Pulmonary Hypertension For the General Internist

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Objectives

1

Define the clinical manifestations of pulmonary hypertension.

2

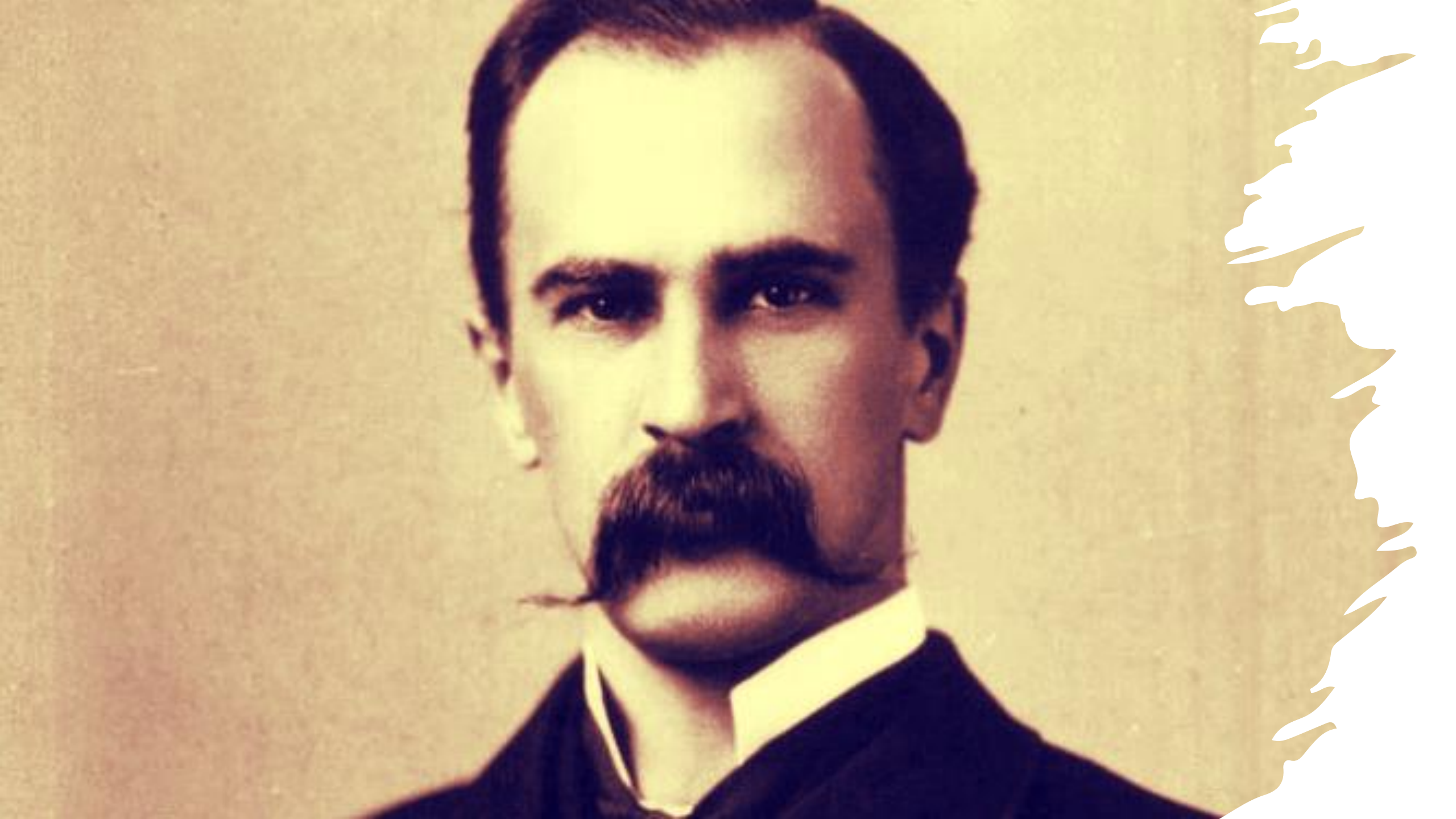
Describe the tests used to make the diagnosis of PAH and the appropriate work up to order in the evaluation of a patient with a new diagnosis of PAH.

3

Discuss the importance of a right heart catheterization in the evaluation of PAH.

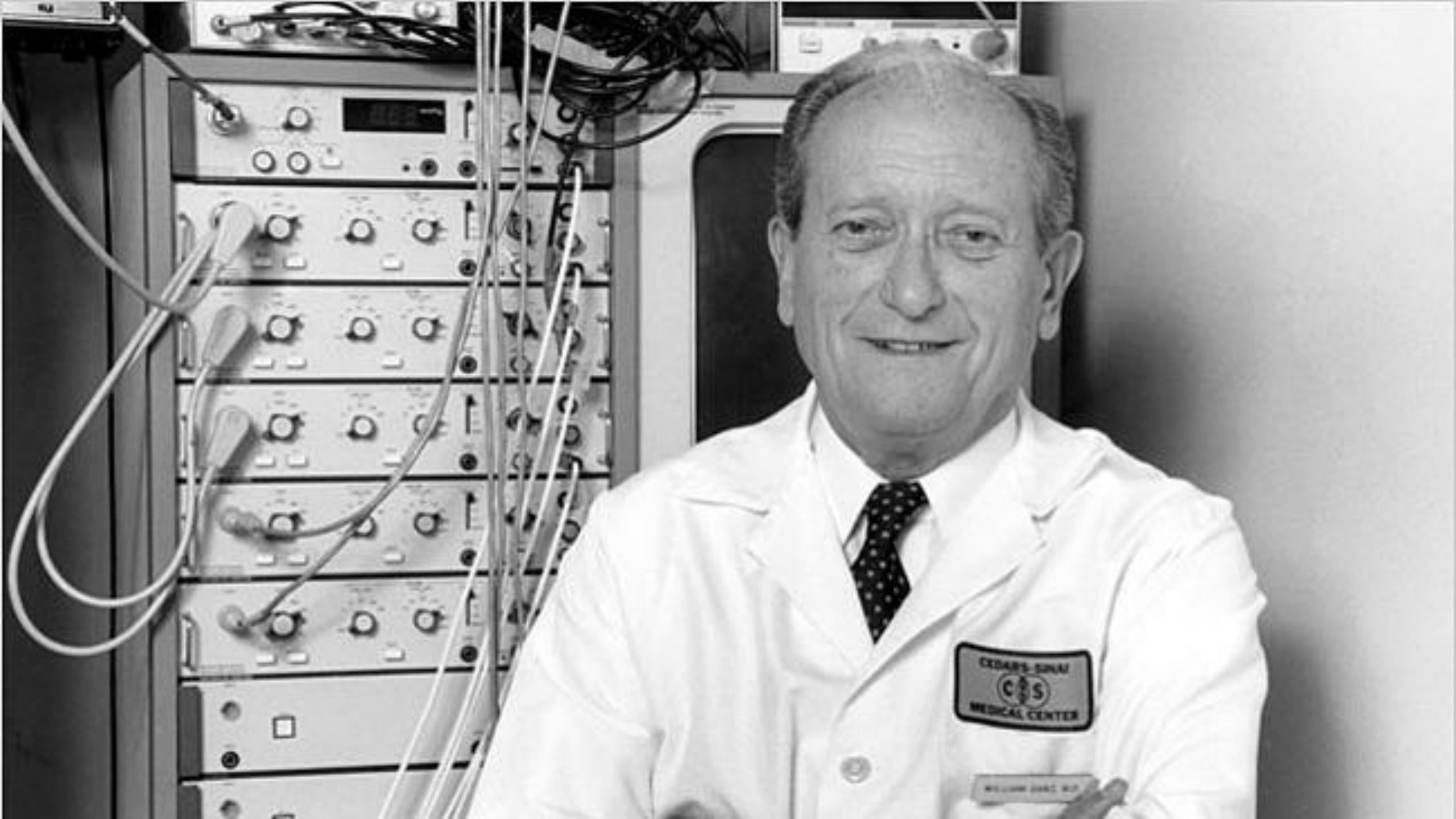
4

Describe the standard treatments for PAH including the endothelin receptor antagonists, the prostacyclins, and the phosphodiesterase type 5 inhibitors and their side effects.



