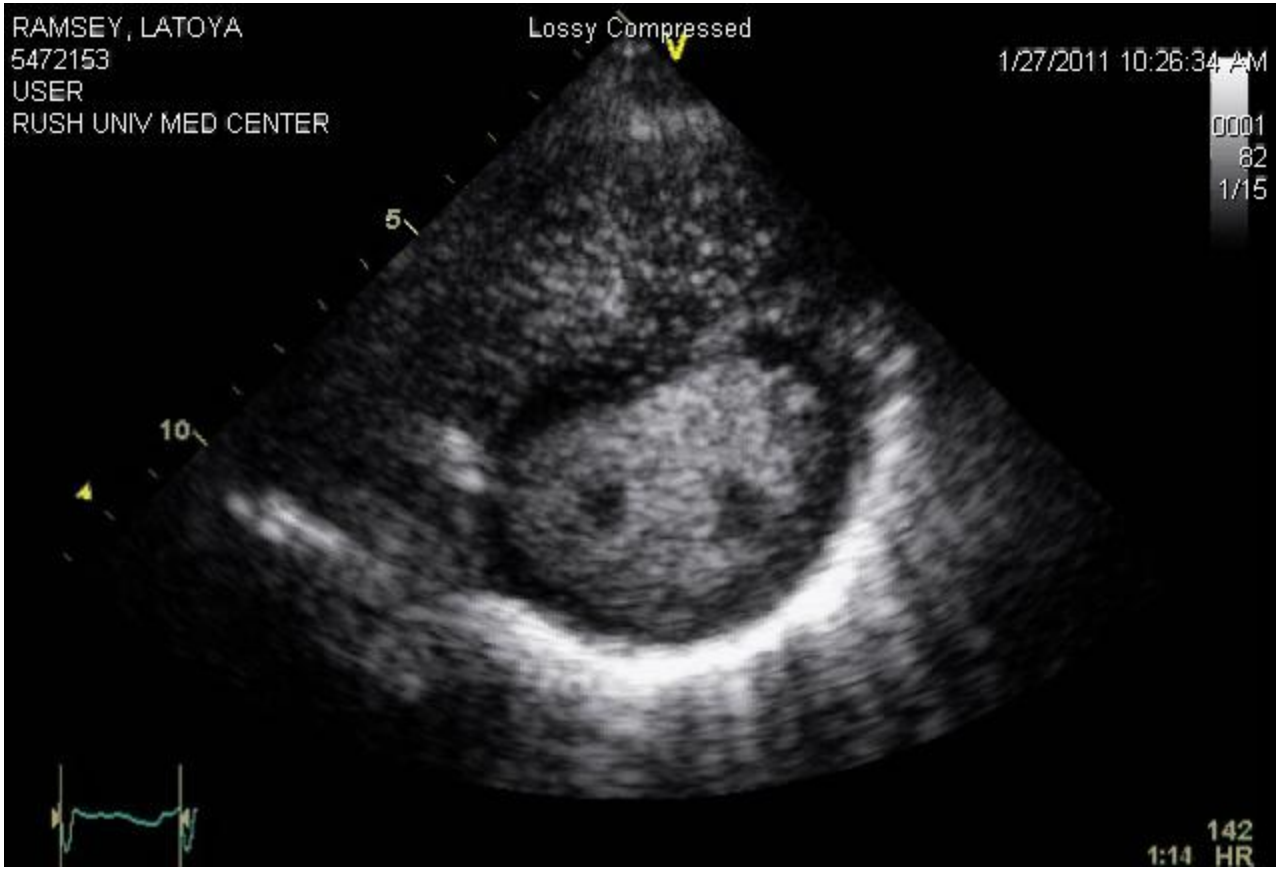
McLaughlin *et al.*
Expert Consensus Document on Pulmonary Hypertension

