IPF: From Pathogenesis to cure

PH in IPF what to do: ERA, PDE5 inhibitors or palliation?

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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 disease**
- 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

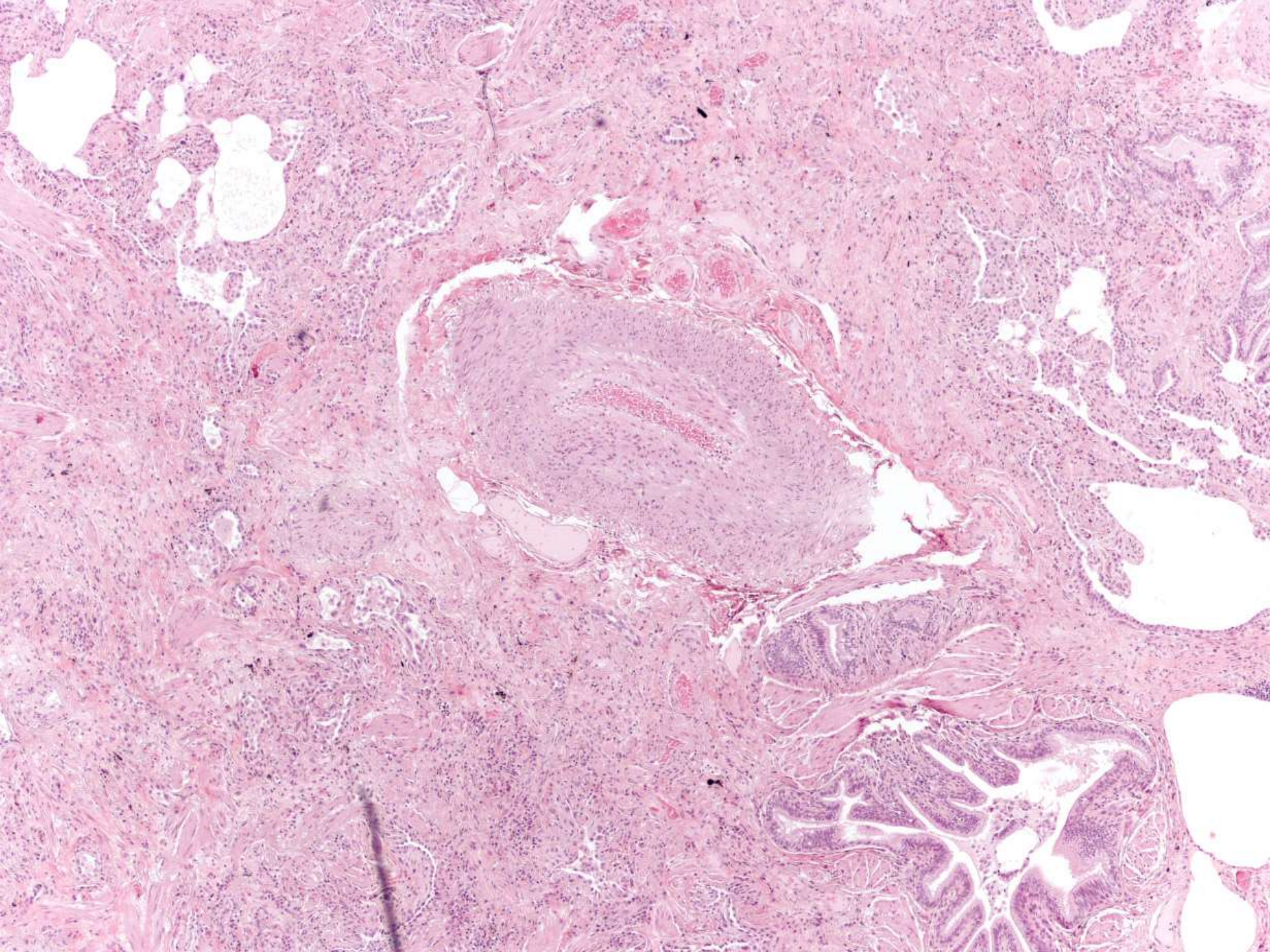
4. Chronic thromboembolic polmonary hypertension (CTEPH)

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

Disorders of the respiratory system and hypoxemia

- PH is generally mild or moderate (PAP < 30 mmHg), is not per se a predominant prognosis factor and not require specific therapeutic intervention (except oxygen therapy)
- Medial hypertrophy and mild intimal fibrosis



Treatment of hypoxic pulmonary hypertension

- Efficacy of vasodilators has never been demonstrated
- Long-term oxygen therapy improves survival in COPD

  24 H > 12 H (NOTT study 1981)

  15 H > 0 H (BMRC study 1981)

  survival improvement due to O_2 is associated with minor changes in PAP
- Beneficial effects of drugs in a subgroup of patients with severe PH?