History

- Drs. Morgagni and Laennec describe “right ventricular hypertrophy” in emphysema in 1762
- Osler describes “sclerosis of the pulmonary artery” due to emphysema
  - Credited first description of pulmonary arterial hypertension
- Drs. White and McGinn coin term “Acute Cor Pulmonale” in decompensated pulmonary embolism 1935
- 1951 Dr. David Dresdale describes hemodynamics and coins term “primary pulmonary hypertension” (PPH)
- 1973, first WHO consensus meeting in Geneva on PPH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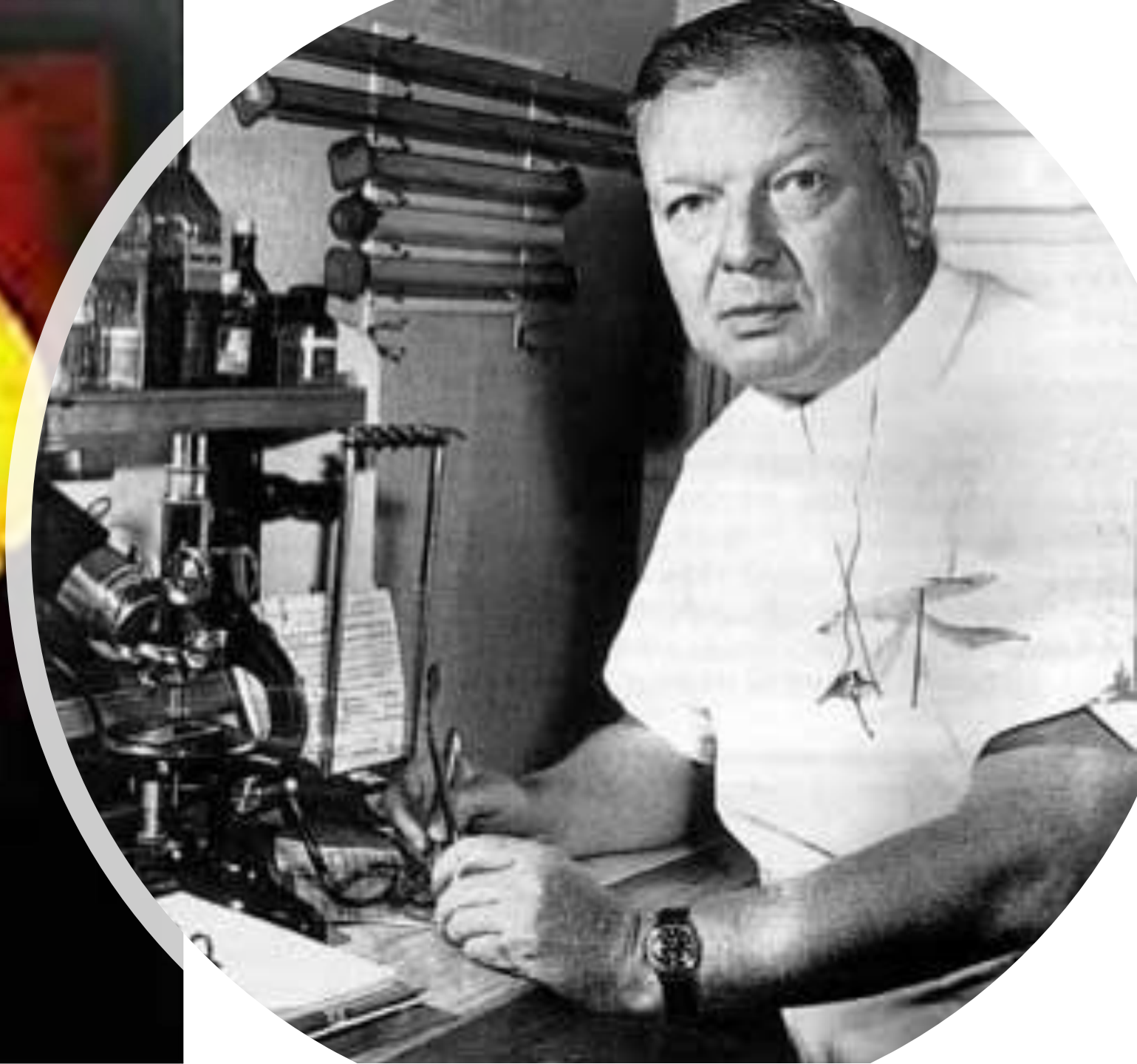
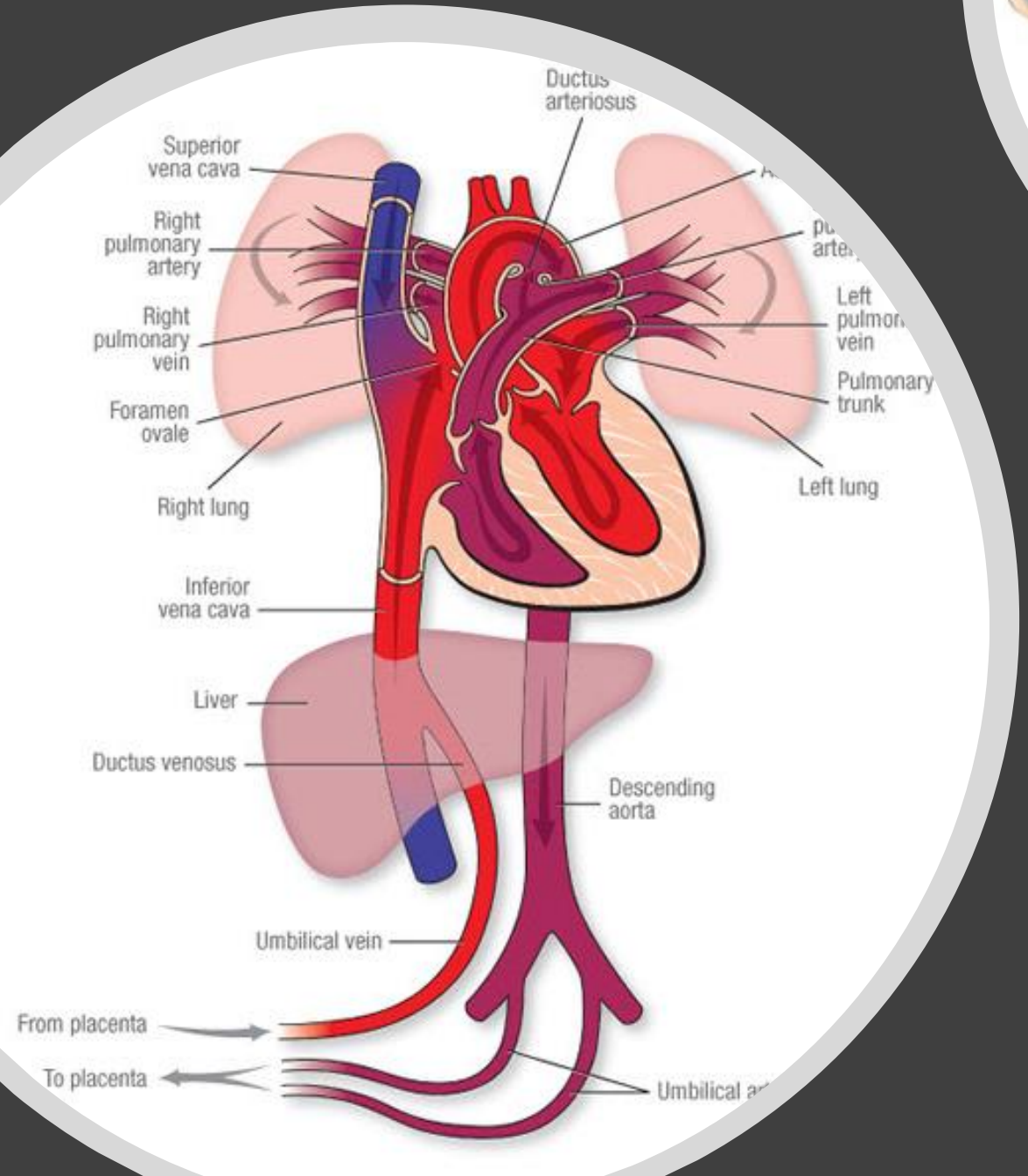
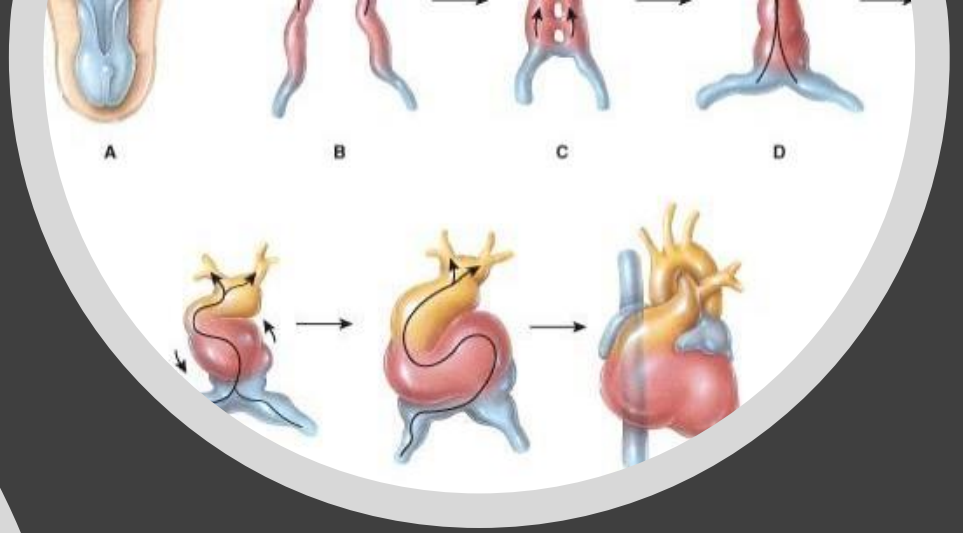
MEDICAL CENTER

Hemodynamics History

- 1929 Dr. Warner Forssman discovers feasibility of cardiac flow directed catheterization
- Dr. Andre Cournand and Dr Dickinson Richards develop the first “pulmonary arterial catheter” design, Cournand Catheter, and win a Nobel Prize in 1956 for their discovery
- 1970 Drs. Swan and Ganz publish use of balloon tipped flow directed catheterization in NEJM
- 1971 Dr RJ Bouchard publishes use of pulmonary arterial balloon occlusion to approximate LVEDP
- 1972 Dr. Swan and HJC Ganz publish use of pulmonary arterial catheter thermodilution to approximate CO







