Clinical Challenges in *Pulmonary Hypertension*

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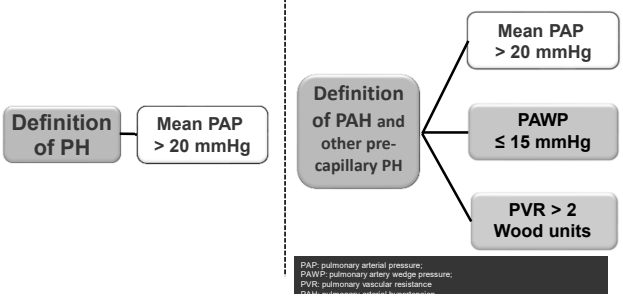
Hemodynamic Definitions of Pulmonary Hypertension



Humbert M, et al. 2022 ESC/ERS Guidelines for Diagnosis and Treatment for Pulmonary Hypertension. European Heart Journal 2022; 00: 1–114 [DOI: 10.1093/eurheartj/ehac237]

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Clinical Classification of Pulmonary Hypertension

1. Pulmonary arterial hypertension
- 1.1 Idiopathic
  - 1.1.1 Non-responders at vasoreactivity testing
  - 1.1.2 Acute responders at vasoreactivity testing
- 1.2 Heritable
- 1.3 Associated with drugs and toxins
- 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

2. PH due to LHD
- 2.1 Heart failure:
  - 2.1.1 with preserved ejection fraction
  - 2.1.2 with reduced or mildly reduced ejection fraction
- 2.2 Valvular heart disease
- 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3. PH due to 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

4. CTEPH and PA obstruction

5. PH with unclear multifactorial mechanisms
- 5.1 Haematological disorders
- 5.2 Systemic disorders
- 5.3 Metabolic disorders
- 5.4 Chronic renal failure with or without haemodialysis
- 5.5 Pulmonary tumour thrombotic microangiopathy
- 5.6 Fibrosing mediastinitis

Humbert M, et al. 2022 ESC/ERS Guidelines for Diagnosis and Treatment for Pulmonary Hypertension. European Heart Journal 2022; 00: 1–114 [DOI: 10.1093/eurheartj/ehac237]

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Suggested new classification of PH (7th WSPH 2024)

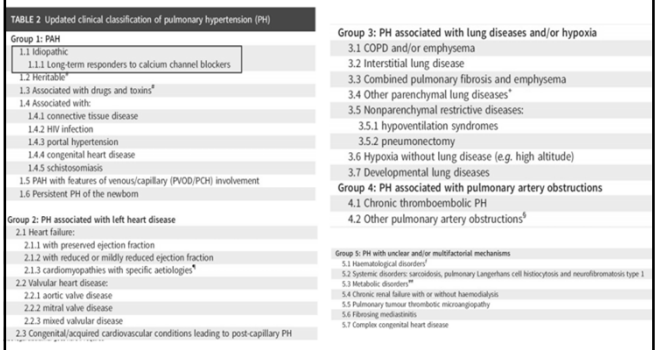

TABLE 2 Updated clinical classification of pulmonary hypertension (PH)

Group 1: PAH
- 1.1 Idiopathic
  - 1.1.1 Long-term responders to calcium channel blockers
- 1.2 Heritable[e]
- 1.3 Associated with drugs and toxins[#]
- 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
  - 2.1.3 cardiomyopathies with specific aetiologies[¶]
- 2.2 Valvular heart disease:
  - 2.2.1 aortic valve disease
  - 2.2.2 mitral valve disease
  - 2.2.3 mixed valvular disease
- 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH

Group 3: PH associated with lung diseases and/or hypoxia
- 3.1 COPD and/or emphysema
- 3.2 Interstitial lung disease
- 3.3 Combined pulmonary fibrosis and emphysema
- 3.4 Other parenchymal lung diseases[+]
- 3.5 Nonparenchymal restrictive diseases:
  - 3.5.1 hypoventilation syndromes
  - 3.5.2 pneumonectomy
- 3.6 Hypoxia without lung disease (e.g. high altitude)
- 3.7 Developmental lung diseases

Group 4: PH associated with pulmonary artery obstructions
- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions[§]

Group 5: PH with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders[‡]
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis and neurofibromatosis type 1
- 5.3 Metabolic disorders[**]
- 5.4 Chronic renal failure with or without haemodialysis
- 5.5 Pulmonary tumour thrombotic microangiopathy
- 5.6 Fibrosing mediastinitis
- 5.7 Complex congenital heart disease

Chin KM, Gaine SP, Gerges C, et al. Treatment algorithm for pulmonary arterial hypertension. Eur Respir J 2024; in press: 2401325 [DOI:10.1183/13993003.01325-2024].

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Hemodynamic Definitions of Pulmonary Hypertension

Definition	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ≤15 mmHg PVR >2 WU
Isolated post-capillary PH	mPAP >20 mmHg PAWP >15 mmHg PVR ≤2 WU
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

Humbert M, et al. 2022 ESC/ERS Guidelines for Diagnosis and Treatment for Pulmonary Hypertension. European Heart Journal 2022; 00: 1–114 [DOI: 10.1093/eurheartj/ehac237]

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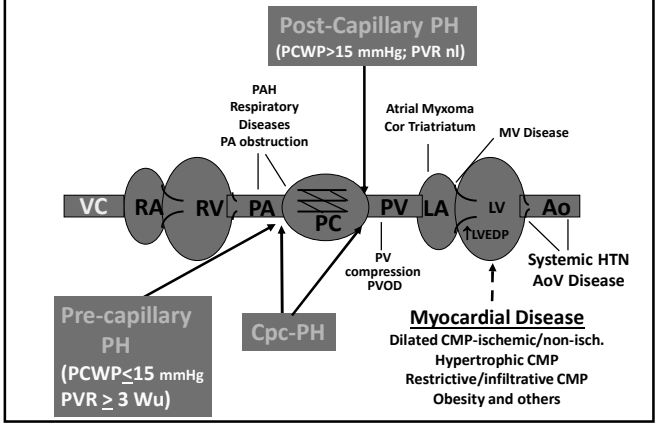
Pulmonary Hypertension: Define Lesion



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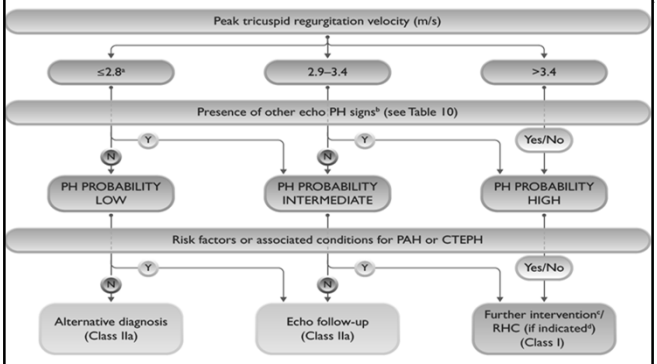
Echocardiographic probability of pulmonary hypertension



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Additional echocardiographic signs suggestive of pulmonary hypertension

A: The ventricles	B: Pulmonary artery	C: Inferior vena cava and RA
RV/LV basal diameter/ area ratio >1.0	RVOT AT <105 ms and/or mid-systolic notching	IVC diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration)
Flattening of the interventricular septum (LVEI >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/s	RA area (end-systole) >18 cm^2
TAPSE/sPAP ratio <0.55 mm/mmHg	PA diameter >AR diameter PA diameter >25 mm	

Humbert M, et al. 2022 ESC/ERS Guidelines for Diagnosis and Treatment for Pulmonary Hypertension. European Heart Journal 2022; 00: 1–114 [DOI: 10.1093/eurheartj/ehac237]

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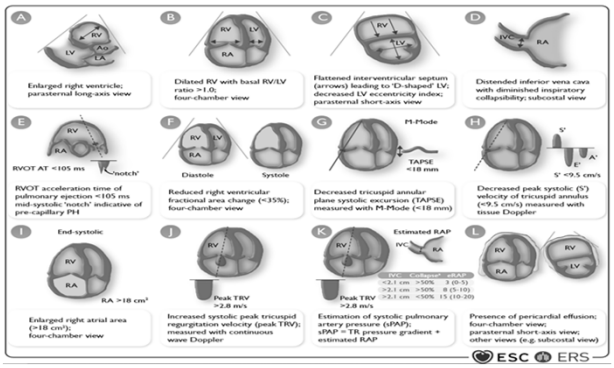
Transthoracic Echocardiographic Parameters in Assessment of PH

- Echocardiography with more detail Right heart imaging for all pt with suspected PH



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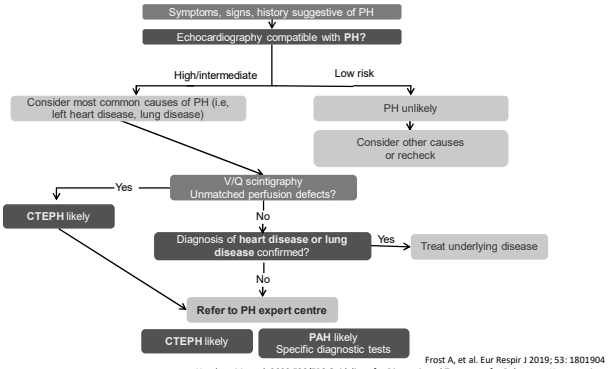
2022 ESC/ERS Guidelines on PH *Diagnosis of PH*



Frost A, et al. Eur Respir J 2019; 53: 1801904

Humbert M, et al. 2022 ESC/ERS Guidelines for Diagnosis and Treatment for Pulmonary Hypertension. European Heart Journal 2022; 00: 1–114 [DOI: 10.1093/eurheartj/ehac237]

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Right Heart Catheterization

Recommendations for right heart catheterization and vasoreactivity testing

ESC ERS

Recommendations	Class	Level
Right heart catheterization (RHC)		
RHC is recommended to confirm the diagnosis of PH (especially PAH or CTEPH), and to support treatment decisions	I	B
In patients with suspected or known PH, it is recommended to perform RHC in experienced centres	I	C
It is recommended that RHC comprises a complete set of haemodynamics, and is performed following standardized protocols	I	C

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2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (European Heart Journal; 2022 – doi: 10.1093/eurheartj/ehac237 and European Respiratory Journal; 2022 – doi: 10.1183/13993003.00879-2022)

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45 y/o female with chronic progressive dyspnea

