PNEUMOMEDICINA 2022

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Ipertensione polmonare in malattie rare non IPF

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TABLE 2 Updated clinical classification of pulmonary hypertension (PH)

1 PAH
- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH (table 3)
- 1.4 PAH 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 long-term responders to calcium channel blockers (table 4)
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement (table 5)
- 1.7 Persistent PH of the newborn syndrome

2 PH due to left heart disease
- 2.1 PH due to heart failure with preserved LVEF
- 2.2 PH due to heart failure with reduced LVEF
- 2.3 Valvular heart disease
- 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3 PH due to lung diseases and/or hypoxia
- 3.1 Obstructive lung disease
- 3.2 Restrictive lung disease
- 3.3 Other lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoxia without lung disease
- 3.5 Developmental lung disorders

CPFE
LAM

4 PH due to pulmonary artery obstructions (table 6)
- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions

5 PH with unclear and/or multifactorial mechanisms (table 7)
- 5.1 Haematological disorders
- 5.2 Systemic and metabolic disorders
- 5.3 Others
- 5.4 Complex congenital heart disease

Istiocitosi a cellule di Langerhans
Sarcoidosi

PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; LVEF: left ventricular ejection fraction.

6th WSPH Nice 2018

Nice 2018 classification

Chronic lung disease (CLD) without PH (mPAP < 20 mmHg)

CLD with PH (PAP >/= 20 mmHg and PVR >/= 3 WU; with supplemental O_2 if needed)

CLD with severe PH (PAP >/= 35 mmHg; supplemental O_2)*

Rationale: - at this level hemodynamics contribute to exercise limitation

- minor subpopulation with “vascular phenotype” (in COPD < 3%)

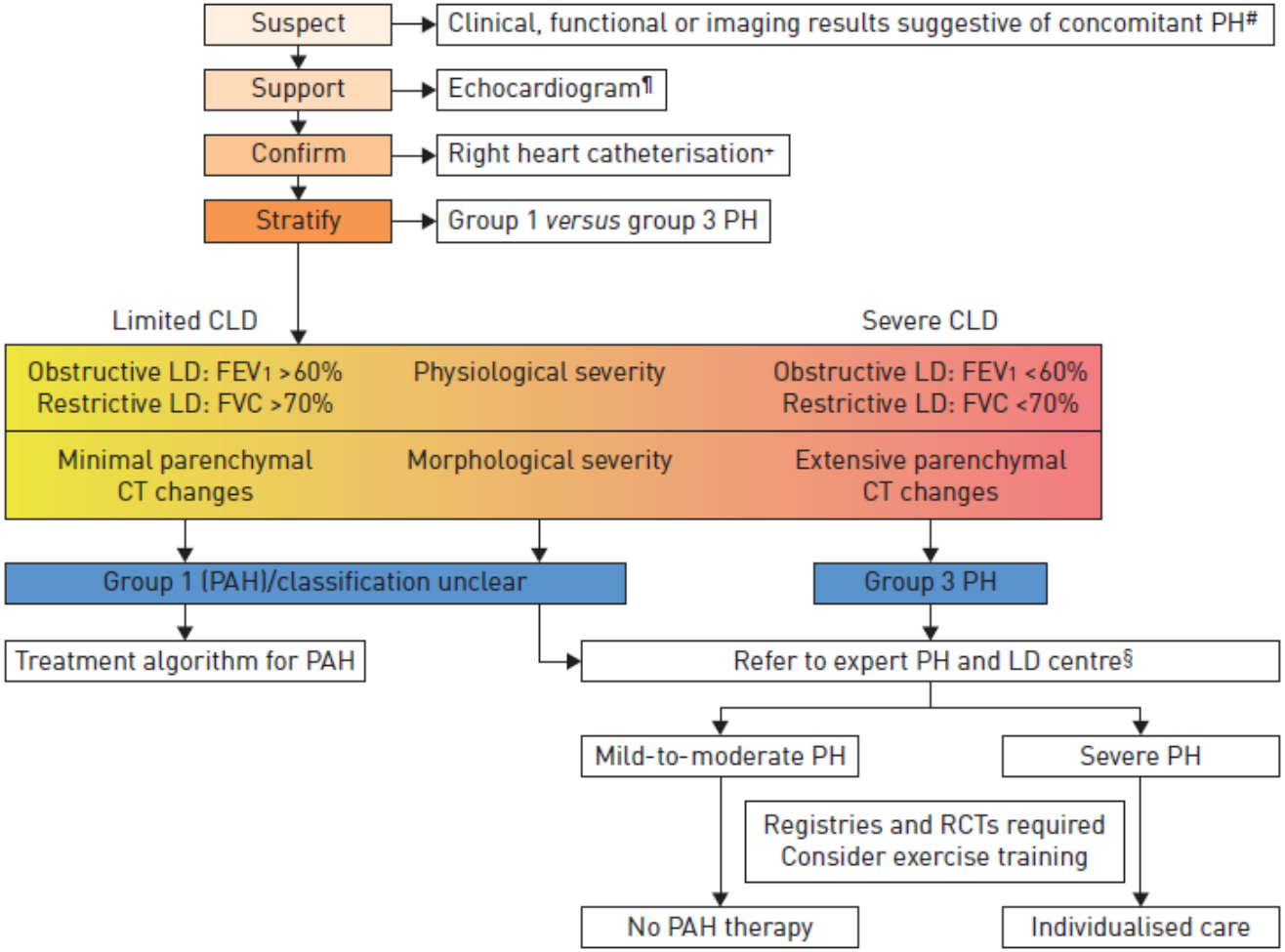
- optimal target population in future RCT addressing PH in CLD

*Lower PA pressures may be clinically significant in COPD/DPLD patients with depressed cardiac index or right ventricular dysfunction

TABLE 1 Criteria favouring group 1 *versus* group 3 pulmonary hypertension (PH)#

Criteria favouring group 1 (PAH)	Testing	Criteria favouring group 3 (PH due to lung disease)
Extent of lung disease		
Normal or mildly impaired: • FEV_1 >60% pred (COPD) • FVC >70% pred (IPF) • Low diffusion capacity in relation to obstructive/restrictive changes	Pulmonary function testing	Moderate to very severely impaired: • FEV_1 <60% pred (COPD) • FVC <70% pred (IPF) • Diffusion capacity "corresponds" to obstructive/restrictive changes
Absence of or only modest airway or parenchymal abnormalities	High-resolution CT scan¶	Characteristic airway and/or parenchymal abnormalities
Haemodynamic profile		
Moderate-to-severe PH	Right heart catheterisation Echocardiogram	Mild-to-moderate PH
Ancillary testing		
Present	Further PAH risk factors (*e.g.* HIV, connective tissue disease, *BMPR2* mutations, *etc.*)	Absent
Features of exhausted circulatory reserve: • Preserved breathing reserve • Reduced oxygen pulse • Low $CO/V'O_2$ slope • Mixed venous oxygen saturation at lower limit • No change or decrease in P_{ACO_2} during exercise	Cardiopulmonary exercise test+ (P_{ACO_2} particularly relevant in COPD)	Features of exhausted ventilatory reserve: • Reduced breathing reserve • Normal oxygen pulse • Normal $CO/V'O_2$ slope • Mixed venous oxygen saturation above lower limit • Increase in P_{ACO_2} during exercise
Predominant haemodynamic profile		Predominant obstructive/restrictive profile

Nathan SD. et al. Eur Respir J 2019



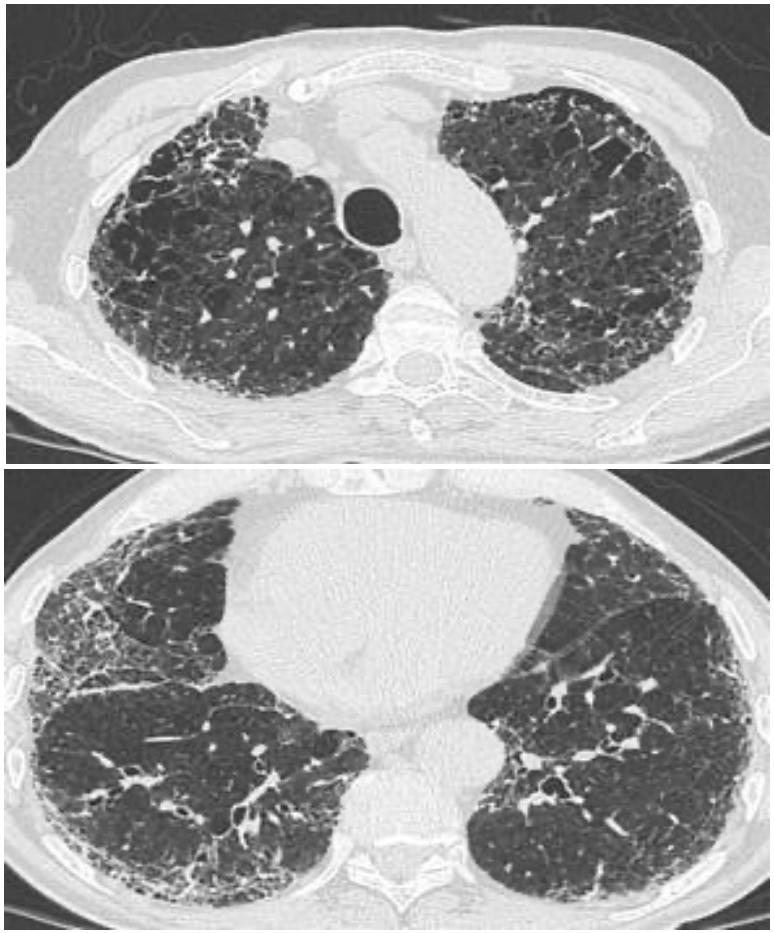
RHC *should be performed* in patients with CLD when significant PH is suspected and the patient's management will likely be influenced by RHC results, including referral for transplantation, inclusion in clinical trials or registries, treatment of unmasked left heart dysfunction, or compassionate use of therapy.

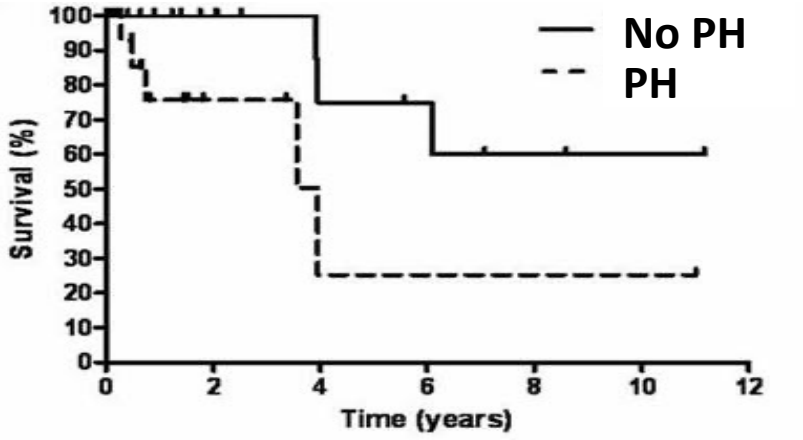
RHC *may be considered* when:

1) Clinical worsening, progressive exercise limitation and/or gas exchange abnormalities are not deemed attributable to ventilatory impairment.
2) An accurate prognostic assessment is deemed sufficiently important.

Nathan SD. et al. Eur Respir J 2019

PH in combined pulmonary fibrosis and emphysema (CPFE)





- ✓ Systolic PAP ≥ 45 mmHg at echocardiography in 47 % of patients
- ✓ Main determinant of prognosis [1,2] (Cox analysis, *p = 0.03*, HR = 4.03 ; IC 95 % : 1.17 – 27.9)[1]

Cottin V *et al.* Eur Respir J 2005
Mejia M *et al*. Chest 2009

Combined pulmonary fibrosis and emphysema (CPFE) is currently defined by the simultaneous presence of emphysema in the upper lobes and fibrosis in the lower lobes on chest CT. Patients with CPFE are particularly prone to develop PH, with estimates suggesting a prevalence of 30–50% [24]. Typically, normal or mildly abnormal lung volumes and the absence of airflow obstruction are accompanied by a markedly impaired diffusion capacity, significant hypoxaemia and PH. The PH appears to contribute to the functional limitation in CPFE and is associated with poor survival [24, 25].

