Pathophysiology of pulmonary vasculature in IPF and Sleep Disorders: the role of pulmonary hypertension

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CLASSIFICATION
4th World Symposium 2008

1. Pulmonary Arterial Hypertension

- ❑ **Idiopathic PAH**

Disorders of the respiratory system and hypoxemia

- Chronic obstructive pulmonary disease
- **Interstitial lung diseases**
- **Sleep disorders**
- Alveolar hypoventilation
- Chronic exposure to high altitude
- Others...

1'. Pulmonary veno occlusive disease (PVO) and/ or pulmonary capillary hemangiomatosis (PCH)

2. Pulmonary hypertension due to left heart disease

- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease

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

- COPD
- Interstitial lung disease
- Others pulmonary diseases
- Sleep-disordered breathing
- Chronic exposure to high altitude
- Developmental abnormalities

4. Chronic thromboembolic polmonary hypertension (CTEPH)

5. PH with unclear or multifactorial mechanisms

1: Hematologic disorders, myeloproliferative disorders, splenectomy
2: Systemic disorders: vasculitis, sarcoidosis, PLCH, LAM, neurofibromatosis
3: Metabolic disorders: GD, thyroid disorders, glycogen storage disease
4: Others: tumoral obstruction , fibrosing mediastinitis, dyalisis

Sleep apnea and PH

Experimental intermittent hypoxia administered for part of the day for just a few weeks in rodents results in

- Pulmonary Hypertension
- Pulmonary arteriolar remodeling
- Right ventricular hypertrophy

- J Appl Physiol 99:2028-2035, 2005
- J Appl Physiol 90:2502-2507, 2001
- Eur Respir J 18:279-285, 2001

OPEN ACCESS Freely available online

PLOS ONE

Effects of Cyclic Intermittent Hypoxia on ET-1 Responsiveness and Endothelial Dysfunction of Pulmonary Arteries in Rats

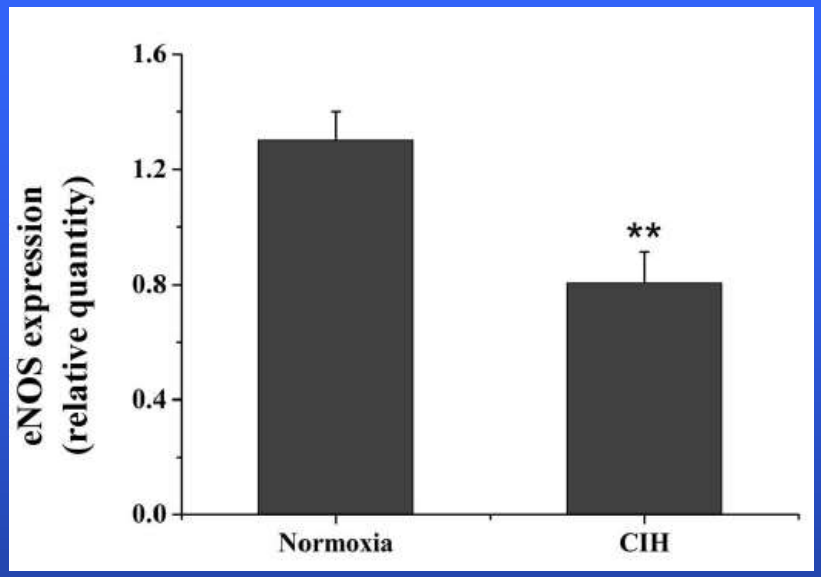
Zhuo Wang[1☯], Ai-Ying Li[2☯], Qiu-Hong Guo[3], Jian-Ping Zhang[3], Qi An[1], Ya-jing Guo[1], Li Chu[3], J. Woodrow Weiss[4*], En-Sheng Ji[1*]

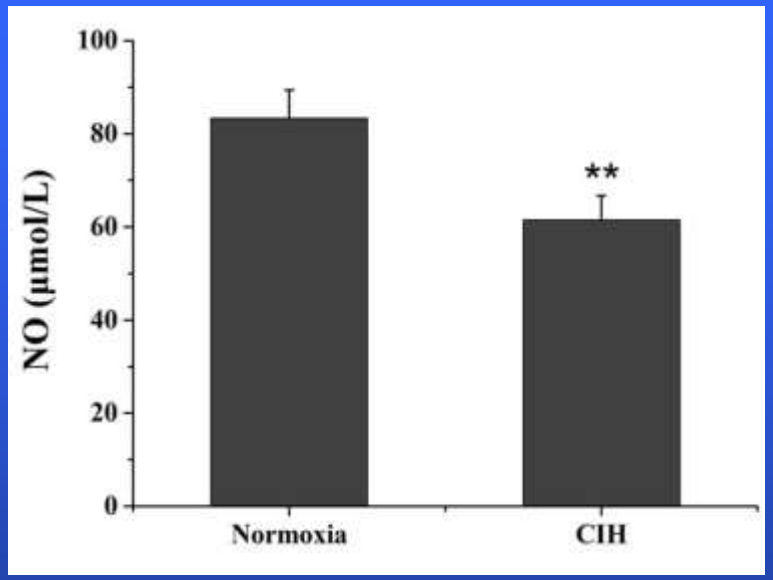
- Exposure to intermittent hypoxia was shown to decrease the relaxation to Acetylcholine, in pulmonary arteries pre-treated with phenylephrine
- ET-1 was found to induce a significant dosedependent contraction of the pulmonary artery
- Vessels from CIH rats were more sensitive to ET-1 than those from normoxia rats.

Thus, the hypoxic conditions used (2 min. cycles of 9%/21% O2, 8 h/day, 3 wks) eventually impaired endothelium-dependent vasodilation and increased vasoconstrictor responsiveness, which is in agreement with the pathology observed in human OSA

PLoS One 2013; 8 (3)

❖ **CIH decreases eNOS expression and NO level in pulmonary arteries**



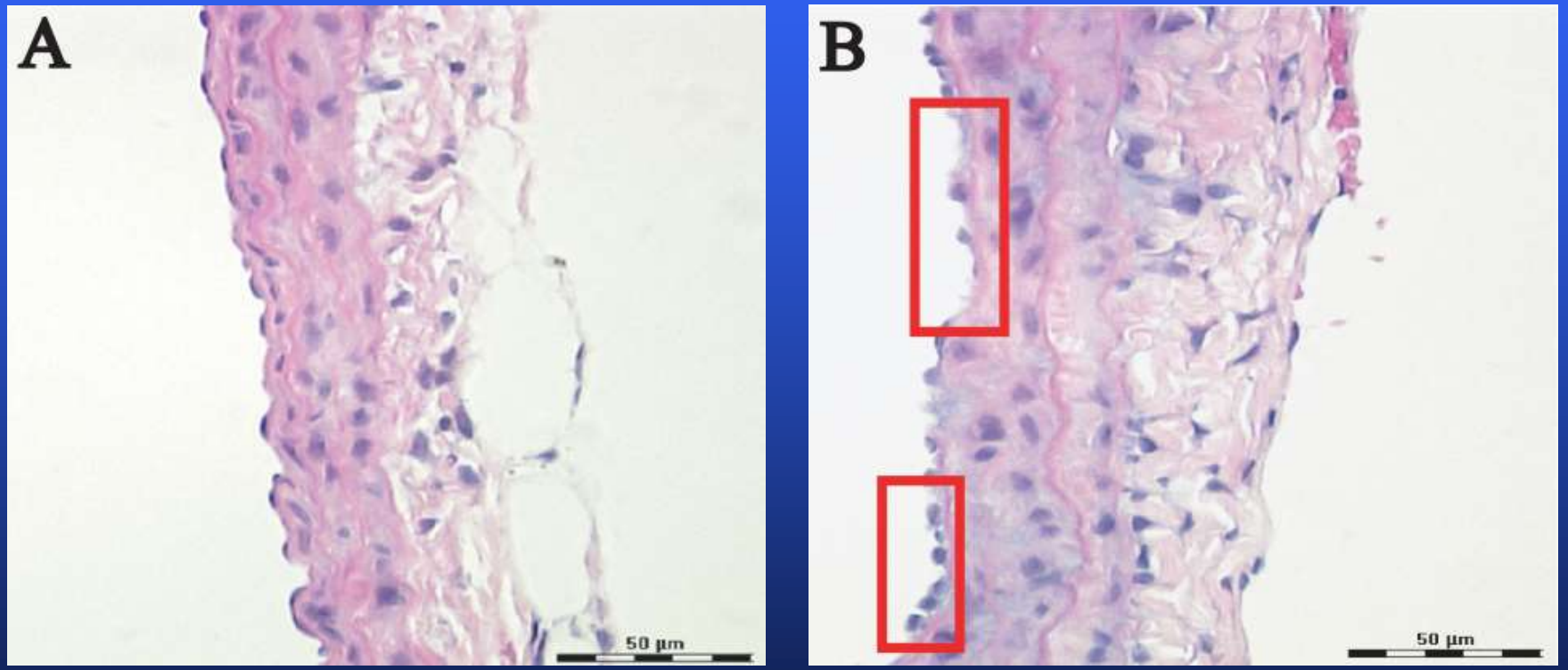


❖ **CIH** increases ET-1 expression in the rat pulmonary artery

PLoS One 2013; 8 (3)

Effects of Cyclic Intermittent Hypoxia (CIH) on pulmonary arteries histopathological changes

Normoxia **CIH**



In the pulmonary artery segments from the CIH group, there were histopathological changes of the endothelial monolayer with cellular enlargement and edema, denudation of some endothelial cells.