- ผู้ป่วยหญิงไทยอายุ **45** ปี
- มาโรงพยาบาลด้วยอาการเหนื่อยง่ายมากขึ้น **6** เดือนก่อนมาโรงพยาบาล **FCIII-IV**
- ประวัติอดีตเป็น **Systemic sclerosis, HT, DVT**
- สูบบุหรี่ **10 packs-year** หยุดสูบมาสามปี

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45 y/o female with chronic progressive dyspnea

- BT 36.7, HR 110 /min, RR 28/min, BP 120/65 mmHg, O2 saturation 87% on room air
- Auscultation revealed a grade III systolic murmur along LLPSB with an accentuated P2
- Dry crackles were noted at both lower lung fields
- Mild liver enlargement and mild pitting edema noted

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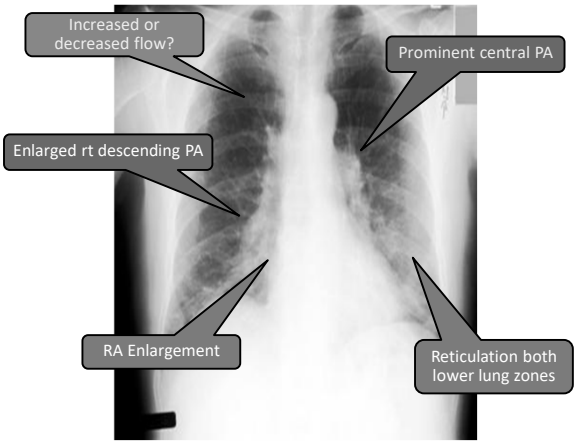

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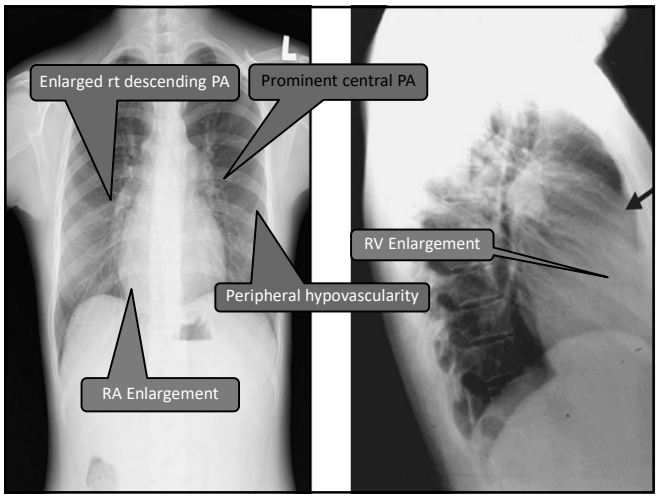

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Reticulation with low lung volume	**L: lymphatic** **I: Infection** **F: Fibrosis** **E: edema**
Lower lobe predominant	**A: Asbestosis, Aspiration** **P: Pulmonary fibrosis** **C: Collagen vascular disease, COP**
PH signs plus:	**Peripheral oligemia** **Increased flow: ASD, VSD, PDA**

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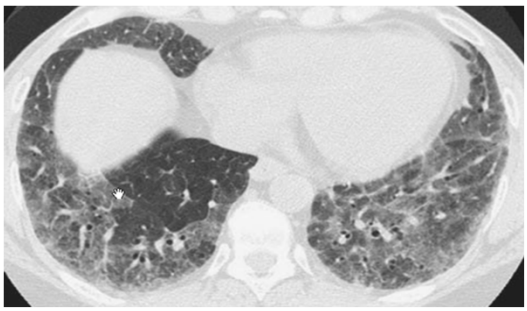

NSIP	Less traction bronchiectasis, more GGO
UIP	More traction bronchiectasis, less GGO

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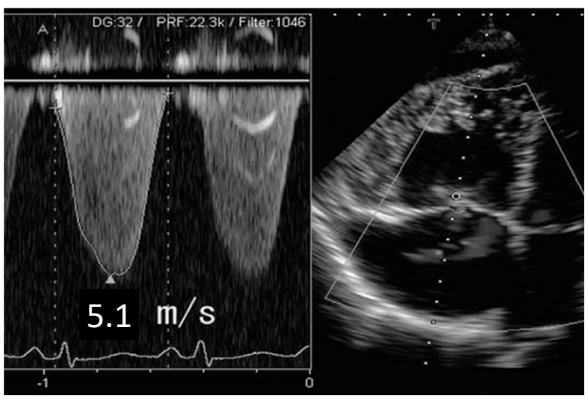

Estimated RAP = 15 mmHg

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Investigation to confirm diagnosis

- **Echocardiogram:**
  - LA and LV are normal, LAVI 22, e/e' 16, LVEF 58%
  - RA and RV are markedly dilated (RV 4.5cm at mid part, RA 24.2 cm2, L=55 mm)
  - Severely impaired RV systolic function (TAPSE =1.0 cm, lateral TDI = 7 cm/sec)
  - Normal MV with mild MR
  - TRV 5.1 m/s, est. RAP 15 mmHg, RVSP 119
  - ASD 1.8 cm

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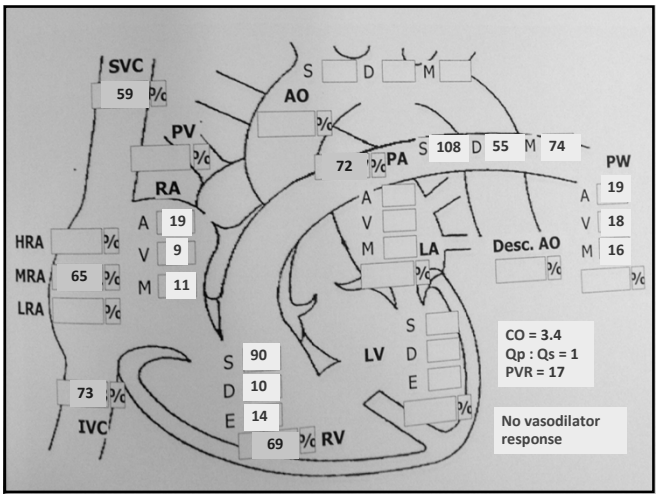

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TABLE 9.1. *Detection of left-to-right shunt by oximetry*

Level of shunt	Criteria for significant step-up: Mean of distal chamber samples	Mean of proximal chamber samples	Highest value in distal chamber	Highest value in proximal chamber	Approximate minimal Q_p/Q_s required for detection (assuming SBFI = 3L/min/M²)	Possible causes of step-up
	O_2% sat	O_2 vol%	O_2% sat	O_2 vol%		
Atrial (SVC/IVC to RA)	≥ 7	≥ 1.3	≥ 11	≥ 2.0	1.5–1.9	Atrial septal defect; partial anomalous pulmonary venous drainage; ruptured sinus of Valsalva; VSD with TR; coronary fistula to RA
Ventricular (RA to RV)	≥ 5	≥1.0	≥ 10	≥1.7	1.3–1.5	VSD; PDA with PR; primum ASD; coronary fistula to RV
Great Vessel (RV to PA)	≥ 5	≥ 1.0	≥5	≥1.0	≥1.3	PDA; aorta-pulmonic window; aberrant coronary artery origin
ANY LEVEL (SVC to PA)	≥ 7	≥1.3	≥ 8	≥1.5	≥1.5	All the above

Abbreviations: SVC and IVC, superior and inferior vena cavae; RA, right atrium; RV, right ventricle; PA, pulmonary artery; VSD, ventricular septal defect; TR, tricuspid regurgitation; PDA, patent ductus arteriosus; PR, pulmonic regurgitation; ASD, atrial septal defect, SBFI, systemic blood flow index; Q_p/Q_s, pulmonary to systemic flow ratio.

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Causes of Oxygen Step Up

- **Step up at atrial level**
  - ASD
  - PAPVC
  - VSD with TR
  - RSOV => RA
  - LV => RA shunt
  - Cor AV Fistula => RA
- **Step up at ventricle level**
  - VSD
  - RSOV => RV
  - Low ASD
  - Cor AV Fistula => RA
  - PDA with PR
  - AVSD
- **Step up at great vessel level**
  - Patent Ductus Arteriosus
  - AP Window
  - Outlet VSD
  - Coronary origin from PA

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Real-Life Situations

- Elevated PAWP (16 mmHg) — **Group 2**: LHD
- NSIP — **Group 3**: NSIP
- Drug?? — **Group 1**: DPAH
- ASD (ASD, step up O2) — **Group 1**: ASD
- Chronic left leg DVT — **Group 4**: CTEPH
- Systemic sclerosis — **Group 1: SSc**

?? Group 5: miscellaneous

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Real-Life Situations

- Elevated PAWP (16 mmHg) — **Group 2**: LHD
- NSIP — **Group 3**: NSIP
- Drug?? — **Group 1**: DPAH
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?? Group 5: miscellaneous

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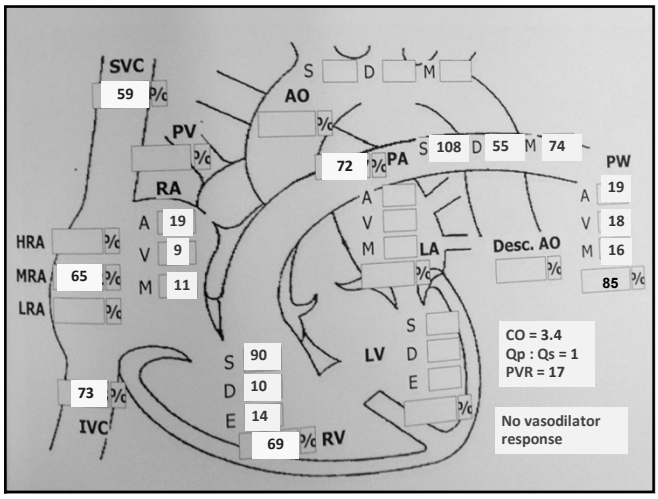

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Errors in Sampling

- Obtaining samples in different physiologic states (arrhythmias, acidosis, hypoventilation)
- Partial wedging of catheter (PA)
  - Overwedge (low O2 saturation)
- Non representative sampling (PVs)

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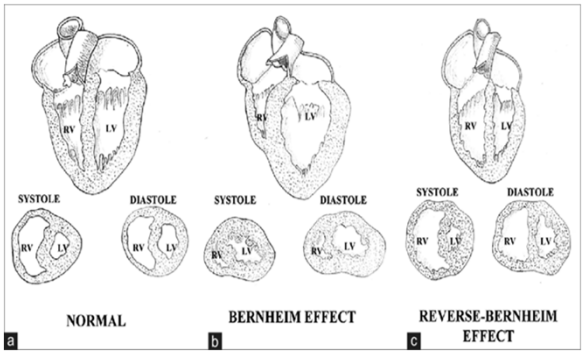
The reverse Bernheim effect



LVEDP > RVEDP RVEDP > LVEDP

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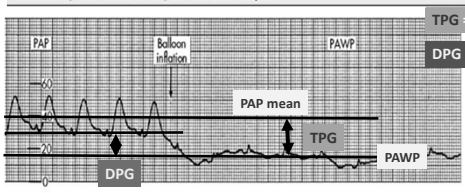
Ipc-PH, Cpc-PH, TPG, DPG

TABLE 1 Haemodynamic criteria of pulmonary hypertension (PH)

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

mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; WU: Wood Units; CO: cardiac output.