Sex male/female n	38/2
Age yrs	68.2±8.9 (47.7–82.2)
Current/ex/never-smokers n	2/37/1
Smoking history pack-yrs	46±23 (17–120)
NYHA class I	0
NYHA class II	6 (15)
NYHA class III	22 (55)
NYHA class IV	12 (30)
6MWD m	244±126 (78–689)
6MWT S_{p,O_2} at end of test	77±10 (62–96)
6MWT S_{p,O_2} decrease during test	-15±8 (-30– -1)
FVC % pred	86±18 (46–116)
FEV_1 % pred	78±19 (38–114)
FEV_1/FVC %	75±18 (29–107)
TLC % pred	84±23 (47–139)
RV % pred	87±47 (41–219)
$D_{L,CO}$ % pred	24±14 (3–52)
K_{CO} % pred	28±16 (4–68)
P_{a,O_2} at rest kPa	7.5±1.6 (5.2–11.7)
P_{a,O_2} at rest mmHg	56.2±12.0 (39–84)
P_{a,CO_2} at rest kPa	4.7±0.6 (3.3–5.9)
P_{a,CO_2} at rest mmHg	35.2±4.5 (25–44)

Eur Respir J 2010; 35: 105–111
DOI: 10.1183/09031936.00038709

Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome

V. Cottin*,f, J. Le Pavec#,f, G. Prévot¶, H. Mal+, M. Humbert#, G. Simonneau#, J-F. Cordier* and GERM"O"P§

f_C beats·min^{-1}	78±15 (50–112)
P_{ra} mmHg	7±4 (0–18)
Mean P_{pa} mmHg	40±9 (24–56)
Diastolic P_{pa} mmHg	26±6 (15–40)
Systolic P_{pa} mmHg	64±14 (39–90)
P_{paw} mmHg	10±3 (2–14)
CO L·min^{-1}	4.7±1.3 (2.8–7.6)
CI L·min^{-1}·m^{-2}	2.5±0.7 (1.5–4.4)
PVR dyn·s·cm^{-5}	521±205 (240–1040)
PVRi dyn·s·cm^{-5}·m^{-2}	947±401 (360–1912)
S_{v,O_2} %	65±9 (47–86)

In conclusion, pulmonary hypertension may appear within a mean of only 16 months after the diagnosis of CPFE syndrome, mostly in patients requiring long-term oxygen therapy. Prognosis is poor, despite moderately severe haemodynamic parameters, with a 1-yr survival of 60% from the diagnosis of pulmonary hypertension.

Eur Respir J 2010; 35: 105–111
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Although the efficacy of drugs specifically indicated in pulmonary arterial hypertension has not been demonstrated in patients with pulmonary parenchymal disorders and associated out-of-proportion pulmonary hypertension, a large number of patients from were treated off-label on an individual basis, thereby providing some preliminary information on the efficacy and safety of pulmonary hypertension therapy in this condition.

No significant effect of treatment was found on survival.

ELSEVIER

The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

Impact of lung morphology on clinical outcomes with riociguat in patients with pulmonary hypertension and idiopathic interstitial pneumonia: A post hoc subgroup analysis of the RISE-IIP study

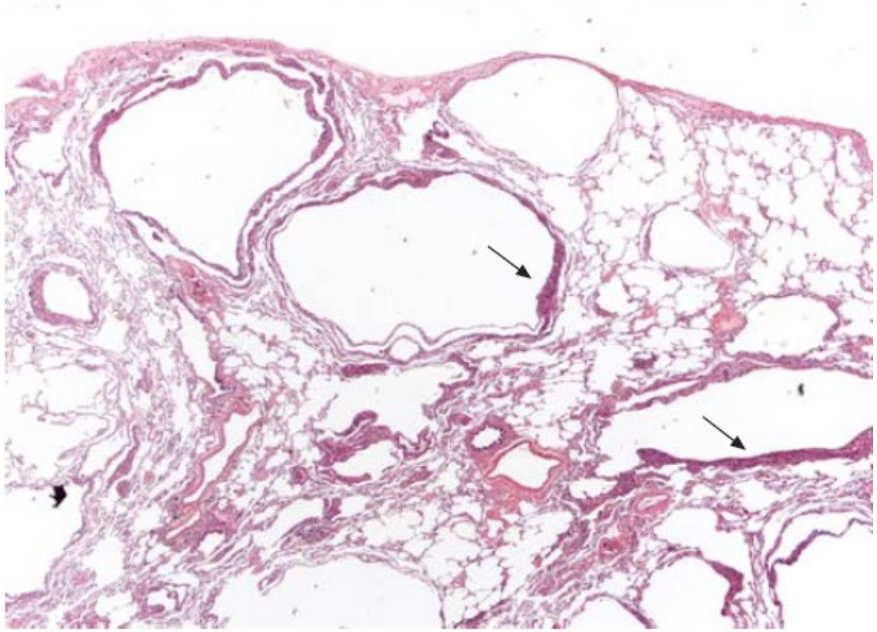
Steven D. Nathan, MD,[a] Vincent Cottin, MD,[b,c] Juergen Behr, MD,[d]

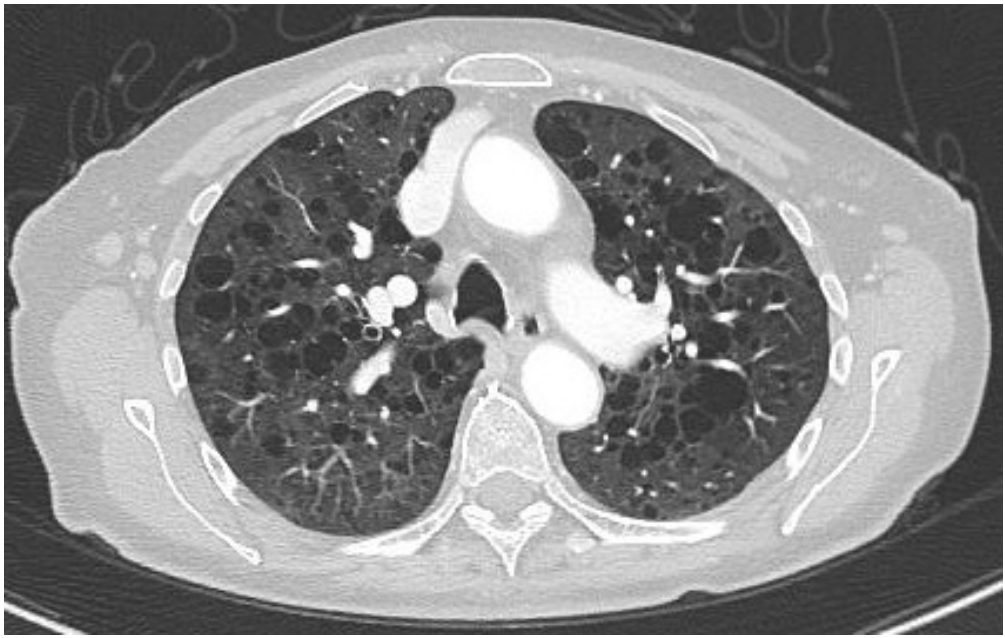
2021

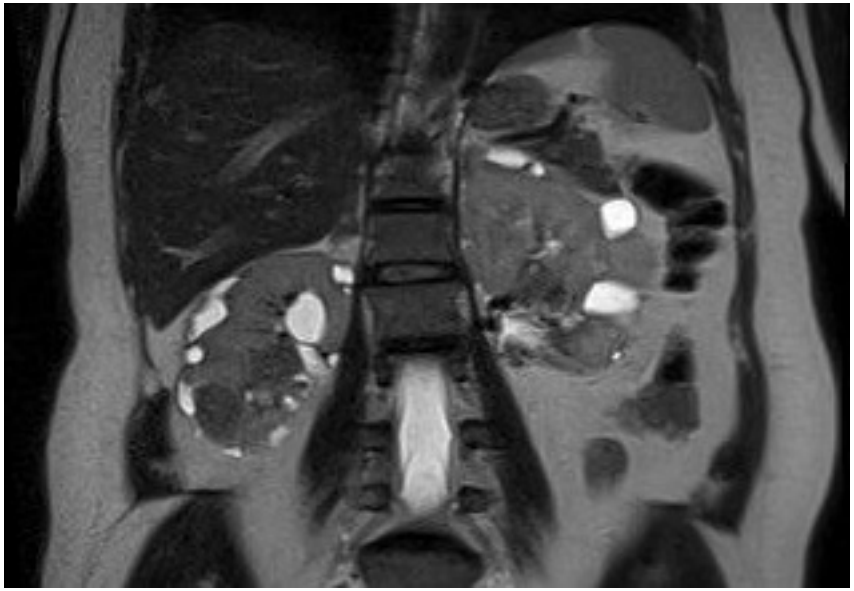
- ✓ Studio randomizzato, controllato, fase 2b
- ✓ Terminato precocemente per aumento della mortalità nel gruppo dei pazienti trattati
- ✓ Analisi retrospettiva post hoc di 65 pz su 147 di cui erano disponibili immagini TC
- ✓ 41 pz su 65 erano CPFE
- ✓ Mortalità più alta nei pz con CPFE (12/41, 29%), rispetto a chi non aveva enfisema (3/24, 13%)

"In conclusion, despite the limitations noted above, the presence of CPFE appears to be a risk factor for mortality in patients with PH-IIP. This mortality risk may be further heightened by a high burden of parenchymal lung disease, and more so perhaps if the extent of emphysema is greater than that of the fibrosis"

PH in linfangioleiomiomatosi (LAM)







Eur Respir J 2012; 40: 630–640
DOI: 10.1183/09031936.00093111

Pulmonary hypertension in lymphangioleiomyomatosis: characteristics in 20 patients

Vincent Cottin, Sergio Harari, Marc Humbert, Hervé Mal, Peter Dorfmüller, et al

TABLE 3 Haemodynamic data at the time of pulmonary hypertension diagnosis

Variable	Patients	
Mean PAP, mmHg	20	32±6 (25–51)
Diastolic PAP, mmHg	19	22±5 (12–30)
Systolic PAP, mmHg	19	48±11 (38–84)
Cardiac output, $L \cdot min^{-1}$	20	5.4±1.9 (3.1–9.5)
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	20	3.4±1.1 (2.1–5.7)
PVR $dyn \cdot s \cdot cm^{-5}$	20	376±184 (118–776)
PVR index $dyn \cdot s \cdot cm^{-5} \cdot m^{-2}$	20	572±307 (190–1433)
Right atrial pressure mmHg	19	7±3 (0–12)
Capillary wedge pressure mmHg	19	10±3 (4–15)
Sv,O_2 %	12	69±7 (59–80)

Data are presented as n or mean± SD (range). PAP: pulmonary arterial pressure; PVR: pulmonary vascular resistance; Sv,O_2: mixed venous oxygen saturation.