- 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

Pulmonary hypertension in IPF

- Frequency
- Prognosis
- Diagnosis
- Treatment

How frequent is it?

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

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

Out-of-Proportion PH
Nice definitions 2013

COPD/IPF/CPFE **without PH** : mPAP <25mmHg

COPD/IPF/CPFE **with PH** mPAP >25mmHg;

COPD/IPF/CPFE **with severe** PH

mPAP >35mmHg or mPAP >25mmHg with low cardiac index (CI <2.0 l/min/m2)

Pulmonary hypertension in IPF

- Frequency
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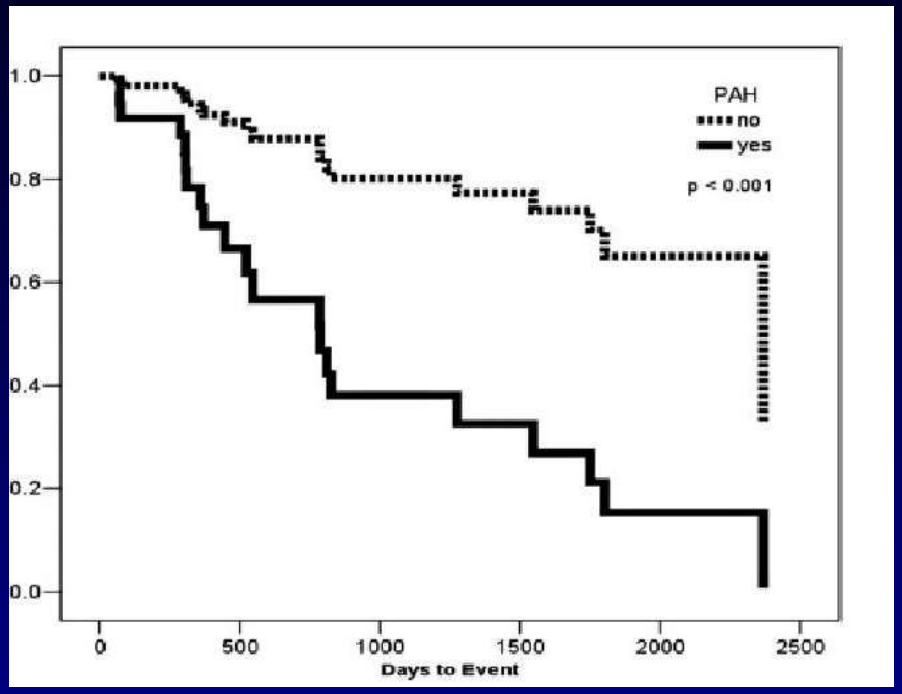
Does it affect the prognosis of IPF?

Pulmonary hypertension in IPF

88 patients with IPF	PASP 0-35 mmHg (n=14)	PASP 36-50 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