Embryology of the Right Ventricle

Embryology of the Right Ventricle

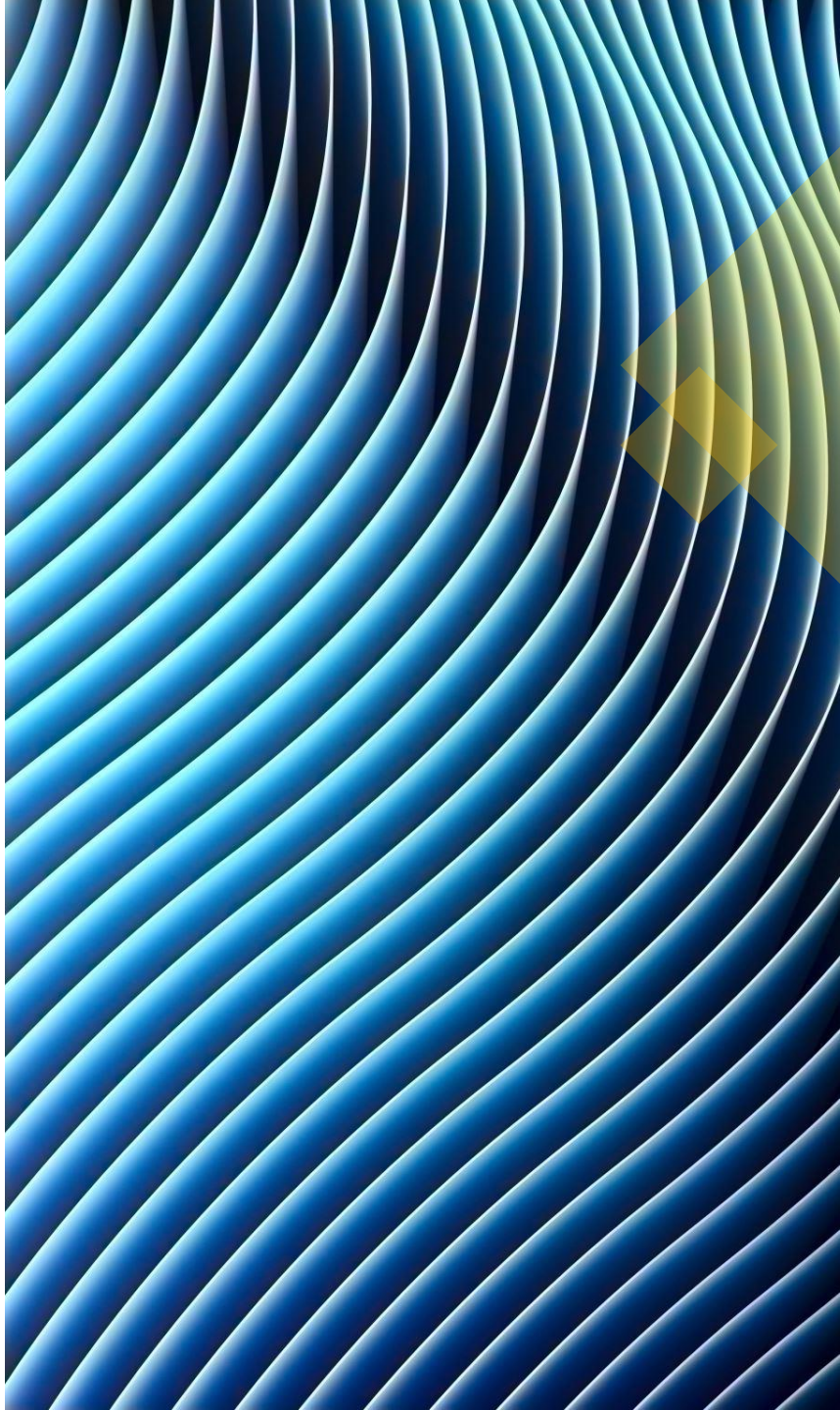
- Bulbus cordis (proximal tube) and the primitive ventricle form the basis for the RV
- The pulmonary artery and aorta develop from a single structure (Truncus Arteriosus)
- Last to develop:
  - Atrioventricular valves
  - Membranous IV Septum
  - Foramen Ovale closure (after birth)
  - Ductus Arteriosus closure (after birth)
- RV > LV systolic pressures prior to birth

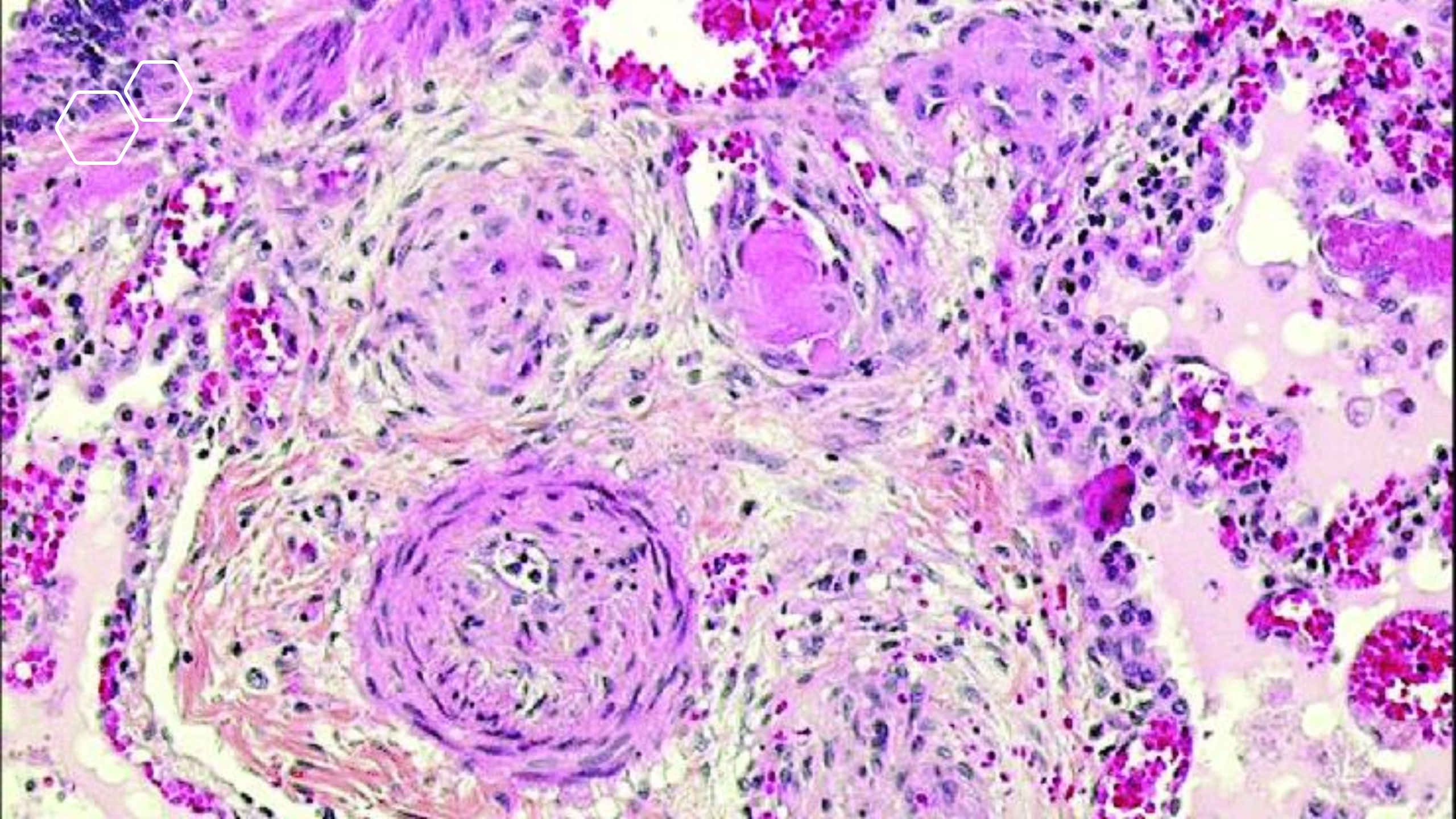
“High Blood Pressure in the Lungs”

- Increased pulmonary vascular resistance
- Intimal fibromuscular hyperplasia
- Dysregulation of mitogenic and antimitogenic endothelial factors
  - Mitogens: Endothelins, Thromboxane, 5-HT
  - Antimitogens: NO (cGMP), PGI (cAMP)
- Genetic dysregulation of pulmonary vascular remodeling
  - BMPR-2 mutation responsible for 80% of HPAH and about 20% of IPAH
  - Others: *ALK1/ACVRL1*, *BMP9*, *ENG*, *SMAD1*, *TBX4*

“We have found what appear to be minute tumors of the lung… These tumors do not line the air spaces in any sense of the word. They are interstitial in position and are characteristically separated by a crown of capillaries from the airspace, thus establishing their interstitial location.”

