Le prospettive terapeutiche: classi 3 e 5

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Clinical classification of pulmonary hypertension (PH)

1. Pulmonary arterial hypertension

1.1 Idiopathic
1.2 Heritable
  1.2.1 BMPR2 mutation
  1.2.2 Other mutations
1.3 Drugs and toxins induced
1.4 Associated with:
  1.4.1 Connective tissue disease
  1.4.2 Human immunodeficiency virus (HIV) infection
  1.4.3 Portal hypertension
  1.4.4 Congenital heart disease (Table 6)
  1.4.5 Schistosomiasis

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

1'.1 Idiopathic
1'.2 Heritable
  1'.2.1 EIF2AK4 mutation
  1'.2.2 Other mutations
1'.3 Drugs, toxins and radiation induced
1'.4 Associated with:
  1'.4.1 Connective tissue disease
  1'.4.2 HIV infection

1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

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

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

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

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

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

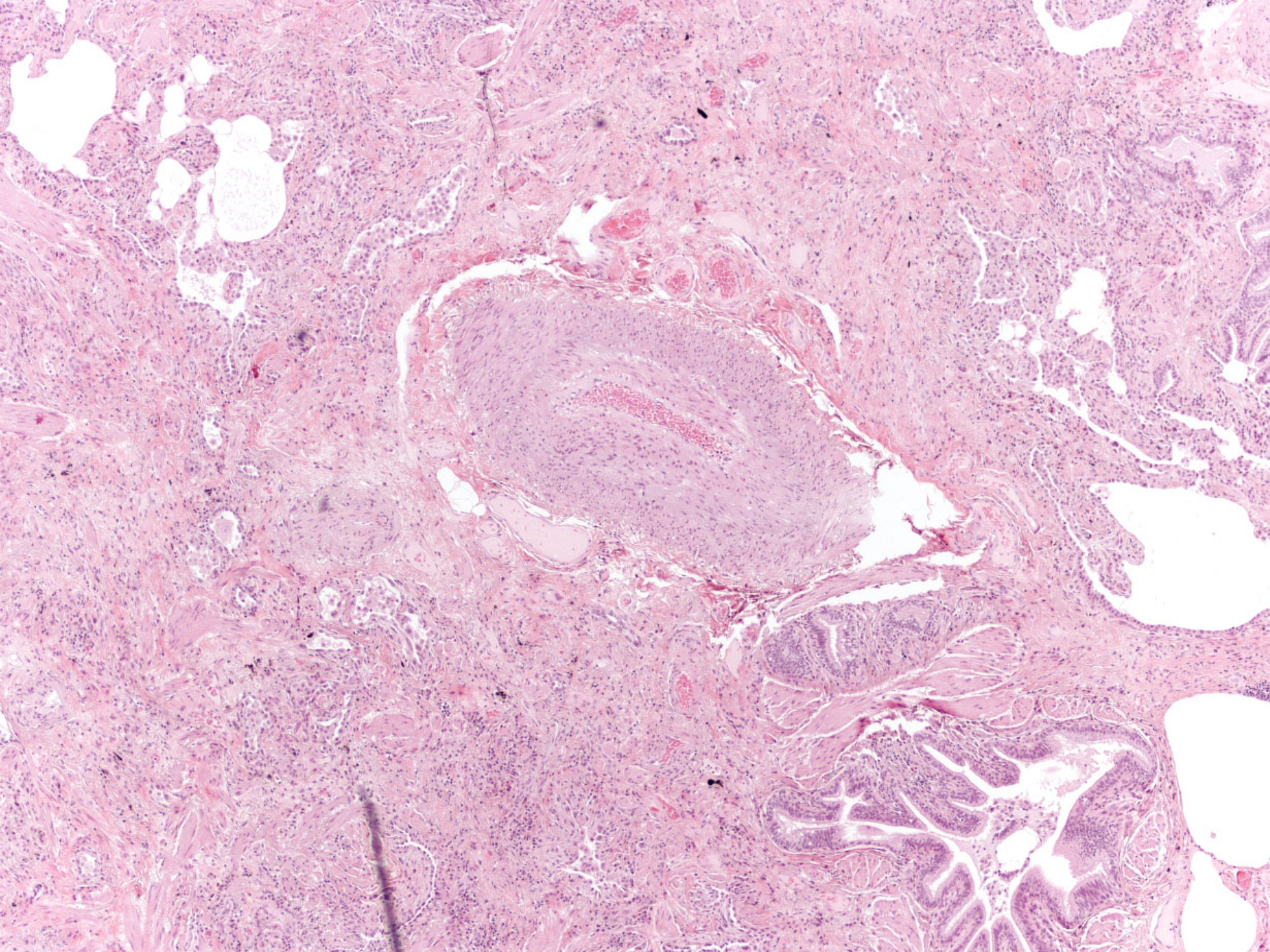
5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

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

Galiè N. et al. ESC/ERS Guidelines. Eur Heart J & Eur Respir J 2015

Disorders of the respiratory system and hypoxemia

- PH is generally mild or moderate (PAP < 30 mmHg), is not per se a predominant prognostic factor and not require specific therapies
- Medial hypertrophy and mild intimal fibrosis



- The prevalence of PH in patients with ILD varies greatly as a function of the underlying disease and the diagnostic mode used to identify PH

- The most extensive data have been published in IPF

Author	Year	Patients	N	Diagnosis	Definition of PH	Prevalence, %
Leutche et al.	2004	IPF	28	RHC	mPAP>35 mmHg	21.4
Nadrous et al.	2005	IPF	88	Echo	sPAP>35 mmHg sPAP>50 mmHg	84 31
Hamada et al.	2007	IPF	70	RHC	mPAP>25 mmHg	8.1
Zisman et al.	2007	IPF	65	RHC	mPAP>25 mmHg	41.5
Patel et al.	2007	IPF	41	RHC	mPAP>25 mmHg +PCWP ≤15 mmHg	20
Shorr et al.	2007	IPF	2.5 k	RHC	mPAP>25 mmHg	46.1
Nathan et al.	2008	IPF	118	RHC	mPAP>25 mmHg	40.7
Song et al.	2009	IPF	131	Echo	sPAP>40 mmHg	25
Minai et al.	2009	IPF	148	RHC	mPAP>25mmHg mPAP>40mmHg	45.9 14.2
Kimura et al.	2012	IPF	101	RHC	mPAP > 20 mmHg	34,6

The incidence and prevalence of PH in IPF remain unclear, with widely varying estimates.

The differences reflect:

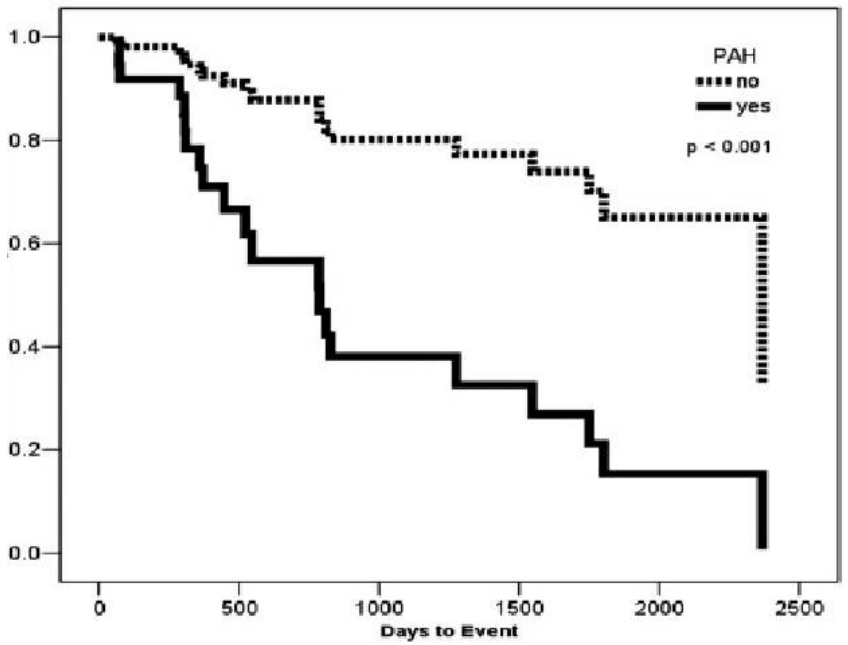
- varying patient populations
- varying underlying disease severity
- differing diagnostic modalities

Pulmonary hypertension in IPF

88 patients with IPF	PASP 0-34 mmHg (n=14)	PASP 35-49 mmHg (n=47)	PASP >50 mmHg (n=27)
Median survival	4.8y	4.1y	0.7y
1 year survival	100%	79%	44%
3 year survival	64%	61%	32%

Nadrous et al Chest 2005: 128;616-7

Pulmonary hypertension in IPF



Variables	MAP ≤ 25 mmHg (n= 10)	MAP > 25 mmHg (n= 24)	P value
MPAP, mmHg	18.2 ± 3.6	29.8 ± 5.1	NA
6MWT distance, m	365.9 ± 81.8	143.5 ± 65.5	< 0.001
SpO2 nadir on 6MWT, %	88.0 ± 3.5	80.1 ± 3.7	< 0.001
Mortality rate, %	37.5	70.0	0.003

Pulmonary vascular resistance predicts early mortality in patients with diffuse fibrotic disease and suspected pulmonary hypertension

Corte TJ et al. Thorax 2009; 64: 883

Table 1 Demographic and clinical data of the study population (n = 66)

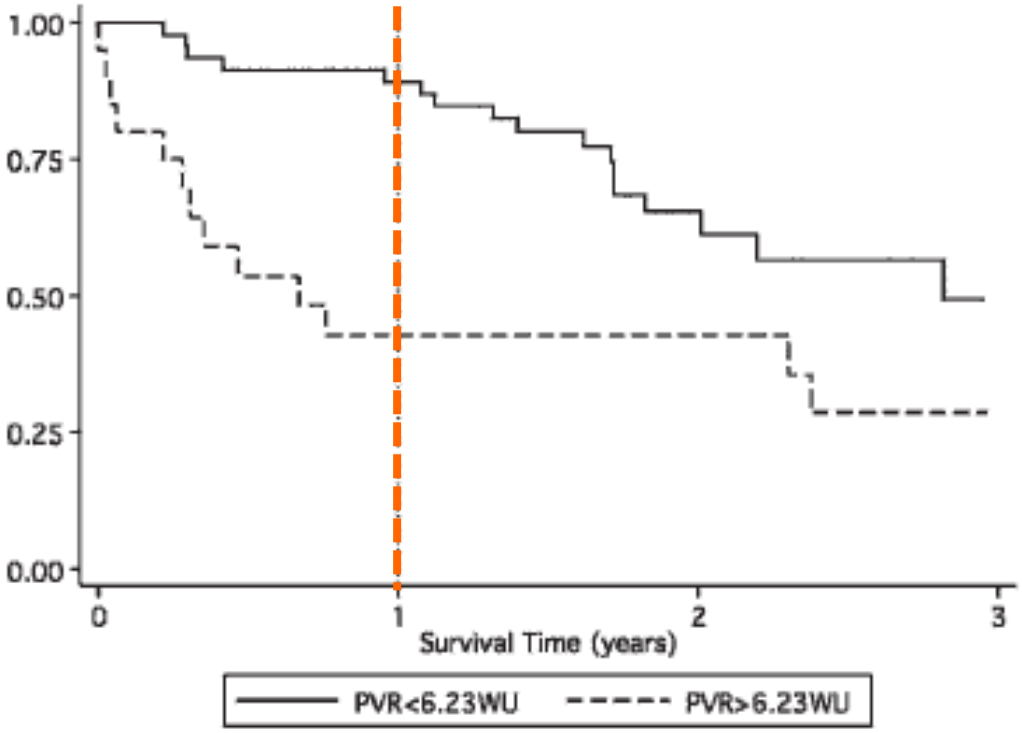
Parameters	No
Clinical parameters*	
Age (years)	57 (12)
Gender (F:M)	28:38
Smoking (pack years)	27 non-smokers, 31 ex-smokers, 7 current smokers, 1 unknown
Time from presentation (months)	33 (4–264)
WHO class	3 (1–4)
Working diagnosis (based on multidisciplinary consensus including lung biopsy when available)	IPF (n = 16) Idiopathic NSIP (n = 6) CTD-related fibrosis (n = 17) Sarcoidosis (n = 12) Other interstitial diseases (n = 15)
Biopsy diagnosis	n = 13 (20%)
Right heart catheter*	
mPAP (mm Hg)	33.6 (11.8)
mRAP (mm Hg)	5.9 (4.2)
mLAP (mm Hg)†	10.7 (5.1)
PVR (Wood units)	5.9 (4.3)
PVR index (Wood units/m²)	10.4 (7.1)
Cardiac output (l/min)	4.3 (1.2)
Cardiac index (l/min/m²)	2.3 (0.5)
Echocardiography	
RVSP (mm Hg, n = 48)	56 (24–102)
PAT (ms, n = 46)	100 (33–144)
Pulmonary function	
T_{LCO} % (n = 65)	29.6 (14.7)
K_{CO} % (n = 65)	52.0 (19.7)
TLC % (n = 61)	72.5 (20.2)
FEV_1 % (n = 62)	62.4 (23.3)
FVC % (n = 62)	67.9 (23.1)
Pao_2 (kPa, n = 61)	8.4 (2.2)
$Paco_2$ (kPa, n = 61)	5.0 (0.9)
CPI (n = 62)	56.9 (14.6)
6MWT (n = 42)	
End Spo_2 (%)	81.4 (8.4)
6MWT distance (m)	254.6 (128.1)

