

PH and lung disease

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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

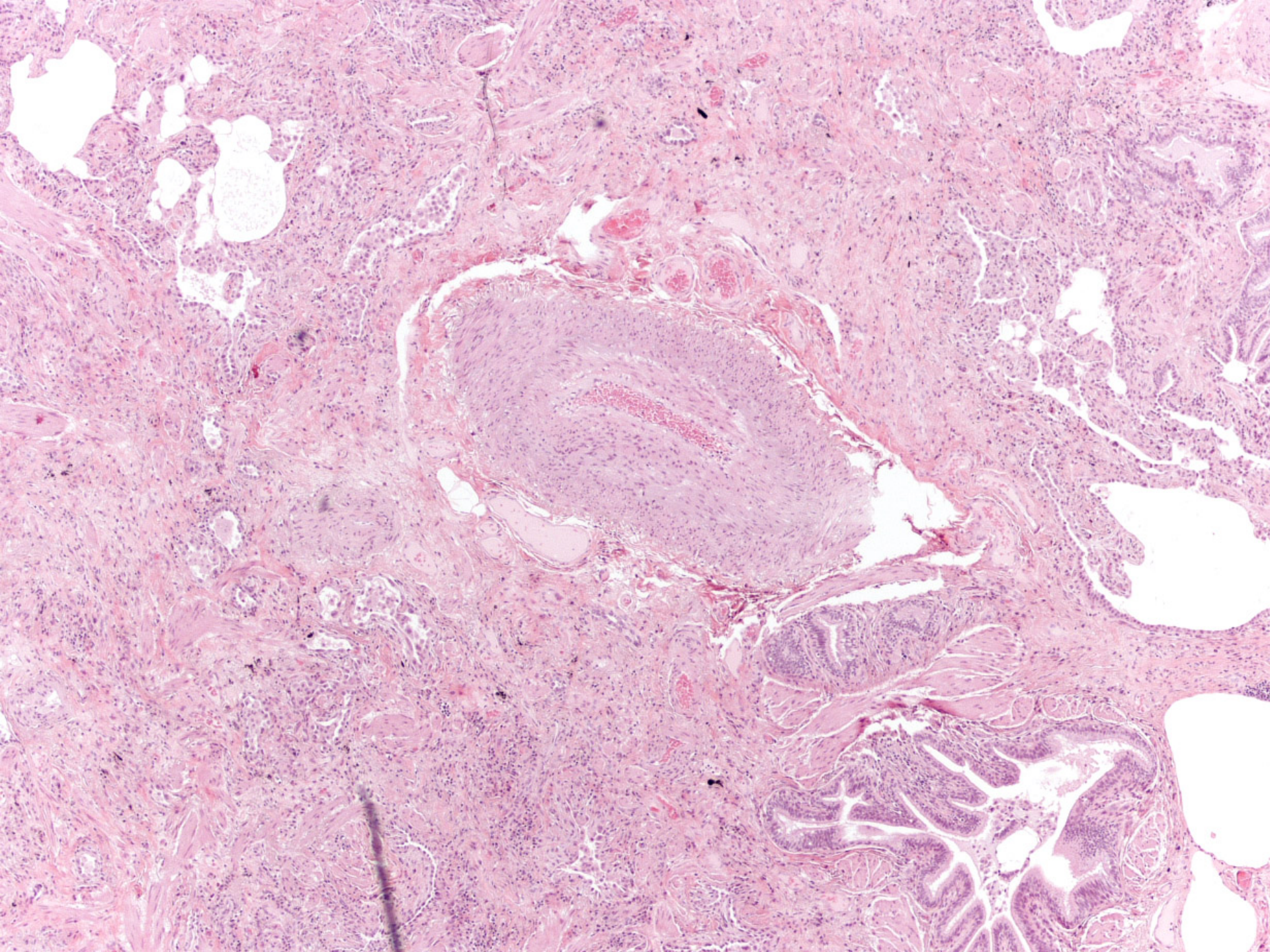
- 4.1 Chronic thromboembolic pulmonary hypertension
- 4.2 Other pulmonary artery obstructions
 - 4.2.1 Angiosarcoma
 - 4.2.2 Other intravascular tumors
 - 4.2.3 Arteritis
 - 4.2.4 Congenital pulmonary arteries stenoses
 - 4.2.5 Parasites (hydatidosis)

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

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.

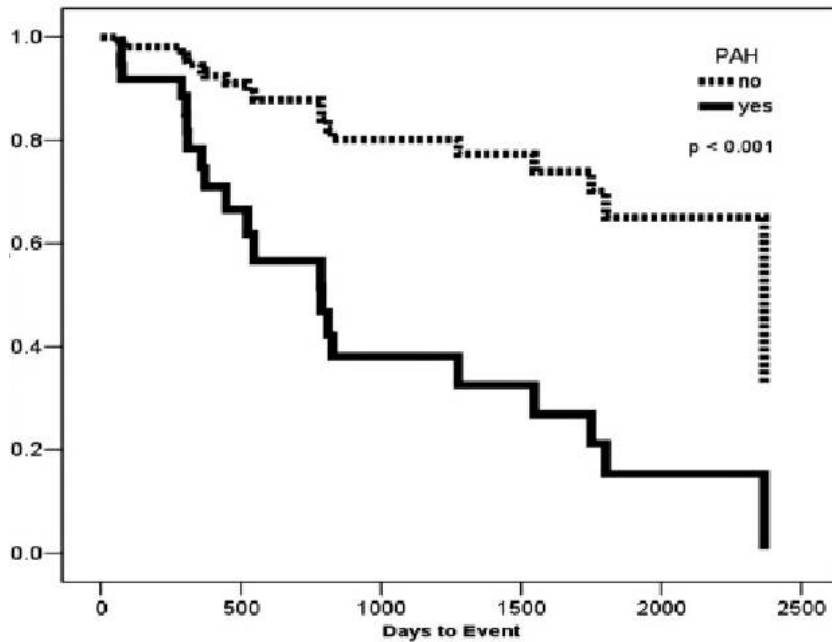
The differences reflect:

- ◆ 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%

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

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/m ²)	10.4 (7.1)
Cardiac output (l/min)	4.3 (1.2)
Cardiac index (l/min/m ²)	2.3 (0.5)
Echocardiography	
RVSP (mm Hg, n = 48)	56 (24–102)
PAT (ms, n = 46)	100 (33–144)
Pulmonary function	
Tlco % (n = 65)	29.6 (14.7)
Kco % (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)

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

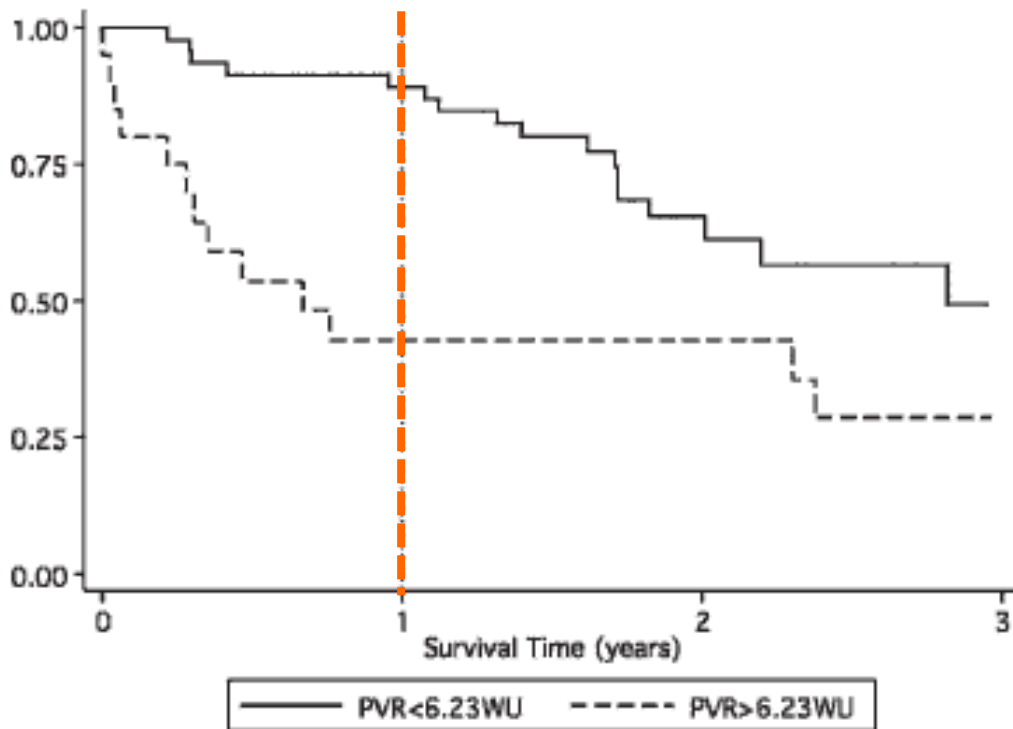
Corte TJ et al. Thorax 2009; 64: 883

Table 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/m ²)	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
- ◆ Primary endpoint:
Change in 6-MWD (defined as $\geq 20\%$ improvement or $\leq 20\%$ improvement)

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.

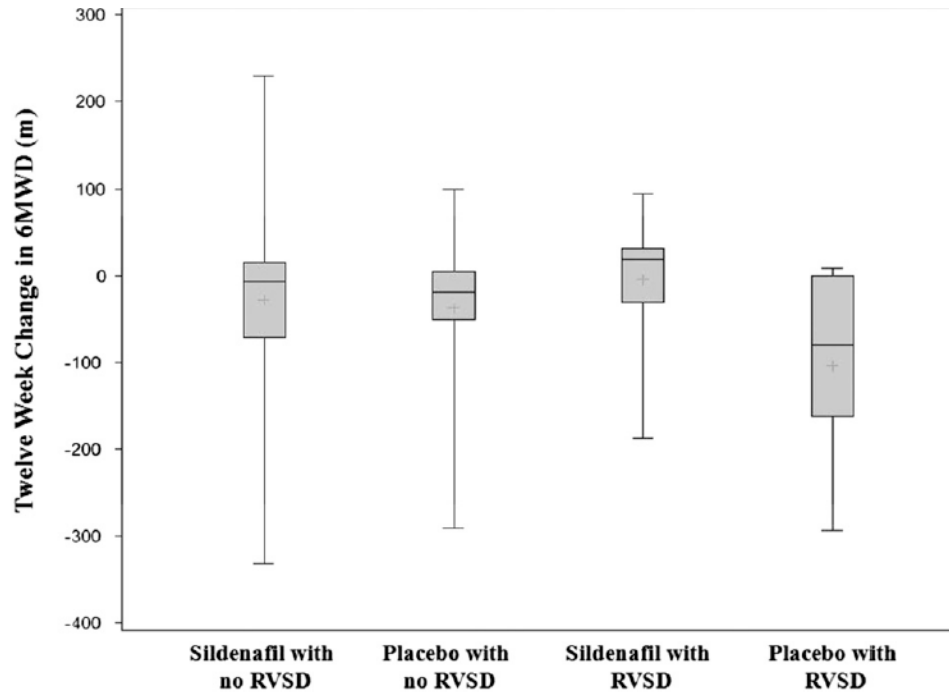
Sildenafil in IPF with Right-sided Ventricular Dysfunction

