UNIVERSITÀ DEGLI STUDI DI BERGAMO | Dipartimento di Ingegneria Gestionale, dell'Informazione e della Produzione

ISTITUTO AUXOLOGICO ITALIANO
Istituto di ricovero e cura a carattere scientifico

Pulmonary hypertension

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10/11/2022

Agenda

- Physiology of the pulmonary circulation and of the right ventricle (RV) → understanding RV failure
- Measures and estimates of pulmonary hemodynamics in clinical practice
- Pulmonary Hypertension (PH): hemodynamic and clinical definition
- Importance of clinical history (risk factors), signs and symptoms
- Overview of instrumental findings in PH
- Diagnostic algorithms
- Frequent forms of PH, associated to cardiac and respiratory diseases:
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    - PH associated with left heart diseases
- «True» Pulmonary Vascular Diseases (PVDs):
    - Pulmonary Arterial Hypertension (PAH)
    - Chronic Thromboembolic Pulmonary Disease (CTED and CTEPH) vs acute Pulmonary Embolism (PE)

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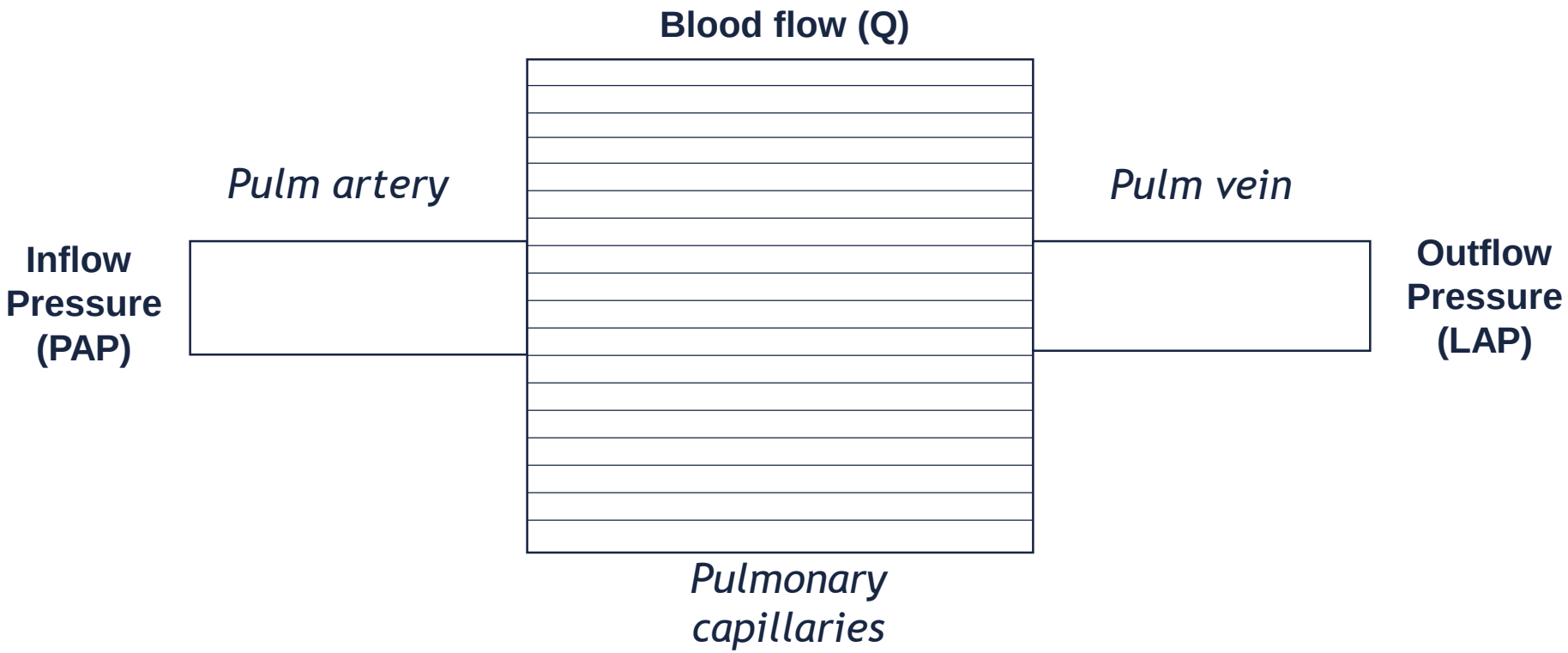
Physiology of the pulmonary circulation and of the right ventricle (RV)

The pulmonary circulation is a low-pressure, high flow system

The right ventricle is a low-pressure flow generator

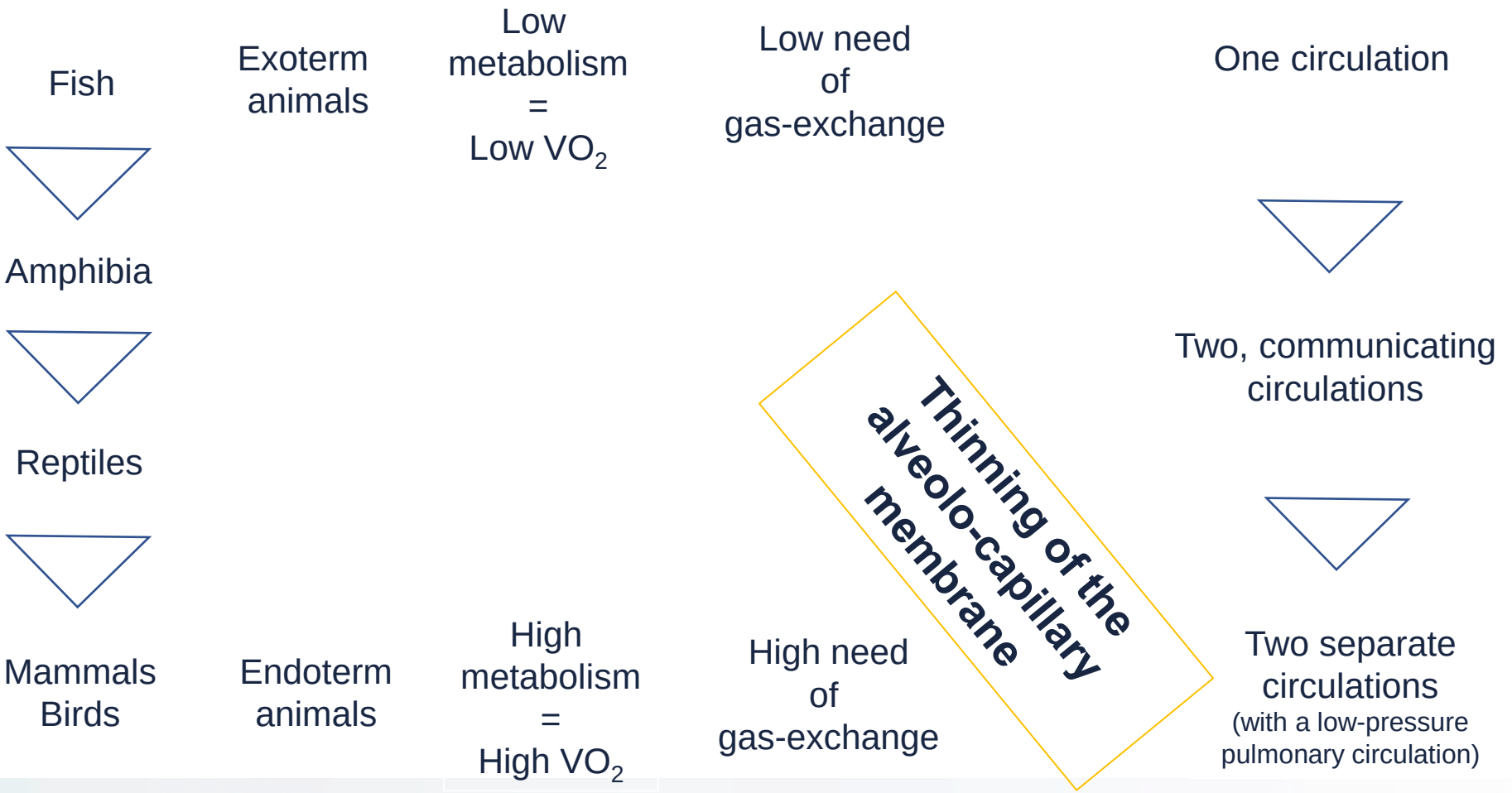
The pulmonary circulation: a hydraulic perspective



$$PVR = (mPAP - LAP) / Q$$

$$mPAP = Q*PVR + LAP$$

Evolution of the pulmonary circulation



West JB. Am J Physiol Regul Integr Comp Physiol 2013

Physiology of the pulmonary circulation

Hemodynamic variables	Normal values
Q, L/min	4.5 - 8.5
HR, bpm	40 - 100
Systolic PAP, mmHg	13 - 26
Diastolic PAP, mmHg	6 - 16
Mean PAP, mmHg	8 - 20
PAWP or LAP, mmHg	5 - 12
P_{cap}, mmHg	8 - 12
RAP, mmHg	1 - 8
PVR, dyne*s*cm^{-5}	12 - 100
PVR, WU	< 1.25

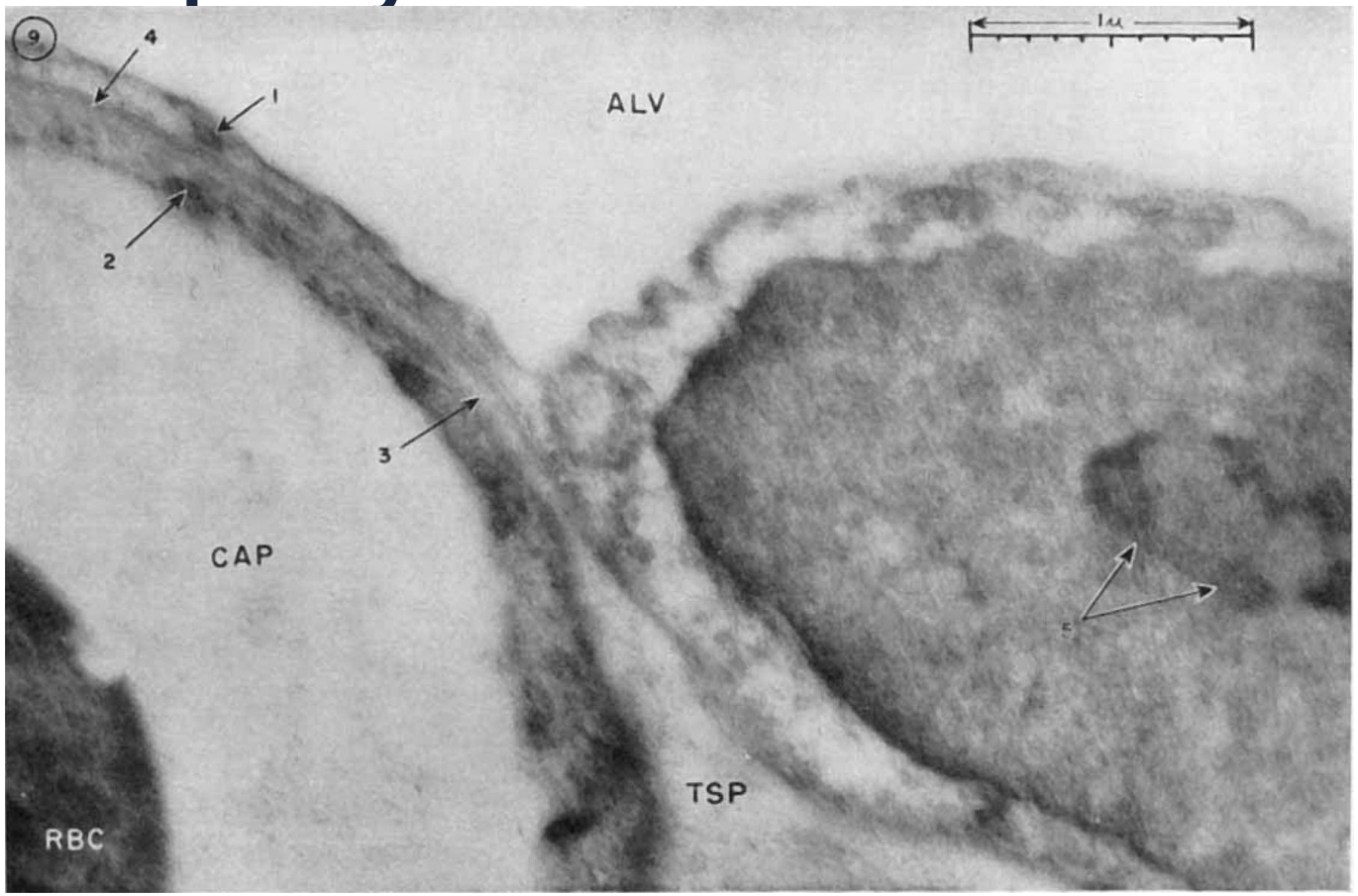
Systemic circulation
x 5-6 times

Systolic SAP, mmHg	90 – 140
Diastolic SAP, mmHg	50 – 90
Mean SAP, mmHg	60 – 105

Q=cardiac output; HR=heart rate; PAP=pulmonary artery pressure; PAWP=pulmonary artery wedge pressure; LAP=left atrial pressure; Pcap=pulmonary capillary pressure; RAP=right atrial pressure; PVR=pulmonary vascular resistance; SAP=systemic arterial pressure

Naeije R et al. Eur Respir J 2013;41:217-23

Alveolo-capillary membrane

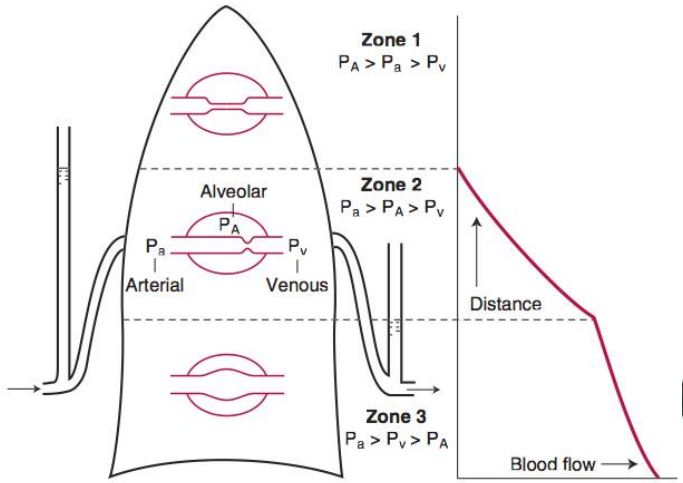


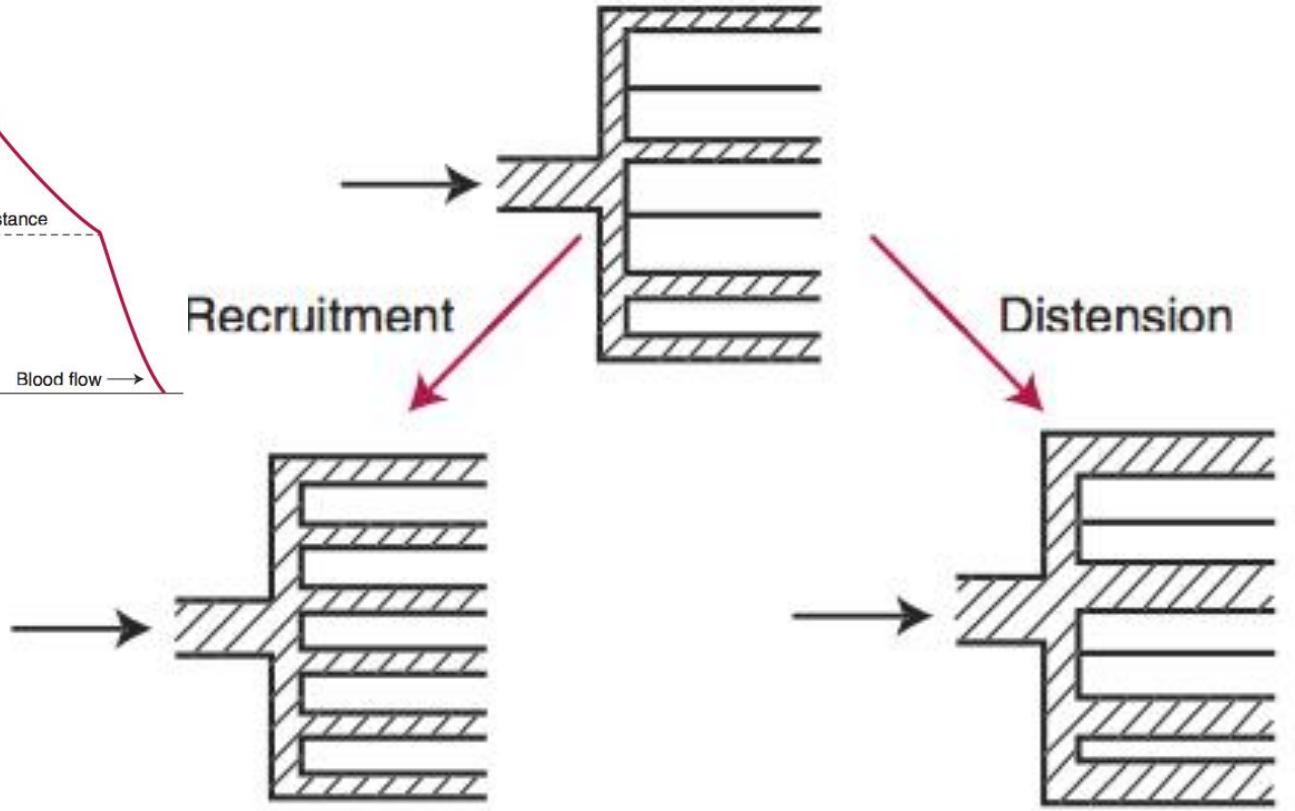
Fick's law of diffusion state that the extent of gas moving through a tissue membrane is proportional to the surface of the membrane and inversely proportional to its thickness.

Alveolo-capillary blood-gas barrier is extraordinarily thin (≈0,3 μm) and covers a surface of 50-100 m^2.

West JB. Book of Respiratory Physiology, 2006
Low FN. Anat Rec 117: 241–263, 195

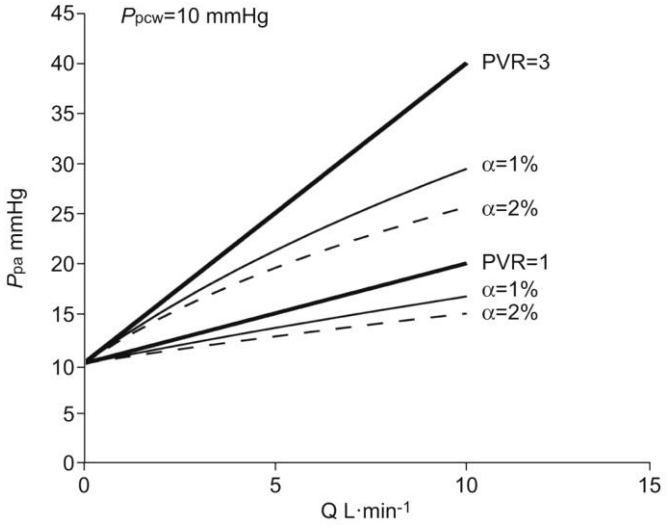
Recrutability of the pulmonary circulation





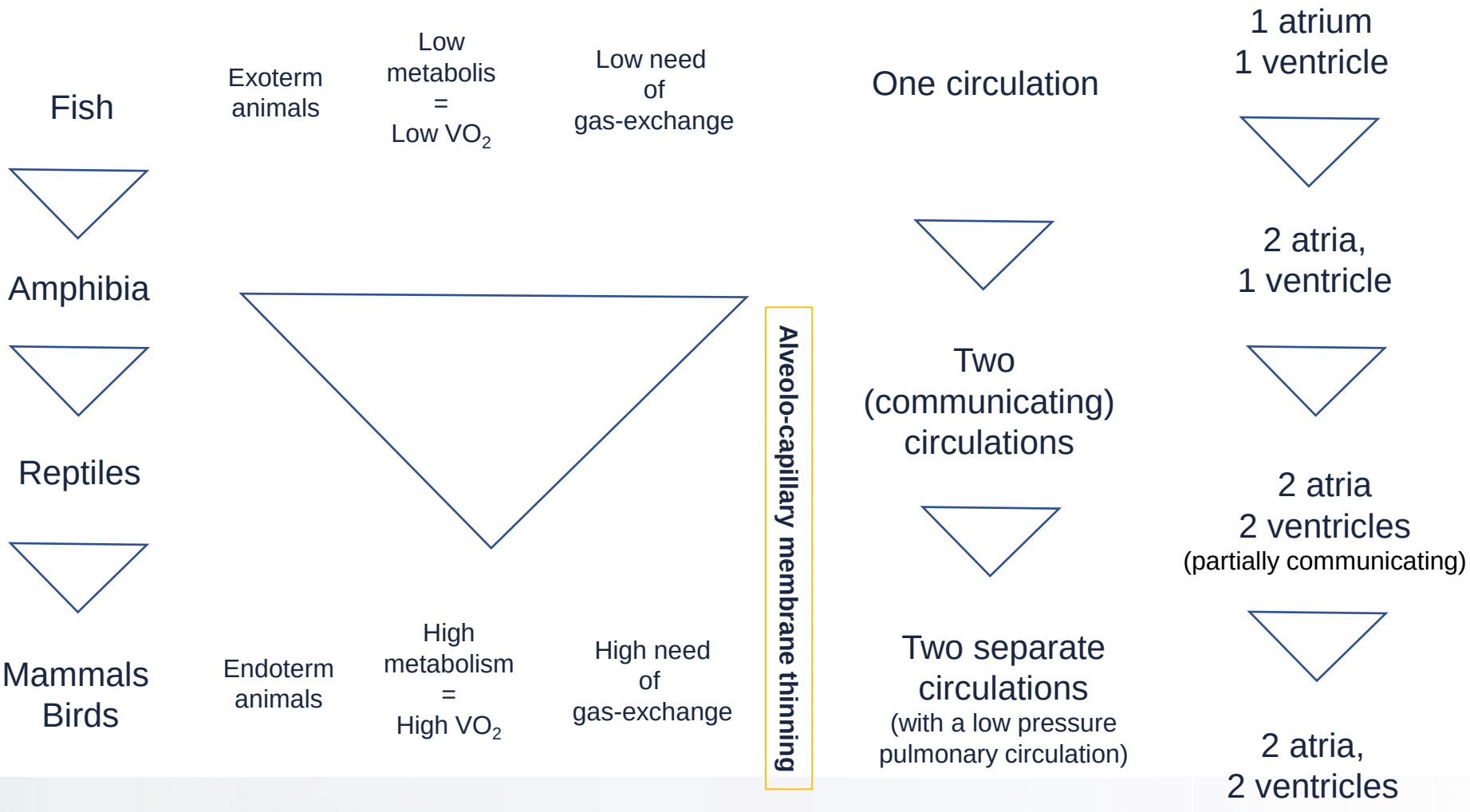
mPAP does not increase linearly with CO increase thanks to distensibility and recrutability of the pulmonary circulation

↑ mPAP = ↑↑ Q * PVR + LAP



West JB. Book of Respiratory Physiology, 2006
Naeije R et al. Eur Respir J 2013;41:217-23

Evolution of the pulmonary circulation (and of the right ventricle)



West JB. Am J Physiol Regul Integr Comp Physiol 2013

Physiology of the pulmonary circulation and of the right ventricle (RV)

The pulmonary circulation is a low-pressure, high flow system…

… and the right ventricle follows !! (*unloaded & reshaped*)

Anatomy of the right ventricle

Anterior position, behind the sternum

Three components

- Inlet (tricuspid valve, chordae tendinae and papillary muscles)
- Trabeculated apical myocardium
- Outlet (infundibolum)

Walls

- Anterior
- Lateral
- Inferior
- (interventricular septum)

Complex shape

- Triangular from a lateral perspective
- Crescent from a transversal section
- Influenced by the interventricular septum

Haddad F et al. Circulation 2008;117:1436-1448

Ventricular interdependence

Continuity between the muscle fibers of the RV and LV:

- functionally binds the ventricles together
- represents the anatomic basis of free ventricular wall traction caused by LV contraction
- contributes, along with the interventricular septum and pericardium, to ventricular interdependence

The RV is connected in series with the LV and is, therefore, obligated to pump on average the same effective stroke volume

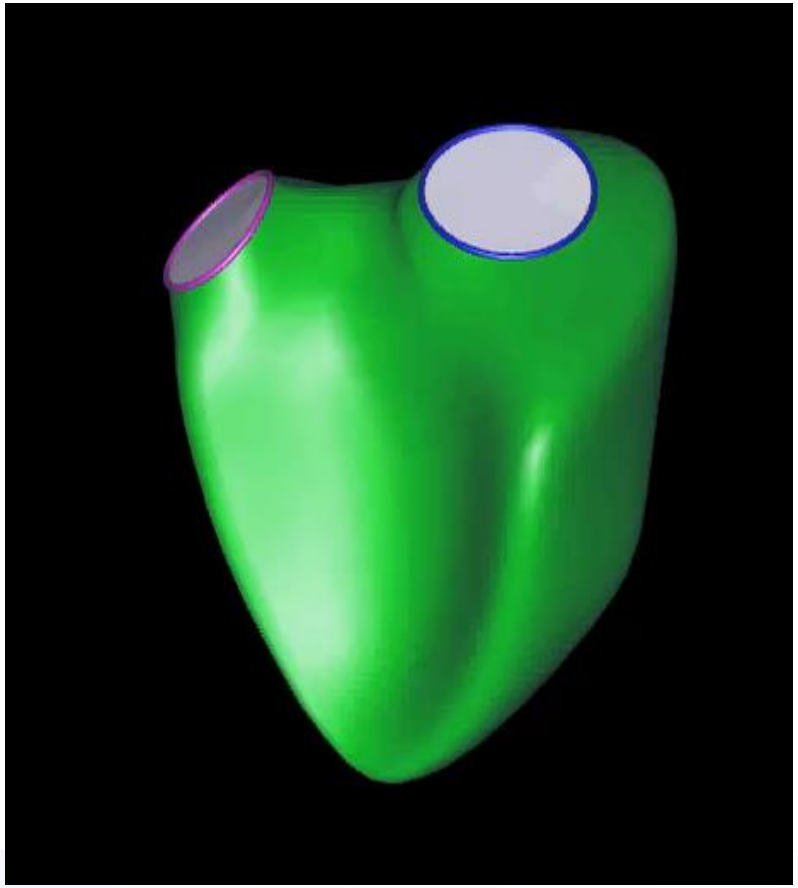
Haddad F et al. Circulation 2008;117:1436-1448

Right ventricular physiology

RV contraction is sequential, starting with the contraction of the inlet and trabeculated myocardium and ending with the contraction of the infundibulum (approximately 25 to 50 ms apart)

- The RV contracts by 3 separate mechanisms:
  1. inward movement of the free wall (bellows effect)
  2. contraction of the longitudinal fibers, (shortens the long axis, draws the tricuspid annulus toward the apex)
  3. LV contraction acting with a traction on RV free wall at the points of attachment (contribution for 20-40% at RV ejection → in the presence of RV scarring, the septum is able to maintain circulatory stability as long as the RV is not dilated)

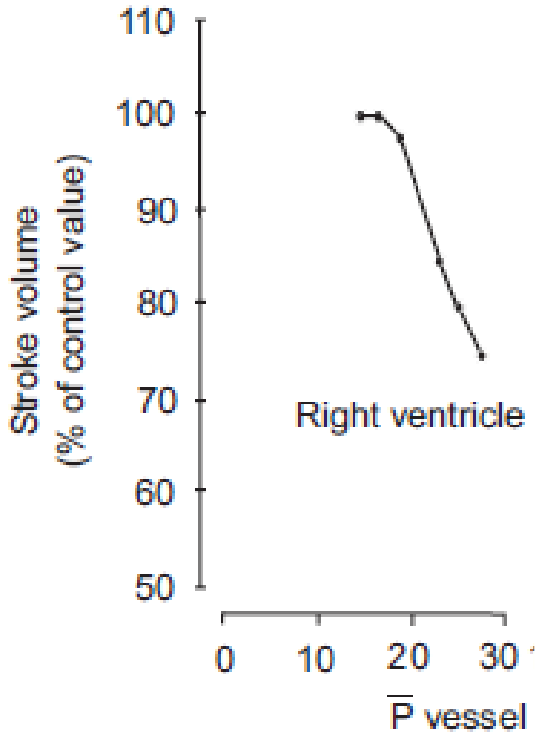
- Shortening of the RV is greater longitudinally than radially



Haddad F et al. Circulation 2008;117:1436-1448

Pathophysiology of RV failure

<u>Acute</u> ↑↑↑ in RV afterload (Pulmonary embolism, PE)



Naeije R et al. Pulm Circ 2014

Pathophysiology of RV failure

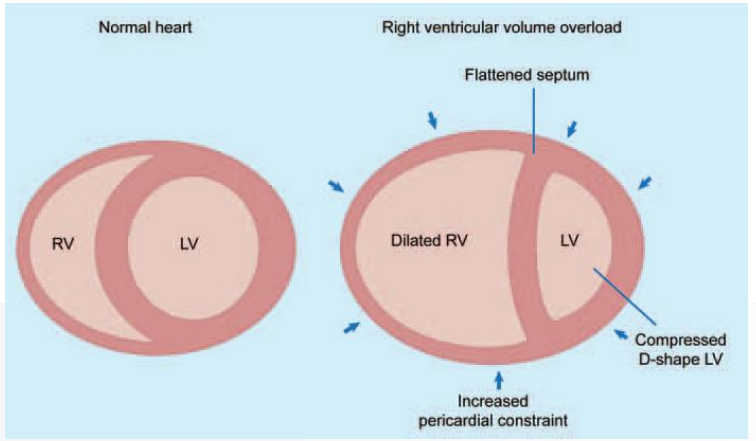
Chronically elevated RV afterload (PAH)

Homeometric (Anrep's) adaptation

↑ intrinsic contractility to maintain SV

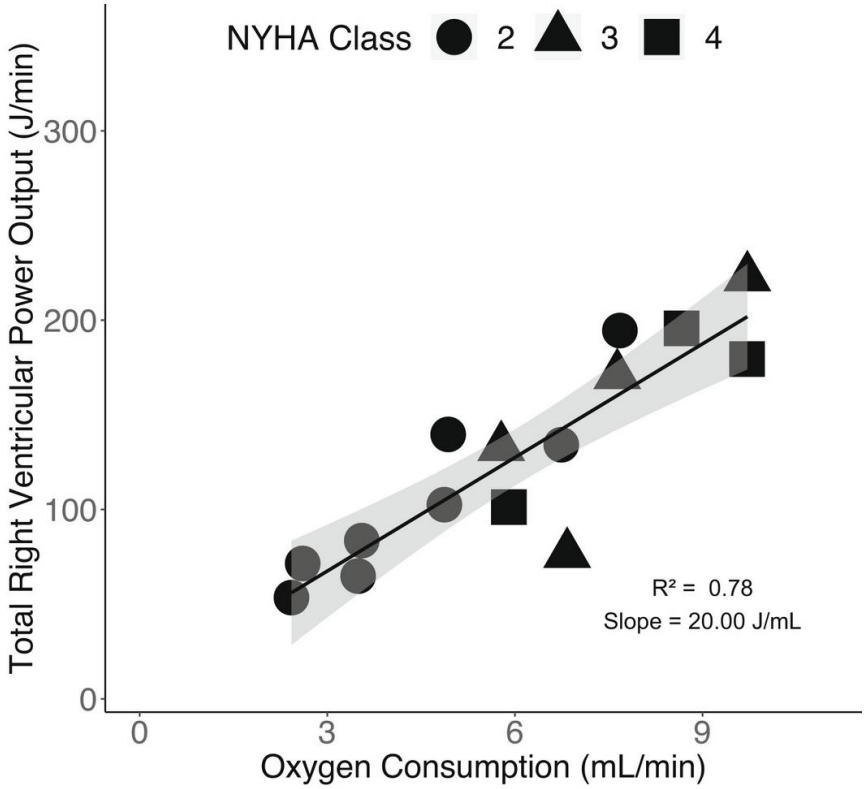
Heterometric adaptation (Starling's law of the heart)

↑ dimension and ↑ filling P to maintain SV

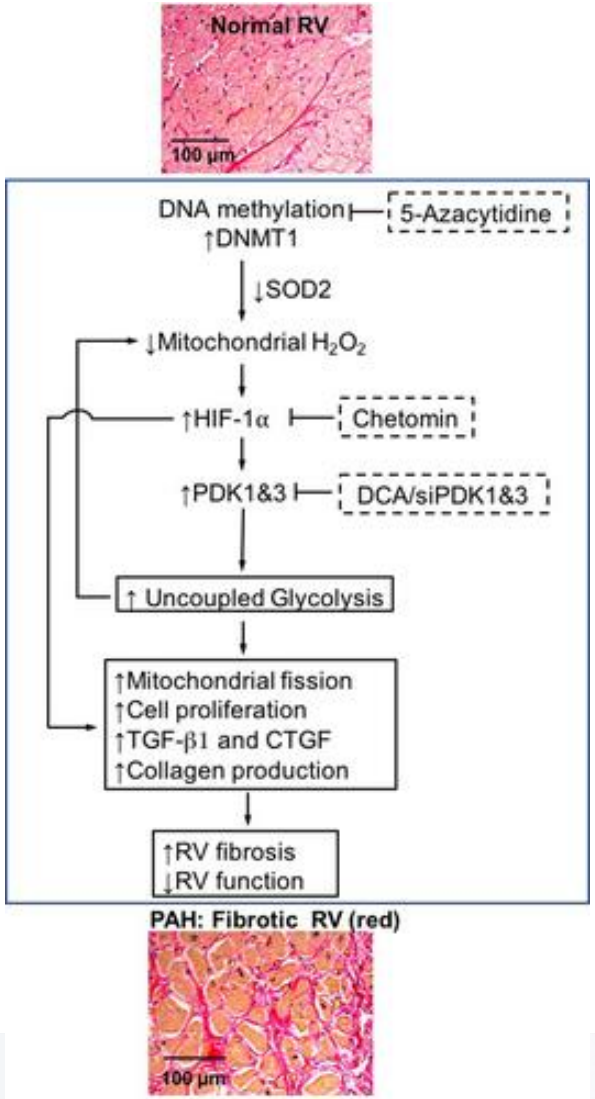


Naeije R et al. Pulm Circ 2014

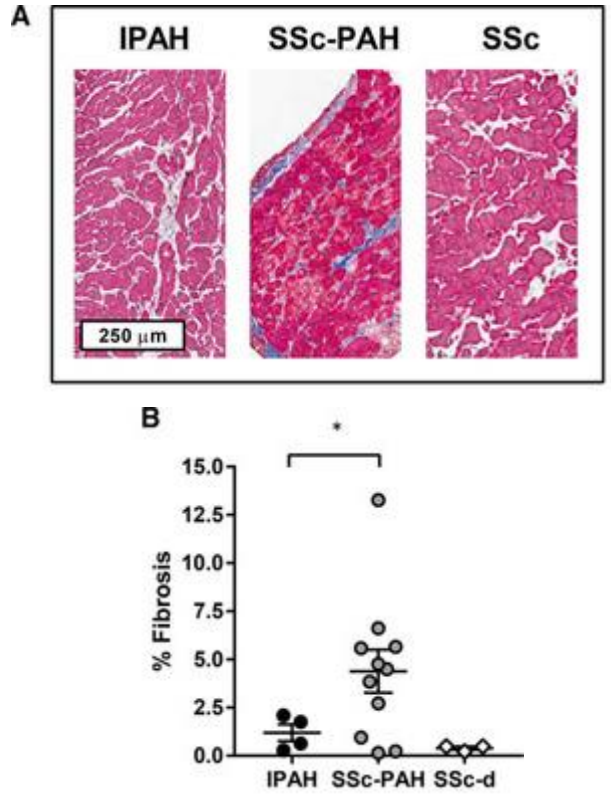
Pathophysiology of RV failure
RV remodeling in chronic pressure overload



Scott JV et al. Phys Rep 2022

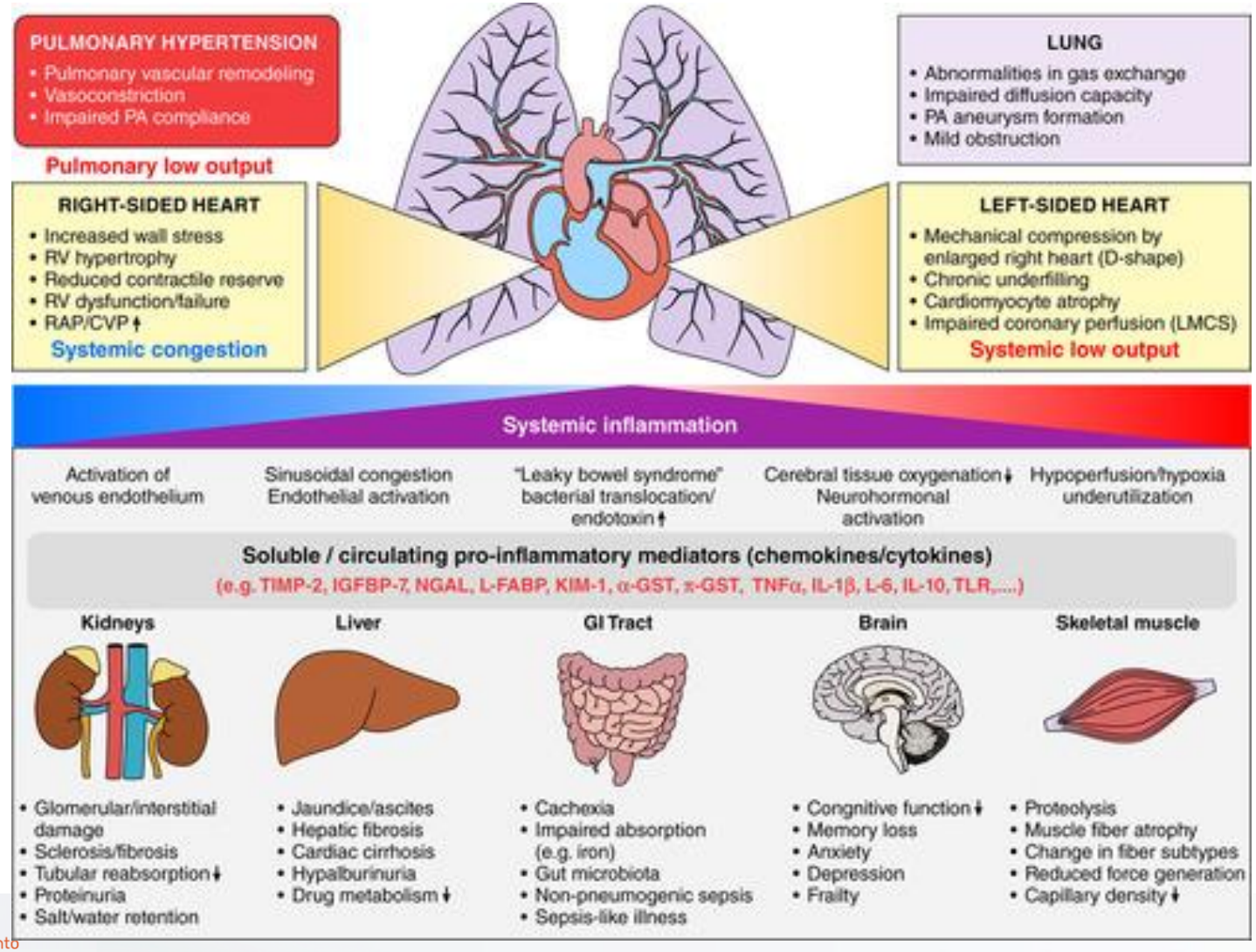


Tian L et al. Circ Res 2020



Hsu S et al. Circulation 2018

RV failure evolves as a systemic syndrome due to low output and venous congestion