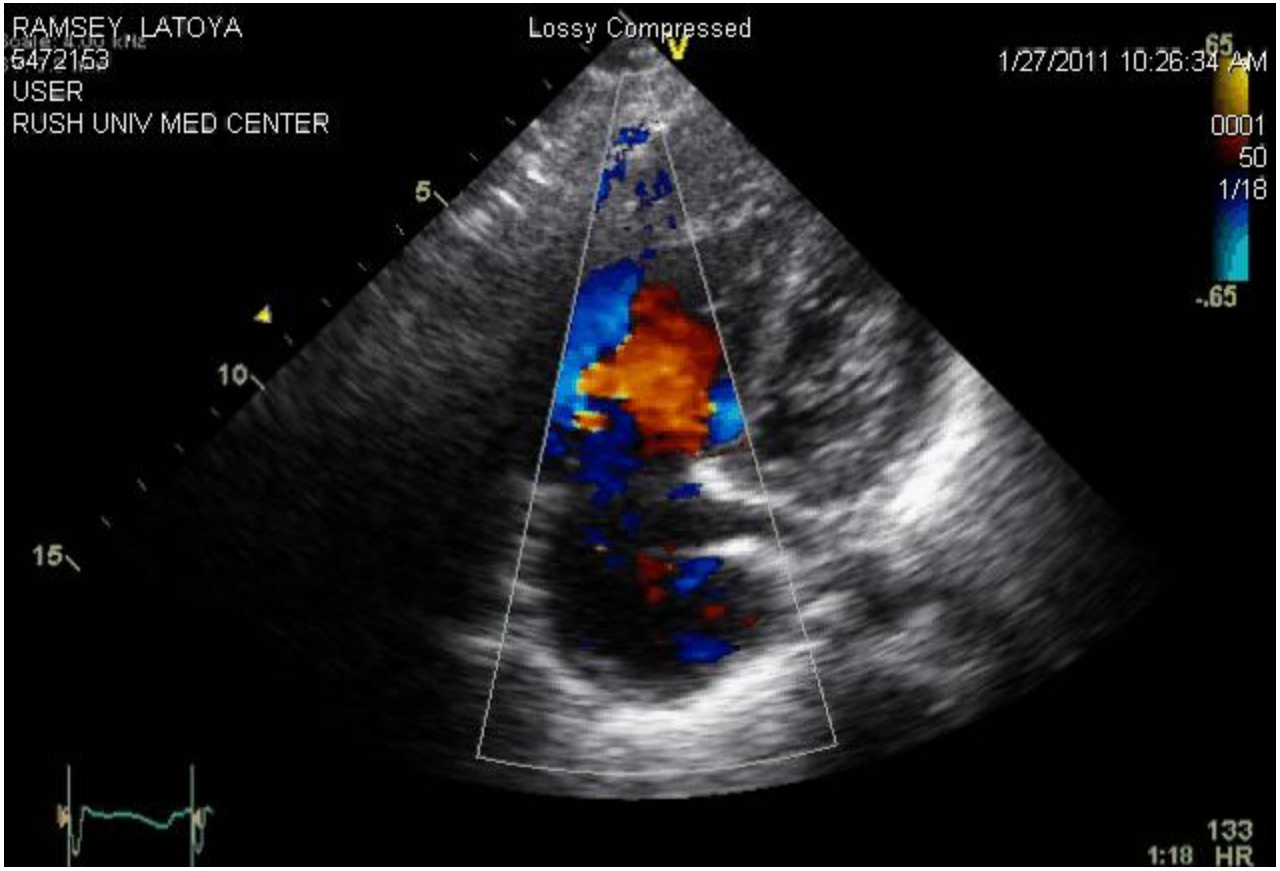
Echocardiography in Pulmonary Hypertension



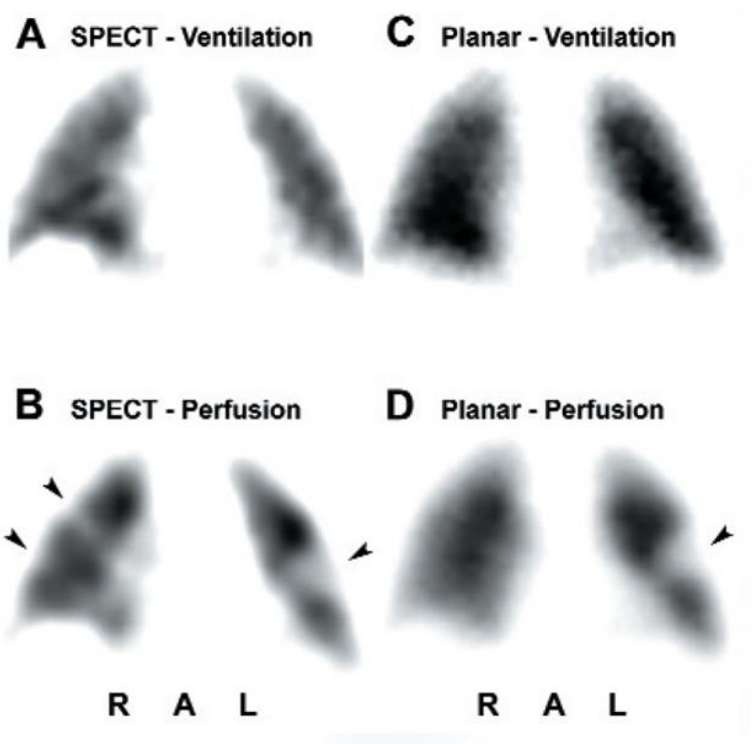
Echocardiography in Pulmonary Hypertension