Chin KM, Gaine SP, Gerges C, et al. Treatment algorithm for pulmonary arterial hypertension. Eur Respir J 2024; in press: 2401325 [DOI:

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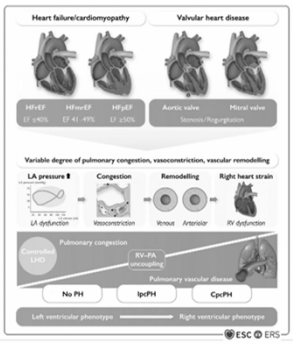
Pulmonary Hypertension Associated with Left Heart Disease

Pulmonary hypertension associated with left heart disease (group 2)



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Recommendations for PH associated with left heart disease

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Recommendations	Class	Level
In patients with LHD, optimizing treatment of the underlying condition is recommended before considering assessment of suspected PH	I	A
RHC is recommended for suspected PH in patients with LHD, if it aids management decisions	I	C
RHC is recommended in patients with severe tricuspid regurgitation with or without LHD prior to surgical or interventional valve repair	I	C
For patients with LHD and suspected PH with features of a severe pre-capillary component and/or markers of RV dysfunction, referral to a PH centre for a complete diagnostic work-up is recommended	I	C

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Recommendations for PH associated with left heart disease

Recommendations	Class	Level
In patients with LHD and CpcPH with a severe pre-capillary component (e.g. PVR >5 WU), an individualized approach to treatment is recommended	I	C
When patients with PH and multiple risk factors for LHD, who have a normal PAWP at rest but an abnormal response to exercise or fluid challenge, are treated with PAH drugs, close monitoring is recommended	I	C
In patients with PH at RHC, a borderline PAWP (13–15 mmHg) and features of HFpEF, additional testing with exercise or fluid challenge may be considered to uncover post-capillary PH	IIb	C
Drugs approved for PAH are not recommended in PH-LHD	III	A

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Characteristic features of PH associated with LV diastolic dysfunction

Factors favouring diagnosis of LV diastolic dysfunction in the presence of PH as assessed by Doppler echocardiography

1. Clinical features
Age > 65 years
Elevated systolic BP
Elevated pulse pressure
Obesity, metabolic syndrome
Hypertension
Coronary artery disease
Diabetes mellitus
Atrial fibrillation

2. Echocardiography
LA enlargement
Concentric remodelling of the LV (relative wall thickness > 0.45)
LV hypertrophy
Presence of echocardiographic indicators of elevated LV filing pressure

3. Interim evaluation (after echocardiography)
Symptomatic response to diuretics
Exaggerated increase in systolic BP with exercise
Re-evaluation of chest radiograph consistent with HF

BP: blood pressure; HF: heart failure;
LA: left atrium; LV: left ventricle/ventricular

Adapted from Galiè N, *et al. Eur Heart J* 2009; 30:2493-537.
ESC guideline 2015. EHJ 2015

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Diastolic dysfunction is associated with increased PH prevalence

- Left-sided heart failure is known to cause PH
- Up to 44% of all HF patients have preserved EF (HFpEF)
- PH is common (83%) in HFpEF
- PH can be severe in patients presenting with HFpEF
  - Suggests that pulmonary vasculopathy may be a contributing factor

But remember:

- PAWP may be normal in HFpEF
- When in doubt do a LVEDP and fluid challenge or excercise RHC

HF: heart failure; HFpEF: heart failure with preserved ejection fraction;
LVEDP: left ventricular end diastolic pressure; PAWP: pulmonary artery wedge pressure

Lam CS, *et al. J Am Coll Cardiol* 2009; 53: 1119-126.

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Trials of PAH-specific therapies in heart failure have been largely disappointing

Drug Author, year	Study acronym	Patients	Design	Primary endpoint	Results
Epoprostenol Califf, 1996	FIRST	*n* = 4 Sev	1:1 randomisation event-driven Mean dose 4 ng/kg/min	Sur val	Early termination (trend to increased survival in treated group)
Bosentan Packer, 2005	REACH-1		domisatio	linical	Early termination (drug-induced fluid retention in the treated group)
Bosentan Kalra, 2002	ENABLE	*n* = 1613 Severe HF		Mortality and hospital stays	No effect
Darusentan Lüscher, 2002	HEAT	*n*	ration s of 30, 100, g	namic	Increased CO No change in PAWP
Darusentan Anand, 2004	EARTH	*n* = NYHA II-IV	5:1 randomisation 6 month duration doses of 10, 25, 50, 100, 300 mg	anges by MRI + clinical events	No effect

CO: cardiac output; HF: heart failure; LV: left ventricular;
MRI: magnetic resonance imaging; NYHA: New York Heart Association; PAWP: pulmonary artery wedge pressure

Vachiéry JL, *et al. J Am Coll Cardiol* 2013; 62:D100-8.

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Real-Life Situations

- Elevated PAWP (16 mmHg) — **Group 2**: LHD
- NSIP — **Group 3**: NSIP
- Drug?? — **Group 1**: DPAH
- ASD (ASD, step up O2) — **Group 1**: ASD
- Chronic left leg DVT — **Group 4**: CTEPH
- Systemic sclerosis — **Group 1: SSc**

?? Group 5: miscellaneous

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Investigation to confirm diagnosis

- **Pulmonary Function Test**
  - FVC 2.56 L (65.7% of predicted value)
  - FEV1 2.16 L (64.4% of predicted value)
  - FEV1/FVC ratio 84%
  - Residual volume 1.73 L (71.3% of predicted value)
  - Carbonmonoxide diffusion capacity (DLCO) 31.0% of predicted value

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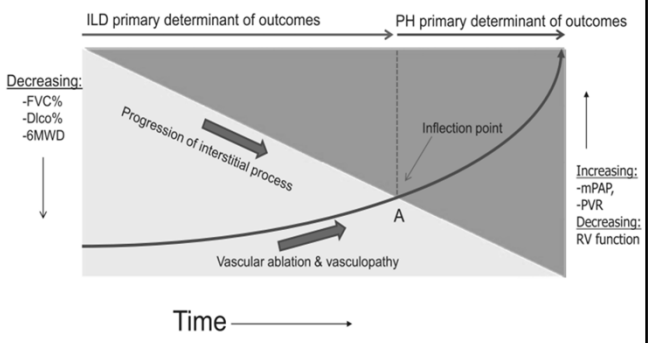
PH-ILD as a Spectrum of Disease



King CS, et al. Curr Opin Pulm Med 2019, 25:459–467

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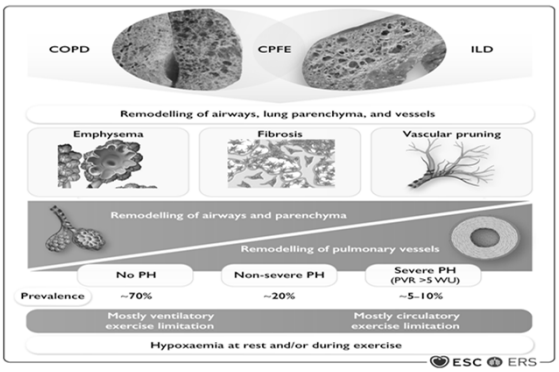
Group 3 Pulmonary Hypertension



2022 ESC/ERS Guidelines for the diagnosis and treatment of PH. European Heart Journal (2022) 00, 1–114

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PH in chronic lung disease: *Differential diagnosis between groups 1 and 3*

Criteria favouring group 1 (PAH)	Parameter	Criteria favouring group 3 (PH due to lung disease)
Normal or mildly impairment: • FEV1 > 60% predicted (COPD) • FVC > 70% predicted (IPF)	**Ventilatory function**	Moderate to very severe impairment: • FEV1 < 60% predicted (COPD) • FVC < 70% predicted (IPF)
Absence of or only modest airway or parenchymal abnormalities	**High-resolution CT scan**	Characteristic airway and/or parenchymal abnormalities
Features of exhausted circulatory reserve: • Preserved breathing reserve • Reduced oxygen pulse • Low CO/VO_2 slope • Mixed venous oxygen saturation at lower limit • No change or decrease in $PaCO_2$ during exercise		Features of exhausted ventilator reserve: • Reduced breathing reserve • Normal oxygen pulse • Normal CO/VO_2 slope • Mixed venous oxygen saturation above lower limit • Increase in $PaCO_2$ during exercise

CO: cardiac output; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity;IPF: idiopathic pulmonary fibrosis; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; VO_2: oxygen consumption

Seeger W, *et al. J Am Coll Cardiol* 2013; 62:D109-16.
ESC guideline 2015. EHJ 2015
Nathan SD , et al. Eur Respir J 2019; 53: 1801914

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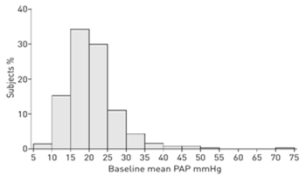
The clinical course of PH in mild to moderate IPF: information from the Artemis-IPF study

- The Artemis-IPF study aimed to study the effects of ambrisentan in IPF
- Stratification was made by mean of RHC:



	All subjects				Group 3# PH subjects			
	Ambrisentan		Placebo		Ambrisentan		Placebo	
	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD	n
Change in mean PAP mmHg	−1.1±5.99	73	0.4±5.85	44	−5.3±4.27	12	−1.1±9.39	7
Change in cardiac output L·min^{-1}	0.56±1.45	72	−0.38±1.30	43	0.03±1.38	12	0.44±0.9	7
Change in PVR mmHg·L^{-1}·min	−0.41±1.19	72	0.14±0.79	43	−0.70±1.31	12	−0.51±1.56	7

RHC at week 48

follow up for all groups

Raghu G, et al. Eur Respir J 2015 (epub)