Studio multicentrico, retrospettivo, che ha valutato 20 pazienti affette da LAM e PH precapillare valutata mediante RHC

Età media ± SD: 49 ± 12 anni

Intervallo di tempo dalla diagnosi di Lam a quella di PH (media ± SD): 9.2 ± 9.8 anni

- ✓ PH precapillare di grado lieve in pz LAM, anche con compromissione funzionale modesta
- ✓ Nelle 6 pz che hanno ricevuto terapia orale la mPAP si è ridotta da 33 ± 9 mmHg a 24 ± 10 mmHg

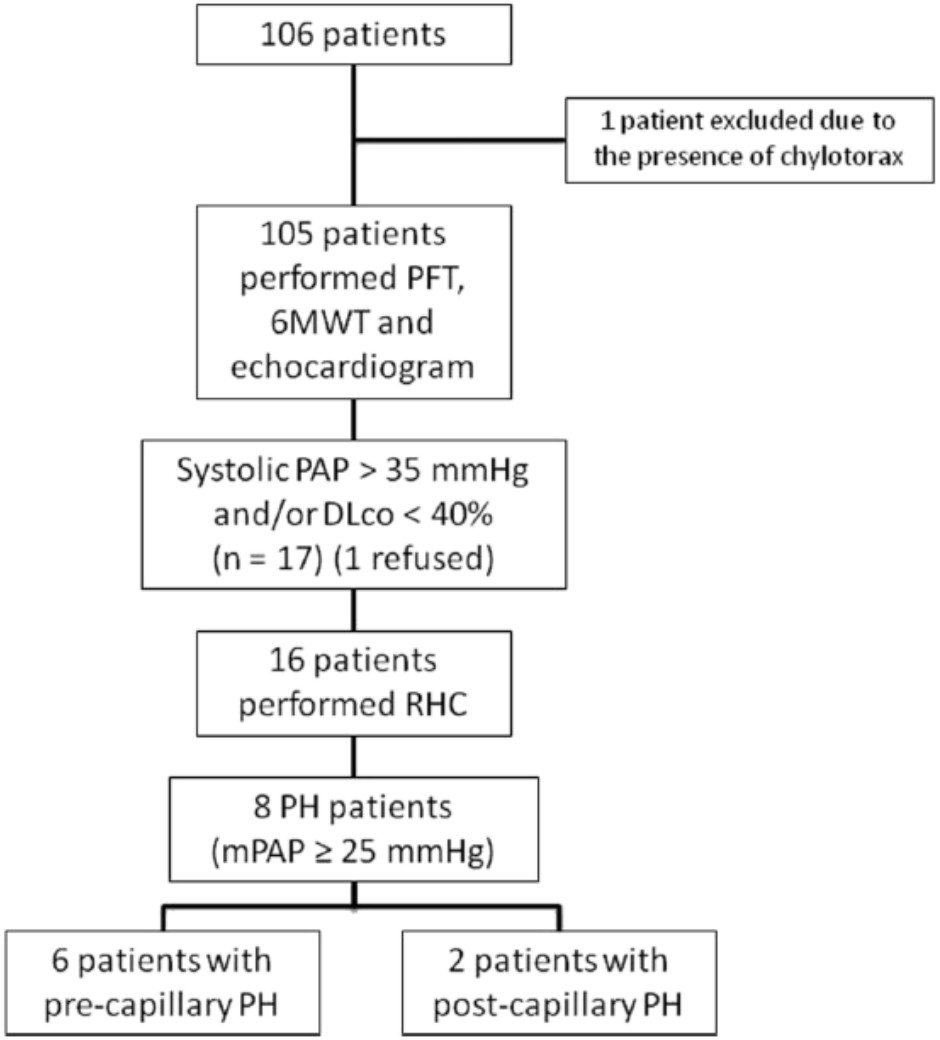
Freitas *et al. Orphanet Journal of Rare Diseases* (2017) 12:74
DOI 10.1186/s13023-017-0626-0

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Pulmonary hypertension in lymphangioleiomyomatosis: prevalence, severity and the role of carbon monoxide diffusion capacity as a screening method

Carolina S. G. Freitas[1], Bruno G. Baldi[1*], Carlos Jardim[1], Mariana S. Araujo[2], Juliana Barbosa Sobral[3], Gláucia I. Heiden[1], Ronaldo A. Kairalla[1], Rogério Souza[1] and Carlos R. R. Carvalho[1]



Clinical, functional and echocardiographic variables	PH ($n = 8$)	Non-PH ($n = 97$)	P
Age (years)	44 ± 6	41 ± 13	0.60
Time from LAM diagnosis (years, IQR)	2 (1.5–11.5)	5 (1–9)	0.75
Use of sirolimus (n, %)	7 (87%)	27 (28%)	0.002
Duration of use of sirolimus (months)	23 ± 7	28 ± 20	0.57
FEV_1 (% predicted)	33 ± 18	76 ± 21	<0.001
DL_{CO} (% predicted)	24 ± 14	72 ± 26	< 0.001
6MWD (m)	371 ± 113	488 ± 110	0.01
Minimum SpO_2	82 ± 6	91 ± 8	0.01
Final Borg dyspnea score	5 (5–7)	2 (0–5)	0.048
Estimated systolic PAP	38 ± 7	26 ± 5	< 0.001
Right heart catheterisation	**PH ($n = 8$)**	**Non-PH ($n = 8$)**	
mPAP (mmHg)	29 ± 5	21 ± 2	<0.001
PAOP (mmHg)	14 ± 4	10 ± 5	0.11
CO (L/min)	4.8 ± 1.2	5.0 ± 0.6	0.70
PVR (IU)	3.4 ± 1.2	2.3 ± 0.8	0.06

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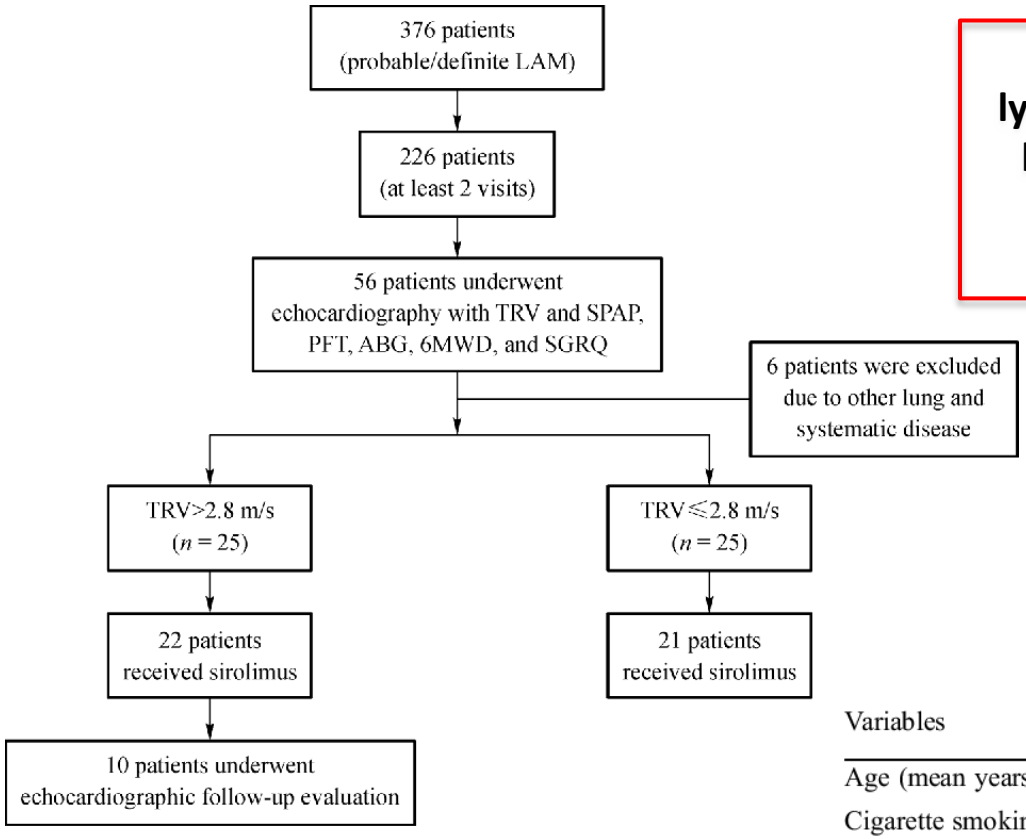
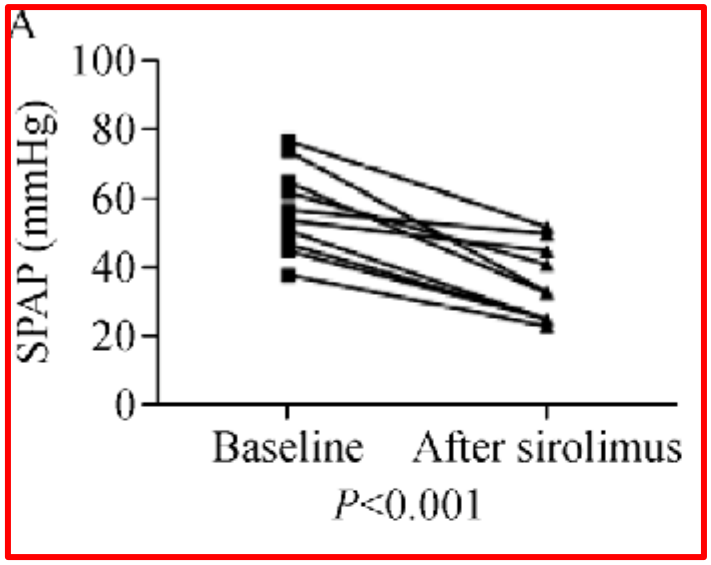
PH. The main findings of this study include the following: 1) The prevalence of PH was low in patients with LAM; 2) PH is of mild severity in LAM and may be pre- or post-capillary; 3) PH was associated with greater impairment of pulmonary function, which suggests that the elevation in PAP is likely associated with the degree of pulmonary parenchymal involvement; 4) Patients with PH had lower exercise performance and greater dyspnea intensity and desaturation during 6MWT; and 5) Reduced DL_{CO} added sensitivity in predicting PH in LAM.

Clinical characteristics in lymphangioleiomyomatosis-related pulmonary hypertension: an observation on 50 patients

Wu X, et al.

Observational Study (2019)





Variables	TRV≤2.8m/s n = 25	TRV>2.8 m/s n = 25
Age (mean years)	38.64±8.10	41.48±8.93
Cigarette smoking	0	0
Weight (kg)	53.66±5.65	51.68±7.15
Body mass index (kg/m^2)	20.97±2.21	20.51±2.71
LAM diagnosis		
Definite (%)	68%	68%
Probable (%)	32%	32%
Tuberous sclerosis complex (%)	8%	8%
Renal angiomyolipoma (%)	20%	12%
History of pneumothorax (%)	32%	28%
History of chylothorax (%)	28%	40%
WHO functional class		
I–II (%)	92%	76%
III–IV (%)	8%	24%
SPAP (mmHg)	30.24±5.25	52.08±12.45
Supplemental oxygen	20%	72%

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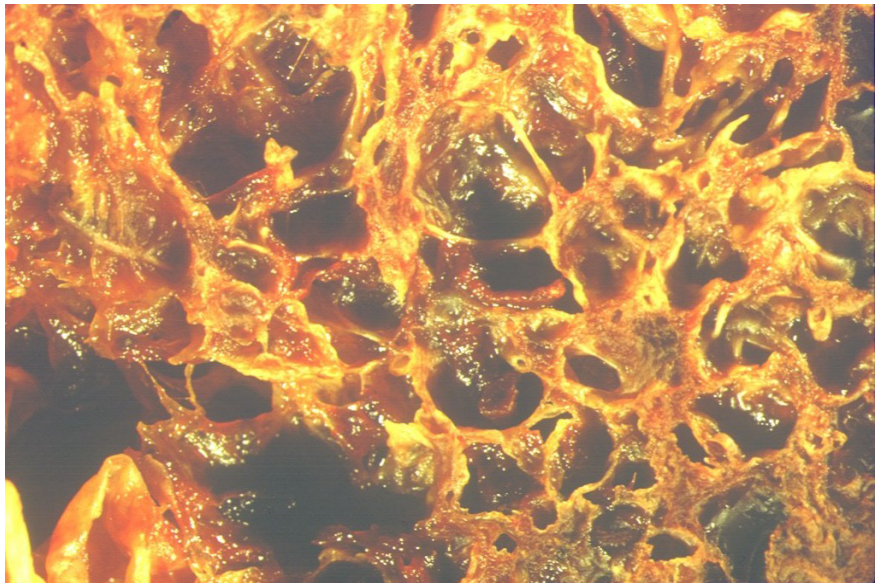
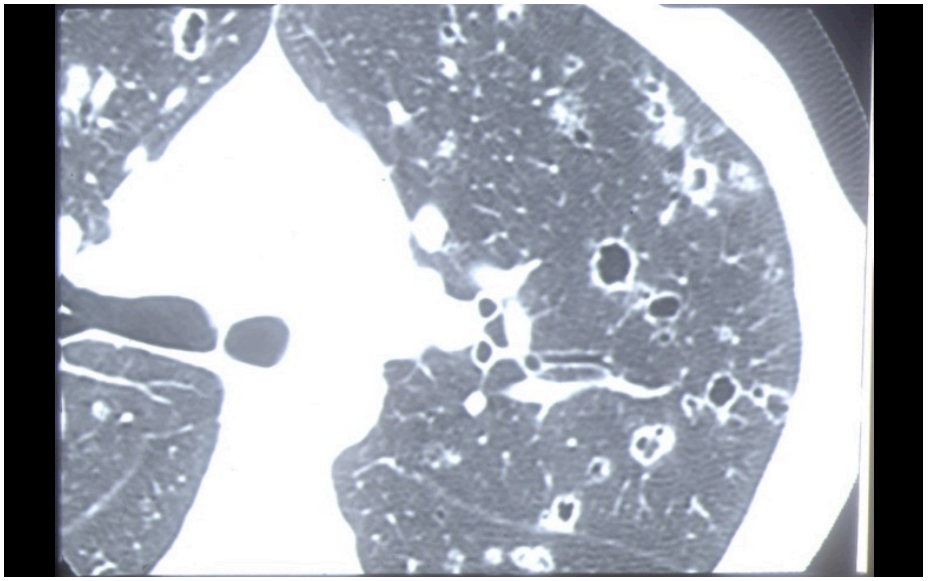
PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; LVEF: left ventricular ejection fraction.