A substudy of STEP-IPF

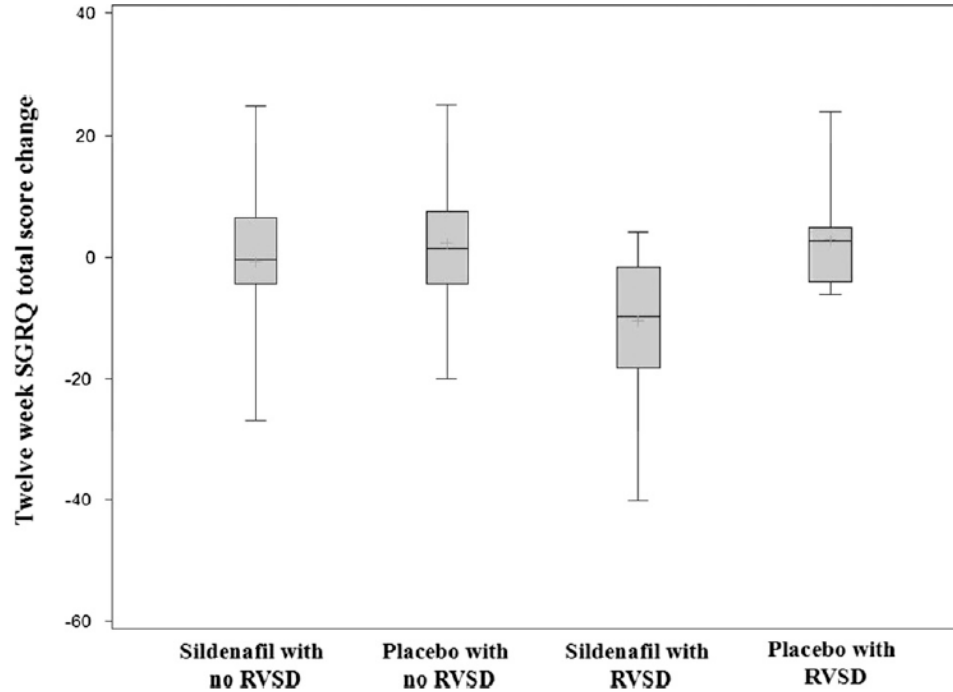
- Of 180 subjects enrolled into STEP-IPF, echocardiograms from 119 were available for independent review (sildenafil, n 56; placebo, n 63)
- Right ventricular hypertrophy (RVH), right ventricular systolic dysfunction (RVSD), and right ventricular systolic pressure (RVSP) were assessed.
- Multivariable 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.

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 of 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 hypertension: a pilot trial

Hoepfer 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
DLCO* 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

Hoepfer 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 \leq 40% at screening)

AND

Intermediate or high probability of Group 3 PH

(defined as a mPAP \geq 20 mmHg with PAWP \leq 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 \geq 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 $\text{DLCO} \leq 35\%$
- 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 guidelines
- 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

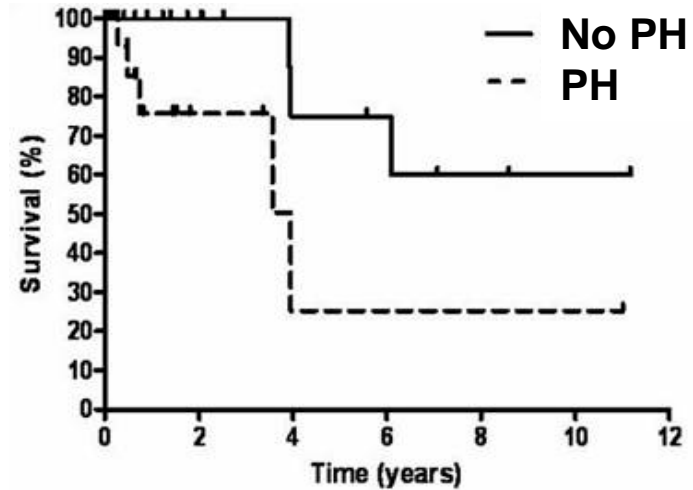
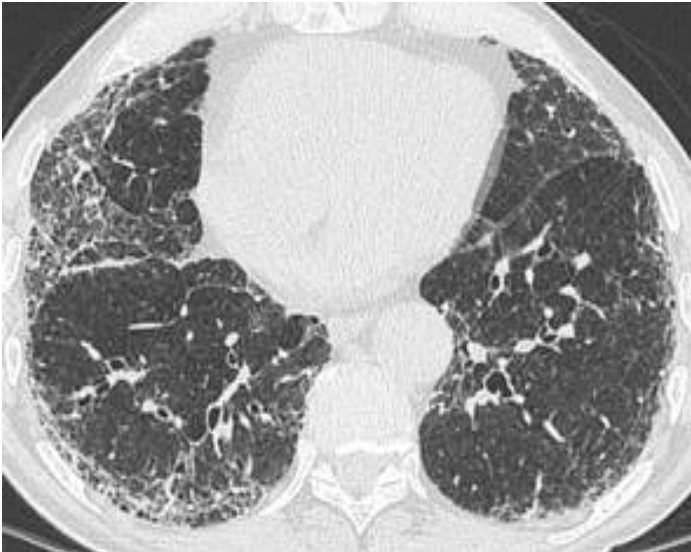
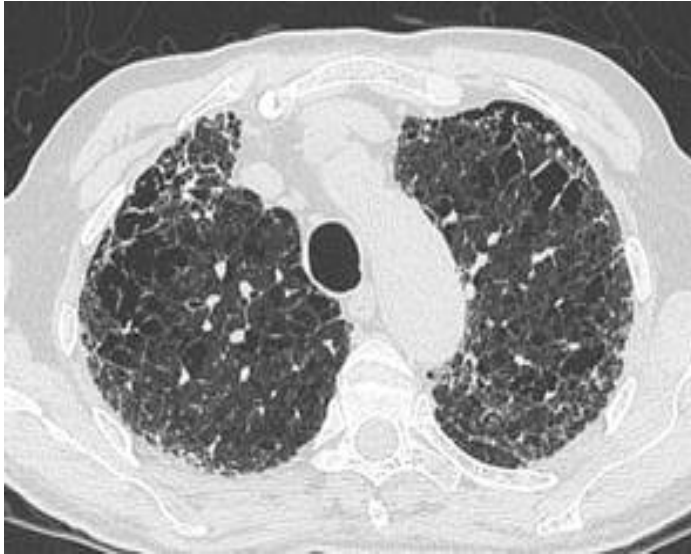
PH in CPFE

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 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

(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 $86 \pm 18\%$, FEV1 $78 \pm 19\%$, and DLCO $28 \pm 16\%$ 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 .

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.