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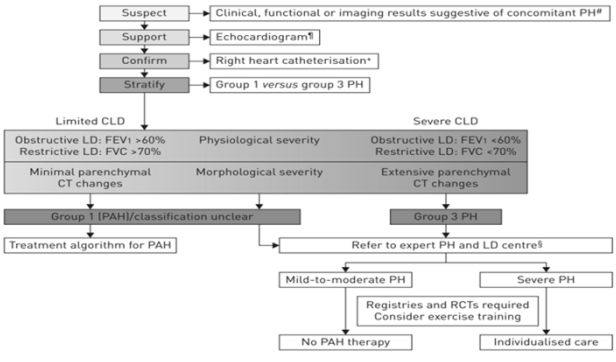
Management of PH in chronic lung disease setting

Underlying lung disease	mPAP < 25 mmHg at rest	mPAP ≥ 25 mmHg and < 35 mmHg at rest	mPAP ≥ 35 mmHg at rest
COPD with FEV1 ≥ 60% of predicted	**No PH**	**PH classification uncertain**	**PH classification uncertain: discrimination between PAH (group 1) with concomitant lung disease or PH caused by lung disease (group 3)** **Refer to a centre with expertise in both PH and chronic lung disease**
IPF with FVC ≥ 70% of predicted CT: absence of or only very modest airway or parenchymal abnormalities	**No PAH treatment recommended**	**No data currently support treatment with PAH-approved drugs**	
COPD with FEV1 < 60% of predicted	**No PH**	**PH-COPD, PH-IPF, PH-CPFE**	**Severe PH-COPD, severe PH-IPF, severe PH-CPFE**
IPF with FVC < 70% of predicted Combined pulmonary fibrosis and emphysema on CT	**No PAH treatment recommended**	**No data currently support treatment with PAH-approved drugs**	**Refer to a centre with expertise in both PH and chronic lung disease for individualised patient care because of poor prognosis; RCTs required**

Seeger W, *et al. J Am Coll Cardiol* 2013; 62:D109-16.
ESC guideline 2015. EHJ 2015
Nathan SD , et al. Eur Respir J 2019; 53: 1801914

48

ILD and Pulmonary Hypertension



Eur Respir J 2019; 53: 1801914 [https://doi.org/10.1183/13993003.01914-2018].

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Treatment of PH in Lung diseases

Recommendations	Class[a]	Level[b]
If PH is suspected in patients with lung disease, it is recommended that echocardiography[c] be performed and the results interpreted in conjunction with ABG, PFTs including DLCO, and CT imaging	I	C
In patients with lung disease and suspected PH, it is recommended to optimize treatment of the underlying lung disease and, where indicated, hypoxaemia, sleep-disordered breathing, and/or alveolar hypoventilation	I	C
In patients with lung disease and suspected severe PH, or where there is uncertainty regarding the treatment of PH, referral to a PH centre is recommended[d]	I	C
In patients with lung disease and severe PH, an individualized approach to treatment is recommended	I	C
It is recommended to refer eligible patients with lung disease and PH for LTx evaluation	I	C
In patients with lung disease and suspected PH, RHC is recommended if the results are expected to aid management decisions	I	C
Inhaled treprostinil may be considered in patients with PH associated with ILD[72-74]	IIb	B
The use of ambrisentan is not recommended in patients with PH associated with IPF[75,76]	III	B
The use of riociguat is not recommended in patients with PH associated with IIP[181]	III	B
The use of PAH medication is not recommended in patients with lung disease and non-severe PH[e]	III	C

	GRADE			
Recommendations	Quality of evidence	Strength of recommendation	Class[a]	Level[b]
PDE5is may be considered in patients with severe PH associated with ILD (individual decision-making in PH centres)	Very low	Conditional	IIb	C
The use of PDE5is in patients with ILD and non-severe PH is not recommended	Very low	Conditional	III	C

2022 ESC/ERS Guidelines for the diagnosis and treatment of PH. European Heart Journal (2022) 00, 1–114

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Real-Life Situations

- Elevated PAWP (16 mmHg) — **Group 2**: LHD
- NSIP — **Group 3**: NSIP
- Drug?? — **Group 1**: DPAH
- ASD (ASD, step up O2) — **Group 1**: ASD
- Chronic left leg DVT — **Group 4**: CTEPH
- Systemic sclerosis — **Group 1: SSc**

?? Group 5: miscellaneous

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Updated Drug and Toxin-induced PAH (7th WSPH 2024)

TABLE 3 Drugs and toxins associated with pulmonary arterial hypertension (PAH)

Definite association	Possible association
Aminorex	Alkylating agents
Benfluorex	Amphetamines
Carfilzomib	Bevacizumab
Dasatinib	Bortezomib
Dexfenfluramine	Bosutinib
Fenfluramine	Cocaine
Methamphetamines	Diazoxide
Mitomycin C[a]	Direct-acting antiviral agents against hepatitis C virus (sofosbuvir)
Toxic rapeseed oil	Indigo naturalis (Chinese herb Qing-Dai)
	Interferon-α and -β
	Leflunomide
	L-tryptophan
	Phenylpropanolamine
	Ponatinib
	Solvents (trichloroethylene)[a]
	St John's wort

[a]: PAH with features of venous (pulmonary veno-occlusive disease)/capillary (pulmonary capillary haemangiomatosis) involvement.

Definite

1) Mitomycin-C[1-3]
- ❑ Alkylating agents
- ❑ Cause PVOD
  (Case series and epidemiological data)

2) Carfilzomib[4]
- ❑ Proteasome inhibitors
- ❑ Cause PAH
  (Analysis of a national PH registry – VigiBase / Meta-analysis)

Possible

1) Bevacizaumab
2) Bortezomib
3) Indigo naturalis (qingadai) = Indirubin

4. Grynblat J, Khouri C, Hlavaty A, et al. Characteristics and outcomes of patients developing pulmonary hypertension associated with proteasome inhibitors. Eur Respir J 2024; 63: 2302158.

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Real-Life Situations

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?? Group 5: miscellaneous

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6th World Symposium & 2015 ESC Guideline on PH
Updated clinical classification of PAH-CHD

Clinical classification of PAH-CHD

Eisenmenger syndrome PVRi > 6-8 WU*m2, resting O2sat <90%; PASP:SBP >0.75, PAWP < 15; PVR:SVR > 0.5:1
Includes large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of PVR and reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis and multiple organ involvement are usually present

Left-to-right shunts QP:QS > 1.5:1, PVR < 2.3-4.6, PVRi <6-8, positive vasoreactivity test
- Correctable*
- Noncorrectable ASD>2 cm, VSD>1 cm, any size PDA

Includes moderate to large defects. PVR is mildly to moderately increased; systemic-to-pulmonary shunting is still prevalent, whereas cyanosis is not a feature

PAH with coincidental CHD
Marked elevation in PVR in the presence of small cardiac defects, which themselves do not account for development of elevated PVR; clinical picture very similar to IPAH. Defect closure is contra-indicated

Post-operative PAH
CHD is repaired but PAH either persists immediately after surgery or recurs/develops months or years after surgery in the absence of significant post-operative haemodynamic lesions. The clinical phenotype is often aggressive

*Correctable with surgery or intravascular non-surgical procedure
CHD: congenital heart disease; IPAH: idiopathic PAH;
PVR: pulmonary vascular resistance

Simonneau G, *et al. Eur Respir J 2019; 53: 1801913*
ESC guideline 2015. EHJ 2015

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Treatment of PAH-CHD

	Symptom	QP:QS	PASP:SBP	PVR:SVR
Correctable	+	≥ 1.5:1	< 50%	< 1/3
	-	≥ 1.5:1	< 50%	< 1/3
	+	Net L to R	≥ 50%	> 1/3
Non-correctable	+	Net R to L	≥ 2/3	≥ 2/3

2018 AHA/ACC Guideline. Circulation 2019

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Treatment of PAH-CHD

Recommendation Table 18 — Recommendations for shunt closure in patients with pulmonary–systemic flow ratio >1.5:1 based on calculated pulmonary vascular resistance

Recommendations	Class[a]	Level[b]
In patients with an ASD, VSD, or PDA and a PVR <3 WU, shunt closure is recommended	I	C
In patients with an ASD, VSD, or PDA and a PVR of 3–5 WU, shunt closure should be considered	IIa	C
In patients with an ASD and a PVR >5 WU that declines to <5 WU with PAH treatment, shunt closure may be considered	IIb	C
In patients with a VSD or PDA and a PVR >5 WU, shunt closure may be considered after careful evaluation in specialized centres	IIb	C
In patients with an ASD and a PVR >5 WU despite PAH treatment, shunt closure is not recommended	III	C

2022 ESC/ERS Guideline. European Heart Journal (2022) 00, 1–114

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Treatment of PAH-CHD

Recommendations	Class[a]	Level[b]
Risk assessment		
Risk assessment is recommended for patients with persistent PAH after defect closure	I	C
Risk assessment should be considered in patients with Eisenmenger syndrome	IIa	C
Treatment		
Bosentan is recommended in symptomatic patients with Eisenmenger syndrome to improve exercise capacity[574]	I	B
In patients with Eisenmenger syndrome, the use of supplemental oxygen therapy should be considered in cases where it consistently increases arterial oxygen saturation and reduces symptoms	IIa	C
Supplemental iron treatment should be considered in patients with iron deficiency	IIa	C
In patients with adult CHD, including Eisenmenger syndrome, other ERAs, PDE5is, riociguat, prostacyclin analogues, and prostacyclin receptor agonists should be considered	IIa	C
In patients with PAH after corrected adult CHD, initial oral combination therapy with drugs approved for PAH should be considered for patients at low and intermediate risk, while initial combination therapy including i.v./s.c. prostacyclin analogues should be considered for patients at high risk	IIa	C[c]
In patients with adult CHD, including Eisenmenger syndrome, sequential combination therapy should be considered if patients do not meet treatment goals	IIa	C
In the absence of significant haemoptysis, oral anticoagulant treatment may be considered in patients with Eisenmenger syndrome with pulmonary artery thrombosis	IIb	C
In women with Eisenmenger syndrome, pregnancy is not recommended	III	C
In patients with Eisenmenger syndrome, routine phlebotomy to lower elevated haematocrit is not recommended	III	C