TABLE 7 Pulmonary hypertension with unclear and/or multifactorial mechanisms

5.1 Haematological disorders	Chronic haemolytic anaemia Myeloproliferative disorders
5.2 Systemic and metabolic disorders	Pulmonary Langerhans cell histiocytosis Gaucher disease Glycogen storage disease Neurofibromatosis Sarcoidosis
5.3 Others	Chronic renal failure with or without haemodialysis Fibrosing mediastinitis
5.4 Complex congenital heart disease	See the Task Force article by Rosenzweig *et al.* [31] in this issue of the *European Respiratory Journal*

Istiocitosi a cellule di Langerhans (PLCH)





Malattia rara in cui le cellule di Langerhans monoclonali CD1a-positive (un tipo di istiocita), accompagnate da linfociti, plasmacellule, neutrofili ed eosinofili, infiltrano i bronchioli e l'interstizio alveolare.

E’ isolata ≥ 85% delle volte. Può interessare cute, ossa, ipofisi, linfonodi

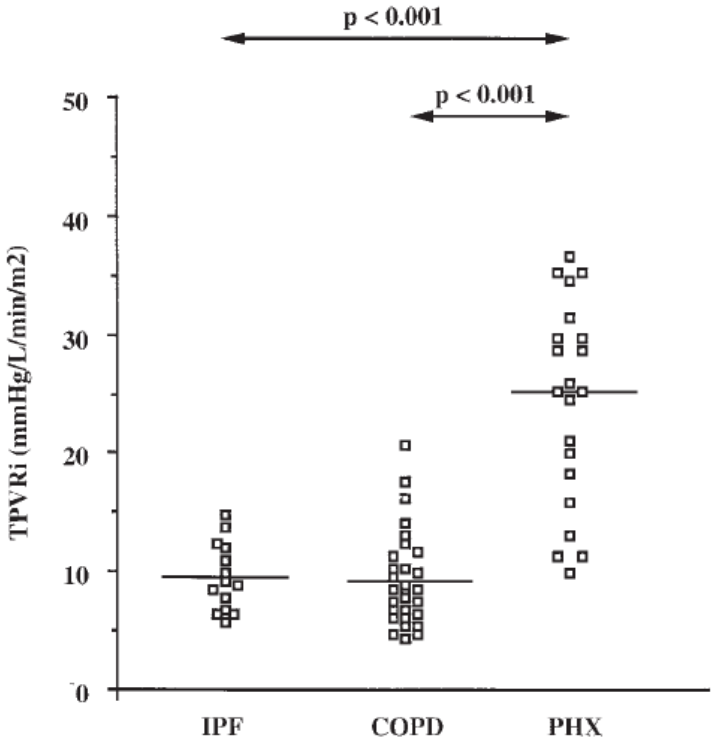
L'eziologia è sconosciuta, ma la malattia si osserva quasi esclusivamente nei fumatori bianchi di 20-40 anni di età (reclutamento e proliferazione delle cellule di Langerhans in risposta a citochine e fattori di crescita secreti dai macrofagi alveolari in risposta al fumo di sigaretta).

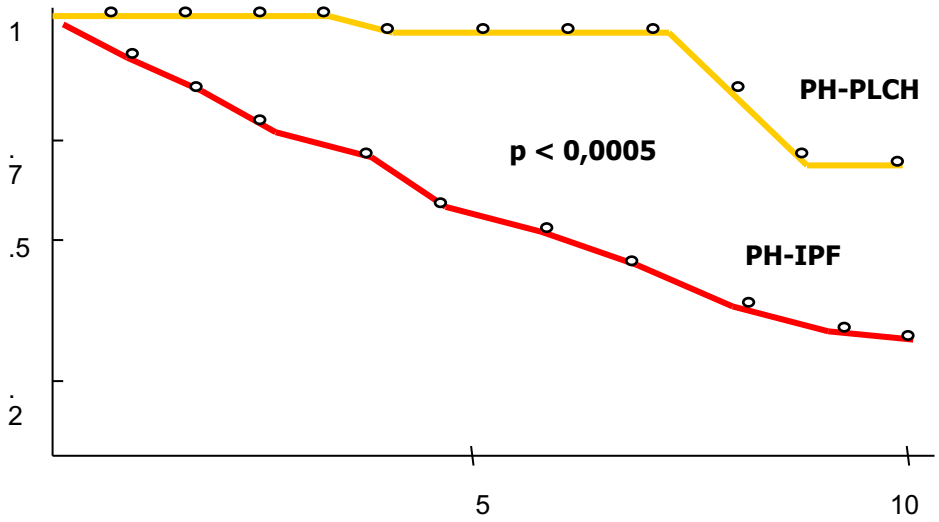
Ipertensione polmonare nella PLCH

- ✓ Rispetto ad altre patologie respiratorie croniche, PLCH è associata ad un'alta prevalenza di ipertensione polmonare (Fartoukh AJRCCM 2000, Harari Chest 1997)

- ✓ PH è stata individuata nel 41-100% dei pazienti con PLCH, con una prevalenza particolarmente elevata (>90%) in quelli valutati per trapianto polmonare (Fartoukh AJRCCM 2000, Wajda Respirology 2020, Chaowalit MCP 2004, Dauriat Transplantation 2006)

- ✓ La presenza di PH è associata ad un'aumentata mortalità nella PLCH (Harari Chest 1997, Chaowalit MCP 2004, Dauriat Transplantation 2006, Bois APLM 2018)





Patofisiologia dell'ipertensione polmonare nella PLCH

- ✓ La vasocostrizione polmonare dovuta dall'ipossia cronica rimane uno dei meccanismi principali coinvolti nella patogenesi della PH nella PLCH

- ✓ Tuttavia, vi sono evidenze che la PH nella PLCH sia correlata anche ad una vasculopatia polmonare intrinseca che si sviluppa indipendentemente dal danno parenchimale e delle piccole vie respiratorie

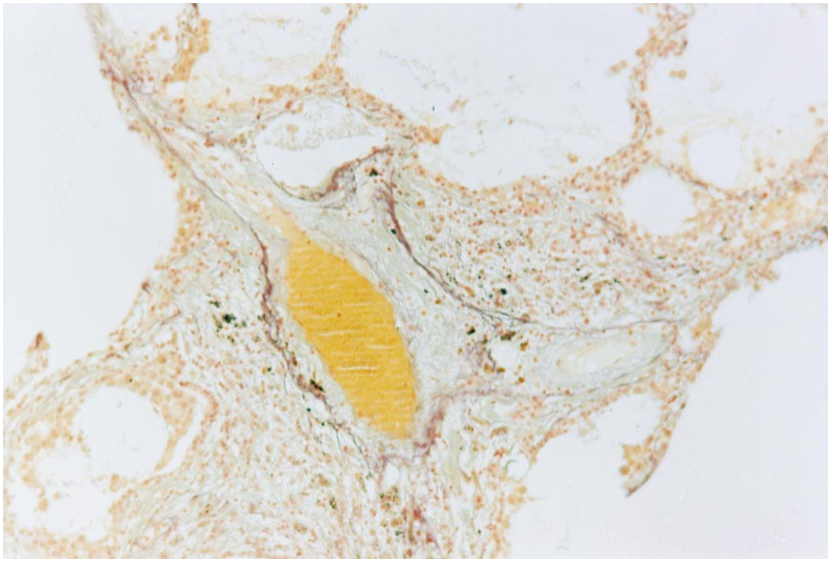
- ✓ Lo sviluppo di PH in alcuni studi sembrerebbe indipendente dal grado di compromissione funzionale e quindi di distruzione del parenchima polmonare

- ✓ Possibile ruolo delle cellule di Langerhans nel rimodellamento vascolare attraverso la produzione di citochine e fattori di crescita e/o invasione diretta anche da parte di altre cellule del sistema immunitario

Travis Am J Surg Pathol 1993
Harari et al JHLT 1997
Fartouk M AJRCCM 2000
Hamada ERJ 2000
Chaowalit MCP 2004
Heiden Chest 2020
Bois MC Arch Pathol Lab Med 2018

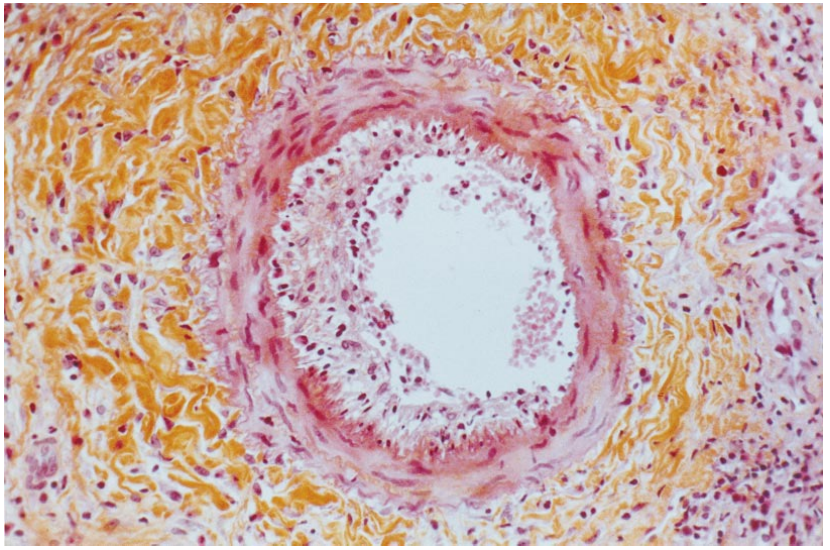
Severe pulmonary hypertension in histiocytosis X
Fartoukh M, Humbert M, et al.
Am J Respir Crit Care Med. (2000) 161:216–23.

- 21 pz con PLCH valutata per trapianto
- PH moderato-severa
- mPAP: 59 ± 4 mm Hg (range 36-74 mmHg)
- Non correlazione tra mPAP e PFR



Venular intimal fibrosis; partial occlusion in a lobular septum.

- Severa vasculopatia polmonare diffusa con interessamento delle arterie polmonari e delle vene intralobari
- Ipertrofia della media, fibrosi intimale e subintimale e/o proliferazione con vari gradi di ostruzione luminale
- Aspetti di patologia veno-occlusiva
- Infiltrazione da parte di cellule di Langerhans in un solo pz



Intimal fibrosis of muscular pulmonary artery within Langerhans' granuloma.