Table 2 Comparison of patients dying within 12 months with those surviving at 12 months

	Death within 12 months	Survival at 12 months	p Value*
mPAP (mm Hg)	39.0 (14.1)	31.7 (10.4)	0.03
PVR (WU)	9.4 (5.8)	4.6 (2.8)	<0.001
PVR index (WU/m²)	16.4 (9.7)	8.5 (4.8)	<0.001
mLAP (mm Hg)	12.2 (6.4)	9.5 (5.0)	0.11
Cardiac output (l/min)	3.8 (1.3)	4.4 (1.1)	0.06
PAT (ms)	69.4 (21.2)	99.5 (28.1)	0.005
Pao_2 (kPa)	7.4 (1.4)	8.8 (2.3)	0.03

Pulmonary vascular resistance predicts early mortality in patients with diffuse fibrotic disease and suspected pulmonary hypertension

Corte TJ et al. Thorax 2009; 64: 883



In severe diffuse lung disease, raised PVR strongly predicts death within 1 year independent of disease severity or diagnosis of IPF.

PVR is superior to other measurements at RHC and also to non-invasive tests (alone or in combination). These findings suggest that, in advanced lung disease, prognostic information that is only obtainable by RHC has important management implications

- The presence of PH in IPF is associated with higher mortality and its development contributes to the deterioration of IPF patients

STEP-IPF - Sildenafil in IPF

- Prospective, randomized, clinical trial:

  to evaluate effectiveness of sildenafil at improving breathing function, exercise capacity and QoL in patients with advanced IPF

- <u>Primary endpoint:</u>

  Change in 6-MWD (defined as ≥ 20% improvement or ≤ 20% improvement)

N Engl J Med 2010;363:620-8

STEP-IPF Results

	Sildenafil	Placebo	P-value
≥ 20% improvement in 6MWD	9/89 (10%)	6/91 (7%)	0.39

No significant change in **6MWD** at 12 or 24 weeks

No difference in mortality or acute exacerbations after 12 or 24 weeks

QOL

- Improvement with treatment on St. George's Respiratory Questionnaire ($P = 0.01$)
- No improvement on SF-36 or EQ-5D tests

Dyspnea

- Improvement with treatment on SOB Questionnaire ($P = 0.006$)
- No improvement on Borg Dyspnea Index after walk test

Gas exchange at 12 weeks

- Improvement in DL_{CO} ($P = 0.04$)
- Improvement in arterial oxygen saturation ($P = 0.05$)

Serious adverse events were similar in the two study groups.

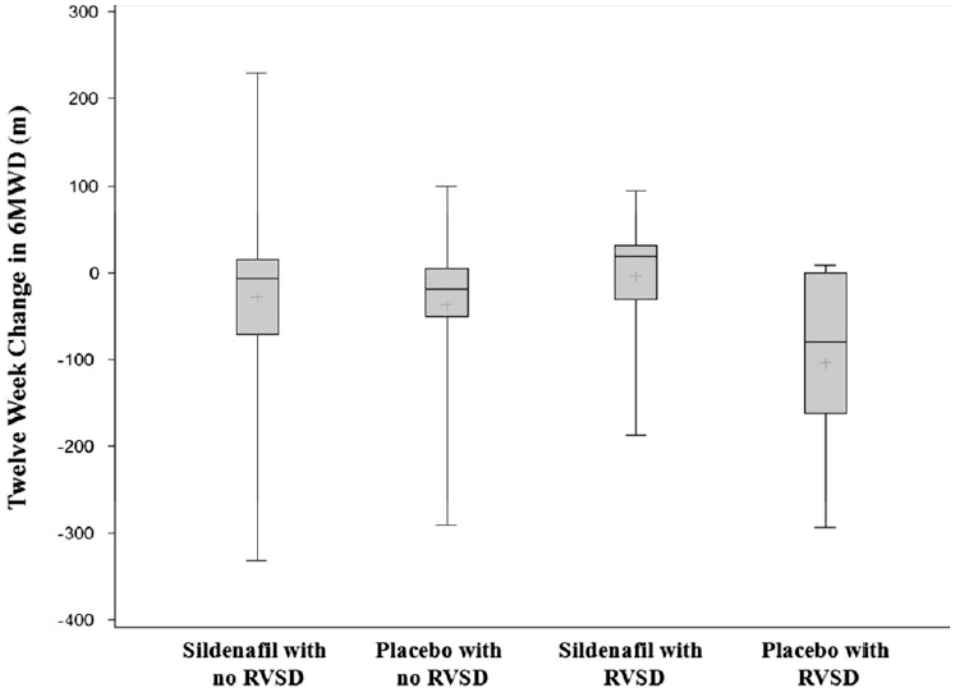
IPF Clinical Research Network. *N Engl J Med*. 2010; 363:620-628.

Sildenafil in IPF with Right-sided Ventricular Dysfunction A substudy of STEP-IPF

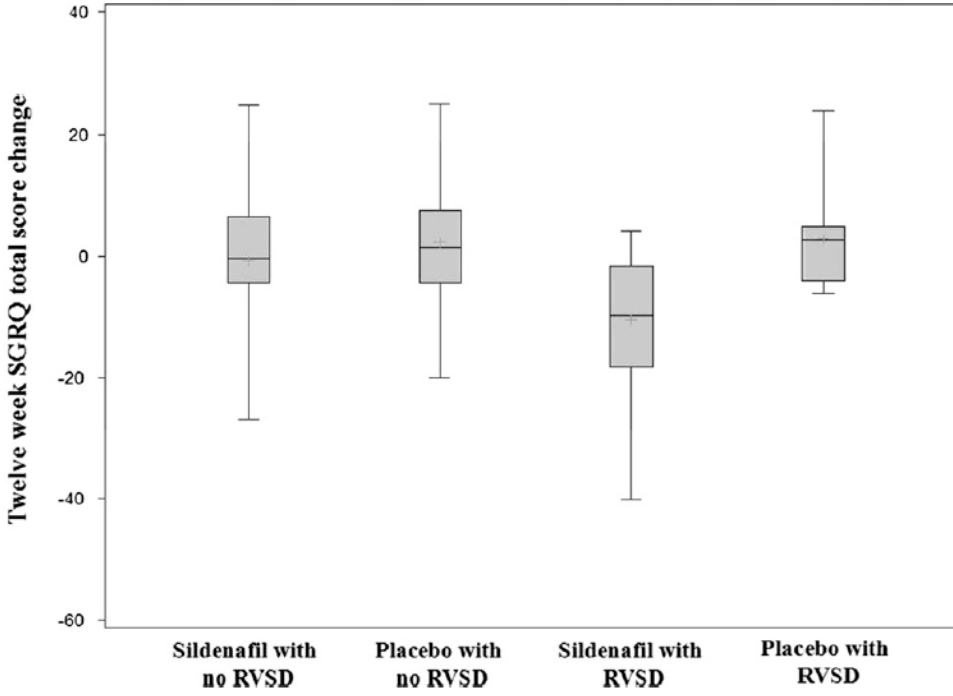
- Of 180 subjects enrolled into STEP-IPF, echocardiograms from 119 were available for independent review (sildenafil, n 56; placebo, n 63)
- Right ventricular hypertrophy (RVH), right ventricular systolic dysfunction (RVSD), and right ventricular systolic pressure (RVSP) were assessed.
- Multivariable linear regression models estimated the relationship between RV abnormality, sildenafil treatment, and changes in 6MWD
- St. George's Respiratory Questionnaire (SGRQ), the EuroQol instrument, and SF-36 Health Survey (SF-36) from enrollment to 12 weeks.

Chest 2013; 143 (6): 1699-1708

Sildenafil in IPF with right-sided ventricular dysfunction
A sub-study of STEP-IPF



Change in 6MWD at 12 weeks by treatment and presence of RVSD



Change in SGRQ total score at 12 weeks by treatment and presence or RVSD

Patients with any evidence of RVSD treated with sildenafil demonstrated a 99.3 m greater 6MWD as compared with those treated with placebo.

Treatment with sildenafil in subjects with RVSD resulted in a significantly lower SGRQ total score

Riociguat for interstitial lung disease and pulmonary hypertension: a pilot trial

Hoeper MM. et al. Eur Respir J 2013;41: 853 - 860

TABLE 1 Baseline demographics and clinical characteristics of the patients

Patients n	22
Age years	60.5 (33.0–80.0)
White ethnicity	22 (100.0)
Male sex	14 (63.6)
BMI kg·m^{-2}	26±4
WHO functional class	
III	19 (86.4)
IV	3 (13.6)
6-min walk distance m	316±96
Underlying disease	
Idiopathic pulmonary fibrosis	13 (59.1)
Non-specific interstitial lung disease	5 (22.7)
Sarcoidosis	3 (13.6)
Systemic sclerosis	1 (4.5)
Pulmonary function	
TLC % pred	67±12
FVC % pred	67±20
FEV_1 % pred	67±17
D_{LCO}# mmol·min^{-1}·kPa^{-1}	2.7±1.5
Haemodynamics and blood gases	
Mean pulmonary artery pressure mmHg	40±10
Pulmonary vascular resistance dyn·s^{-1}·cm^{-5}	656±201
Cardiac output L·min^{-1}	4.3±1.4
Systolic blood pressure# mmHg	136±16
Heart rate¶ beats per minute	78±14
SpO_2 %	94±3
SvO_2¶ %	62±12
$PaCO_2$ mmHg	39±7

Riociguat for interstitial lung disease and pulmonary hypertension: a pilot trial

Hoeper MM. et al. Eur Respir J 2013;41: 853 - 860

Objective: to assess the safety, tolerability and preliminary efficacy of riociguat, in patients with PH-ILD

Design: open-label, uncontrolled pilot trial

Intervention: patients received oral riociguat (1.0–2.5 mg three times daily) for 12 weeks (n=22), followed by an ongoing long-term extension (interim analysis at 12 months) in those eligible (n=15)

Conclusions: Riociguat was well tolerated by most patients and improved cardiac output and PVR, but not mPAP. Further studies are necessary to evaluate the safety and efficacy of riociguat in patients with PH-ILD.

