Left sided Pulmonary Hypertension

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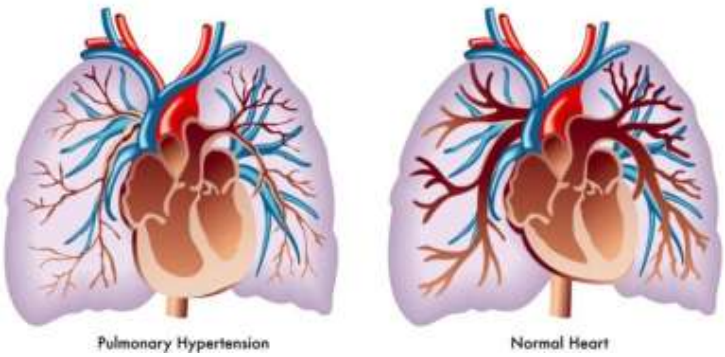
Left sided Pulmonary Hypertension



Question

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- **Among elderly patients referred for the evaluation of pulmonary hypertension, what is the most commonly missed diagnosis?**

1. **OSA**
2. **CLD**
3. **HFpEF**
4. **PE**

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4. **PE**

Key Message

Patients with PH and occult LHD are frequently misclassified as PAH and treated with PAH-specific drugs.

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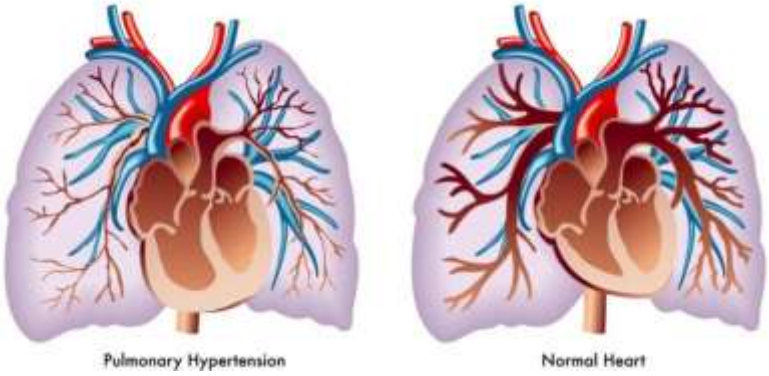

Classification

Comprehensive clinical classification of pulmonary hypertension

1. Pulmonary arterial hypertension

1.1 Idiopathic
1.2 Heritable
- 1.2.1 BMPR2 mutation
- 1.2.2 Other mutations

1.3 Drugs and toxins induced
1.4 Associated with:
- 1.4.1 Connective tissue disease
- 1.4.2 human immunodeficiency virus (HIV) infection
- 1.4.3 Portal hypertension
- 1.4.4 Congenital heart disease (Table 5)
- 1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

1'.1 Idiopathic
1'.2 Heritable
- 1'.2.1 EIF2AK4 mutation
- 1'.2.2 Other mutations

1'.3 Drugs, toxins and radiation induced
1'.4 Associated with:
- 1'.4.1 Connective tissue disease
- 1'.4.2 HIV infection

1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
2.5 Congenital/acquired pulmonary veins stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia

3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

4.1 Chronic thromboembolic pulmonary hypertension
4.2 Other pulmonary artery obstructions
- 4.2.1 Angiosarcoma
- 4.2.2 Other intravascular tumors
- 4.2.3 Arteritis
- 4.2.4 Congenital pulmonary arteries stenoses
- 4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

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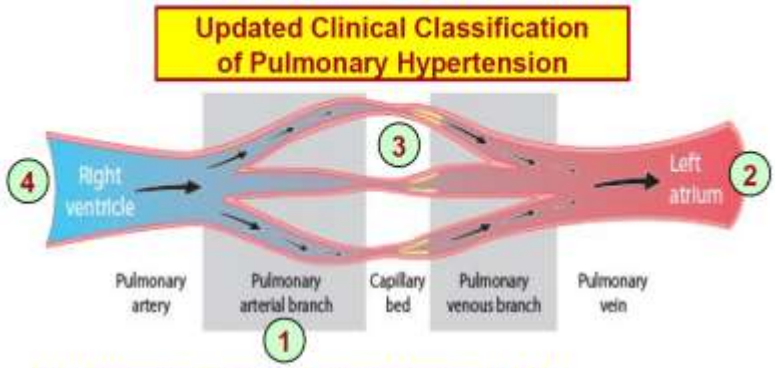
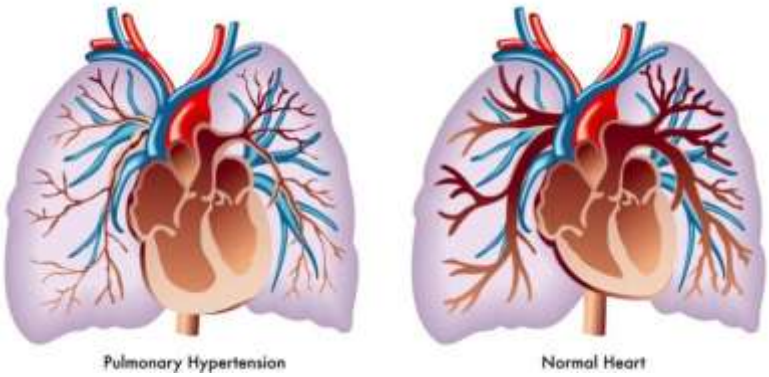
European Respiratory Journal 2015;46:903–975