Rosenkranz S et al. Circulation 2020

Chronic elevation in RV afterload and mortality

Hemodynamic variables	Normal values
Q, L/min	4.5 - 8.5
HR, bpm	40 - 100
Systolic PAP, mmHg	13 - 26
Diastolic PAP, mmHg	6 - 16
Mean PAP, mmHg	8 - 20
PAWP or LAP, mmHg	5 - 12
P_{cap}, mmHg	8 - 12
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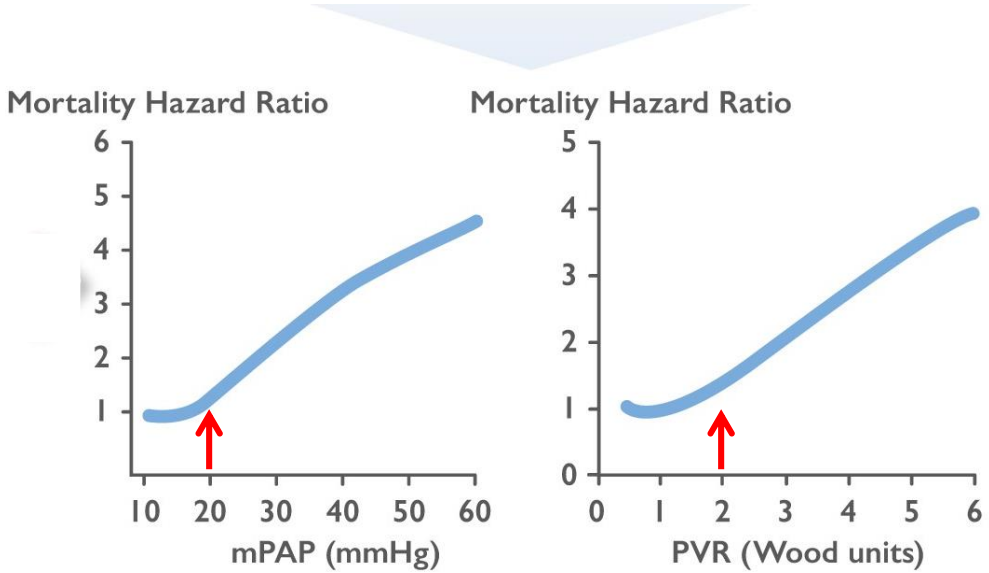
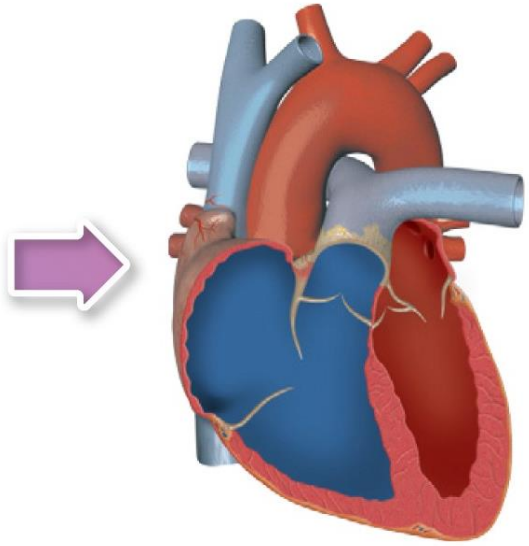
PVR, WU	< 1.25





Right heart failure

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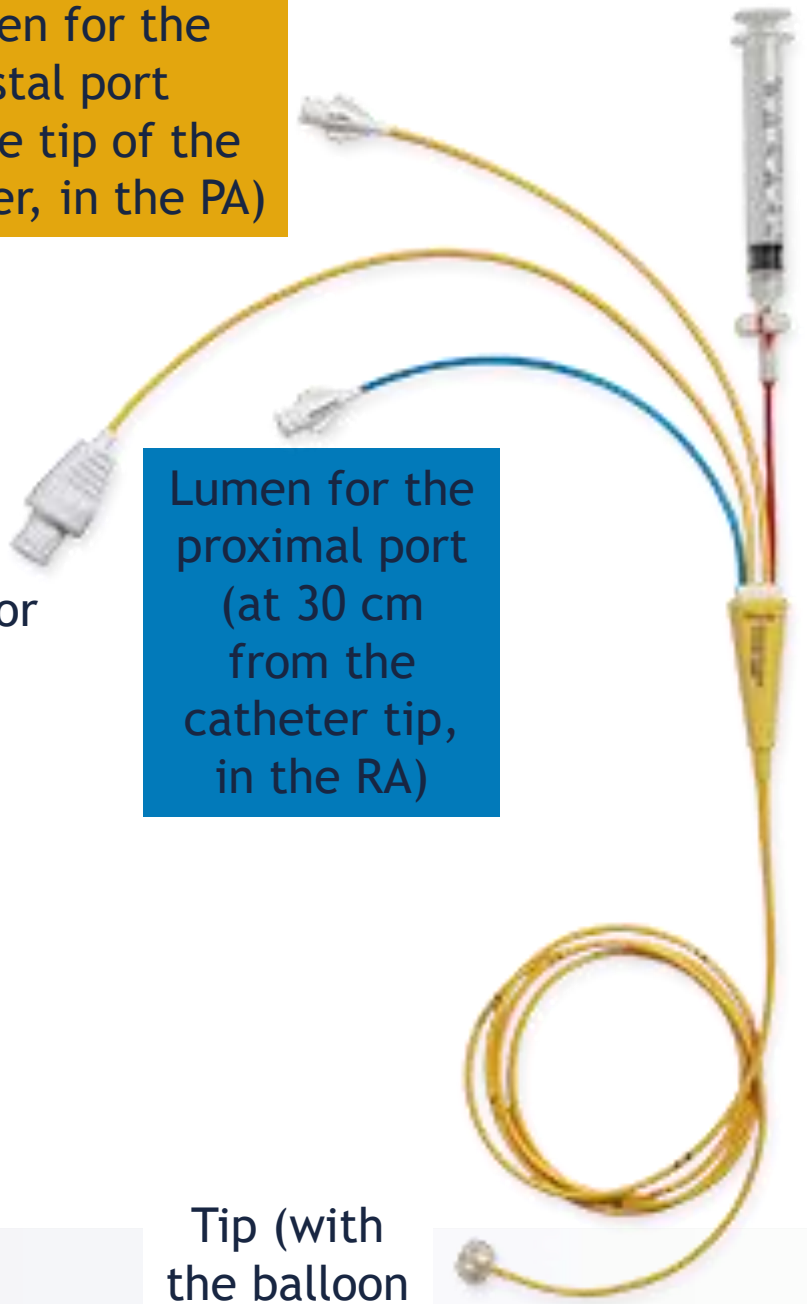
Swan-Ganz catheter

Lumen for the distal port (at the tip of the catheter, in the PA)



Thermistor

Lumen for the proximal port (at 30 cm from the catheter tip, in the RA)

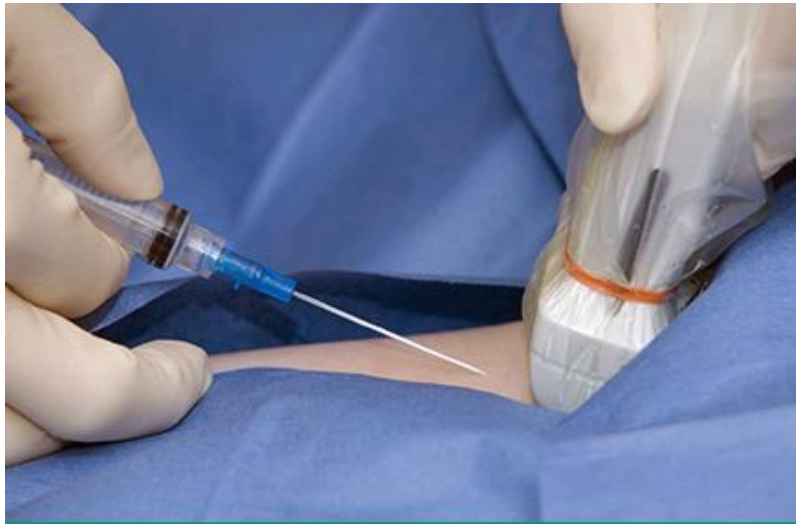
Tip (with the balloon inflated)

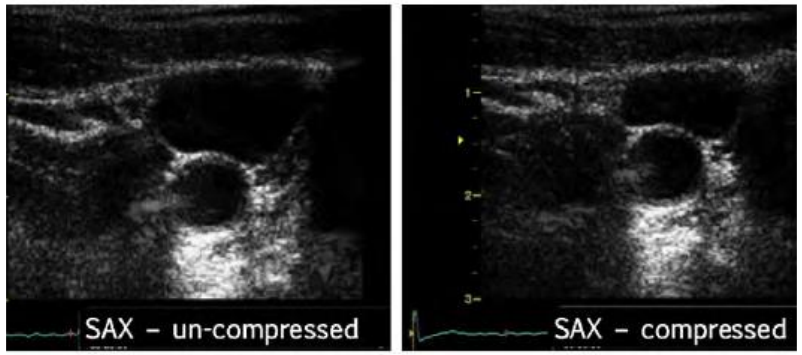
Measuring pulmonary hemodynamics

William Ganz and H.J.C. Swan

"In the fall of 1969, I was on the beach in Santa Monica, California, with my young children and noted a sailboat with a large spinnaker making good progress in a calm sea.

I wondered whether a sail or parachute at the tip of a flexible catheter would solve the problem"





Troianos CA et al. J Am Soc Echocardiogr 2011

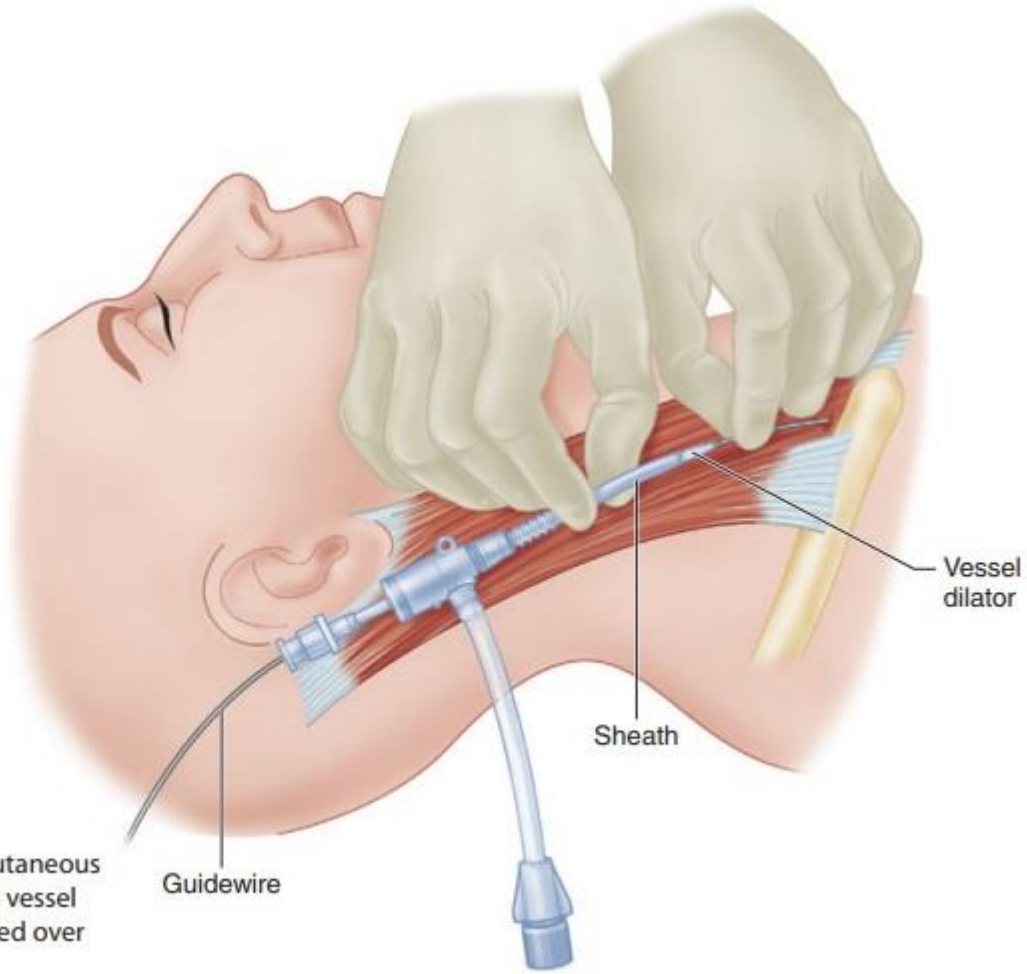
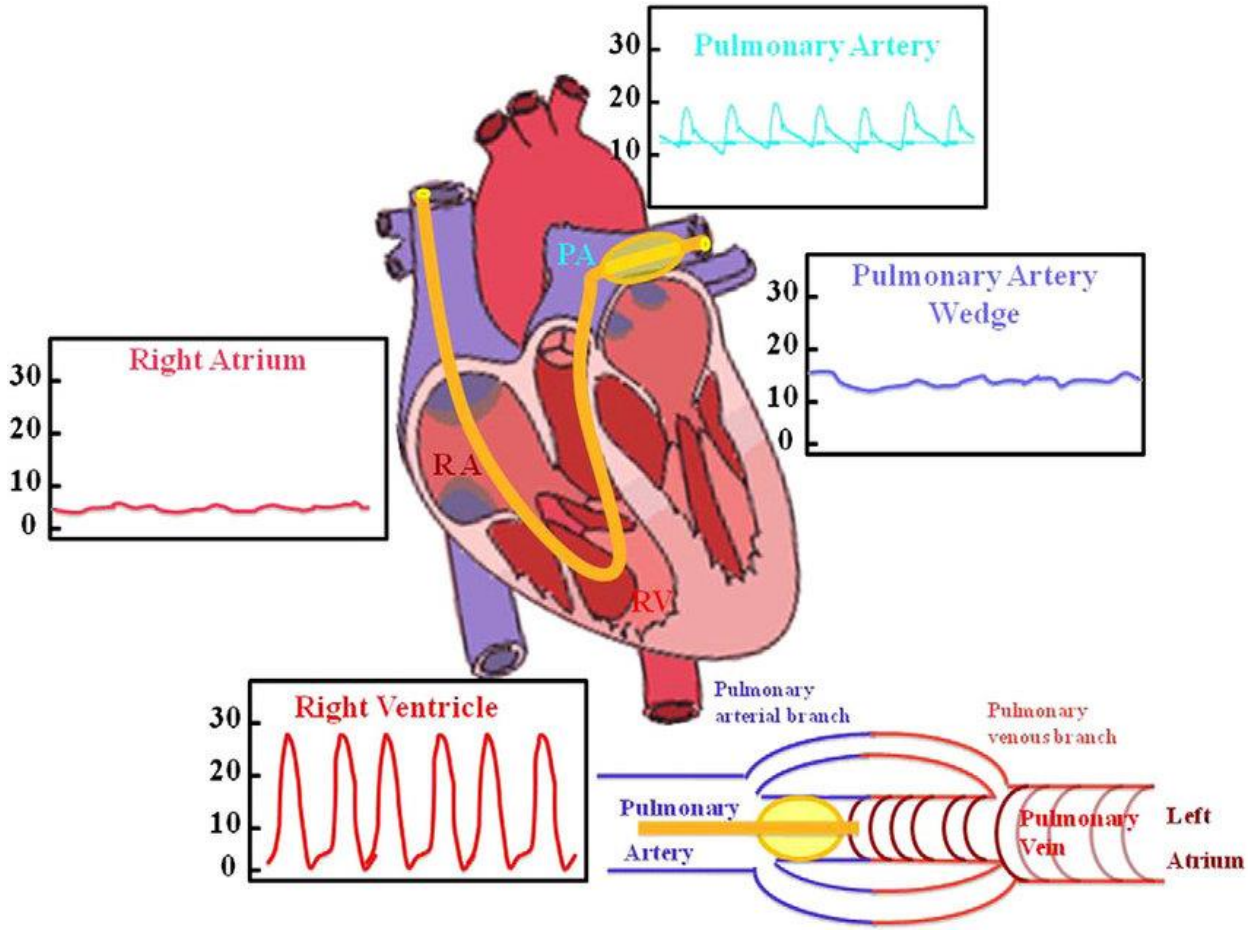
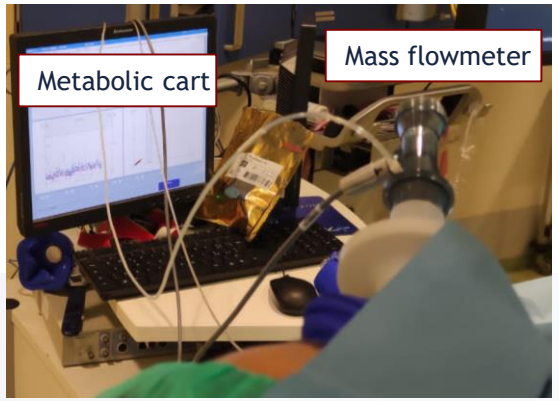


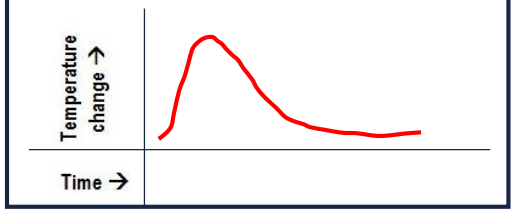
FIGURE 5–21 A percutaneous introducer consisting of a vessel dilator and sheath is passed over the guidewire.



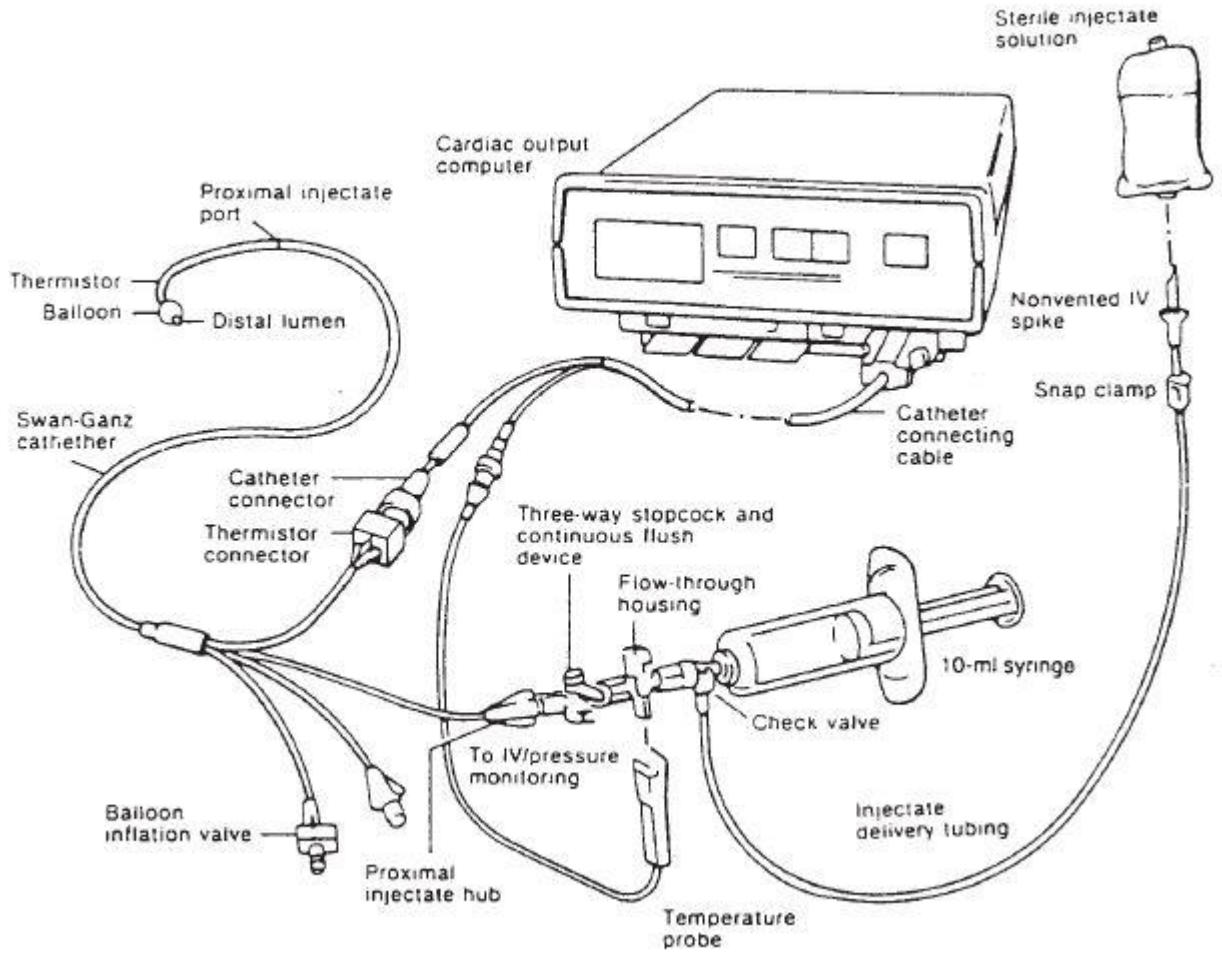
Cardiac output (direct Fick)



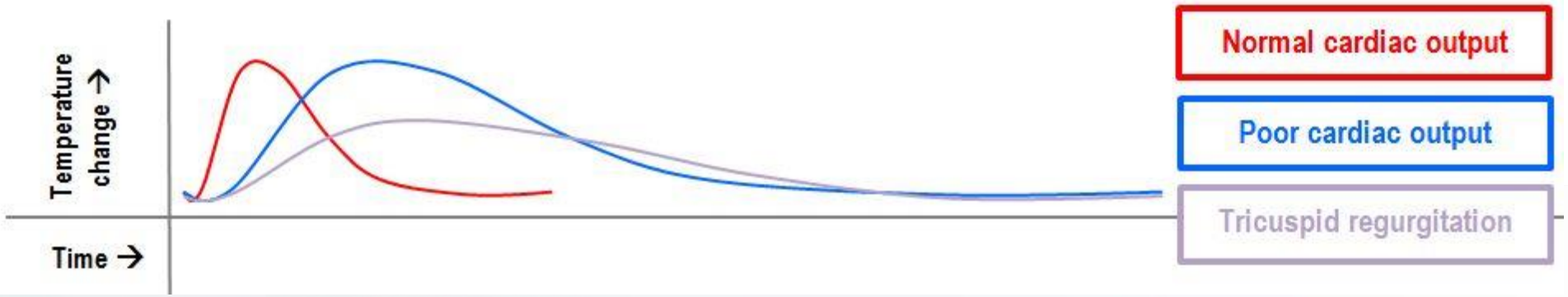
Cardiac output (thermodilution)



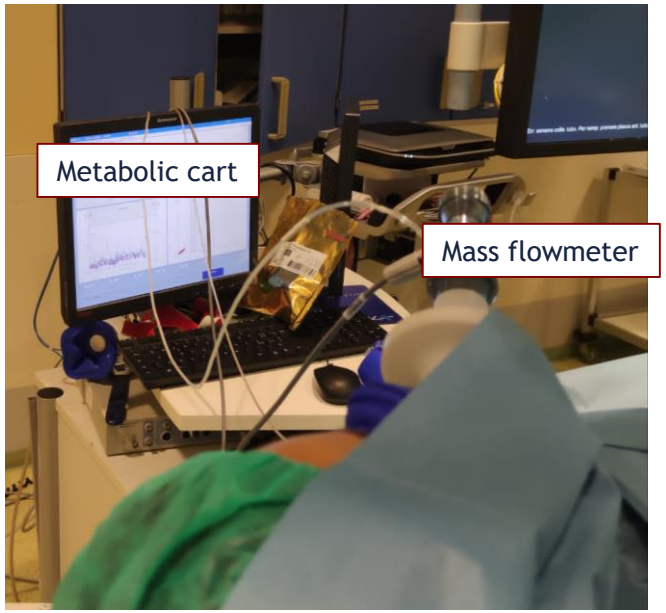
CO measurement thermodilution



Triplicate TD measurement with < 10% changes



CO measurement
Direct Fick method



$VO_2 = CO \times d(a\text{-}v)O_2$

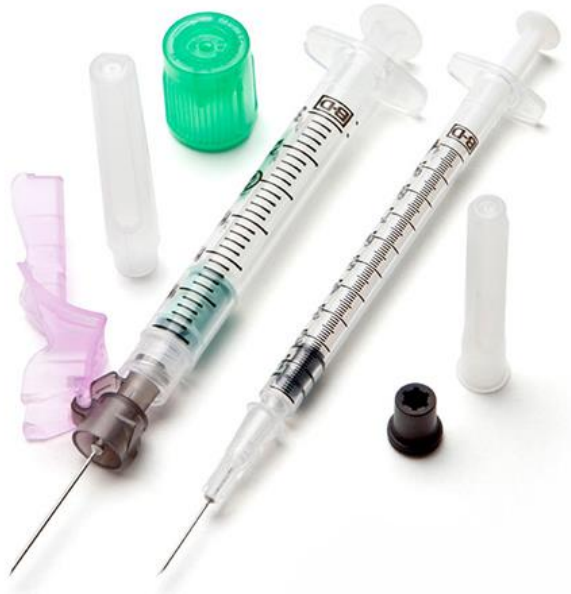
$CO = VO_2 / d(a\text{-}v)O_2$

$CO = VO_2 / [Hb*1.37*(SaO_2\text{-}SvO_2)] / 10 * 1000$

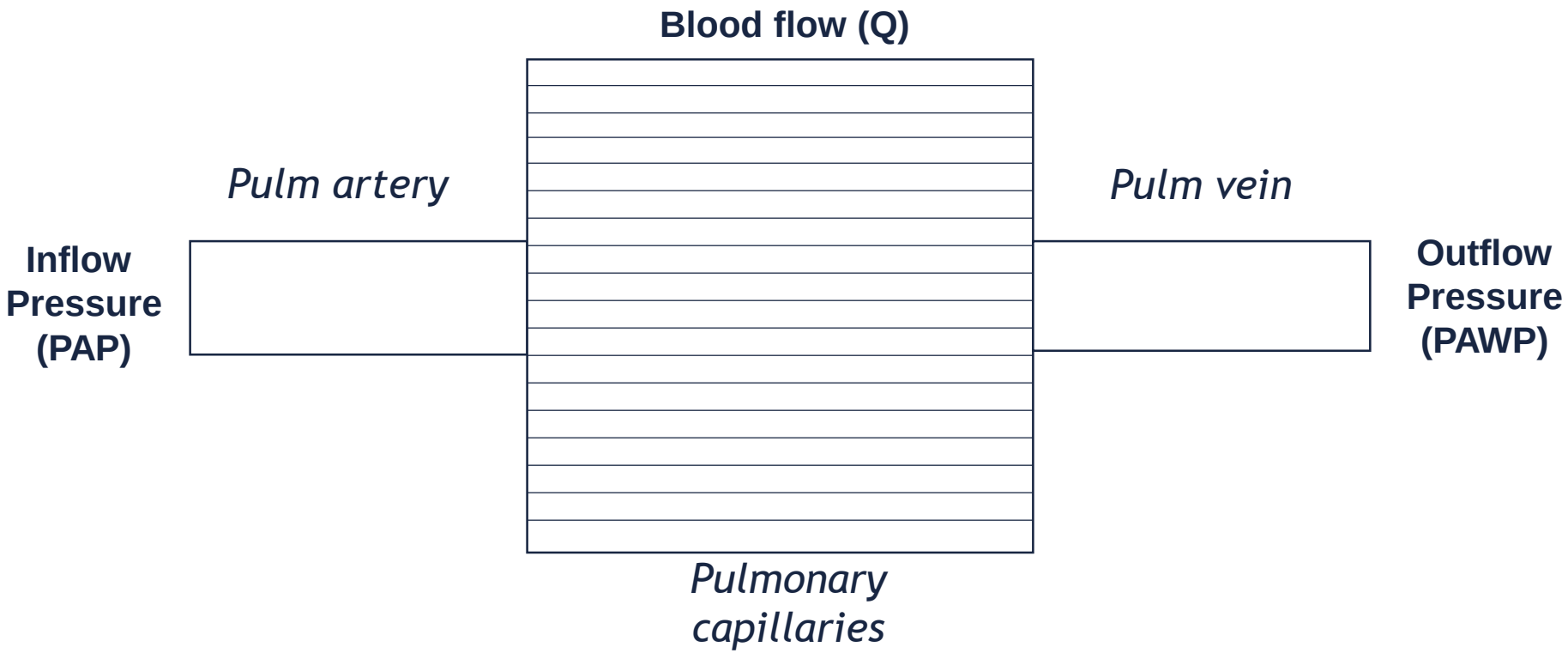
VO_2= oxygen consumption

CO=cardiac output

$d(a\text{-}v)O_2$=arteriovenous oxygen difference



The pulmonary circulation: a hydraulic perspective



$$PVR = (mPAP - LAP) / Q$$

Estimating pulmonary artery and filling pressures
Echocardiography

Non - invasive

Low cost

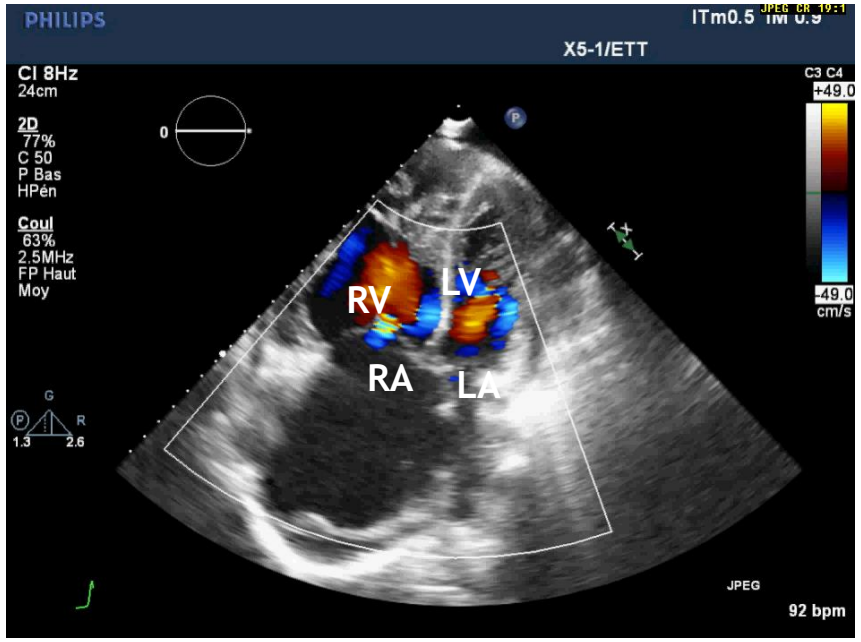
Dedicated personnel

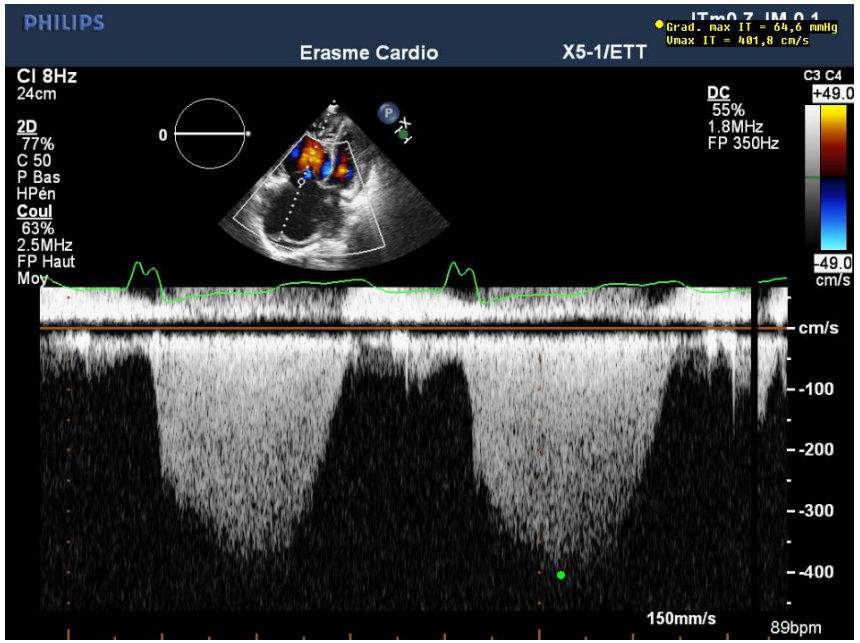
Pulmonary artery pressure estimation

Indirect signs of pulmonary pressure increase: right heart dimensions and function

Morphology and function of left heart chamber and valves

Estimating pulmonary artery and filling pressures
Systolic PAP



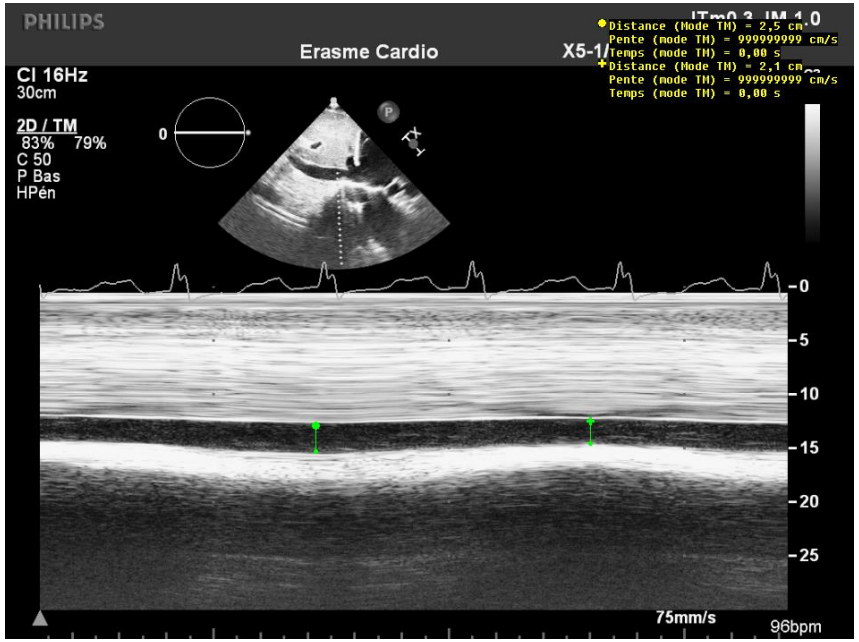


RV-RA systolic pressure gradient = 4 x TRV^2

Systolic PAP = RV-RA systolic pressure gradient + RAP

PAP=pulmonary artery pressure
RA=right atrium
RAP=right atrial pressuer
RV=right ventricle
TRV=tricuspid regurgitant jet velocity measured with CW Doppler

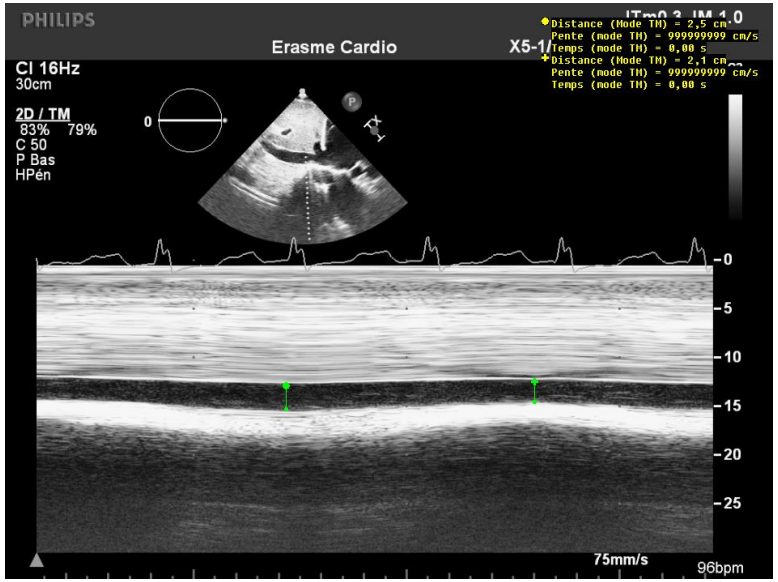
Estimating pulmonary artery and filling pressures
Right atrial pressure (RAP)



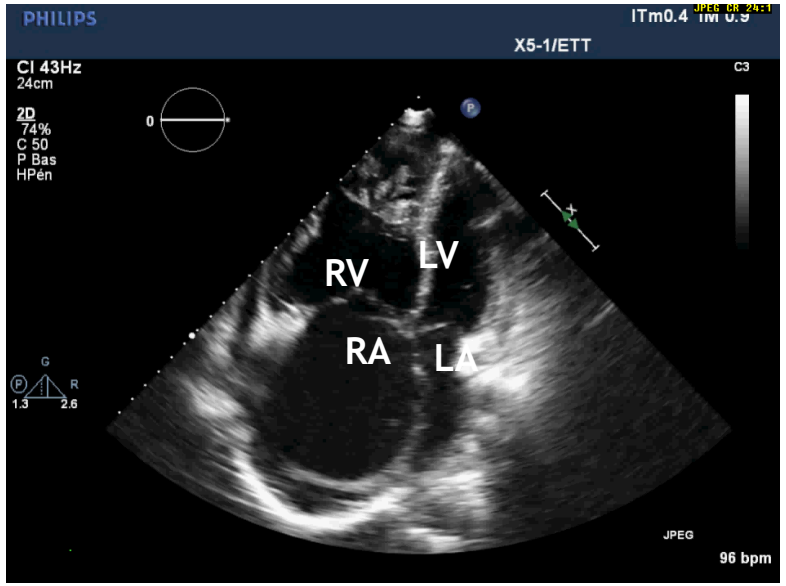
Inferior vena cava (IVC) diameter and collapsibility:

- Normal diameter and collapsibility → RAP 0-5 mmHg
- Dilated IVC or reduced collapsibility → RAP 5-10 mmHg
- Dilated IVC and reduced collapsibility → RAP 10-15 mmHg

Estimating pulmonary artery and filling pressures
Additional signs of PH – right heart dimensions

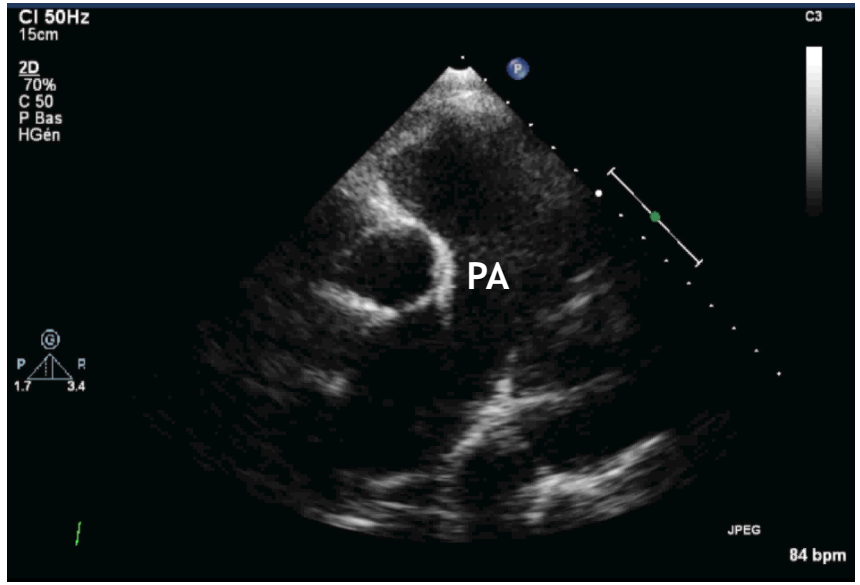


Dilated IVC and/or ↓collapsibility



Dilated RV, RV > LV, septal shift

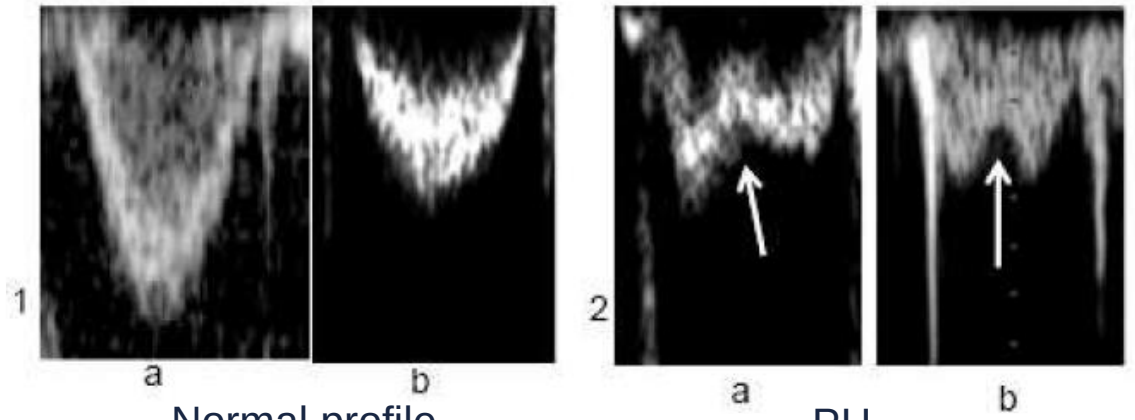
Dilated RA



Dilated PA

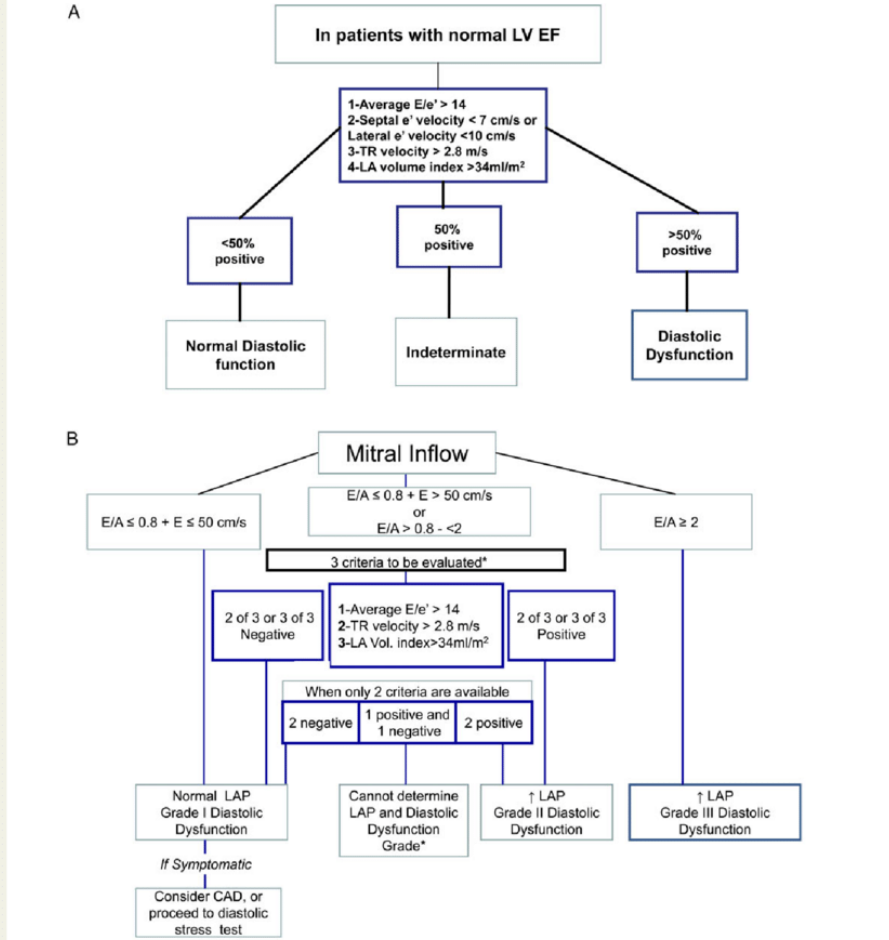
Estimating pulmonary artery and filling pressures
Additional signs of PH – Doppler study of the RV outflow tract