In summary

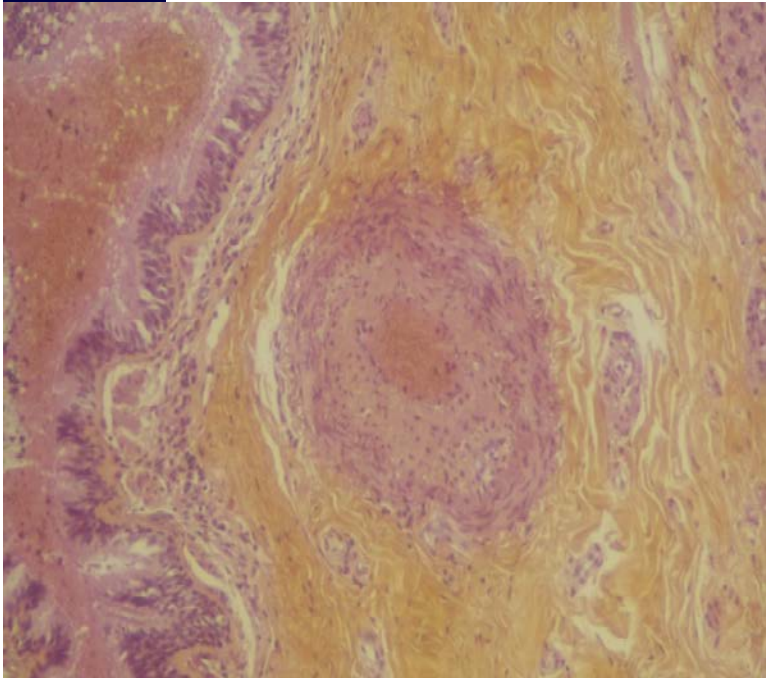
Combined pulmonary fibrosis with emphysema

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

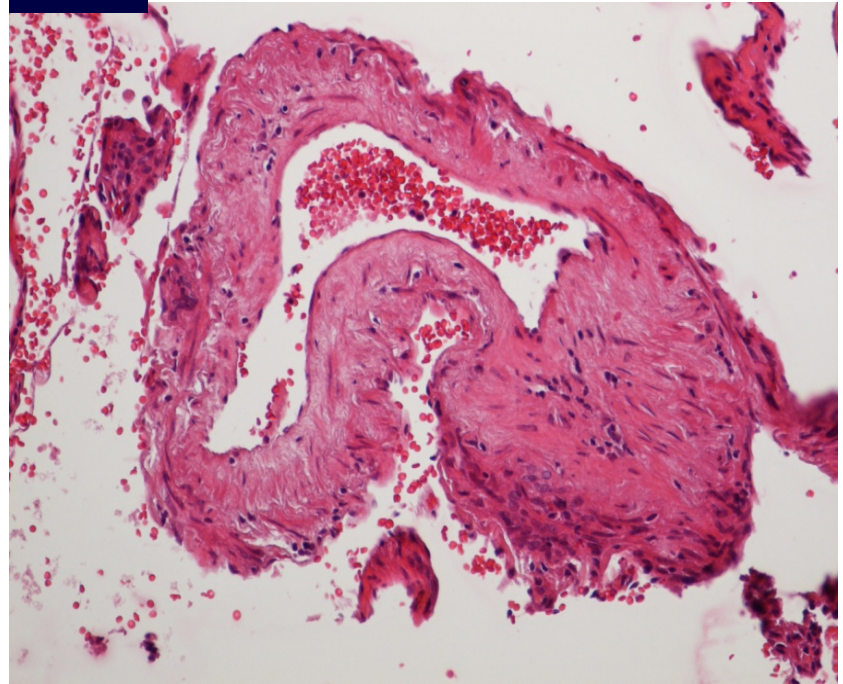
Involvement of pulmonary vessels by the disease process: the example of Cystic Lung Disease

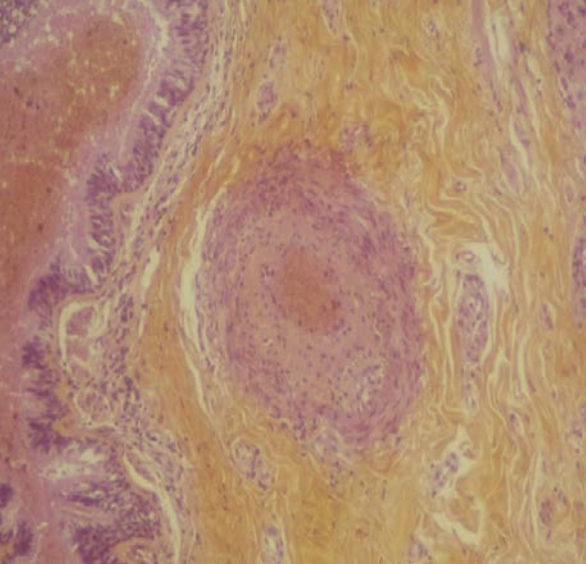
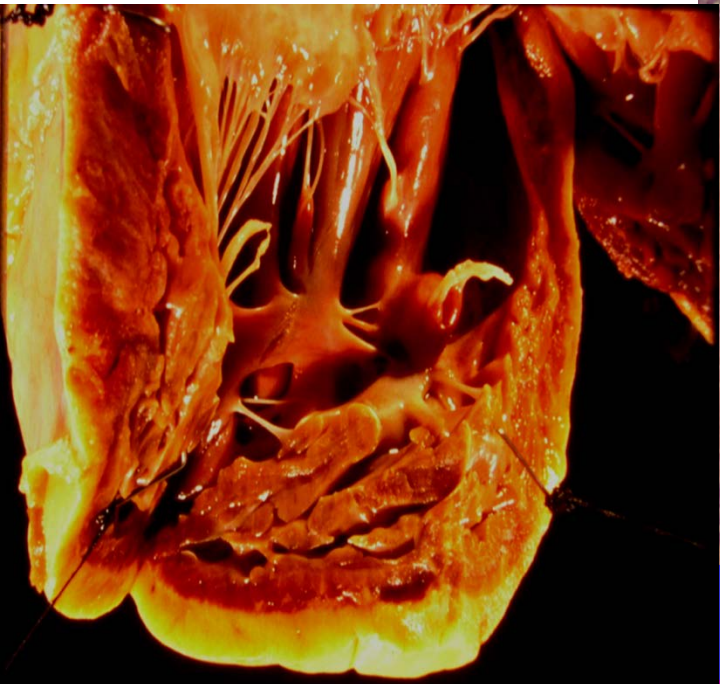
- ◆ Pulmonary Langerhans cell histiocytosis
- ◆ Lymphangioleiomyomatosis