PLoS One 2013; 8 (3)

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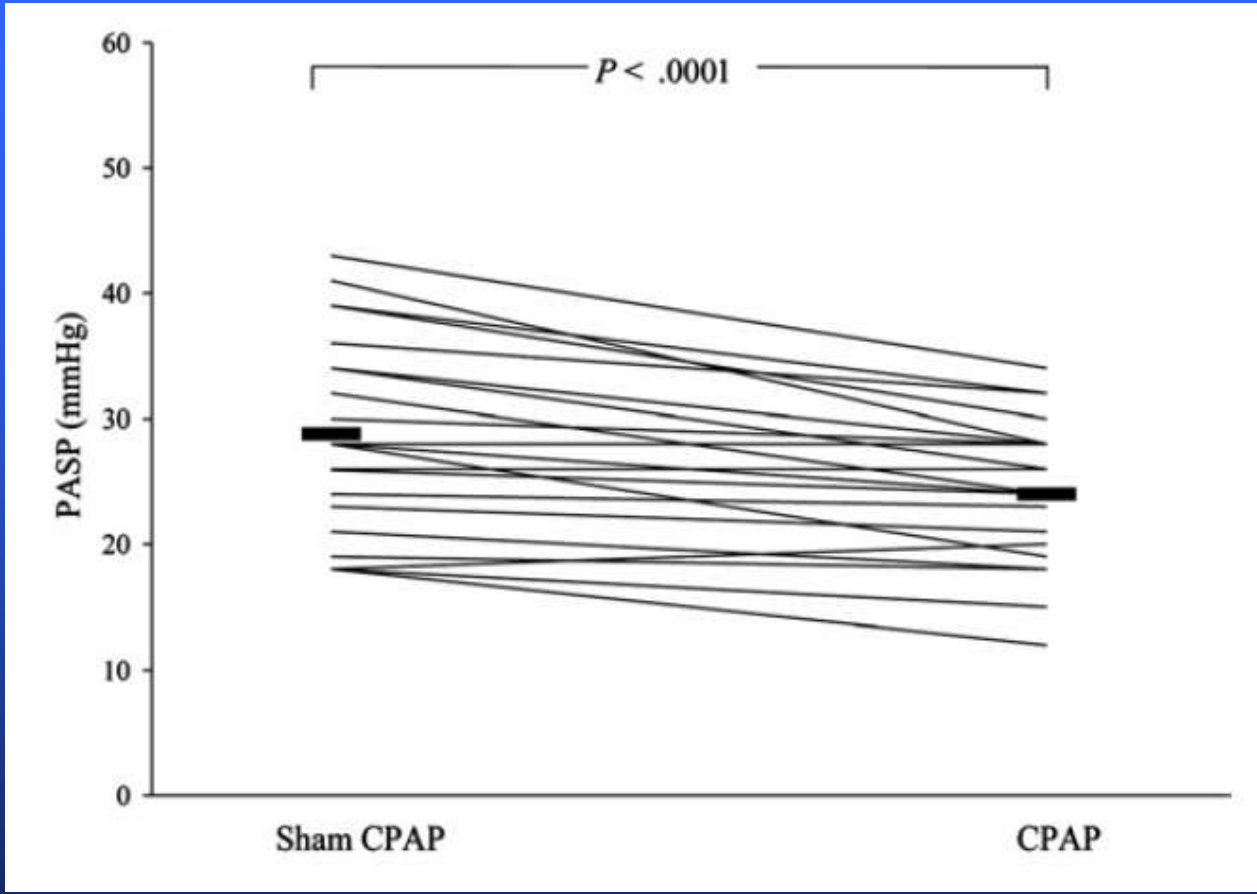
The imbalance of between NO and ET pre-disposes the vasculature to increased tone, altered remodeling, proliferation and endothelial injury

PLoS One 2013; 8 (3)

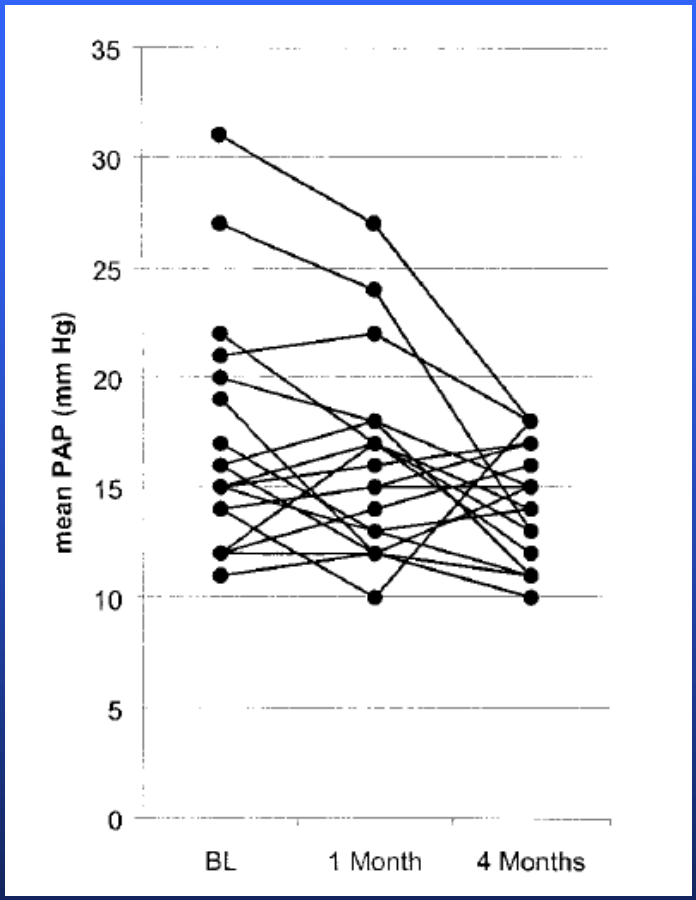
PH and CPAP treatment of OSA



Individual values for the Doppler echocardiography-derived pulmonary artery systolic pressure (PASP) after crossover trial of 3-month sham vs 3-month effective CPAP treatment in 21 patients with OSA

Eur Heart J 2006. 27:1106-1113
2006

PH and CPAP treatment of OSA



Daytime mean Ppa (estimated by Pulsed Doppler echocardiography) during room air breathing in 20 patients with OSA over 4 mo of CPAP treatment.

During CPAP treatment there was a fall of daytime Ppa (room air breathing) in the 20 compliant patients with OSA, which reached statistical significance after 4 mo of treatment

The biggest drop in Ppa was observed in pulmonary hypertensive patients with mean Ppa ≥ 20 mm Hg.

Total pulmonary vascular resistance (TPVR) fell significantly during CPAP treatment.

Am J Respir Crit Care Med 2002; 165: 152-158

Frequency of PH in patients with OSAS

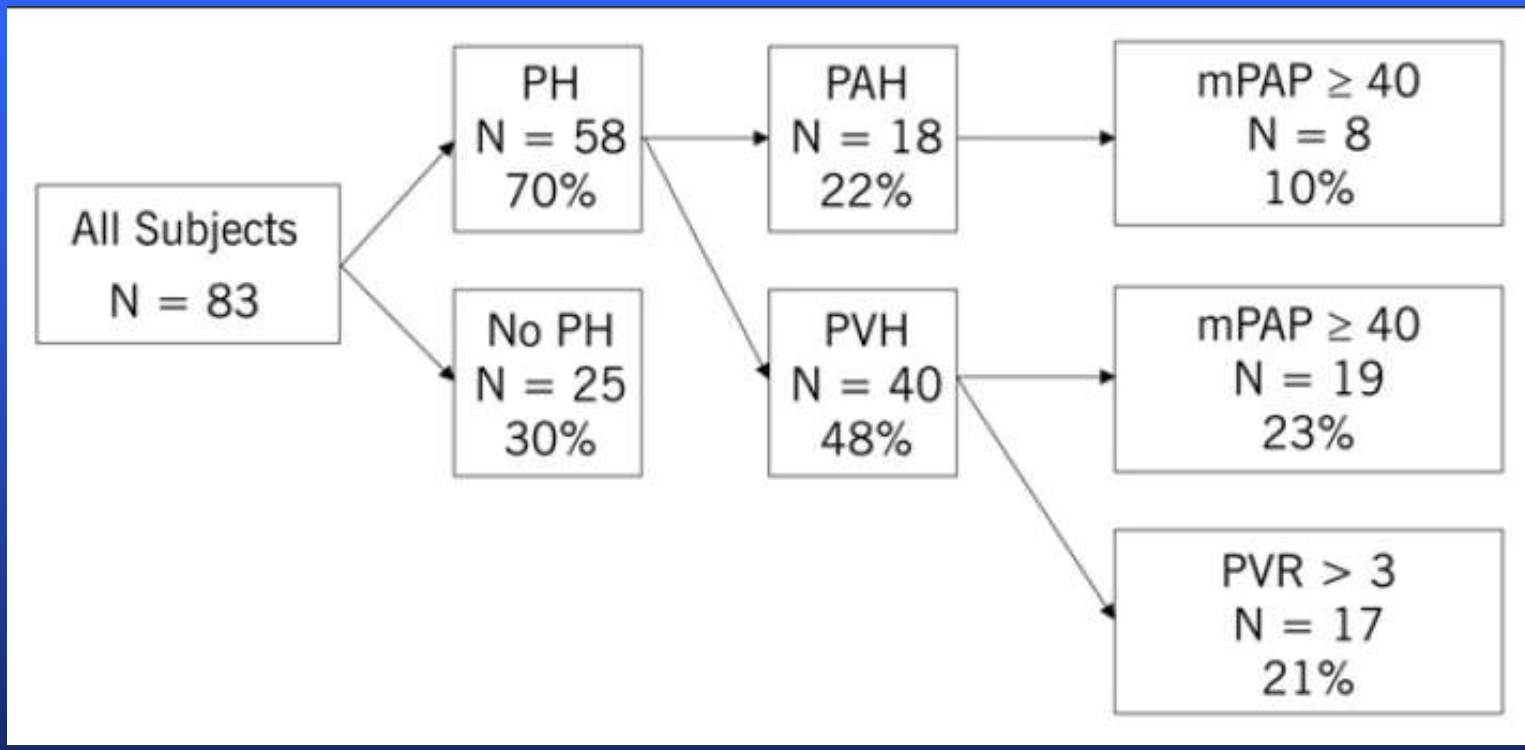
Table 1. Prevalence of PHT in OSAs

Study	Sample size	PH prevalence (%)	mPAP (mm Hg)	mPAP in PH	FEV_1 (% predicted)	PaO_2 (mm Hg)	$PaCO_2$ (mm Hg)
Schroeder et al[64]	22	59	21	25	-	80	-
Tilkian et al[28]	12	67	20	23	-	77	41
Fletcher et al[65]	24	79	28	32	62	66	46
Podszus et al[36]	65	20	19	29	-	-	-
Weitzenblum et al[54]	46	20	16	23	66	73	39
Krieger et al[53]	114	19	16	-	65	72	39
Sajkov et al[59]	27	41	18	23	89	75	41
Laks et al[56]	100	42	21	29	73	74	45
Chaouat et al[52]	220	17	-	-	-	73	39
Sanner et al[61]	92	20	15	22	92	83	36
Bady et al[58]	44	27	20	28	92	81	41
Sajkov et al[60]	32	34	18	24	102	78	40
Alchanatis et al[57]	29	21	17	26	92	90	40
Arias et al[63]	23	43	22	28	111	-	40