PW Doppler on RVOT



Normal profile PH

Estimating pulmonary artery and filling pressures
Left heart filling pressures



Normal diastolic function → normal left heart filling pressures

Grade I diastolic dysfunction → normal left heart filling pressures

Grade II diastolic dysfunction → ↑ LAP

Grade III diastolic dysfunction → ↑↑ LAP

Echocardiographic probability of PH

TABLE 1 Echocardiographic probability of pulmonary hypertension (PH) in symptomatic patients with a suspicion of PH

Peak tricuspid regurgitation velocity m·s^{-1}	Presence of other echocardiographic "PH signs"#	Echocardiographic probability of PH
≤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	

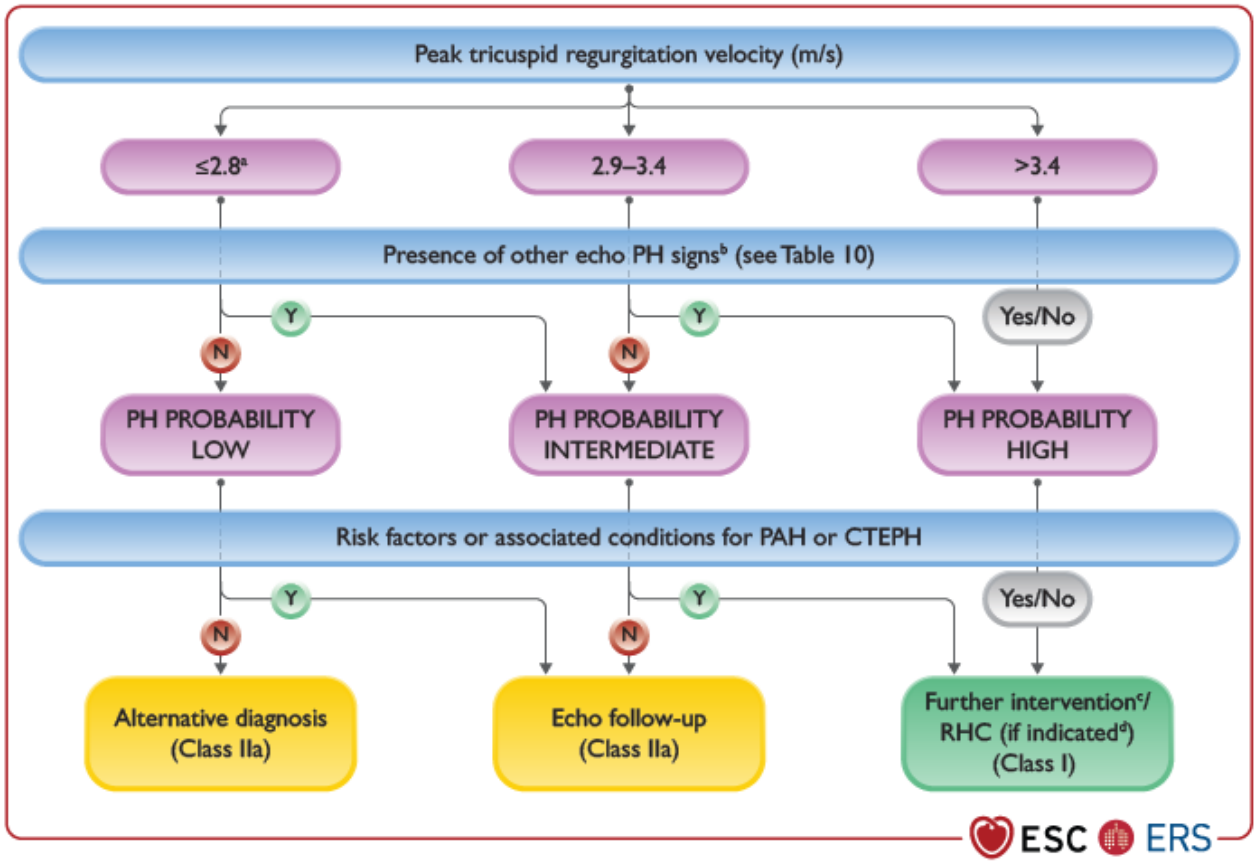


Figure 5 Echocardiographic probability of pulmonary hypertension and recommendations for further assessment. CPET, cardiopulmonary exercise testing; CTEPH, chronic thrombo-embolic pulmonary hypertension; echo, echocardiography; LHD, left heart disease; N, no; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RHC, right heart catheterization; TRV, tricuspid regurgitation velocity; Y, yes. [a]Or unmeasurable. The TRV threshold of 2.8 m/s was not changed according to the updated haemodynamic definition of PH. [b]Signs from at least two categories in *Table 10* (A/B/C) must be present to alter the level of echocardiographic probability of PH. [c]Further testing may be necessary (e.g. imaging, CPET). [d]RHC should be performed if useful information/a therapeutic consequence is anticipated (e.g. suspected PAH or CTEPH), and may not be indicated in patients without risk factors or associated conditions for PAH or CTEPH (e.g. when mild PH and predominant LHD or lung disease are present).

Agenda

- Physiology of the pulmonary circulation and of the right ventricle (RV) → understanding RV failure
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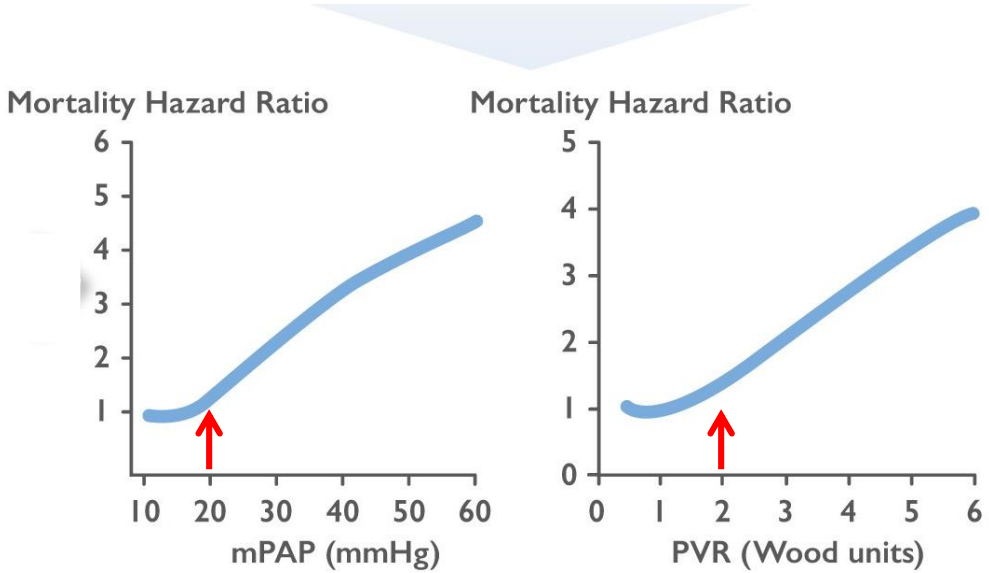
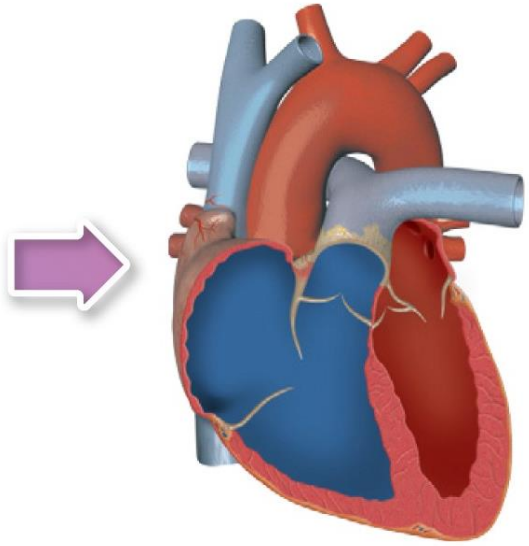
Chronic elevation in RV afterload and mortality

Hemodynamic variables	Normal values
Q, L/min	4.5 - 8.5
HR, bpm	40 - 100
Systolic PAP, mmHg	13 - 26
Diastolic PAP, mmHg	6 - 16
Mean PAP, mmHg	8 - 20
PAWP or LAP, mmHg	5 - 12
P_{cap}, mmHg	8 - 12
RAP, mmHg	1 - 8
PVR, dyne*s*cm^{-5}	12 - 100
PVR, WU	< 1.25





Right heart failure

PH: hemodynamic definition(s)

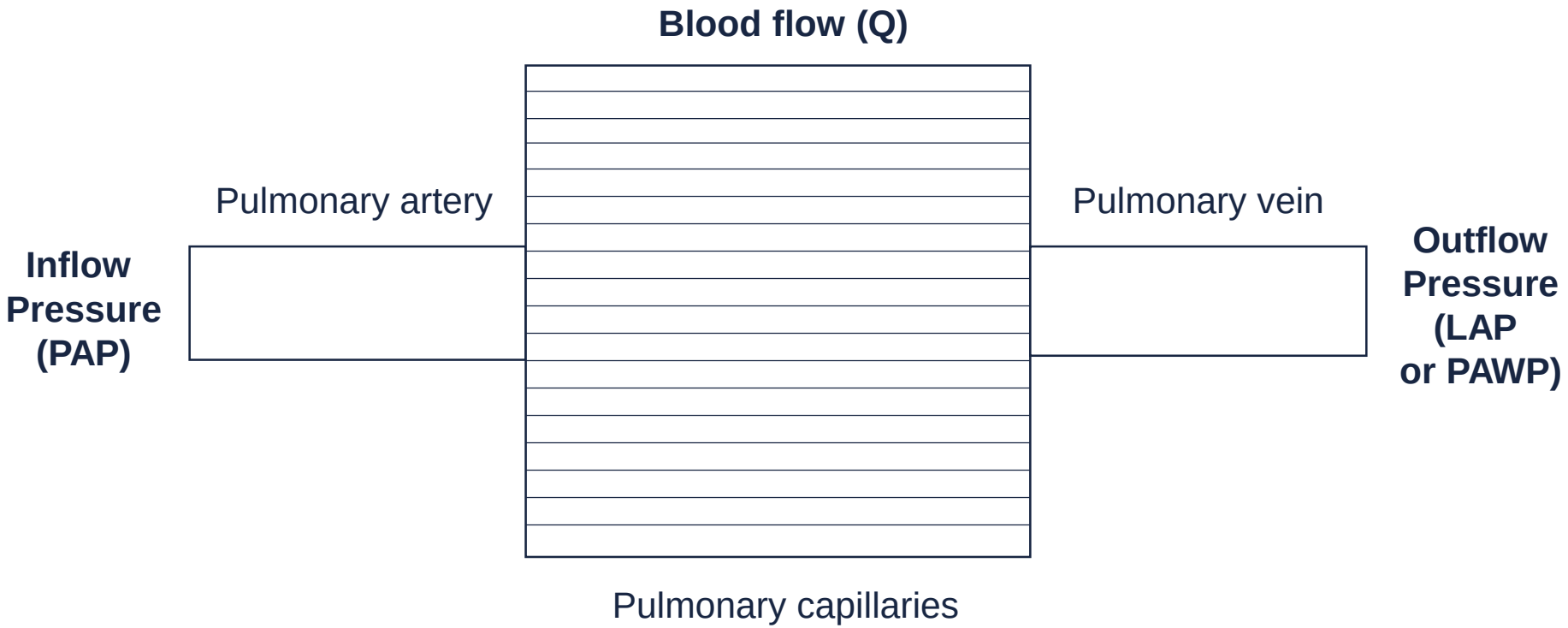
Definition	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ≤15 mmHg PVR >2 WU
IpcPH Isolated post-capillary PH	mPAP >20 mmHg PAWP >15 mmHg PVR ≤2 WU
CpcPH Combined post- and pre- capillary PH	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU
Exercise PH	mPAP/CO slope between rest and exercise >3 mmHg/L/min

Post-capillary PH

CO, cardiac output; CpcPH, combined post- and pre-capillary pulmonary hypertension; IpcPH, isolated post-capillary pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WU, Wood units.

Some patients present with elevated mPAP (>20 mmHg) but low PVR (≤2 WU) and low PAWP (≤15 mmHg); this haemodynamic condition may be described by the term 'unclassified PH' (see text for further details).

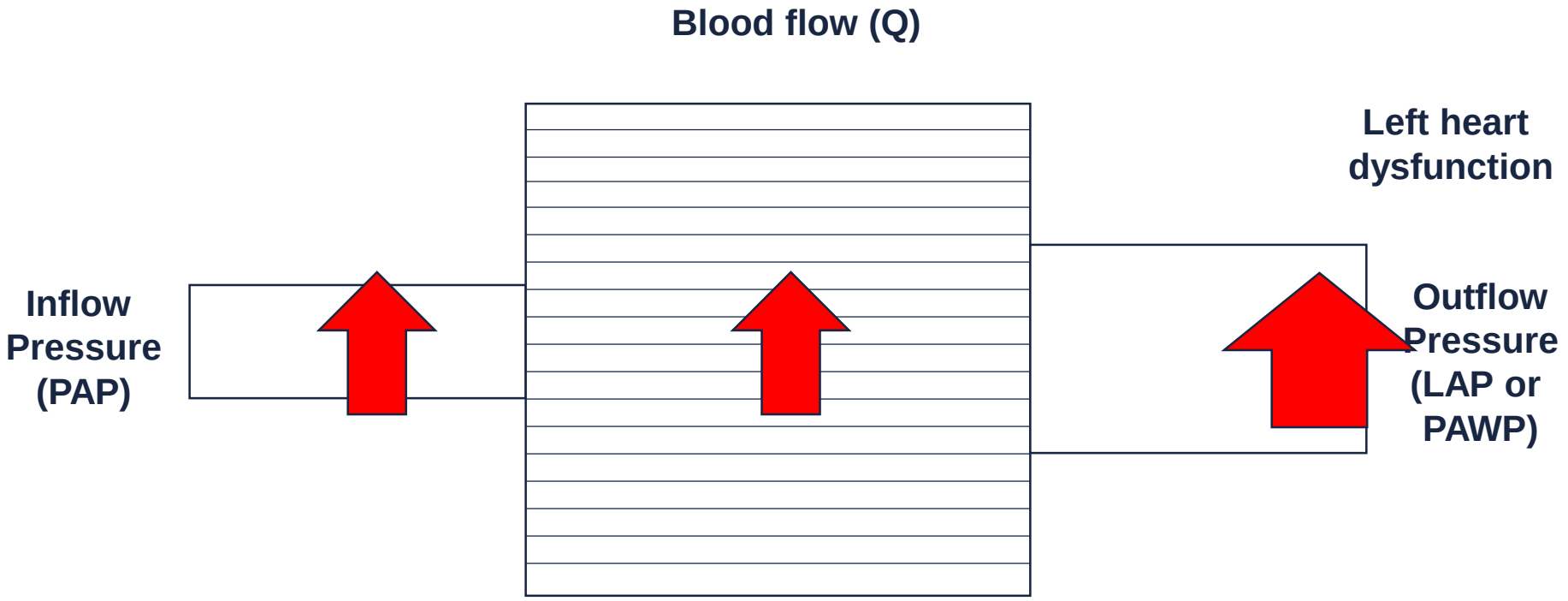
Pulmonary circulation



- PVR = (mean PAP - LAP) / Q
- mean PAP = PVR x Q + LAP

PAP=pulmonary artery pressure
PAWP=pulmonary artery wedge pressure
PVR=pulmonary vascular resistance
Q=cardiac output

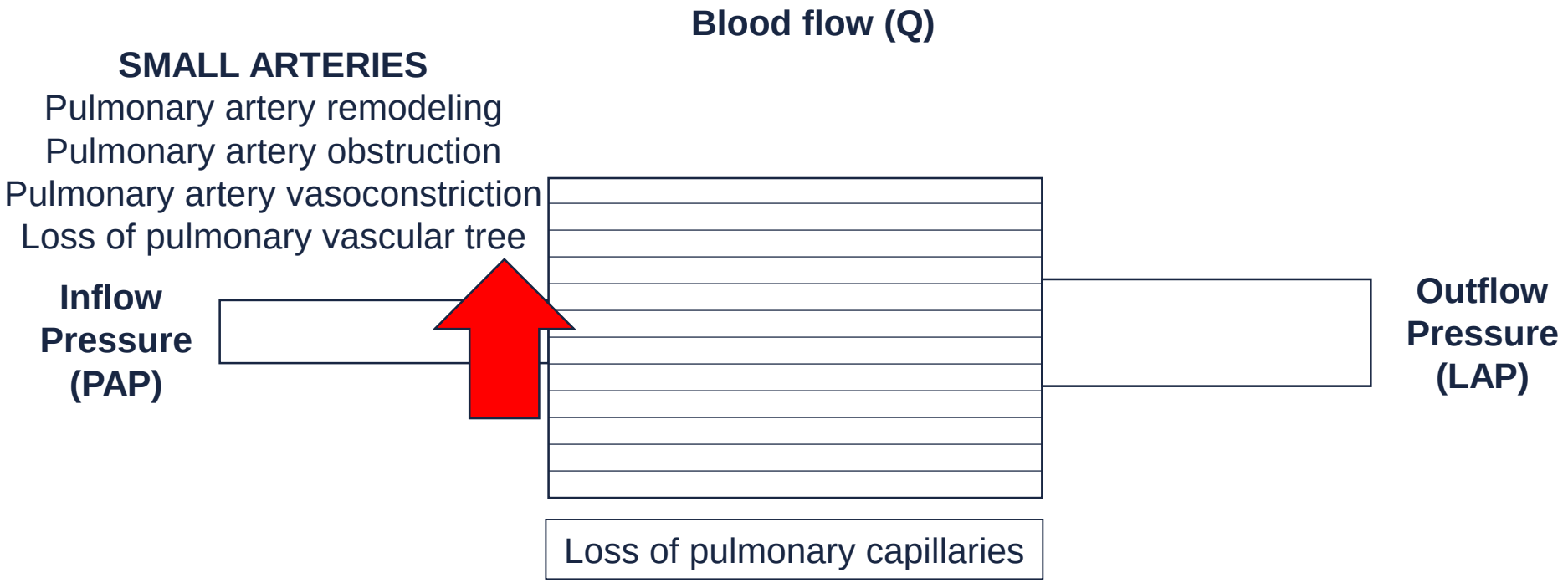
Pulmonary circulation



↑↑ mPAP = PVR x Q + ↑↑ LAP

Post-capillary PH

Pulmonary circulation



↑↑ mPAP = ↑↑ PVR x Q + LAP

Pre-capillary PH

PH: hemodynamic definition(s)

	Definition	Haemodynamic characteristics
	PH	mPAP >20 mmHg
	Pre-capillary PH	mPAP >20 mmHg PAWP ≤15 mmHg PVR >2 WU
Post-capillary PH	IpcPH Isolated post-capillary PH	mPAP >20 mmHg PAWP >15 mmHg PVR ≤2 WU
Post-capillary PH	CpcPH Combined post- and pre- capillary PH	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU
	Exercise PH	mPAP/CO slope between rest and exercise >3 mmHg/L/min

CO, cardiac output; CpcPH, combined post- and pre-capillary pulmonary hypertension; IpcPH, isolated post-capillary pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WU, Wood units.

Some patients present with elevated mPAP (>20 mmHg) but low PVR (≤2 WU) and low PAWP (≤15 mmHg); this haemodynamic condition may be described by the term 'unclassified PH' (see text for further details).

PH: clinical classification

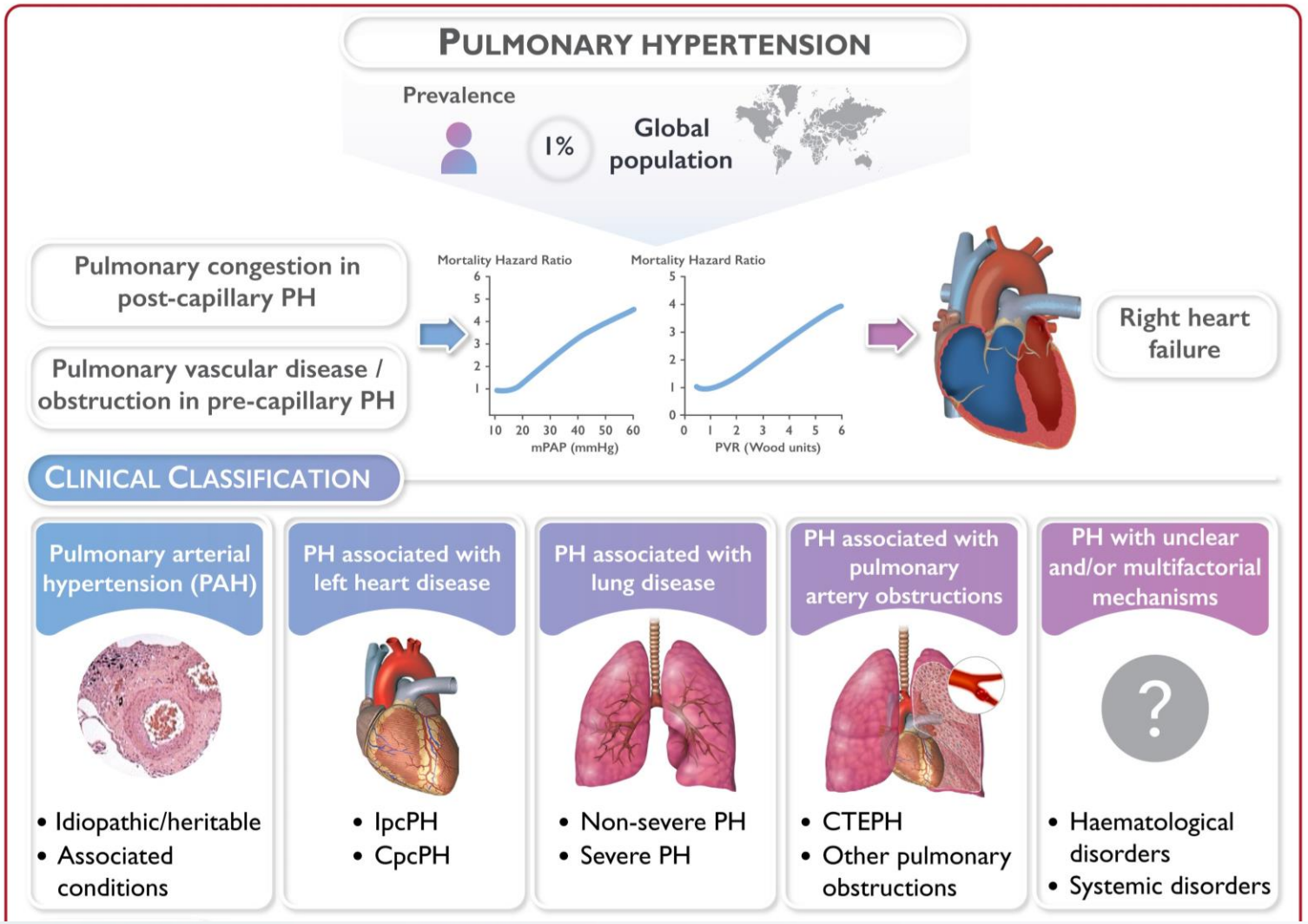


Table 6 Clinical classification of pulmonary hypertension

GROUP 1 Pulmonary arterial hypertension (PAH)
- 1.1 Idiopathic
  - 1.1.1 Non-responders at vasoreactivity testing
  - 1.1.2 Acute responders at vasoreactivity testing
- 1.2 Heritable[a]
- 1.3 Associated with drugs and toxins[a]
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
- 1.6 Persistent PH of the newborn

GROUP 2 PH associated with left heart disease
- 2.1 Heart failure:
  - 2.1.1 with preserved ejection fraction
  - 2.1.2 with reduced or mildly reduced ejection fraction[b]
- 2.2 Valvular heart disease
- 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH

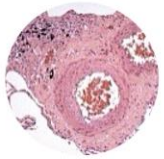
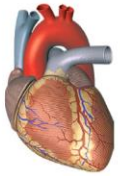
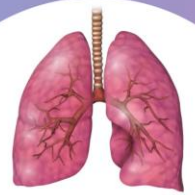
GROUP 3 PH associated with lung diseases and/or hypoxia
- 3.1 Obstructive lung disease or emphysema
- 3.2 Restrictive lung disease
- 3.3 Lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoventilation syndromes
- 3.5 Hypoxia without lung disease (e.g. high altitude)
- 3.6 Developmental lung disorders

GROUP 4 PH associated with pulmonary artery obstructions
- 4.1 Chronic thrombo-embolic PH
- 4.2 Other pulmonary artery obstructions[c]

GROUP 5 PH with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders[d]
- 5.2 Systemic disorders[e]
- 5.3 Metabolic disorders[f]
- 5.4 Chronic renal failure with or without haemodialysis
- 5.5 Pulmonary tumour thrombotic microangiopathy
- 5.6 Fibrosing mediastinitis

PH: clinical classification

Clinical Classification

Pulmonary arterial hypertension (PAH)	PH associated with left heart disease	PH associated with lung disease	PH associated with pulmonary artery obstructions	PH with unclear and/or multifactorial mechanisms
				
• Idiopathic/heritable • Associated conditions	• IpcPH • CpcPH	• Non-severe PH • Severe PH	• CTEPH • Other pulmonary obstructions	• Haematological disorders • Systemic disorders

Prevalence

Rare	Very common	Common	Rare	Rare
				

Therapeutic Strategies

Medical therapy • PAH drugs • CCB in responders **Lung transplantation**	**IpcPH:** • Treatment of LHD[a] **CpcPH:** • Treatment of LHD[a] • Potentially: PAH drugs (trials)	**PH-lung disease:** • Optimized care of underlying lung disease **Severe PH:** • Potentially: PAH drugs (trials)	**Surgical therapy:** • PEA **Interventional:** • BPA **Medical therapy:** • PH drugs	**Optimized treatment of underlying disease** • Potentially: PAH drugs (trials)

ESC ERS

Agenda

- Physiology of the pulmonary circulation and of the right ventricle (RV) → understanding RV failure
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- Diagnostic algorithms
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Clinical manifestations and findings

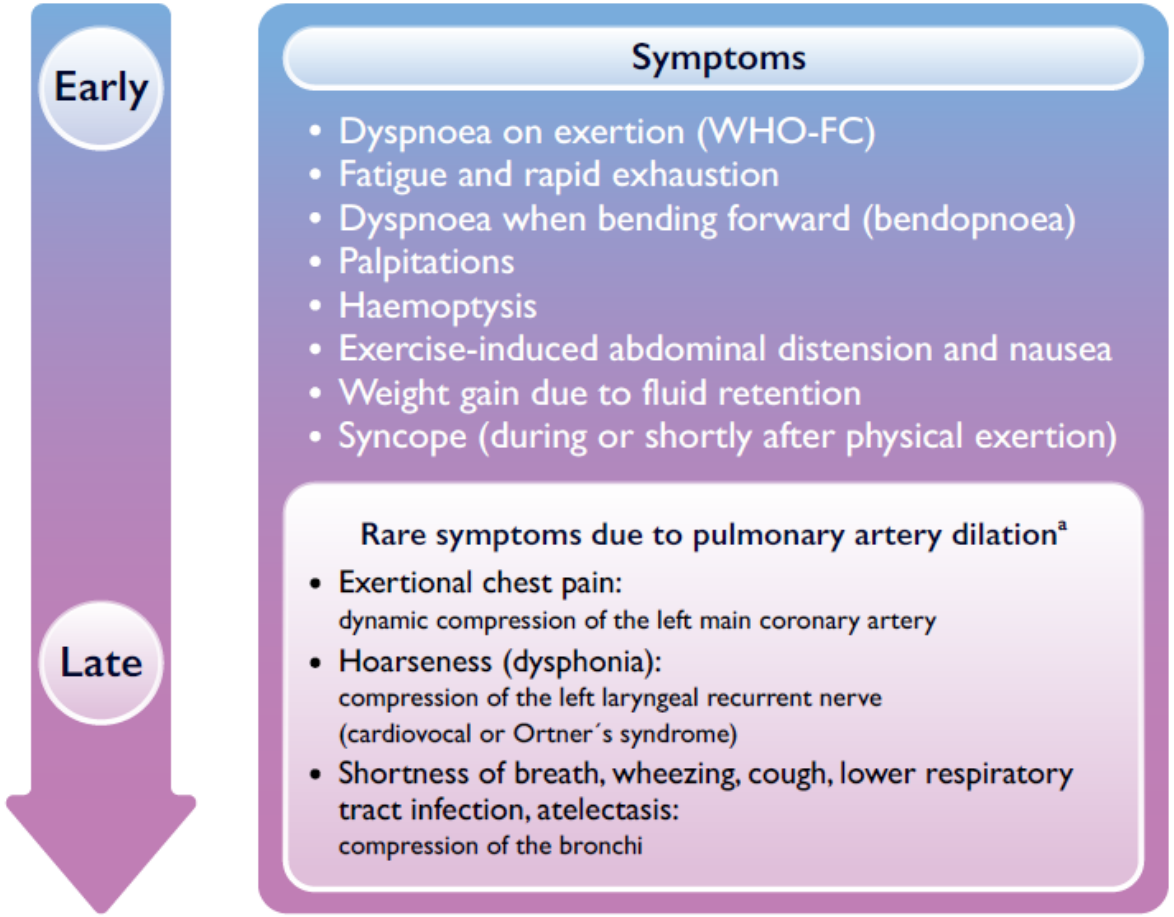
Clinical manifestations and findings depend upon:

- the degree of RV dysfunction
- the presence of conditions associated with PH development

PH: symptoms

Symptoms of PH are mainly **linked to right ventricle (RV) dysfunction**, and typically associated with exercise in the earlier course of the disease

Additional symptoms may be linked to an underlying disease associated with PH



PH: signs

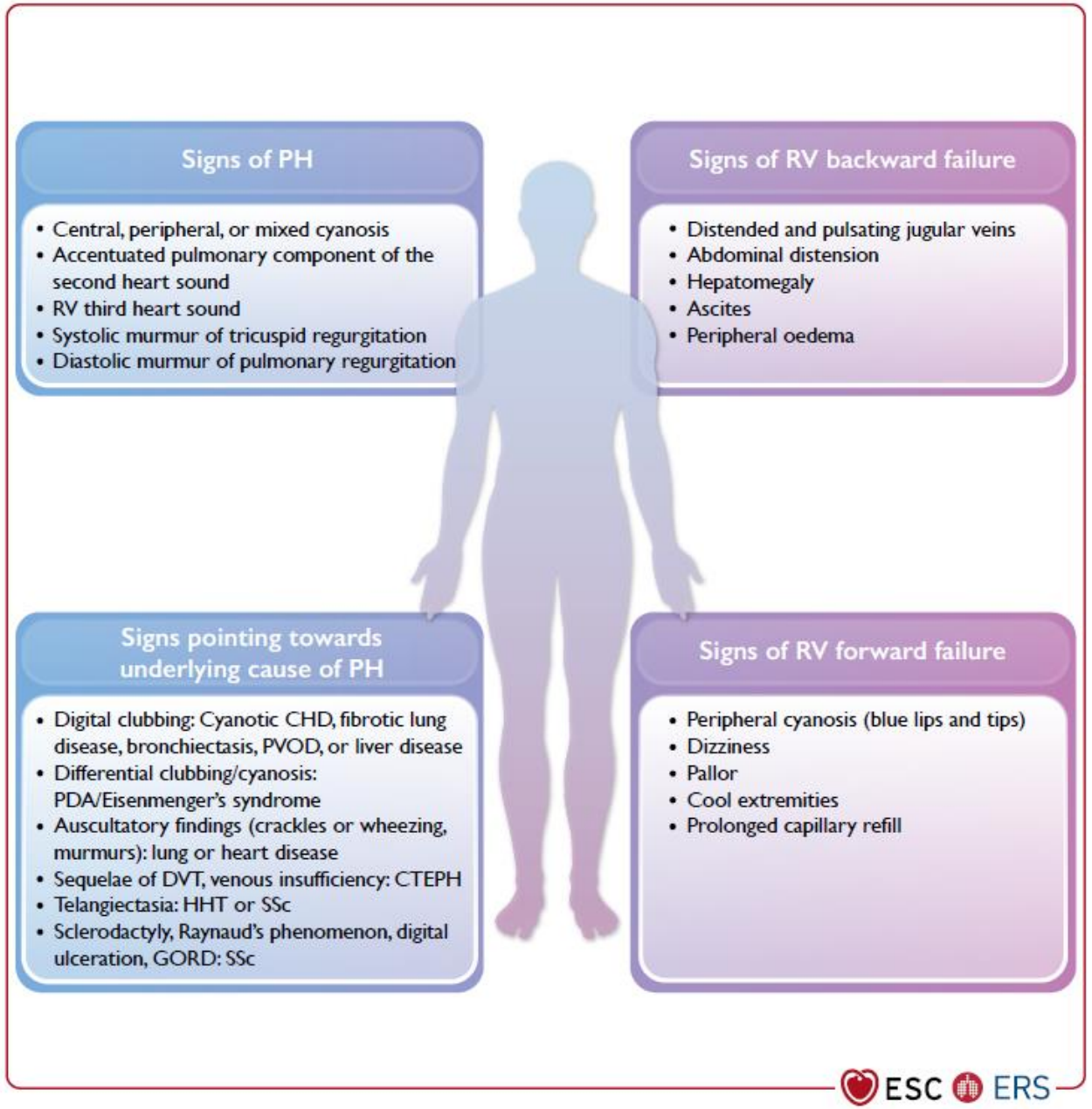


Figure 3 Clinical signs in patients with pulmonary hypertension. CHD, congenital heart disease; CTEPH, chronic thrombo-embolic pulmonary hypertension; DVT, deep venous thrombosis; GORD, gastro-oesophageal reflux disease; HHT, hereditary haemorrhagic telangiectasia; PDA, patent ductus arteriosus; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; RV, right ventricle; SSc, systemic sclerosis.

Electrocardiogram

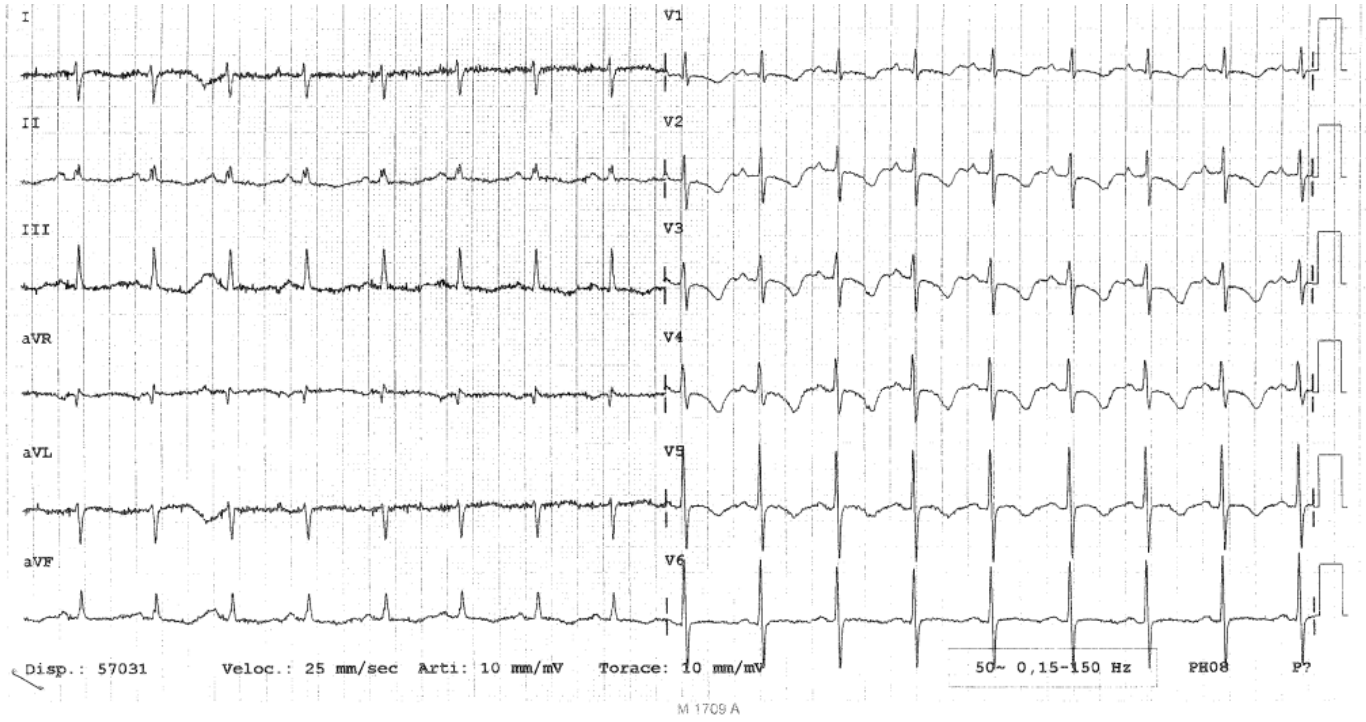
Table 8 Electrocardiogram abnormalities in patients with pulmonary hypertension

Typical ECG abnormalities in PH[66]
• P pulmonale (P >0.25 mV in lead II)
• Right or sagittal axis deviation (QRS axis >90° or indeterminable)
• RV hypertrophy (R/S >1, with R >0.5 mV in V1; R in V1 + S in lead V5 >1 mV)
• Right bundle branch block—complete or incomplete (qR or rSR patterns in V1)
• RV strain pattern[a] (ST depression/T-wave inversion in the right pre-cordial V1–4 and inferior II, III, aVF leads)
• Prolonged QTc interval (unspecific)[b]

ECG, electrocardiogram; PH, pulmonary hypertension; QTc, corrected QT interval; RV, right ventricular.

[a]Present in advanced PH.