PLCH

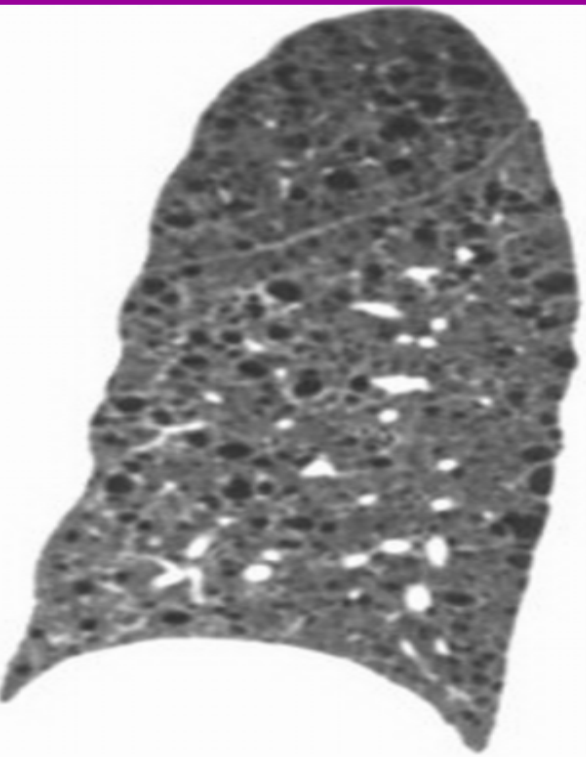
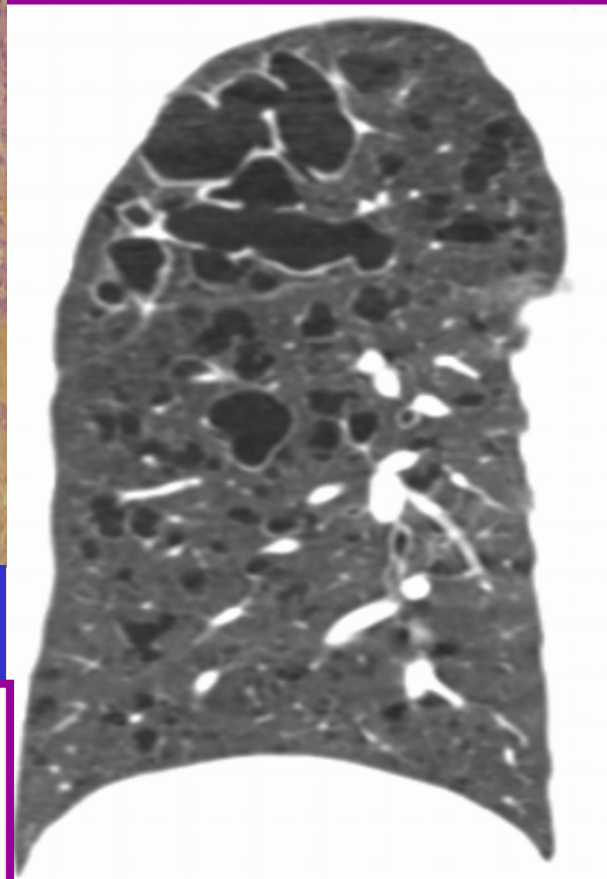