1) Pulmonary arterial hypertension (PAH).
2) PH due to left sided heart disease.
3) PH due to lung disease and/or hypoxia.
4) Thromboembolic PH.
5) Multifactorial PH. (as in sarcoidosis)

Left sided Pulmonary Hypertension



Definition

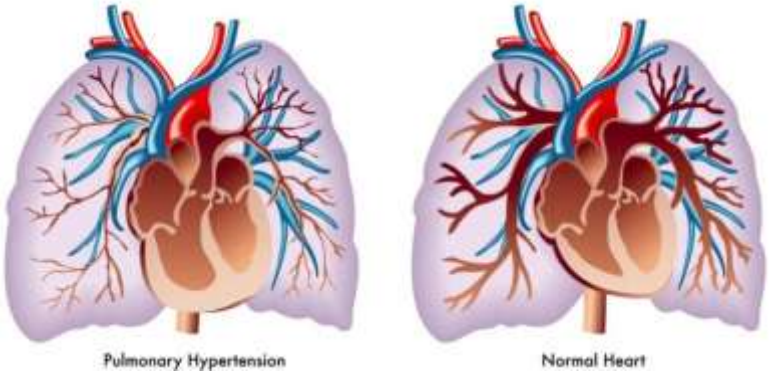
Definition:

- Left-sided heart disease is probably the most frequent cause of PH.
- The key hemodynamic factor that differentiates group 2 PH from others is the elevation in the left-sided heart filling pressure, PAWP.

Definition:

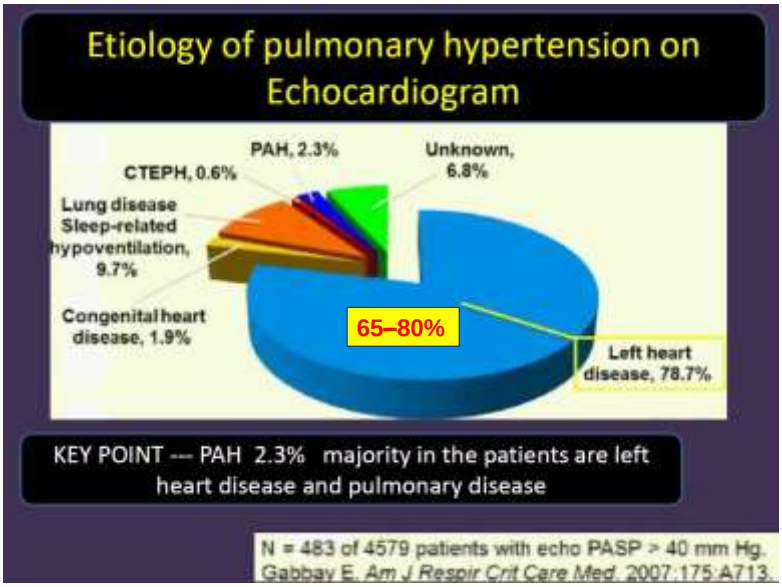
- Left sided ventricular or valvular dysfunction may result in chronic left atrial hypertension, with passive backward transmission of this pressure to the pulmonary vasculature leading to PH.

Left sided Pulmonary Hypertension



Prevalence of LHD-PH

Prevalence of LHD-PH



Prevalence of LHD-PH

- In HFrEF, the prevalence of PH as assessed by RHC was reported to be between 40 and 75%.
- In patients with HFpEF, recent studies utilizing either echocardiography or RHC indicated a PH prevalence in a range between 36 and 83%.

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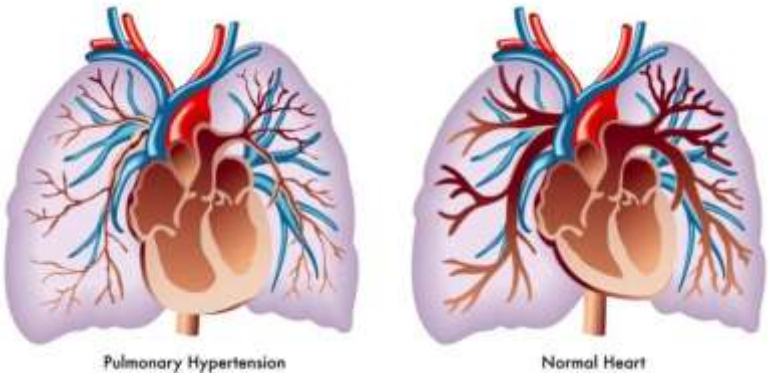