[b]Patients with pulmonary arterial hypertension can present with a prolonged QTc interval (although non-specific), which may reflect RV dysfunction and delayed myocardial repolarization, and is an independent predictor of mortality.[67]

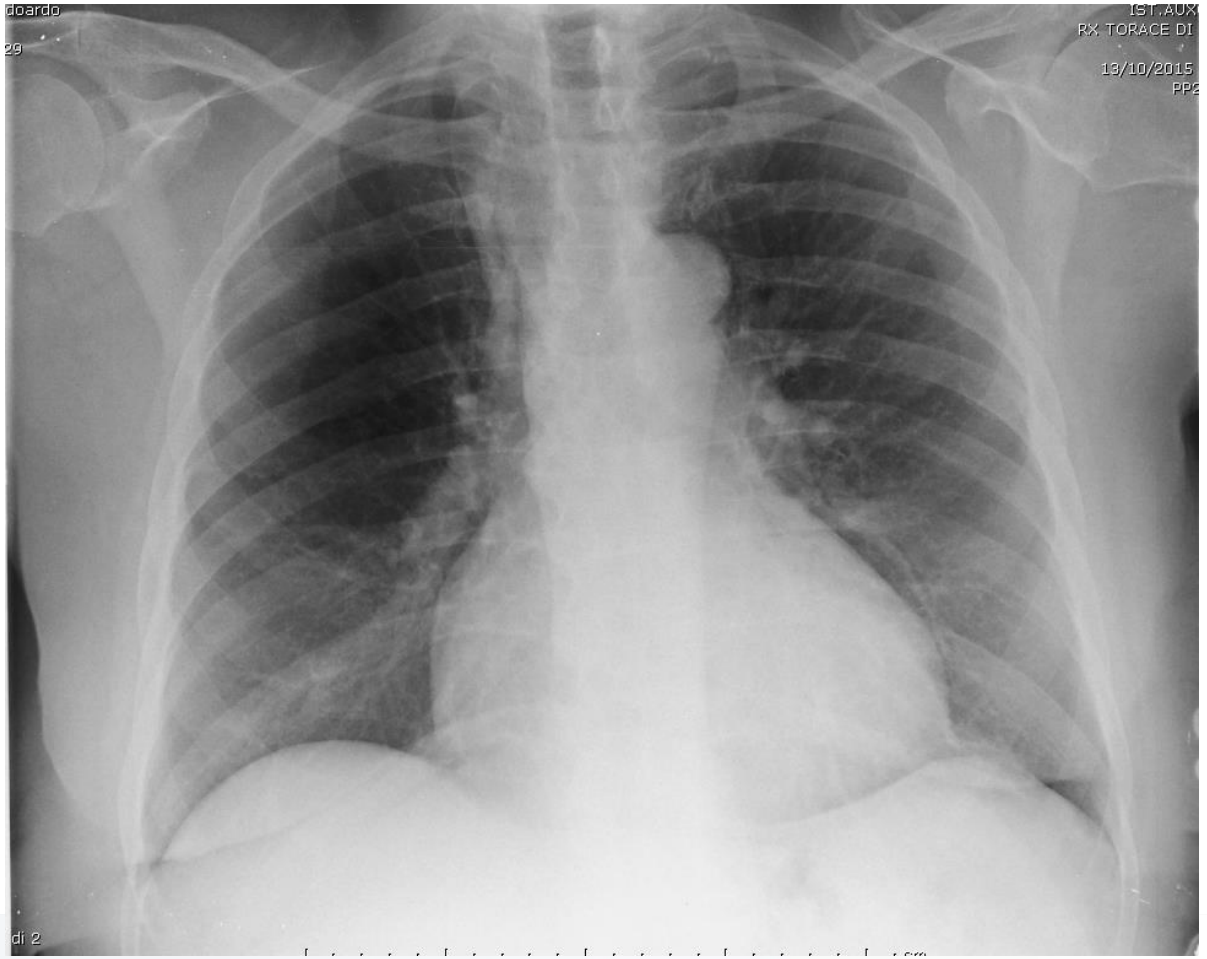


Chest X-ray

Table 9 Radiographic signs of pulmonary hypertension and concomitant abnormalities

Signs of PH and concomitant abnormalities	Signs of left heart disease/ pulmonary congestion	Signs of lung disease
Right heart enlargement	Central air space opacification	Flattening of diaphragm (COPD/ emphysema)
PA enlargement (including aneurysmal dilatation)	Interlobular septal thickening 'Kerley B' lines	Hyperlucency (COPD/ emphysema)
Pruning of the peripheral vessels	Pleural effusions	Lung volume loss (fibrotic lung disease)
'Water-bottle' shape of cardiac silhouette[a]	Left atrial enlargement (including splayed carina) Left ventricular dilation	Reticular opacification (fibrotic lung disease)

COPD, chronic obstructive pulmonary disease; PA, pulmonary artery; PH, pulmonary hypertension.
[a]May be present in patients with PH with advanced right ventricular failure and moderate pericardial effusion.



Agenda

- Physiology of the pulmonary circulation and of the right ventricle (RV) → understanding RV failure
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- Pulmonary Hypertension (PH): hemodynamic and clinical definition
- Clinical manifestations and findings
- **Diagnostic approach**
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    - PH associated with left heart diseases
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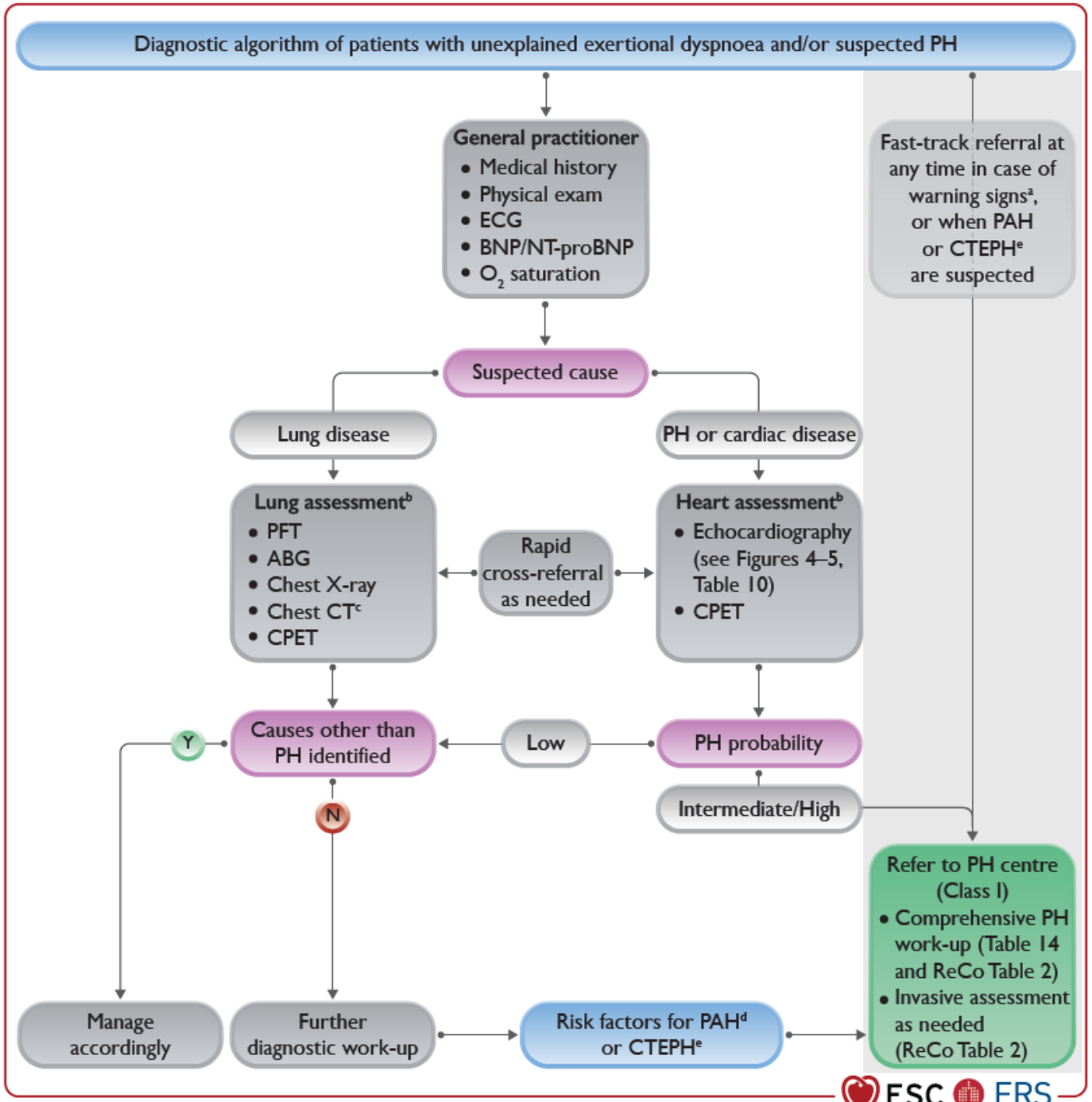
PH: diagnostic approach

The diagnostic approach to PH is mainly focused on two tasks.

The primary goal is to raise **early suspicion** of PH and ensure **fast-track referral** to PH centres in patients with a high likelihood of PAH, CTEPH, or other forms of severe PH.

The second objective is to **identify underlying diseases**, especially LHD (group 2 PH) and lung disease (group 3 PH), as well as comorbidities, to ensure proper classification, risk assessment, and treatment.


Diagnostic algorithm of patients with unexplained exertional dyspnoea and/or suspected PH
General practitioner
• Medical history
• Physical exam
• ECG
• BNP/NT-proBNP
• O_2 saturation
Fast-track referral at any time in case of warning signs[a], or when PAH or CTEPH[e] are suspected
Suspected cause
Lung disease
PH or cardiac disease
Lung assessment[b]
• PFT
• ABG
• Chest X-ray
• Chest CT[c]
• CPET
Rapid cross-referral as needed
Heart assessment[b]
• Echocardiography (see Figures 4–5, Table 10)
• CPET
Y
Causes other than PH identified
Low
PH probability
N
Intermediate/High
Refer to PH centre (Class I)
• Comprehensive PH work-up (Table 14 and ReCo Table 2)
• Invasive assessment as needed (ReCo Table 2)
Manage accordingly
Further diagnostic work-up
Risk factors for PAH[d] or CTEPH[e]
ESC ERS

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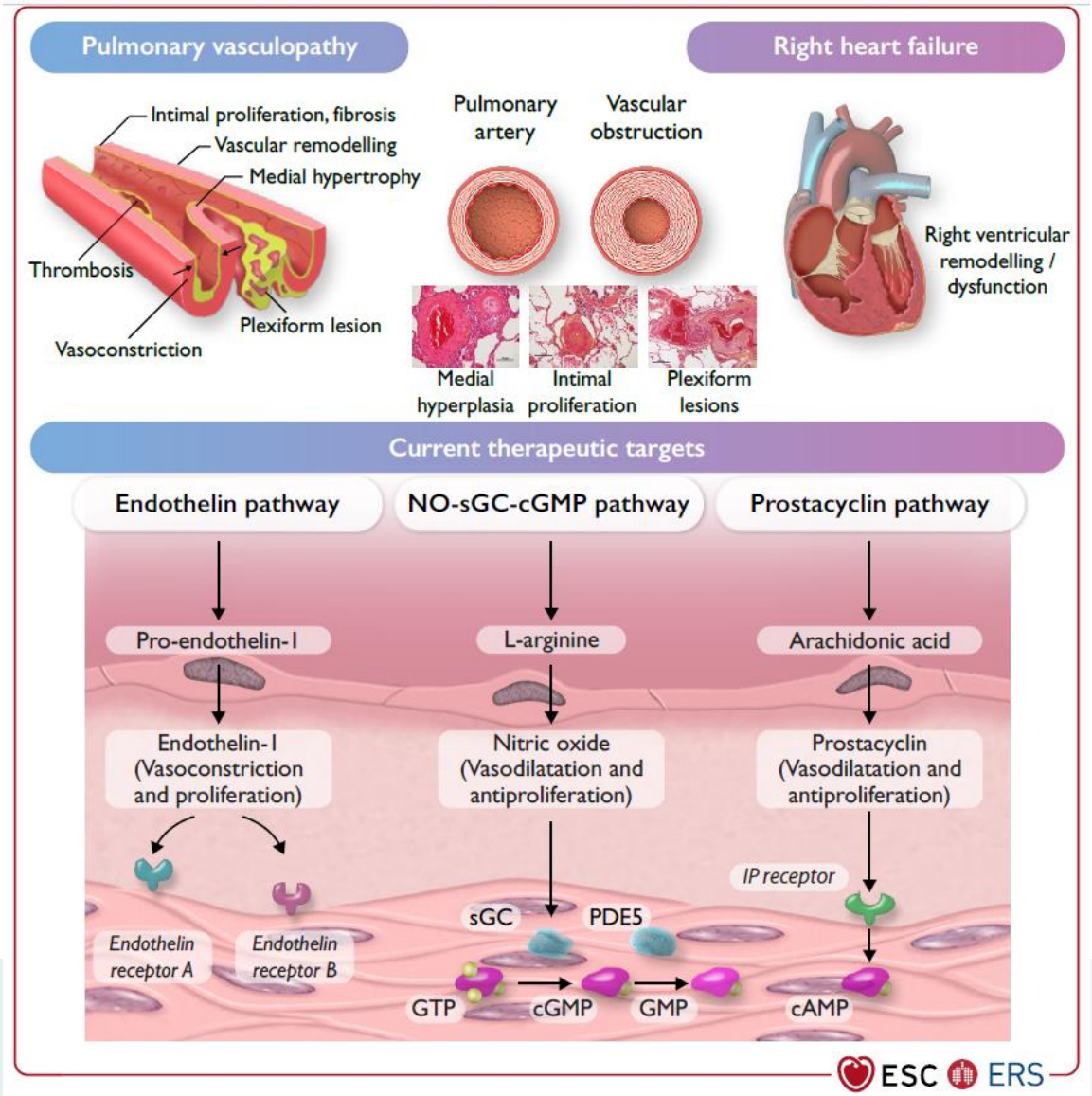
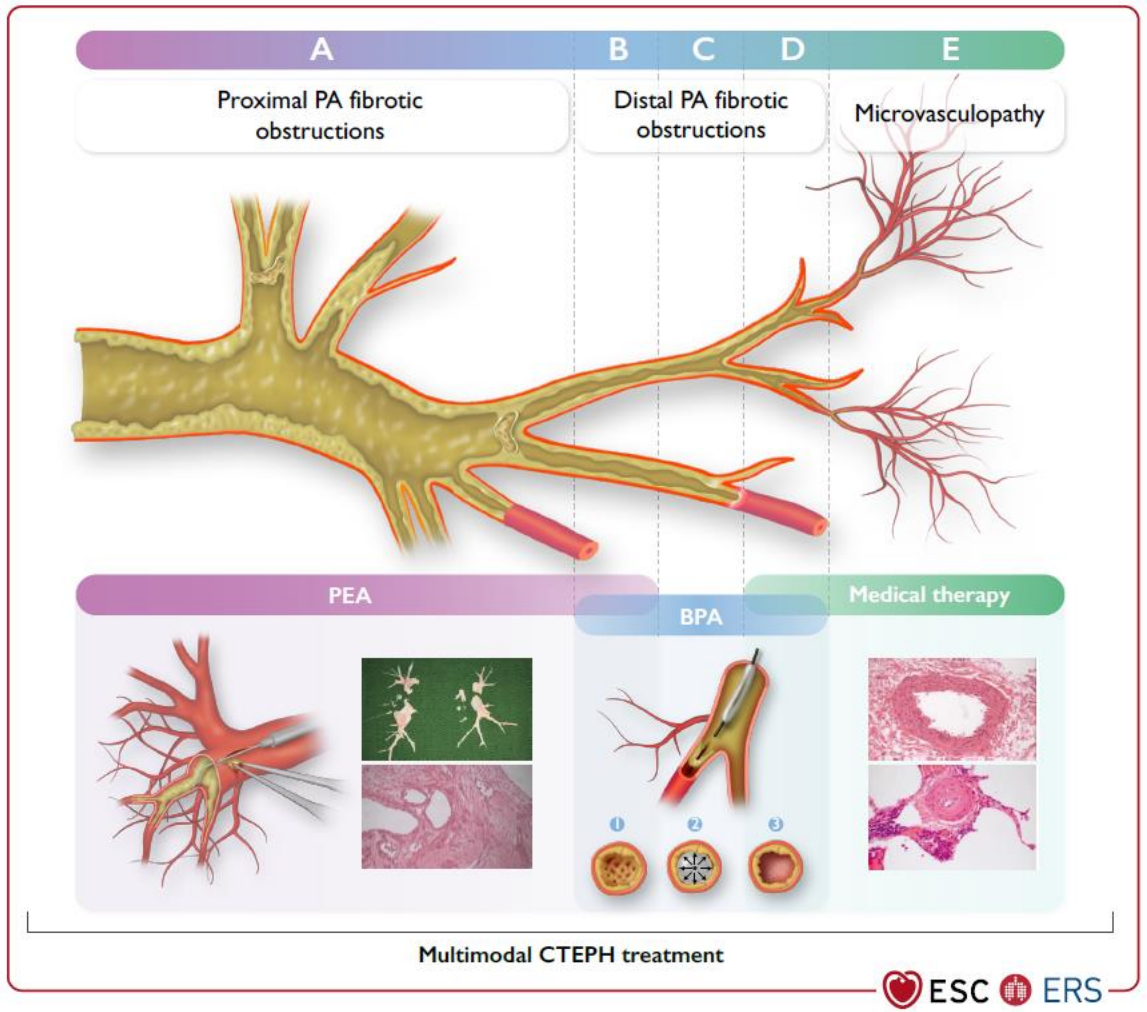
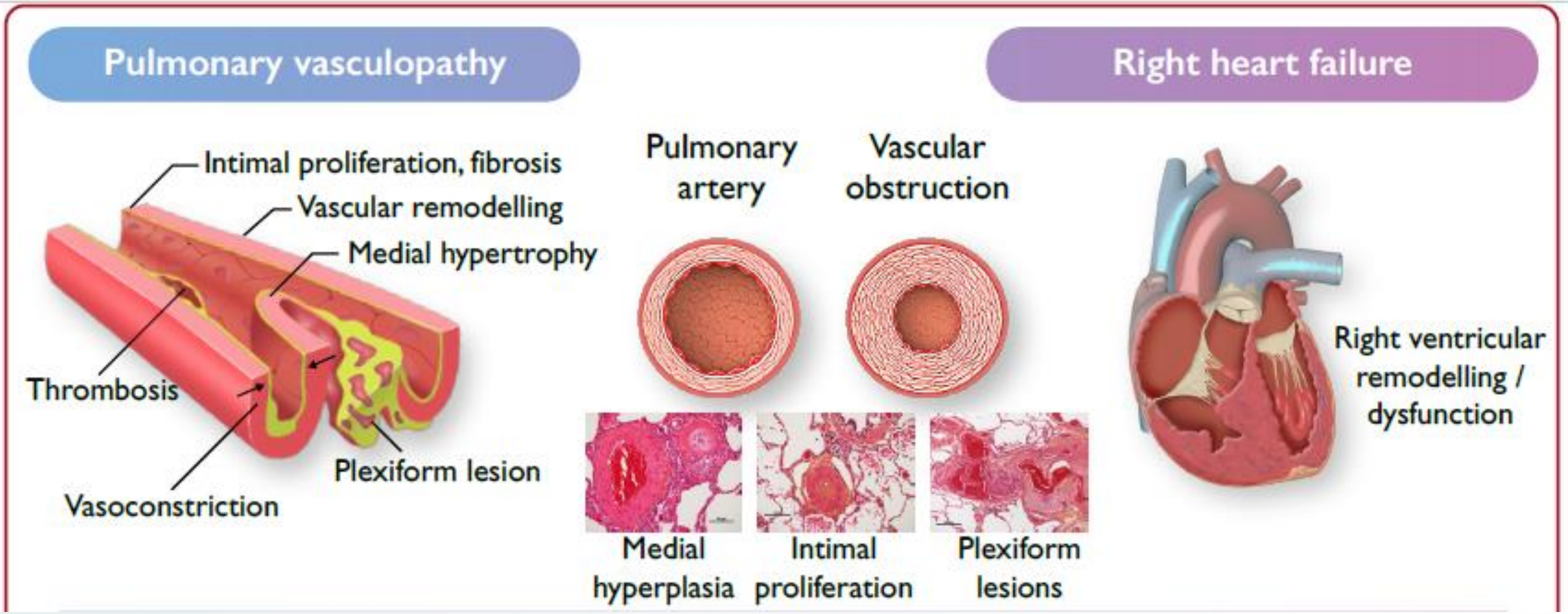
Pulmonary vascular diseases: PAH and CTEPH





Pulmonary Arterial Hypertension (PAH)



Pulmonary arterial hypertension (PAH) Epidemiology

In Europe, PAH prevalence and incidence are in the range of 15–60 subjects per million population and 5–10 cases per million per year, respectively

Mean age at diagnosis between 50 and 65 years in current registries.

Female predominance is quite variable among registries and may not be present in elderly patients

Pulmonary Arterial Hypertension (PAH)
Clinical classification

GROUP 1 Pulmonary arterial hypertension (PAH)

- 1.1 Idiopathic
  - 1.1.1 Non-responders at vasoreactivity testing
  - 1.1.2 Acute responders at vasoreactivity testing
- 1.2 Heritable[a]
- 1.3 Associated with drugs and toxins[a]
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
- 1.6 Persistent PH of the newborn

IPAH: 50-60% of PAH

Table 13 Phenotypic features associated with pulmonary arterial hypertension mutations

Gene	Pulmonary hypertension phenotypic association	Putative molecular mechanism	Inheritance pattern	Potential distinguishing clinical and examination features	Investigations	Populations	Reference
BMPR2	Heritable and idiopathic PAH	Haploinsufficiency	Autosomal dominant	No specific or diagnostic clinical features described	No discriminative investigations described	Paediatric and adult	152
ATP13A3		Unknown	Autosomal dominant			Adult	149
AQP1		Unknown	Autosomal dominant			Adult	149
ABCC8		Haploinsufficiency	Autosomal dominant			Adult	153
KCNK3		Haploinsufficiency	Autosomal dominant			Adult	154
SMAD9		Haploinsufficiency	Autosomal dominant			Adult	155
Sox17	Heritable and idiopathic PAH Congenital heart disease	Unknown	Autosomal dominant			Paediatric and adult	149
CAV1	Heritable and idiopathic PAH Lipodystrophy	Gain of function; dominant negative	Autosomal dominant	Deficiency of subcutaneous adipose tissue	Fasting triglyceride and leptin levels	Paediatric and adult	156
TBX4	Heritable and idiopathic PAH Small patella syndrome (ischiopatellar dysplasia) Parenchymal lung disease Bronchopulmonary dysplasia Persistent pulmonary hypertension of the neonate	Unknown	Autosomal dominant	Patellar aplasia Skeletal abnormalities, particularly pelvis, knees, and feet	Skeletal X-rays: pelvis, knees, and feet CT chest: diffuse parenchymal lung disease	Paediatric and (less commonly) adult	149,157
EIF2AK4	Pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis	Loss of function	Autosomal recessive	Distal phalangeal clubbing	Reduced DLCO CT chest: interlobular septal thickening and mediastinal lymphadenopathy, and centrilobular ground-glass nodular opacities	Adult	158
KDR	Heritable and idiopathic PAH	Loss of function	Autosomal dominant	No specific or diagnostic clinical features described	Possible reduced DLCO	Older-onset adult	159
ENG	Heritable and idiopathic PAH Hereditary haemorrhagic telangiectasia	Unknown	Autosomal dominant	Telangiectasia Abnormal blood vessel formation Visceral arteriovenous malformations Bleeding diathesis	Iron-deficiency anaemia Presence on imaging of pulmonary, hepatic, cerebral, or spinal arteriovenous malformations Invasive endoscopic assessment of gastrointestinal telangiectasia	Adult and paediatric	160
ACVRL1		Haploinsufficiency	Autosomal dominant			Adult and paediatric	160
GDF2		Haploinsufficiency	Autosomal dominant			Adult and paediatric	149

CT, computed tomography; DLCO, Lung diffusion capacity for carbon monoxide; PAH, pulmonary arterial hypertension.

Drugs and toxins associated with PAH

Definite association	Possible association
Aminorex	Alkylating agents (cyclophosphamide, mitomycin C)[a]
Benfluorex	Amphetamines
Dasatinib	Bosutinib
Dexfenfluramine	Cocaine
Fenfluramine	Diazoxide
Methamphetamines	Direct-acting antiviral agents against hepatitis C virus (sofosbuvir)
Toxic rapeseed oil	Indirubin (Chinese herb Qing-Dai)
	Interferon alpha and beta
	Leflunomide
	L-tryptophan
	Phenylpropanolamine
	Ponatinib
	Selective proteasome inhibitors (carfilzomib)
	Solvents (trichloroethylene)[a]
	St John's Wort

Medical conditions associated with PAH

GROUP 1 Pulmonary arterial hypertension (PAH)

- 1.1 Idiopathic
  - 1.1.1 Non-responders at vasoreactivity testing
  - 1.1.2 Acute responders at vasoreactivity testing
- 1.2 Heritable[a]
- 1.3 Associated with drugs and toxins[a]
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease **Annual incidence: 0,7-1,5%; prevalence: 5-19% → SCREENING**
  - 1.4.2 HIV infection **Prevalence: 0,5%**
  - 1.4.3 Portal hypertension **Prevalence: 1-2%**
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
- 1.6 Persistent PH of the newborn

Medical conditions associated with PAH

Table 21 Clinical classification of pulmonary arterial hypertension associated with congenital heart disease

(1) Eisenmenger syndrome
Includes all large intra- and extracardiac defects that begin as systemic-to-pulmonary shunts and progress to severely elevated PVR and to reverse (pulmonary-to-systemic) or bidirectional shunting. Cyanosis, secondary erythrocytosis, and multiple organ involvement are usually present. Closing the defects is contraindicated.

(2) PAH associated with prevalent systemic-to-pulmonary shunts
- Correctable[a]
- Non-correctable

Include moderate-to-large defects. PVR is mildly to moderately increased and systemic-to-pulmonary shunting is still prevalent, whereas cyanosis at rest is not a feature.

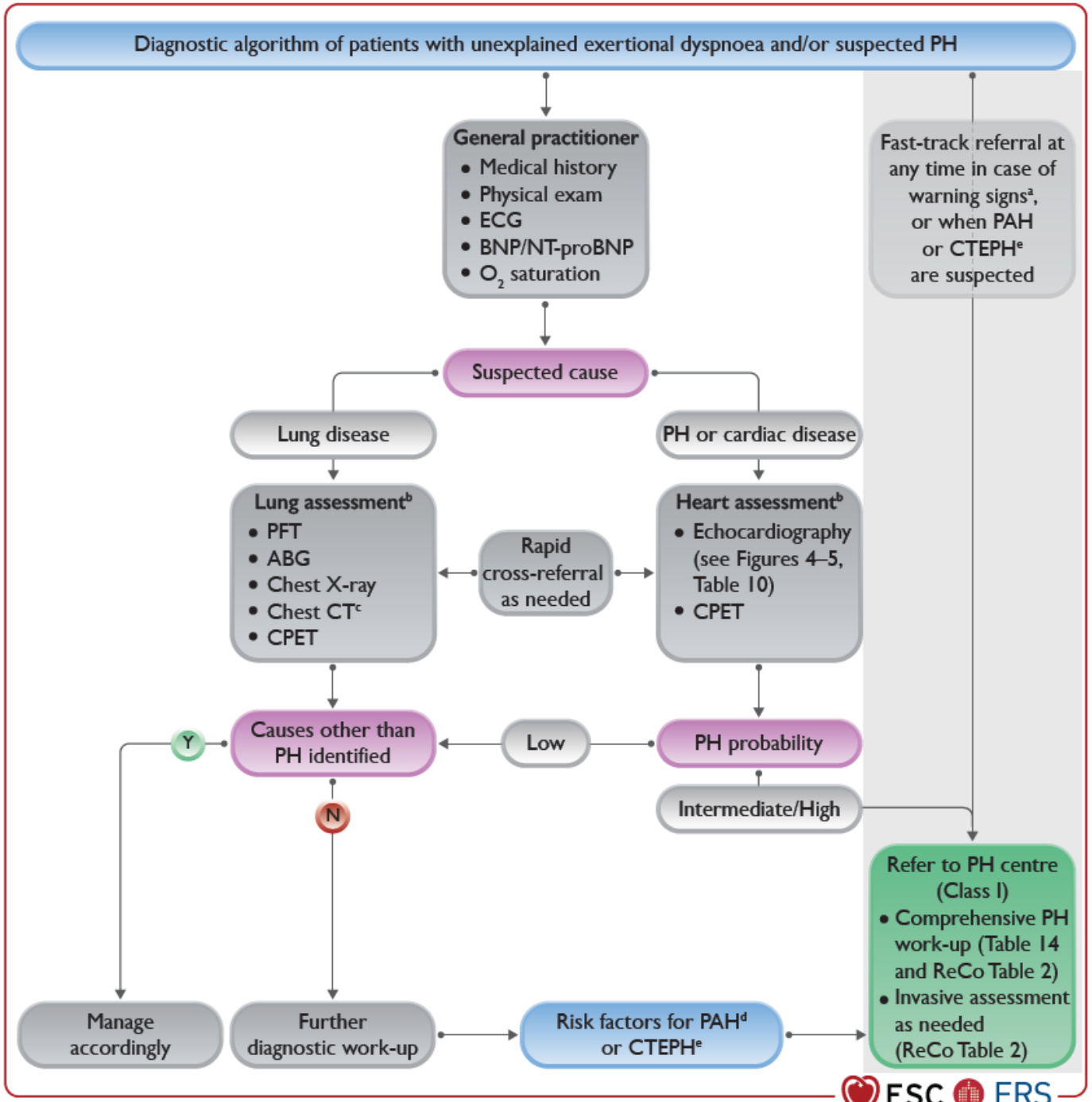
(3) PAH with small/coincidental[b] defects
Markedly elevated PVR in the presence of cardiac defects considered haemodynamically non-significant (usually ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echocardiography), which themselves do not account for the development of elevated PVR. The clinical picture is very similar to IPAH. Closing the defects is contraindicated.

(4) PAH after defect correction
Congenital heart disease is repaired, but PAH either persists immediately after correction or recurs/develops months or years after correction in the absence of significant, post-operative, haemodynamic lesions.

IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance.

Pulmonary arterial hypertension associated with adult CHD is included in group 1 of the PH clinical classification and represents a heterogeneous patient population.

Post-capillary PH in adult CHD should be excluded to determine further management.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• Physical exam
• ECG
• BNP/NT-proBNP
• O_2 saturation
Fast-track referral at any time in case of warning signs[a], or when PAH or CTEPH[e] are suspected
Suspected cause
Lung disease
PH or cardiac disease
Lung assessment[b]
• PFT
• ABG
• Chest X-ray
• Chest CT[c]
• CPET
Rapid cross-referral as needed
Heart assessment[b]
• Echocardiography (see Figures 4–5, Table 10)
• CPET
Y
Causes other than PH identified
Low
PH probability
N
Intermediate/High
Refer to PH centre (Class I)
• Comprehensive PH work-up (Table 14 and ReCo Table 2)
• Invasive assessment as needed (ReCo Table 2)
Manage accordingly
Further diagnostic work-up
Risk factors for PAH[d] or CTEPH[e]
ESC ERS

Comprehensive work-up

Clinical history

Oxygen requirement for hypoxemia

Chest radiograph

Pulmonary function test and arterial blood gas analysis

Echocardiography

Lung scintigraphy

Chest CT

Cardiopulmonary exercise testing

Right heart catheterization

Comprehensive work-up

Clinical history

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Right heart catheterization

Vasoreactivity testing

GROUP 1 Pulmonary arterial hypertension (PAH)

1.1 Idiopathic

1.1.1 Non-responders at vasoreactivity testing

1.1.2 Acute responders at vasoreactivity testing

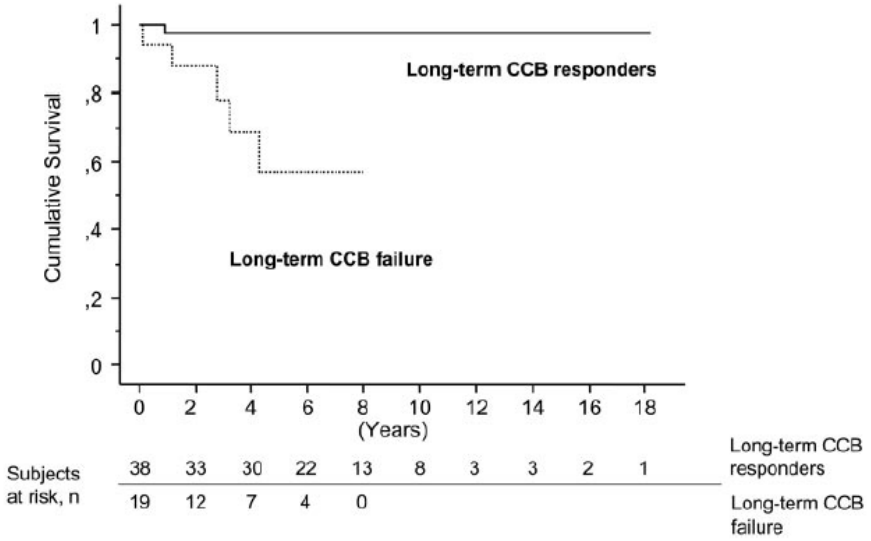
Candidates:

Pre-capillary PH (suspicion of idiopathic/heritable PAH or PAH associated to drugs or toxins)

Which molecule(s):

Inhaled nitric oxide 10-20 ppm

(IV Epoprostenol 2–12 ng/kg/min)



Responder to vasoreactivity testing:

mPAP reduction ≥ 10 mmHg, with a mPAP ≤ 40 mmHg and increased/stable cardiac output

Galiè N et al. PH ESC Guidelines 2015
Sitbon O et al. Circulation 2005

Comprehensive work-up

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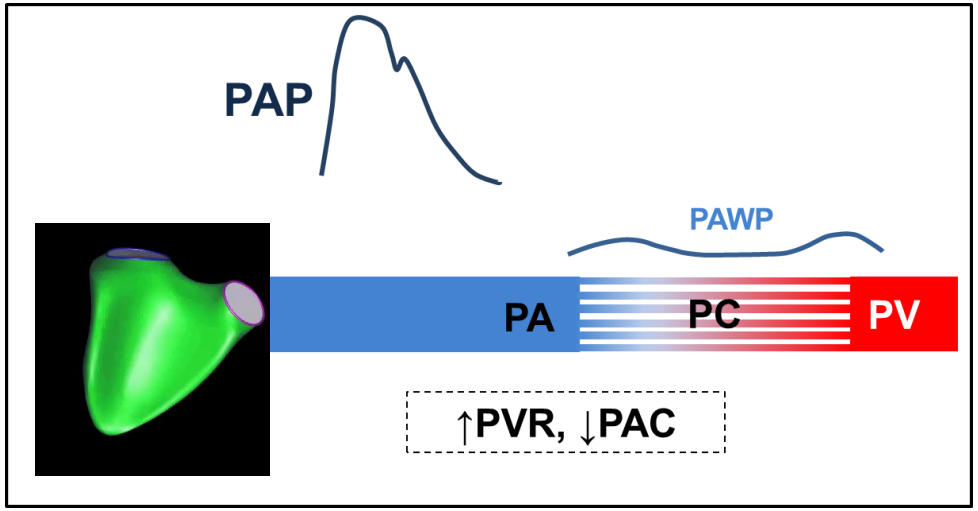
Right heart catheterization

Multiparametric risk stratification in PAH at diagnosis

	Determinants of prognosis (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
	Clinical observations and modifiable variables			
clinical	Signs of right HF	Absent	Absent	Present
clinical	Progression of symptoms and clinical manifestations	No	Slow	Rapid
clinical	Syncope	No	Occasional syncope[a]	Repeated syncope[b]
clinical	WHO-FC	I, II	III	IV
functional	6MWD[c]	>440 m	165–440 m	<165 m
functional	CPET	Peak VO_2 >15 mL/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 mL/min/kg (35–65% pred.) VE/VCO_2 slope 36–44	Peak VO_2 <11 mL/min/kg (<35% pred.) VE/VCO_2 slope >44
lab	Biomarkers: BNP or NT-proBNP[d]	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–800 ng/L NT-proBNP 300–1100 ng/L	BNP >800 ng/L NT-proBNP >1100 ng/L
imaging	Echocardiography	RA area <18 cm^2 TAPSE/sPAP >0.32 mm/mmHg No pericardial effusion	RA area 18–26 cm^2 TAPSE/sPAP 0.19–0.32 mm/mmHg Minimal pericardial effusion	RA area >26 cm^2 TAPSE/sPAP <0.19 mm/mmHg Moderate or large pericardial effusion
imaging	cMRI[e]	RVEF >54% SVI >40 mL/m^2 RVESVI <42 mL/m^2	RVEF 37–54% SVI 26–40 mL/m^2 RVESVI 42–54 mL/m^2	RVEF <37% SVI <26 mL/m^2 RVESVI >54 mL/m^2
haemo	Haemodynamics	RAP <8 mmHg CI ≥2.5 $L/min/m^2$ SVI >38 mL/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 $L/min/m^2$ SVI 31–38 mL/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 $L/min/m^2$ SVI <31 mL/m^2 SvO_2 <60%

Clinical	Clinical signs of HF
	Progression of symptoms
	Syncope
	WHO functional class
Functional	6MWD
	CPET
	Peak VO_2
	Peak VO_2
	VE/VCO_2 slope
Lab	NT-proBNP
	BNP
Imaging	Echo, CMR
	RA area
	Pericardial effusion
Hemodynamics	RHC
	RAP
	CI
	SvO2

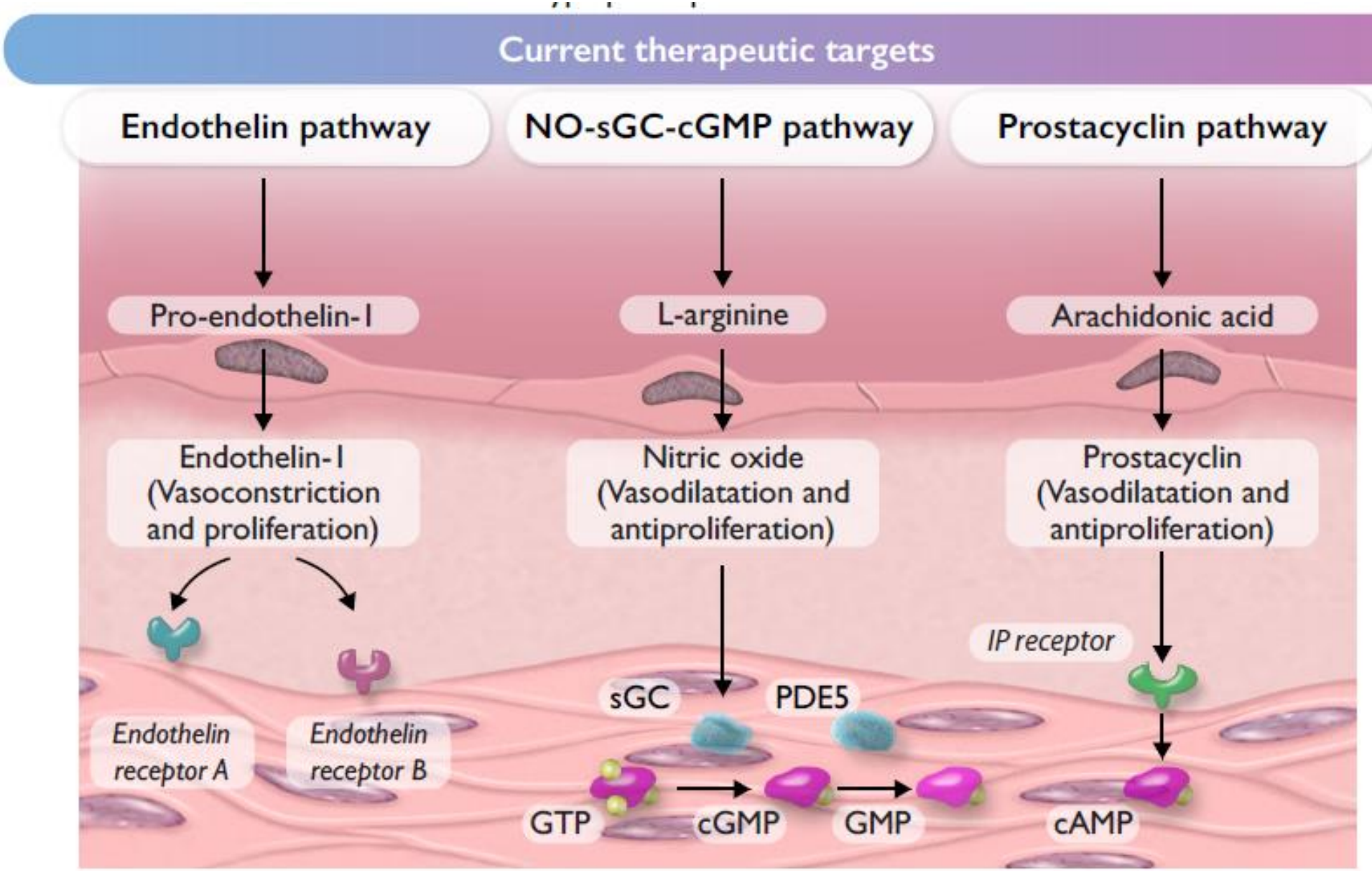


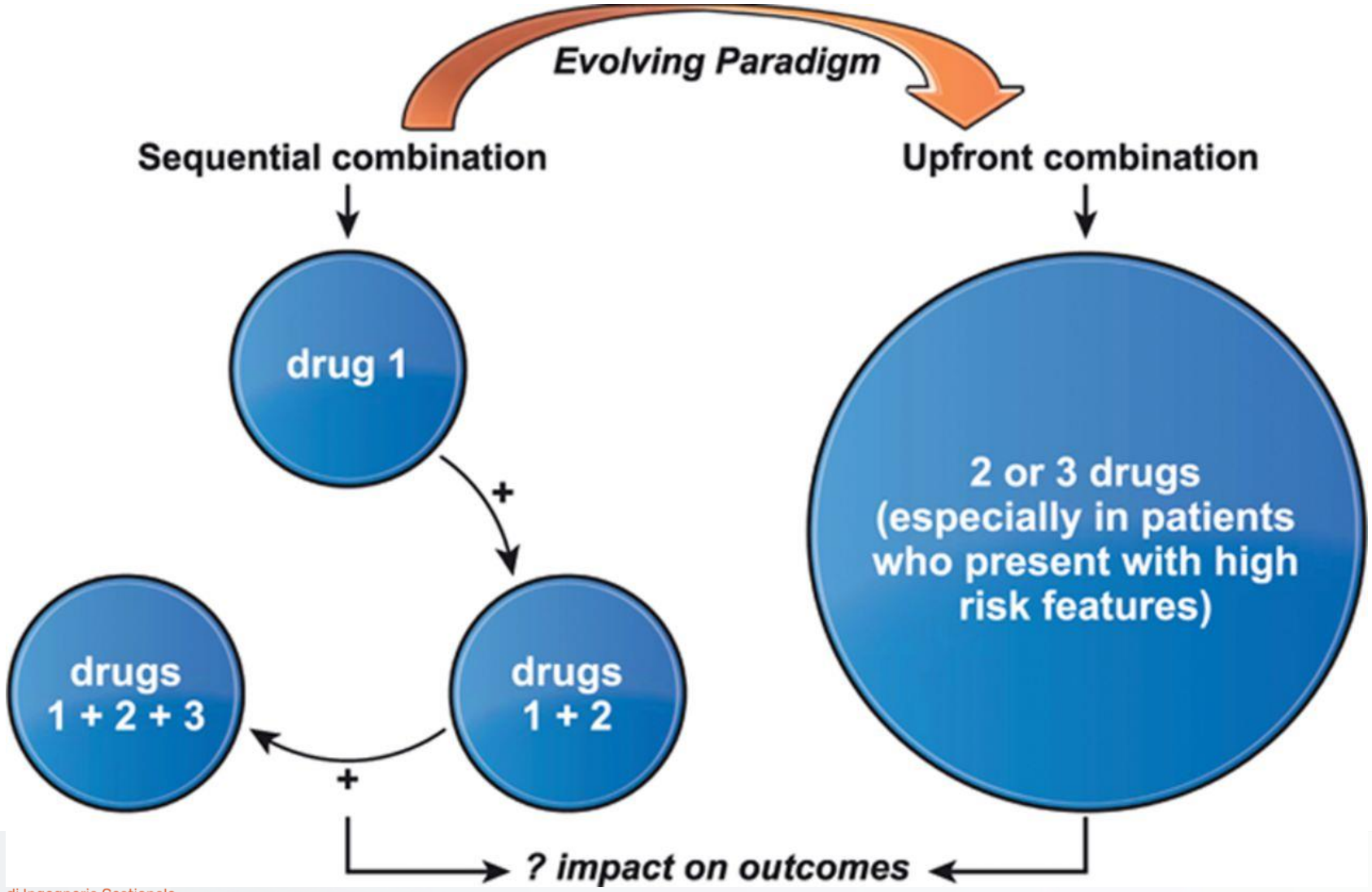
Complementary parameters reflecting **right heart failure**