LAMs

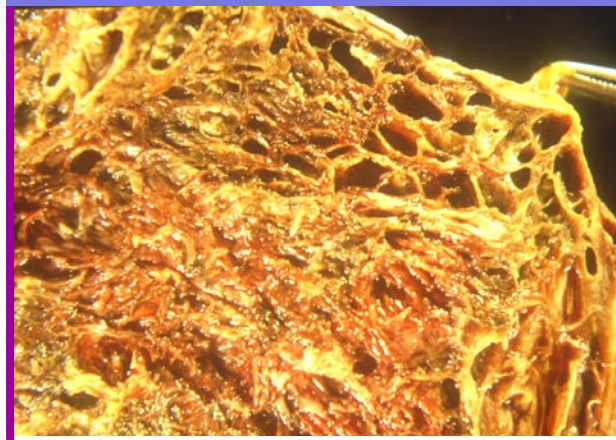




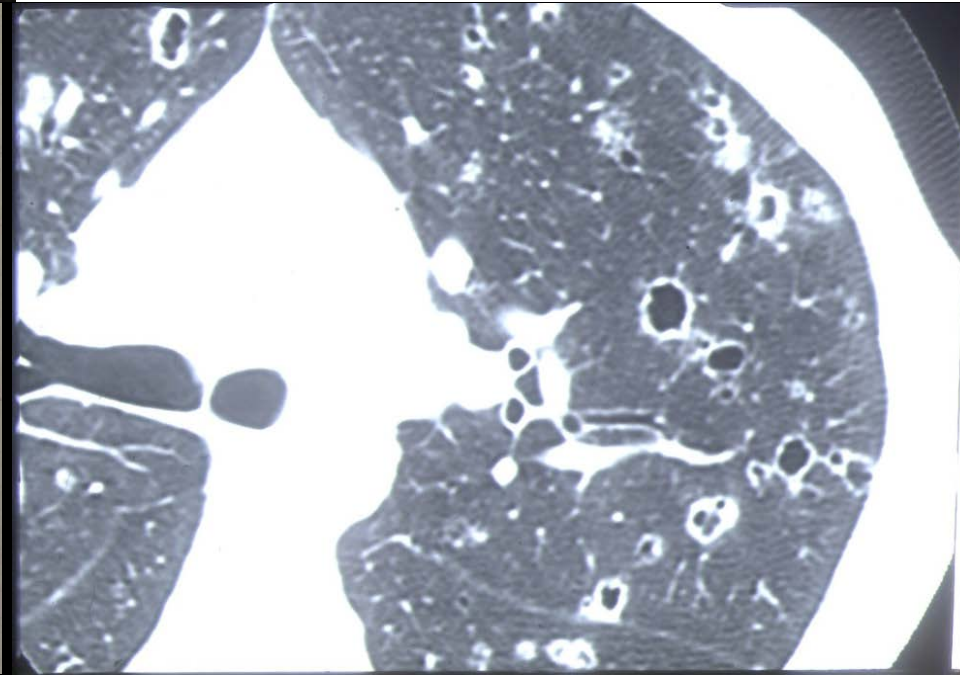
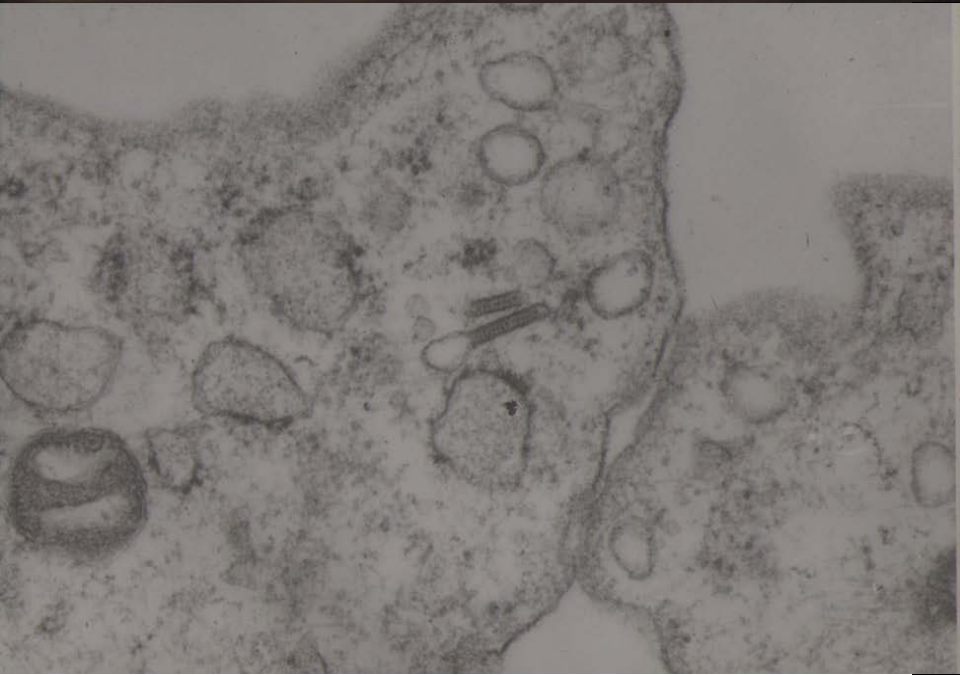
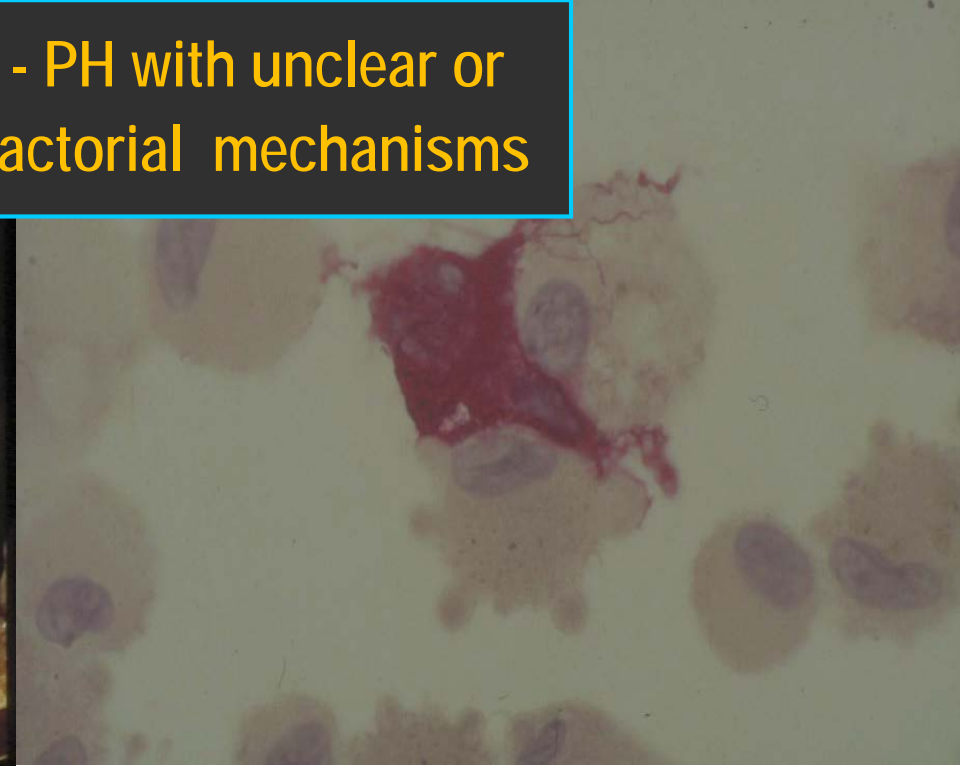
PLCH



LAM



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.