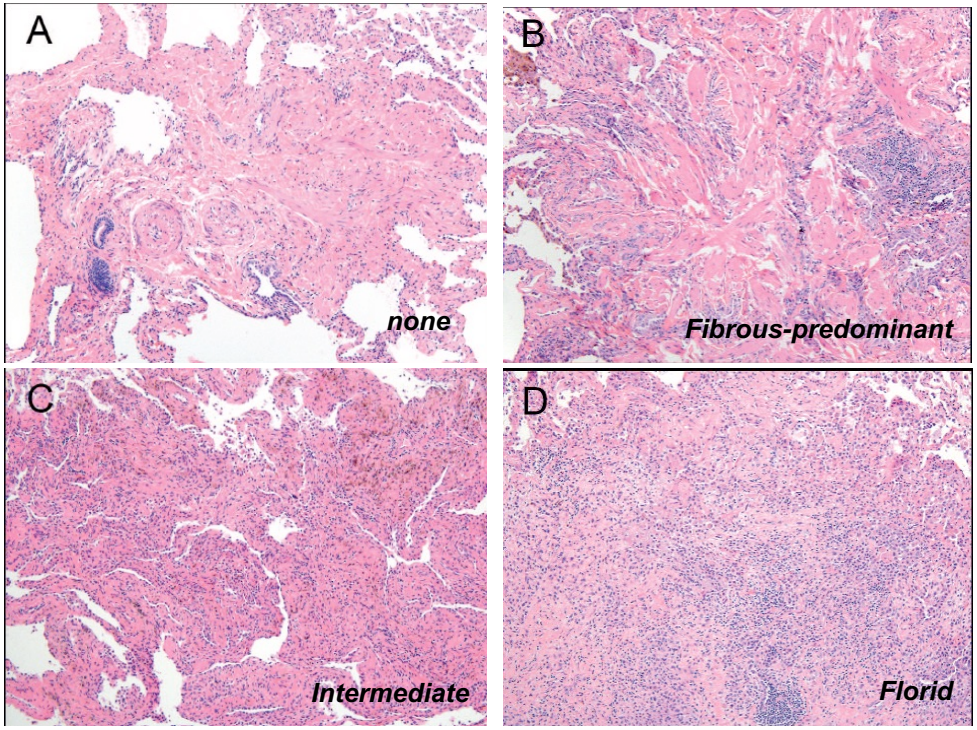
Morphometric Study of Pulmonary Arterial Changes in Pulmonary Langerhans Cell Histiocytosis

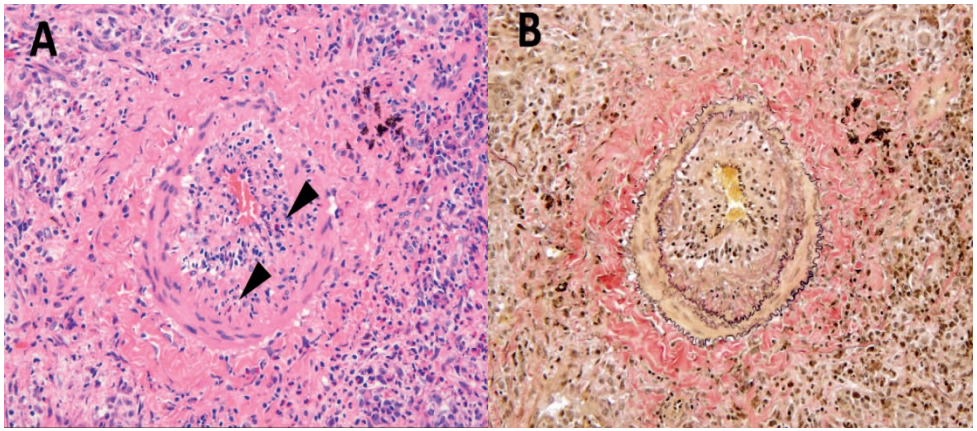
Bois MC, et al.

Arch Pathol Lab Med. (2018)

Table 2. Histologic Features of Patients With Pulmonary Langerhans Cell Histiocytosis (PLCH)

Histopathologic Characteristic	PLCH Cases, n = 25
Cellularity, n (%)	
Florid	9 (36)
Intermediate	6 (24)
Fibrous-predominant	4 (16)
None	6 (24)
Vascular invasion by immune cells, n (%)	
Extensive	2 (8)
Moderate	4 (16)
Few	5 (20)
None	14 (56)
Cystic changes present, n (%)	20 (80)
Bronchiolocentric scars present, n (%)	20 (80)
Emphysema[a], n (%)	
Severe	1 (4)
Moderate	4 (16)
Mild	11 (44)
None	9 (36)
BRAF V600E positive, n (%)[b]	3 (23)





Intimal thickening and extensive vascular involvement by immune and lesional cells, including eosinophils (arrowheads)

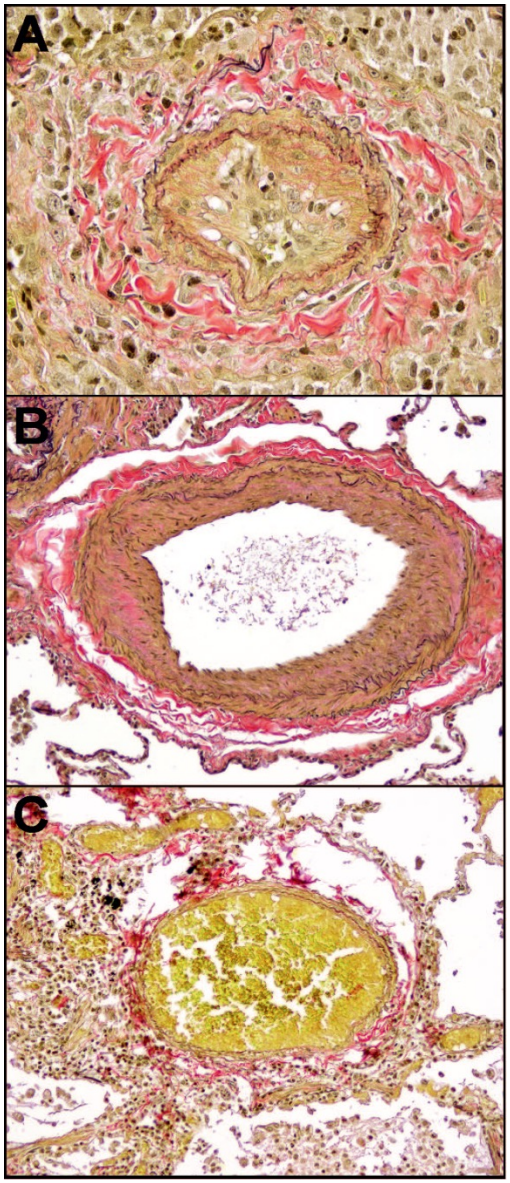
Morphometric Study of Pulmonary Arterial Changes in Pulmonary Langerhans Cell Histiocytosis

Bois MC, et al.

Arch Pathol Lab Med. (2018)

”Using morphometry techniques we find that arterial media and intima are substantially thicker in lesional arteries than in nonlesional pulmonary arteries in patients with PLCH. We furthermore find non lesional arteries to be significantly thicker than those of matched controls. Although our findings do not correlate with other clinical metrics defining PHT severity, the results of our study provide unique insight into the potential pathogenesis of PHT in patients with PLCH.”

“Our findings suggest that factors other than direct vascular obstruction or inflammatory cell infiltration contribute, at least in part, to the vascular remodeling in PLCH.”



An arteriole within a PLCH lesion, showing marked intimal thickening (A). A pulmonary artery in a patient with PLCH, but within unaffected lung, demonstrating intimal thickening without significant medial thickening (B). Pulmonary artery in a control patient (C)

Terapia dell'ipertensione polmonare nella PLCH

- ✓ In un case report è stata descritta una completa risoluzione della PH in un pz affetto da PLCH con la cessazione dall'abitudine tabagica (Kinosita Intern Med. 2016)
- ✓ In un case report è stato descritto un miglioramento della mPAP e delle PVR in un pz trattato con terapia steroidea (Benyounes Chest 1996)
- ✓ Casistiche di pazienti trattati con terapia specifica per PH:

Respiratory Medicine Case Reports 18 (2016) 54–57

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case report

Long-term improvement during tadalafil therapy in a patient with pulmonary hypertension secondary to pulmonary Langerhans cell histiocytosis

Kenji Nemoto [a, *], Shuji Oh-ishi [a], Toshihide Inui [a], Mariko Nakazawa [a], Kentaro Hyodo [a], Masayuki Nakajima [a], Jun Kanazawa [a], Yukiko Miura [a], Takio Takaku [a], Yuko Minami [b], Kenji Hayashihara [a], Takefumi Saito [a], Yoshinori Kawabata [c]

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case report

Dramatic and sustained responsiveness of pulmonary Langerhans cell histiocytosis-associated pulmonary hypertension to vasodilator therapy

Adam May [a], Garvan Kane [b], Eunhee Yi [c], Robert Frantz [b], Robert Vassallo [d, *]

Eur Respir J 2010; 36: 202–211
DOI: 10.1183/09031936.00004810

LETTERS

Severe pulmonary hypertension in histiocytosis X: long-term improvement with bosentan

INTERNAL MEDICINE

CASE REPORT

Severe Pulmonary Hypertension in Adult Pulmonary Langerhans Cell Histiocytosis: The Effect of Sildenafil as a Bridge to Lung Transplantation

Takayuki Yoshida[1], Satoshi Konno[1], Ichizo Tsujino[1], Takahiro Sato[1], Hiroshi Ohira[1], Fengshi Chen[2], Hiroshi Date[2], Akihiro Ishizu[3], Hironori Haga[4], Mishie Tanino[5] and Masaharu Nishimura[1]

Pulmonary Langerhans Cell Histiocytosis-Associated Pulmonary Hypertension

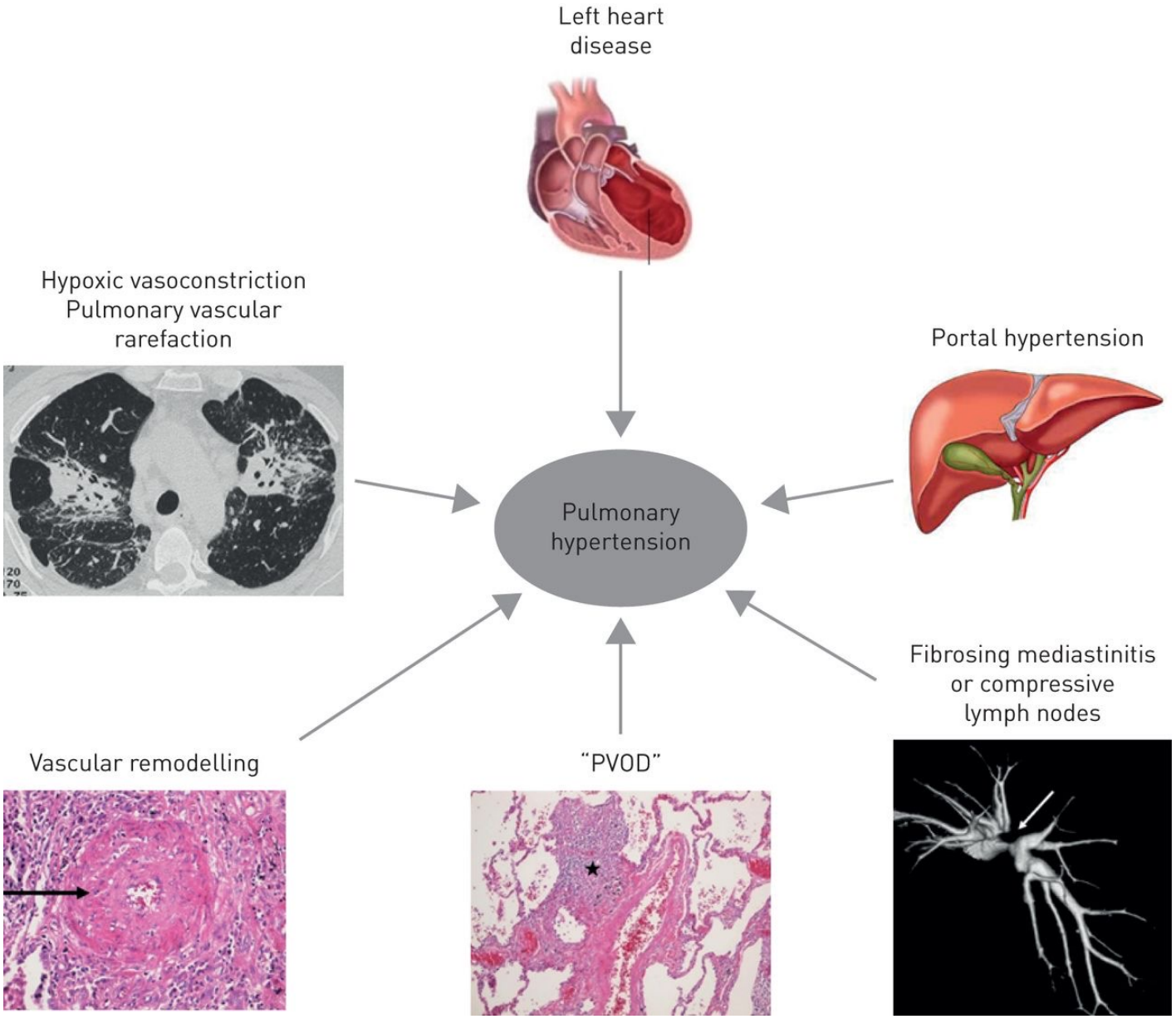
Clinical Characteristics and Impact of Pulmonary Arterial Hypertension Therapies