- Dr. John H Vogel, 1962





Manifestations of pulmonary Hypertension

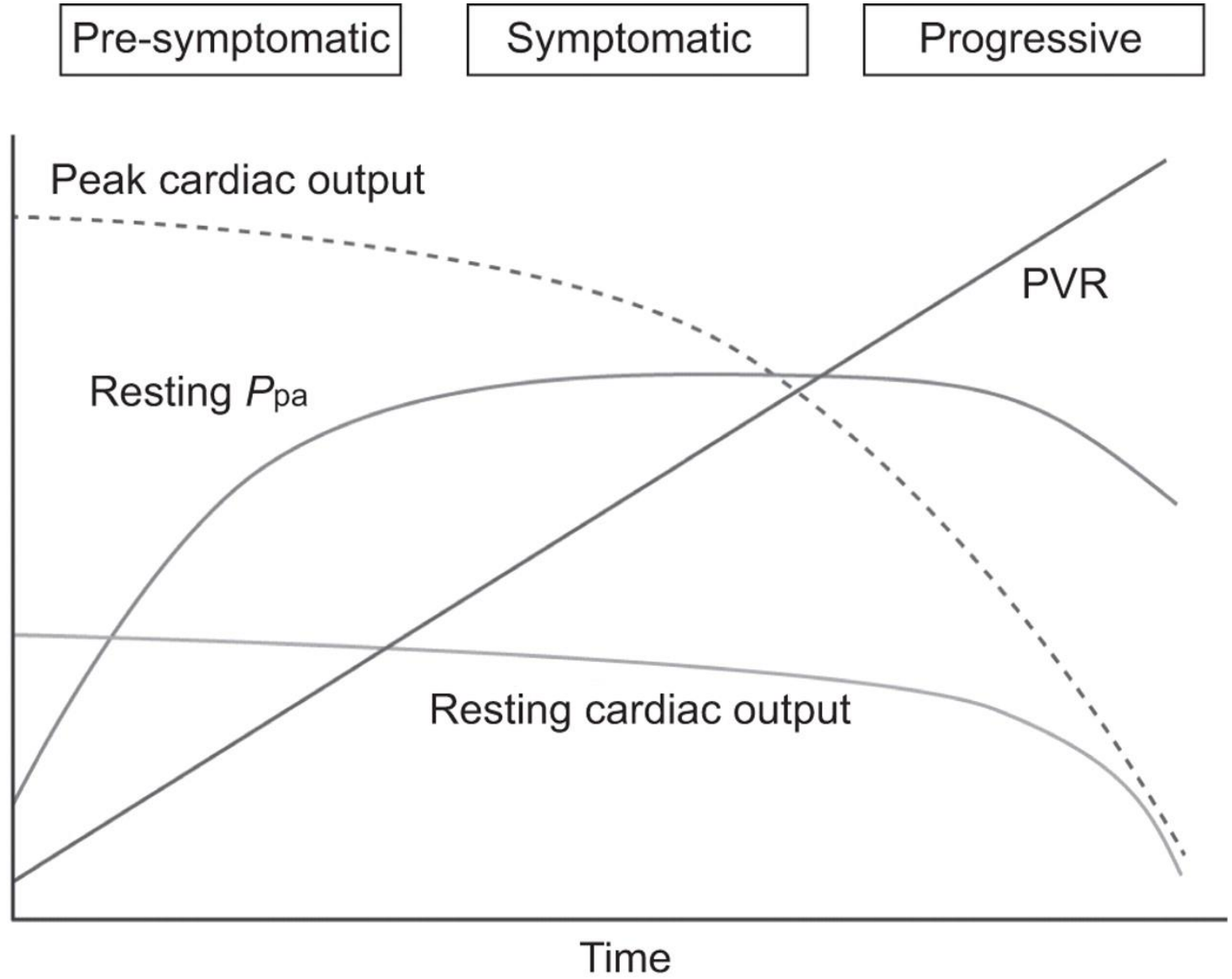
Early disease symptoms are subtle

Common symptoms:

- Shortness of breath
- Edema/weight gain
- General fatigue
- Palpitations
- Presyncope/syncope
- Chest Pain/Tightness
- Orthopnea
- Cough

Delay in Diagnosis

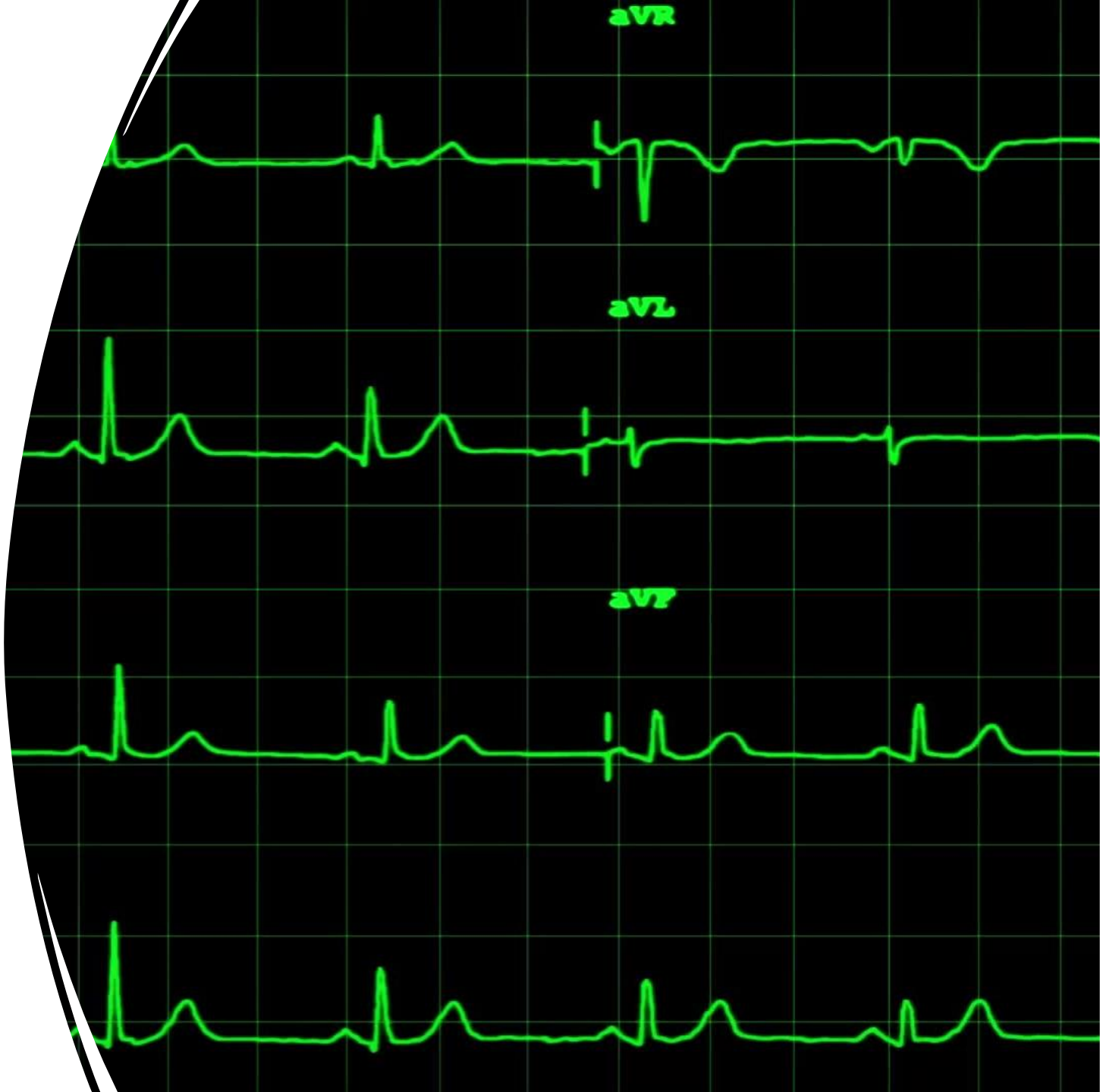
- Diagnosis typically made 2-5 years after symptom onset
- Most diagnosed with WHO-fc III-IV symptoms
- Subspecialist “hot potato”
- Mild echo findings treated with diuretics or monitoring


Pre-symptomatic
Symptomatic
Progressive
Peak cardiac output
PVR
Resting P_{pa}
Resting cardiac output
Time