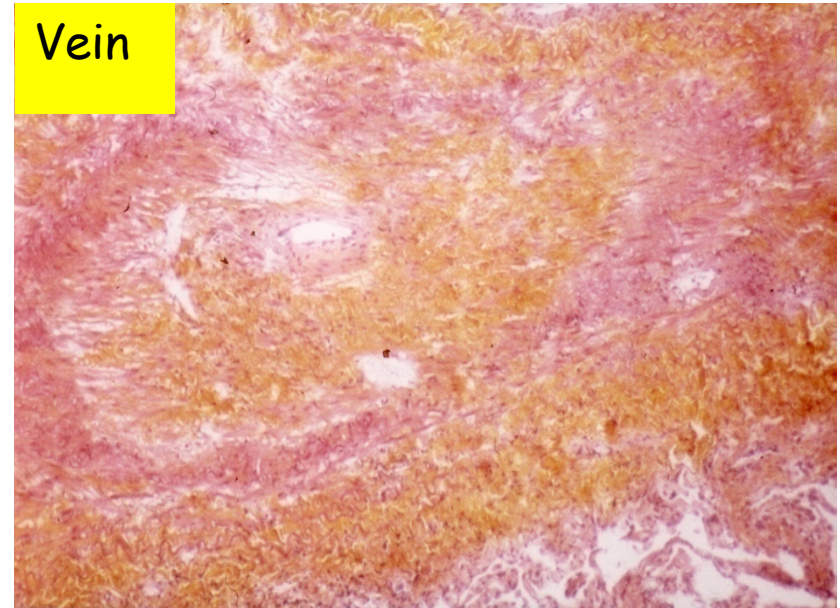
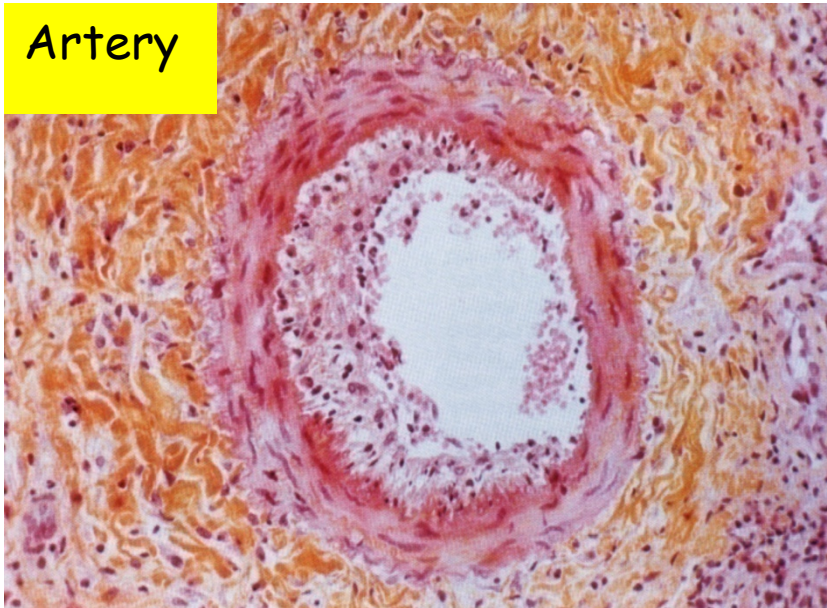


PULMONARY VASCULAR INVOLVEMENT IN HISTIOCYTOSIS X

- ◆ 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

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?)



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

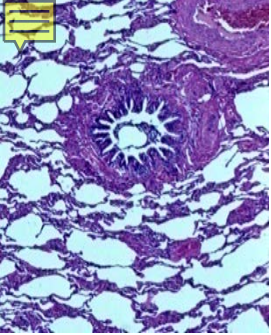
Le Pavec et al. Chest 2012; 142: 1150

- ◆ 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 \pm SD 6MWD: $355 \text{ m} \pm 95 \text{ m}$
- ◆ 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