Causes of LHD-PH

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Table 2.—Causes of Pulmonary Venous Hypertension

Location	Condition
Aorta	Coarctation
	Supravalvular aortic stenosis
Left ventricle	Left ventricular failure of any cause
	Aortic stenosis
	Aortic regurgitation
	Congenital subaortic stenosis
	Hypertrophic cardiomyopathy
	Constrictive pericarditis
	Restrictive cardiomyopathy
	Dilated cardiomyopathy
	Mitral stenosis
	Mitral regurgitation
Left atrium	Ball-valve thrombus
	Myxoma
	Cor triatriatum
Pulmonary veins	Congenital pulmonary vein stenosis
	Mediastinitis
	Mediastinal fibrosis
	Mediastinal neoplasm

Causes of LHD-PH

- Although mitral stenosis was a common cause of pulmonary venous hypertension decades ago, heart failure with a preserved ejection fraction (HFpEF) is a common cause of pulmonary venous hypertension currently.

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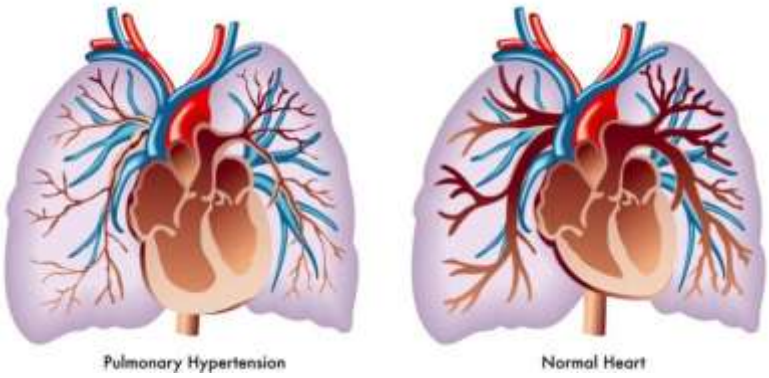


Pathophysiology

Pathophysiology

- Primary vascular changes in the arterial wall may be absent in group 2 PH.
- Capillary and arterial remodelling develop as a result of backward transmission of increased pulmonary venous pressure.

Pathophysiology

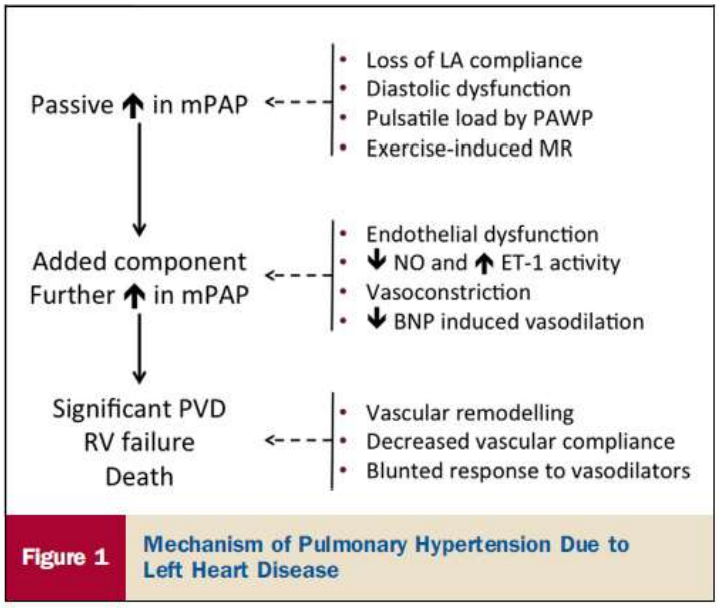
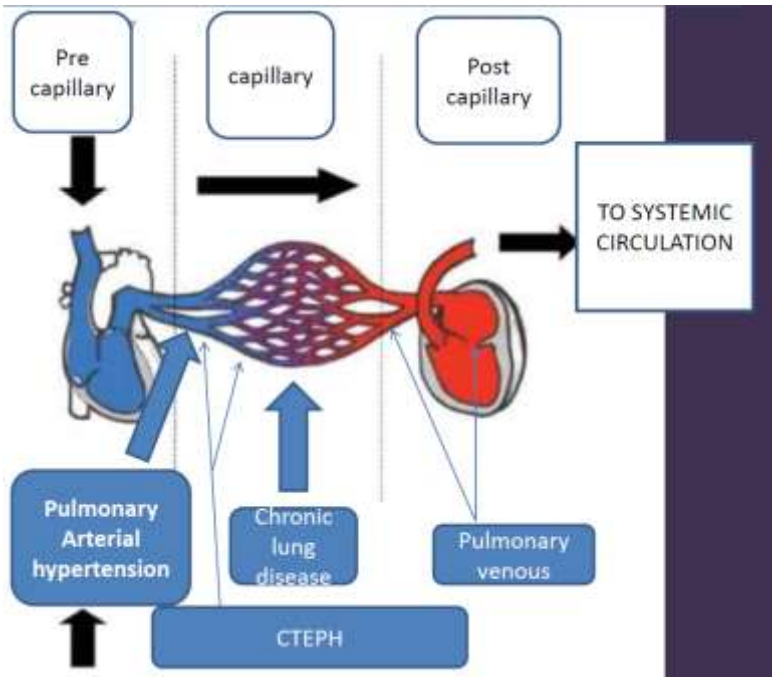