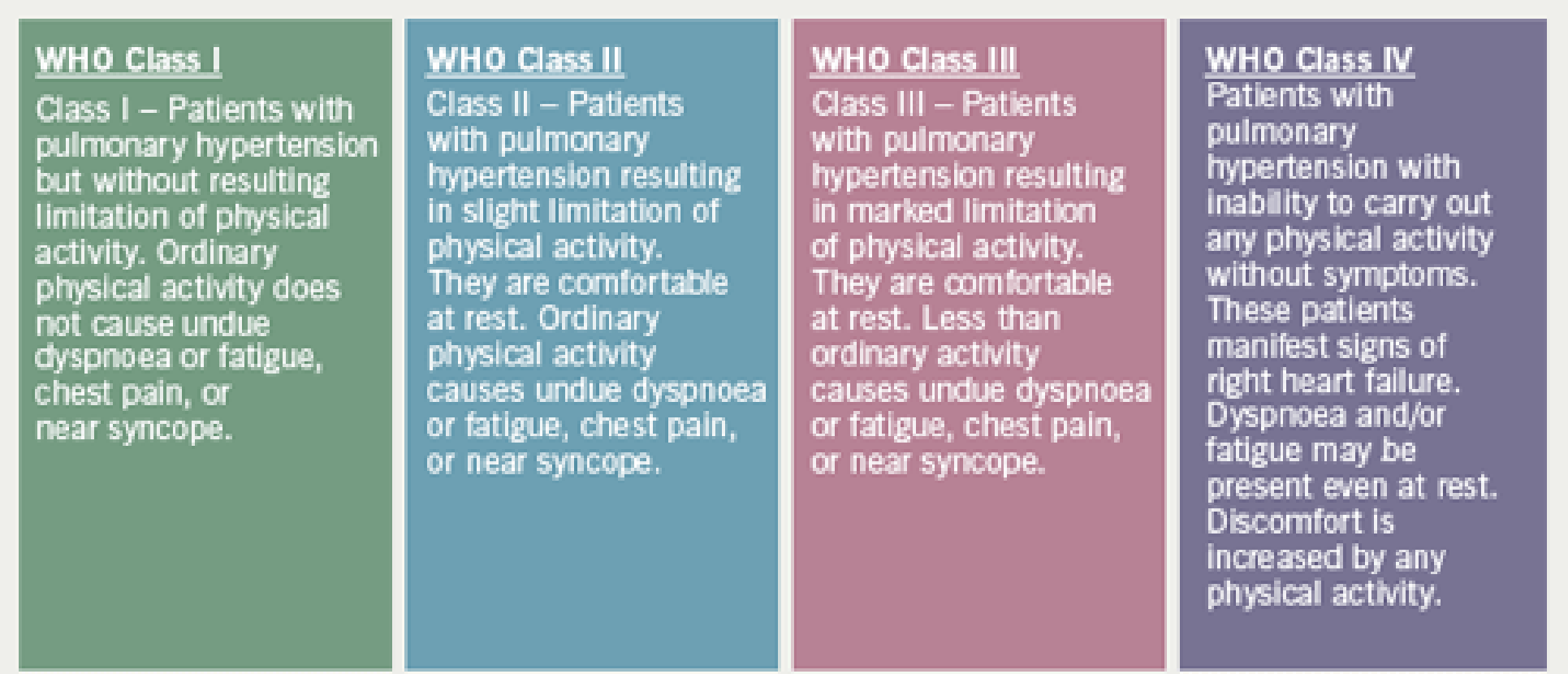

Referrals

Basic Testing

- Echocardiogram
- PA-Lat Chest X-ray
- Labs: CBC, CMP, NT-ProBNP



WHO Functional Classification



Adapted from: Barst RJ, McGoon M, Torbicki A *et al. J Am Coll Cardiol* 2004;43:40S–47S.

WHO Group Classification

- WHO I – PAH
  - Idiopathic
  - Heritable
  - Congenital Heart Disease
  - CTD
  - Sickle Cell
  - Portal Pulmonary Hypertension
  - Schistosomiasis
- WHO IV – CTEPH

- WHO II – LV Disease
  - Systolic HF
  - Diastolic HF
  - Valvular HF
- WHO III – Hypoxic Lung Disease
  - COPD
  - ILD
  - OSA
  - Altitude Sickness
- WHO V – Other
  - Sarcoidosis
  - Chronic Hemolytic Anemia
  - Glycogen Storage Disease
  - Splenectomy
  - Hyperthyroidism

Basic Treatment Algorithm

- WHO group classification I
  - Pulmonary Vasodilators
- WHO group classification IV
  - Surgery (pulmonary endarterectomy)
  - +/- Pulmonary vasodilators
- Everything Else
  - Work-up and treat the underlying cause
  - Reassess for out-of proportion disease once optimized

Question:

62 year morbidly obese male with 50 pack year history of smoking and a past medical history significant for GOLD III COPD and untreated Obstructive Sleep Apnea. He presents to the office from his PCP office after echocardiogram reveals an RVSP of 42. RHC is performed which shows hemodynamic profile of: MPAP 28, PCWP 15, and CO of 8 by ficks equation. Which of the following is the most appropriate step in management.

A. Evaluated for exertional hypoxia

B. Initiate sildenafil for mild pulmonary hypertension

C. Repeat Pulmonary Function Testing

D. Refer for bariatric surgery evaluation

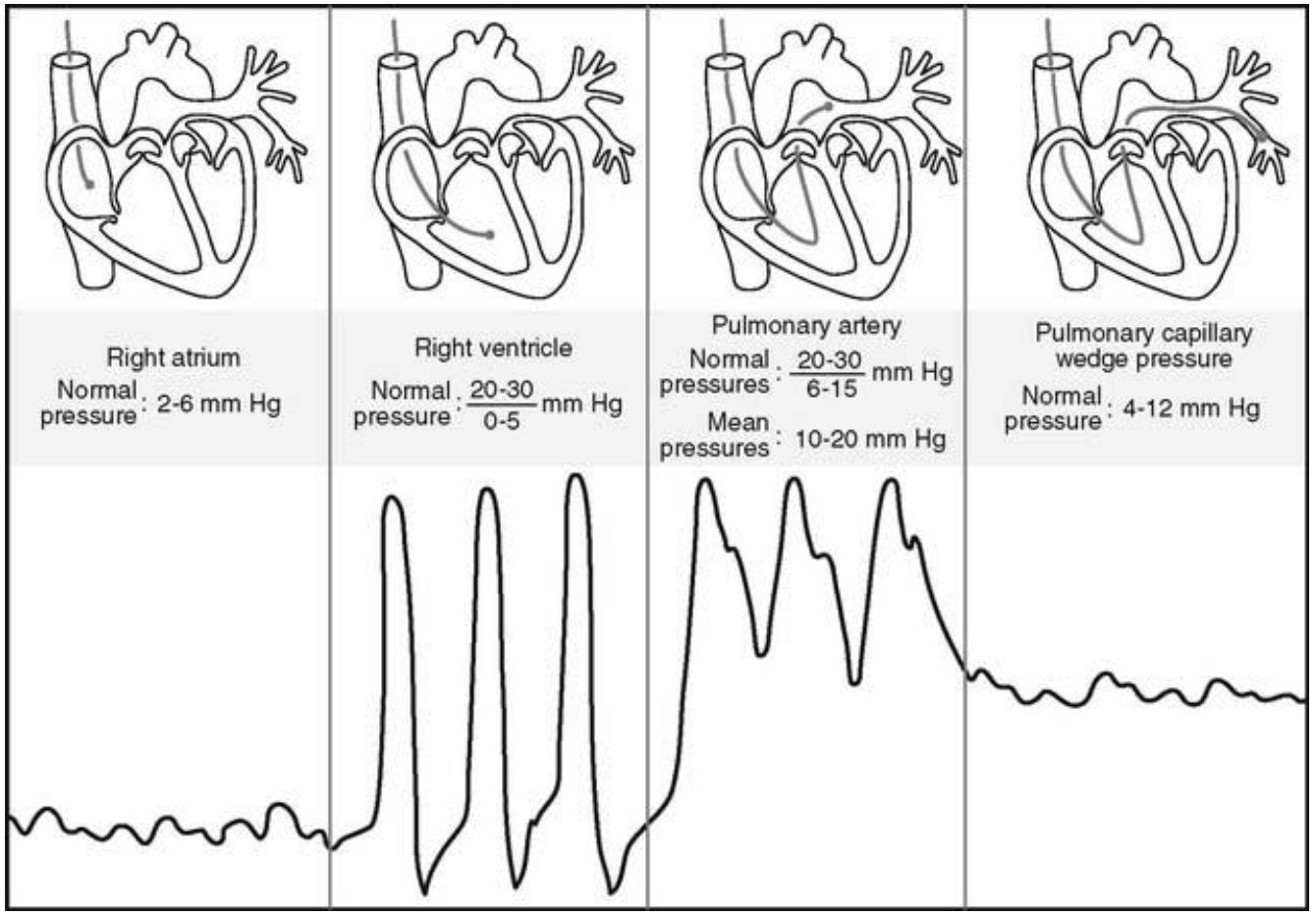
Table 1.

Hemodynamic profiles of pulmonary hypertensio.