Efficacy and safety of riociguat in patients with symptomatic pulmonary hypertension (PH) associated with idiopathic interstitial pneumonias (IIP) (RISE-IIP)

Phase 2 clinical study is terminated on 2016

The DMC recommended the study's immediate termination after observing that patients receiving riociguat were at a possibly increased risk of death and other serious adverse events as compared to patients receiving placebo

Pirfenidone and sildenafil

- A phase IIb multicenter, randomized, double-blind placebo controlled study to evaluate the **efficacy**, **safety and tolerability** of sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and intermediate or high probability of group 3 pulmonary hypertension
- Clinical phase: II b

Primary endpoint

- The primary efficacy endpoint is will be evaluated based on a comparison of the proportion of patients showing disease progression over 52 weeks of treatment period, as evidenced by reaching the following combined endpoint:
  - Relevant decline in 6MWD of at least 15% from baseline (as defined per protocol), respiratory – related non-elective hospitalization, or all cause mortality

Key inclusion criteria

For the purpose of this study, patients have to present with:

Advanced IPF

(defined as a measurable %DLCO≤40% at screening)

AND

Intermediate or high probability of Group 3 PH

(defined as a mPAP≥ 20 mmHg with PAWP≤15 mmHg) on a previous RHC of acceptable quality

OR

In the absence of a previous RHC, patients with ECHO intermediate or high probability of PH, as defined by the 2015 ESC/ERS guidelines (peak TVR ≥ 2.9 m/s), will be considered eligible for the study

Efficacy and Safety of Nintedanib When Co-administered With Sildenafil in Idiopathic Pulmonary Fibrosis Patients With Advanced Lung Function Impairment

Nintedanib and sildenafil

- A 24-week, double-blind randomized parallel group study evaluating the **efficacy and safety** of oral nintedanib co-administered with oral sildenafil
- Clinical phase: III b
- **Objective:** To assess efficacy and safety of concomitant treatment with nintedanib and sildenafil in IPF patients with advanced lung **function impairment**

Nintedanib and sildenafil

- 300 patients to be included, ≥ 40 years and with DLCO ≤ 35%
- Randomization 1:1
- Nintedanib 150 mg bid with the possibility to reduce to 100 mg bid to manage adverse events or placebo and sildenafil 20 mg tid
- 24 weeks of randomized treatment
- **Primary Endpoint**: Change from baseline in SGRQ total score at week 12

Other key inclusion criteria

- Age 40-80 years
- Diagnosis of IPF for at least 3 months prior the screening
- Confirmation of IPF diagnosis by the Investigator, in accordance with the 2011 international consensus giudelines
- WHO Functional class II/III
- 6MWD of 100-450 m

Future direction for Treatment of IPF + PH

- Association of antifibrotic drugs with PAH medications
- Evaluate the real effect on survival and QOL not only 6 MWT and/or RHC

IPF + PH

- **Long-term oxygen therapy**
  Palliation of dyspnea
- Lung transplantation
- Drug therapy
  - No proven benefit of PAH-specific drugs (not recommended)
  - IPF regardless of PH : no benefit (bosentan, macitentan), deleterious (ambrisentan, riociguat), unclear benefit (sildenafil)
  - Possible improvement of hemodynamics with unclear clinical benefit and risk of deterioration of gas exchange

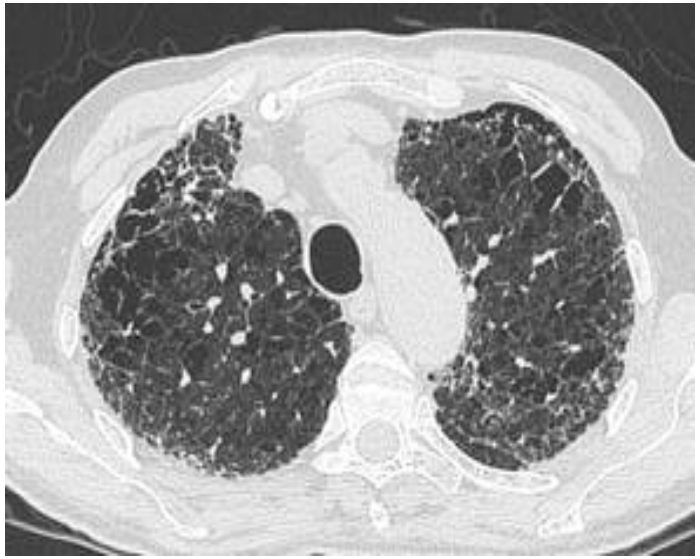
PH in CPFE

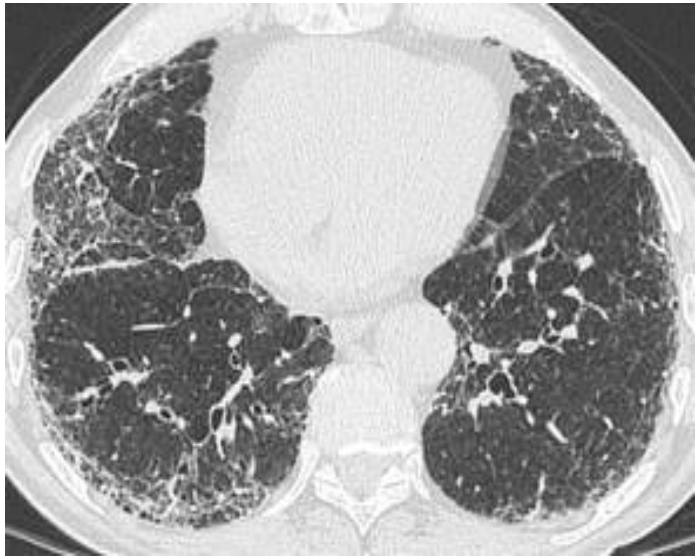
PH is frequent in patients with the CPFE syndrome, with 47% of patients with estimated systolic right ventricular pressure ≥45 mmHg at echocardiography.

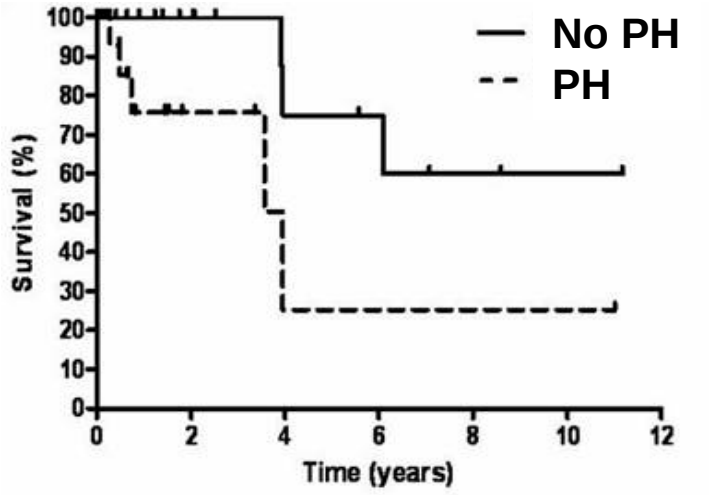
The risk of developing pulmonary hypertension is much higher in CPFE than in IPF without emphysema

The prognosis of CPFE is worse than that of IPF without emphysema, an outcome determined by severe pulmonary hypertension and not only by the presence of associated emphysema

PH in the syndrome of combined pulmonary fibrois 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]

(1) Cottin V *et al.* Eur Respir J 2005.
(2) Mejia M *et al*. Chest 2009.

PH in patients with CPFE

A retrospective multicentre study was conducted in 40 patients (38 males; age 68 ± 9 yrs; 39 smokers)

Dyspnoea was functional class II in 15%, III in 55% and IV in 30%. 6-min walk distance was 244±126 m. FVC was 86 ± 18%, FEV1 78 ± 19%, and DLCO 28 ± 16% of predicted.

PaO2 on room air was 56 ± 12 mmHg).

Mean pulmonary artery pressure was 40 ± 9 mmHg, cardiac index 2.5 ± 0.7 and pulmonary vascular resistance 521 ± 205.

Cottin V et al Eur Respir J 2010; 35; 105

PH in patients with CPFE

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.

Coffin V et al Eur Respir J 2010; 35; 105

In summary

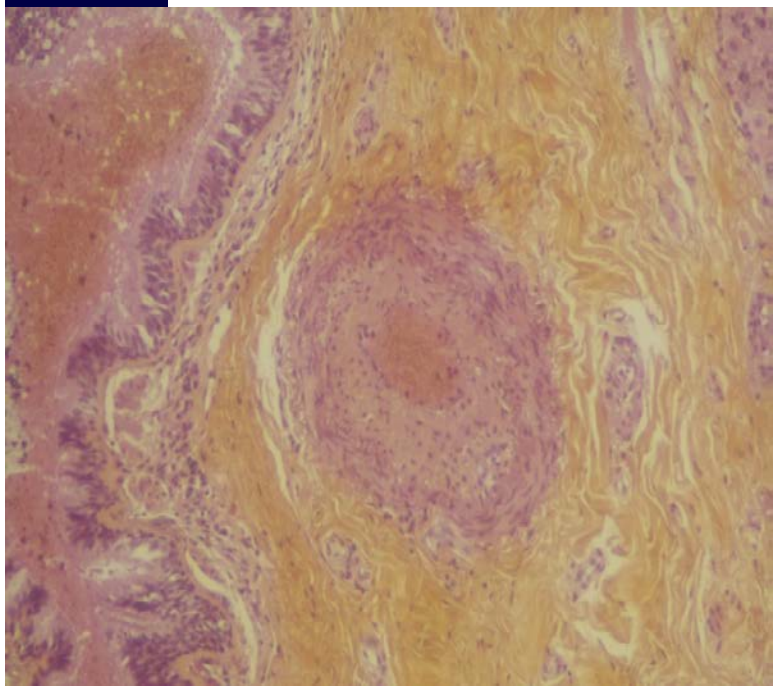
Combined pulmonary fibrosis with emphysema

- Males
- Smokers
- Severe PH
- Worse survival than IPF

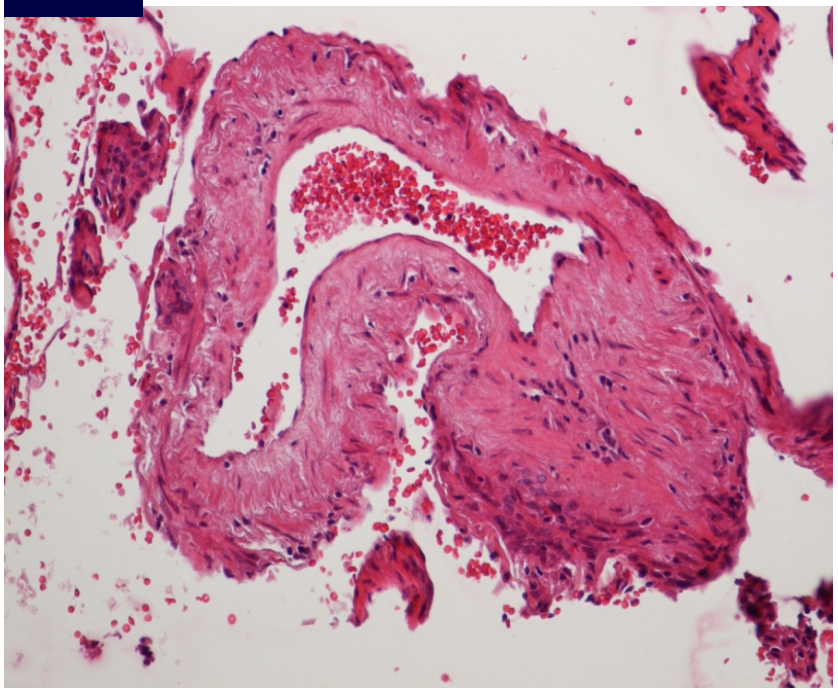
Involvement of pulmonary vessels by the disease class V

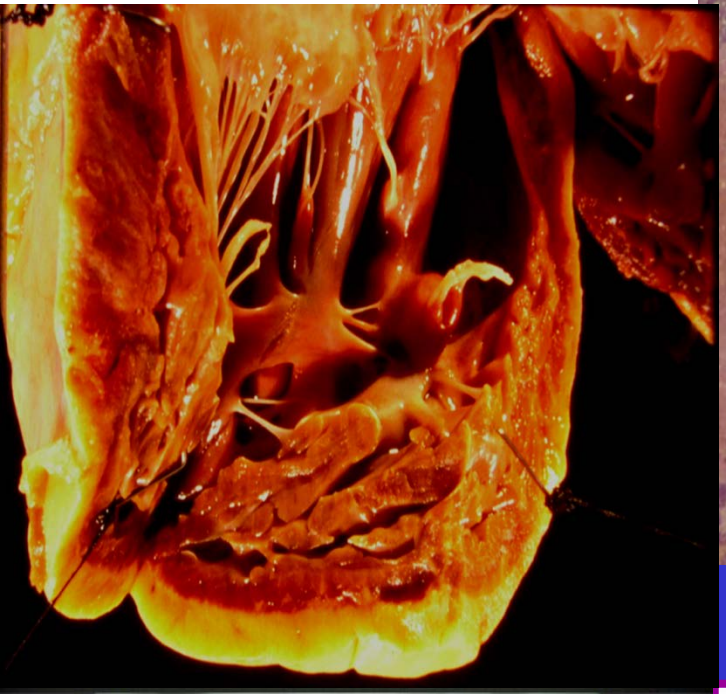
- Pulmonary Langerhans cell histiocytosis
- Lymphangioleiomyomatosis
- Sarcoidosis