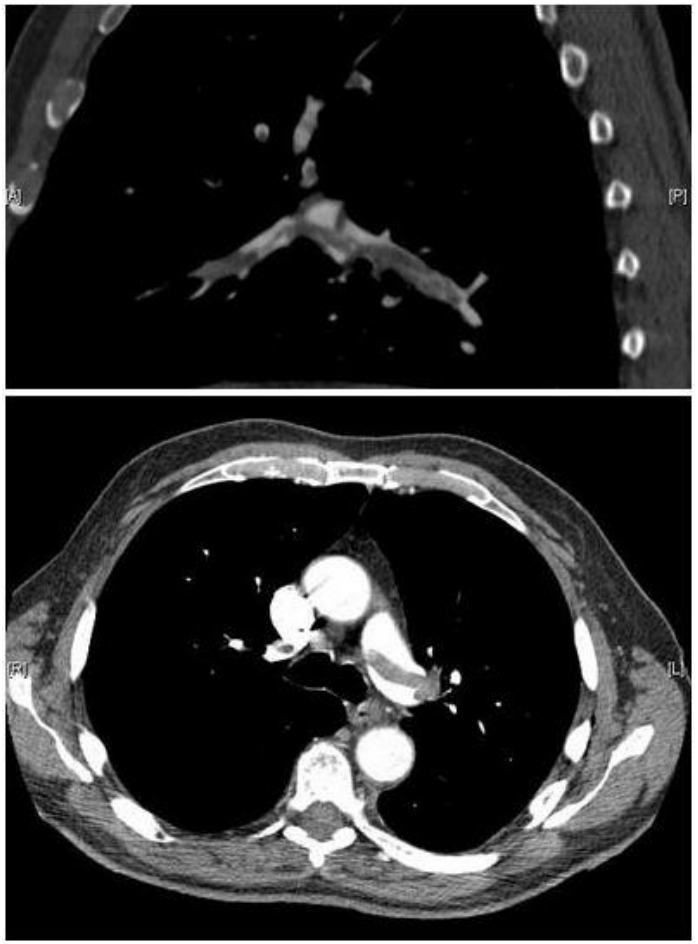


Echocardiography in Pulmonary Hypertension



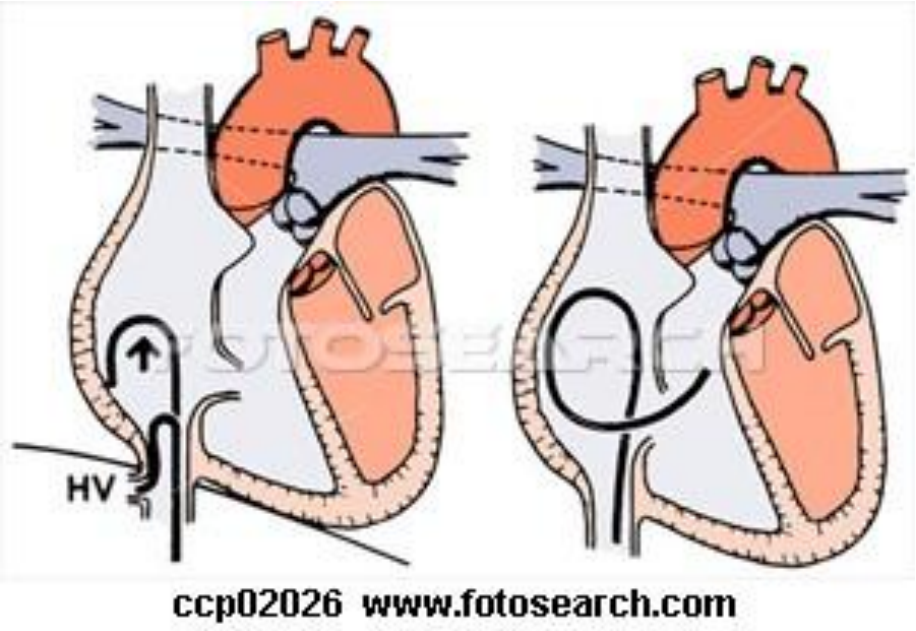
Diagnosis of Chronic and Acute Pulmonary Embolism