Jérôme Le Pavec, MD, PhD; Gwenaël Lorillon, MD; Xavier Jaïs, MD; Colas Tcherakian, MD; Séverine Feuillet, MD; Peter Dorfmüller, MD, PhD; Gérald Simonneau, MD; Marc Humbert, MD, PhD; and Abdellatif Tazi, MD, PhD

Chest 2012; 142; 1150-1157

- ✓ 29 pazienti affetti da PLCH con PH confermata al cateterismo cardiaco dx
- ✓ 83% dei pazienti in classe funzionale WHO III e IV; intervallo dalla diagnosi di PLCH a quella di PH associata di 9.2 ± 9.8 anni
- ✓ Test del cammino: 355 m ± 95 m, mPAP: 45 ± 14 mmHg
- ✓ 14 pz trattati con farmaci specifici per PH: 10 ERA, 5 PH5i (2 pz con tp combinata), 1 iloprost inalatorio
- ✓ in 12 pz miglioramento della mPAP (56±14 mmHg → 45±12 mmHg) e delle PVR (701±239 dyne/s/cm5 → 469±210 dyne/s/cm5)
- ✓ In questo gruppo di pz la terapia specifica per la PH ha determinato un miglioramento emodinamico senza peggioramento dell'ossigenazione o edema polmonare

PH in sarcoidosi



Vis D Eur Respir J 2020

EUROPEAN RESPIRATORY REVIEW
REVIEW
L. SAVALE ET AL.

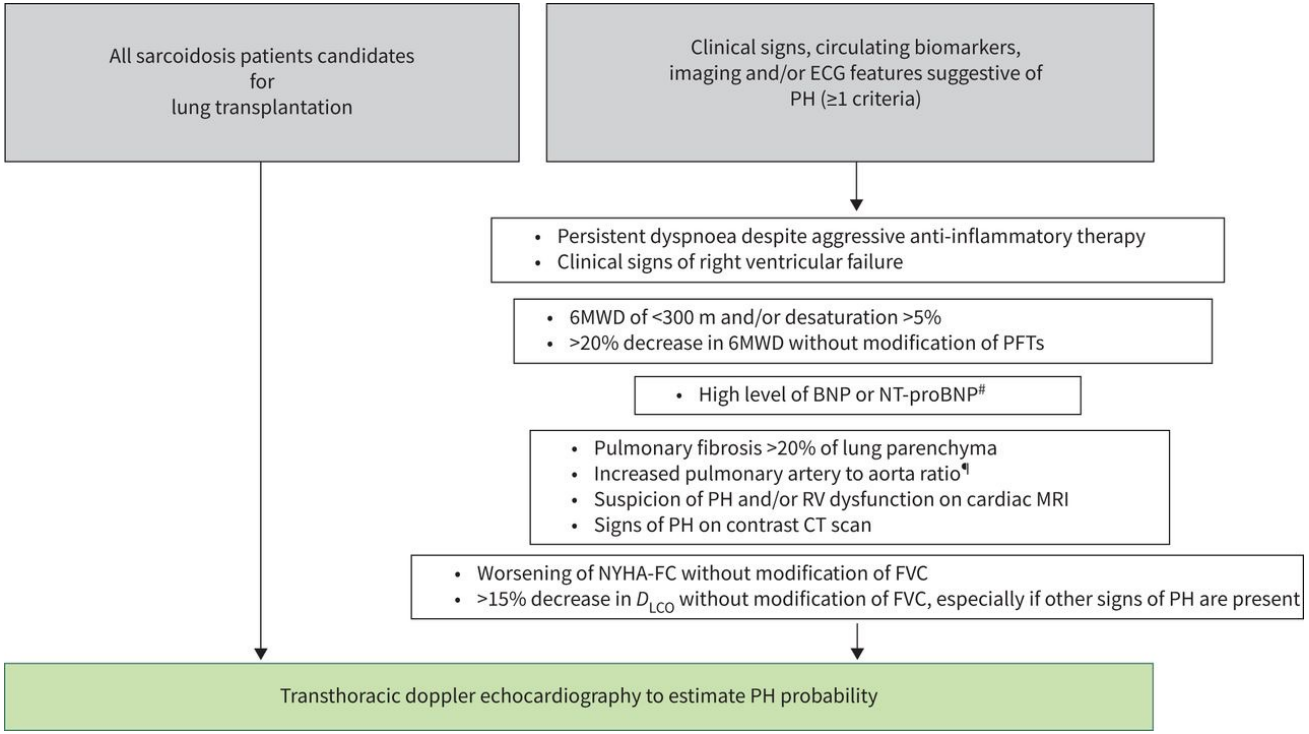
WASOG statement on the diagnosis and management of sarcoidosis-associated pulmonary hypertension

Laurent Savale[1], Marloes Huitema[2], Oksana Shlobin[3], Vasilis Kouranos[4,5], Steven D. Nathan[3], Hiliaro Nunes[6], Rohit Gupta[7], Jan C. Grutters[8], Daniel A. Culver[9], Marco C. Post[2], Daniel Ouellette[10], Elyse E. Lower[11], Tamara Al-Hakim[12], Athol U Wells[4,5], Marc Humbert[1] and Robert P. Baughman[11]

- ✓ La presenza di SAPH è associata ad un significativo peggioramento della sintomatologia, come evidenziato dalla classe funzionale WHO, dalla riduzione di metri al test del cammino e/o dalla maggiore desaturazione con necessità di ossigenoterapia

- ✓ SAPH è un fattore indipendente di mortalità

- ✓ Necessità di effettuare ecocardio di screening



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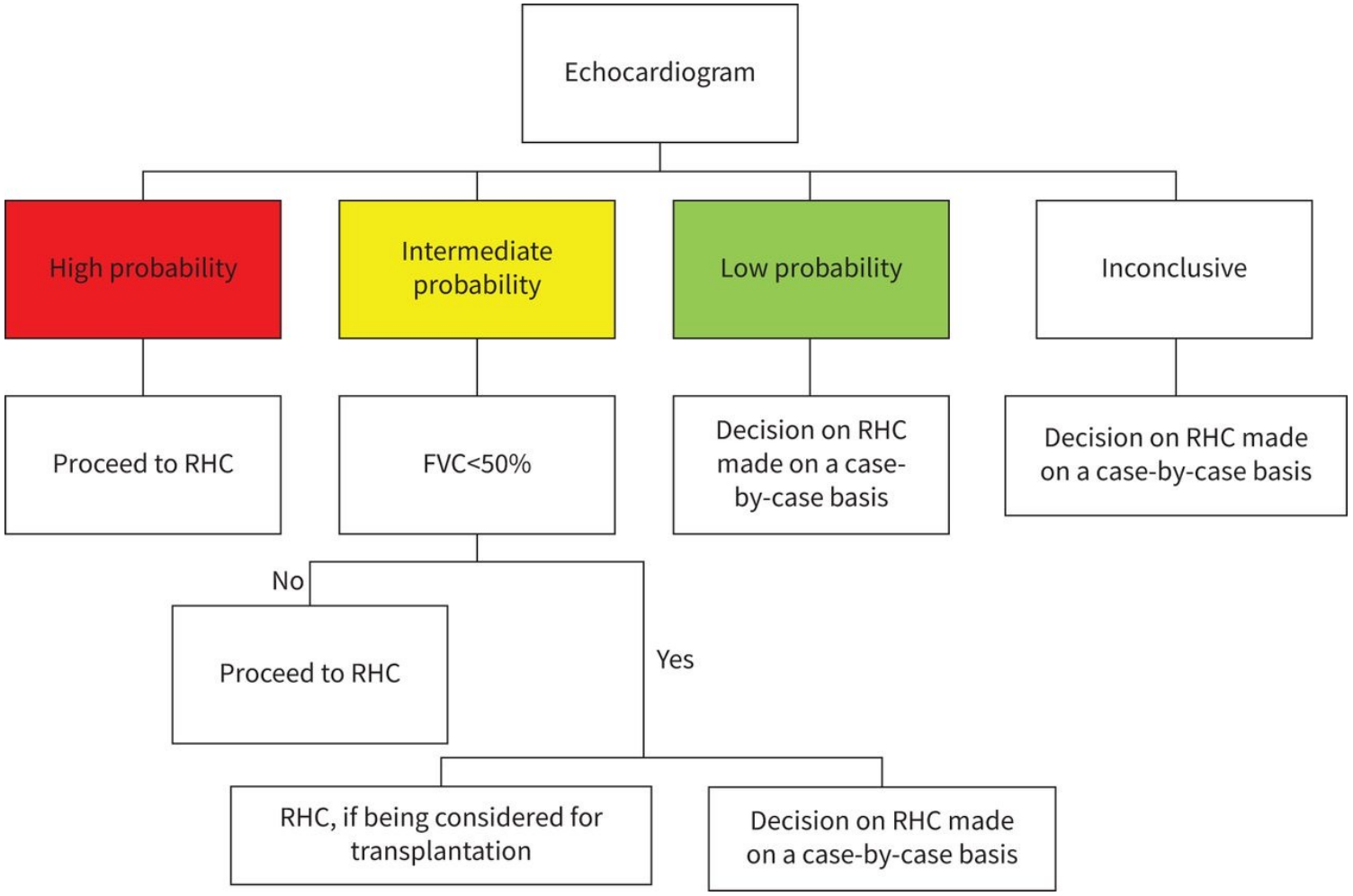
✓ Quando effettuare un cateterismo cardiaco destro?



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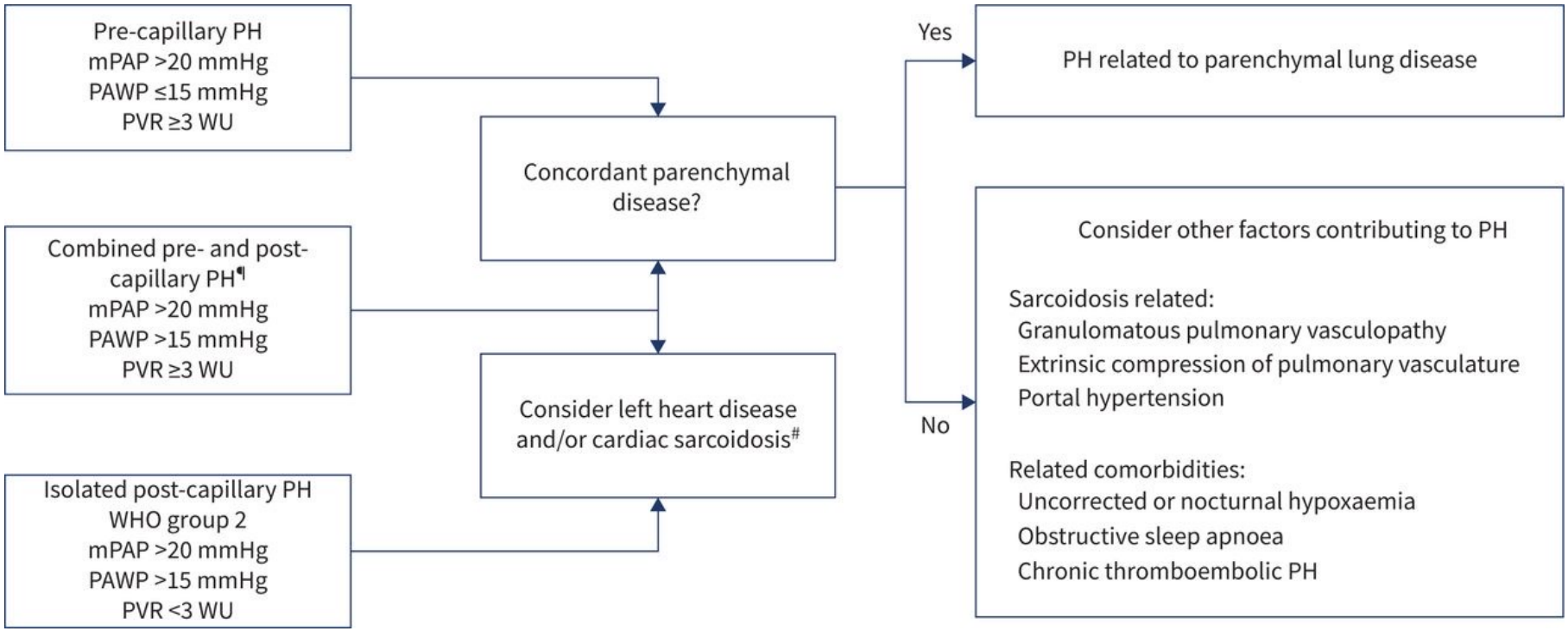