Am J Cardiol. 2009;104:1300-6

Frequency and impact of PH in patients with OSAS

A retrospective study



Flow diagram showing hemodynamic characteristics (measured by right heart catheterization) in a cohort of 83 patients with OSA

Am J Cardiol. 2009;104:1300-6

Frequency and impact of PH in patients with OSAS

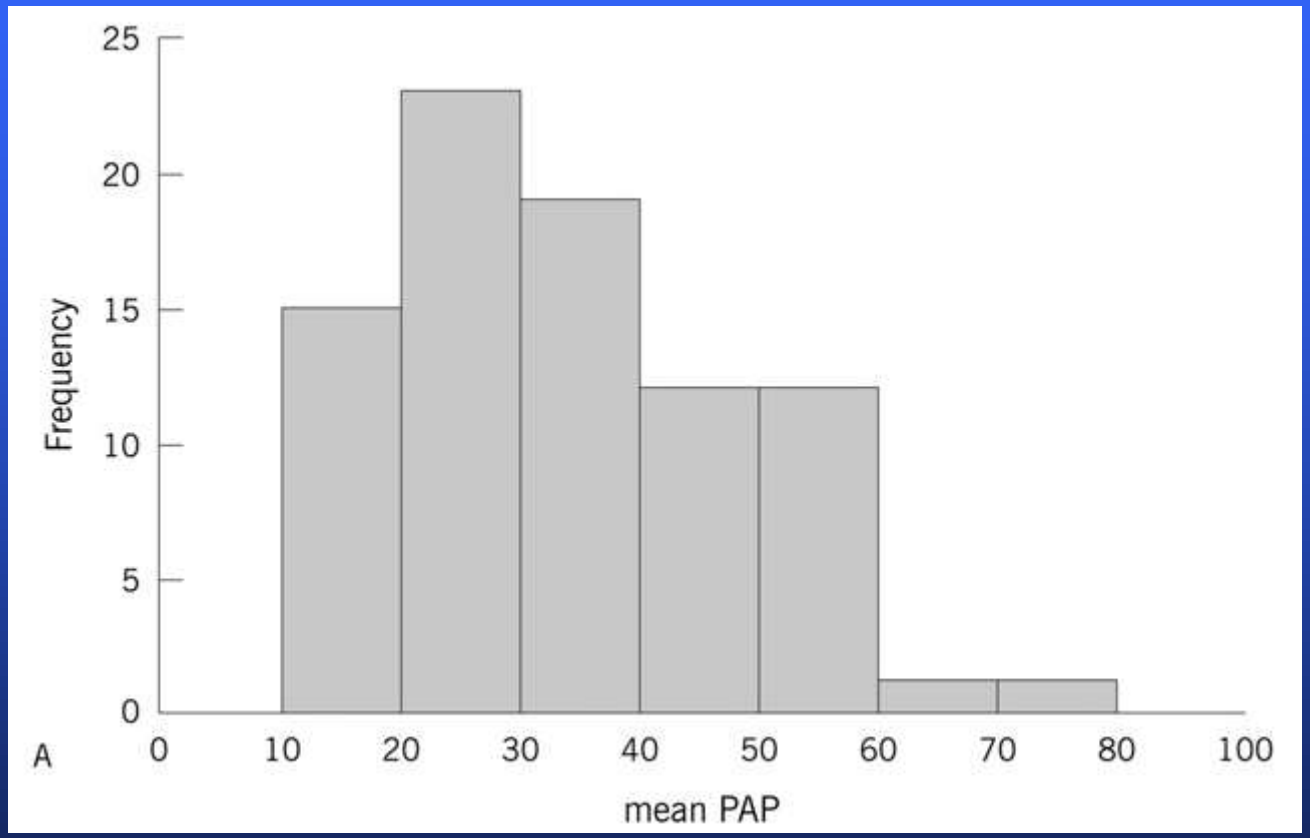
❖ All PH groups experienced significantly more frequent nocturnal desaturation than did the non-PH group (p 0.05 for PH and PAH compared to non-PH group).

❖ The PH group had the longest duration of nocturnal desaturation (i.e., percentage of total sleep time with oxygen saturation 90%; PAH 34 33% vs PVH 14 24% of total sleep time).

❖ No significant difference was observed in the depth of desaturation (i.e., no significant difference was found in the minimum recorded oxygen saturation) and apnea-hypopnea index

Am J Cardiol. 2009;104:1300-6

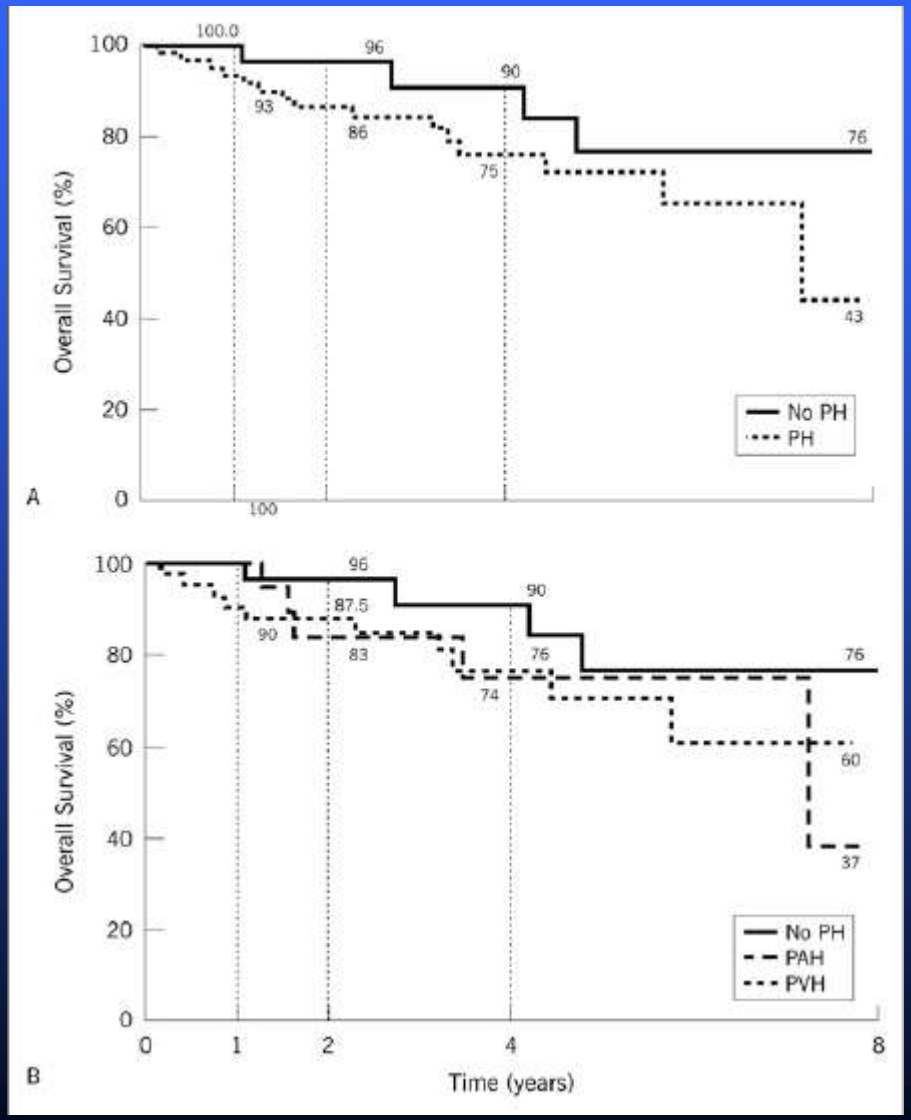
Frequency and impact of PH in patients with OSAS



Most patients had mild or moderate elevations in pulmonary arterial pressure; however, 33% of patients had a mean pulmonary arterial pressure ≥ of 40 mm Hg

Am J Cardiol. 2009;104:1300-6

Frequency and impact of PH in patients with OSAS



Kaplan-Meier survival estimates in 83 patients with OSA
(A)with and without PH and
***(B) those without PH compared to those with* PAH and PVH.**

Am J Cardiol. 2009;104:1300-6

Frequency and impact of PH in patients with OSAS

❖ In addition to factors such as age, forced expiratory volume in 1 second, diffusion capacity for carbon monoxide, and the apneahypopnea index, pulmonary hemodynamics are important correlates of increased mortality in patients with OSA

❖ Functional capacity is decreased and dyspnea is greater in patients with OSA and PH than in those with OSA but without PH agrees with observations regarding PH in other diseases such as idiopathic pulmonary fibrosis and sarcoidosis.

Am J Cardiol. 2009;104:1300-6

How many patients with PH suffer from sleep apnea?

Original Article

Sleep apnea in precapillary pulmonary hypertension ☆

Rio Dumitrascu [a], Henning Tiede [a], Jan Eckermann [a], Konstantin Mayer [a], Frank Reichenberger [b], Hossein Ardeschir Ghofrani [a], Werner Seeger [a], Jörg Heitmann [a], Richard Schulz [a,*]

[a] *University of Giessen Lung Center, Germany*
[b] *Department of Pneumology, Asklepios Lung Center, Munich-Gauting, Germany*

Methods: 169 patients with a diagnosis of PH confirmed by right heart catheterisation and clinically stable in NYHA classes II or III were prospectively investigated by polygraphy. Recruitment was independent of sleep-related symptoms and the use of vasodilator drugs or nasal oxygen.