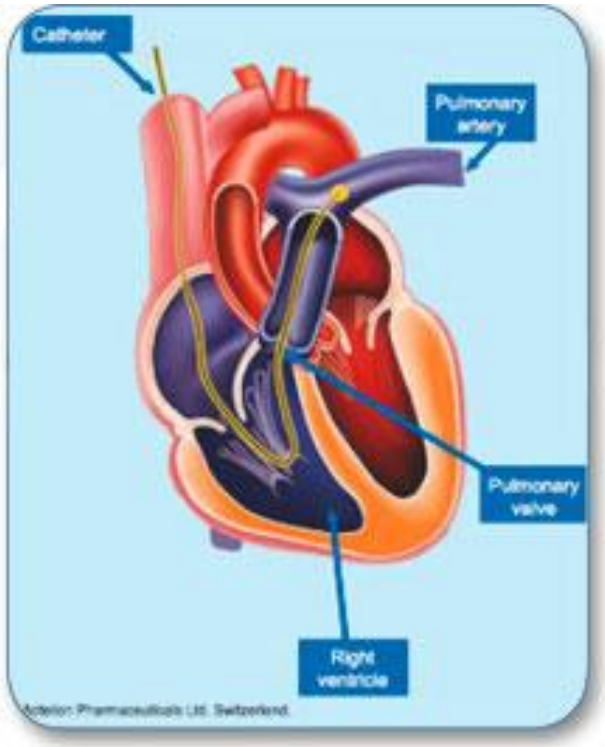




Right Heart Catheterization with acute vasoreactivity testing

The gold-standard





Right Heart Catheterization with acute vasoreactivity testing

The gold-standard

Diagnosis of PAH by Right Heart Catheterization

- Gold standard to confirm diagnosis
  - echo may underestimate pulmonary pressures
  - echo can miss congenital anomalies
  - echo may underestimate LV disease
- Only proven tool to accurately assess hemodynamic response to treatment
  - repeat catheterization indicated before changing therapy

PAH definition:

- mPAP >25 mm Hg at rest or >30 mm Hg during exercise
- Normal PCWP ≤15 mm Hg
- PVR >3 wu

Gaine et al. Lancet. 1998;352:719.

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Right Heart Catheterization with acute vasoreactivity testing

The gold-standard

Right Heart Catheterization

Example:

- Mean RAP: 12 mm Hg
- RV: 90/6 (RVEDP = 14)
- PAP: 89/36 (mean 54) mm Hg
- PAOP: 14 mm Hg
- Mixed venous saturation: 64%
- Cardiac output (Fick): 4.3 L/min
- Cardiac index: 2.2 L/min/m^2
- PVR: 9 Wood units (744)

RAP = right atrial pressure; *RV* = right ventricle; *RVEDP* = right ventricular end-diastolic pressure; *PAP* = pulmonary artery pressure; *PAOP* = pulmonary artery occlusion pressure; *PVR* = pulmonary vascular resistance

Medscape

Invasive Hemodynamic Assessment

Table 6. Essential Components of Invasive Hemodynamic Assessment

Oxygen saturations (SVC, IVC, RV, PA, SA)
Right atrial pressure
Right ventricular pressure
Pulmonary artery pressure, systolic, diastolic, mean
Pulmonary arterial wedge pressure, left atrial pressure, or left ventricular end-diastolic pressure
Cardiac output/index
Pulmonary vascular resistance
Systemic blood pressure
Heart rate
Response to acute vasodilator

IVC indicates inferior vena cava; PA, pulmonary artery; RA, right atrium; RV, right ventricle; SA, systemic artery; and SVC, superior vena cava.

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Acute Vasoreactivity Test

Table 7. Agents for Acute Vasodilator Testing

	Epoprostenol	Adenosine	Nitric Oxide
Route of Administration	Intravenous infusion	Intravenous infusion	Inhaled
Dose Titration	2 ng/kg/min every 10 to 15 min	50 mcg/kg/min every 2 min	None
Dose Range	2 to 10 ng/kg/min	50 to 250 mcg/kg/min	10 to 80 ppm
Side Effects	Headache, nausea, lightheadedness	Dyspnea, chest pain, AV block	Increased left heart filling pressure in susceptible patients

Who is an acute responder?