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

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

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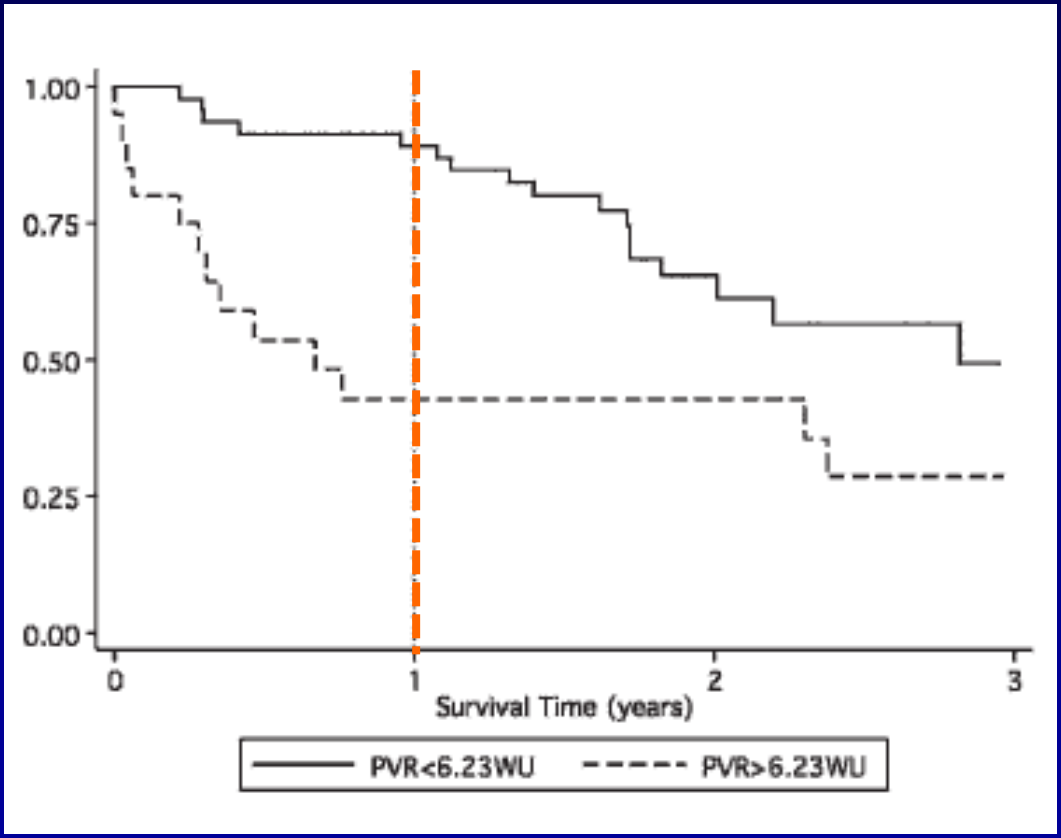


In severe diffuse lung disease, raised PVR strongly predicts death within 1 year independent of disease severity or diagnosis of IPF.

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

Pulmonary hypertension in IPF

- Frequency
- Prognosis
- Diagnosis
- Treatr

How can we investigate these patients?

- PH in IPF patients is more frequent when the underlying fibrosis is severe (secondary PH)
- However, PH may occur in milder disease, raising the possibility of therapeutic intervention
- Thus, screening IPF patients for the early identification of PH is essential

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

Assessment of PH in IPF

Patients with IPF should be evaluated for PH when:

- The symptoms are more severe than one would expect from lung function data (dyspnea and fatigue are symptoms of IPF as well as PH)
- When signs of right heart failure develop
- If clinical deterioration is not matched by a decline in pulmonary function
- Profound hypoxemia, and a low DLCO are indicators of PH