Sleep Medicine 2013; 14: 247–251

Original Article

Sleep apnea in precapillary pulmonary hypertension ☆

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- Based on the AHI cutoff value of >10/hour of sleep, 45 PH patients (i.e. 26.6%) were found to suffer from sleep-disordered breathing. Of these, 27 patients (i.e. 16%) had OSA and 18 patients (i.e. 10.6%) had CSA
- the severity of sleep-disordered breathing was mild-to-moderate with a mean AHI of 20/hour
- OSA mainly occurred in patients with chronic thromboembolic PH (CTEPH) and COPD-associated PH. The majority of cases with CSA were seen in patients with IPAH, CTEPH and ‘‘other’’ diagnoses of PH

Sleep Medicine 2013; 14: 247–251

IPF and sleep disorders

Poor sleep quality and daytime sleepiness are extremely common in patients with IPF

Poor sleep quality however does not seem to be associated to the degree of lung impairment

Chest 2008; 134: 693-698

Strong correlation has been found between oxygen saturation during sleep and Fatigue Severity Scale

Med Princ Pract 2009; 18: 10-15

IPF and sleep disorders

Several studies show that nocturnal hypoxiemia is often present in DPLD and that these desaturations may lead to sleep fragmentation and impairment of sleep quality

Pulmonary hypertension in IPF

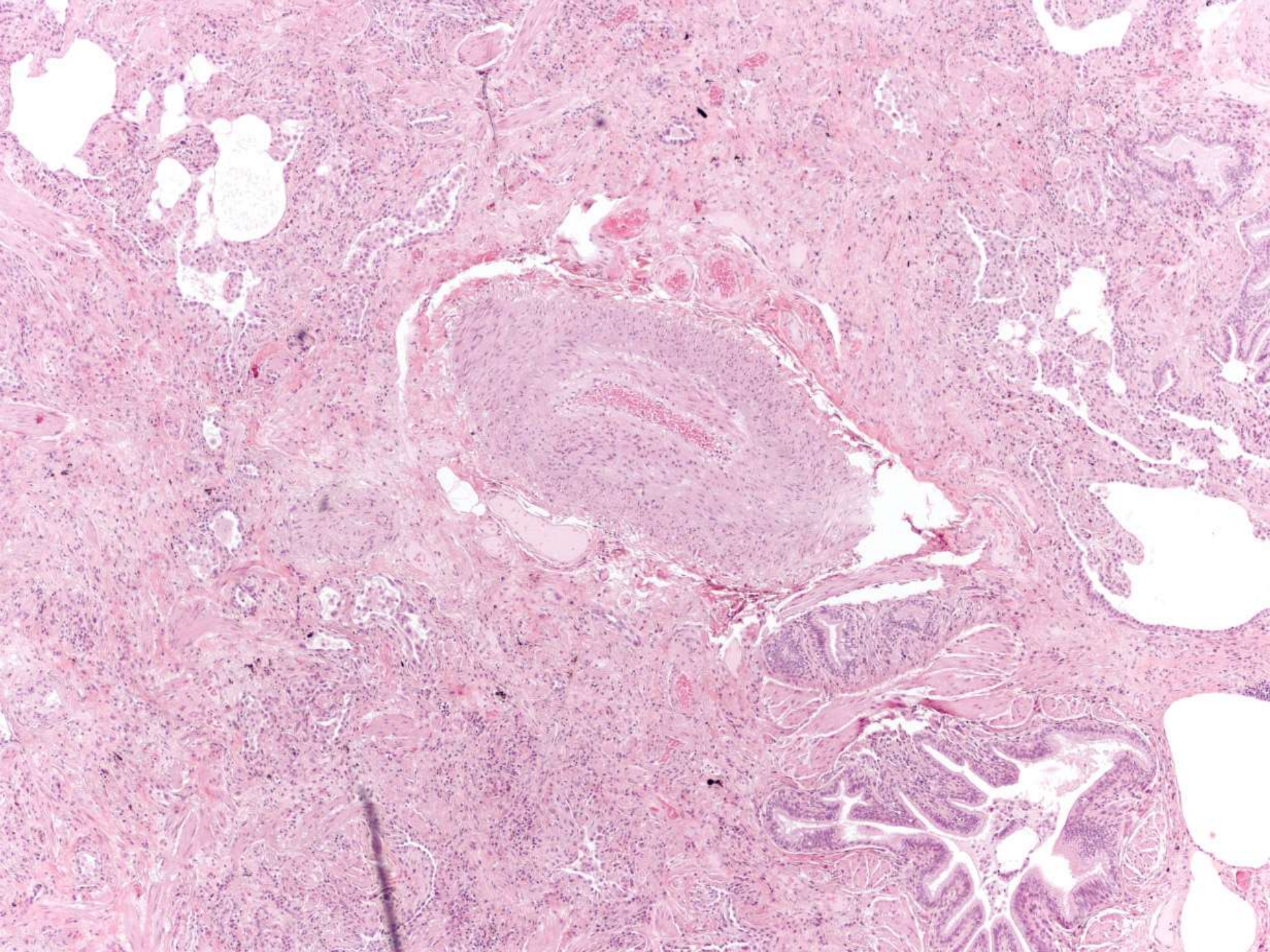
- Frequency
- Prognosis
- Diagnosis
- Treatment

Prevalence of PH in IPF

- The prevalence of PH complicating the course of patients with IPF has been reported as occurring in 32 to 85% of patients
- 9% of patients having a mPAP of greater than 40 mm Hg
- initial prevalence of 41% increasing to more than 90% at follow-up

Correlates of PH in IPF

- it appears that PH may not correlate with lung volumes in patients with IPF
- factors aside from progressive fibrosis are responsible for PH in IPF
- pulmonary artery remodeling might play a more relevant role than vasoconstriction, yet the two pathogenetic processes might be intimately interrelated



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

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	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

Pulmonary hypertension in IPF

Nathan SD, et al. Chest 2007, 131: 657-663

- 118 patients with IPF and RHC (FVC% 54.6 and Dlco% 36.3)
- 48 patients (40.7%) qualified as having PH

Lettieri CJ et al. Chest 2006, 129:746-52

- 79 patients with IPF and RHC (FVC% 49.3 and Dlco% 31.1)
- 25 patients (31.6%) qualified as having PH

Hamada K et al. Chest 2007, 131:650-656

- 70 patients with IPF and RHC (early stage of IPF: FVC% 76 and Dlco% 45)
- 6 patients (8.1%) qualified as having PH

Shorr AF et al. Eur Respir J 2007;30:715–721

- 2525 patients with IPF and RHC (FVC% 48.4) Patients undergoing assessment for lung transplantation
- 932 patients (46.1%) qualified as having PH

Patients assessed at the time of transplantation evaluation: PH prevalence of 36%

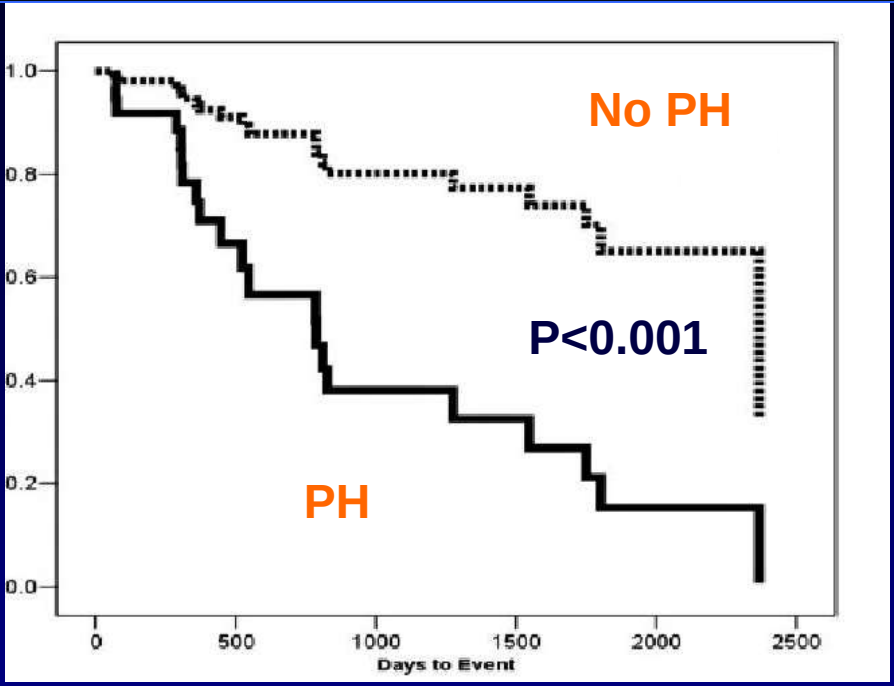
At the time of transplantation, 85% of the same patient cohort had PH

Conclusions

PH is progressive and the prevalence and severity of PH is temporally related to the progression of IPF