- decrease in mPAP of at least 10mmHg to an absolute mPAP ≤ 40mmHg without a decrease in cardiac output

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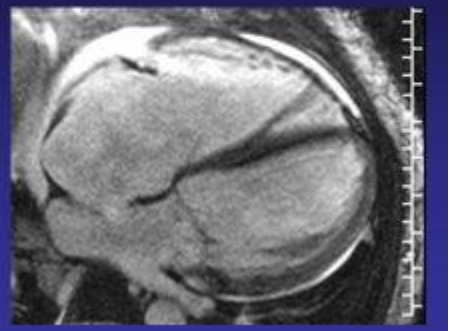
Cardiac MRI

Early Signs of PAH: Cardiac MRI

- Cardiac MRI measures:
  - RV volume and mass, stroke volume, CO
  - myocardial fibrosis
  - pulmonary perfusion



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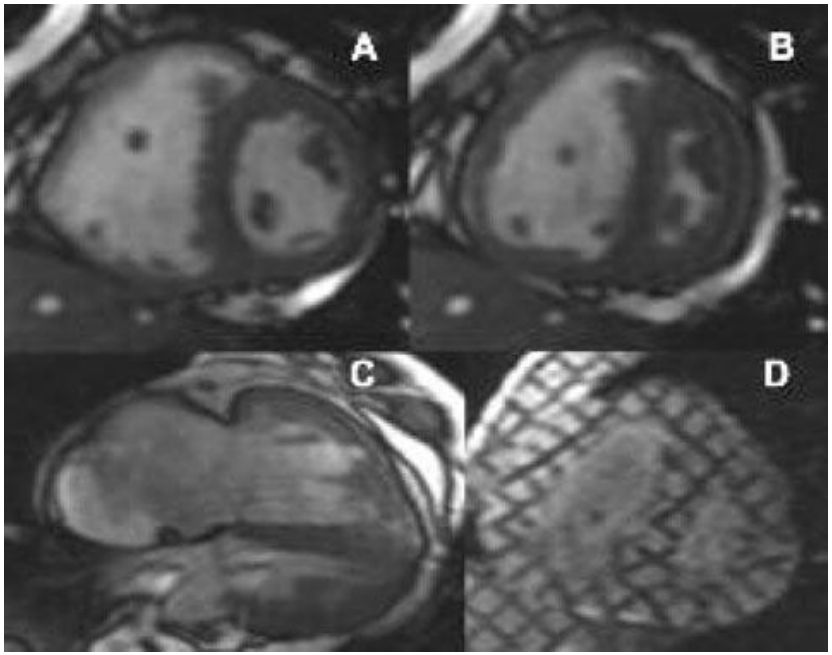
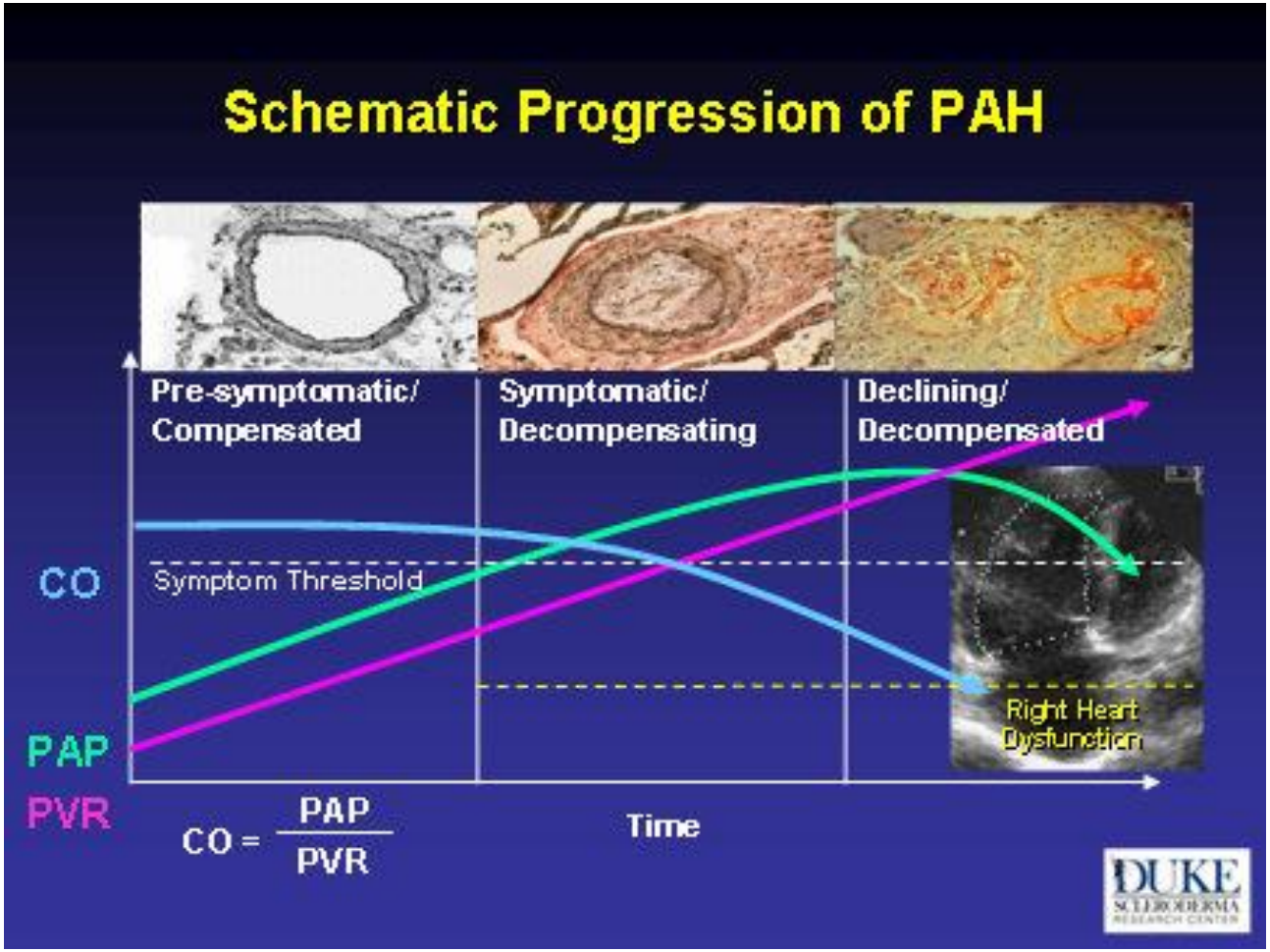