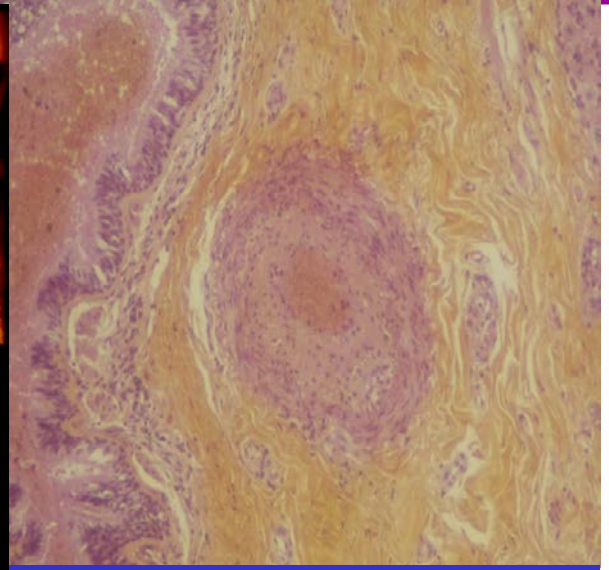
PLCH



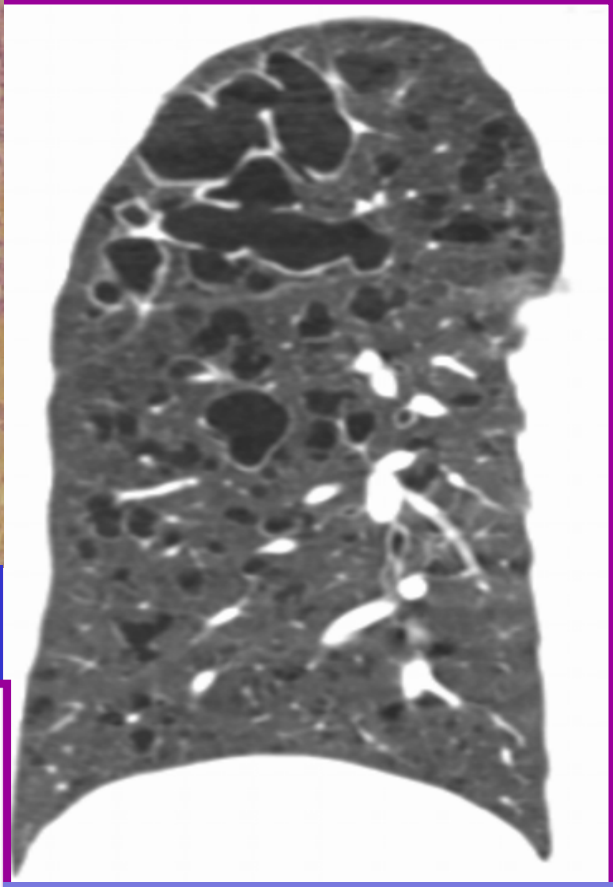
LAMs







PLCH



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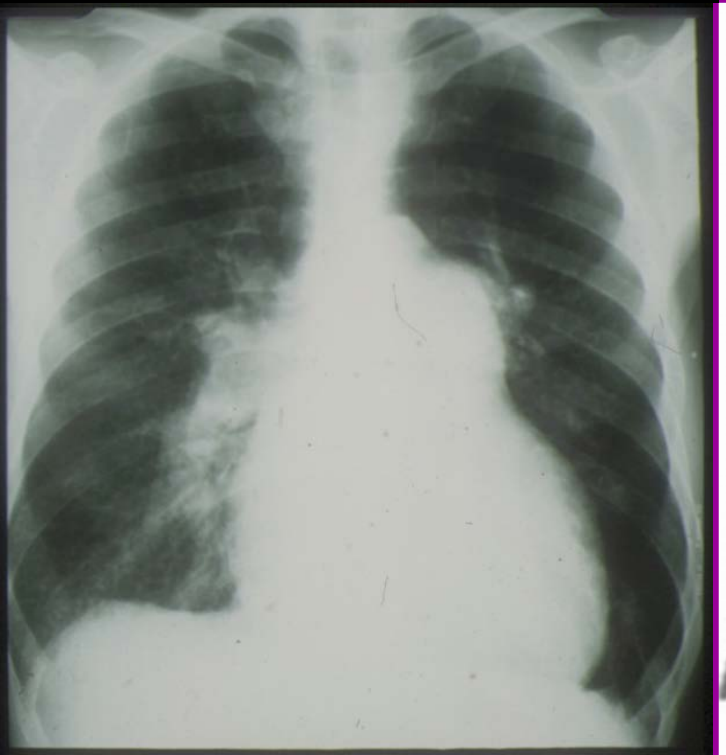
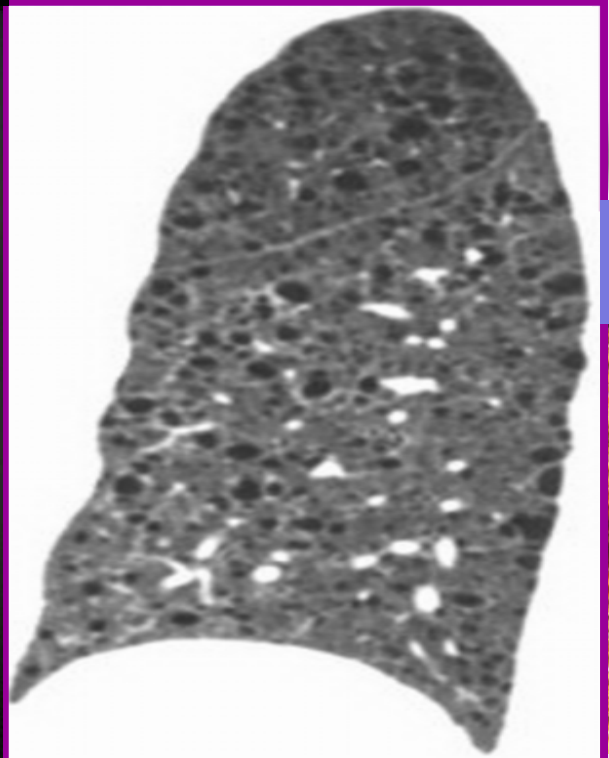
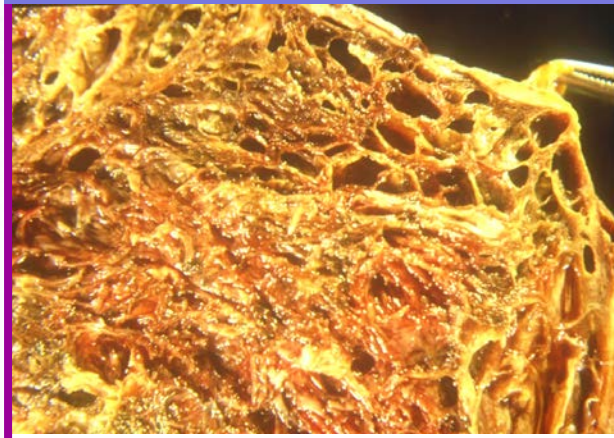
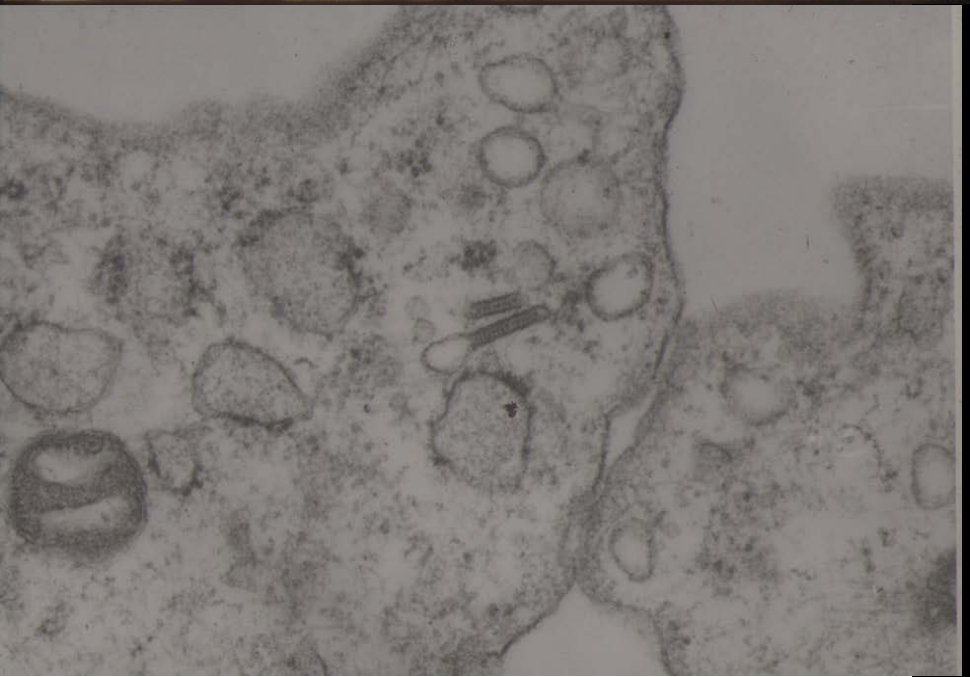
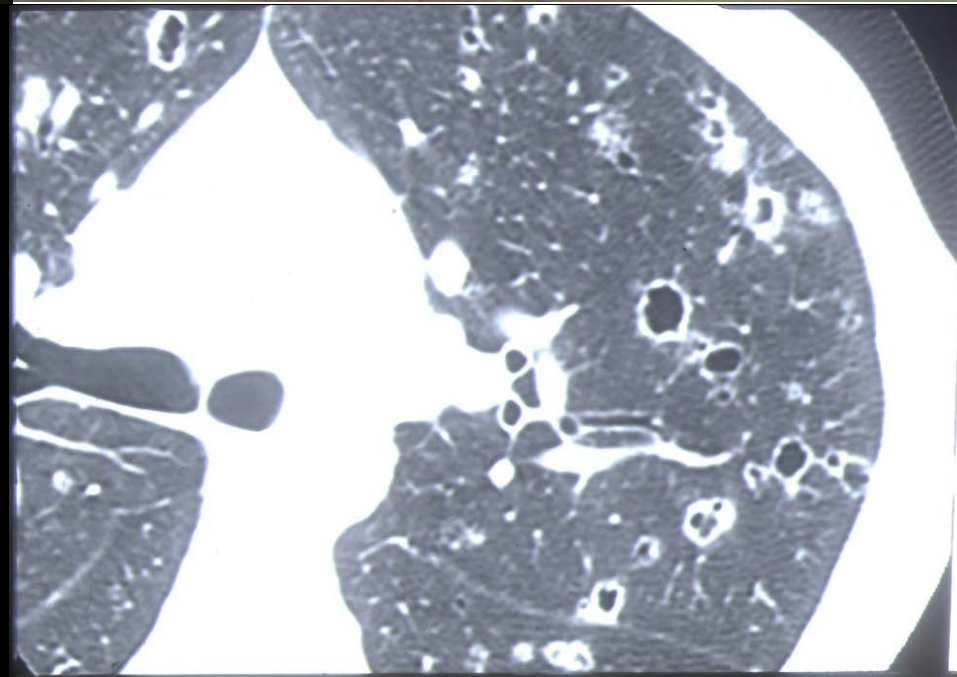






PLCH - PH with unclear or multifactorial mechanisms





IS PULMONARY LCH A HYPERTENSIVE DISEASE?

18 LCH PATIENTS

FEV1	42.8% ± 15.5 S.D.
TLC	99.9% ± 18.8 S.D.
Tiffenau	55.4% ± 13.9 S.D.
PaO2	57.7 ± 10.6 S.D.
PAPm	55.9 ± 12 S.D.
C.I.	2.77 ± 0.71 S.D.
PVRi	17.6 ± 6.5 S.D.