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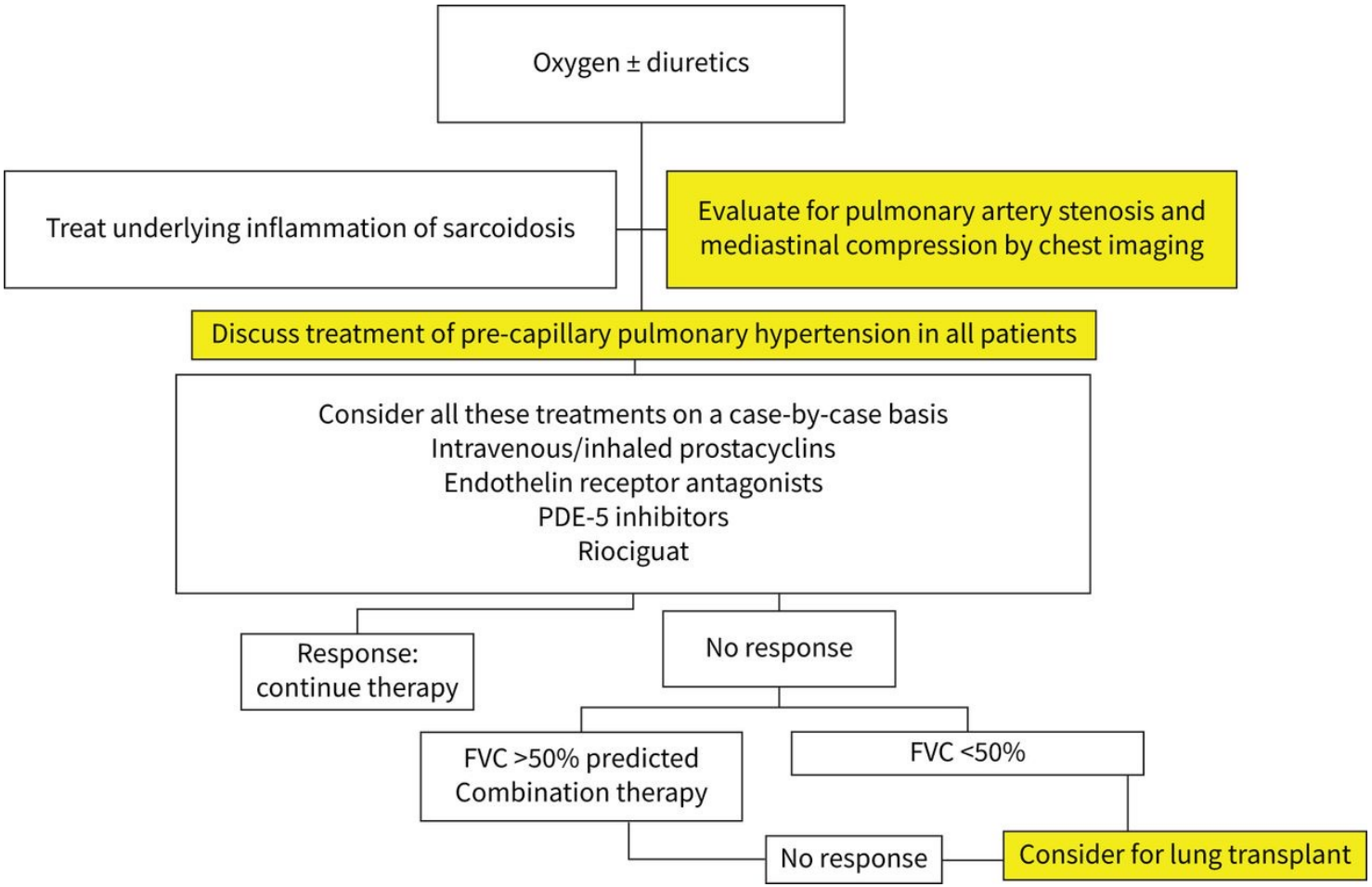
✓ Terapia



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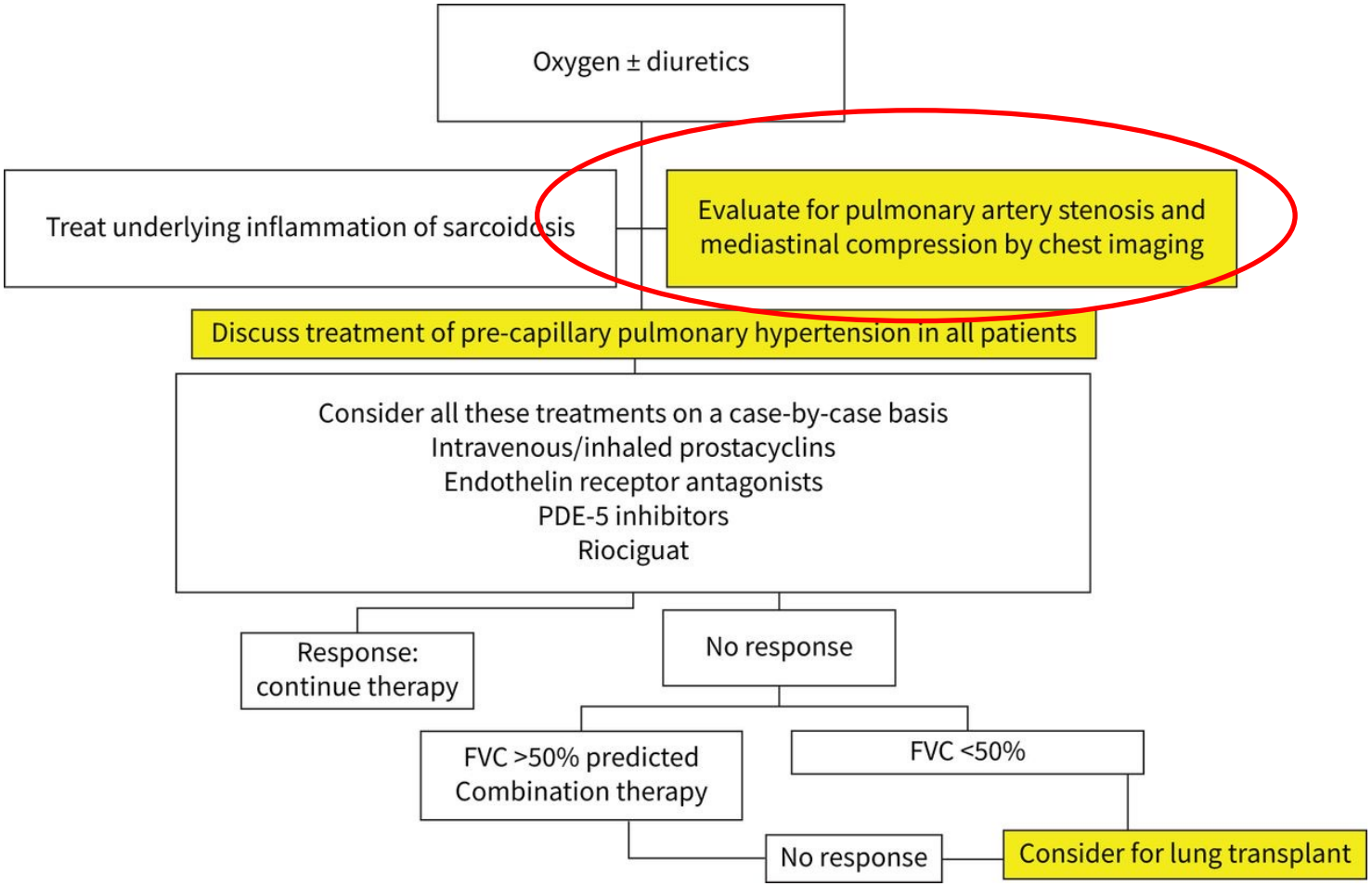
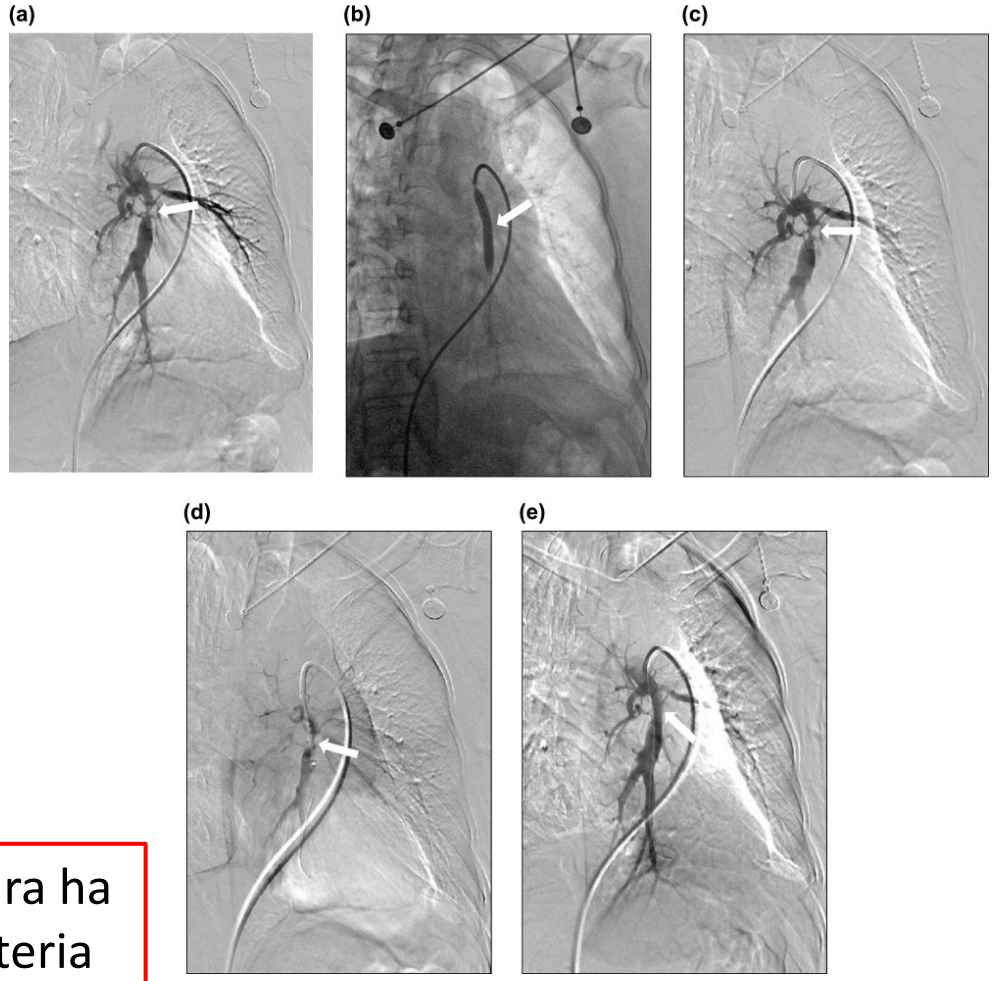
- ✓ Terapia