Nathan SD et al. Respiration 2008; 76: 288-94

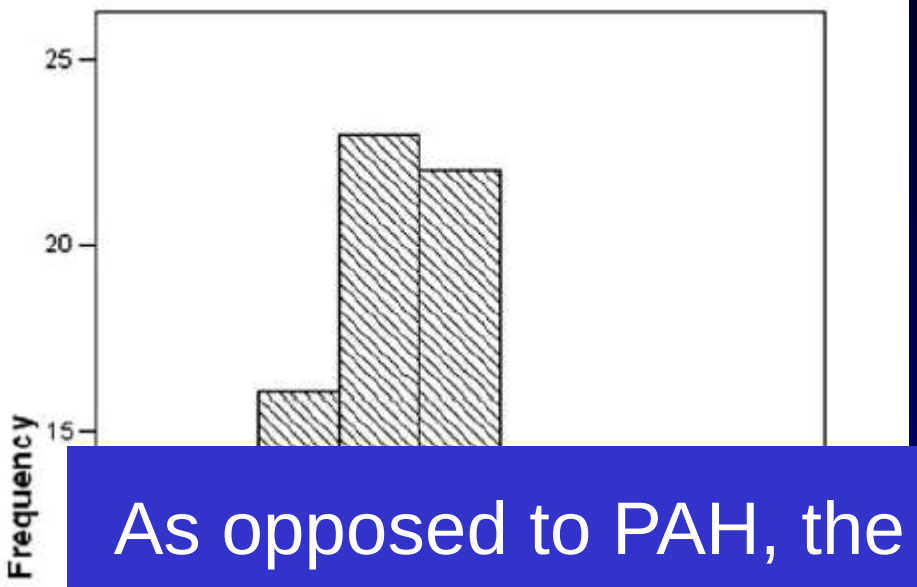
Pulmonary hypertension in IPF

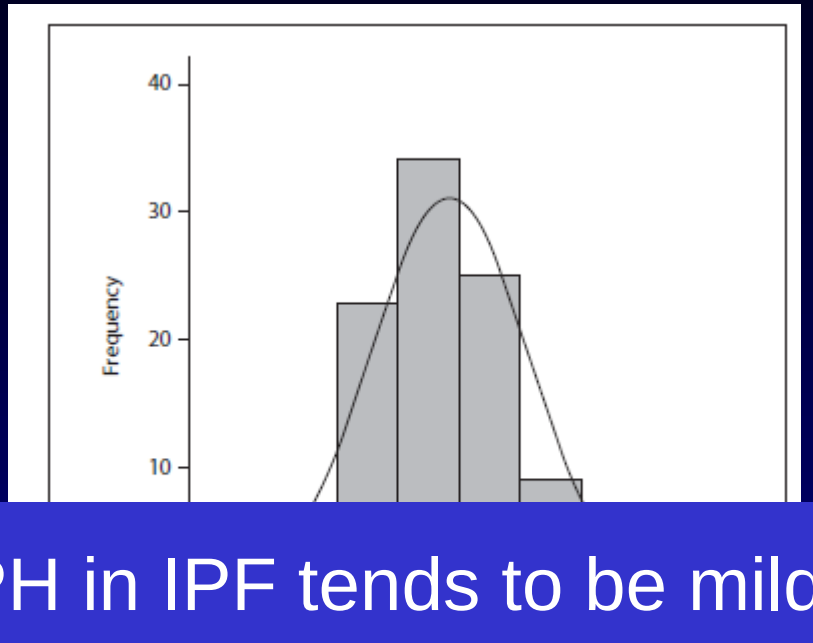


Variables	MAP ≤ 25 mmHg (n= 10)	MAP > 25 mmHg (n= 24)	P value
MPAP, mmHg	18.2 ± 3.6	29.8 ± 5.1	NA
6MWT distance, m	365.9 ± 81.8	143.5 ± 65.5	< 0.001
SpO2 nadir on 6MWT, %	88.0 ± 3.5	80.1 ± 3.7	< 0.001
Mortality rate, %	37.5	70.0	0.003

Lettieri CJ et al. Chest 2006, 129:746-52

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





As opposed to PAH, the PH in IPF tends to be mild in most patients.

In one series, approximately 50% of the patients with PH had an mPAP in the 25 to 30 mmHg range, while only about 10% of patients with IPF listed for transplantation have severe PH as defined by a mPAP > 40 mmHg

Lettieri CJ et al. Chest 2006;129: 746-752

Shorr AF et al. Eur Respir J 2007;30:715-721

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)

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

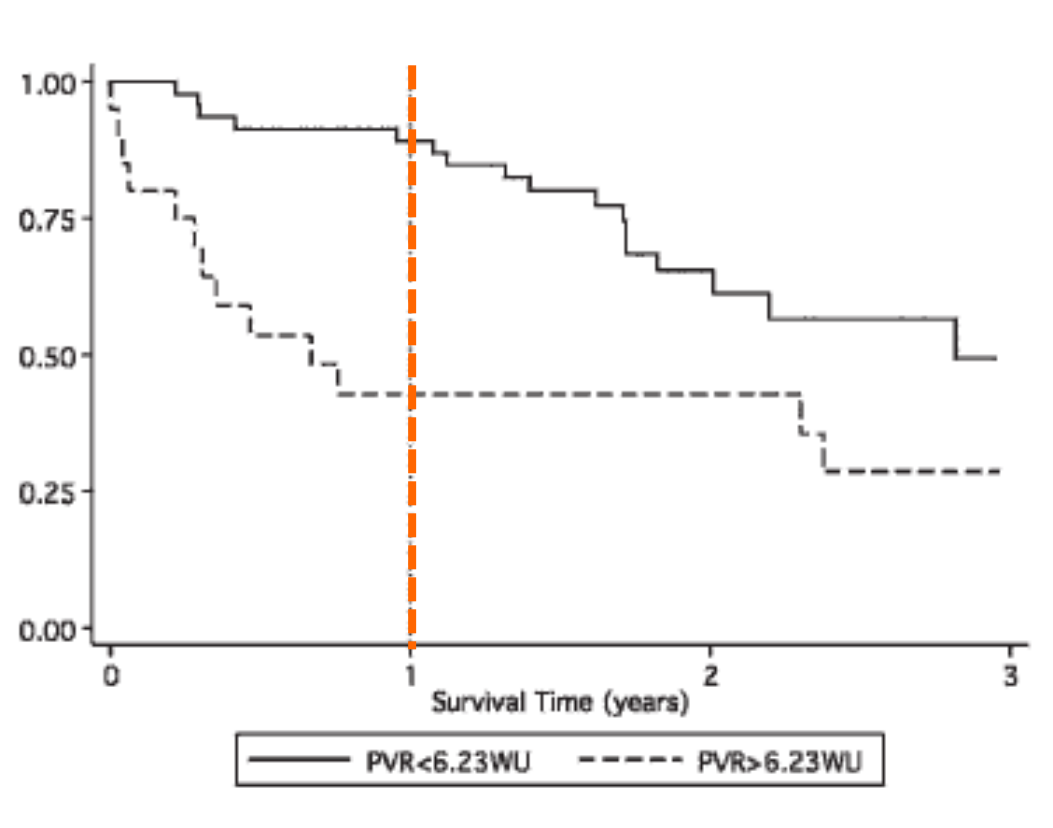
Corte TJ et al. Thorax 2009; 64: 883

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/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



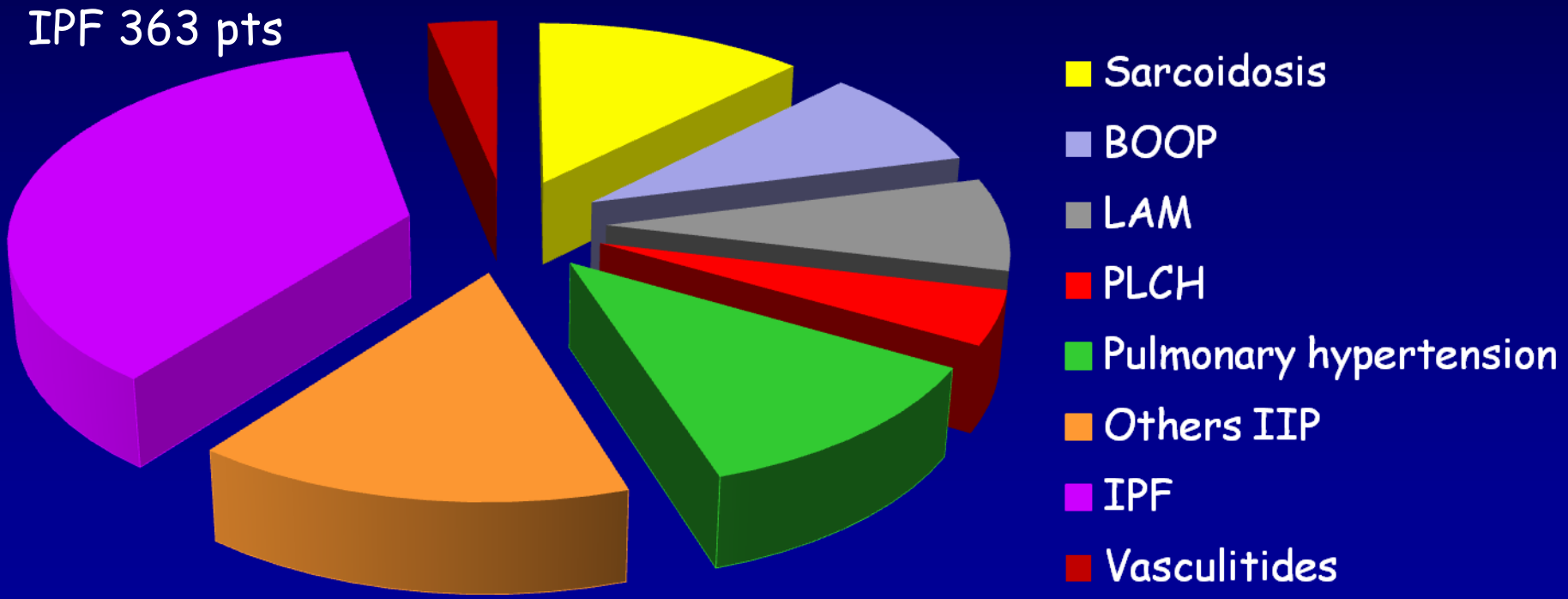
In severe diffuse lung disease, raised PVR strongly predicts death within 1 year independent of disease severity or diagnosis of IPF.

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

Pulmonary rare diseases

Ospedale San Giuseppe Experience (2001- 2012)

Tot. 996 patients



RHC and 6MWD in IPF

Variables	MAP ≤ 25 mmHg (n= 17)	MAP > 25 mmHg (n= 13)	MAP > 35 mmHg (n= 4)	P value
MPAP, mmHg	19.4 ± 3.6	32.4 ± 6	40,5 ± 2,6	NA
6MWT distance, m	222.0 ± 118.5	222.3 ± 118.5	203.7 ± 128.3	>0.1
FVC, %	51.6 ± 13.8*	63.8 ± 16*	56.0 ± 6.7	<0.05
FEV1, %	58.3 ± 16.3	65.8 ± 18.8	55.2 ± 3.7	>0.05
DLCO, %	31.4 ± 9.6	24.2 ± 13.0	29.0 ± 7.4	>0.05
CI, l/min/m2	3.4 ± 0.55*	2.9 ± 0.7*	2.8 ± 0.6	<0.05
PVR, wood units	3.5 ± 1.1*	6.9 ± 1.4*	10.3 ± 2.0	<0.05

Harari S. submitted

In the PH group 4 pts had out of proportion PH (mean PAP >35 mmHg) and walked 203.7 meters ±128.3 that did not statistically differ from the latters - mean survival in those pts was 8 months

Our data suggest that meters walked during 6MWT are not statistically different in IPF patients with or without PH.
6MWD should not be used as surrogate end point in clinical study in IPF-PH pts.