2022 ESC/ERS Guideline. European Heart Journal (2022) 00, 1–114

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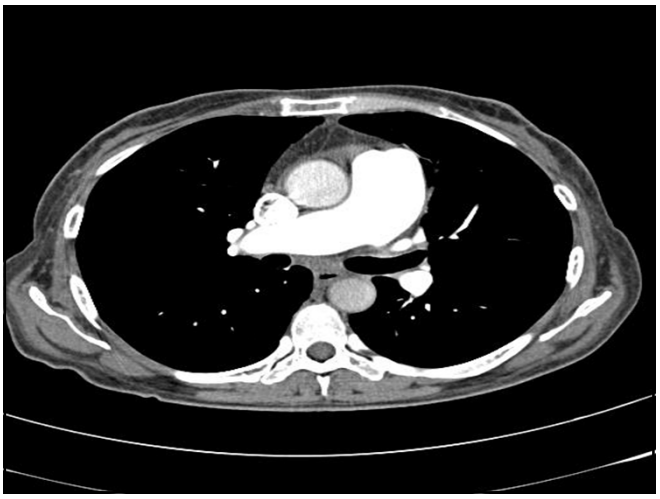
- Systemic sclerosis — **Group 1: SSc**

?? Group 5: miscellaneous

60



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Real-Life Situations

- Elevated PAWP (16 mmHg) — **Group 2**: LHD
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- ASD (ASD, step up O2) — **Group 1**: ASD
- Chronic left leg DVT — **Group 4**: CTEPH
- Systemic sclerosis — **Group 1: SSc**

?? Group 5: miscellaneous

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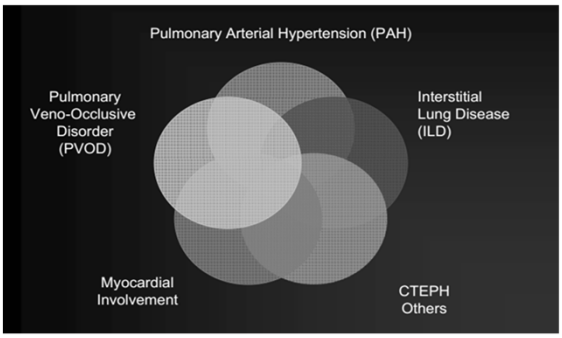
Potential Causes of PH in SSc (CTD)



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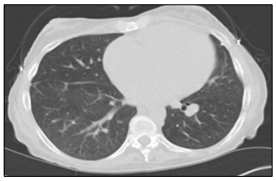
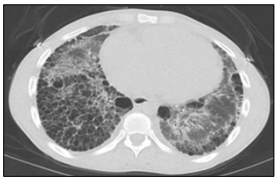
Two Types of PH in SSc



- Limited >> Diffuse
- Anti centromere Ab
- Minimal abnormal lung architecture
- Severe elevation of mPAP (mostly > 40 mmHg)



- Diffuse >> limited
- Anti topoisomerase Ab
- Very abnormal lung architecture
- Mild to moderate elevation of mPAP

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Risk Factors for Developing SSc-PAH

- Limited scleroderma
- Long standing of Raynaud phenomenon
- Low DLCO
- FVC %predicted / DLCO %predicted > 1.6
- Anti-centromere
- U3-RNP antibody

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Final Diagnosis

- Disproportionate pulmonary hypertension in SSc with NSIP, likely due to pulmonary arterial hypertension
  - –SSc-PAH
- NSIP
- SSc
- HT
- History of DVT

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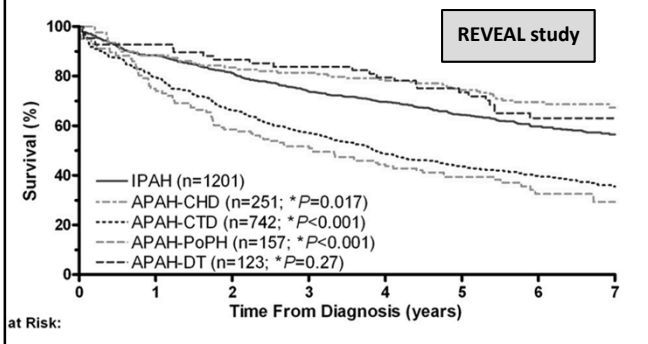
Survival from time of diagnostic RHC



Benza RL, *et al*. *Chest* 2012;142(2):448-56.

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RV adaptation in IPAH versus PAH-CHD

- Compared with IPAH, Eisenmenger's syndrome patients have higher CI and lower mRAP (despite having a higher mPAP)[1]

Elevated mPAP

IPAH
RV inability to adapt = *Worse prognosis*

Decompensation[2]:
- **RV dilation**
- **RV failure**

PAH-CHD
RV adaptation = *Better prognosis*

Compensation[2]:
- **Increased RV wall thickness**
- **Mild RV dilation**

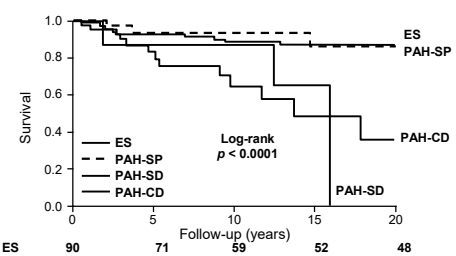
CHD: congenital heart disease; CI: cardiac index; IPAH: idiopathic PAH; mPAP: mean pulmonary arterial pressure; mRAP: mean right atrial pressure; RV: right ventricle/ventricular

1. Chin KM, *et al. Coron Artery Dis* 2005; 16:13-8.
2. Bristow MR, *et al. Chest* 1998; 114:S101-6.

71

Survival rates of clinical subgroups of PAH-CHD

Survival rates in a predominantly adult population (*n* = 192) over a 20-year period



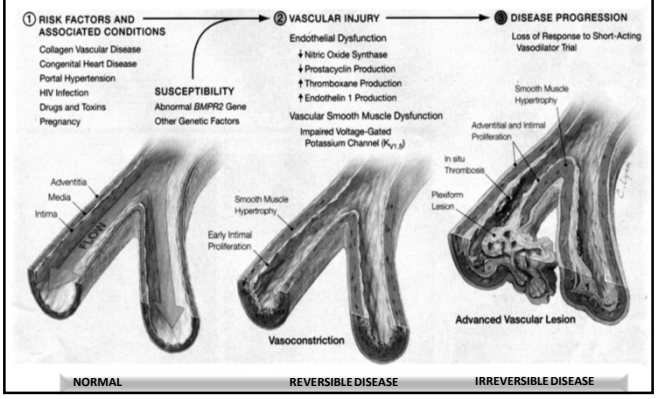
Patients at risk:					
ES	90	71	59	52	48
PAH-SP	48	22	18	11	10
PH-SD	10	4	4	2	0
PAH-CD	44	22	12	4	3

CD: cardiac defect correction; CHD: congenital heart disease;
ES: Eisenmenger syndrome; SD: small defects; SP: systemic-to-pulmonary shunts

Manes A, *et al. Eur Heart J* 2013; Epub ahead of print.

72

Pathogenesis of PAH



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Pathophysiology

Pulmpnary hypertension
↓
Pressure overload
↓
RV hypertrophy
Dec. wall stress
} Compensatory phase
Normal CO, RAP
↓
RV failure
RV ischemia
TVR
Inc. wall stress
Pre&afterload mismatch
Decrease LV compliance
} Decompensatory phase
↓ CO, ↑RAP,↑PcWP
Hypoxia, Acidosis
Arrhythmias

Dilated RV- Intact pericardium
↑ RAP
⇓
↑ Intrapericardial pressure (IPP)
⇓
↓ LV transmural filling pressure
LVEDP-IPP
+
Shift of IV septum toward LV
⇓
↓LV preload and
↓↓ LV distensibility
⇓
↓↓ Systemic Cardiac Output

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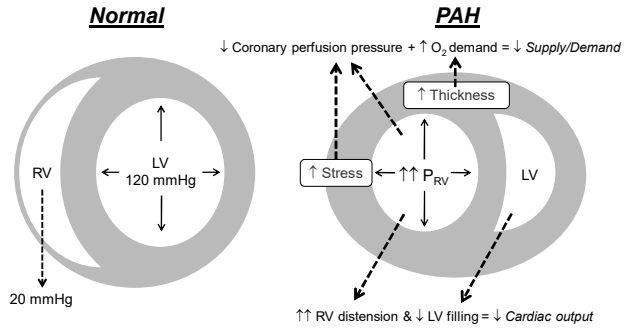
RV anatomy: *Normal versus PAH*



LV: left ventricle/ventricular; RV: right ventricle/ventricular

Chin KM, *et al. Coron Artery Dis* 2005; 16:13-8.

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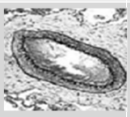
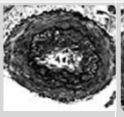
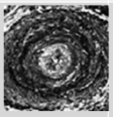
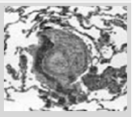
PAH: Clinical course and progression

	Asymptomatic compensated	Symptomatic decompensating		Advanced decompensated
		Subtle	Overt	
S&S	None	SOB, Fatigue	SOB, edema	RVF, syncope, death
FC	I	II	III	IV
Hemodynamic trends		CO, PAP, PVR, RAP		
Pathologic appearance				

Minai OA, et al. Cleveland Clincal J Med 2007;74:737-47

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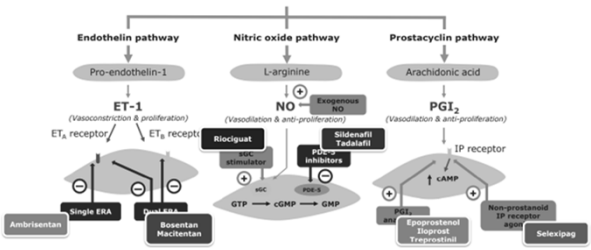
Therapies are available to target three key pathological pathways in PAH



cAMP: cyclic adenosine monophosphate; cGMP: cyclic guanosine monophosphate; ERA: endothelin receptor antagonists; ET-1: endothelin-1; ET_A: endothelin receptor A ; ET_B: endothelin receptor AB; GTP: guanosine triphosphate; IP: prostacyclin receptor; NO: nitric oxide; PDE-5: phosphodiesterase-5; PGI_2: prostacyclin sGC: soluble guanylate cyclase
Figure adapted from Humbert M, et al. Circulation 2014; 130:2189-208.