Progression of Pulmonary Hypertension



Prognostic Factors in Pulmonary Hypertension

Table 2. PAH*: Determinants of Prognosis

Determinants of Risk	Lower Risk (Good Prognosis)	Higher Risk (Poor Prognosis)
Clinical evidence of RV failure	No	Yes
Progression of symptoms	Gradual	Rapid
WHO class†	II, III	IV
6MW distance‡	Longer (greater than 400 m)	Shorter (less than 300 m)
CPET	Peak VO_2 greater than 10.4 mL/kg/min	Peak VO_2 less than 10.4 mL/kg/min
Echocardiography	Minimal RV dysfunction	Pericardial effusion, significant RV enlargement/dysfunction, right atrial enlargement
Hemodynamics	RAP less than 10 mm Hg, CI greater than 2.5 L/min/m^2	RAP greater than 20 mm Hg, CI less than 2.0 L/min/m^2
BNP§	Minimally elevated	Significantly elevated

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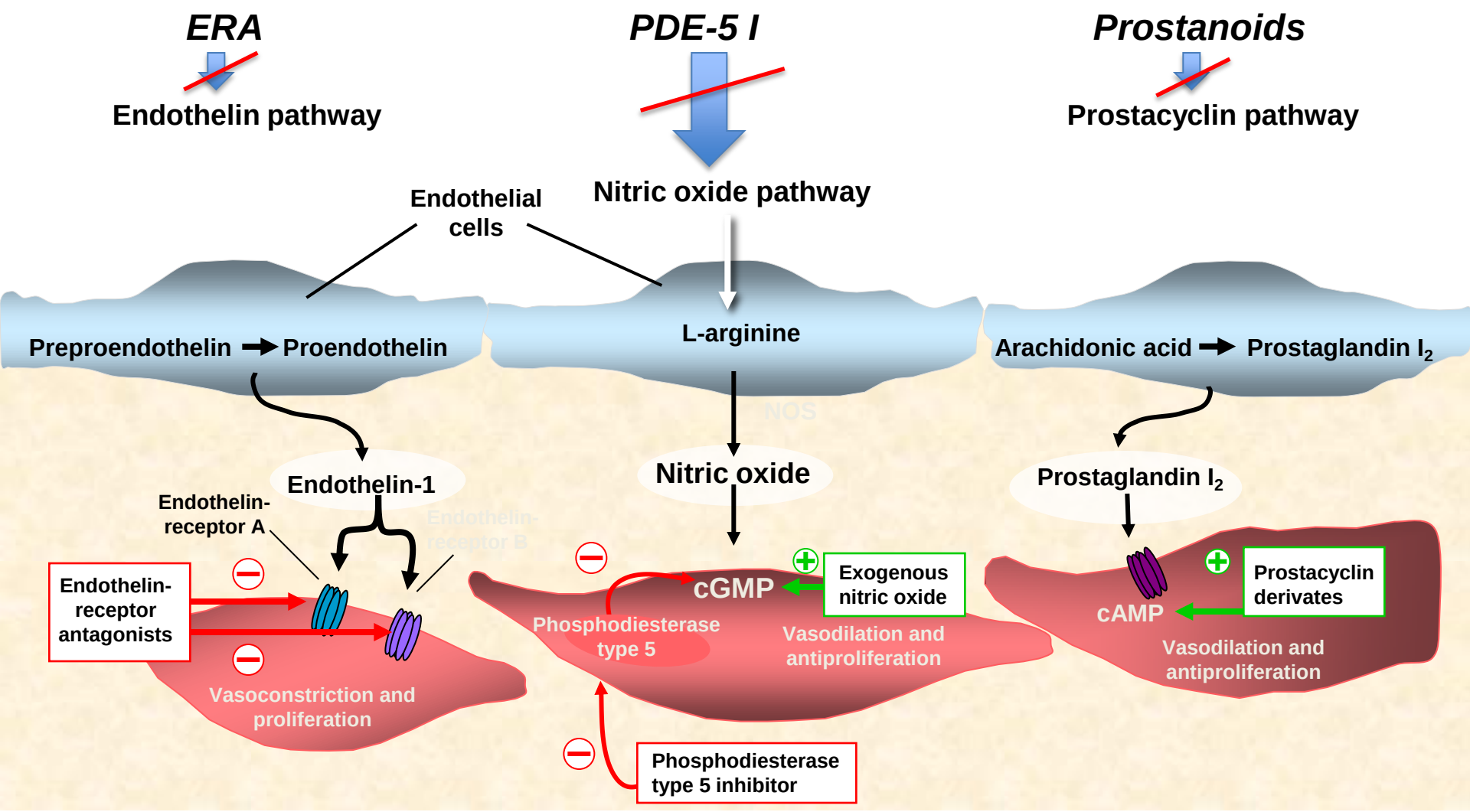
Therapy