Harari S., Simonneau G., Brenot F. et Coll. JHLT 1997 Apr;16(4):460-463

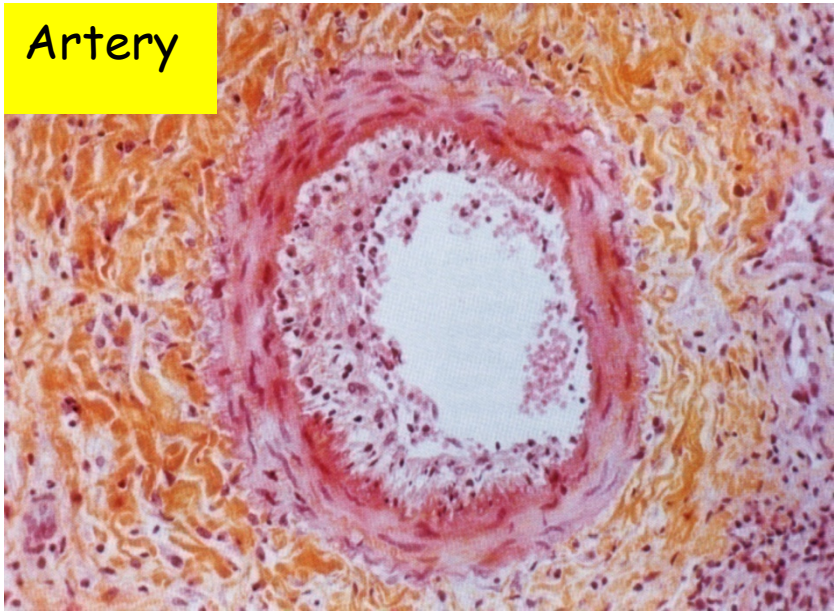
PULMONARY VASCULAR INVOLVEMENT IN HISTIOCYTOSIS X

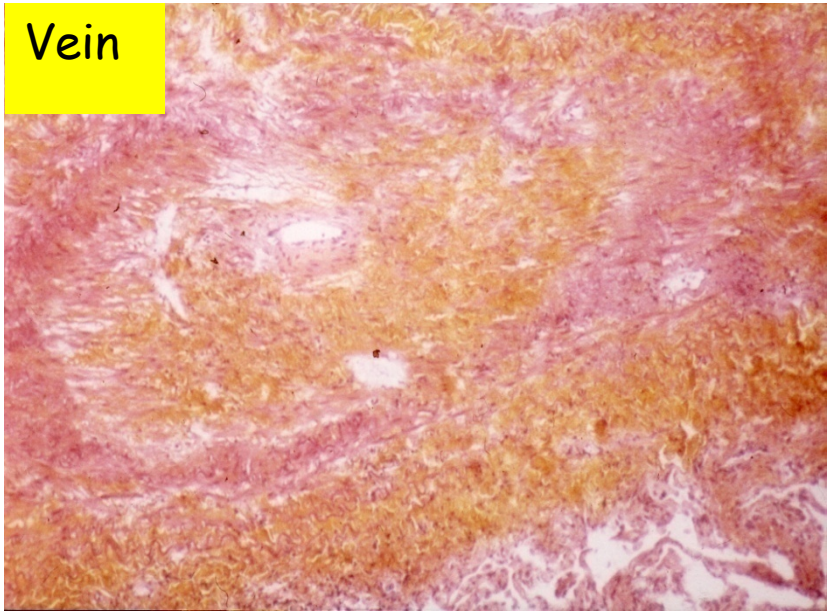
- 21 pts with advanced PLCH referred for LTx
- All of them had moderate-to-severe PH
- mPAP: 59 ± 4 mm Hg (range 36-74 mmHg)
- No correlation between mPAP and PFT
- Pathological findings (n = 12): intrinsic proliferative vasculopathy involving both small to medium-sized arteries and septal veins. VOD in 1/3 of pts

Fartoukh et al. Am J Respir Crit Care Med 2000; 161:216-23

PULMONARY VASCULAR INVOLVEMENT IN HISTIOCYTOSIS X

- Pulmonary histiocytosis X = marked pulmonary vascular remodeling predominantly affecting pulmonary veins
- In patients with sequential histologies, this pulmonary vasculopathy was progressing with time (while parenchymal lesions were stable)
- A case of steroid-sensitive pulmonary hypertension has been reported (specific steroid-sensitive vasculopathy?)





Fartoukh et al. Am J Respir Crit Care Med 2000; 161:216-23

Pulmonary Langerhans cell histiocytosis-associated pulmonary hypertension: clinical characteristics and impact of pulmonary arterial hypertension therapies

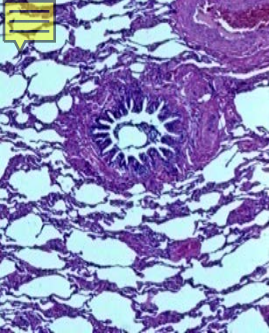
Le Pavec et al. Chest 2012; 142: 1150

- 29 consecutive patients with PLCH and PH confirmed with RHC were included
- 83% of patients were in WHO functional class III to IV interval between PLCH and PH diagnosis of 9.2 ± 9.8 yrs
- Mean ± SD 6MWD: 355 m ± 95 m
- mPAP: 45 ± 14 mmHg
- Use of PAH therapy in 12 patients was followed by an improvement in mPAP (56 ± 14 mmHg and 45 ± 12 mmHg, p> 0.05) between baseline and follow-up evaluations

Pulmonary Langerhans cell histiocytosis-associated pulmonary hypertension: clinical characteristics and impact of pulmonary arterial hypertension therapies

Le Pavec et al. Chest 2012; 142: 1150

- In this group of patients, PAH therapies improved hemodynamics without oxygen worsening or pulmonary edema
- WHO functional class was the only prognostic factor identified
- Prospective clinical trials focusing on this population of patients are warranted

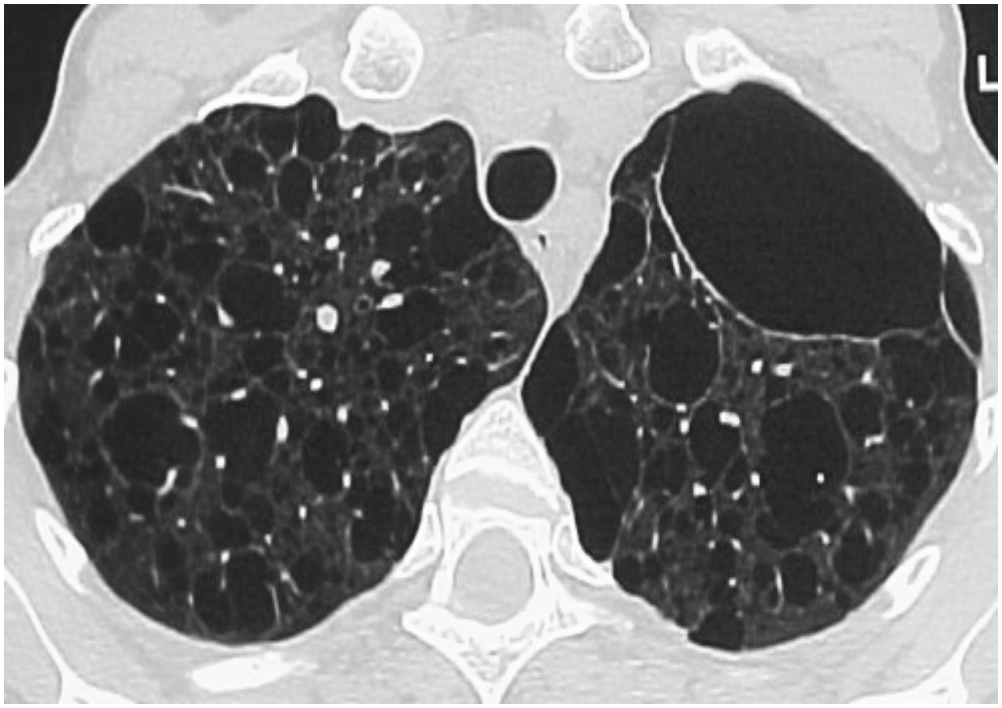


PULMONARY HYPERTENSION DIAGNOSTIC CLASSIFICATION

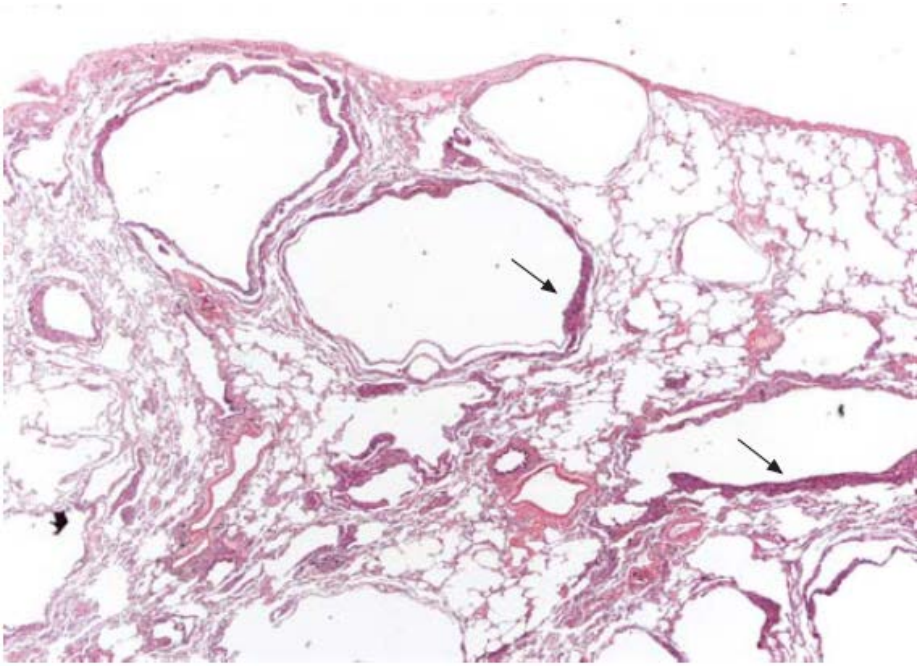
(updated 4th WSPAH-Dana Point 2008)

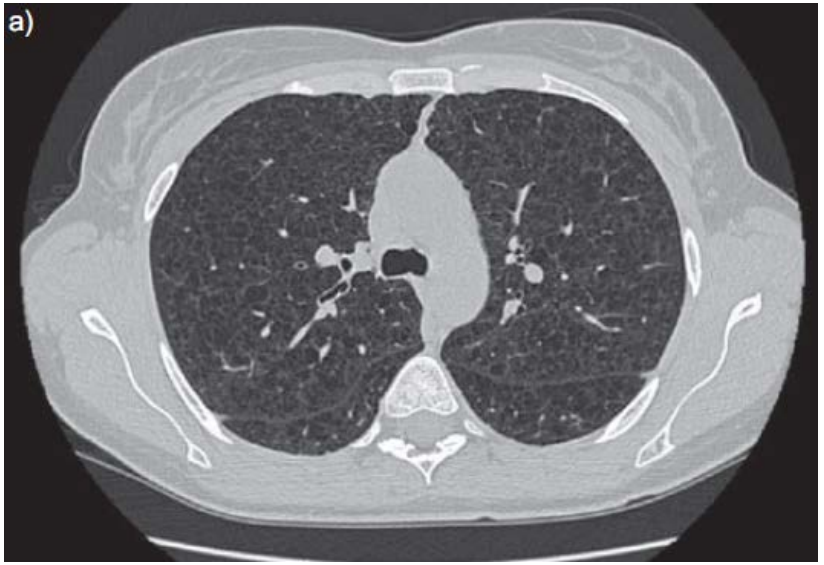
5. PH with unclear or multifactorial mechanisms

Lymphangioleiomiomatosis

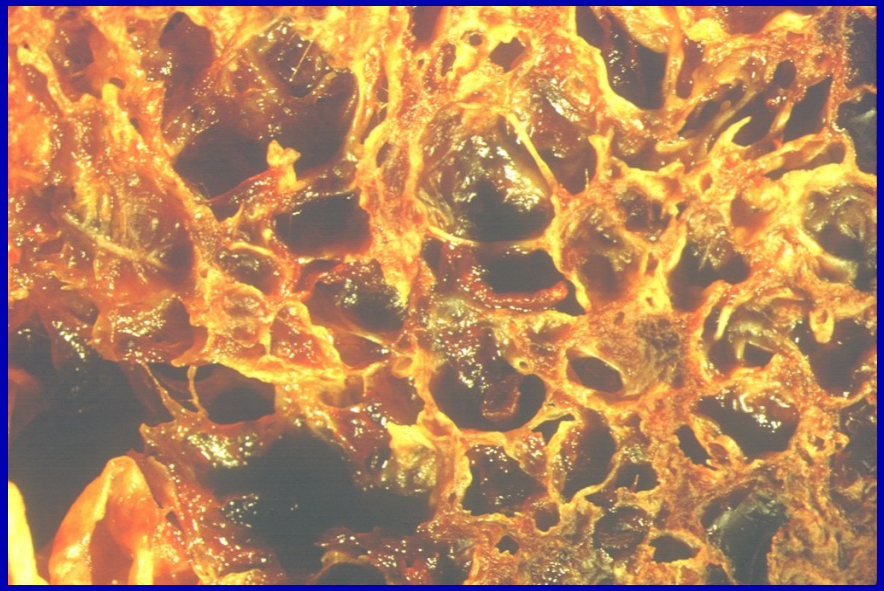


Lymphangioleiomyomatosis (LAM)