Harari S. submitted

Trials of therapy for PH in IPF

Type of lung disease	Investigator/year	Type of study	N	Therapy	Outcome
Lung fibrosis	Ghofrani et al, 2002	OL-RCT	**16 (IPF=7)**	Sildenafil, iNO, epoprostenol	Sildenafil improved pulmonary hemodynamics and gas exchange
IPF	Krowka et al, 2007 (multicenter)	DB-RCT	**51**	Inhaled iloprost	No improvement in 6MWT, NYHA/WHO Class
IPF	Collard et al, 2007	OL trial	**14**	Sildenafil	57% had significant increase in 6MWT

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 ≥ 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.

STEP-IPF

- This study was intended to examine the effects of sildenafil in a population with advanced IPF, defined as a DLCO of less than 35% of the predicted value, not a population with IPF and documented PH.
- PH is common, although not universally present, in patients with advanced IPF.
- The lack of RHC before and after the study intervention precluded the ability to determine whether the potential benefits of sildenafil in patients with advanced IPF (e.g., decreased dyspnea, improved quality of life, and improved gas transfer) were driven by the subgroup with elevated PAP

N Engl J Med 2010;363:620-8

Sildenafil in IPF with Right-sided Ventricular Dysfunction

A substudy of STEP-IPF

Methods:

Of 180 subjects enrolled into STEP-IPF, echocardiograms from 119 were available for independent review (sildenafil, n 56; placebo, n 63)

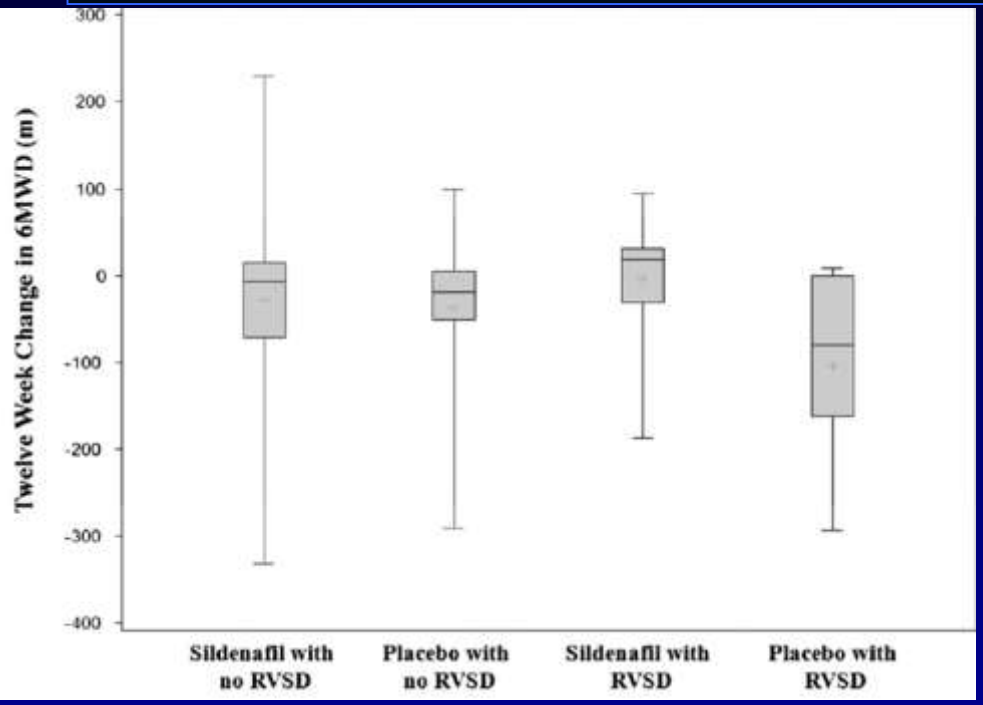
Right ventricular hypertrophy (RVH), right ventricular systolic dysfunction (RVSD), and right ventricular systolic pressure (RVSP) were assessed.

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.

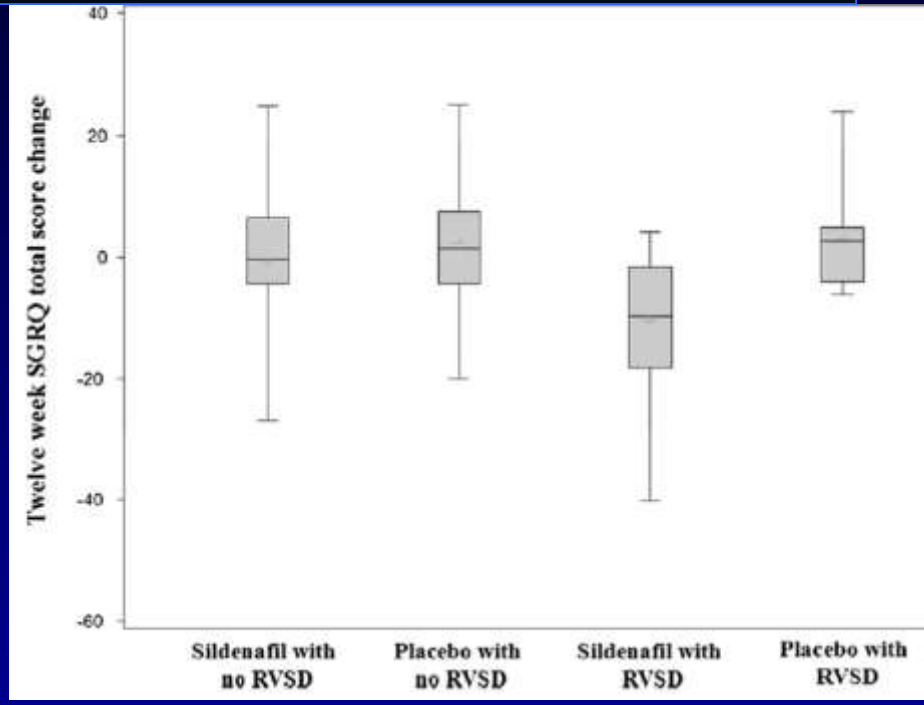
Chest 2013; 146: 1699

Sildenafil in IPF with Right-sided Ventricular Dysfunction

A substudy of STEP-IPF



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

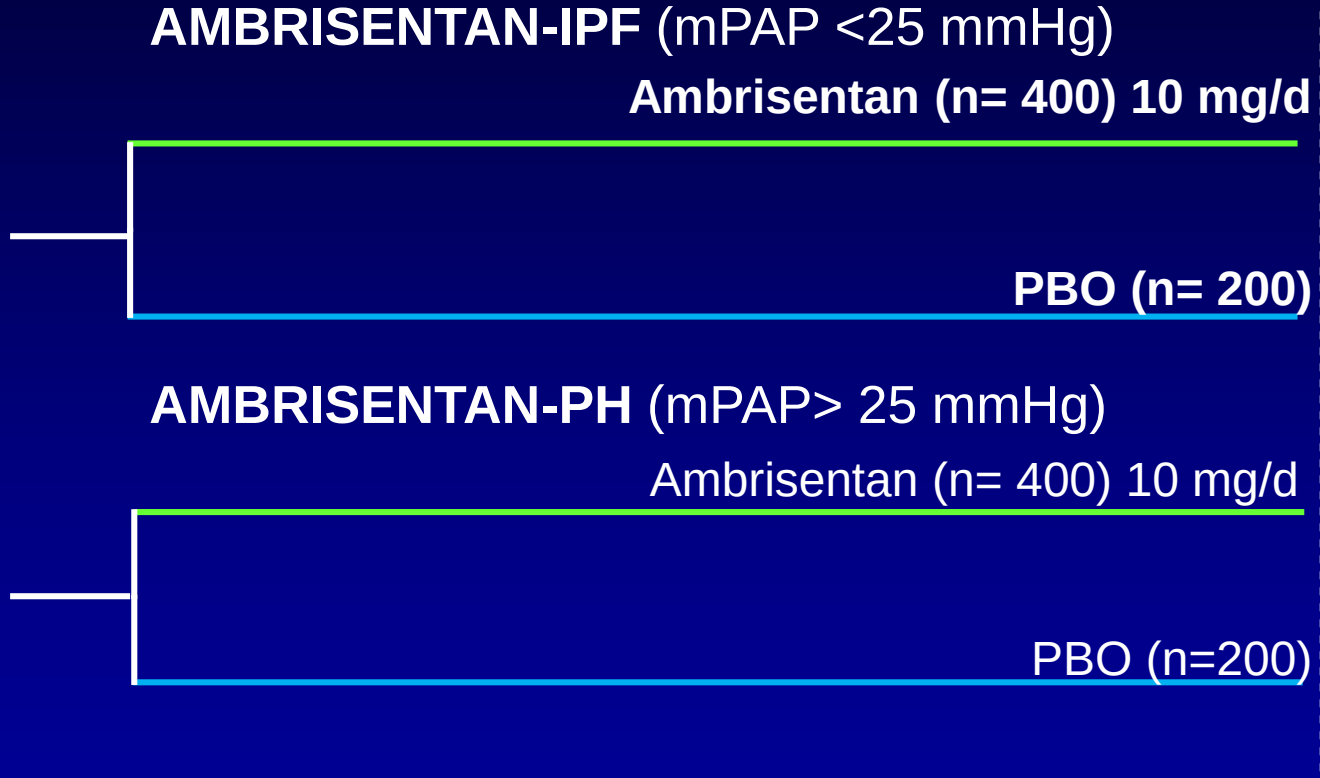


Change in SGRQ total score at 12 weeks by treatment and presence or RVSD

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

ARTEMIS STUDIES
Study design



Primary endpoint Change in % predicted FVC and DLCO at 12 months

Primary endpoint Change in 6MWT at 12 months

Ambrisentan PH-IPF trial was interrupted prematurely because of a lack of superior activity of the experimental arm (unpublished data)

Treatment of idiopathic pulmonary fibrosis with ambrisentan A parallel, randomized trial

Raghu G. et al. Ann Inter Med 2013;158: 641 - 649

Objective: To determine whether ambrisentan, an ETA receptor– selective antagonist, reduces the rate of IPF progression

Design: Randomized, double-blind, placebo-controlled, event driven trial (ClinicalTrials.gov: NCT00768300)

Participants: Patients with IPF aged 40 to 80 years with minimal or no honeycombing on HRCT

Intervention: Ambrisentan, 10 mg/d, or placebo

Measurements: Time to disease progression, defined as death, respiratory hospitalization, or a categorical decrease in lung function.