Targets for Therapy for Pulmonary Hypertension



Humbert M, et al. *N Engl J Med*. 2004;351:1425-1436.

Pulmonary Hypertension Therapy

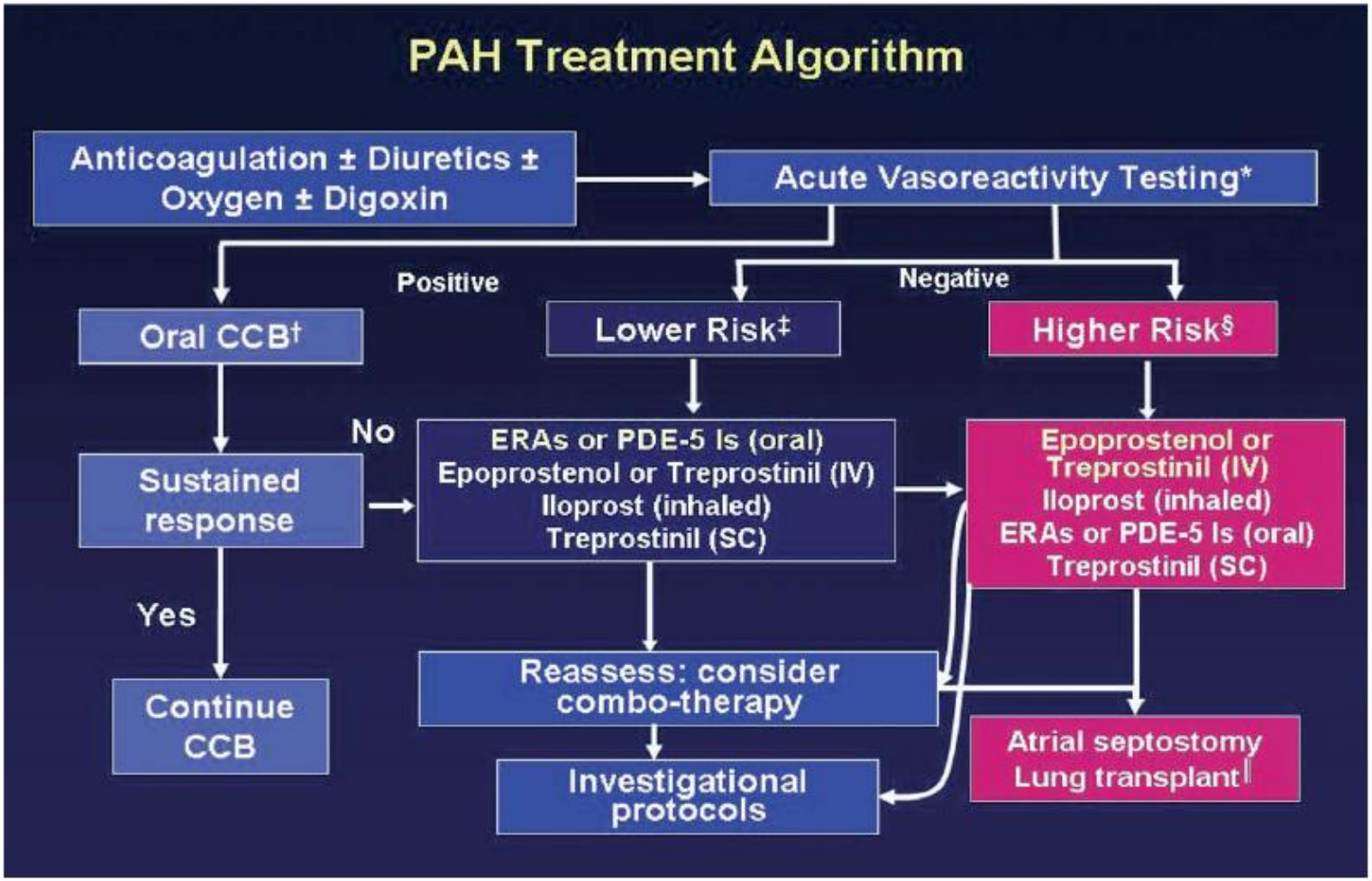


Figure 6. Treatment Algorithm for PAH

Endothelin Receptor Antagonists

Agents

- Bosentan (Tracleer)
  - nonselective ERA
- Ambrisentan
  - relative selective ERA
- Sitaxsentan
  - selective on ET_A ERA

Effects

- Improve 6-min walk distance
- Improve functional class
- Monitor liver enzymes

Phosphodiesterase inhibitors (PDE-5 I)

Agents

- Sildenafil
  - specific PDE-5 I
- Tadalafil
  - long acting PDE-5 I

Effects

- Improve 6-min walk distance (benefit seen at 1year)
- Improve functional class
- Side effects:
  - flushing
  - dyspnea
  - epistaxis

Prostanoids

Agents

- Epoprostenol
  - continuous i.v pump
  - improves survival
- Treprostenil
  - used i.v or s.q
- Iloprost
  - intranasally
-

Effects

- Improve 6-min walk distance
- Improve functional class
- Side effects:
  - flushing
  - Jaw pain
  - naseau/diarrhea
  - infections (gram (-) organisms)
  - Infusion and pump interruption – life threatening

General agents

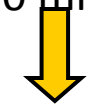
- Calcium channel blockers
  - verapamil, diltiazem
- Anticoagulation with coumadin
  - INR=1.5-2.5
- Diuretics
- Digoxin

Combination Therapy: Treatment Algorithm

Baseline and 2- to 6-Month Evaluation for Treatment Goals

6-Minute Walk Distance >380 meters; Peak VO_2 >10.4 mL/min/kg

Peak systolic BP >120 mm Hg during exercise



Oral Monotherapy

Dual-Class Oral Combination Therapy

Addition of Inhaled Prostanoid