Figure 1 Mechanism of Pulmonary Hypertension Due to Left Heart Disease



Haemodynamic definitions of pulmonary hypertension

Definition	Characteristics[a]	Clinical group(s)[b]
PH	PAPm ≥25 mmHg	All
Pre-capillary PH	PAPm ≥25 mmHg PAWP ≤15 mmHg	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	PAPm ≥25 mmHg PAWP >15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR ≤3 WU[c]	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥7 mmHg and/or PVR >3 WU[c]	

CO = cardiac output; DPG = diastolic pressure gradient (diastolic PAP - mean PAWP); mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WU = Wood units.

[a]All values measured at rest; see also section 7.
[b]According to Table 4.
[c]Wood Units are preferred to dynes.s.cm^{-5}.

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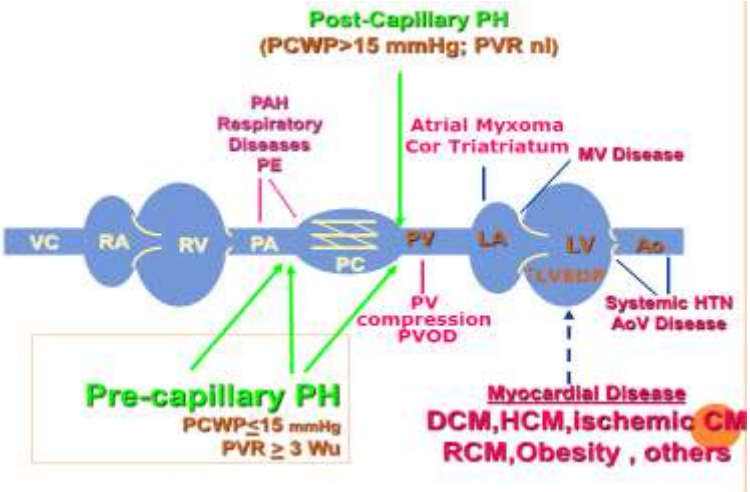
Pathophysiology



Pathophysiology

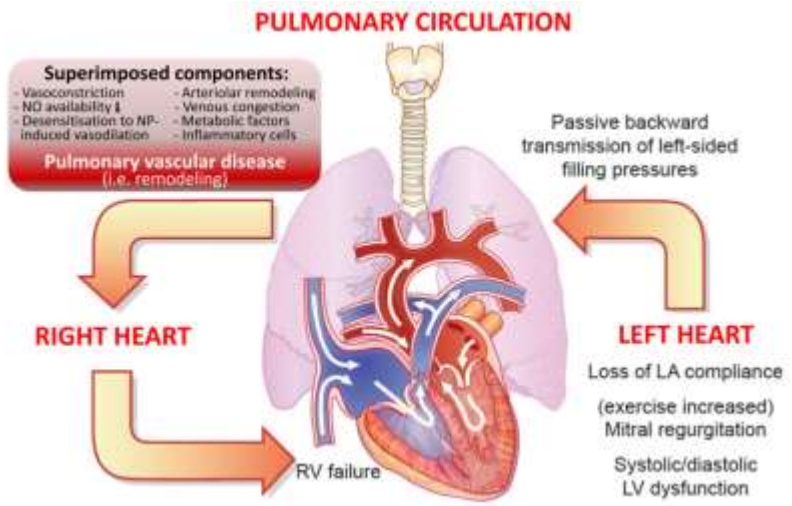
Table 2 Proposed Definition and Classification of PH-LHD

Terminology	PAWP	Diastolic PAP – PAWP
Isolated post-capillary PH	>15 mm Hg	<7 mm Hg
Combined post-capillary and pre-capillary PH	>15 mm Hg	≥7 mm Hg

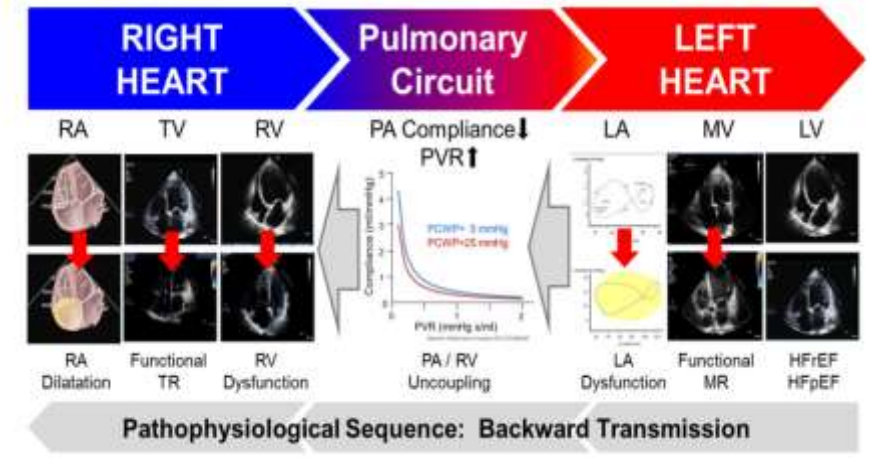
Hemodynamic measurements are taken under resting conditions.