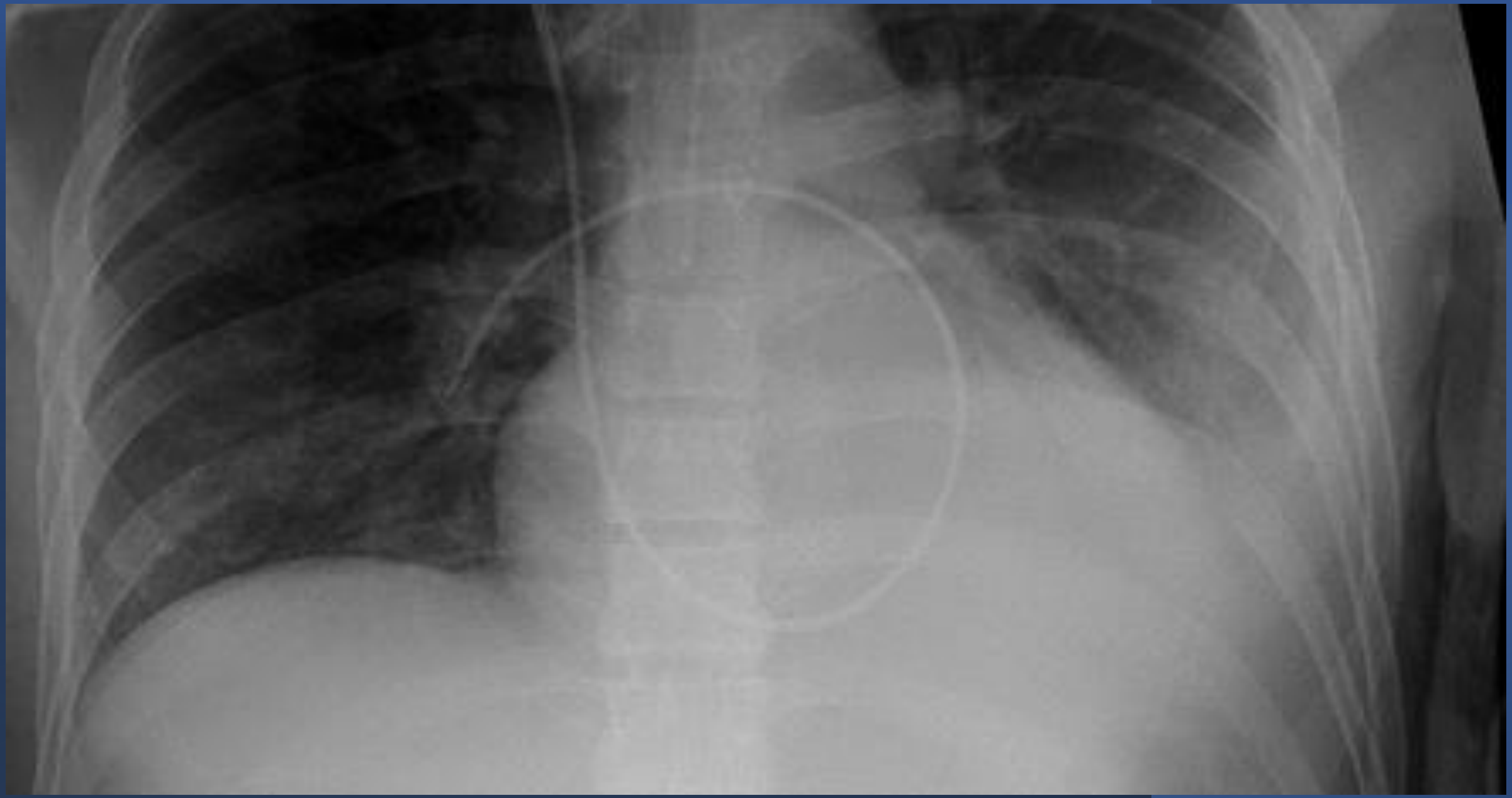
Classification	Mean pulmonary artery pressure	Pulmonary capillary wedge pressure	Pulmonary vascular resistance
Isolated pre-capillary PH	>20 mm Hg	<15 mm Hg	>3 WU
Combined pre- and post-capillary PH		>15 mm Hg	>3 WU
Isolated post-capillary PH		>15 mm Hg	<3 WU

The 6th World Symposium on Pulmonary Hypertension defined three hemodynamic profiles of pulmonary hypertension (PH): isolated pre-capillary PH, combined pre- and post-capillary PH, and isolated post-capillary PH. WU, Wood units.

Hemodynamics



Hemodynamics



Question:

45-year-old male with a 10-year history of methamphetamine use presents with dyspnea to your clinic. States symptoms have been progressive for the past 2 years. He also complains of difficulty with lying flat and weight gain. Echocardiogram shows a decreased LVEF of 45% with mild left atrial enlargement. The right ventricle is moderately enlarged with decreased function (TAPSE 1.4cm). Which of the following hemodynamic profiles on right heart catheterization would be most concerning for primary pulmonary arterial hypertension

A. MPAP 35, PCWP 18, PVR 2.8, CO 6.1
B. MPAP 35, PCWP 12, PVR 2.8, CO 8.2
C. MPAP 35, PCWP 14, PVR 3.1, CO 6.8
D. MPAP 35. PCWP 20, PVR 3.1, CO 4.8
E. None of the above

PAH Treatment Goals

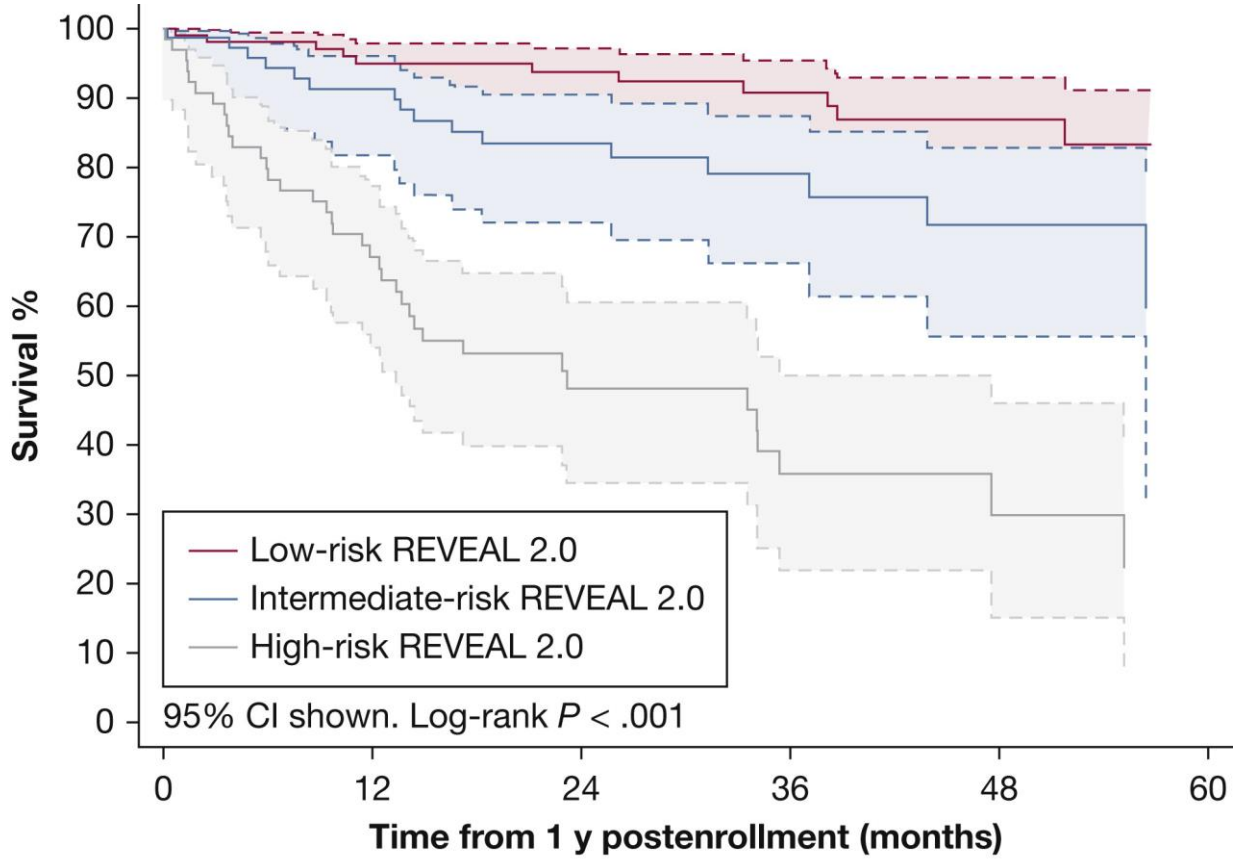
- Lower Risk (Improve Survival)
- Prevent adverse outcomes (Hospitalization, Lung transplant, Death)
- Improve quality of life
- Improve Exercise Capacity
  - 6MWT
  - WHO-FC
- Improved Hemodynamics

2015 ESC Guidelines: Risk Assessment

- Clinical Symptoms
- Functional Assessment
- Biomarkers
- Imaging
- Hemodynamics

Determinant of Prognosis (Estimated 1-Year Mortality)	Low Risk (<5 Percent)	Intermediate Risk (5-10 Percent)	High Risk (>10 Percent)
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional	Repeated
WHO FC	I, II	III	IV
6MWD	>440 m	165-440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 mL/min/kg (>65 percent predicted) VE/VCO_2 slope <36	Peak VO_2 11-15 mL/min/kg (35-65 percent predicted) VE/VCO_2 slope 36-44.9	Peak VO_2 <11 mL/min/kg (>35 percent predicted) VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50-300 ng/L NT-proBNP 300-1,400 ng/L	BNP >300 ng/L NT-proBNP >1,400 ng/L
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18-26 cm^2 No or minimal pericardial effusion	RA area >26 cm^2 Pericardial effusion
Hemodynamics	RAP <8 mmHg CI ≥2.5 L/min/m^2 SvO_2 >65 percent	RAP 8-14 mmHg CI 2.0-2.4 L/min/m^2 SvO_2 60-65 percent	RAP >14 mmHg CI <2.0 L/min/m^2 SvO_2 <60 percent