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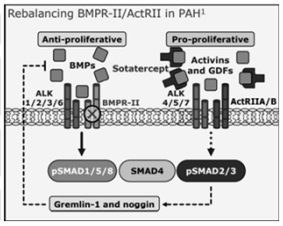
Therapeutic developments in rebalancing BMPR-II/ActRII in PAH

Understanding the role of BMPR-II/ActRIIA signaling has paved the way for novel therapeutic approaches[2]

Sotatercept is a novel, first-in-class fusion protein that acts by rebalancing signaling between pro- and anti-proliferative pathways, thereby reversing the characteristic vascular remodeling seen in PAH[1]

In preclinical studies, sotatercept treatment improved hemodynamics, RV hypertrophy, RV function and arteriolar remodeling[3]

Sotatercept is under current investigation in clinical trials[1]



ALK: anaplastic lymphoma kinase; BMP: bone morphogenic protein; BMPR-II: bone morphogenic protein receptor type II; GDF: growth-differentiation factor; TGF-β: transforming growth factor beta. 1. Adapted from Humbert M, et al. N Engl J Med 2021; 384:1204-15; 2. Guignabert C, and Humbert M, Eur Respir J 2021; 57:2002341; 3. Yung L-M, et al. Sci Transl Med 2020; 12:eaaz5660.

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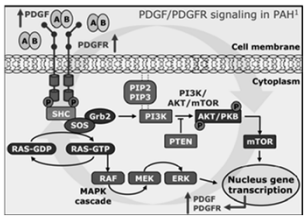
Overexpression of PDGF/PDGFR has been implicated in the development of PAH

Aberrant PDGF signaling occurs in PAH[1]

Increased expression of PDGFs and PDGFR has been observed in patients with PAH[2,3]

PDGF/PDGFR overexpression drives pulmonary vascular remodeling, leading to further upregulation of PDGF and PDGFR[2]

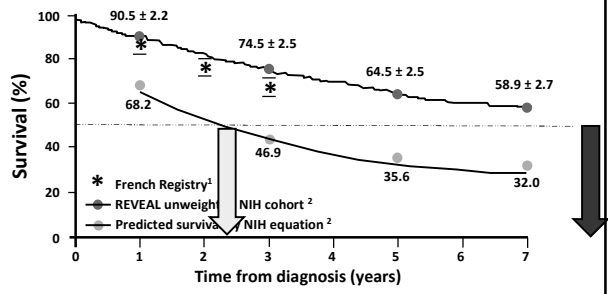
Potential for reverse remodeling therapy by inhibiting PDGFR in PAH patients[2]



MAPK: mitogen-activated protein kinase; PDGF: platelet-derived growth factor; PDGFR: platelet-derived growth factor receptor 1. Adapted from Kanaan R, and Strange C. Eur Respir Rev 2017; 26:170061; 2. Parnes F, et al. Am J Respir Crit Care Med 2008; 178:81–8; 3. Hennes A, and Humbert M. Eur Respir Rev 2017; 26:170093.

79

Long-term outcomes are improved in the modern treatment era

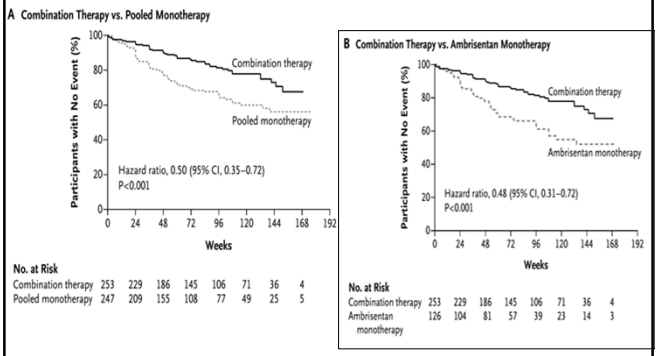


No. at risk: 279 377 390 388 328 240 153 88

1. Humbert M, *et al. Eur Respir J* 2010; 36:549–555.
2. Benza RL, *et al. Chest* 2012;142(2):448-56.

81

Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension



Galiè N, et al. N Engl J Med 2015;373:834-44.

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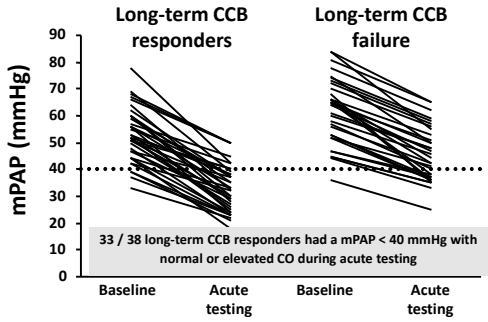
Mean PAP reached during acute vasodilator testing



O. Sitbon *et al. Circulation* 2005

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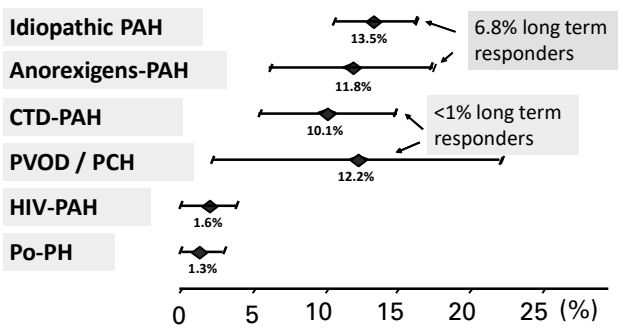
Acute Responders: By diagnosis



Familial PAH and CHD-PAH: 0 %

O. Sitbon *et al.* Circulation 2005

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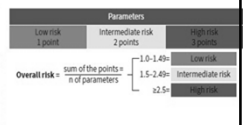
7th World Symposium on PH

Risks Stratification

- At diagnosis:

Determinants of prognosis (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
Clinical observations and modifiable variables			
Signs of right HF	Absent ✓	Absent	Present
Progression of symptoms and clinical manifestations	No	Slow ✓	Rapid
Syncope	No ✓	Occasional syncope*	Repeated syncope*
WHO-FC	I, II	III ✓	IV
6MWD† (159 m)	>440 m	165–440 m	<165 m ✓
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
Biomarkers: BNP or NT-proBNP‡	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
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
cMRI‖	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
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% ✓



Parameters
- Low risk: 5
- Intermediate risk: 3
- High risk: 2

Overall risk = **1.7**

[(5 x 1) + (3 x 2) + (2 x 3)]/10

Chin KM, Gaine SP, Gerges C, et al. Treatment algorithm for pulmonary arterial hypertension. Eur Respir J 2024; in press: 2401325 [DOI:10.1183/13993003.01325-2024].

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7th World Symposium on PH
Risks Stratification

- 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	<50	50–199	200–800	>800
NT-proBNP,[a] ng/L	<300 ✓	300–649	650–1100	>1100

Parameters			
Low risk 1 point	Intermediate-low risk 2 points	Intermediate-high risk 3 points	High risk 4 points

Overall risk = sum of the points = n of parameters

1.0–1.49=	Low risk
1.5–2.49=	Intermediate-low risk
2.5–3.49=	Intermediate-high risk
≥3.5=	High risk

Parameters
- Low risk: 2
- Intermediate-low risk: 1

Overall risk = **1.3**
[(2 x 1) + (1 x 2)]/3

Chin KM, Gaine SP, Gerges C, et al. Treatment algorithm for pulmonary arterial hypertension. Eur Respir J 2024; in press: 2401325 [DOI:10.1183/13993003.01325-2024].

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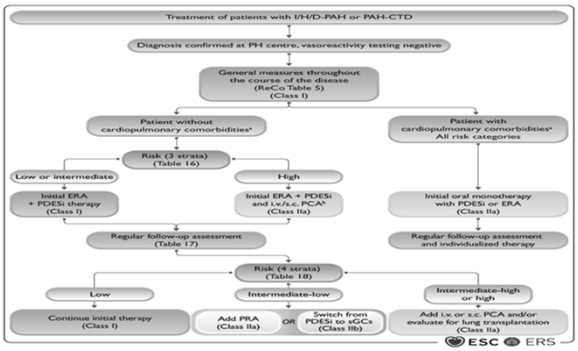
6th World Symposium and 2022 ESC Guideline on PH
Evidence-based treatment algorithm
Initial therapy with PAH approved drugs



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Potential Role for Initial Monotherapy

- IPAH, HPAH and DAH patient responders to acute vasoreactivity tests and with FC I/II and sustained haemodynamic improvement after at least 1 year on CCBs only
- Long-term-treated historical PAH patients with monotherapy (>5–10 years) stable with low-risk profile
- IPAH >75 years old with multiple risk factors for HFpEF
- PAH patients with suspicion or high probability of PVOD/PCH
- PAH-HIV infection or Portop-PH or uncorrected CHD, as they were not included in RCTs of initial combination therapy
- PAH patients with very mild disease (e.g. WHO FC I, PVR 3–4 WU, mPAP <30 mmHg, normal RV at echocardiography)
- Combination therapy unavailable or contraindicated

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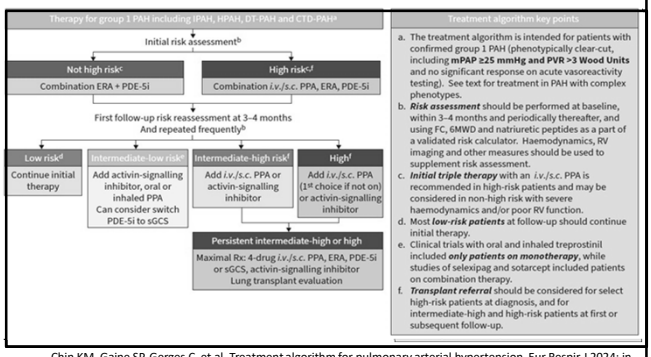
7th World Symposium on PH 2024
Evidence-based treatment algorithm
Follow up therapy with PAH approved drugs



Chin KM, Gaine SP, Gerges C, et al. Treatment algorithm for pulmonary arterial hypertension. Eur Respir J 2024; in press: 2401325 [DOI:10.1183/13993003.01325-2024].

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Heart Rate Recovery Predicts Clinical Worsening in Patients with PAH?

- 75 patients
- HRR 1 defined as the difference in HR at the end of 6MW and at 1 minute after completion
  - HRR≤16 more likely to show clinical worsening
  - Report HRR<16 and mPAP as the best predictors via multivariate analysis
  - Compared with 6MWD, HRR1 < 16 a better predictor of CW and TCW
  - The addition of HRR1 to 6 MWD increases the capacity of 6MWD to predict clinical worsening and TCW in patients with PAH

Minai OA et al. AJRCCM 2012;185:400

93

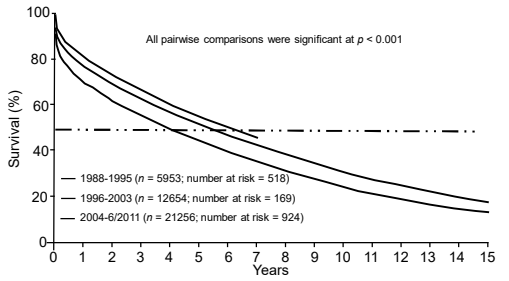
Atrial septostomy as a bridge to transplant

- Creation of inter-atrial right-to-left shunt can:
  - Decompress right heart chambers
  - Increase left ventricle pre-load
  - Increase cardiac output
- A pre-procedural risk assessment reduces mortality
- Atrial septostomy should be avoided in end-stage patients with:
  - Baseline mean right atrial pressure > 20 mmHg
  - O_2 saturation at rest of < 85% on room air

Galiè N, *et al. J Am Coll Cardiol* 2013; 62:D60-72.