The prevalence of Cpc-PH in patients with HF is 12–38%

Pathophysiology



Pathophysiology



Pathophysiology

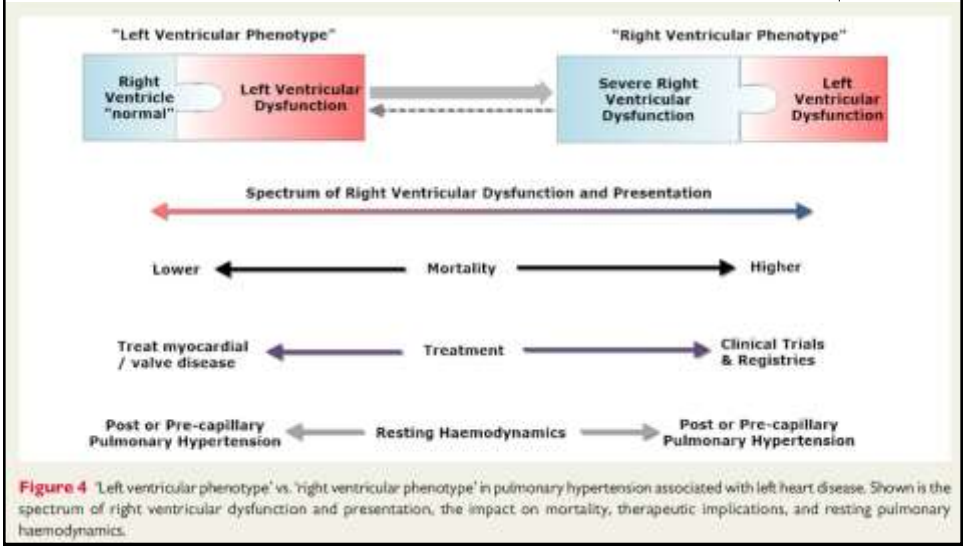
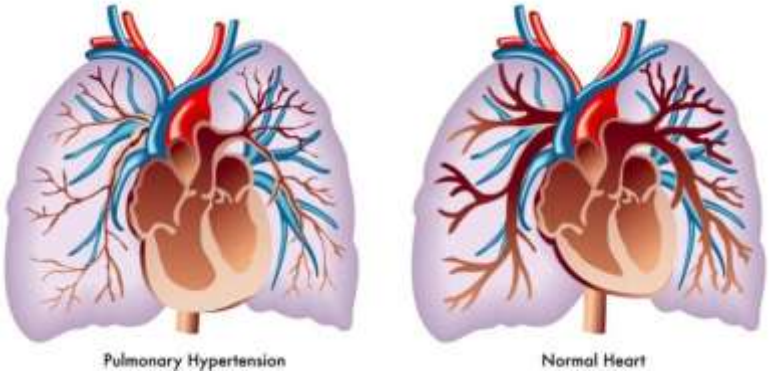
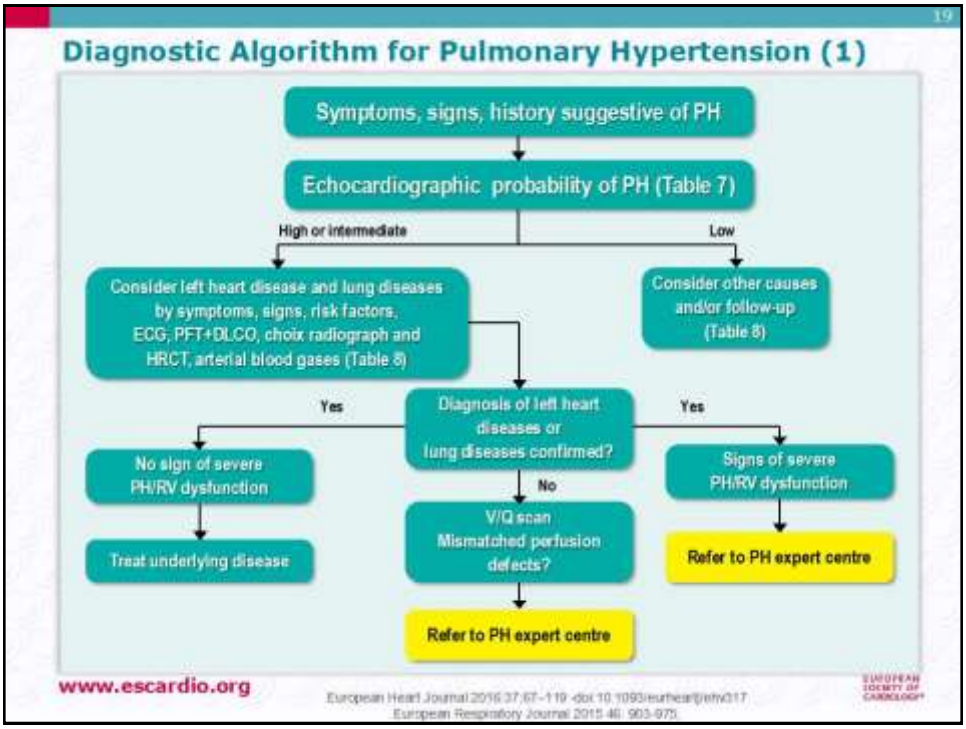