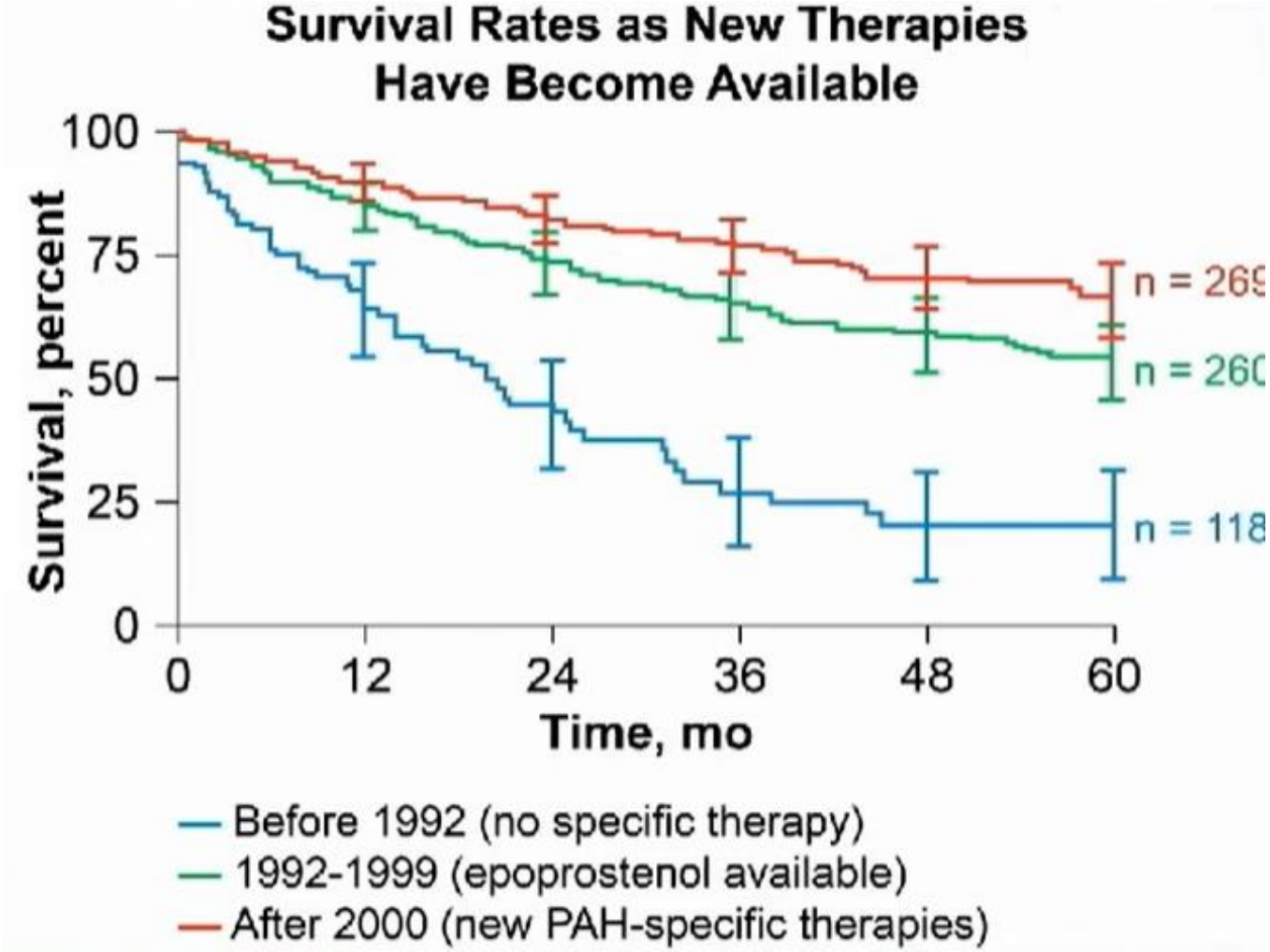
Galie N et al; ESC Scientific Document Group, Eur Heart J 2015;37:67-119



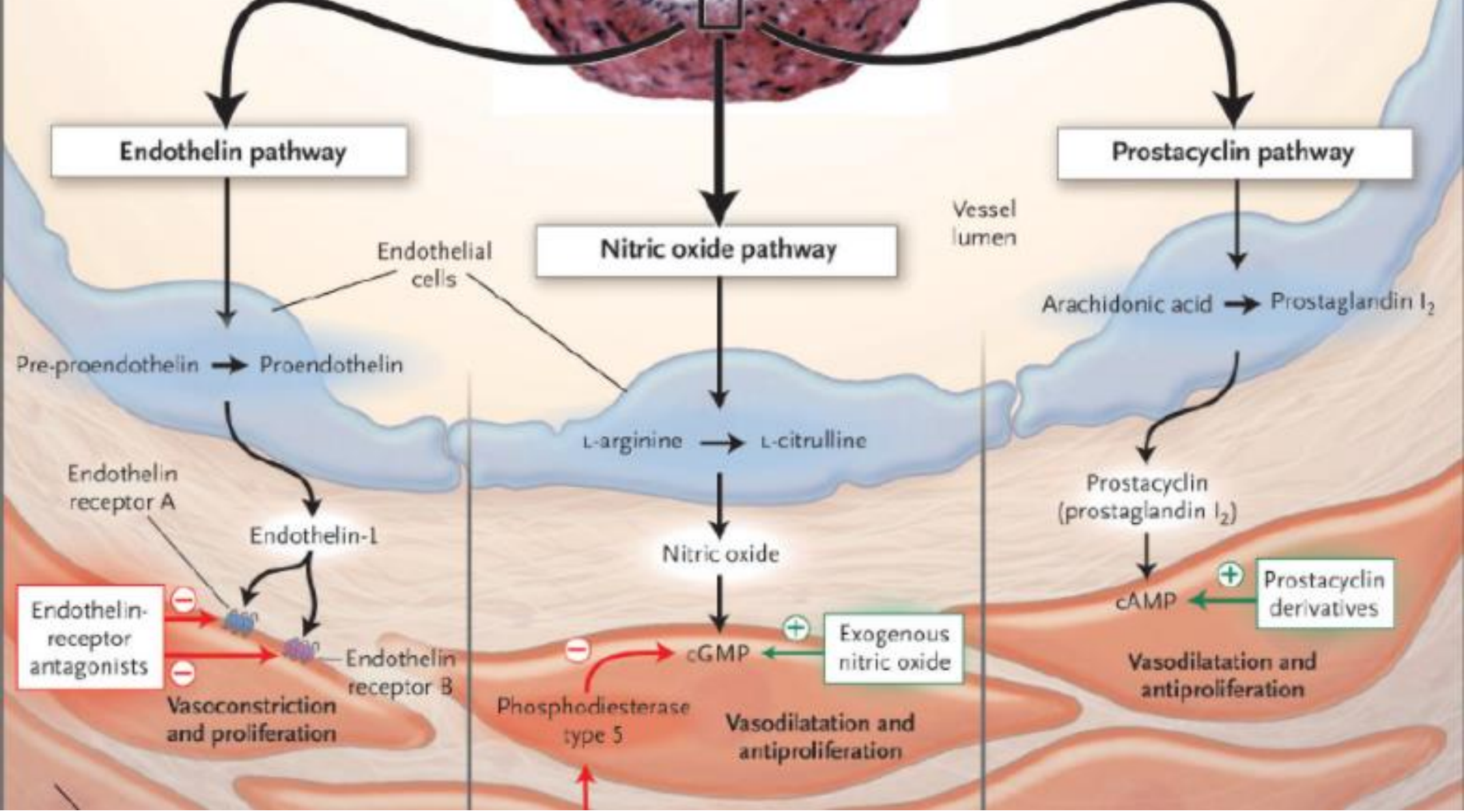
No. at risk						
Low-risk REVEAL 2.0	111	90	74	52	29	16
Intermediate-risk REVEAL 2.0	76	59	42	25	16	5
High-risk REVEAL 2.0	66	40	18	11	5	3