Transition to Intravenous Prostanoid

Refer for Lung Transplantation

Hoeper MM, et al. *Eur Respir J.* 2005;26(5):858-863.

Follow up of Patients with Pulmonary Hypertension

Table 8. Longitudinal Evaluation of the PAH Patient*

Clinical Course	Stable; no increase in symptoms and/or decompensation	Unstable; increase in symptoms and/or decompensation
Physical Examination	No evidence of right heart failure	Signs of right heart failure
Functional Class	I/II	IV†
6MWD	Greater than 400 m	Less than 300 m
Echocardiogram	RV size/function normal	RV enlargement/dysfunction
Hemodynamics	RAP normal	RAP high
	CI normal	CI low
BNP	Near normal/remaining stable or decreasing	Elevated/increasing
Treatment	Oral therapy	Intravenous prostacyclin and/or combination treatment
Frequency of Evaluation	Q 3 to 6 months‡	Q 1 to 3 months
FC Assessment	Every clinic visit	Every clinic visit
6MWT	Every clinic visit	Every clinic visit
Echocardiogram§	Q 12 months or center dependent	Q 6 to 12 months or center dependent
BNP‖	Center dependent	Center dependent
RHC	Clinical deterioration and center dependent	Q 6 to 12 months or clinical deterioration

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Summary

- Pulmonary Hypertension is a rare disease
- Despite extensive advances in diagnosis and therapy it is a disease with high mortality
- Due to its complex nature, patients with pulmonary hypertension should be managed at or in conjunction with a PAH Center of Excellence
- PAH Centers of Excellence offer multidisciplinary programs (cardiology pulmonology, rheumatology, ID, transplant services)

Thank you!