RV-PA uncoupling

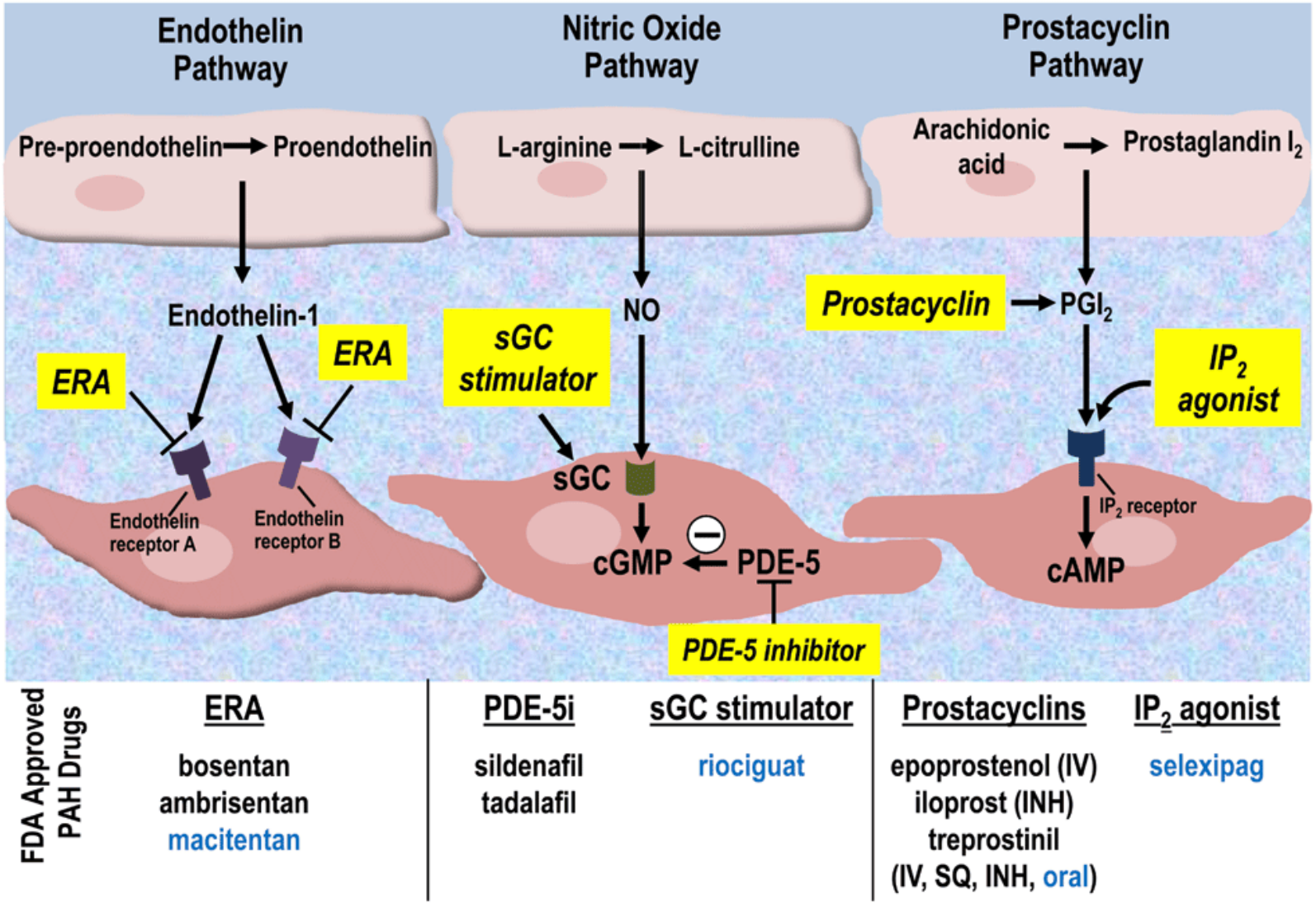
→ «**Failure** of the heart **to pump blood** commensurate with end-organ needs, **or to do so at the expense of high filling pressure**» (at rest or during exercise)

Galiè N et al. Eur Heart J 2015
Braunwald E et al. In: Braunwald E (ed). Heart Disease: A Textbook of Cardiovascular Medicine 1992
Naeije R et al. In: The Right Ventricle in Health and Disease. Springer Science 2015


Current therapeutic targets
Endothelin pathway
NO-sGC-cGMP pathway
Prostacyclin pathway
Pro-endothelin-1
L-arginine
Arachidonic acid
Endothelin-1 (Vasoconstriction and proliferation)
Nitric oxide (Vasodilatation and antiproliferation)
Prostacyclin (Vasodilatation and antiproliferation)
Endothelin receptor A
Endothelin receptor B
IP receptor
sGC
PDE5
GTP
cGMP
GMP
cAMP



10.1161/CIRCULATIONAHA.114.006974



DOI: 10.12688/f1000research.9739.1

PAH: natural history of the disease (1980s)

The estimated median survival of these patients was 2.8 years (95% Cl, 1.9 to 3.7 years).

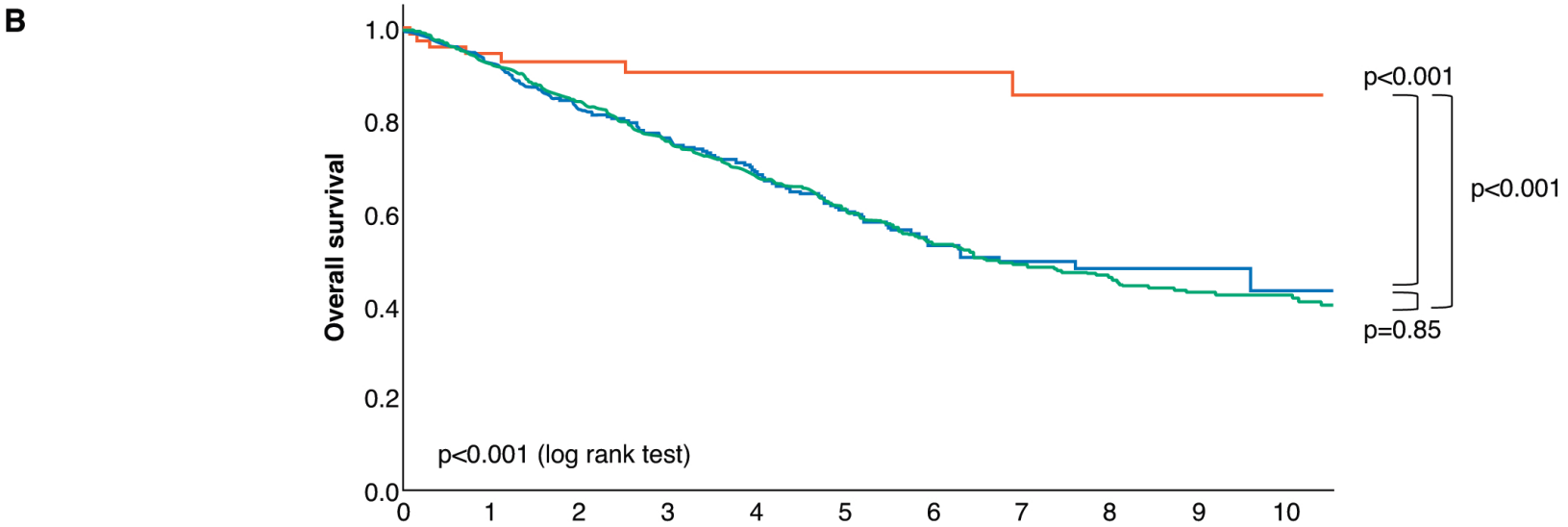
Estimated single-year survival rates were as follows:

at 1 year, 68% (Cl, 61% to 75%);

at 3 years, 48% (Cl, 41% to 55%);

at 5 years, 34% (Cl, 24% to 44%)

The role of triple PAH combination therapy



Patients, at risk (n)

Triple combo	76	59	52	40	30	26	22	17	10	6	1
Dual combo	551	418	299	225	169	115	79	46	24	12	7
Monotherapy	984	786	630	484	369	284	210	161	123	85	61

Overall survival (95% CI)

Triple combo	94% (0.89 – 1.00)	91% (0.83 – 0.98)	91% (0.83 – 0.98)			86% (0.74 – 0.97)
Dual combo	93% (0.90 – 0.95)	76% (0.72 – 0.80)	61% (0.55 – 0.66)			43% (0.33 – 0.54)
Monotherapy	92% (0.91 – 0.94)	76% (0.73 – 0.79)	61% (0.57 – 0.65)			43% (0.38 – 0.47)

Boucly A et al. Am J Respir Crit Care Med 2021

Multiparametric risk stratification in PAH at follow-up

Determinants of prognosis	Low risk	Intermediate–low risk	Intermediate–high risk	High risk
Points assigned	1	2	3	4
WHO-FC	I or II[a]	-	III	IV
6MWD, m	>440	320–440	165–319	<165
BNP or NT-proBNP,[a] ng/L	<50 <300	50–199 300–649	200–800 650–1100	>800 >1100

		Low risk 1-year mortality < 5%
Clinical	Clinical signs of HF	Absent
	Progression of symptoms	No
	Syncope	No
	WHO functional class	I, II
Functional	6MWD	> 440 m
	CPET	
	Peak VO_2	> 15 mL/Kg/min
	Peak VO_2	> 65 of predicted
	VE/VCO_2 slope	< 36
Lab	NT-proBNP	< 300
	BNP	< 50
Imaging	Echo, CMR	
	RA area	< 18 cm^2
	Pericardial effusion	No
Hemodynamics	RAP	< 8 mmHg
	CI	≥ 2.5 L/min/m^2
	SvO2	> 65%

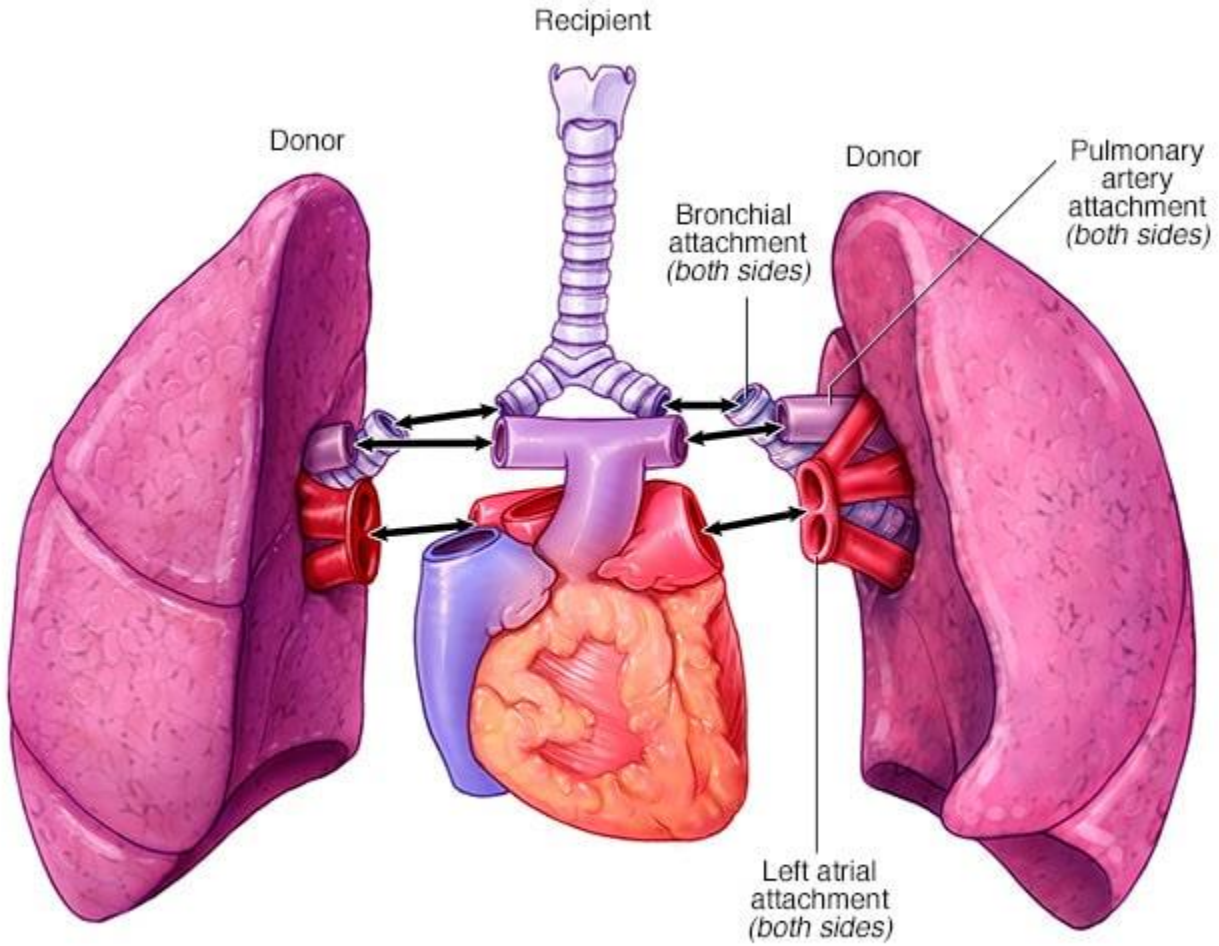
If we are able to modify risk profile with PAH-specific treatments, **we can modify prognosis.**

These treatment goals are **not always realistic** and

- may not be achievable in patients with advanced disease, patients with severe co-morbidities, or very old patients
- should take into account expectations of properly informed patients

Galiè N et al. Eur Respir J 2019
Galiè N et al. Eur Heart J 2015

High risk patients should be evaluated for lung transplant



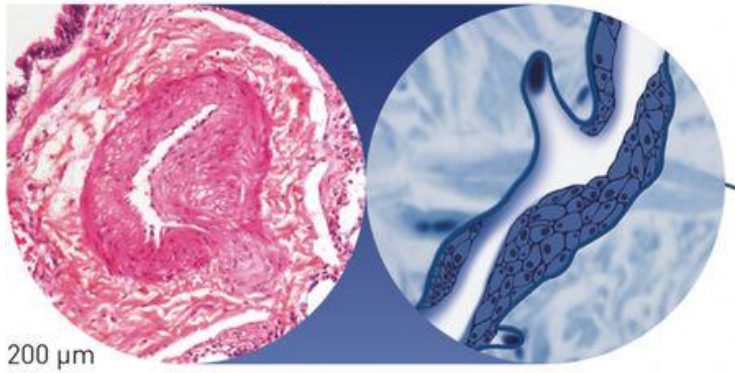
PVOD

GROUP 1 Pulmonary arterial hypertension (PAH)

- 1.1 Idiopathic
  - 1.1.1 Non-responders at vasoreactivity testing
  - 1.1.2 Acute responders at vasoreactivity testing
- 1.2 Heritable[a]
- 1.3 Associated with drugs and toxins[a]
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
- 1.6 Persistent PH of the newborn

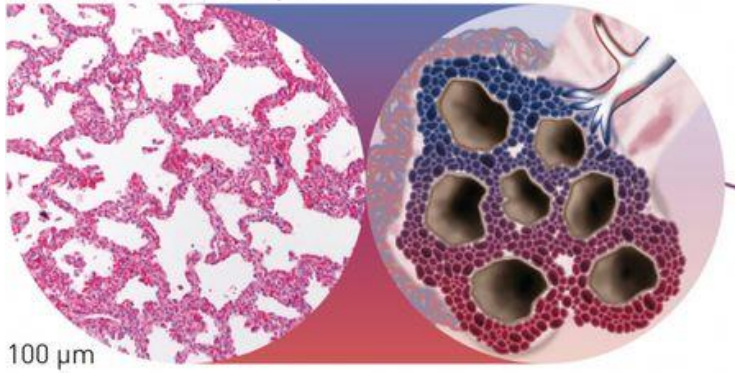
Lesions of PVOD

Pulmonary artery



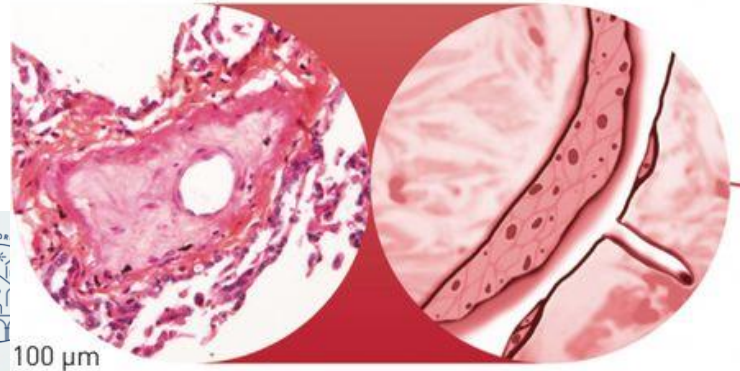
200 µm

Pulmonary capillaries

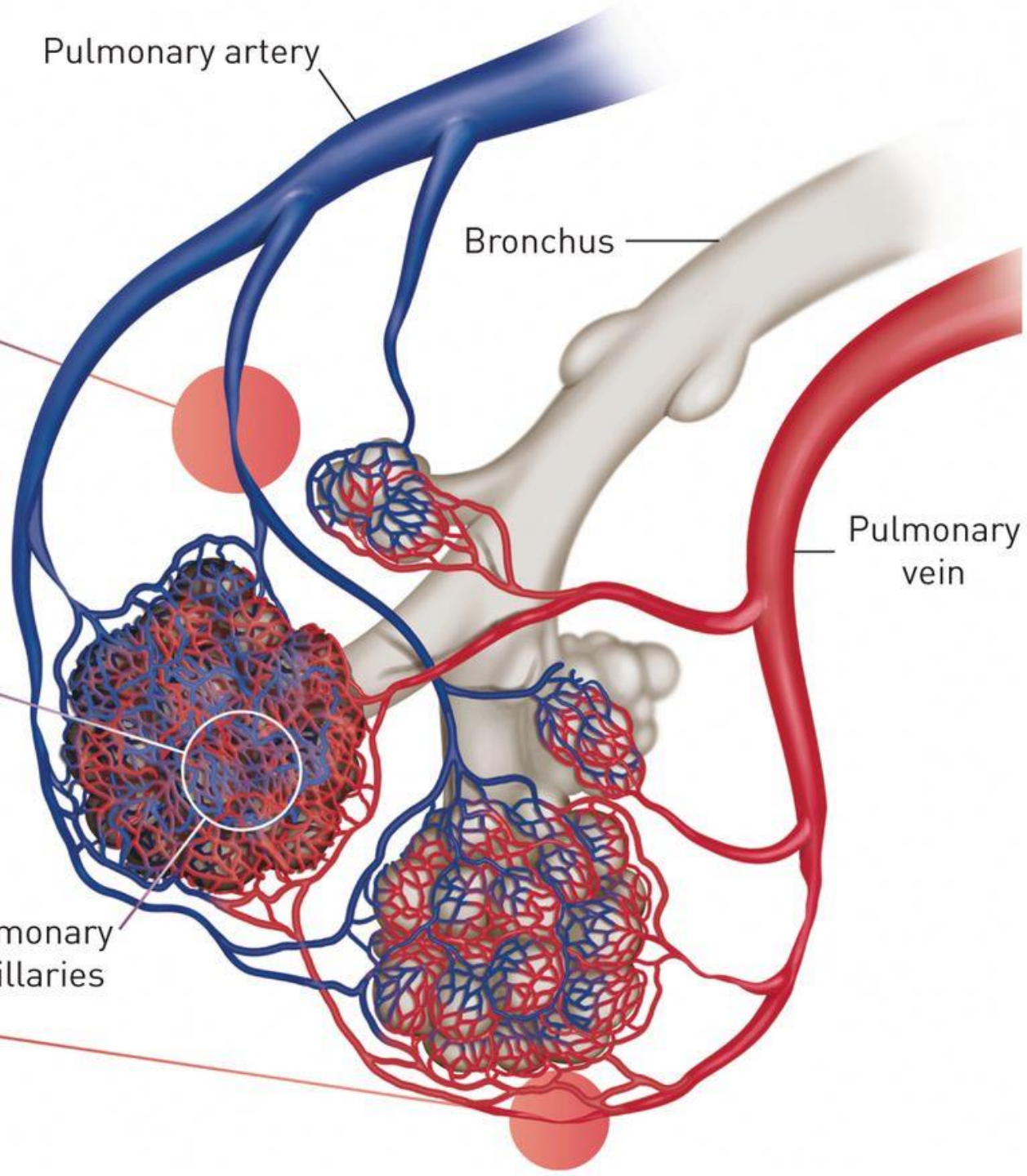


100 µm

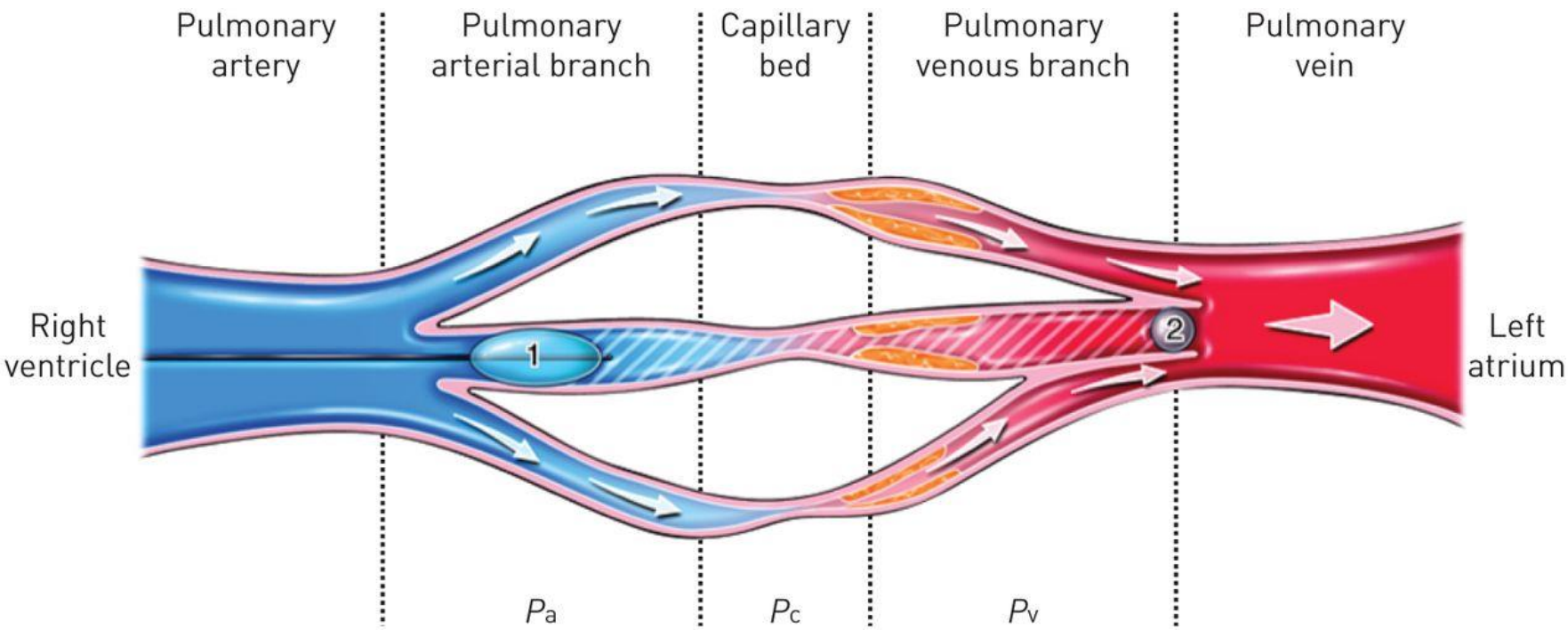
Pulmonary vein



100 µm



PVOD


Pulmonary artery
Pulmonary arterial branch
Capillary bed
Pulmonary venous branch
Pulmonary vein
Right ventricle
1
2
Left atrium
Pa
Pc
Pv

Comprehensive work-up

Clinical history

Oxygen requirement for hypoxemia

Chest radiograph

Pulmonary function test (with **DLCO**) and arterial blood gas analysis

Echocardiography

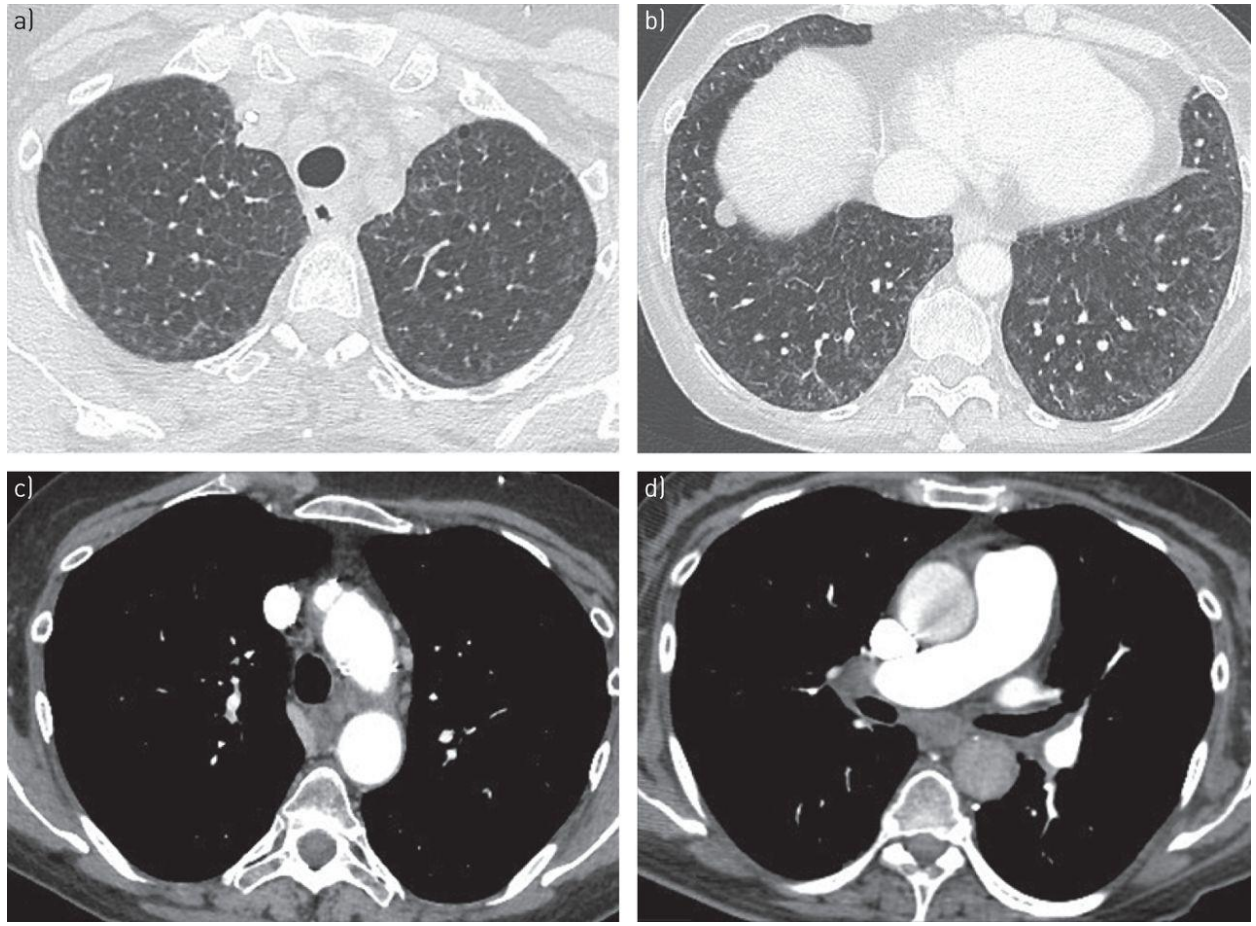
Lung scintigraphy

Chest CT

Cardiopulmonary exercise testing

Right heart catheterization

PVOD



Additional clinical features:
Low pO2
Low DLCO

HRCT features of pulmonary veno-occlusive disease.
a, b) Presence of septal lines and centrilobular ground-glass opacities.
c, d) latero-aortic and subcarinal lymph node enlargement.

Agenda

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- Measures and estimates of pulmonary hemodynamics in clinical practice
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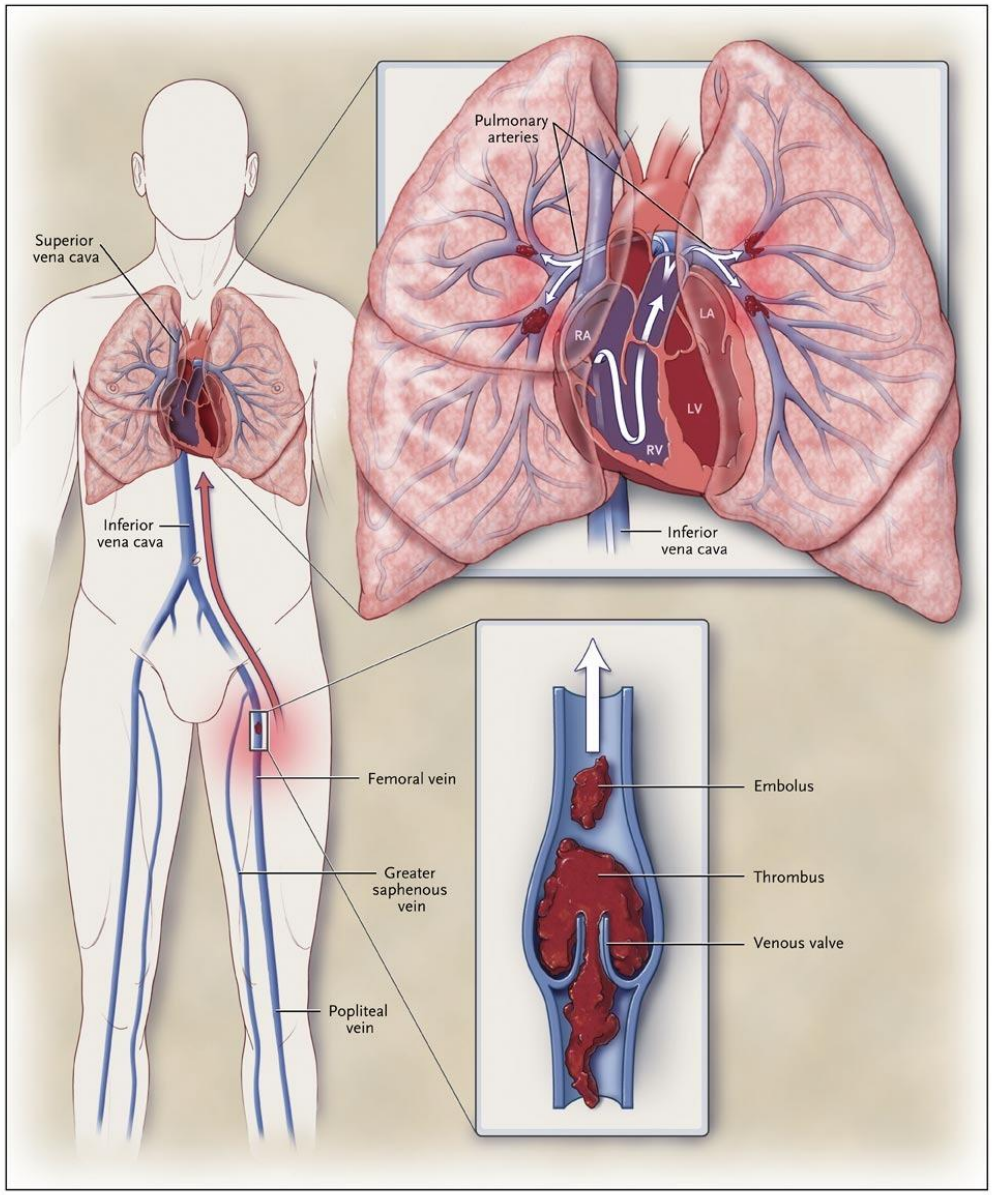
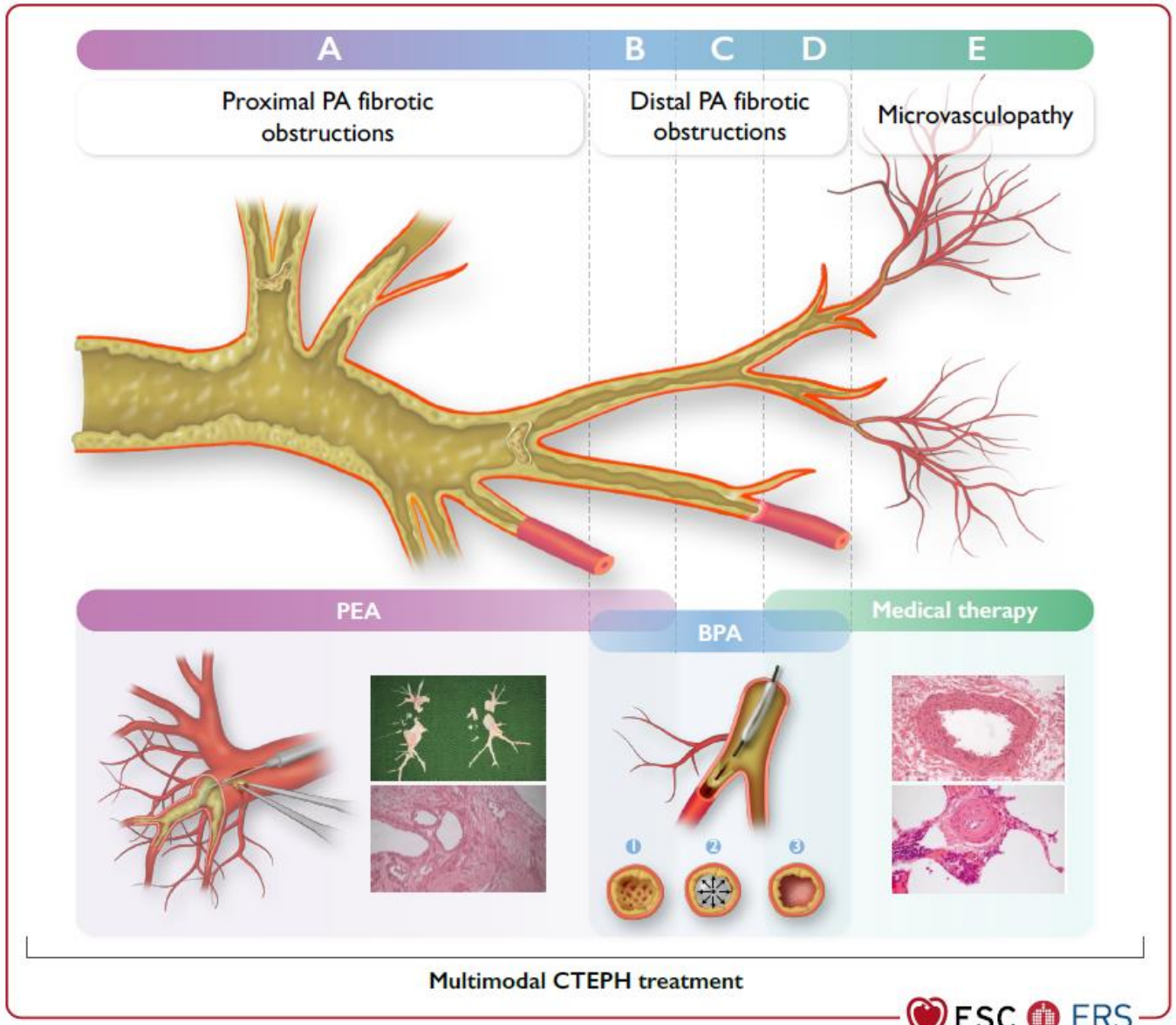
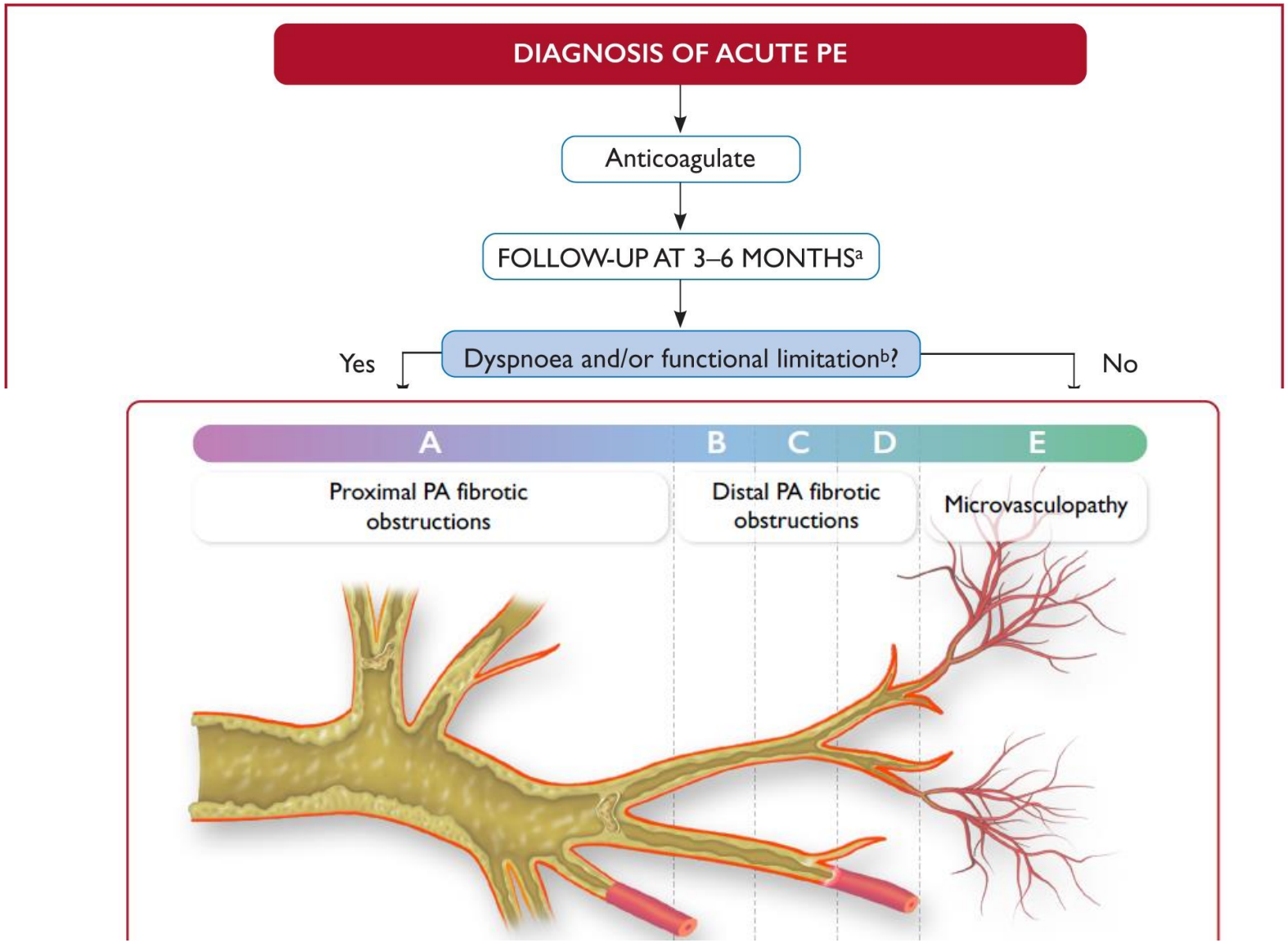
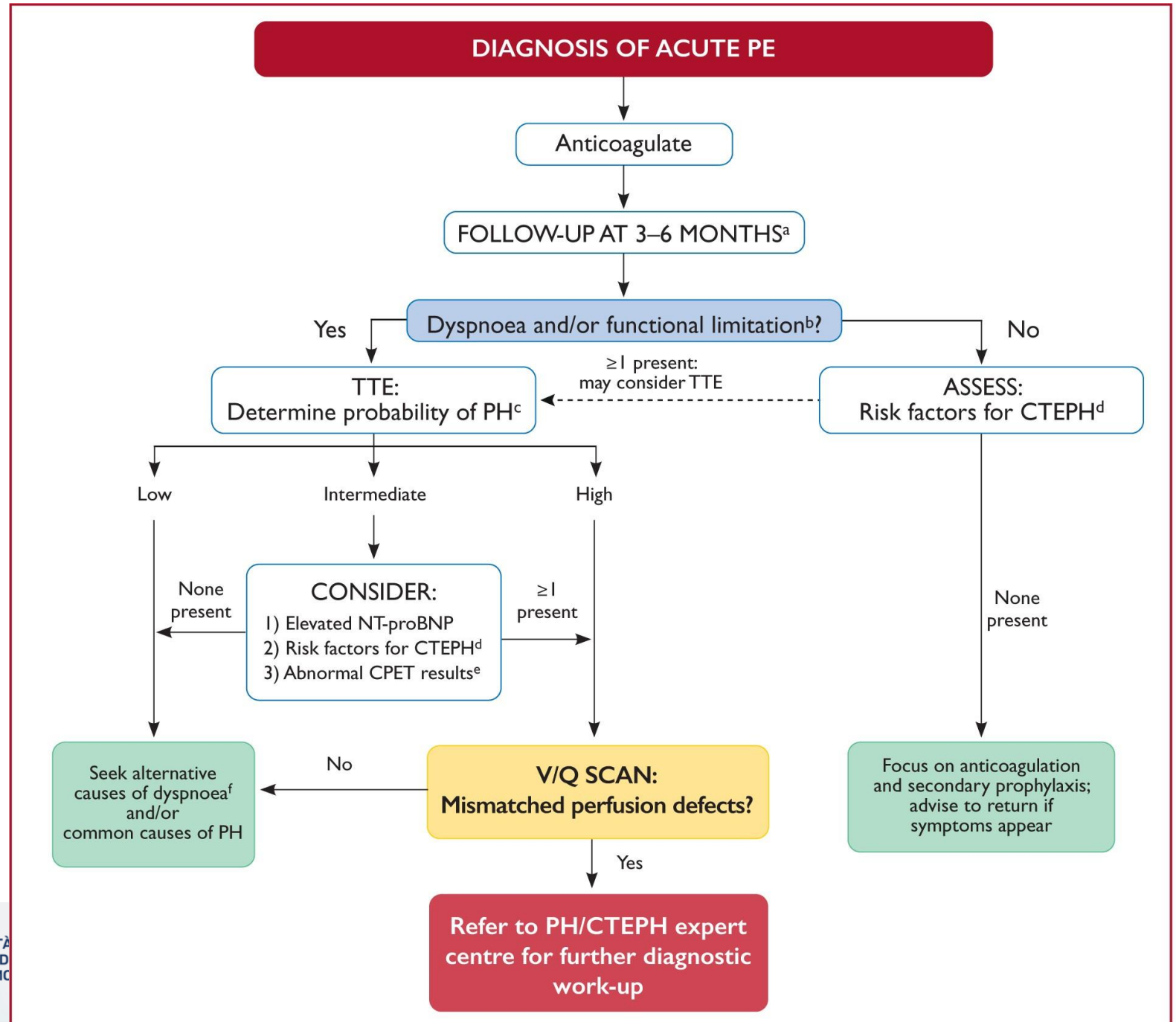
- Importance of clinical history (risk factors), signs and symptoms
- Overview of instrumental findings in PH
- Diagnostic algorithms
- Frequent forms of PH, associated to cardiac and respiratory diseases:
    - PH associated with lung diseases and/or hypoxia
    - PH associated with left heart diseases
- **«True» Pulmonary Vascular Diseases (PVDs):**
    - Pulmonary Arterial Hypertension (PAH)
    - **Chronic Thromboembolic Pulmonary Disease (CTED and CTEPH) vs acute Pulmonary Embolism (PE)**