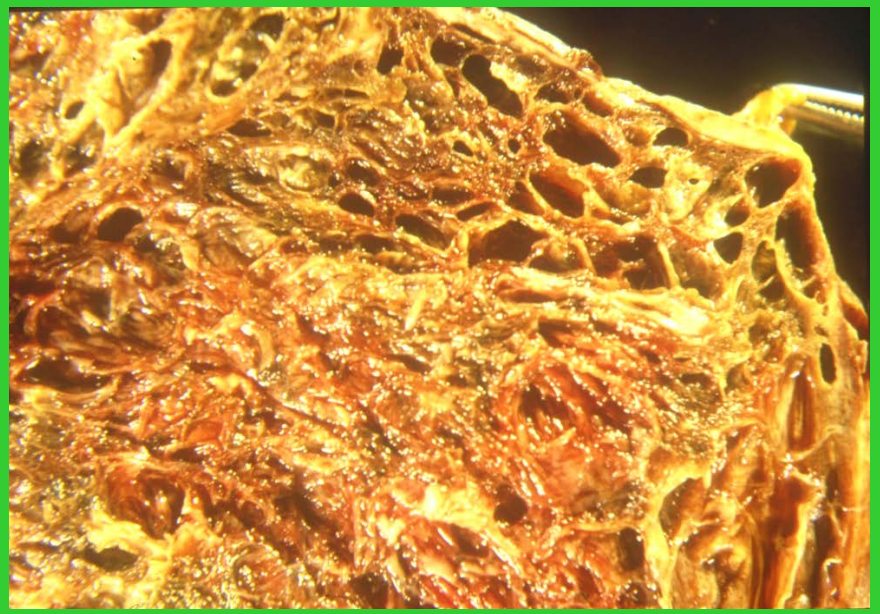


Lymphangioleiomyomatosis (LAM) is a rare multisystem disorder affecting predominantly young females in their reproductive years. It is characterised by progressive cystic destruction of the lung, lymphatic abnormalities and abdominal tumours(e.g. angiomyolipomas)



PLCH

LAM



Pulmonary Hypertension in Lymphangioleiomyomatosis: Characteristics in 20 patients

- This retrospective, multicenter study evaluated patients with LAM and pre-capillary PH by RHC
- Mean ± SD age: 49 ± 12 years and mean ± SD time interval between LAM and PH diagnosis of 9.2 ± 9.8 yrs
- All, except for one patient, were receiving supplemental oxygen
- Mean ± SD 6MWD: 340 m ± 84 m
- mPAP: 32 ± 6 mmHg
- mPAP > 35 mmHg in only 20% of cases
- Mean ± SD FEV1: 42 ± 25%; DLCO 29 ± 135

Cottin V. , Harari S. et al. Eur Respir J 2012; 40: 630

Pulmonary Hypertension in Lymphangioleiomyomatosis: Characteristics in 20 patients

- In six patients who received oral PAH therapy , the PAP decreased from 33 ± 9 mmHg to 24 ± 10 mmHg

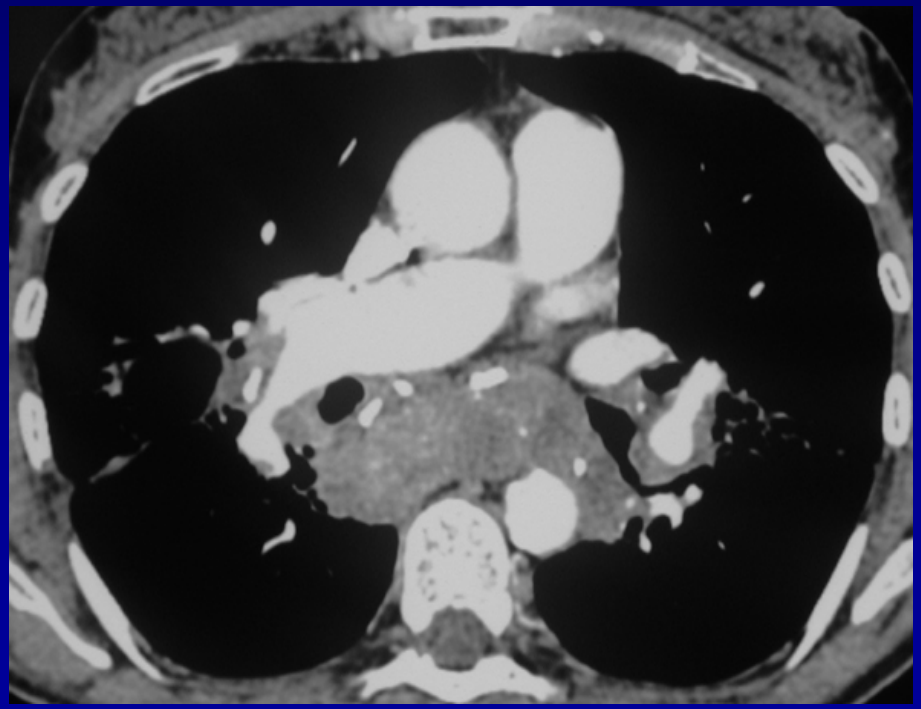
Pre-capillary PH of mild haemodynamic severity may occur in patients with LAM, even with mild pulmonary function impairment.
PAH therapy might improve the haemodynamics in PH associated with LAM.

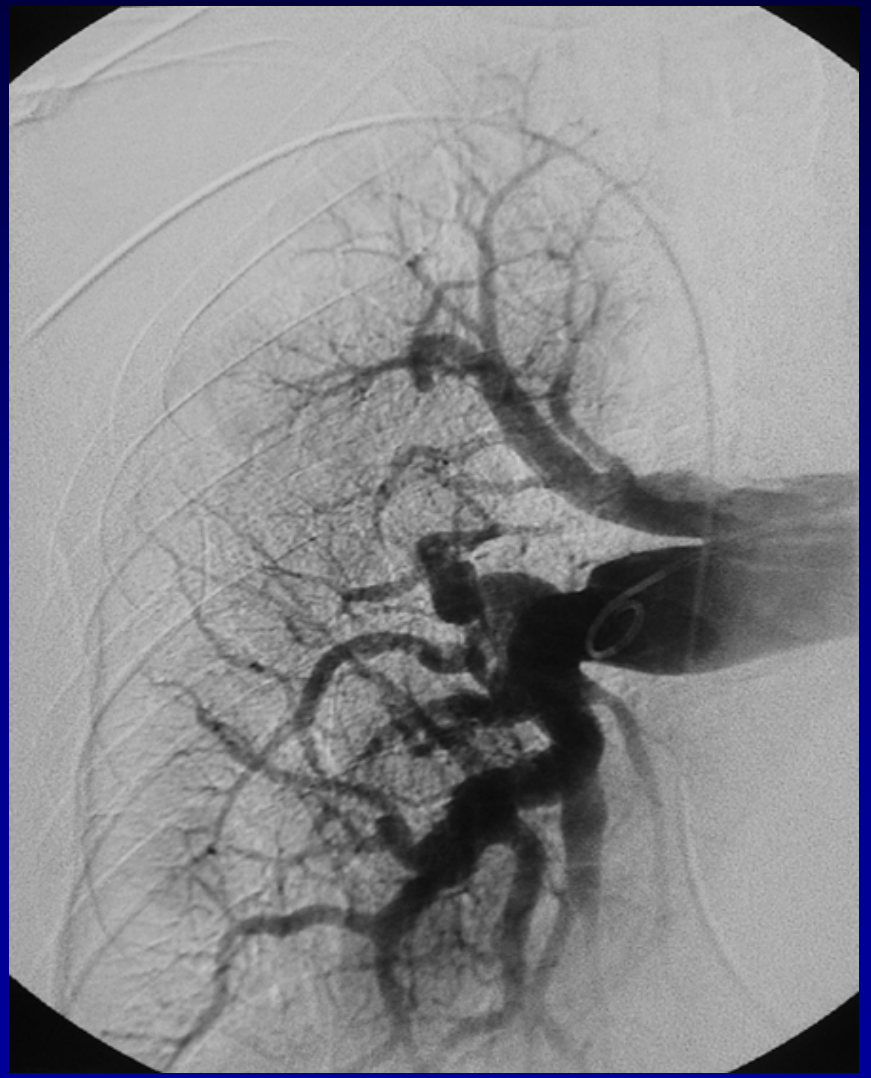
Cottin V. , Harari S. et al. Eur Respir J 2012; 40: 630