94

Survival rates for lung transplant recipients have improved significantly



ISHLT registry data showing adult lung transplant recipients Kaplan-Meier survival by era (transplants January 1988-June 2011)

ISHLT: International Society for Heart and Lung Transplantation

Yusen RD, *et al. J Heart Lung Transplant* 2013; 32: 965-78.

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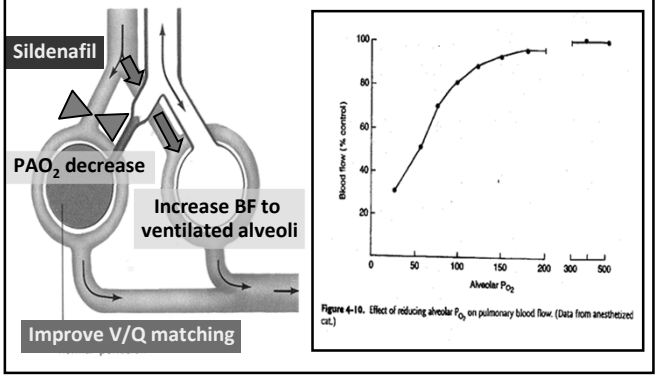
Hypoxic pulmonary vasoconstriction



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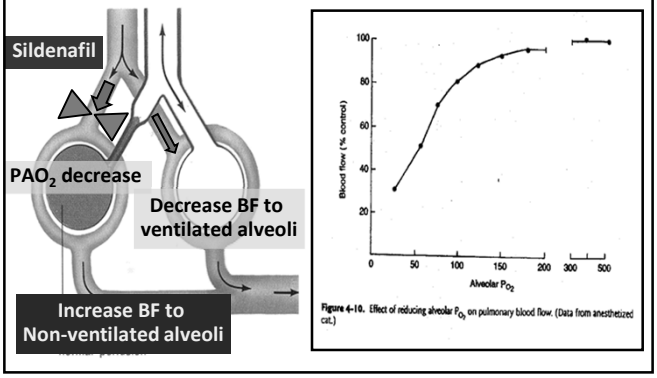
Hypoxic pulmonary vasoconstriction



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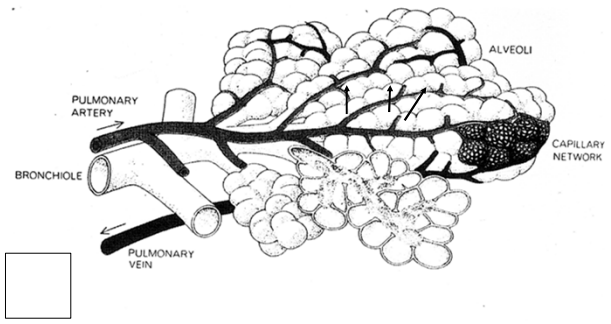
Inhaled Iloprost



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New insights into CTEPH management

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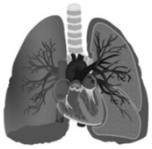
Background
Pathophysiology

- CTEPH is a rare complication of acute PE[a]
  - Characterized by fibrothrombotic obstructions of large pulmonary arteries, combined with small vessel arteriopathy,[a] → redistribution of blood flow and high intravascular pressures lead to remodeling and hypertension[b]
- Potentially fatal; poor prognosis if untreated[b]
  - Survival rates at 5 years: 30% for patients with mPAP > 40 mmHg; 10% for patients w/mPAP > 50 mmHg[c]
  - mPAP > 30 mmHg may be associated with poor prognosis[d]
- Management of CTEPH has advanced in recent years



a. Delcroix M, et al. *Circulation*. 2016;133:859-871; b. Hoeper MM. *Eur Respir Rev*. 2015;24:272-282; c. Riedel M, et al. *Chest*. 1982;81:151-158; d. Lewczuk J, et al. *Chest*. 2001;119:818-823.

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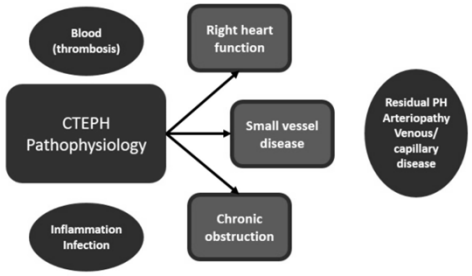
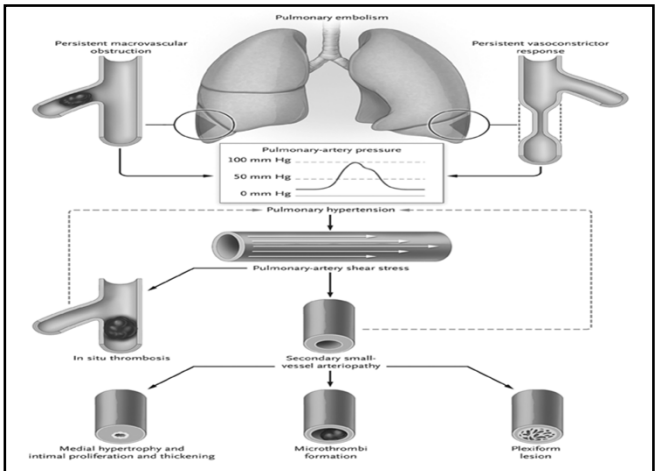
CTEPH Is Not Just a Clot Problem



- Individual patients are likely to display > 1 of these disease manifestations
- Patients may benefit from a combination of treatment strategies (eg, use of medical therapy before or after surgery)

Kim NH. *Cardiol Clin*. 2016;34:435-441.

114



Piazza G, et al. N Engl J Med 2011;364:351-60.

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Findings of pre-existing CTEPH

Direct vascular signs
Eccentric wall-adherent filling defect(s), which may calcify; different from the central filling defects within a distended lumen, which are the hallmark of acute PE
Abrupt tapering and truncation
Complete occlusion and pouch defects
Intimal irregularity
Linear intraluminal filling defects (intravascular webs and bands)
Stenosis and post-stenotic dilatation
Vascular tortuosity
Indirect vascular signs
Significant RV hypertrophy, RA dilatation
Pericardial effusion
Dilatation of pulmonary artery (>29 mm in men and >27 mm in women) and/or calcifications of pulmonary artery
Systemic collateral arterial supply (bronchial arterial collaterals towards pulmonary post-obstructive vessels)
Parenchymal changes
Mosaic attenuation of the lung parenchyma resulting in geographical variation in perfusion

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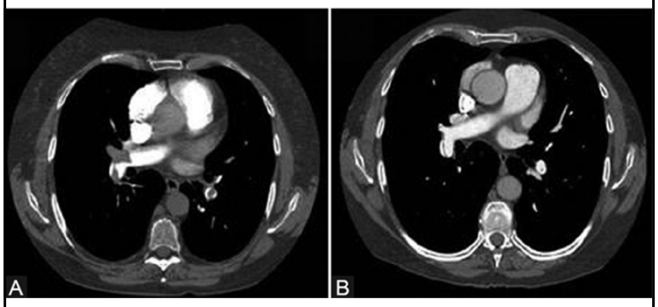
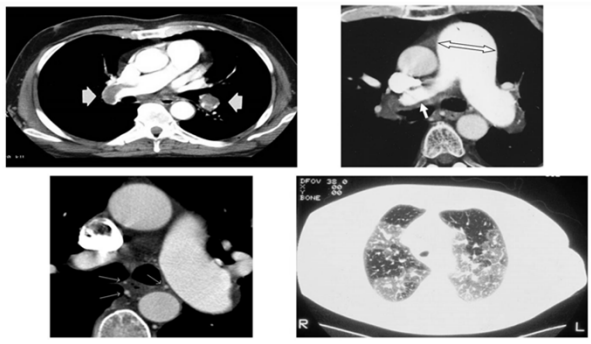
CT Angiography



Auger WR, et al. Pulmo Cir 2012;2:155-62

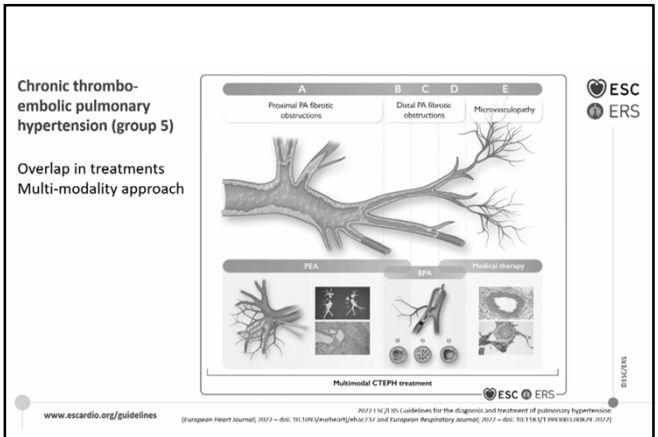
120

CT Angiography



Auger WR, et al. Pulmo Cir 2012;2:155-62

121



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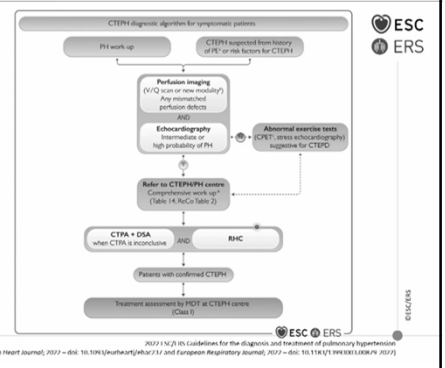
Chronic Thromboembolic Pulmonary Hypertension