Acute PE vs CTEPH

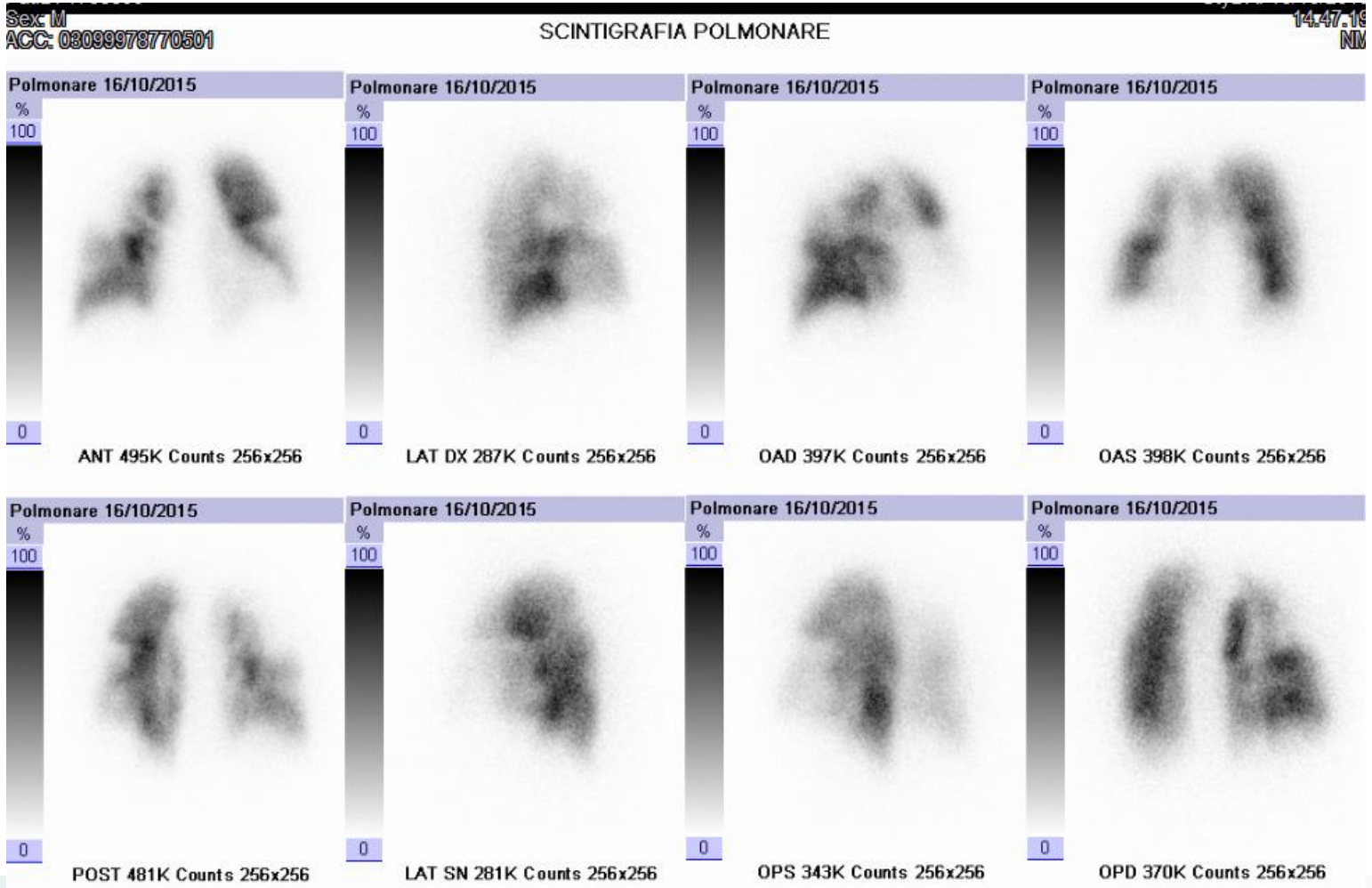





DIAGNOSIS OF ACUTE PE
Anticoagulate
FOLLOW-UP AT 3–6 MONTHS[a]
Dyspnoea and/or functional limitation[b]?
Yes
No
A
B
C
D
E
Proximal PA fibrotic obstructions
Distal PA fibrotic obstructions
Microvasculopathy



Lung scintigraphy



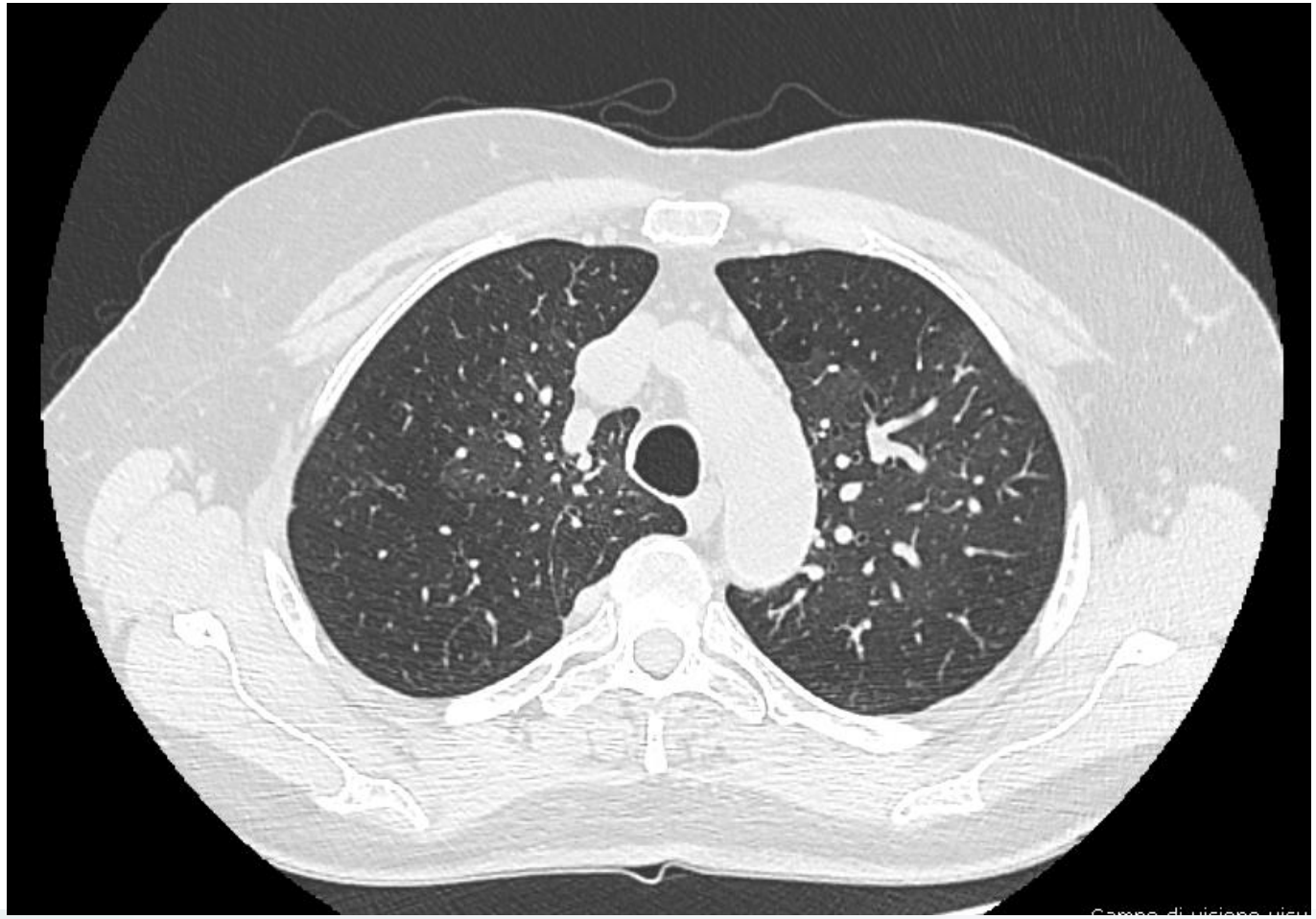
Lung scintigraphy

A ventilation/perfusion (V/Q) lung scan should be performed in patients with PH to look for CTEPH

The V/Q scan has been the screening method of choice for CTEPH because of its higher sensitivity compared with CT pulmonary angiogram (CTPA),

A normal- or low-probability V/Q scan effectively excludes CTEPH with a sensitivity of 90–100% and a specificity of 94–100%;

Chest CT



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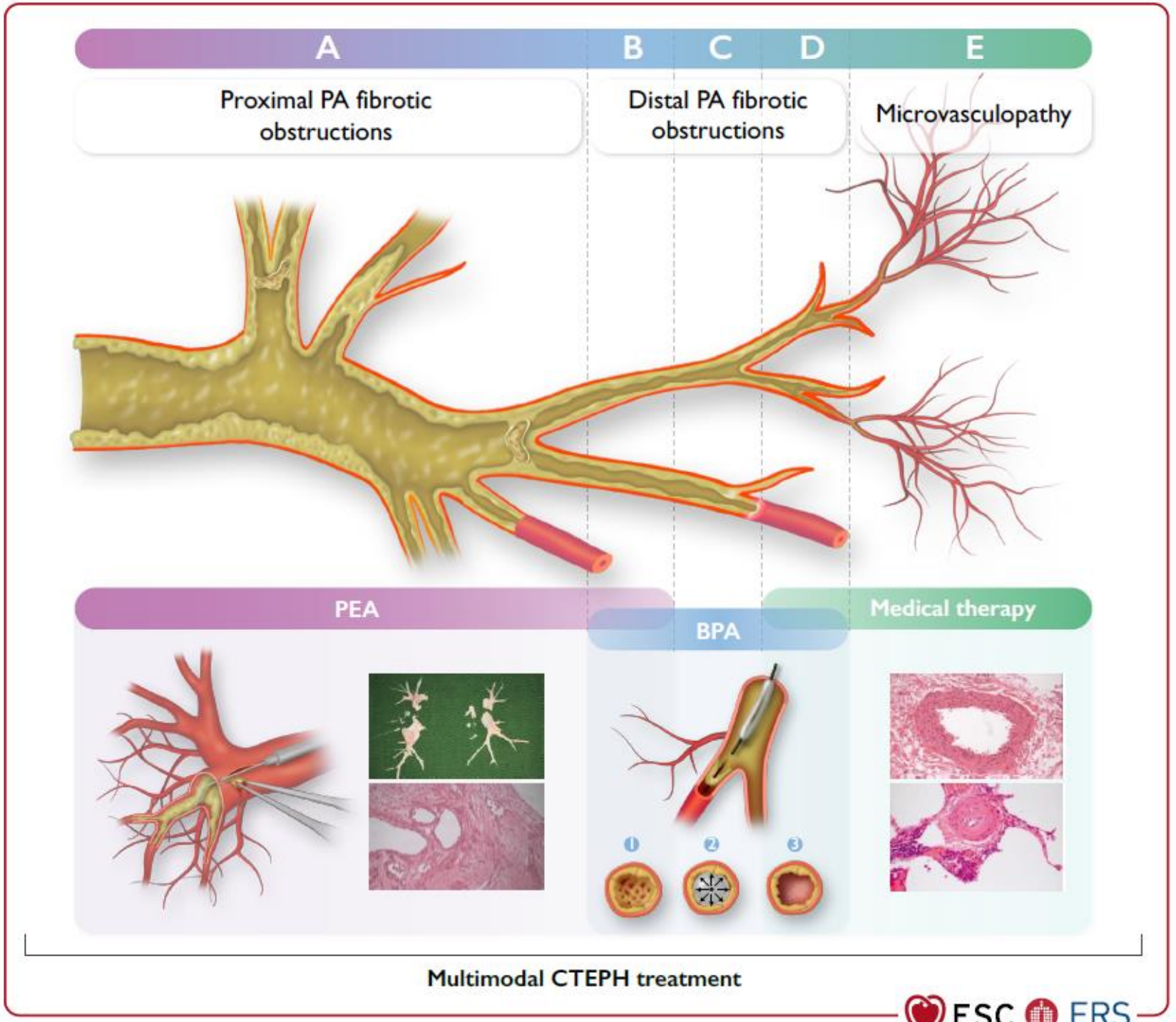
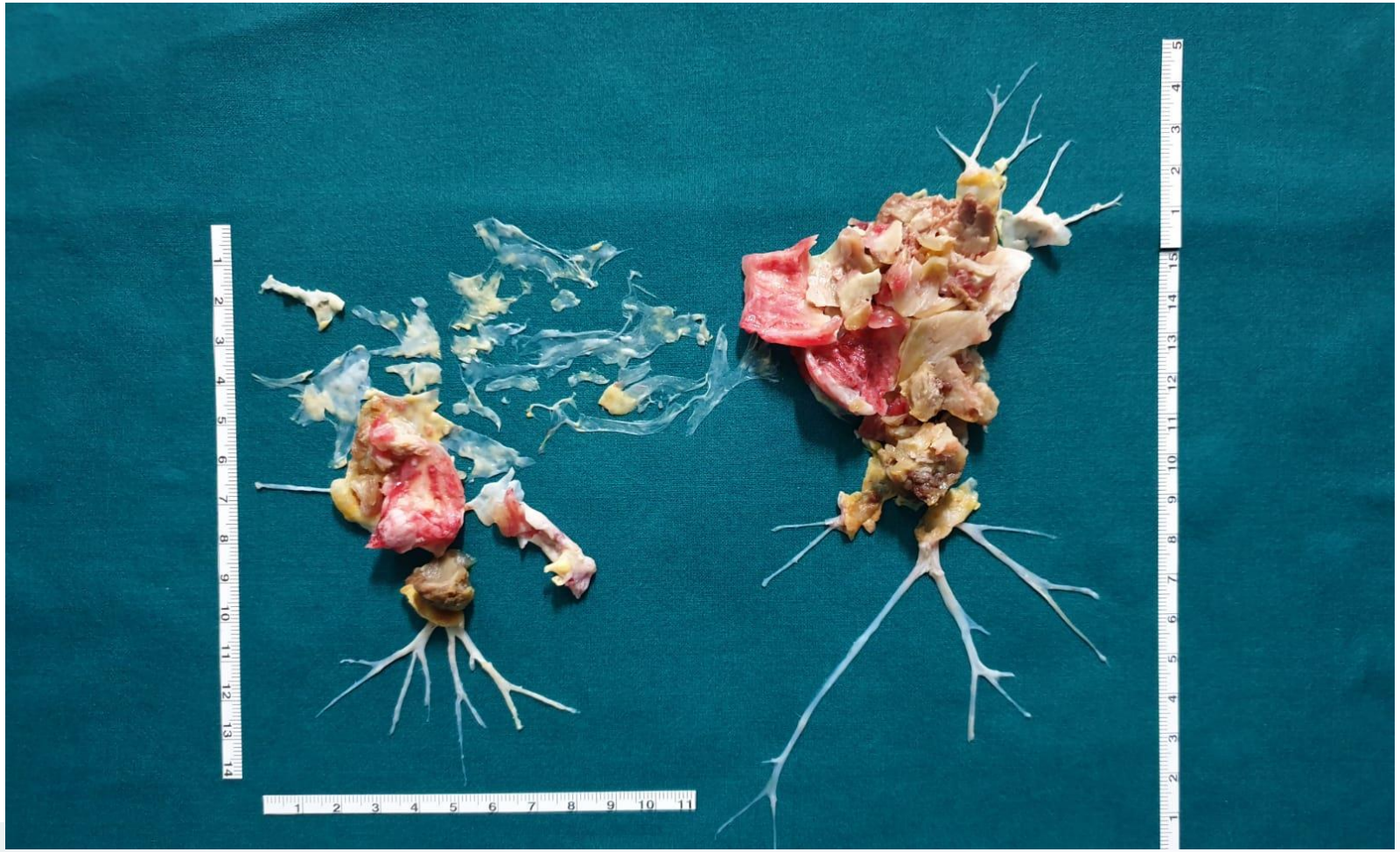
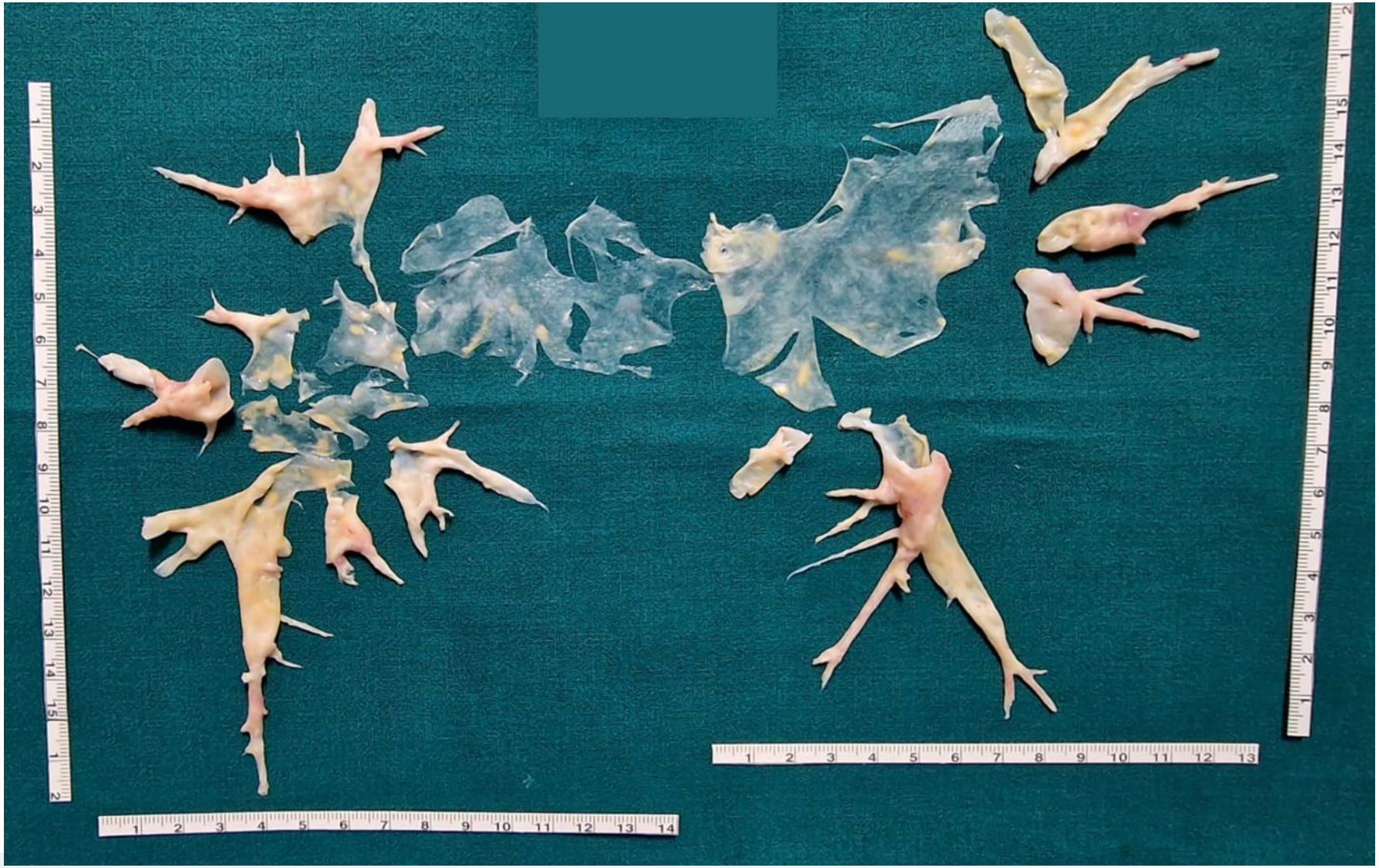
Right heart catheterization



CTEPH treatment



Courtesy of Prof Andrea D'Armini



Courtesy of Prof Andrea D'Armini

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PH *associated* with Left Heart Disease (PH-LHD)

2.1 left ventricular systolic dysfunction

2.2 left ventricular diastolic dysfunction

2.3 valvular heart disease

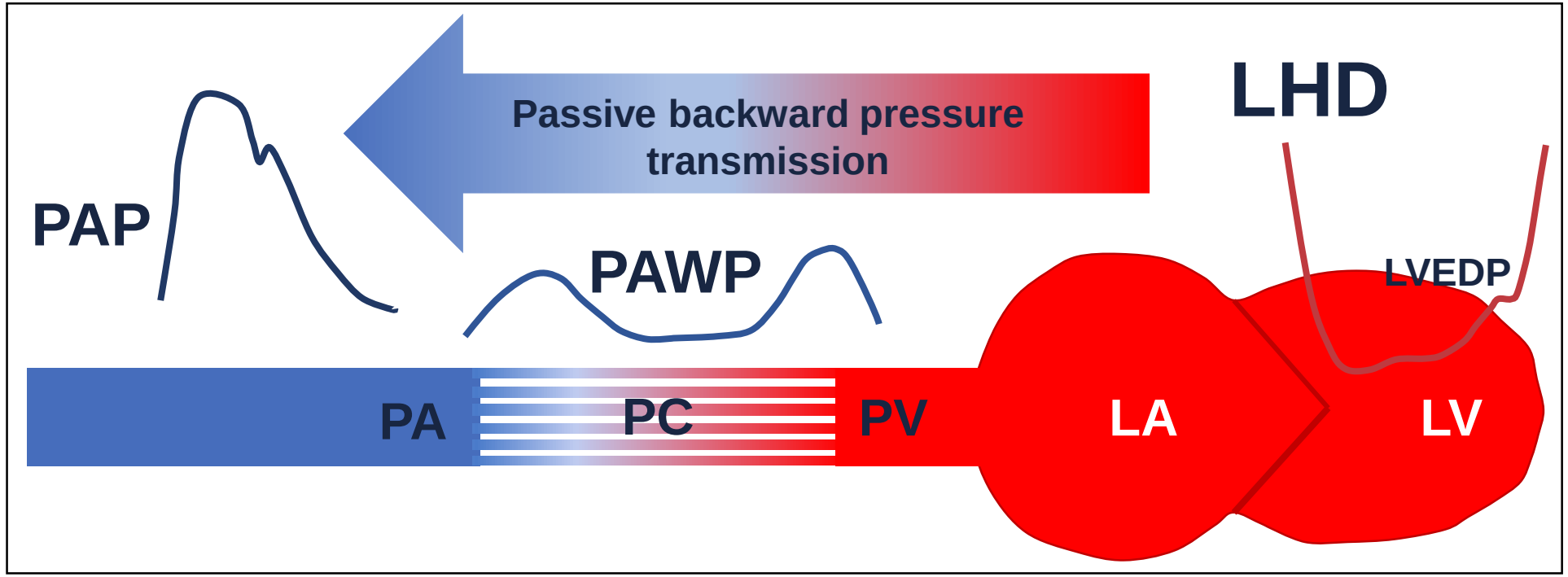
…

Prevalence of PH increases with worsening of functional class

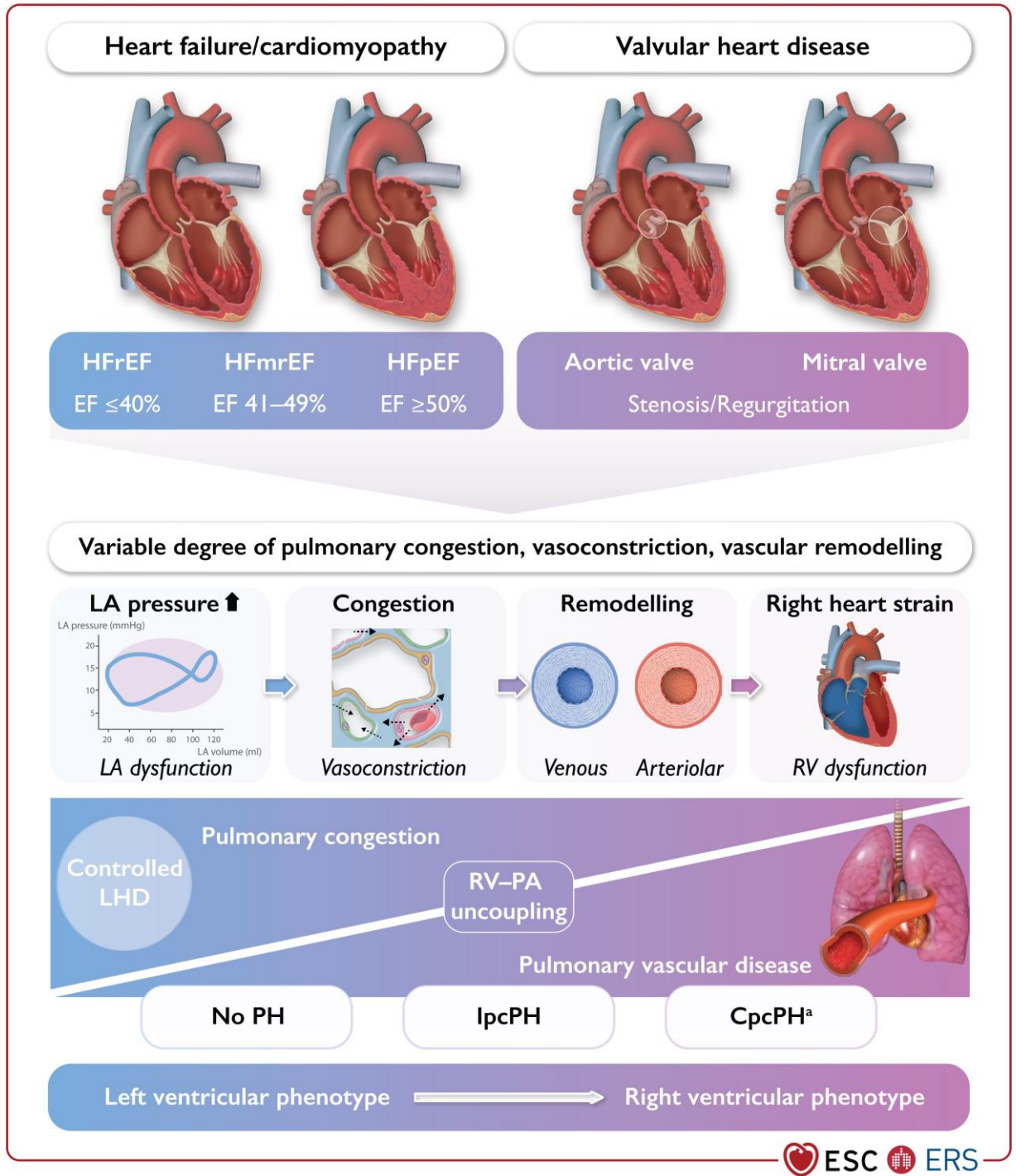
Up to 60% of patients with LV systolic dysfunction and up to 70% of patients with LV diastolic dysfunction can present with PH

In the presence of mitral or aortic valve disease (left heart), prevalence of PH increases in parallel to the severity of the valvular disease and in association with symptoms

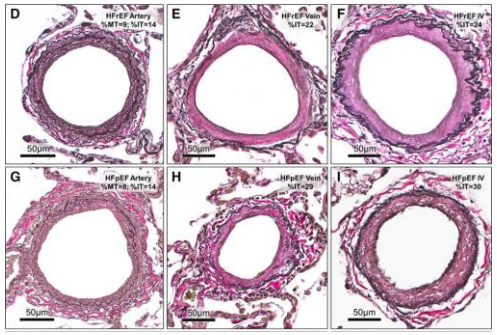
PH-LHD: post-capillary PH



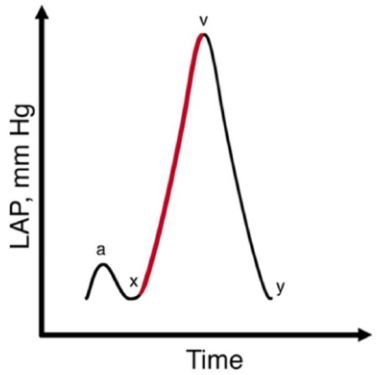
Vachiéry JL et al. J Am Coll Cardiol 2013
Naeije R et al. Circ Heart Fail 2017
Vachiéry JL et al. Eur Respir J 2019


Heart failure/cardiomyopathy
Valvular heart disease
HFrEF
EF ≤40%
HFmrEF
EF 41–49%
HFpEF
EF ≥50%
Aortic valve
Mitral valve
Stenosis/Regurgitation
Variable degree of pulmonary congestion, vasoconstriction, vascular remodelling
LA pressure
LA pressure (mmHg)
LA volume (ml)
LA dysfunction
Congestion
Vasoconstriction
Remodelling
Venous
Arteriolar
Right heart strain
RV dysfunction
Controlled LHD
Pulmonary congestion
RV–PA uncoupling
Pulmonary vascular disease
No PH
IpcPH
CpcPH[a]
Left ventricular phenotype
Right ventricular phenotype
ESC ERS

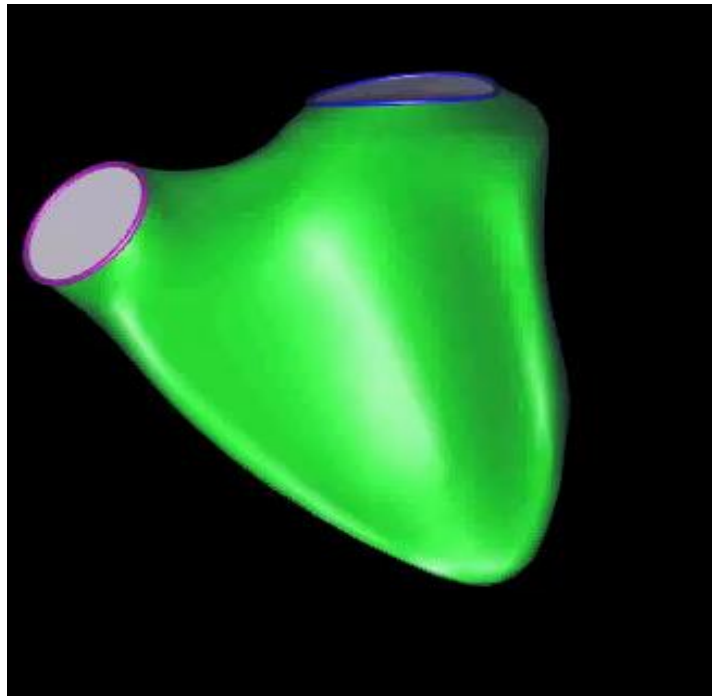
Load-dependent RV remodeling and dysfunction in PH-HF



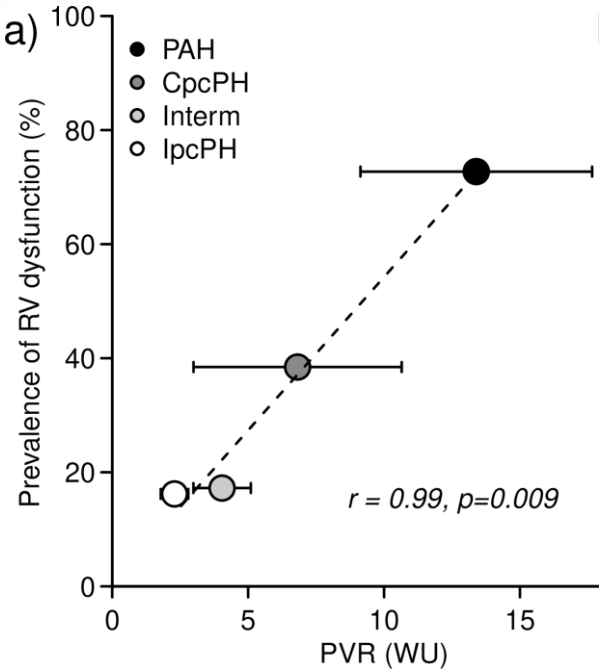
↑ Resistive afterload (↑ PVR)

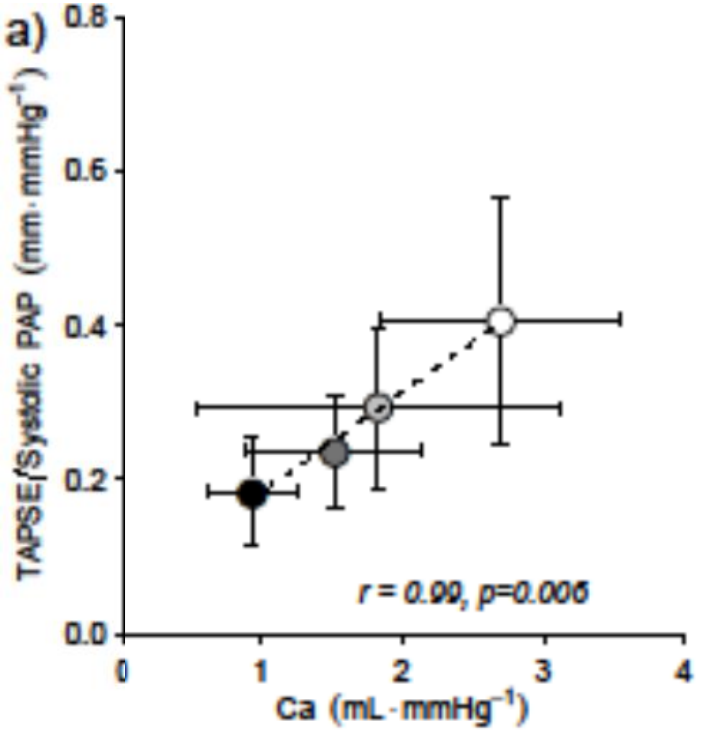


↑ Pulsatile afterload (↓ PAC)



RV dysfunction = ↑ proBNP,
↓ exercise capacity, ↓ survival

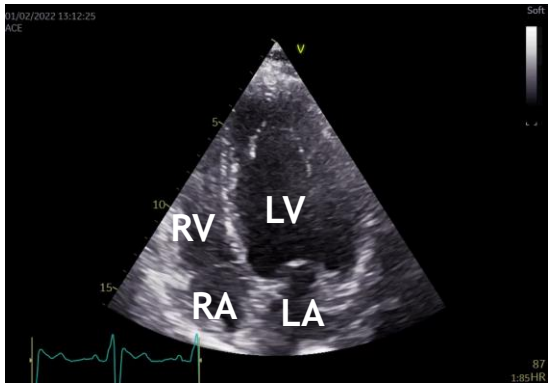




Naeije et al CircHF 2018; Vonk-Noordegraaf et al JACC 2017; Guazzi et al JACC CVImaging 2017; Caravita et al PlosOne 2018