Figure 4 'Left ventricular phenotype' vs. 'right ventricular phenotype' in pulmonary hypertension associated with left heart disease. Shown is the spectrum of right ventricular dysfunction and presentation, the impact on mortality, therapeutic implications, and resting pulmonary haemodynamics.

Left sided Pulmonary Hypertension



Diagnosis



Examples of key factors suggestive of Group 2 pulmonary hypertension

Clinical presentation	Echocardiography	Other features
Age >65 years	Structural left heart abnormality · Disease of left heart valves · LA enlargement (>4.2 cm) · Bowing of the IAS to the right · LV dysfunction · Concentric LV hypertrophy and/or increased LV mass	ECG · LVH and/or LAH · AF/Afib · LBBB · Presence of Q waves
Symptoms of left heart failure	Doppler indices of increased filling pressures · Increased E/e' · >Type 2-3 mitral flow abnormality	Other imaging · Kerley B lines · Pleural effusion · Pulmonary oedema · LA enlargement
Features of metabolic syndrome	Absence of: · RV dysfunction · Mid systolic notching of the PA flow · Pericardial effusion	
History of heart disease (past or current)		
Persistent atrial fibrillation		

AF = atrial flutter; Afib = atrial fibrillation; ECG = electrocardiogram; IAS = inter-atrial septum; LA = left atrium; LAH = left anterior hemiblock; LBBB= left bundle branch block; LV = left ventricle; LVH = left ventricular hypertrophy; PA = pulmonary artery; RV = right ventricle.

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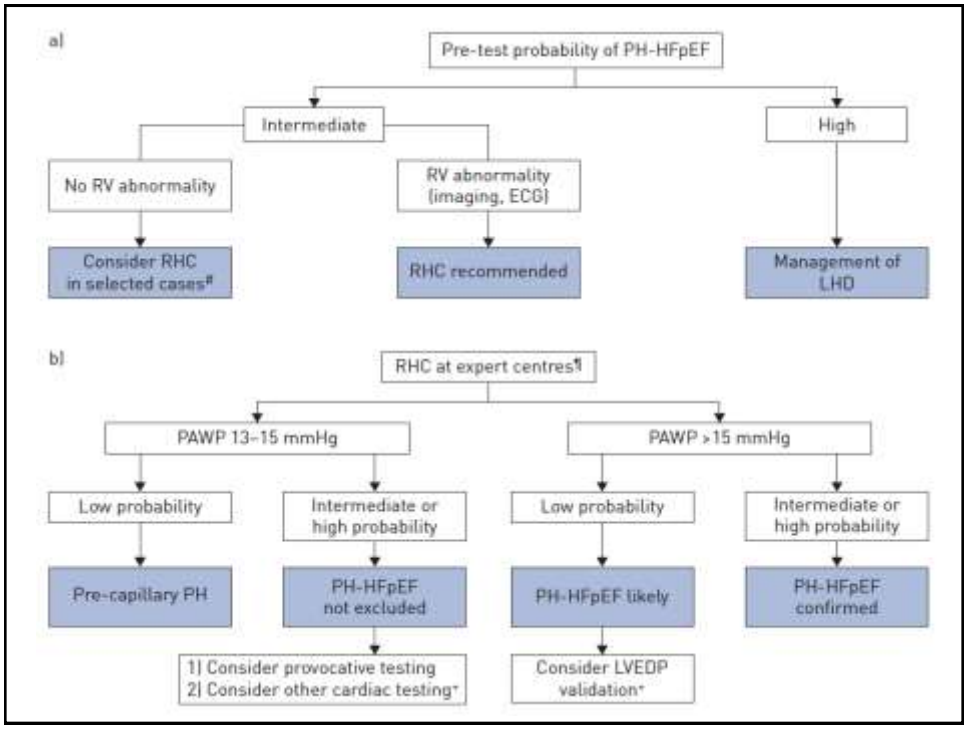
Recognition of PH resulting from HFpEF is more challenging, and HFpEF is commonly mistaken for IPAH.