Recommendation for PH due to lung diseases

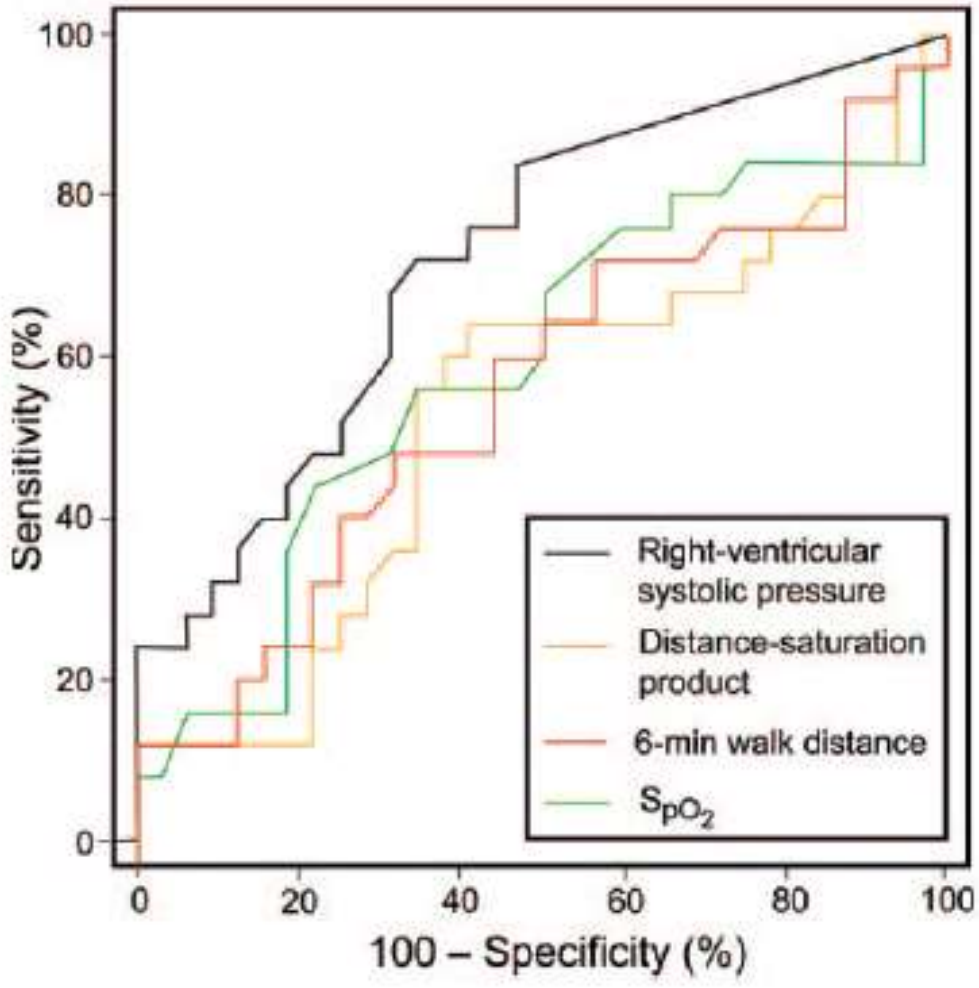
Statement	Class#	Level *f*
Echocardiography is recommended as a screening tool for the assessment of PH due to lung diseases	I	C
RHC is recommended for a definite diagnosis of PH due to lung diseases	I	C
should be enrolled in RCTs targeting PAH specific drugs		
The use of PAH-specific drug therapy is not recommended in patients with PH due to lung diseases	III	C

Once PH is suspected, patients should be evaluated by echocardiography

class of recommendations
f level of evidence

Eur Respir J 2009; 34:1219

Echocardiography, 6-Minute Walk Distance, and Distance-Saturation Product as Predictors of Pulmonary Arterial Hypertension in Idiopathic Pulmonary Fibrosis



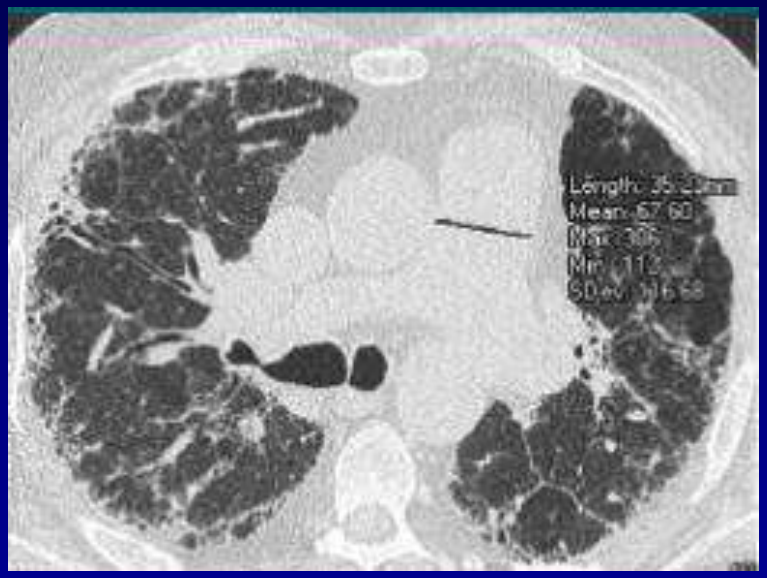
The main findings of this study are:

1. Noninvasive diagnostic tests such as echocardiogram, 6MWT distance, DSP, and SpO2 perform poorly in detecting PH in IPF patients.
2. The diagnostic accuracy of the echocardiogram for the detection of PAH exceeds that of the other variables, with a sensitivity of 72% and a positive predictive value of 62%.
3. The prevalence of PH in our cohort of patients with IPF was 43%.