Implications of PH in LHD

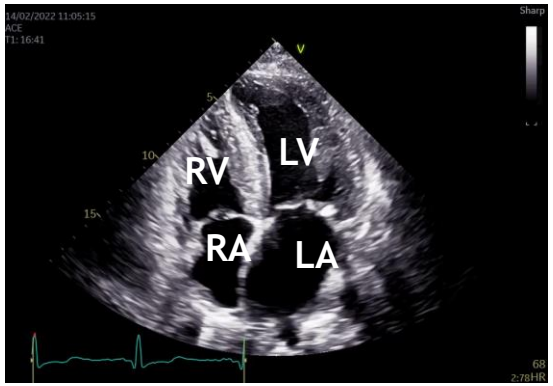
HFrEF



Almost no diagnostic uncertainties in regards of PH etiology (low LVEF)

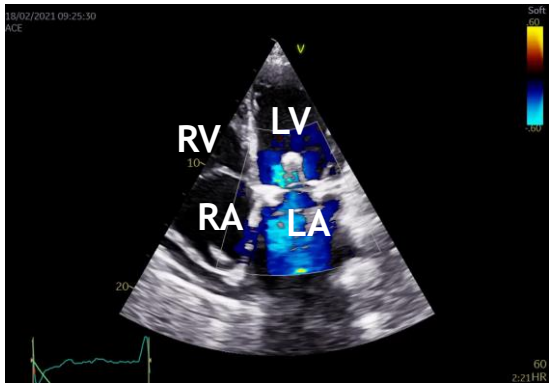
RHC indicated in advanced cases when evaluating indication for heart transplantation

HFpEF



RHC may be indicated to discriminate between PH-HFpEF and pulmonary vascular disease

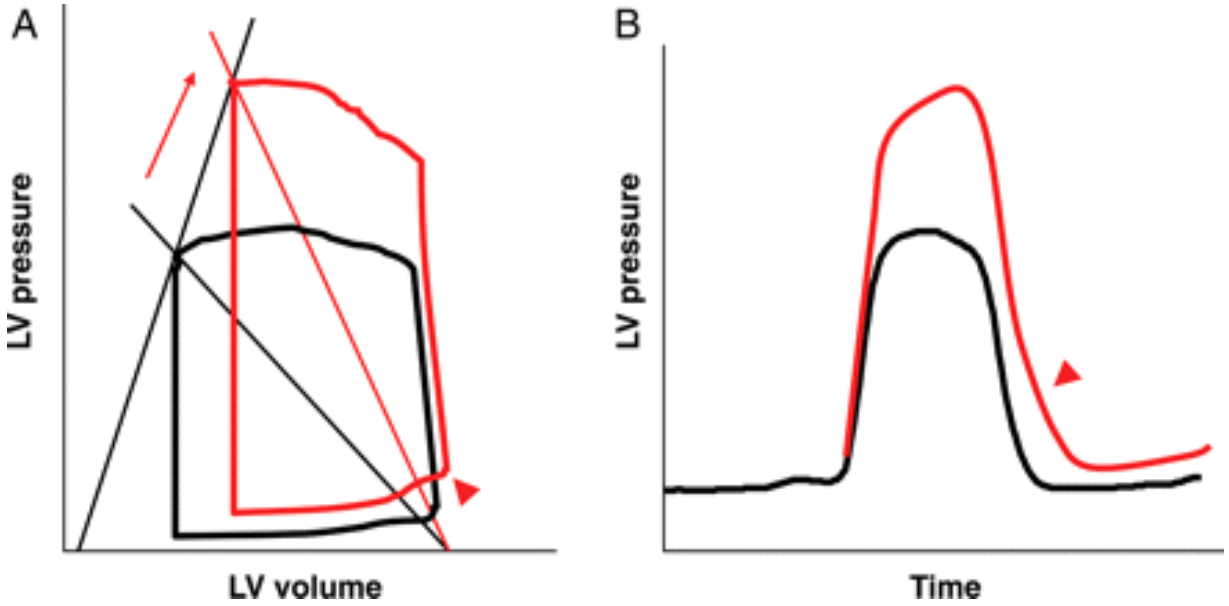
Left-sided VHD



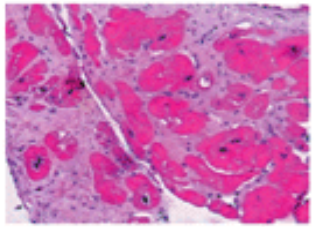
Almost no diagnostic uncertainties in regards of PH etiology (VHD)

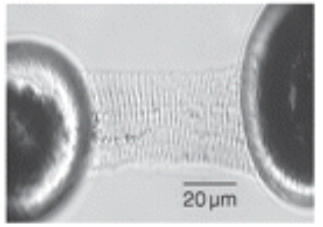
RHC might be indicated in some cases before surgery / transcatheter intervention

HFpEF ≈ ↑ LV stiffness



Borlaug, Paulus. EHJ 2011

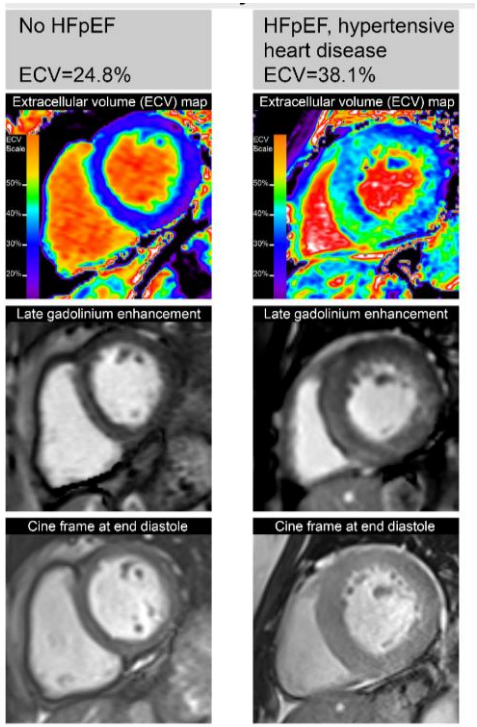




Extracellular matrix
- Amount of collagen
- Abundance of collagen type 1
- Collagen cross-linking

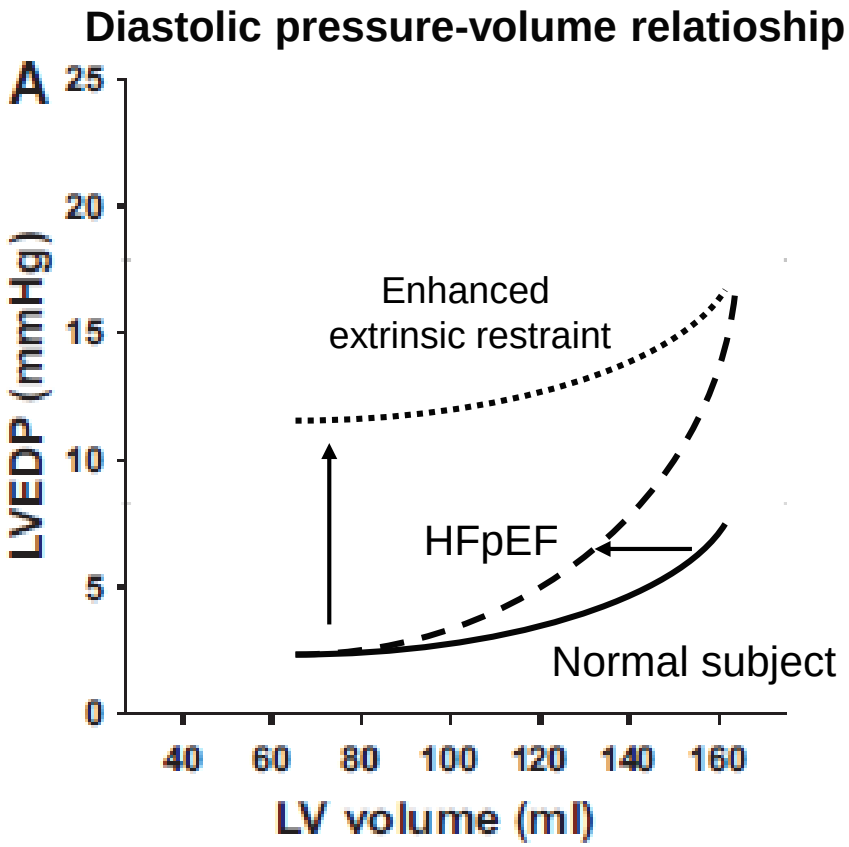
Cardiomyocytes
- Ca^{2+} removal
- Cross-bridge detachment
  - High-energy phosphates
- Cytoskeletal protein titin
  - Isoform shifts
  - Phosphorylation
  - Oxidation

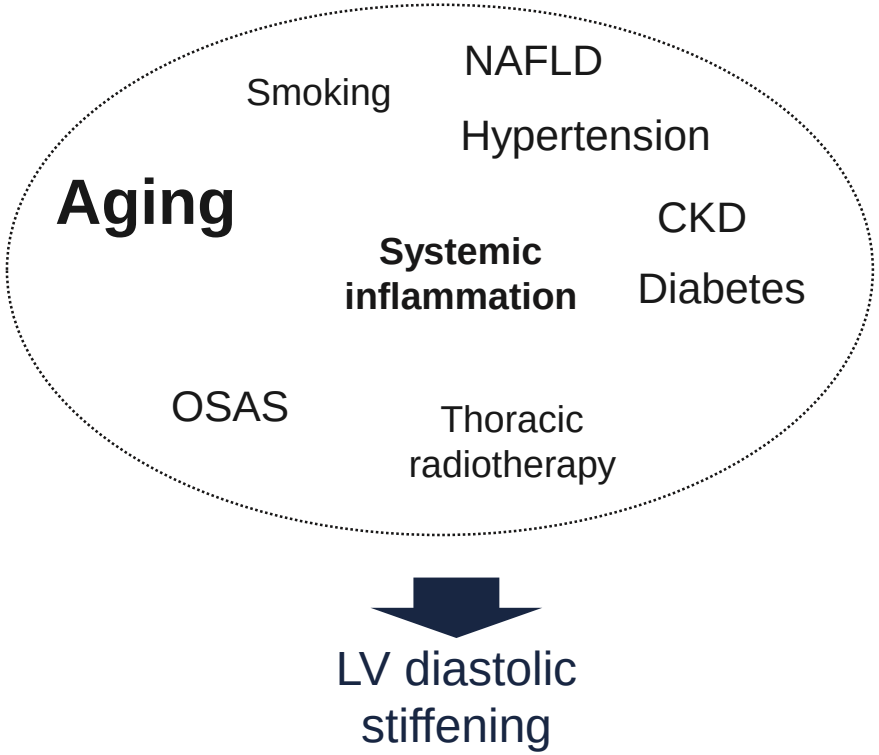
Matricellular proteins



Borlaug, Paulus. EHJ 2011
Quarta et al. EJHF 2020

What is HFpEF and where does it starts



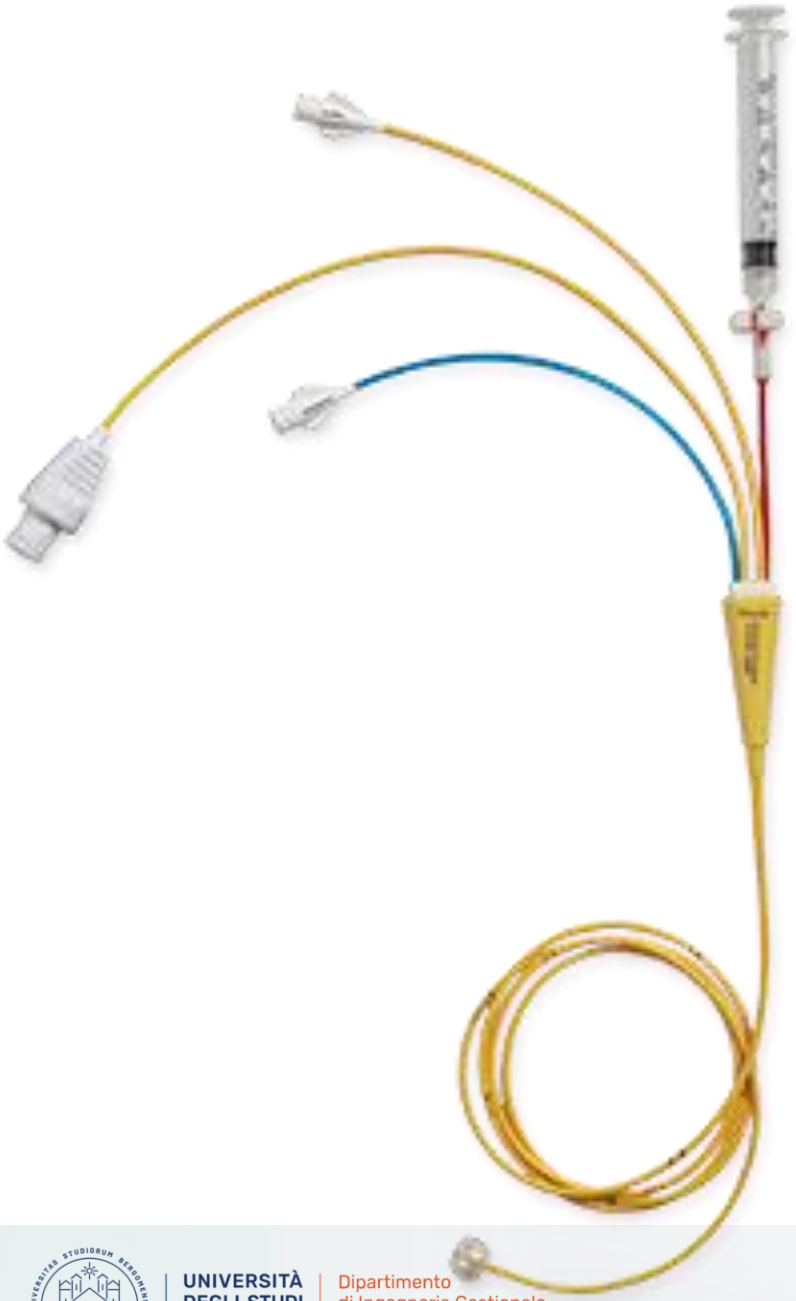


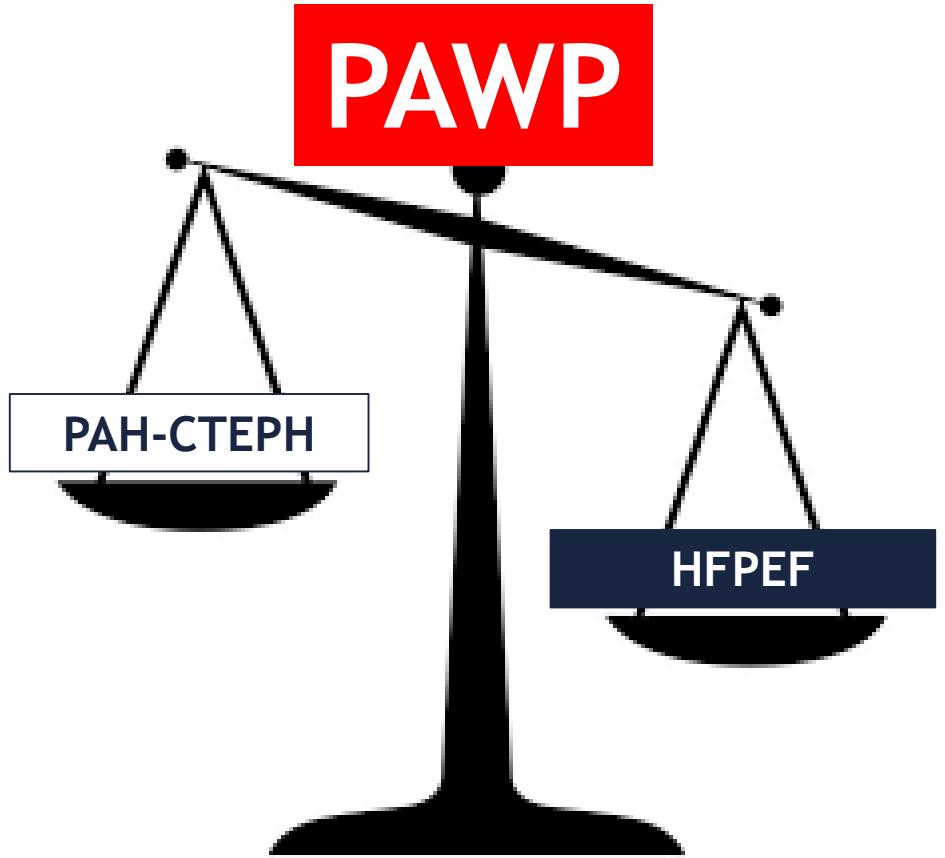
Borlaug BA. Circ Heart Fail 2014
Eur J Heart Fail 2021
Cardiovasc Dis 2021
Baratto C et al Circ HF 2021

	Low probability of PH-HFpEF	Intermediate probability of PH-HFpEF	High probability of PH-HFpEF
	Required features		
Age	<60 years	60-70 years	>70 years
Cardiovascular risk factors (obesity, systemic hypertension, dyslipidemia, glucose intolerance or diabetes mellitus)	None	1-2 factors	>2 factors
Previous cardiac intervention	No	No	Yes
Atrial fibrillation	No	Paroxysmal	Persistent or permanent
Structural LHD	No	No	Present
EKG	Normal or sign of RV strain	Mild LVH	LBBB or LVH
Resting echocardiography	• No LVH • No mitral or aortic disease • No LA dilation • No diastolic dysfunction • LA strain > 40%	• Mild LVH • Mild left mitral or aortic regurgitation • No LA dilation • Diastolic dysfunction grade I • LA strain 20-30%	• LVH • Moderate mitral or aortic regurgitation • any mitral or aortic stenosis • LA dilation • Diastolic dysfunction grade ≥ 2 • LA strain < 20%
	Additional features		
Cardiac MRI	No left heart abnormalities		• LVH • LGE + • ↑ LV ECV • LA dilation • Perfusion defects
Exercise echocardiography	E/e' < 10	E/e' 10-14	E/E' > 14
CPET	• Normal or high VE/VCO2 slope • No EOV	Elevated VE/VCO2 slope or EOV	• Mildly elevated VE/VCO2 slope • EOV

CPET=cardiopulmonary exercise test; EOV=exercise oscillatory ventilation; LA=left atrium; LBBB=left bundle branch block; LGE=late gadolinium enhancement; LHD=left heart disease; LV=left ventricle; MRI=magnetic resonance imaging; PH=pulmonary hypertension; VE =minute ventilation; VCO2=carbon dioxide production

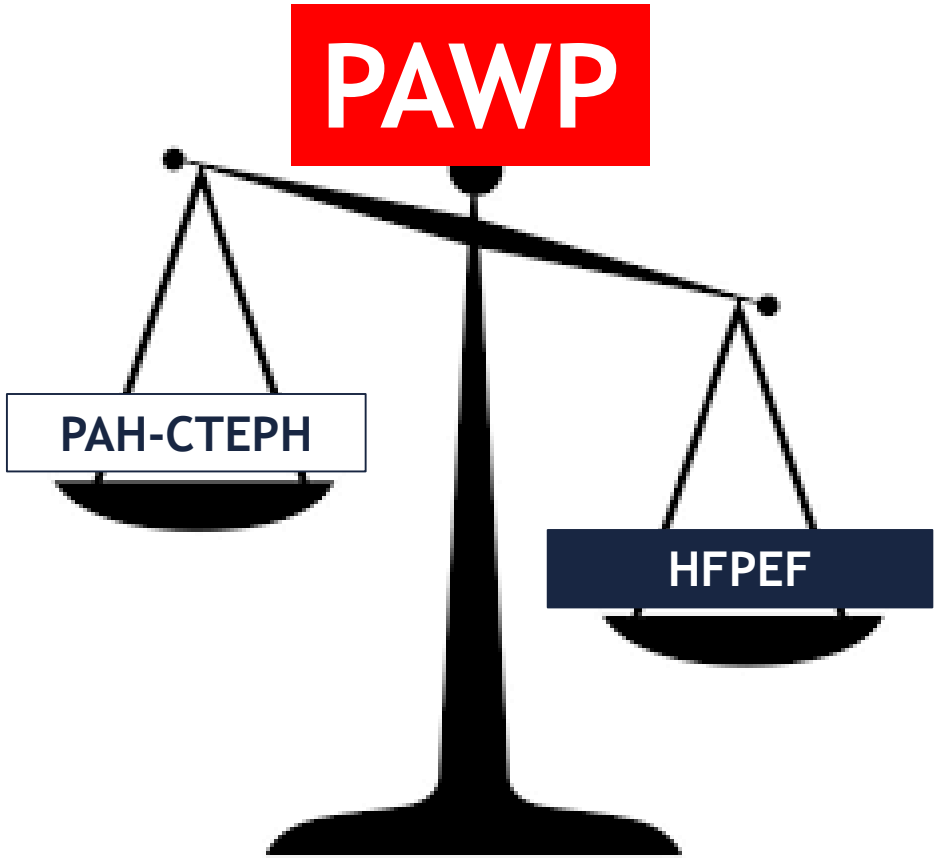
Vachiéry JL, Caravita S. Encyclopedia of Respiratory Medicine, in press
Vachiéry JL et al, Eur Respir J 2019





≤ 12 mmHg 13-15 mmHg > 15 mmHg

Pre-capillary Post-capillary



≤ 12 mmHg 13-15 mmHg > 15 mmHg

Pre-capillary Post-capillary

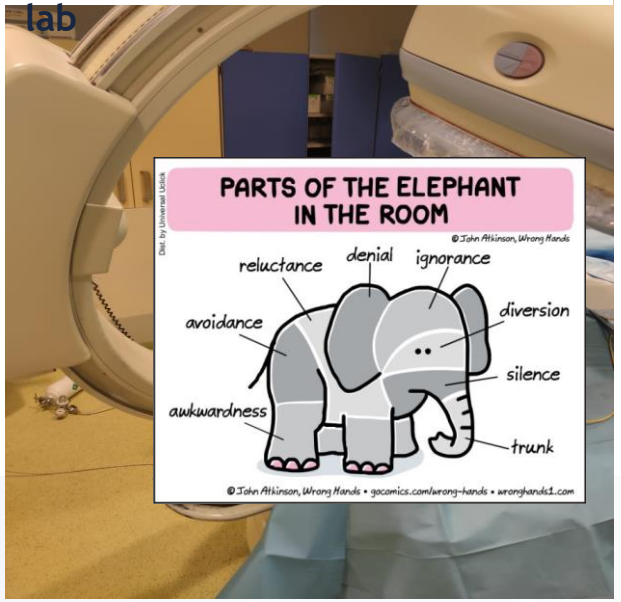
Rare disease

Improvement with PAH specific therapy

Frequent disease

Potential harm with PAH specific therapy

HFpEF: the elephant in the cath lab



Ageing
Atrial fibrillation
CV risk factors
History of LHD
SSc
…

Provocative tests in the cath lab

Fluid load

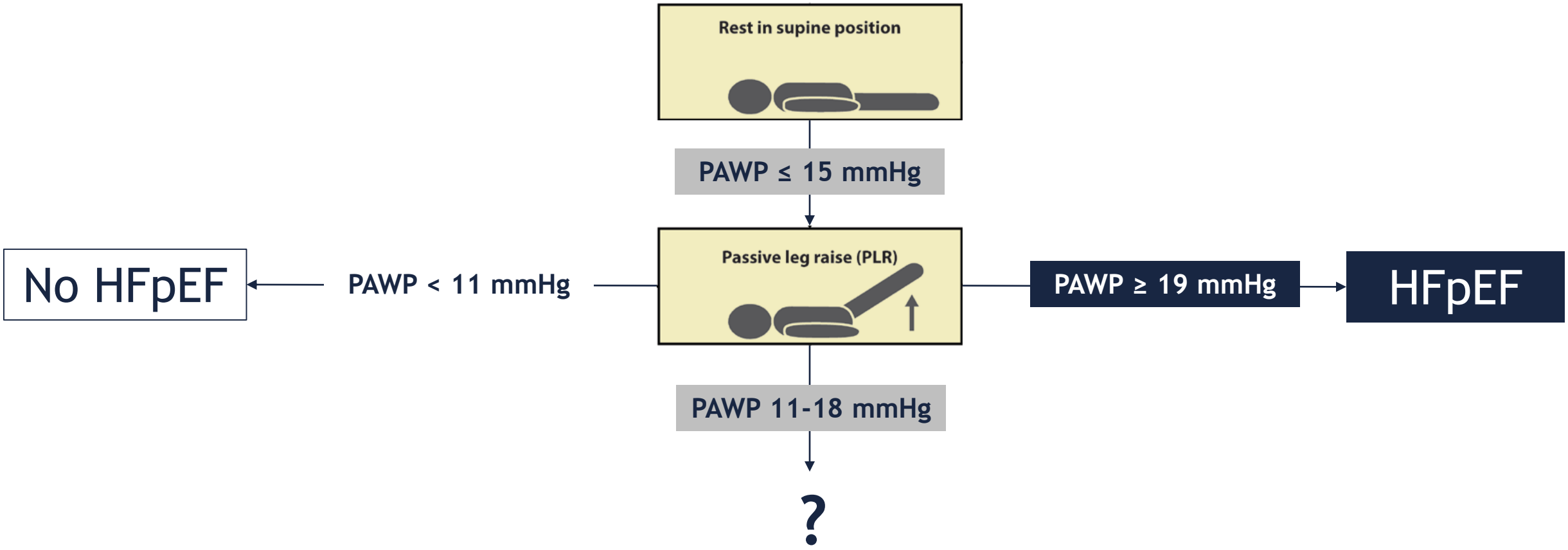
500 mL or 7 mL/Kg in 5-10’

≈

Passive leg raise

1’ passive leg raise

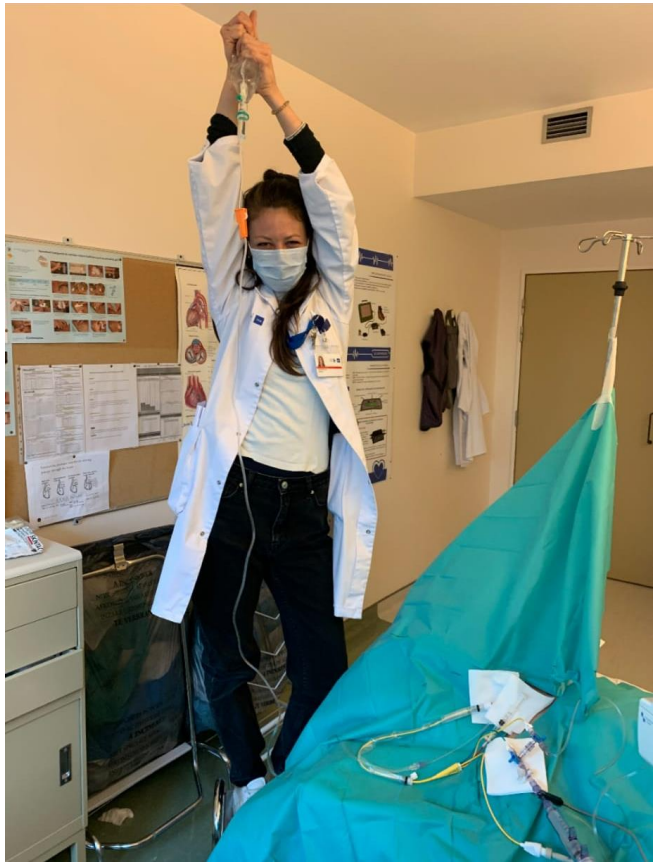
Vachiéry JL et al. Eur Respir J, 2018
Humbert M et al. Eur Heart J 2022



Modified from van de Bovenkamp AA et al. Circ HF 2022

Provocative tests in the cath lab

Fluid load



500 mL or 7 mL/Kg in 5-10’

≈

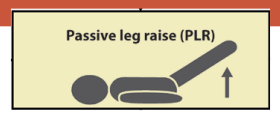
Passive leg raise

1’ passive leg raise

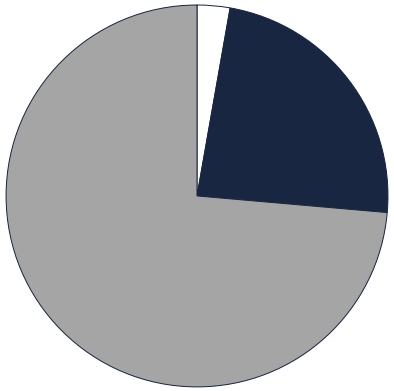
Exercise

Step or ramp protocol up to exhaustion

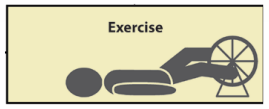
Vachiéry JL et al. Eur Respir J, 2018
Humbert M et al. Eur Heart J 2022



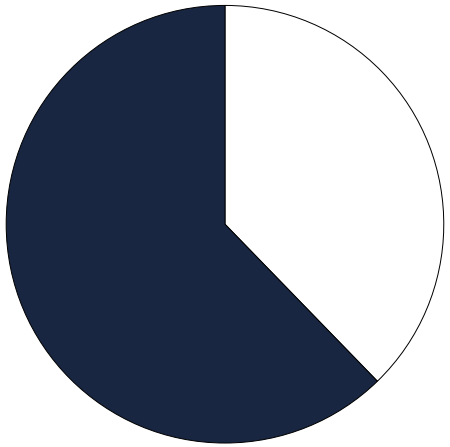
PAWP after Passive Leg Raise (PLR)



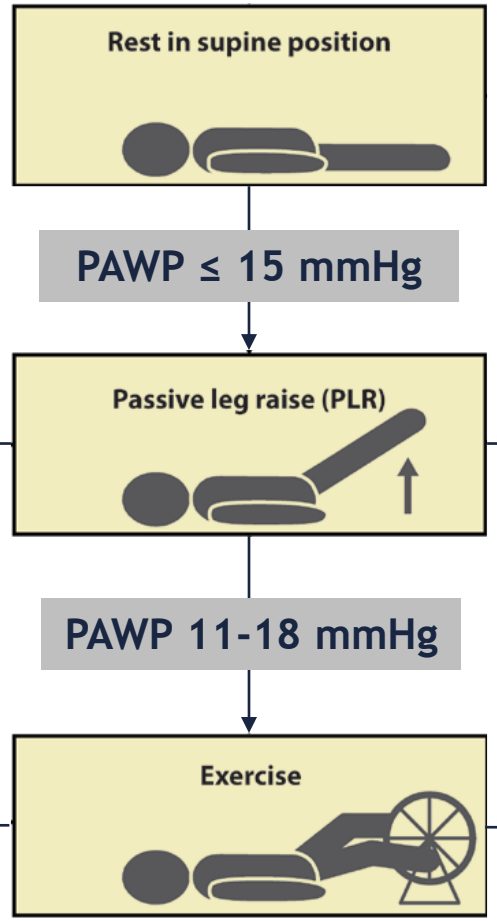
- PAWP-PLR < 11 (no HFpEF)
- PAWP-PLR ≥ 19 (HFpEF)
- PAWP-PLR 11-18



PAWP during exercise (EX)

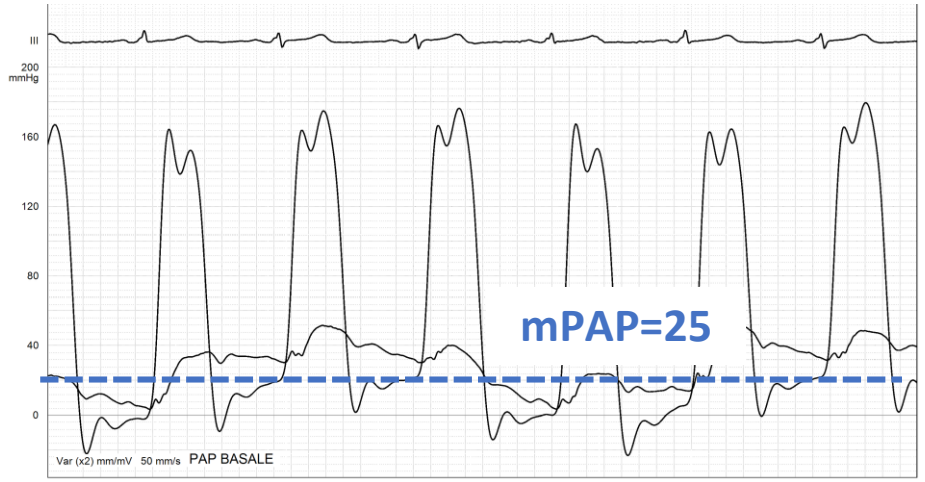


- PAWP-EX < 25 (no HFpEF)
- PAWP-EX ≥ 25 (HFpEF)

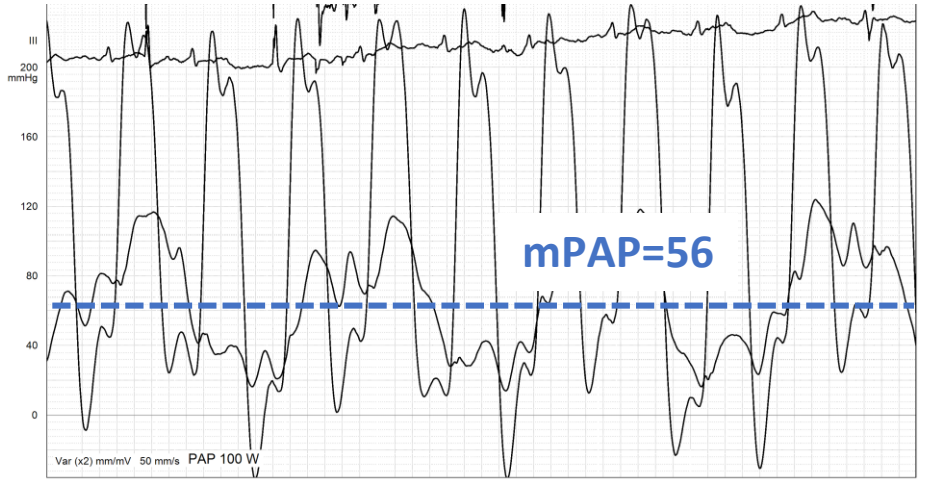


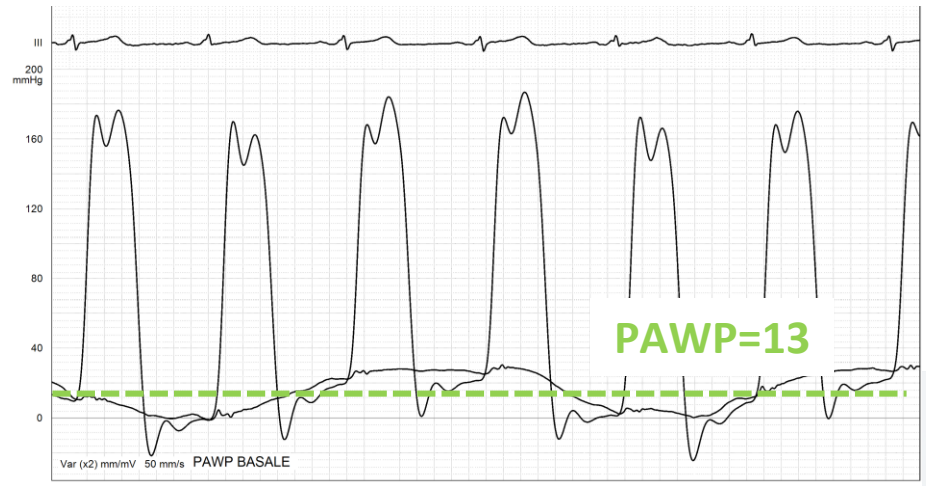
Modified from van de Bovenkamp AA et al. Circ HF 2022

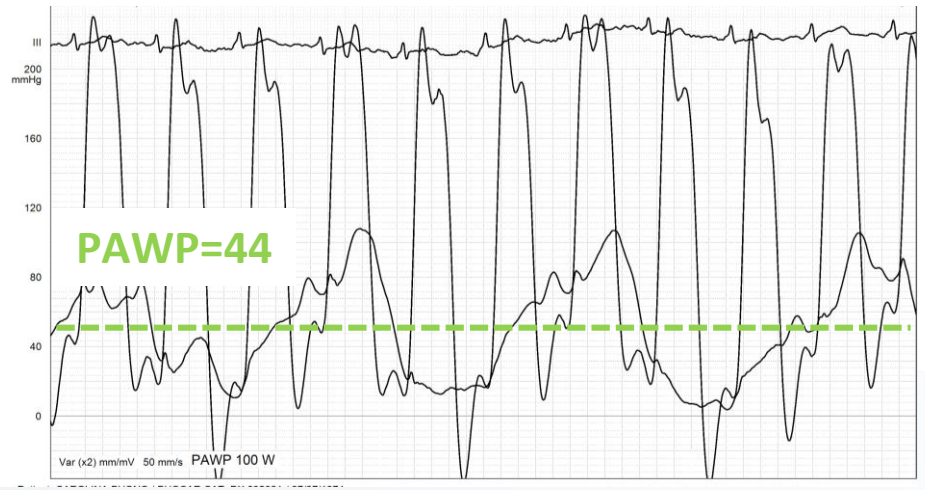
REST

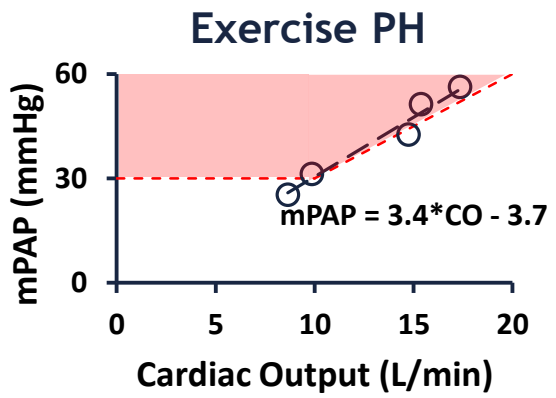

III
200 mmHg
160
120
80
40
0
mPAP=25
Var (x2) mm/mV 50 mm/s PAP BASALE

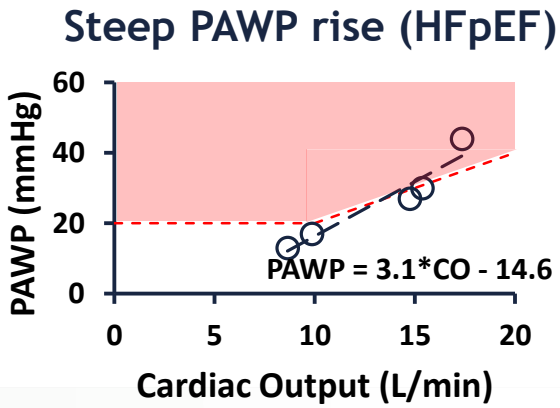
100 W


III
200 mmHg
160
120
80
40
0
mPAP=56
Var (x2) mm/mV 50 mm/s PAP 100 W


III
200 mmHg
160
120
80
40
0
PAWP=13
Var (x2) mm/mV 50 mm/s PAWP BASALE


III
200 mmHg
160
120
80
40
0
PAWP=44
Var (x2) mm/mV 50 mm/s PAWP 100 W


Exercise PH
mPAP (mmHg)
60
30
0
0
5
10
15
20
Cardiac Output (L/min)
mPAP = 3.4*CO - 3.7


Steep PAWP rise (HFpEF)
PAWP (mmHg)
60
40
20
0
0
5
10
15
20
Cardiac Output (L/min)
PAWP = 3.1*CO - 14.6

Post-capillary PH: implications

Development of PH is frequent in LHD

It generally reflects severity of LHD (**but be aware of the potential overlap with PH-LD, PAH and CTEPH!**)

It is associated with worse prognosis, in particular when a pre-capillary component develops

There is **no specific treatment for PH associated with LHD**, except optimizing/intensifying treatment for LHD itself

Drugs targeting the pulmonary circulation may cause harm in patients with LHD!!!!!!