Distinguishing Pulmonary Arterial Hypertension From Heart Failure With Preserved Ejection Fraction

CHARACTERISTIC	PULMONARY ARTERIAL HYPERTENSION MORE LIKELY	HFPEF MORE LIKELY
Age	Younger	Older
Comorbid conditions: diabetes mellitus, hypertension, coronary artery disease, obesity (metabolic syndrome)	Often absent	Often present and multiple
Symptoms: paroxysmal nocturnal dyspnea, orthopnea	Often absent	Often present
Cardiac examination	Right ventricular heave, loud P_2, tricuspid regurgitation murmur	Sustained left ventricular impulse, S_4
Chest x-ray	Clear lung fields	Pulmonary vascular congestion, pleural effusions, pulmonary edema
Chest CT	Often clear lungs	Mosaic perfusion pattern, ground-glass opacities consistent with chronic interstitial edema
ECG	Right axis deviation, right ventricular enlargement	Left atrial enlargement, left ventricular enlargement atrial fibrillation, no right axis deviation
Natriuretic peptides	Often elevated	Often elevated
Echocardiography showing left atrial enlargement, left ventricular hypertrophy	Absent	Often present
Echocardiography showing diastolic dysfunction	Grade 1 common	Grade 2, 3 common
Echocardiography of right ventricle	Often enlarged, may share the apex	Often normal, mildly enlarged
Echocardiography showing pericardial effusion	Sometimes	Rare



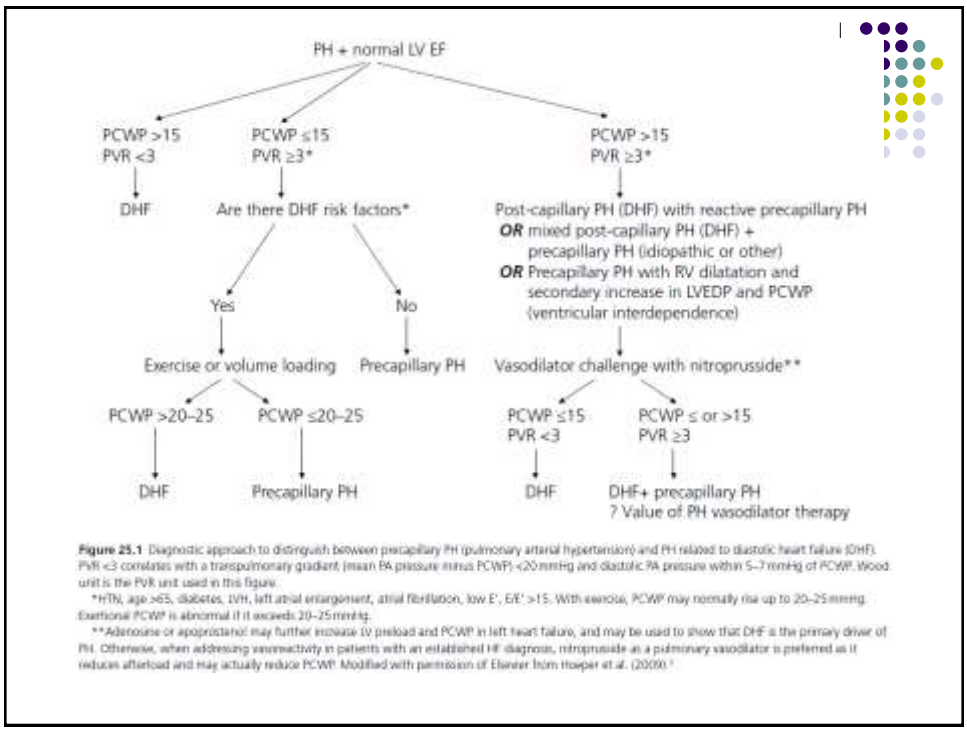


Figure 25.1 Diagnostic approach to distinguish between precapillary PH (pulmonary arterial hypertension) and PH related to diastolic heart failure (DHF). PVR <3 correlates with a transpulmonary gradient (mean PA pressure minus PCWP) <20 mmHg and diastolic PA pressure within 5–7 mmHg of PCWP. Wood unit is the PVR unit used in this figure.

*HTN, age >65, diabetes, LVH, left atrial enlargement, atrial fibrillation, low E', E/E' >15. With exercise, PCWP may normally rise up to 20–25 mmHg. Exertional PCWP is abnormal if it exceeds 20–25 mmHg.

**Adenosine or epoprostenol may further increase LV preload and PCWP in left heart failure, and may be used to show that DHF is the primary driver of PH. Otherwise, when addressing vasoreactivity in patients with an established HF diagnosis, nitroprusside as a pulmonary vasodilator is preferred as it reduces afterload and may actually reduce PCWP. Modified with permission of Elsevier from Hoeper et al. (2009).[1]

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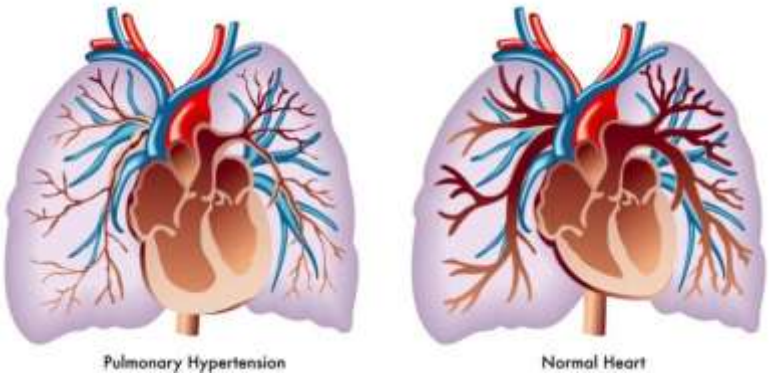

Management

Management

- Whereas targeted therapies are available for pulmonary arterial hypertension (PAH), these treatments have not been adequately evaluated or are not indicated and may even be harmful in patients with PH related to LHD.