Conclusion: Ambrisentan was not effective in treating IPF and may be associated with an increased risk for disease progression and respiratory hospitalizations

Out-of-proportion pulmonary hypertension

A paradigm for rare diseases

..we can highlight some of the limitations of this study design, which have also been observed in other studies

First, patients who were deemed eligible for enrollment included not only those with a PAP> 35 mm Hg, but also subjects with a mPAP >25 mm Hg

Second, the 6-MWT, which is a non validated and probably misleading test, was chosen as the primary end point

This test has not yet been validated as a useful screen for PH in IPF, and its prognostic significance is still unknown

Harari S. Chest, 2012*;* 142:1087-1088

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.

Conclusions

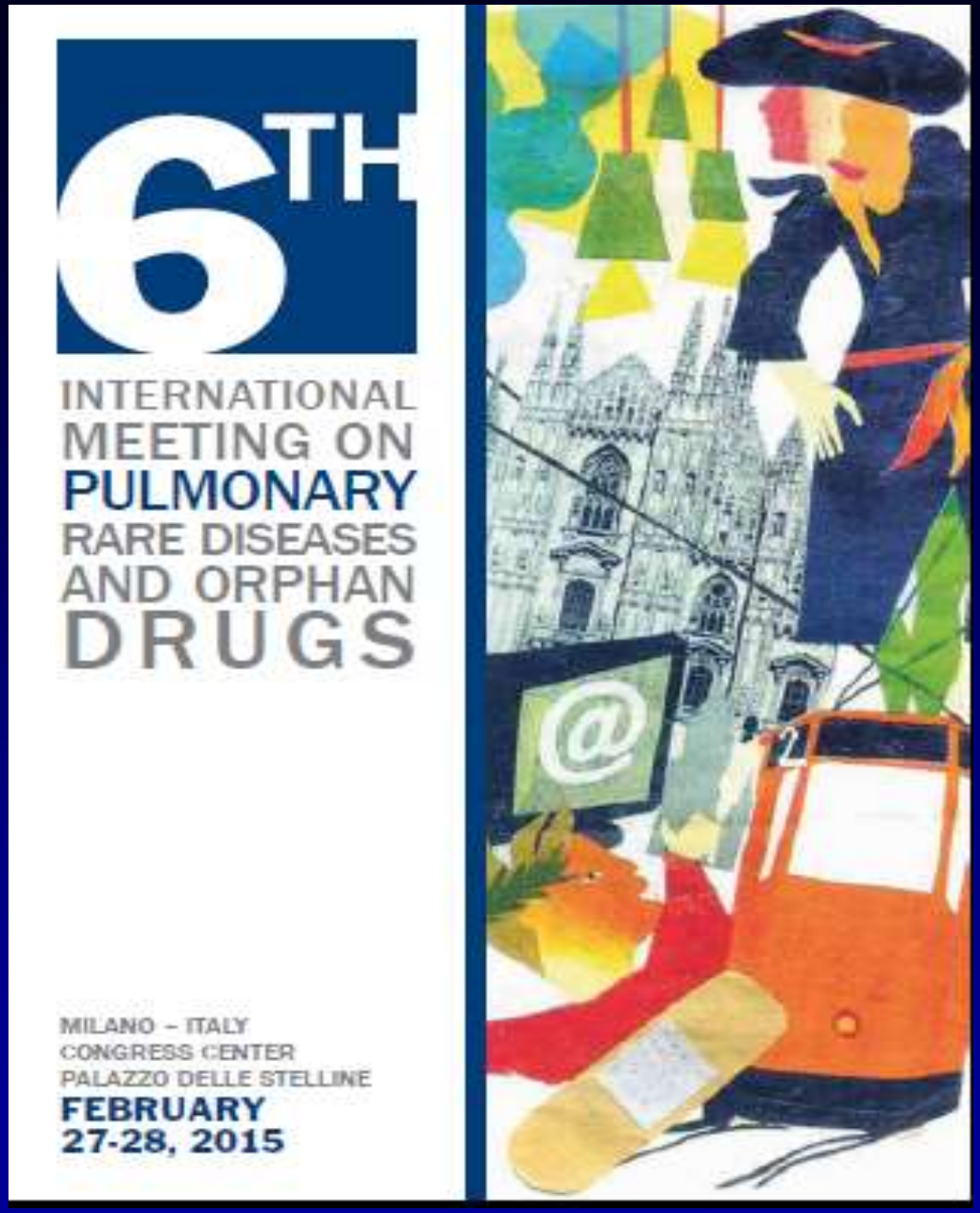
- OSA can be complicated by the development of PH
- PH in the context of OSA has prognostic implications for the patient
- PH in OSA is usually mild-moderate, but sometimes it can be severe
- CPAP treatment can reduce PH values

Conclusions

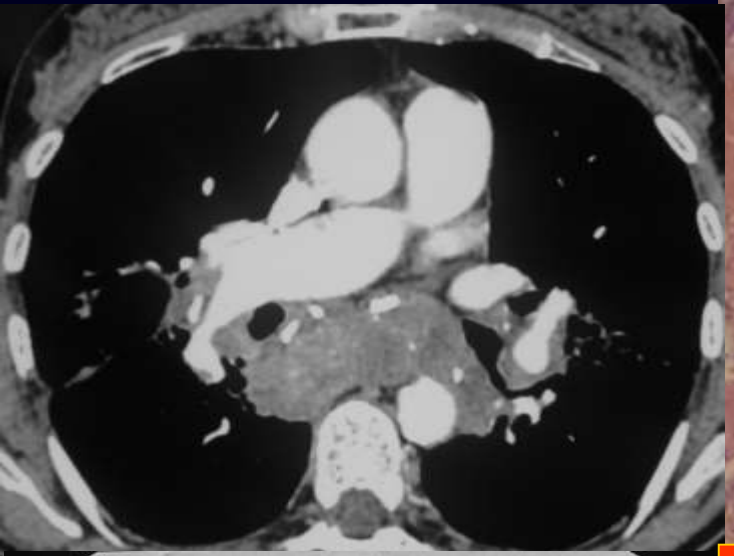
- IPF is commonly complicated by the development of PH
- PH in the context of IPF has functional and prognostic implications for the patient
- There is no sufficient evidence that the drugs currently used for PAH are safe and effective in patients with PH associated with IPF
- Patients with PH and IPF disease should be treated in the setting of clinical trials whenever possible

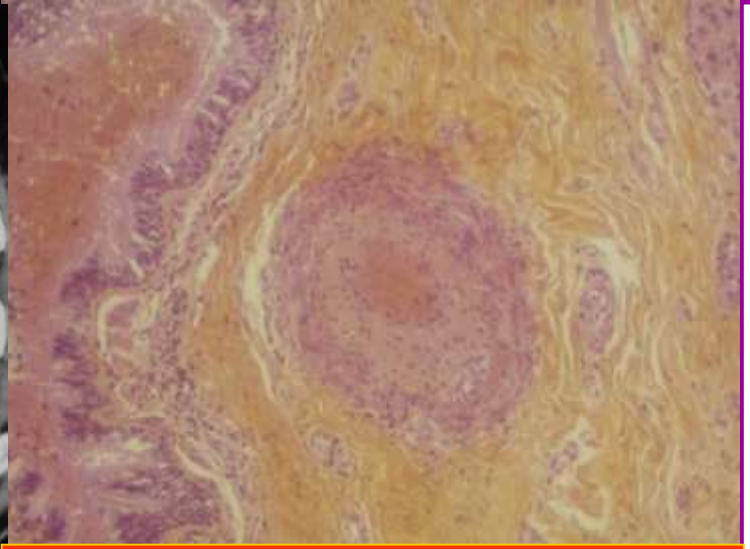
Conclusions

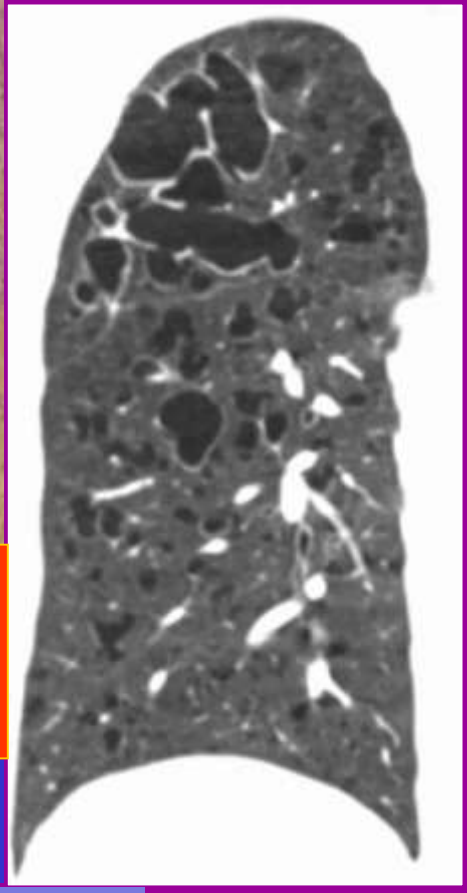
- The use of drugs currently approved for PAH, in patients with IPF is not recommended until further data are available
- Lung transplantation is the best option for these patients