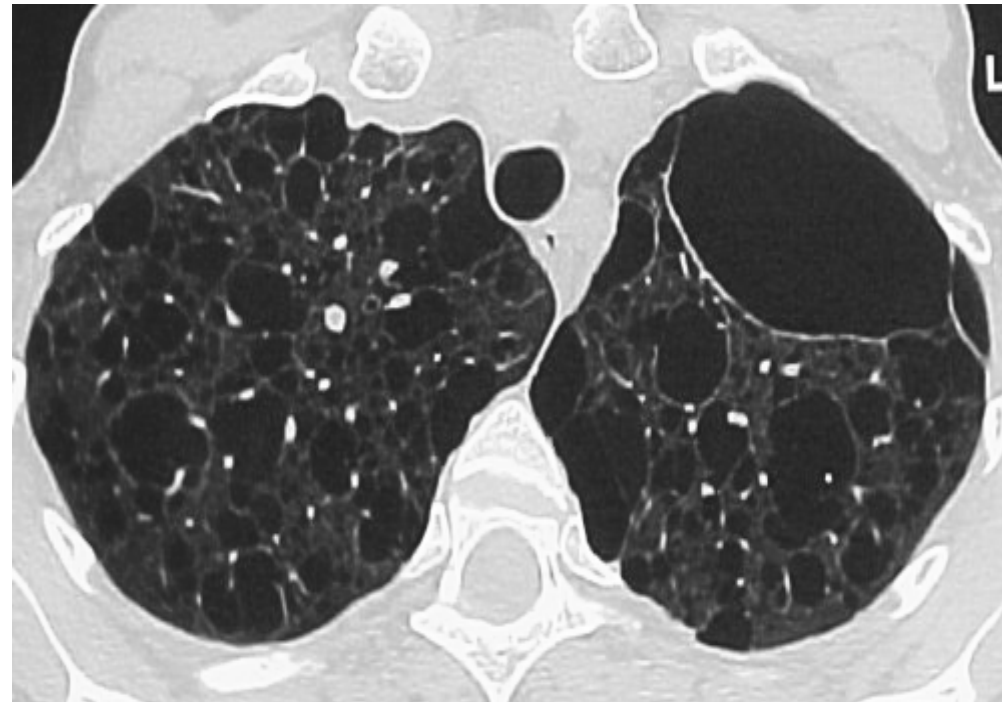


PULMONARY HYPERTENSION DIAGNOSTIC CLASSIFICATION

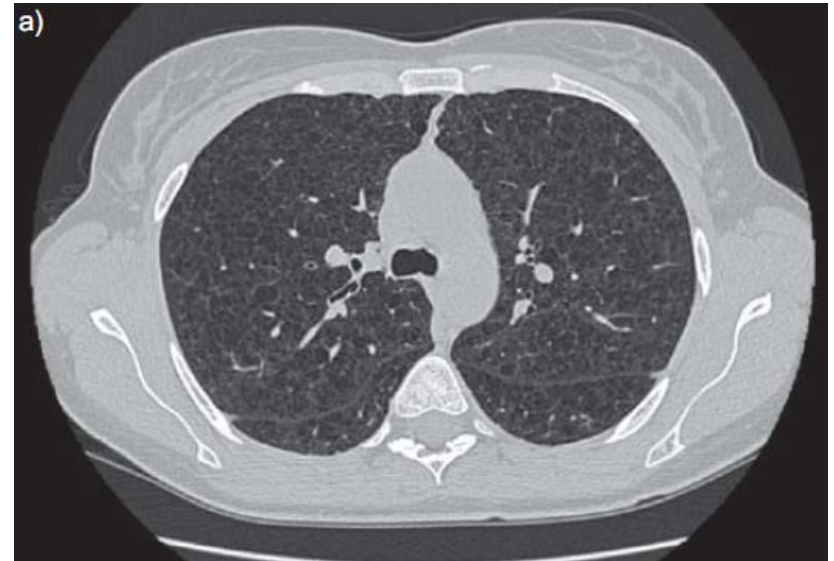
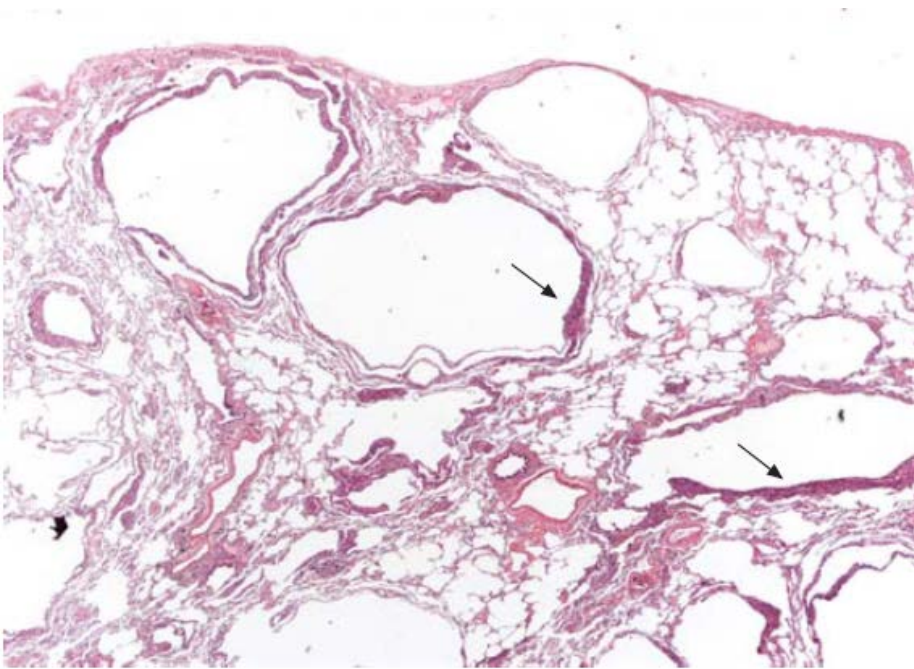
(updated 4th WSPAH-Dana Point 2008)

5. PH with unclear or
multifactorial mechanisms

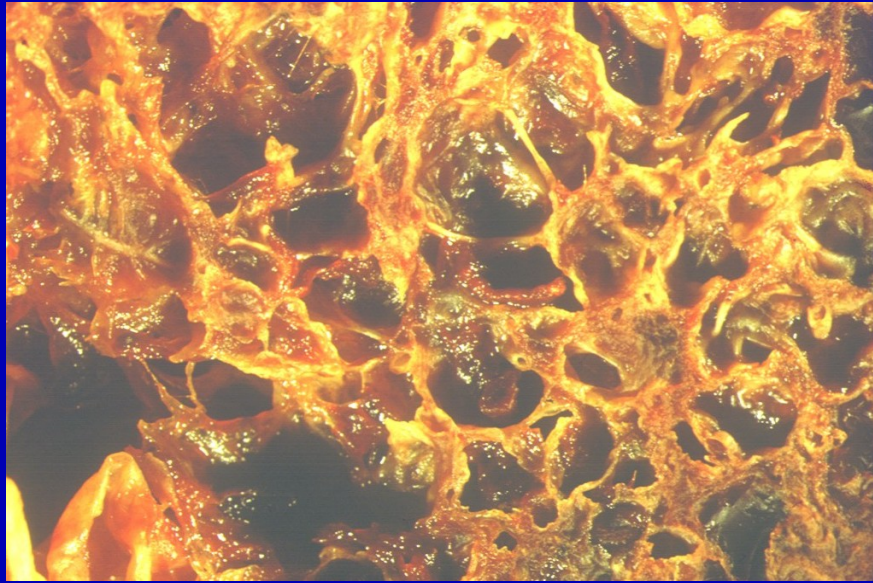
Lymphangioleiomyomatosis



Lymphangiomyomatosis (LAM)



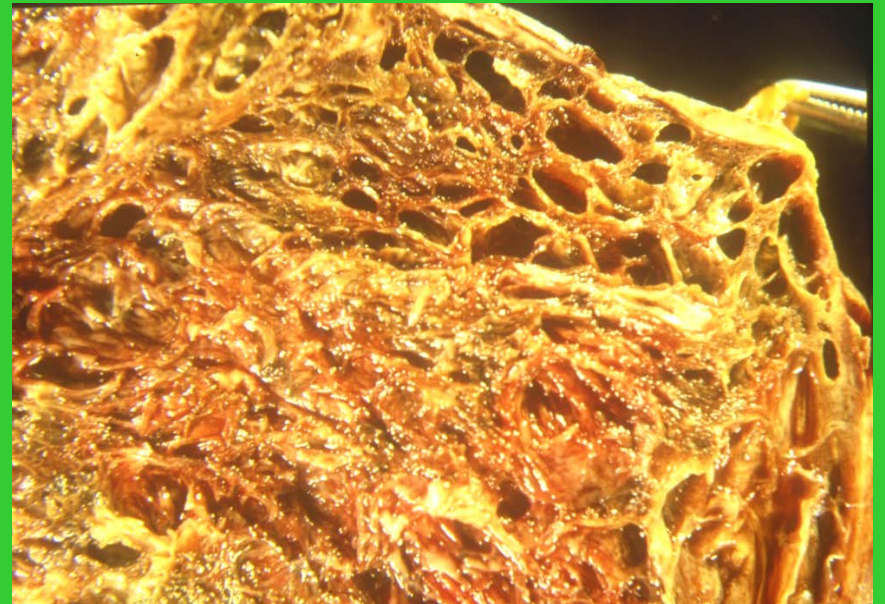
Lymphangiomyomatosis (LAM) is a rare multisystem disorder affecting predominantly young females in their reproductive years. It is characterised by progressive cystic destruction of the lung, lymphatic abnormalities and abdominal tumours (e.g. angiomyolipomas)



PLCH



LAM



Pulmonary Hypertension in Lymphangiomyomatosis: Characteristics in 20 patients

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

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- ◆ 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.

- ◆ 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.