Agenda

- Physiology of the pulmonary circulation and of the right ventricle (RV) → understanding RV failure
- Measures and estimates of pulmonary hemodynamics in clinical practice
- Pulmonary Hypertension (PH): hemodynamic and clinical definition
- Importance of clinical history (risk factors), signs and symptoms
- Overview of instrumental findings in PH
- Diagnostic algorithms
- Frequent forms of PH, associated to cardiac and respiratory diseases:
    - **PH associated with lung diseases and/or hypoxia**
    - PH associated with left heart diseases
- «True» Pulmonary Vascular Diseases (PVDs):
    - Pulmonary Arterial Hypertension (PAH)
    - Chronic Thromboembolic Pulmonary Disease (CTED and CTEPH) vs acute Pulmonary Embolism (PE)

Photo courtesy of Prof Grzegorz Bilo

Pulmonary hypertension
Clinical classification

3. Pulmonary Hypertension due to Lung Disease and/or hypoxia (PH-LD)
   - COPD
   - Interstital lung disease
   - Mixed obstructive and restrictive disorders
   - …

Pre-capillary

Clinical classification – group 3

3. Pulmonary Hypertension due to Lung Disease and/or hypoxia

Pre-capillary PH

3.1 Chronic obstructive pulmonary disease (obstructive disorder)
3.2 Interstital lung disease (restrictive disorder)
3.3 Mixed obstructive and restrictive lung diseases
3.4 Sleep disordered breathing
3.5 Alveolar hypoventilation
3.6 Chronic exposure to high altitude
3.7 Pulmonary development disorders

Complication of respiratory disease rather than a disease *per se*

PH due to lung disease is «severe» if:
mPAP > 35 mmHg
mPAP > 25 mmHg + Cardiac Index < 2.5 L/min/m^2

Clinical classification – group 3

- **Chronic obstructive pulmonary disease (COPD)**
  - 90% of advanced COPD (GOLD IV) have mPAP > 20 mmHg (20 - 35 mmHg)
  - Only 3-5% of patients has mPAP > 35 mmHg

- **Pulmonary fibrosis**
  - 8-15% of patients have mPAP > 25 mmHg
  - Prevalence of PH increases in end-stage patients (30-60%)
  - In end-stage patients, less than 10% has a mPAP > 40 mmHg

- **Combined fibrosis and emphysema**
  - Patients with paradoxically normal lung volumes at pulmonary function tests
  - 30-50% of patients present with PH
  - PH is severe in more than half of cases

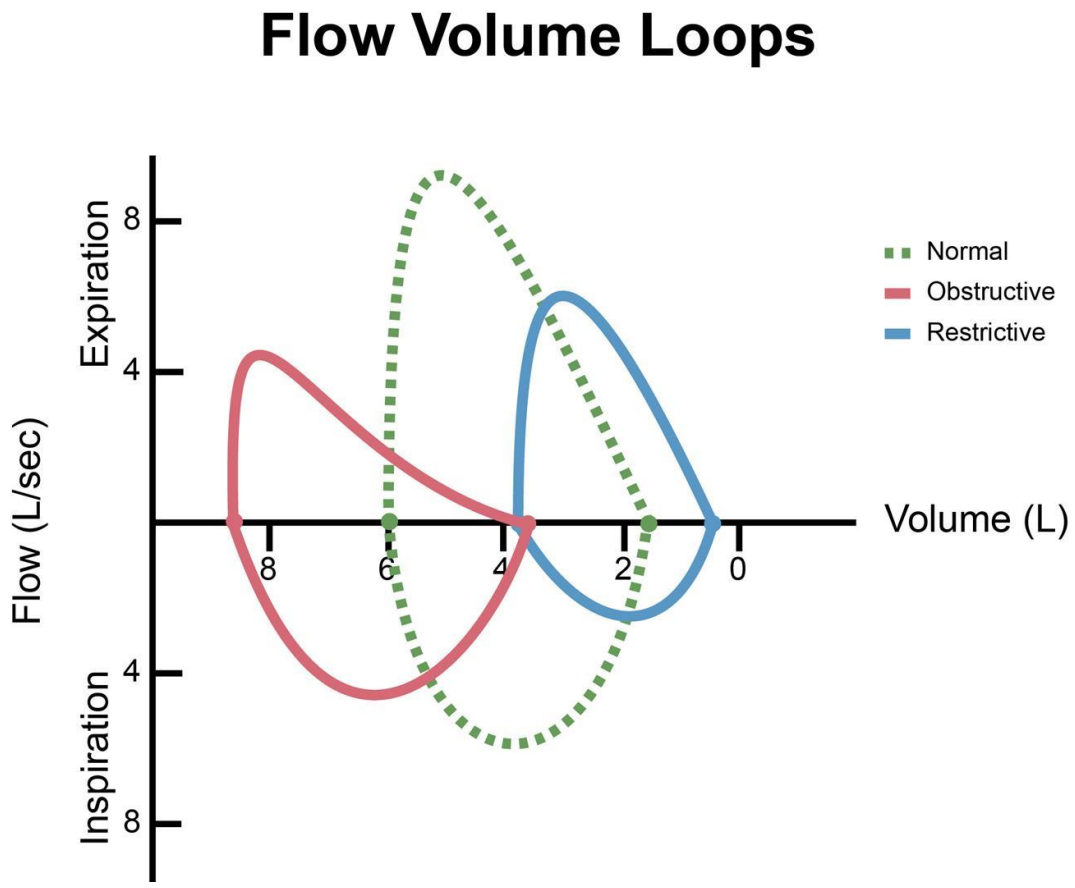
Exclusion of lung disease

Pulmonary function test (lung spirometry) + DLCO

Computed tomography of the chest

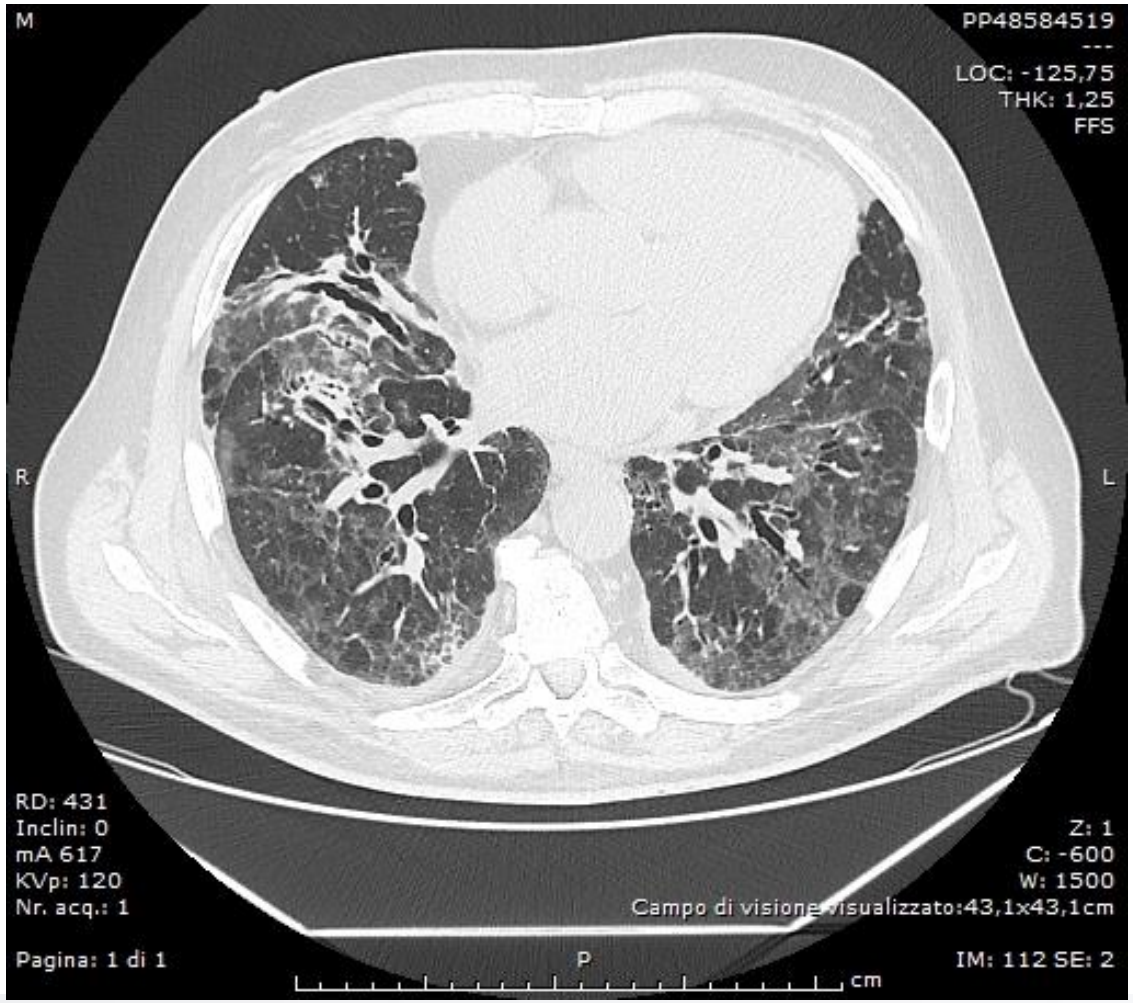
…

Pulmonary function test



Measure of pulmonary volumes and lung physiology

Computed tomography (CT) of the chest



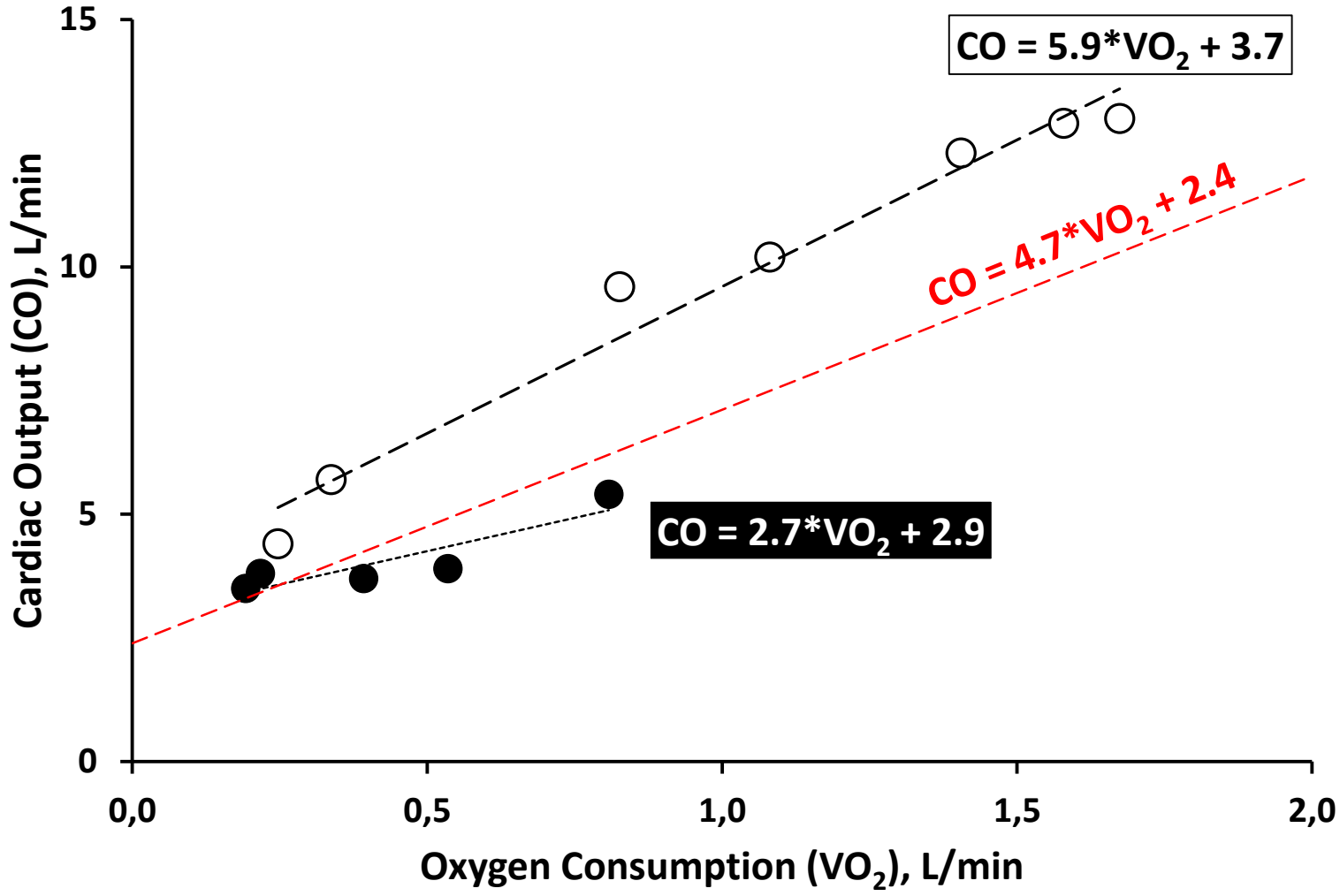
Visualization of lung parenchyma

PAH vs PH-LD

	PAH	PH-LD
Pulmonary function tests		
FEV1 (% predicted), in obstructive diseases	> 60	< 60
FVC (% predicted), in restrictive diseases	> 70	< 70
HR CT of the chest		
Parenchimal and/or airway abnormalities	= ↑	↑↑↑
Hemodynamic / cardiac profile		
RV dysfunction (echo, MRI, natriuretic peptide)	↑↑↑	=↑
Cardiac index	↓	=
(Invasive) CPET		
Respiratory reserve	=	↓
$PaCO_2$	= ↓	↑
Oxygen pulse	↓	=
CO/VO_2 relationship	↓	=
SvO_2	↓	=

Seeger W et al, J Am Coll Cardiol 2013; Galié N et al. Eur Heart J 2015; Nathan SD et al. Eur Respir J 2019

CO reserve (cardiovascular limitation to exercise)

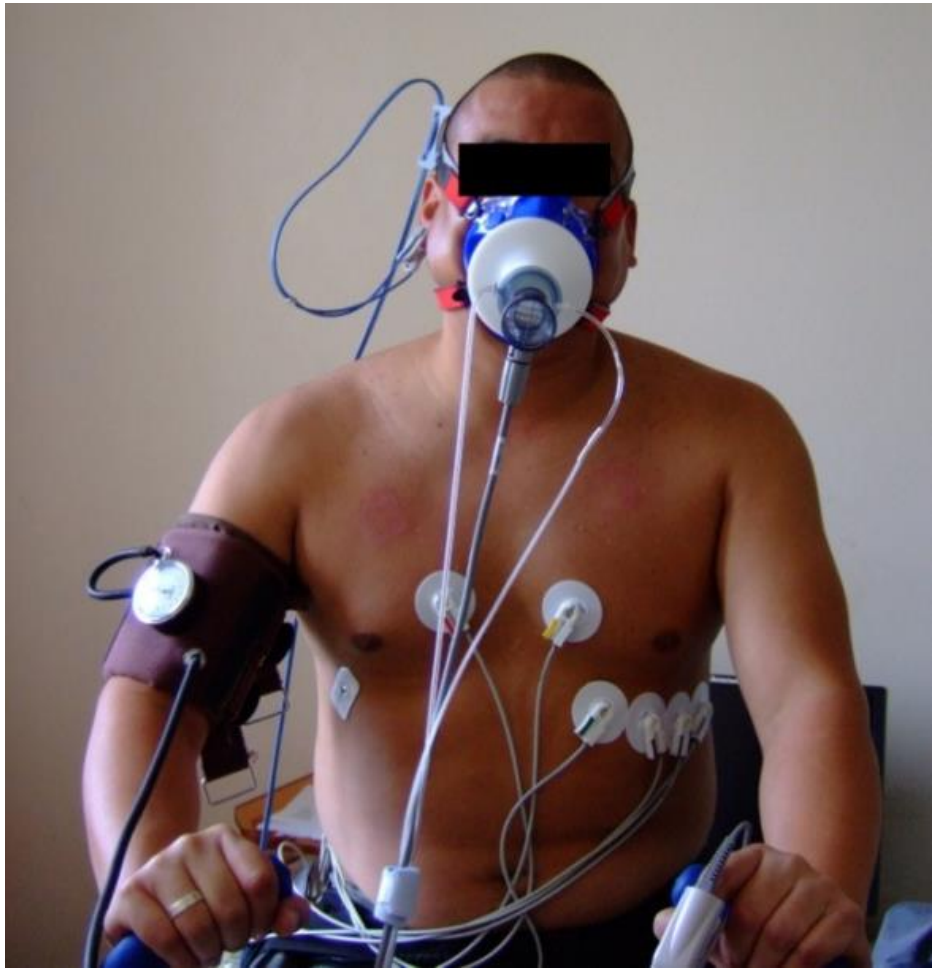


$VO_2 = CO * (a\text{-}v)O_2$ diff

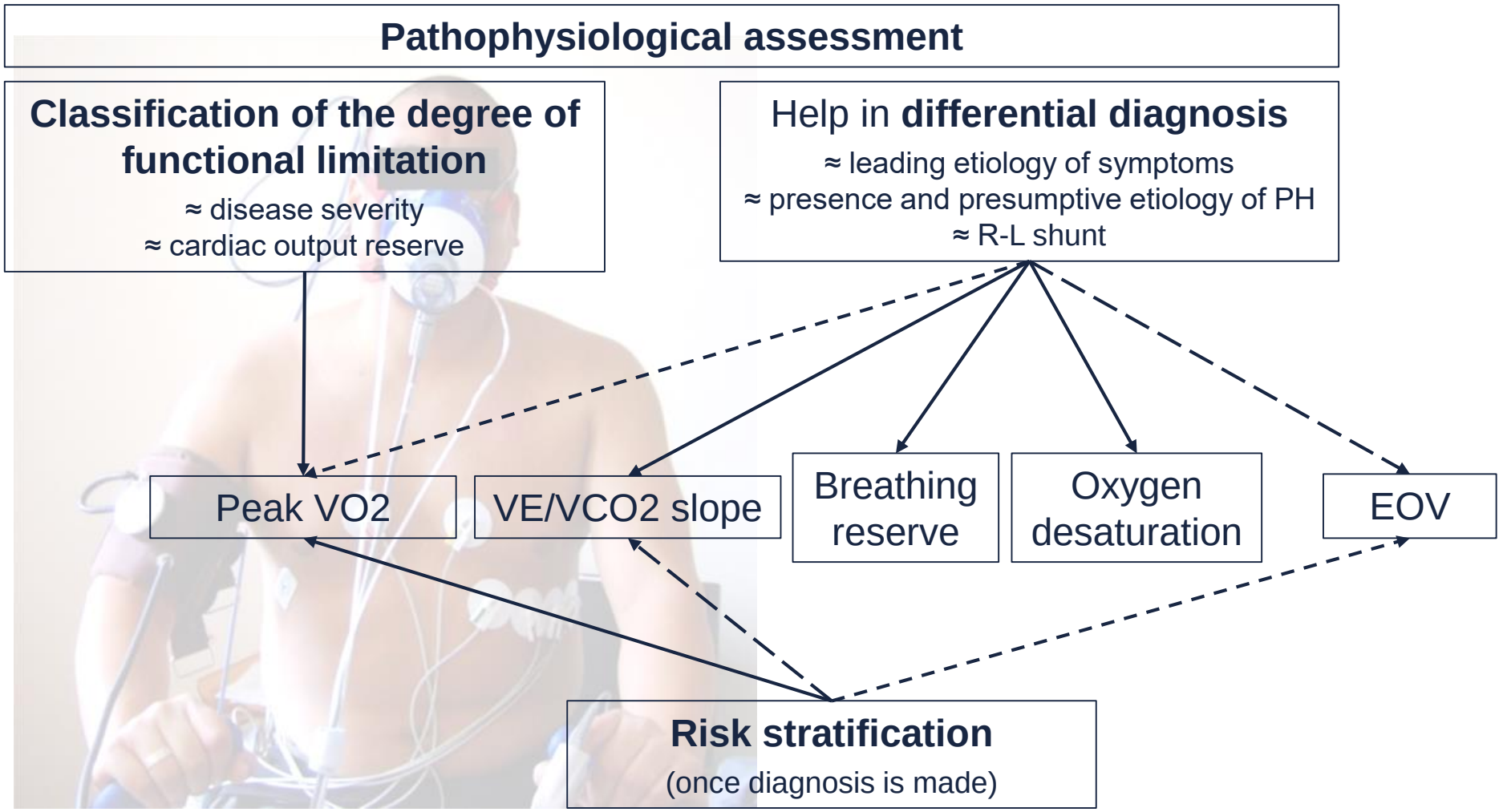
Sorajja P et al. Catheter Cardiovasc Interv 2017; 89:E223-47

CPET

Standard CPET vs invasive CPET



Gas-exchange parameters

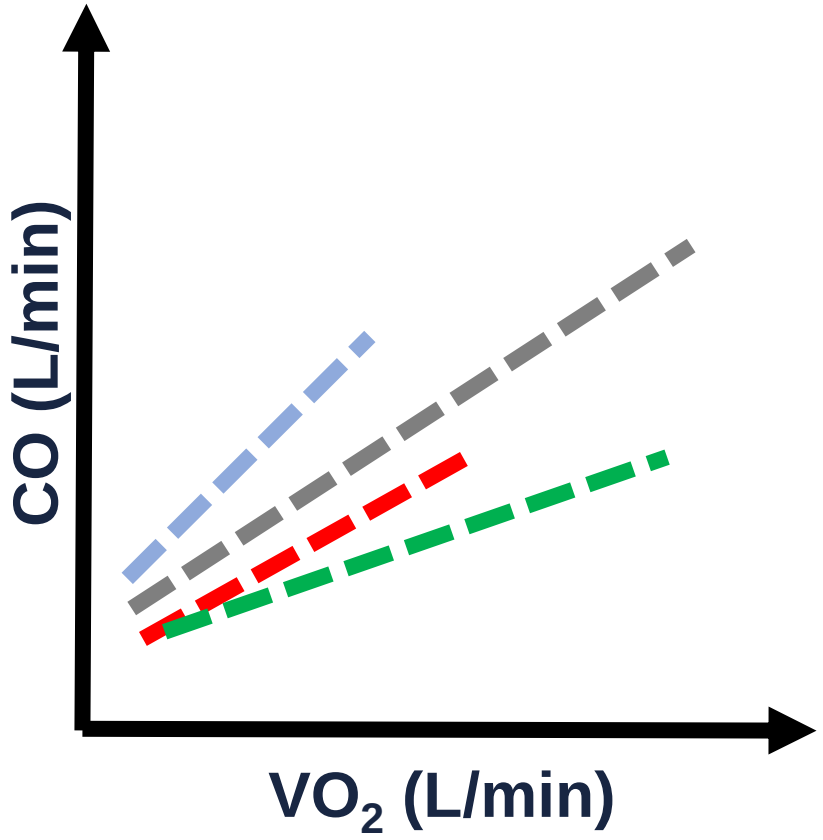


Oxygen uptake (VO_2), i.e.: *how much my patient is limited*

$$VO_2 = CO \times O_2(A\text{-}V)diff$$

Cardiac output

RV systolic reserve | **LV systolic reserve**



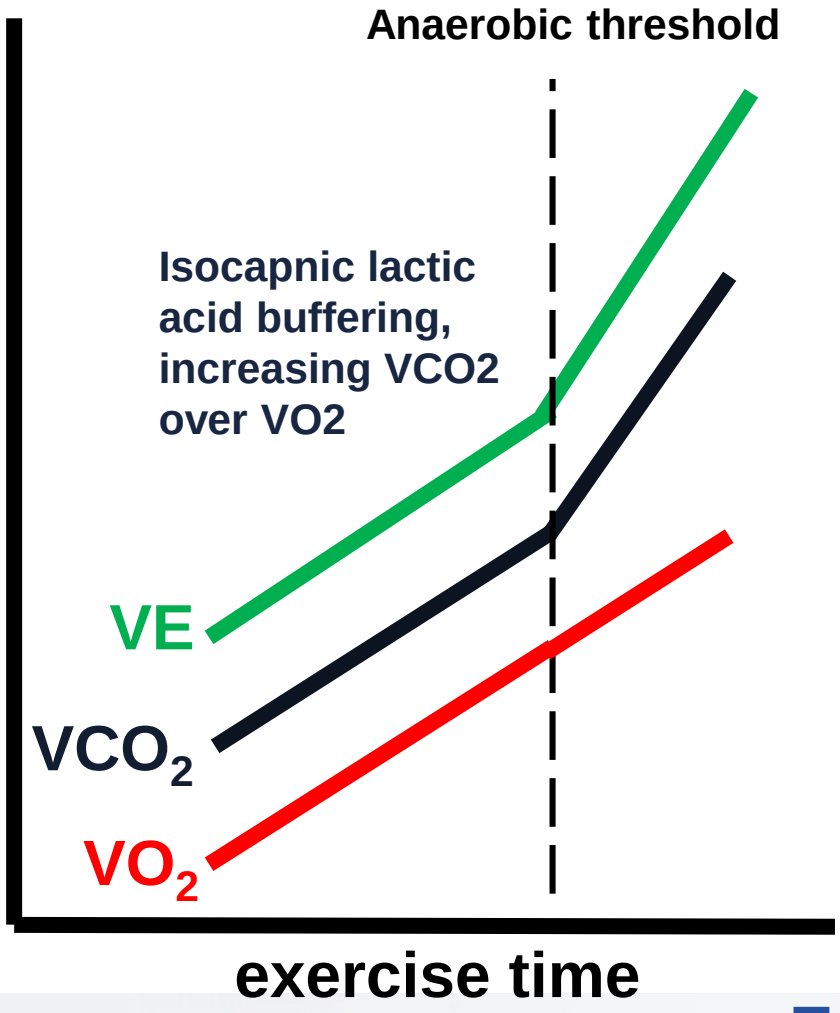
VO_2 is a quite good noninvasive surrogate of CO response to exercise in HF and PAH.

Potential exceptions:

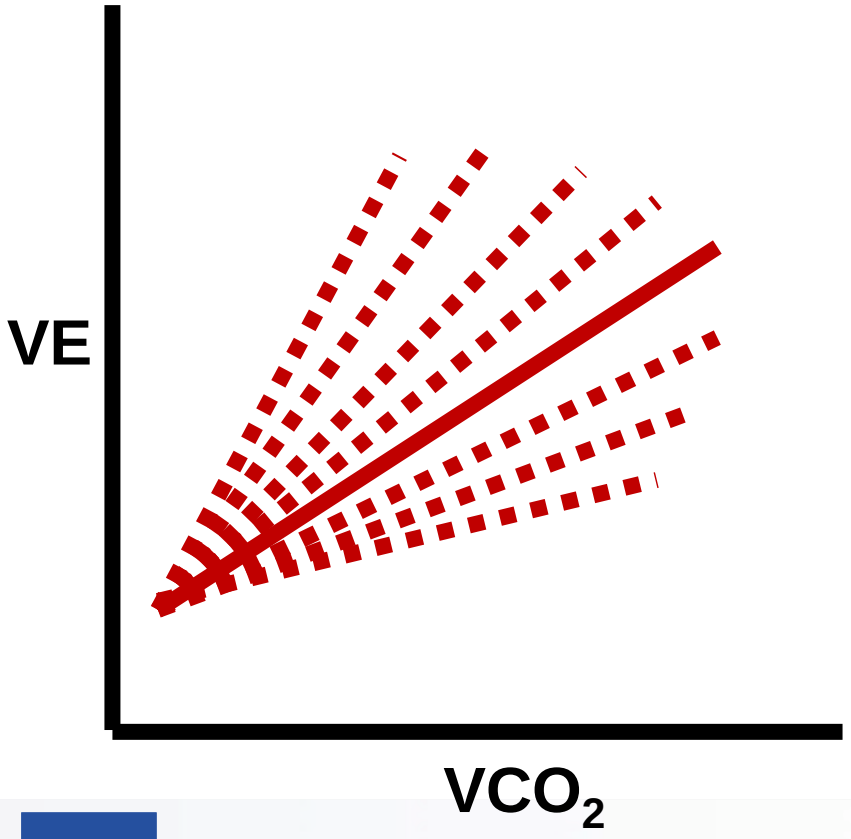
- **Well trained or «hyper O_2 extractor» subjects** (can compensate cardiac output deficit with superoptimal peripheral O_2 extraction)
- **Respiratory diseases** (↓ aO_2 availability)

Guyton, Texbook of Medical Physiology
Guazzi M et al. Circulation 2012;126:2261-74
Guazzi M et al. J Am Coll Cardiol 2017
Caravita S et al. J Heart Lung Transpl 2017;36:754-62

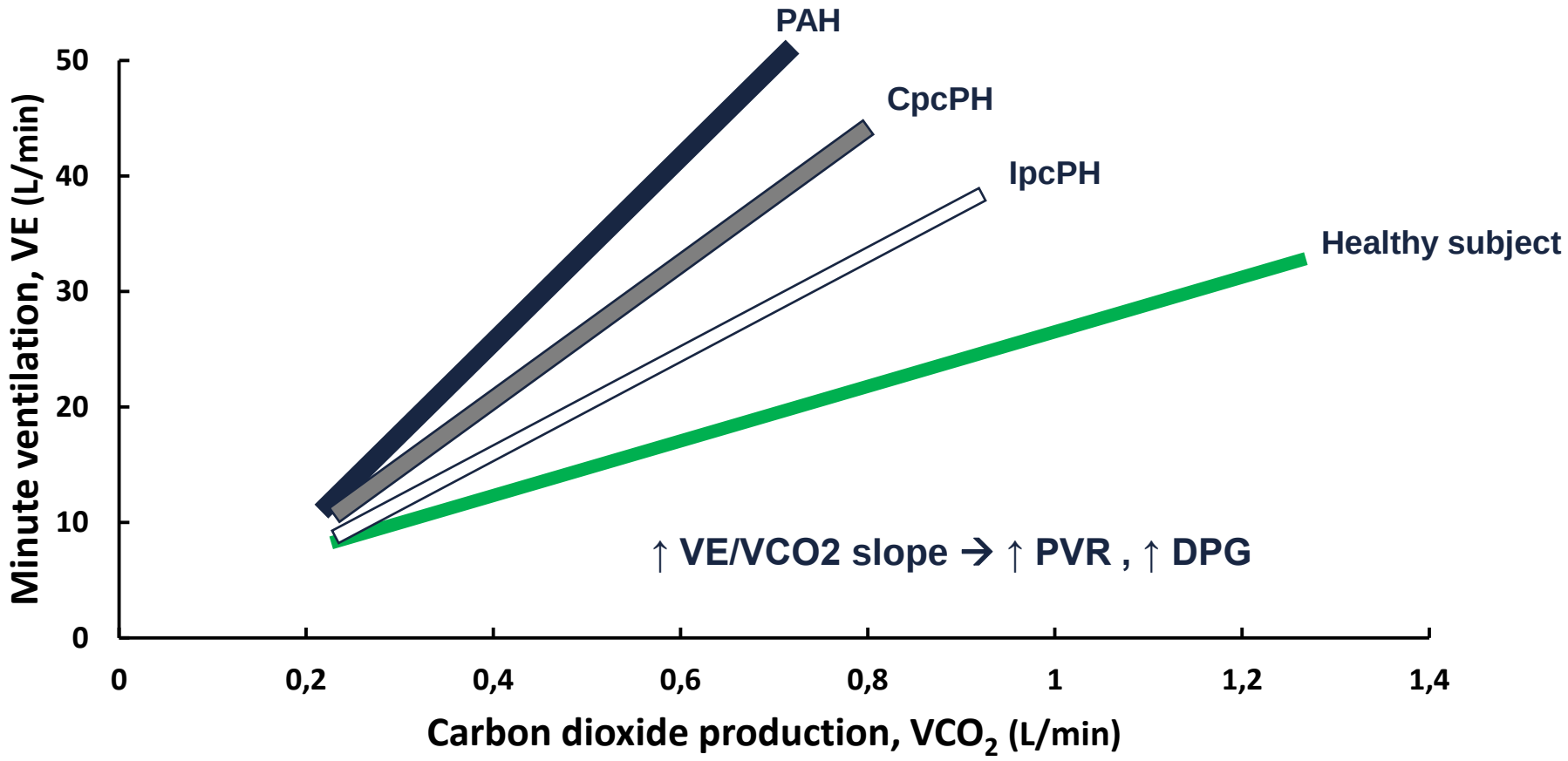
VE/VCO2 slope
Control of ventilation during exercise



$$\frac{V_E}{VCO_2} = \frac{863}{PaCO_2 * (1 - v_D/v_\tau)}$$

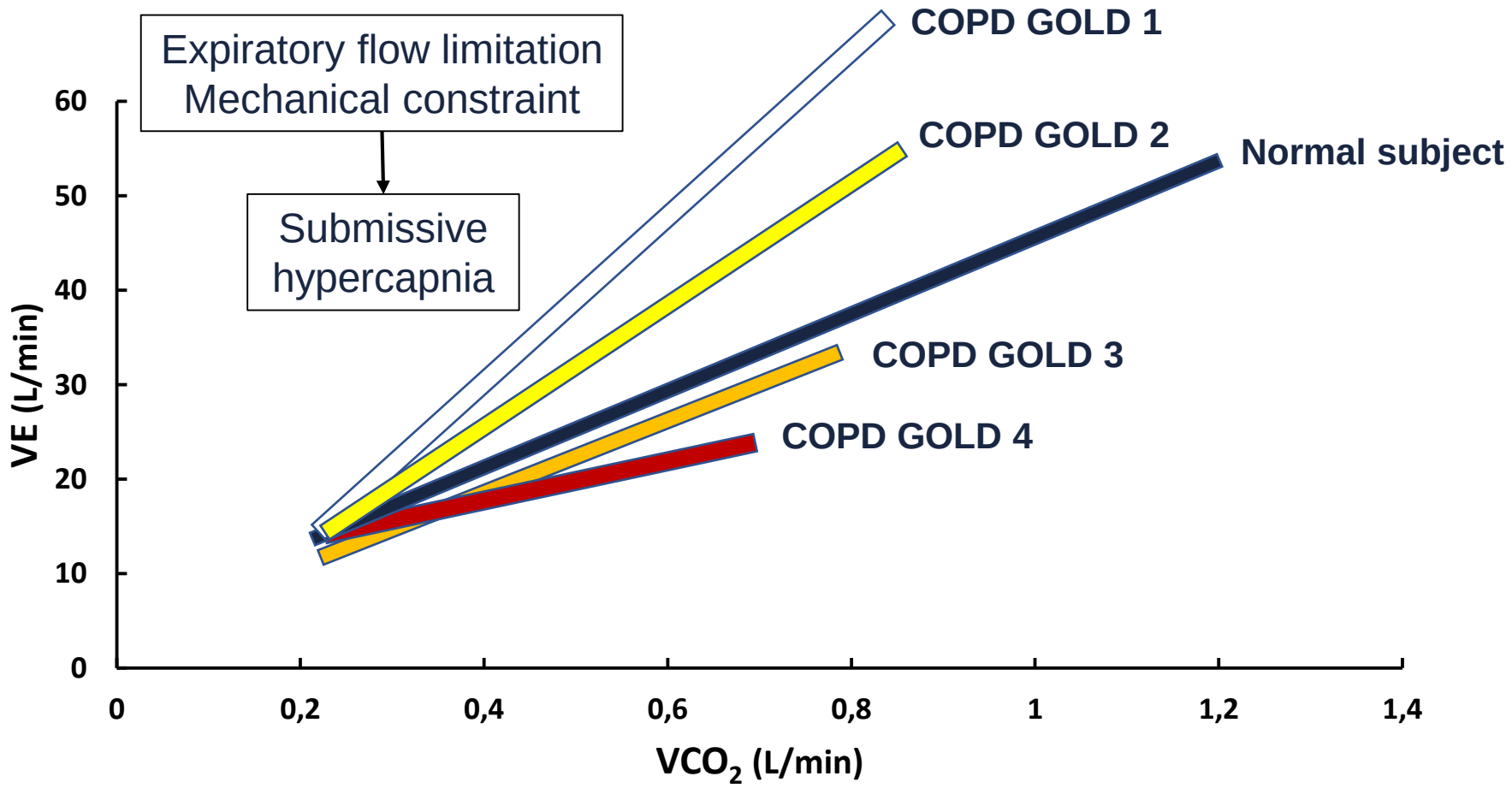


Exercise hyperventilation in PH
IpcPH vs CpcPH vs PAH



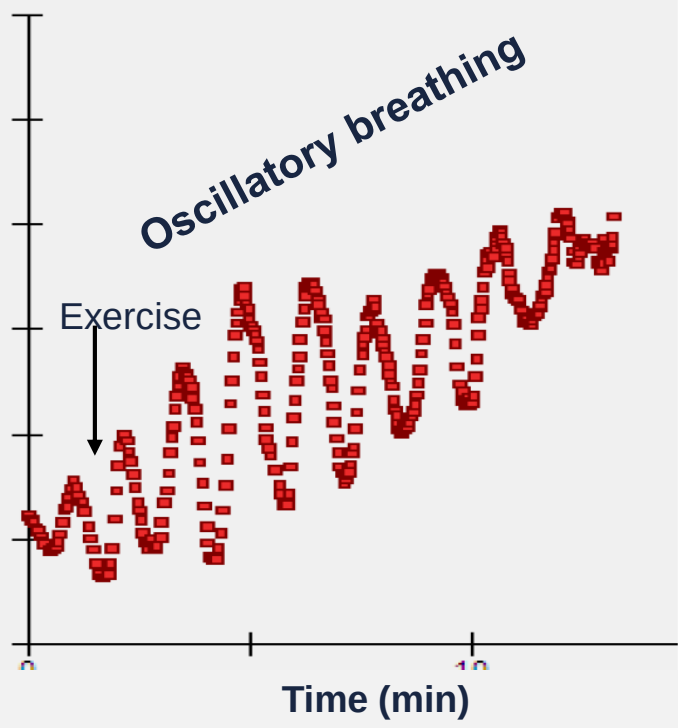
Caravita S et al. J Heart Lung Transpl 2017;36:754-62
Farina S et al. Int J Cardiol 2018
Sun XG et al. Circulation 2001;104:429-35
Taylor BJ et al. J Card Fail 2015;21:647-55
Lewis GD et al. Circ Heart Fail 2008;1:227-33

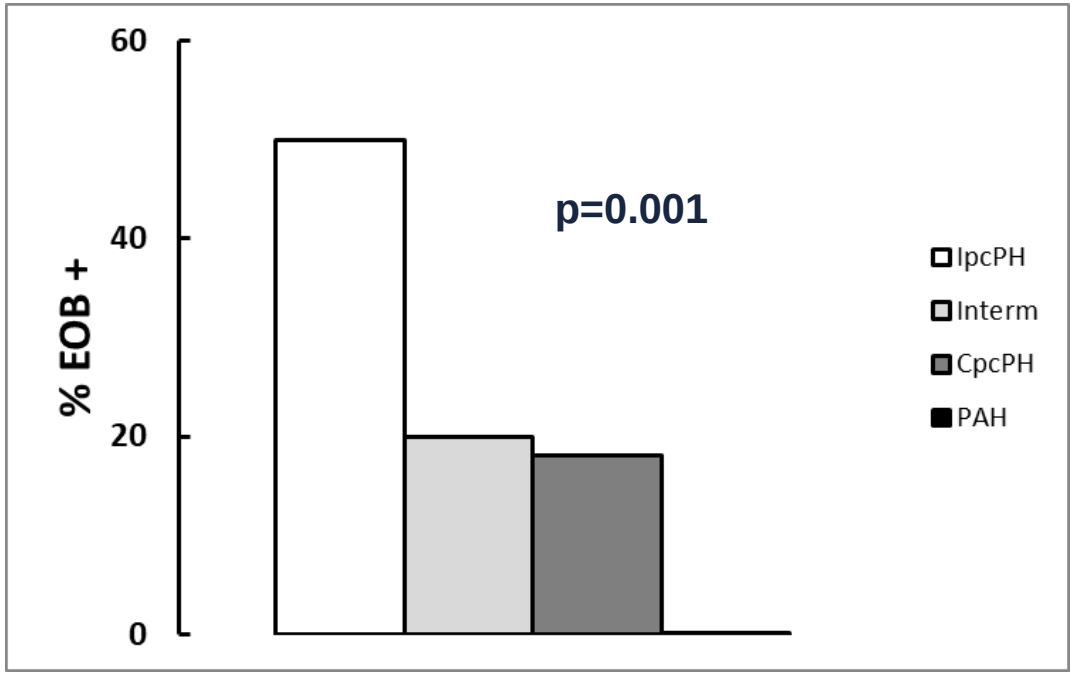
VE/VCO2 slope: mind the comorbidities!



Neder JA et al. Eur Respir J 2015;45:377-87
Poon CS et al. Respir Physiol Neurobiol 2015;216:86-93

Exercise oscillatory breathing (EOB)





Caravita S et al. J Heart Lung Transpl 2017
Vicenzi M et al. Int J Cardiol 2016

Standard CPET in PVD

DIFFERENTIAL DIAGNOSIS

	PH-HFpEF IpcPH	PH-HFpEF CpcPH	PAH	PH-LD
VO_2	↓	↓(↓)	↓(↓)	↓
VE/VCO_2	↑	↑↑	↑↑↑	↑
EOV	↑↑	↑	-	-
Ventilatory reserve	↑	↑	=↓	↓↓
SaO_2	=	=	=↓	↓

PROGNOSIS

	Low risk 1-year mortality < 5%	Intermediate risk 1-year mortality 5-10%	High risk 1-year mortality > 10%
Peak VO_2 (mL/Kg/min)	> 15	11 - 15	< 11
Peak VO_2 (% of predicted)	> 65	35 - 65	< 35
VE/VCO_2 slope	< 36	36 - 45	> 45

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