Liu L, et al. Clin Respir J 2015

Una recente metanalisi della letteratura ha dimostrato che l'angioplastica dell'arteria polmonare con o senza stenting ha determinato un miglioramento al test del cammino

(daSilva-deAbreu A, et al. Curr Probl Cardiol 2021)

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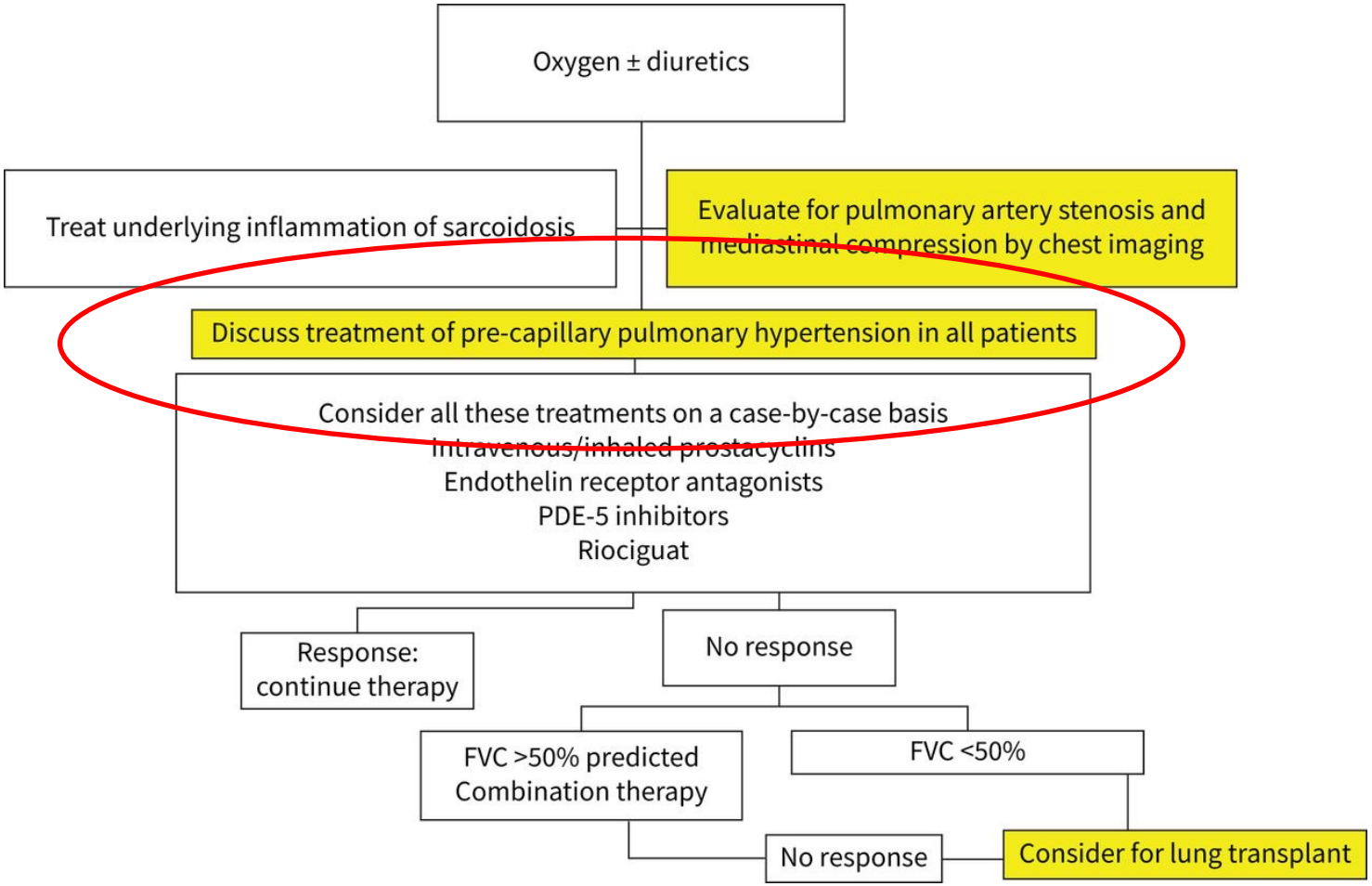

TABLE 3 Treatment of pre-capillary SAPH

	Highest level of evidence study in patients with SAPH	Total number of patients with SAPH treated	Results in sarcoidosis
Prostenoids			
Epoprostenol	Retrospective OL positive [78, 79]	12	Haemodynamics improved [78, 79]
Iloprost	Prospective, OL [72]	15 of 22 enrolled completed 16 weeks' therapy	In sarcoidosis, haemodynamics and QoL improved [72]
Endothelin receptor antagonists			
Bosentan	DBPC [71]	23	Haemodynamics improved, no change in 6MWD [71]
Ambrisentan	Prospective OL [73]	21	Nonsignificant improved QoL, no change 6MWD [73]
Macitentan	Retrospective OL [82]	6	WHO FC improved in 4/6 treated patients [82]
Phosphodiesterase 5 inhibitors			
Sildenafil	Retrospective OL [16]	12	Haemodynamics improved, 6MWD no changes
Tadalafil	Prospective OL [74]	12	No significant changes in 6MWD and QoL
Others			
Riociguat	DBPC [70]	16	TCW and 6MWD significantly better compared with placebo
Combination therapy	Retrospective OL positive [8, 21, 77]	29	Haemodynamics and 6MWD improved in some

SAPH: sarcoidosis-associated pulmonary hypertension; OL: open-label; QoL: quality of life; DBPC: double-blind, placebo-controlled; 6MWD: 6-min walk distance; WHO FC: World Health Organization functional class; TCW: time to clinical worsening.

Summary

In SAPH, treatment decision and follow-up should be made by a multidisciplinary team with a sarcoidosis and a PH expert. Off-label use of PAH therapy may be considered for symptomatic patients on a case-by-case basis (figure 7). As noted above, nearly three-quarters of sarcoidosis patients listed for lung transplant have SAPH [16, 19]. It has been observed that post-transplant survival in patients with pulmonary sarcoidosis was similar to that in patients with other indications for lung transplantation [52, 81].

SPHINX: Selexipag

TITOLO:

Studio clinico, multicentrico, randomizzato, in doppio cieco, controllato con placebo in pazienti affetti da ipertensione polmonare associata a sarcoidosi (SAPH) per valutare l'efficacia e la sicurezza di selexipag assunto per via orale.

OBBIETTIVO PRIMARIO:

Valutare alla Settimana 26 l'effetto di selexipag rispetto al placebo sulla resistenza vascolare polmonare (PVR) in partecipanti con ipertensione polmonare associata a sarcoidosi (SAPH).

ENDPOINT PRIMARIO:

PVR alla Settimana 26 espressa come percentuale del valore rispetto alla baseline

SPHINX: Selexipag

Criteri di inclusione

- Età compresa tra **18 anni e 75 anni**
- Diagnosi di sarcoidosi confermata in base ai criteri ATS
- Sarcoidosi associata a ipertensione polmonare precapillare, confermata da RHC (a riposo) **entro i 90 giorni precedenti** la randomizzazione:

a. PVR ≥320 din*sec/cm5 (≥4,0 unità Wood)

b. Pressione arteriosa polmonare media (mPAP) ≥25 mmHg

c. Pressione di incuneamento arteriosa polmonare (PAWP) ≤15 mmHg oppure, se non disponibile o non affidabile, pressione diastolica e ventricolare sinistra (LVEDP) ≤15 mmHg.

- Gravità della PH in base alla classificazione modificata **FC WHO II–IV,** allo Screening e alla randomizzazione; i partecipanti appartenenti alla classa funzionale IV devono presentare una condizione stabile ed essere in grado di effettuare un 6MWT.
- **Nessun trattamento con terapia specifica per PH o monoterapia orale per PH (**cioè Riociguat, PDE5i, ERA); se in trattamento con uno specifico farmaco orale per PH in monoterapia orale, la terapia dovrà essere stabile (cioè nessuna introduzione di nuove terapie o variazione di dosaggio).) per almeno 90 giorni prima della randomizzazione e della RHC qualificante per l'arruolamento
- Regime di trattamento stabile per la sarcoidosi, cioè nessun nuovo trattamento antinfiammatorio specifico per sarcoidosi da almeno 90 giorni e dose stabile da almeno 30 giorni prima della randomizzazione e della RHC qualificante per l'arruolamento.
- **6MWT tra 50 e 450** m sia allo Screening, sia al momento della randomizzazione.
- Capacità vitale forzata **(FVC) >50%** del valore previsto allo Screening.
- **FEV1/FVC ≥60%**
- Per i pazienti arruolati o per i quali è previsto l'arruolamento in un programma di riabilitazione cardio-polmonare

TABLE 3 Recommendations and questions for the future direction of research in chronic lung disease (CLD)-associated pulmonary hypertension (PH)

Development of better animal models of PH in both COPD and ILD encouraged
- Differential molecular mechanisms (parenchymal *versus* vascular)
- Identification of novel molecular targets

Novel techniques employing *ex vivo* cultured human lung tissue to identify the key cellular and molecular drivers of pathological lung and vascular remodelling and for individualised drug testing
- (Co-)cultured human pulmonary vascular cells, viable human lung slices, *ex vivo* grown or iPSC-derived human lung organoids

Research into biomarkers for group 3 PH encouraged
- Classical circulating peptides, circulating RNA subsets, monocyte/leukocyteomics, volatile exhaled compounds, exhaled "genomic fingerprint"
- Shared access to existing biobanks/biosamples from disparate registries, trials including industry-sponsored studies, regulatory agency involvement
- Patients enrolled into future clinical trials should be consented to enable sharing of their biospecimens

Clinical variables for enrolment in group 3 clinical trials require more sophisticated "deep phenotyping"
- Image phenotyping of parenchymal *and* vascular changes, novel imaging techniques including CT "vascular morphometry", SPECT/CT, PET "metabolomics", four-dimensional MRI, artificial intelligence machine learning ("radiomics")
- Nature, extent and spatial distribution of the parenchymal and vascular abnormalities

Optimal patient phenotype for trials of therapy
- Best haemodynamic variable(s) and threshold to define the patient phenotype; evaluation of right ventricular dysfunction for enrolment; extent of permissible parenchymal lung disease?
- Combination of pulmonary function testing, haemodynamic profile and imaging required

Clinical trial end-points in PH with underlying lung disease
- Phase 2 studies: physiological variables (*e.g.* right ventricular function, haemodynamics, 6MWT) and biomarkers (*e.g.* BNP) acceptable
- Phase 3 studies: comprehensive patient centric clinical outcomes preferable: composite end-point, time to clinically meaningful change (clinical worsening and/or improvement)
- Clinical worsening events may include: mortality, hospitalisation (cardiopulmonary), categorical changes in a functional test (*e.g.* 6MWT), QoL measures, NYHA Functional Class change, need for supplemental oxygen, disease exacerbation, lung transplantation

6MWT: improve its group 3 informative value ("integrate" distance, deoxygenation, Borg dyspnoea score, heart rate recovery?)

Encourage cardiopulmonary exercise testing for more elaborate distinction between respiratory *versus* circulatory limitation (problem: supplemental oxygen dependency)

Haemodynamic assessment while exercising is encouraged and is to be standardised

Inclusion spectrum in group 3 in view of different aetiology, molecular pathology and clinical course: "narrow *versus* broad"?

IIP can be studied together with chronic hypersensitivity pneumonitis and occupational lung disease

Sarcoidosis-PH sufficiently different and should be studied independently

COPD-PH should be studied independently

CPFE-PH included in ILD-PH studies; permissible provided the extent of their emphysema is not too great; or risk for confounding signal?

Studies employing inhaled PH therapies are an attractive option as this may enable better ventilation/perfusion matching and limit systemic side-effects

Future studies should focus on the prevention/inhibition/reversal of vascular remodelling in addition to vasodilation CLD-PH

Future studies should also target role of the vascular compartment in driving parenchymal abnormalities ("vascular therapy beyond PH")

Further studies of the role of pulmonary rehabilitation (exercise training) in lung disease complicated by PH are encouraged

Nathan SD. et al. Eur Respir J 2019