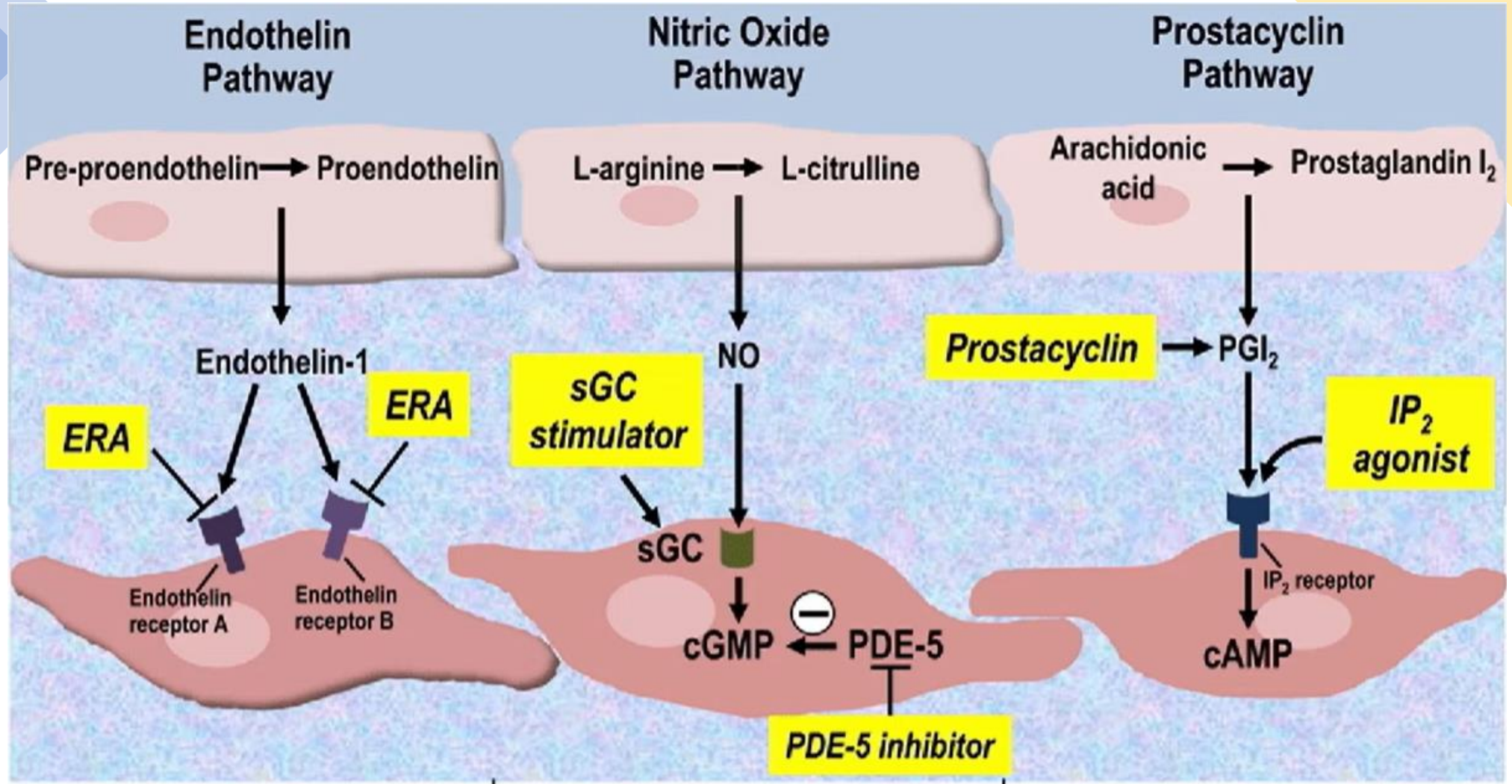
Therapy Options

- 15% annual mortality rate despite newer therapies
- RVF remains primary driver of mortality



Sitbon O et al. Annual Congress 2007 of the ERS

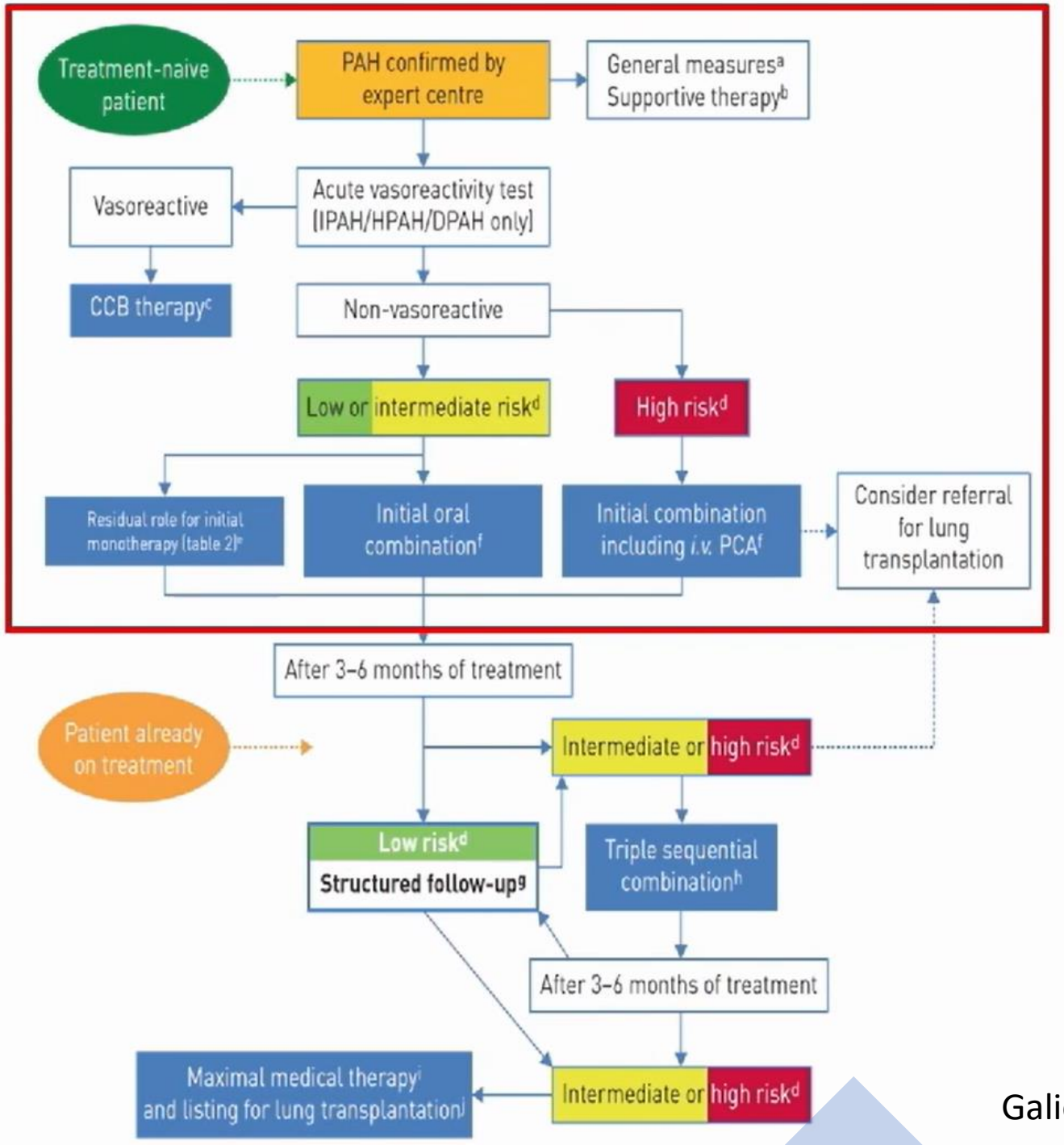

Endothelin pathway
Nitric oxide pathway
Prostacyclin pathway
Vessel lumen
Endothelial cells
Pre-proendothelin → Proendothelin
Endothelin receptor A
Endothelin-1
Endothelin-receptor antagonists
Endothelin receptor B
Vasoconstriction and proliferation
L-arginine → L-citrulline
Nitric oxide
cGMP
Exogenous nitric oxide
Phosphodiesterase type 5
Vasodilatation and antiproliferation
Arachidonic acid → Prostaglandin I2
Prostacyclin (prostaglandin I2)
cAMP
Prostacyclin derivatives
Vasodilatation and antiproliferation



FDA Approved PAH Drugs	ERA	PDE-5i	sGC stimulator	Prostacyclins	IP_2 agonist
	bosentan ambrisentan macitentan	sildenafil tadalafil	riociguat	epoprostenol (IV) iloprost (INH) treprostinil (IV, SQ, INH, oral)	selexipag

Side Effects

Common Side Effects:	ERAs	Riociguat	PDE-5	Prostaglandins
• Hypotension • Hypoxia • Body Aches	• Teratogenic • Edema • Contraindicated in severe hepatic dysfunction	• Teratogenic • Contraindicated in severe renal/hepatic dysfunction • Contraindicated in combination with nitrates/PDE-5	• Caution in ischemic vascular disease (CAD, ischemic optic neuropathy, cva, etc) • Contraindicated in sickle cell disease • Contraindicated in combination with nitrates and protease inhibitors (CYP3A4i)	• Contraindicated in severe hepatic impairment (oral Treprostinil) • Increased bleeding risk



Galie et al 6th WSPH ERJ 2018

Therapy Overview

- Therapy should be performed at high volume PAH centers
- Combination therapy > Sequential monotherapy
- Avoid within class combinations (2 ERAs, 2 PDE-5s, ect) due to lack of additional efficacy
- Side effect profiles are similar and additive
  - Example: Riociguat + PDE-5i contraindicated due to hypotension ADE
- Pulmonary Hypertension is incurable and progressive despite therapy
- All high risk patients should be referred to a lung transplant center

Question:

34-year female with history of mixed connective tissue disease. Presents to your office as a referral from the community cardiologist. Patient symptoms include shortness of breath with all activity including ADLs. He is asymptomatic at rest. He uses 2LPM 24/7 and does not check his oximetry readings regularly. Echo shows LVEF of 60%, normal diastolic function, severe TR with estimated RVSP of 65+RAP. IVC is dilated. RHC from the cardiology office reveals a MPAP of 36, PCWP 18, and CO of 3.9 by triplicate thermodilution. Of the following what is the most appropriate next step for this patient.

- Hold therapy. Further work-up for etiology of his pulmonary hypertension
- Initiate two drug therapy with sildenafil and Abrisentan
- Initiate one drug therapy with sildenafil alone
- Diuresis and repeat catheterization once euvolemic

Take Homes

- The Right Ventricle is way cooler than the left ventricle
- Pulmonary hypertension symptoms are non-specific and insidious
- Early referral saves lives
- Risk determines outcomes and therefore therapy
- Therapy should be performed at a high-volume center with expertise in treating pulmonary hypertension patients

Objectives (again)

1

Define the clinical manifestations of pulmonary hypertension.

2

Describe the tests used to make the diagnosis of PAH and the appropriate work up to order in the evaluation of a patient with a new diagnosis of PAH.

3

Discuss the importance of a right heart catheterization in the evaluation of PAH.

4

Describe the standard treatments for PAH including the endothelin receptor antagonists, the prostacyclins, and the phosphodiesterase type 5 inhibitors and their side effects.


Any
Questions

References

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