PULMONARY HYPERTENSION DIAGNOSTIC CLASSIFICATION

5. PH with unclear or multifactorial mechanisms

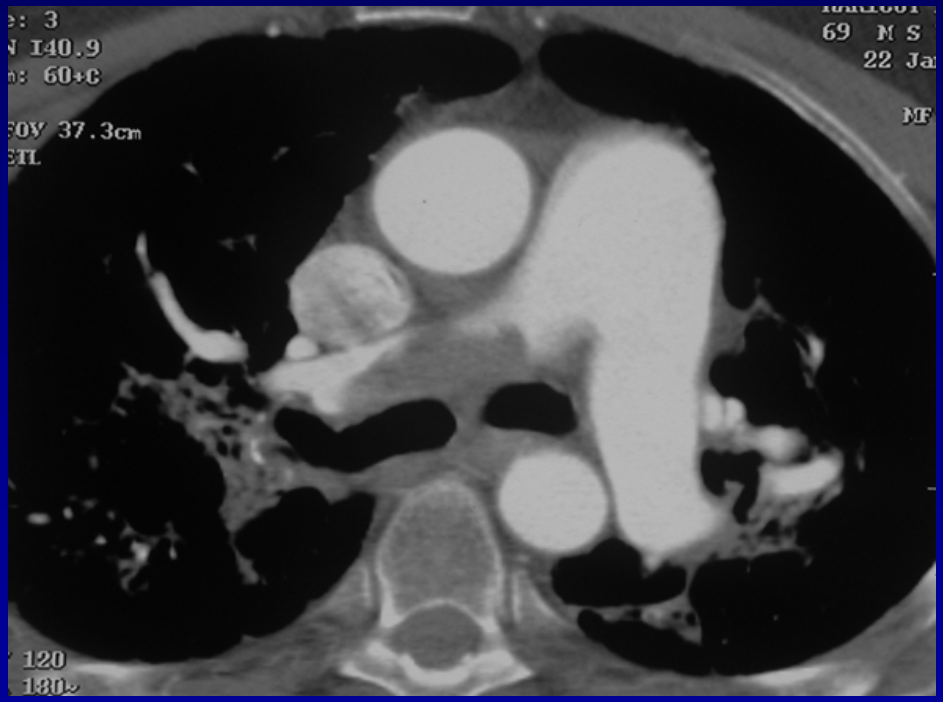
- **Sarcoidosis**

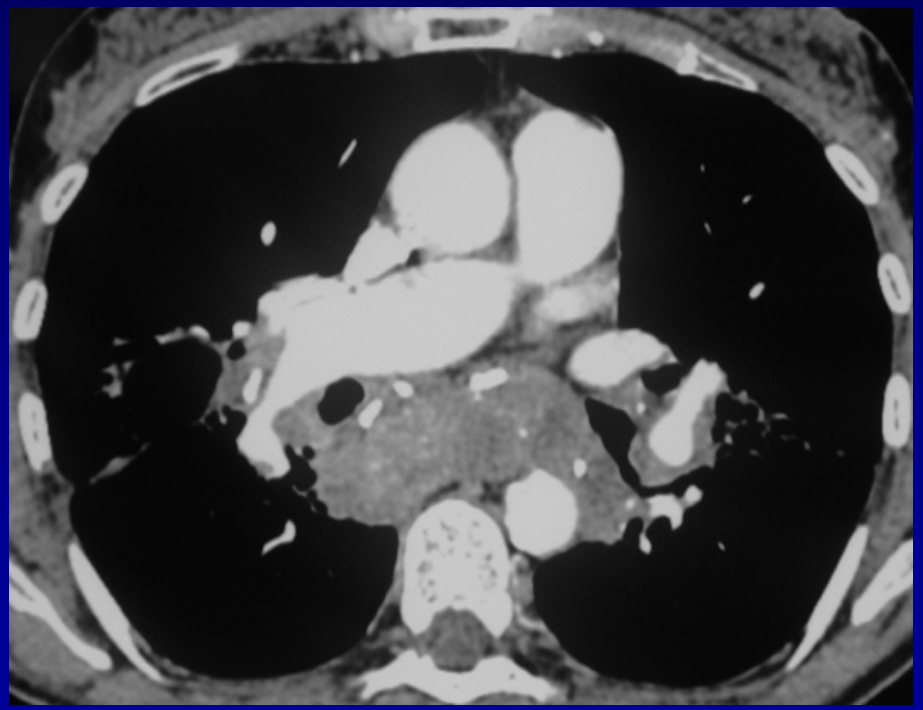




PULMONARY VASCULAR INVOLVEMENT IN SARCOIDOSIS

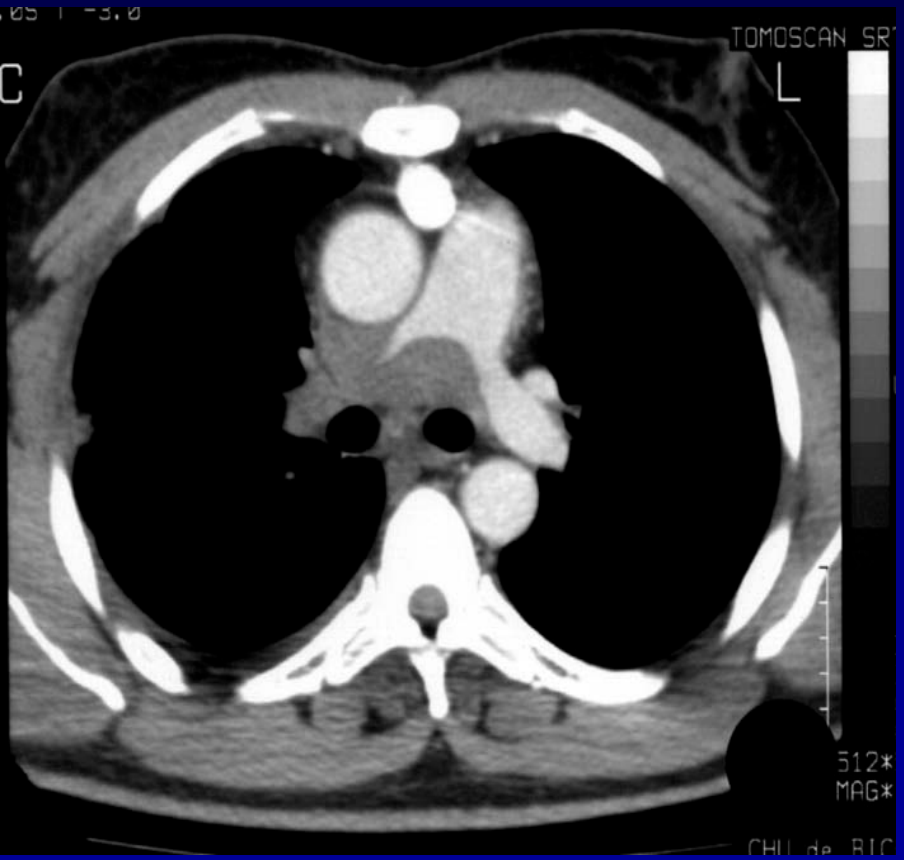
- Extrinsic compression of large pulmonary arteries by mediastinal or hilar adenopathies or fibrosis was detected in 4 out of 15 patients in stage IV

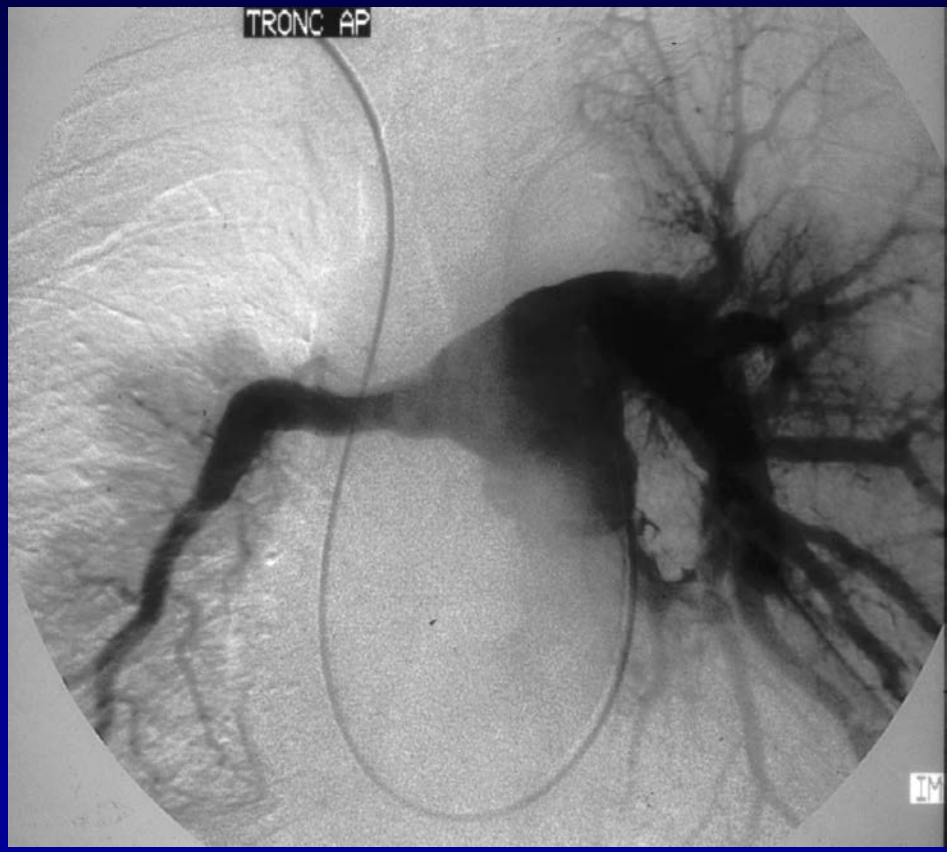




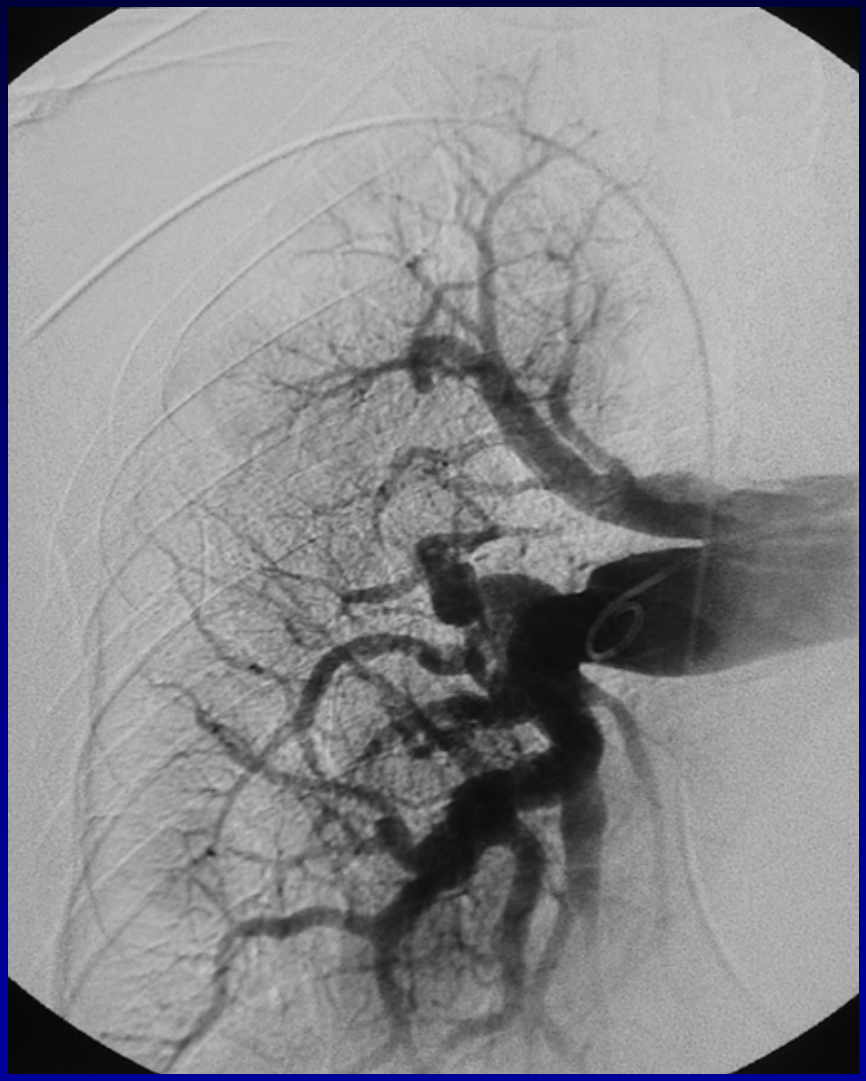
Nunes et al. Thorax 2006

FIBROSING MEDIASTINITIS IS A CAUSE OF PULMONARY HYPERTENSION IN SARCOIDOSIS





PULMONARY VASCULAR INVOLVEMENT IN SARCOIDOSIS



Pulmonary angiography

(9 patients)

- Vascular distorsion associated with extrinsic compression: n = 4 (stage IV in all the cases)

Nunes et al. Thorax 2006

PULMONARY VASCULAR INVOLVEMENT IN SARCOIDOSIS

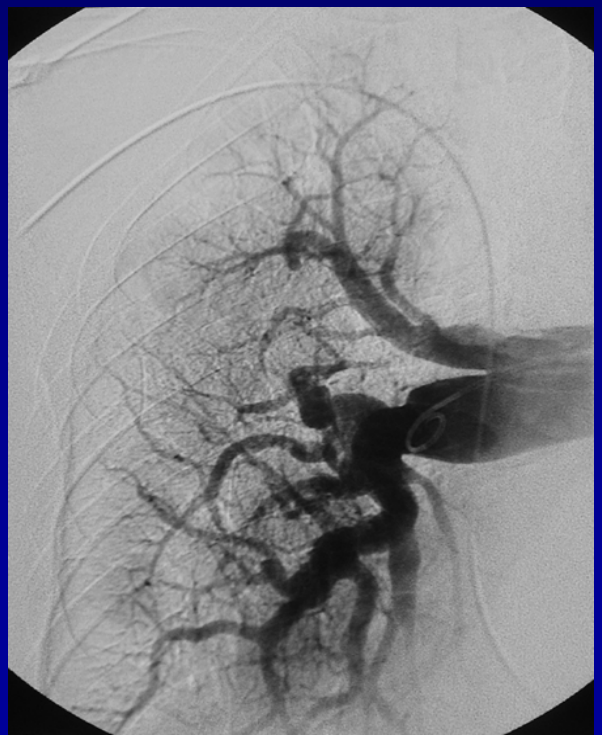
Precapillary pulmonary hypertension in the context of sarcoidosis may be due at least in part to:

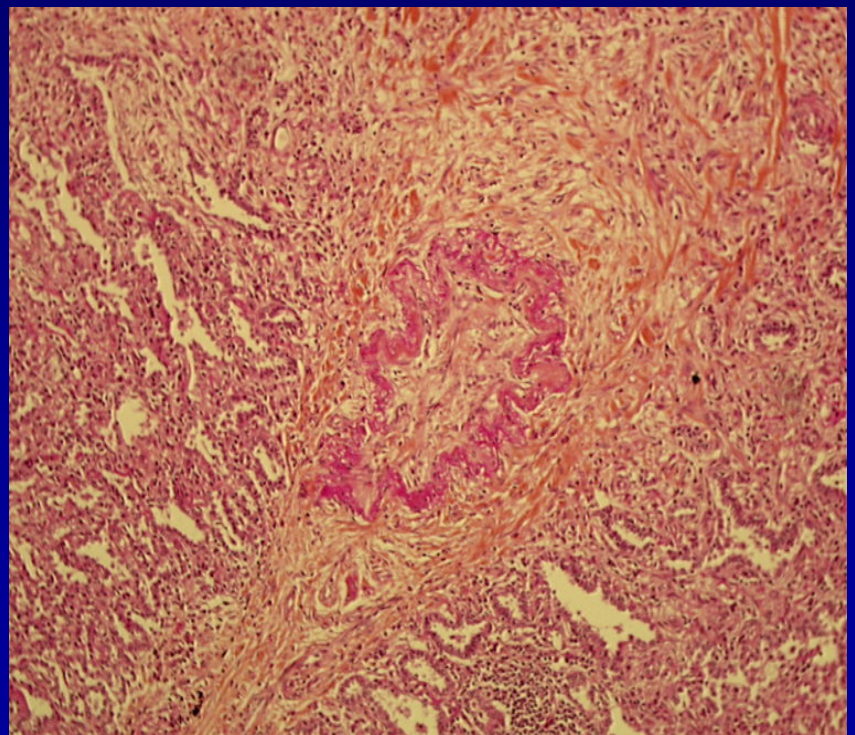
- Extrinsic compression of large pulmonary arteries by mediastinal or hilar adenopathies or fibrosis
- Destruction of the distal capillary bed by fibrotic process and resulting hypoxia (stage IV)
- Specific vasculitis, with infiltration of the walls of pulmonary arteries and/or veins by granulomas (steroid sensitive ?)