Management of pulmonary hypertension in left heart disease

Recommendations	Class	Level
Optimization of the treatment of the underlying condition is recommended before considering assessment of PH-LHD (i.e. treating structural heart disease).	I	C
It is recommended to identify other causes of PH (i.e. COPD, SAS, PE, CTEPH) and to treat them when appropriate before considering assessment of PH-LHD.	I	C
It is recommended to perform invasive assessment of PH in patients on optimized volume status.	I	C
Patients with PH-LHD and a severe pre-capillary component as indicated by a high DPG and/or high PVR should be referred to an expert PH centre for a complete diagnostic work-up and an individual treatment decision.	IIa	C
The importance and role of vasoreactivity testing is not established in PH-LHD, except in patients who are candidates for heart transplantation and/or LV assist device implantation.	III	C
The use of PAH approved therapies is not recommended in PH-LHD.	III	C

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Management

- Optimized treatment of the underlying LHD including medical treatments (reaching the target dosages) and interventional therapies (e.g. CRT, ICD, LVAD, MitraClip) usually helps to lower left-sided filling pressure and is always the primary aim in HF patients.

Management

- There is good evidence in patients with LV HF and functional MR, that proper treatment of the mitral valve including catheter-based approaches such as Mitral Clipping or Cardio-Band lead to substantial improvement of pulmonary haemodynamics, including reductions of the mean PAP and PAWP (mainly via reduction of the v-wave), and a profound improvement of cardiac index.

Key Message

Hence, MR has to be considered as the potential cause of PH in LV HF, and appropriate valve repair should be initiated in patients who are on optimized medical treatment.

Management

- Reductions of PAP were not achieved by targeted PAH drugs in this trial, but by optimized HF treatment including adjustment of diuretics (CHAMPION Trial).

Management

- The results of the **ENABLE trials** with bosentan were recently published, confirming that blocking endothelin-1 has no effect on outcome in patients with HFrEF.
- The **SOCRATES programme** assessed the role of vericiguat, a guanylate cyclase stimulator, in HFrEF and HFpEF.

Management

- In **SOCRATESReduced**, vericiguat did not change the NT-proBNP level at 12 weeks compared with placebo.
- Similar results were observed in **SOCRATES-Preserved**, with no effect on left atrial volume index.

Key Message

Based on the current evidence, the use of targeted PAH therapies in patients with PH related to left HF is discouraged, and selected patients with Cpc-PH and/or RV phenotype should be referred to centres with expertise in both HF and PH, and should—whenever possible—be included into clinical trials.

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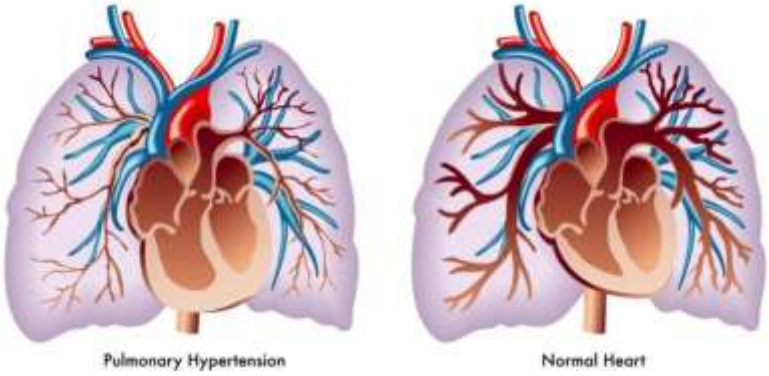
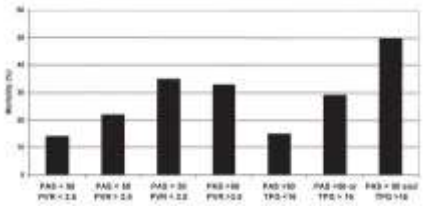


Prognosis

Pre-transplant pulmonary hypertension, even when reversible to a PVR of <2.5 WU, is associated with a higher mortality



Pre-Transplant Reversible Pulmonary Hypertension Predicts Higher Risk for Mortality After Cardiac Transplantation

J Heart Lung Transplant 2005;24:170 –7

Key Message

HF is often associated with PH and RV dysfunction, which have an important impact on disease progression, morbidity, and mortality, and this tends to be underestimated in the field of HF.