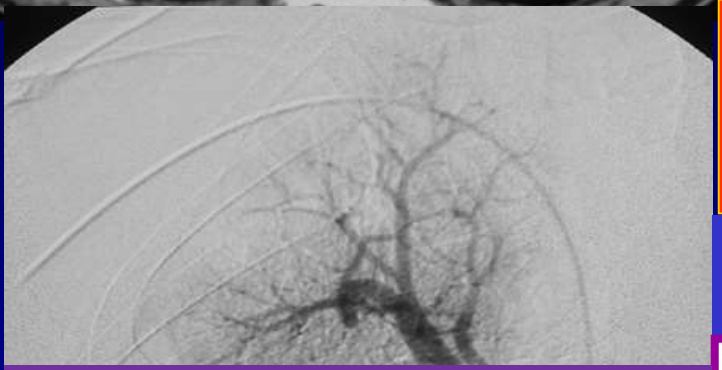


www.pulmonaryrarediseases.com







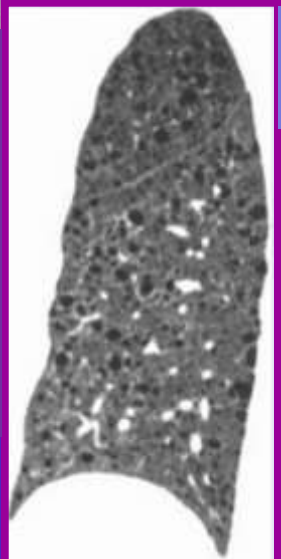


Occlusion of a vascular lumen by intimal hyperplasia and fibrosis

PLCH

PH due to:
-granulomatous vasculitis
-mechanical compression of the large pulmonary artery
-distortion of the vascular bed

Sarcoidosis



LAM

PH in LAM is rare and mild

PULMONARY HYPERTENTION IN LUNG TRANSPLANT CANDIDATES WITH INTERSTITIAL LUNG DISEASE

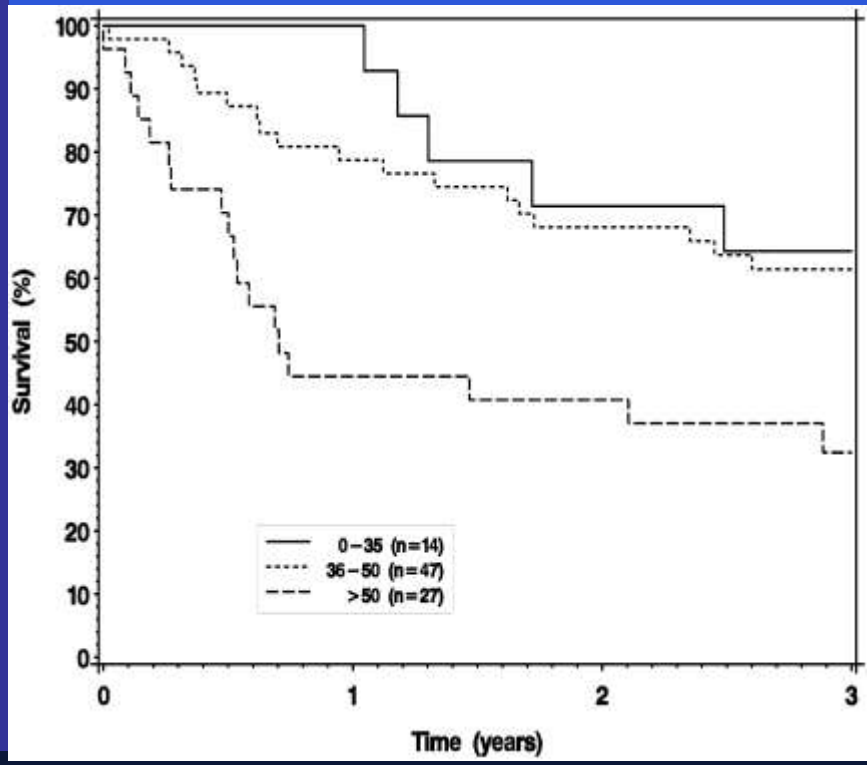
43 IDIOPATHIC FIBROSIS

FEV1	43.6% ± 13.8 S.D.
TLC	52.3% ± 21.7 S.D.
Tiffenau	93.7% ± 18.7 S.D.
PaO2	56.8% ± 14.09 S.D.
PAPm	33.6% ± 9.8 S.D.
C.I.	3.18% ± 0.69 S.D.
PVRi	8.3% ± 3.45 S.D.

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

The impact of pulmonary hypertension on survival in patients with idiopathic pulmonary fibrosis

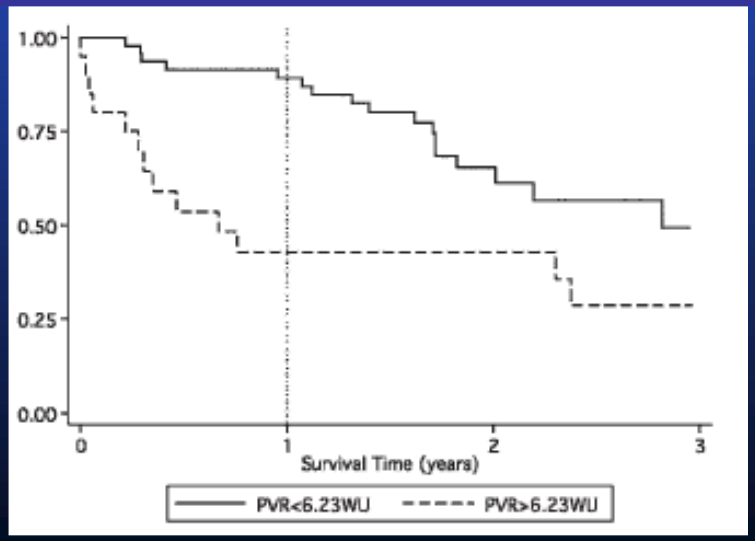
- 88 pts with IPF submitted to EcoCG
- sPAP = 48 ± 16 mmHg
- sPAPs correlated to DLco
- Pts with sPAP > 50 mmHg have bad survival than the others (p=0.009)



Nadrous HF et al. Chest 2005;128:2393-99

Pulmonary vascular resistance predicts early mortality in patients with diffuse fibrotic lung disease and suspected PH

- 66 pts with RVSP > 40 mmHg and/or RVD with dyspnea or hypoxia not correlated to fibrosis
- 50 pts (76%) with mPAP >25 mmHg (mPAP 33.5±11.8 mmHg, PVR 5.9±4.3 Wood units)
- Elevated PVR values are prognostic factor of mortality



	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

Corte TJ. Thorax 2009; 64:883–888.

Sildenafil

CHEST

Sildenafil Improves Walk Distance in Idiopathic Pulmonary Fibrosis*

Harold B. Collard, MD, FCCP; Kevin J. Anstrom, PhD; Marvin I. Schwarz, MD, FCCP; and David A. Zisman, MD, FCCP

(*CHEST 2007; 131:897–899*)

Table 1—*Clinical Characteristics

Variables	Values
Age, yr	72 (7); 71 (63, 85)
Female gender	6 (43)
Smoking history	10 (71)
Duration of symptoms, mo	40.4 (30.0); 34.5 (10, 84)
Surgical lung biopsy-proven disease	6 (43)
Right-heart catheterization performed	10 (71)
Mean PA pressure,† mm Hg	30.7 (5.7); 29.5 (29.0, 43.0)
FVC	
L	2.65 (1.18); 2.39 (0.99, 5.31)
% predicted	69.6 (18.4); 71.5 (41.0, 100.0)
D_{LCO}	
mL/min/mm Hg	7.39 (3.92); 7.25 (2.90, 17.80)
% predicted	32.4 (17.0); 33.0 (13.0, 79.0)

Patient No.	RHC	Dose (tid), mg	6MWD, m			BDI		AEs
			Baseline	Follow-up	Change	Baseline	Follow-up	
1	Y	50	40	60	20	15	13	None
2	Y	50	60	100	40	15	13	None
3	Y	50	382	374	-8	7	7	None
4	N	50	100	140	40	11	13	None
5	N	50	135	95	-40	12	12	None
6	Y	20	55	100	45	12	11	None
7	Y	20	75	90	15	10	7	Headache and diarrhea
8	Y	20	60	185	125	11	9	None
9	N	50	518	525	7	6	6	None
10	Y	20	70	85	15	13	12	Headache
11	Y	40	65	270	205	6	7	Blurry vision
12	Y	40	155			15		Chest pain during follow-up 6MWT†
13	Y	20	105			11		Diarrhea (medication stopped)
14	N	25	250			8		Transient hypotension (medication stopped)

The use of sildenafil to treat pulmonary hypertension associated with interstitial lung disease

TAMERA J. CORTE, MICHAEL A. GATZOULIS, LISA PARFITT, CARL HARRIES, ATHOL U. WELLS AND S. JOHN WORT

Respirology (2010) **15**, 1226–1232

15 ILD pts and PAH submitted to six month-therapy of sildenafil:

1 IPF

5 NSIP

5 Sarcoidosis

2 ILD associated to polymiositis

1 histyocitosis

1 chronic hypersensitivity pneumonia

Table 1 Clinical data before and after 6-month sildenafil therapy

	n	Pre-sildenafil†	*n*	Post-sildenafil†	*P*-value‡
Brain natriuretic peptide (pmol/L)	15	37 (5–452)	12	15.5 (3–220)	0.03§
6MWD (m)	13	156 ± 101	6	256 ± 57	<0.05
Right ventricular systolic pressure (mm Hg)	11	73.8 ± 17.8	11	72.6 ± 28.0	NS
DL_{CO} (%)	14	23.8 ± 12.8	9	26.4 ± 16.5	NS
FVC (%)	14	52.6 ± 15.4	11	55.9 ± 13.8	NS
PaO_2 (kPa)	11	7.3 ± 1.8	9	7.8 ± 2.4	NS

In this retrospective review of intention to treat ILD patients with PH, we report that 6-month oral sildenafil therapy was safe and well tolerated, and was associated with a significant improvement in 6MWD and BNP levels, but no change in echocardiographic haemodynamic values (RVSP). Our results suggest that sildenafil may have a role in the management of PH in ILD patients. However, prospective placebo-controlled trials in patients with PH and ILD are warranted before therapeutic recommendations can be made for this patient group.