Diagnostic strategy in chronic thrombo-embolic pulmonary hypertension



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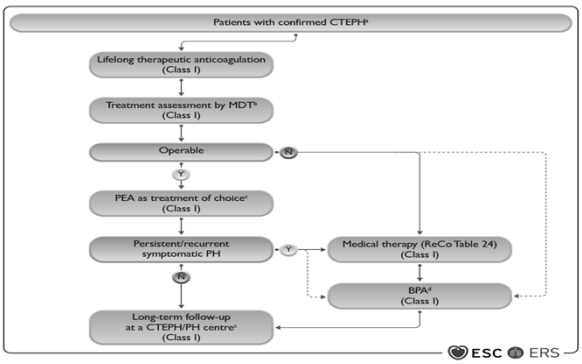
Chronic Thromboembolic Pulmonary Hypertension



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Factors that affect decisions about operability

- The location of the disease/clot
- The correlation between hemodynamic compromise and the clot burden
- Disease concordant (CTPA and VQ scan)
- The surgical experience (center and individual surgeon)
- The patient's condition and comorbidities

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Favorable risk–benefit assessment for PEA

Characteristics	Lower risk with predictable good long-term outcome	Higher risk with less predictable long-term outcome (not contraindications)
History	History of DVT/PE	No history of DVT/PE
Examination	No signs of right heart failure	Signs of right heart failure
Comorbidity	None	Significant concomitant lung or left heart disease
Functional limitation	Functional class II or III	Functional class IV
Imaging	Clear disease concordant on all images	Inconsistency on imaging modalities
Type of disease	Bilateral lower lobe disease	No disease appreciable in lower lobes
Haemodynamics	PVR <1000 dyn·s·cm^{-5}, in proportion to site and number of obstructions on imaging; higher PA pulse pressure	PVR >1200 dyn·s·cm^{-5}, out of proportion to site and number of obstructions on imaging; higher PA diastolic pressure

Kim NH, et al. CTEPH. Eur Respir J 2019; 53: 1801915

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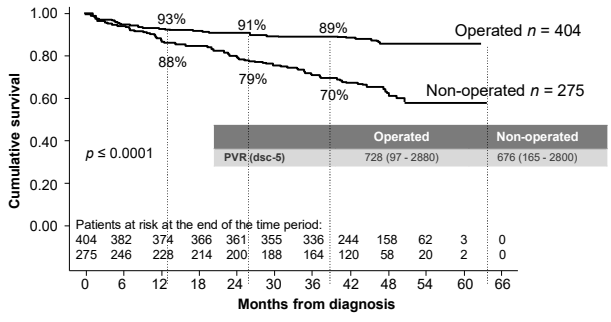
CTEPH registry: *Survival is significantly improved following PEA*



CTEPH: chronic thromboembolic pulmonary hypertension;
PEA: pulmonary endarterectomy; PVR: pulmonary vascular resistance

Simonneau G, *et al. Am J Respir Crit Care Med* 2013; 187:A5365.

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How do we treat inoperable CTEPH or persistent PH after PEA

- Continues anticoagulants
- Ensure adequate oxygenation
- Ensure adequate diuresis
- Pulmonary rehabilitation
- Balloon pulmonary angioplasty?
- PAH-specific treatment ?

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Balloon Pulmonary Angioplasty (BPA)

- Alternative option for some patients when lesions are too distal for PEA
- No longer considered experimental or desperation modality
- Evolving fast: patient selection, vessel target, imaging/guide
- High-risk procedure; reserved for experienced centers

Madani M, et al. *Eur Respir Rev*. 2017;26:170105.

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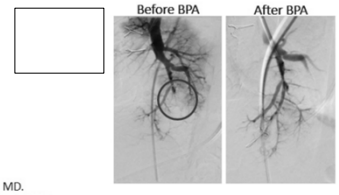
Balloon Pulmonary Angioplasty (BPA)

- Catheter-based alternative for patients deemed inoperable or unsuitable for PEA, and who have recurrent PH after PEA
  - Distal segmental and subsegmental arteries
- High-risk procedure but less invasive than PEA
- No current guidance or standardization to determine eligibility for BPA
- Reserved for experienced centers
- Normally performed over multiple sessions
- Potential complications: micro ruptures of the vessels that can lead to a pulmonary hemorrhage, or sometimes major bleeding



Images courtesy of Ardeschir Ghofrani, MD.
Madani M, et al. *Eur Respir Rev*. 2017;26:170105.

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Summarizing PEA and BPA

PEA	BPA
• Can be used to remove thromboembolic lesions in expert centers[a] – Proximal main, (diameter of ~3 cm), lobar, and distally located midsegmental and subsegmental branches[a] • Typically, treatment of choice for patients with accessible lesions and who are suitable for surgery[a] • 10% to 50%* of patients are inoperable with PEA[a] • Potentially curable[b] or 35% of patients may have persistent/ recurrent PH† after PEA[a]	• Catheter-based alternative for patients deemed inoperable or unsuitable for PEA, and who have recurrent PH after PEA[a] – Distal segmental and subsegmental arteries[a] • High-risk procedure but less invasive than PEA[a] – Has been shown to improve symptoms, function, and hemodynamics[a] • No current guidance or standardization to determine eligibility for BPA[a] • Reserved for experienced centers[a]

*May be an overestimation due to misdiagnosis of CTEPH. †Having hemodynamic signs of PH.
a. Madani M, et al. *Eur Respir Rev*. 2017;26:170105; b. Delcroix M, et al. *Circulation*. 2016;1;133:859-871.

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Recommendations for CTEPH

ESC
ERS

PICO 4: Should patients with CTEPH who are considered inoperable but candidates for BPA receive medical therapy before interventional therapy is initiated?

	GRADE			
Recommendations	Quality of evidence	Strength of recommendation	Class	Level
In patients with CTEPH who are candidates for BPA, medical therapy should be considered prior to the intervention	Very low	Conditional	IIa	B

www.escardio.org/guidelines

2017 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (European Heart Journal; 2017 – doi: 10.1093/eurheartj/ehx179 and European Respiratory Journal; 2017 – doi: 10.1183/13993003.00879-2017)

SEP2018

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CTEPH: *The potential role of medical therapy*

When is medical therapy for CTEPH appropriate?

- Patients with predominantly distal disease that is not surgically accessible[1] → ?
- Patients with persistent or residual PH post-PEA[1,2] → ?
- PEA contraindicated due to prognostically significant comorbidity[1]
- Patients who are 'high-risk' due to extremely poor haemodynamics prior to PEA[1]

CTEPH: chronic thromboembolic pulmonary hypertension; PEA: pulmonary endarterectomy

1. Hoeper MM, *et al. J Am Coll Cardiol* 2009; 54:S85-96.
2. Kim NH, *et al. J Am Coll Cardiol* 2013; 62:D92-9.

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CHEST-1: *Treatment of CTEPH with riociguat*

- Phase III multicentre, double-blind, placebo-controlled study
- 261 patients with inoperable CTEPH or persistent/recurrent PH after PEA
  - Randomised to receive riociguat or placebo
- Significantly improved 6MWD and PVR after 16 weeks
  - **6MWD**: 39 m ↑ in riociguat group
    6 m ↓ in placebo group
  - **Mean PVR**: 226 dyn·sec·cm^{-5} ↓ in riociguat group
    23 dyn·sec·cm^{-5} ↑ in placebo group

6MWD: 6-minute walk distance; CTEPH: chronic thromboembolic pulmonary hypertension; PEA: pulmonary endarterectomy; PVR: pulmonary vascular resistance

Ghofrani HA, *et al. New Engl J Med* 2013; 369:319-29.

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Chronic Thromboembolic Pulmonary Hypertension

Recommendations	Class[a]	Level[b]
CTEPH		
Lifelong, therapeutic doses of anticoagulation are recommended in all patients with CTEPH[760]	I	C
Antiphospholipid syndrome testing is recommended in patients with CTEPH	I	C
In patients with CTEPH and antiphospholipid syndrome, anticoagulation with VKAs is recommended[703,764,765]	I	C
It is recommended that all patients with CTEPH are reviewed by a CTEPH team for the assessment of multimodality management[54]	I	C
PEA is recommended as the treatment of choice for patients with CTEPH and fibrotic obstructions within pulmonary arteries accessible by surgery[54,760]	I	B
BPA is recommended in patients who are technically inoperable or have residual PH after PEA and distal obstructions amenable to BPA[54,102,780,784,789,793,798,811]	I	B
Riociguat is recommended for symptomatic patients with inoperable CTEPH or persistent/recurrent PH after PEA[775]	I	B
Long-term follow-up is recommended after PEA and BPA, as well as for patients with CTEPH established on medical therapy[780,805,806,812]	I	C
A multimodality approach should be considered for patients with persistent PH after PEA and for patients with inoperable CTEPH[804,805,812]	IIa	C
Treprostinil s.c. may be considered in patients in WHO-FC III–IV who have inoperable CTEPH or persistent/recurrent PH after PEA[776]	IIb	B
Off-label use of drugs approved for PAH may be considered in symptomatic patients who have inoperable CTEPH[53,777–779,801,803]	IIb	B
In patients with inoperable CTEPH, a combination of sGC stimulator/PDE5i, ERA,[777] or parenteral prostacyclin analogues[778] may be considered	IIb	C
BPA may be considered for technically operable patients with a high proportion of distal disease and an unfavourable risk:benefit ratio for PEA	IIb	C
CTEPD without PH		
In patients with CTEPD without PH, long-term anticoagulant therapy should be considered on an individual basis[a]	IIa	C
PEA or BPA should be considered in selected symptomatic patients with CTEPD without PH	IIa	C

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Parting Thoughts…

- PH is a serious, complex, & underrecognized condition
- A comprehensive evaluation is needed to determine what type of PH is present
- Current and emerging therapies can alleviate symptoms and maybe starting to influence longer-term outcomes

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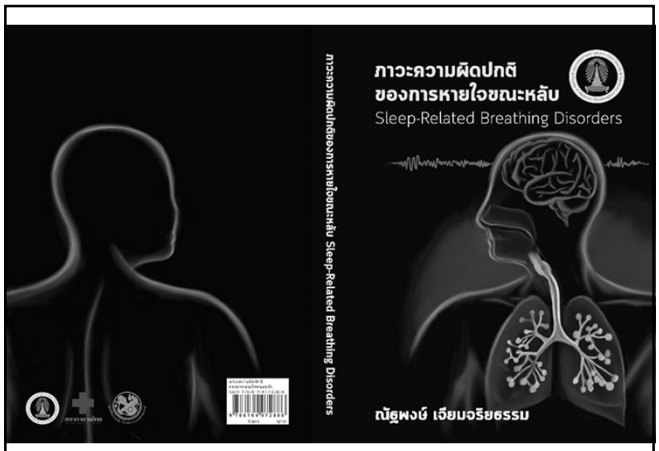

Thank you for your attention

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