Nunes et al. Thorax 2006

PULMONARY VASCULAR INVOLVEMENT IN SARCOIDOSIS

- Pulmonary hypertension in sarcoidois occurs in two very different settings
- In the absence of pulmonary fibrosis, PH appears to be related to a specific vasculopathy and may be steroid-sensitive
- In case of pulmonary fibrosis, the mechanism of PH is complex, but certainly involves at least in part a specific vasculopathy as PH is out of proportion with alterations in lung fuction. In these patients, physicians have to consider lung transplantation sooner than they would have solely on the basis of lung function





ACTION

Pneumologi in azione
nell'ipertensione arteriosa polmonare (PAH)

ORIGINAL ARTICLE
PULMONARY VASCULAR DISEASES AND SARCOIDOSIS

Management and long-term outcomes of sarcoidosis-associated pulmonary hypertension

Athénaïs Boucly[1,2,3], Vincent Cottin[4,15], Hilario Nunes[5,15], Xavier Jaïs[1,2,3], Abdelatif Tazi[6], Grégoire Prévôt[7], Martine Reynaud-Gaubert[8], Claire Dromer[9], Catherine Viacroze[10], Delphine Horeau-Langlard[11], Christophe Pison[12], Emmanuel Bergot[13], Julie Traclet[4], Jason Weatherald[1,2,3,14], Gérald Simonneau[1,2,3], Dominique Valeyre[5], David Montani[1,2,3], Marc Humbert[1,2,3], Olivier Sitbon[1,2,3,16] and Laurent Savale[1,2,3,16]

PH secondary to sarcoidosis

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18 French Pulmonary hypertension centers were involved from 2004 to 2014

Only patients with severe PH-sarcoidosis were recruited

In 156 patients was diagnosed PH-sarcoidosis, 126 of them had a severe PH

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The median time between the diagnosis of sarcoidosis and the diagnosis of PH was 17 years

The median survival time of PH-sarcoidosis patients was 6,8 years

Sex ratio was 1:1 and the median age was 57,5 years

The majority of the patients (72%) had a radiological stage IV of sarcoidosis disease at the time of PH-sarcoidosis diagnosis

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A baseline visit and a follow-up visit after six months, including 6MWT and RHC, was performed

When pulmonary vascular compression was suspected, an angio Tc or a PET scan was collected

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In 97 patients (77%) PAH-targeted therapy was prescribed

Most of them (83 pts) received an initial monotherapy

- 54 bosentan
- 6 ambrisentan
- 5 sildenafil
- 5 tadalafil
- 2 epoprostenol iv
- 1 inhaled iloprost

14 pts initiated with combination therapy

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At the time of diagnosis of PH-sarcoidosis in 33 pts was initiated immunosoppressive therapy (including steroid)

In 22 of them was associated PAH therapy

in 11 of them was not associated PAH therapy

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After six months, in 81 pts was found a significant improvement of haemodynamics variables with an increase of CI and a reduction of PVR improvement of NYHA functional class

No improvements of 6MWT

No correlation between pulmonary haemodynamics variables and lung function

PH secondary to sarcoidosis

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After 24 months of follow-up,

42 patients died
9 underwent to lung transplantation
39 needed treatment escalation with PAH- targeted medications

In these patients, safety and tolerability of PH drugs was similar to those of PAH patients.

PH secondary to sarcoidosis

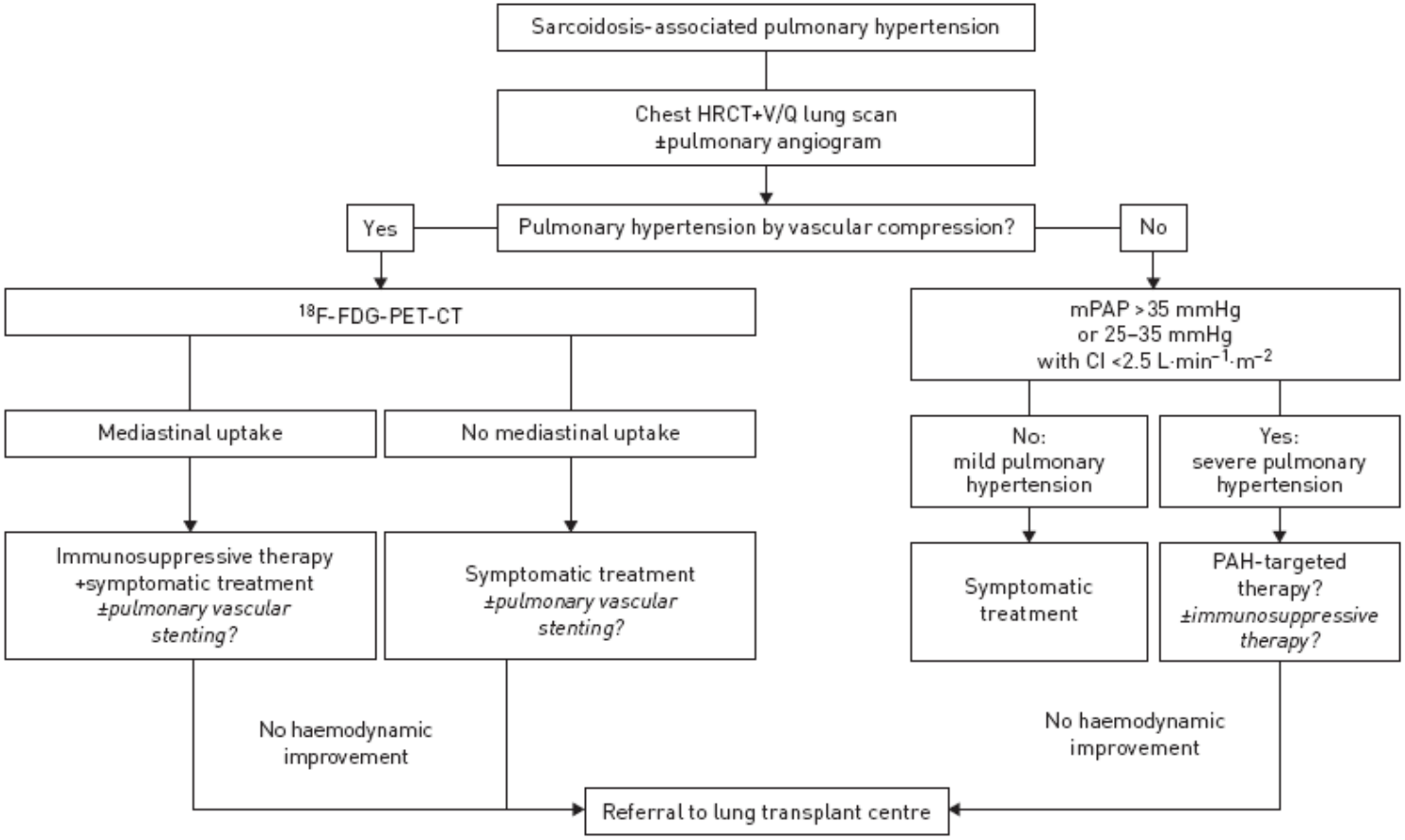
The impact of immunosopressive therapy in patient with pH-sarcoidosis is not well known

In this study, 4 of 11 patients treated only with steroid and/or immunosopressive therapy alone improved their short-term pulmonary haemodynamics

Two patients that had an extrinsic compression of pulmonary arteries (detected with a PET scan) by mediastinal lymphonodes responded to immunosoppressive therapy alone

So, PET scan can be helpful to detect these patients and it can represent a baseline test in PH-sarcoidosis pts

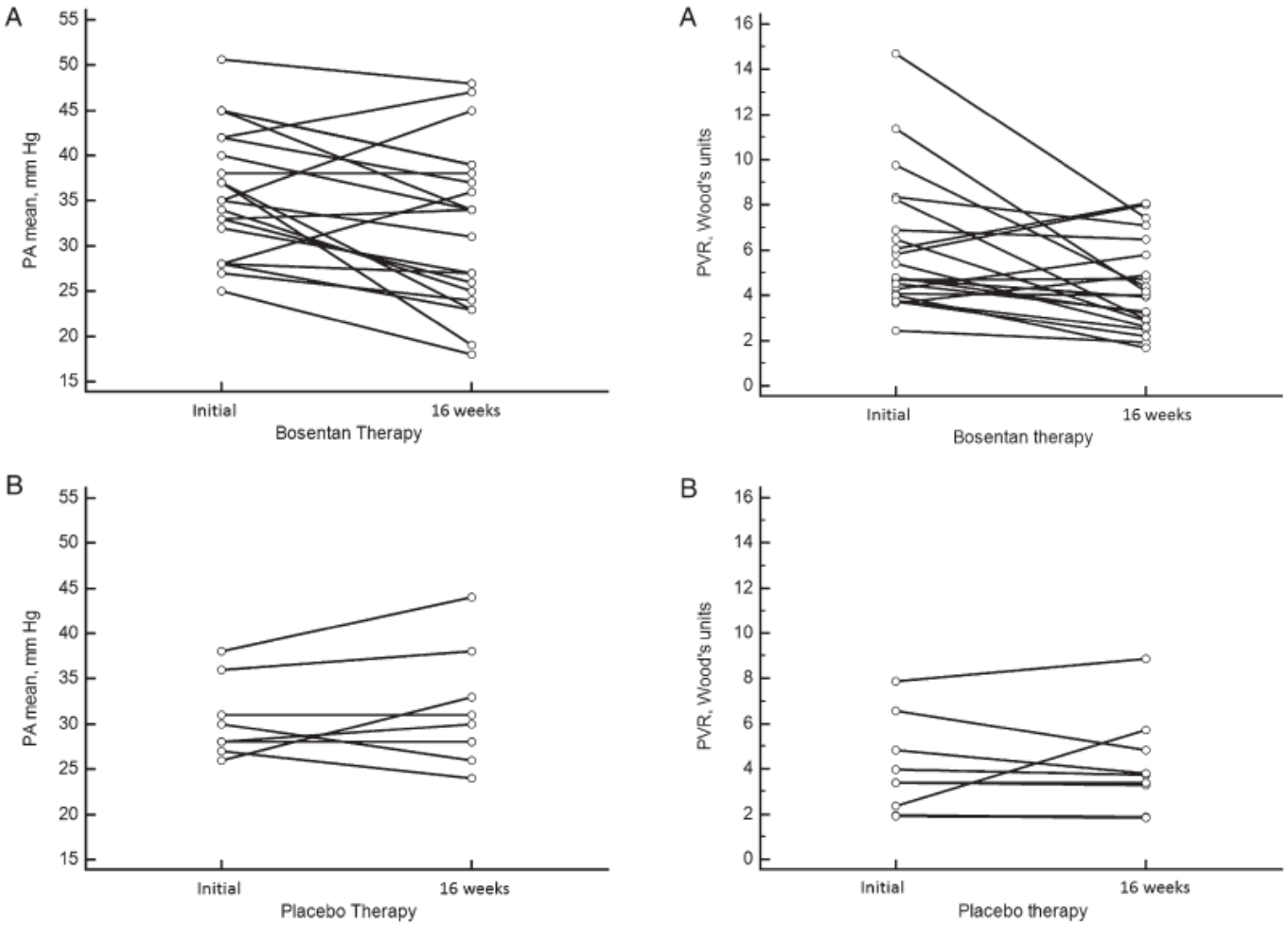
PH secondary to sarcoidosis



Original research

Bosentan for Sarcoidosis-Associated Pulmonary Hypertension A Double-Blind Placebo Controlled Randomized Trial

Baughman RP, et al. Chest 2014; 145; S10



Original research

Bosentan for Sarcoidosis-Associated Pulmonary Hypertension A Double-Blind Placebo Controlled Randomized Trial

Baughman RP, et al. Chest 2014; 145; S10

In conclusion, we found that 16 weeks of bosentan therapy in patients with SAPH is associated with a significant improvement in PA mean pressure and PVR. The level of improvement was similar to that reported in other WHO groups treated with bosentan. The treatment was well tolerated. The effect of treatment over longer periods will require further investigation.

PH secondary to sarcoidosis

CONCLUSIONS

PAH therapy improves haemodynamic variables but not exercise capacity

In selected patients we can use steroids and/or immunosoppressive therapies

The long-term survival remains poor

Lung transplantation is a reasonable option too

- Currently there is no specific therapy for PH associated with lung diseases.

- Published experience with targeted PAH drug therapy is scarce, and so far there is no evidence from RCTs suggesting that PAH drugs result in improved symptoms or outcomes in patients with lung disease.

- The use of drugs approved for PAH is not recommended for patients with PH due to lung disease.

ESC/ERS 2015 Guidelines on PH