Modrykamien AM et al. Respir Care 2010; 55: 584

The effect of diffuse pulmonary fibrosis on the reliability of CT signs of pulmonary hypertension

Conclusion: PA dilatation occurs in the absence of PH in patients with pulmonary fibrosis and is therefore an unreliable sign of PH in these patients



Transverse CT scan shows dilatated main PA (diameter 35.23 mm) in 53-year-old patient with IPF and normal PAP

Radiology; 2008; 249:1042-9

Statement	Class#	Level *f*
Echocardiography is recommended as a screening tool for the assessment of PH due to lung diseases	I	C
RHC is recommended for a definite diagnosis of PH due to lung diseases	I	C

Given the limitations of echocardiography, RHC remains the standard for the diagnosis of PH

Patients with "out of proportion" PH due to lung diseases should be enrolled in RCTs targeting PAH specific drugs	IIa	C
The use of PAH-specific drug therapy is not recommended in patients with PH due to lung diseases	III	C

Eur Respir J 2009; 34:1219

Pulmonary hypertension in IPF

- Frequency
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Therapeutic options for PH in IPF are limited

ESC/ERS GUIDELINES

Guidelines for the diagnosis and treatment of pulmonary hypertension

The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and European Respiratory Society (ERS) endorsed by the International Society of Heart and Lung Transplantation (ISHLT)

Statement	Class#	Level *f*
Echocardiography is recommended as a screening tool for the assessment of PH due to lung diseases	I	C
RHC is recommended for a definite diagnosis of PH due to lung diseases	I	C
The optimal treatment of the underlying lung disease including long-term O2 therapy in patients with chronic hypoxaemia is recommended in patients with PH due to lung diseases	I	C

The benefit of reversing intermittent hypoxia (at night or on exercise) is unclear and needs further study

Eur Respir J 2009; 34:1219

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.

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

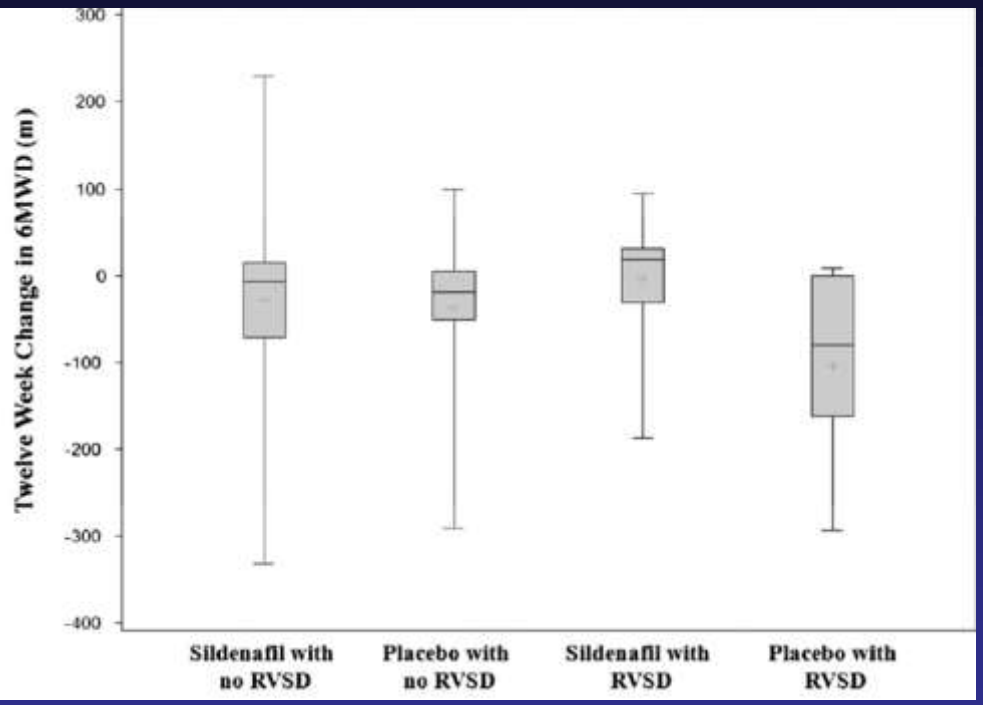
- Of 180 subjects enrolled into STEP-IPF, echocardiograms from 119 were available for independent review (sildenafil, n 56; placebo, n 63)

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

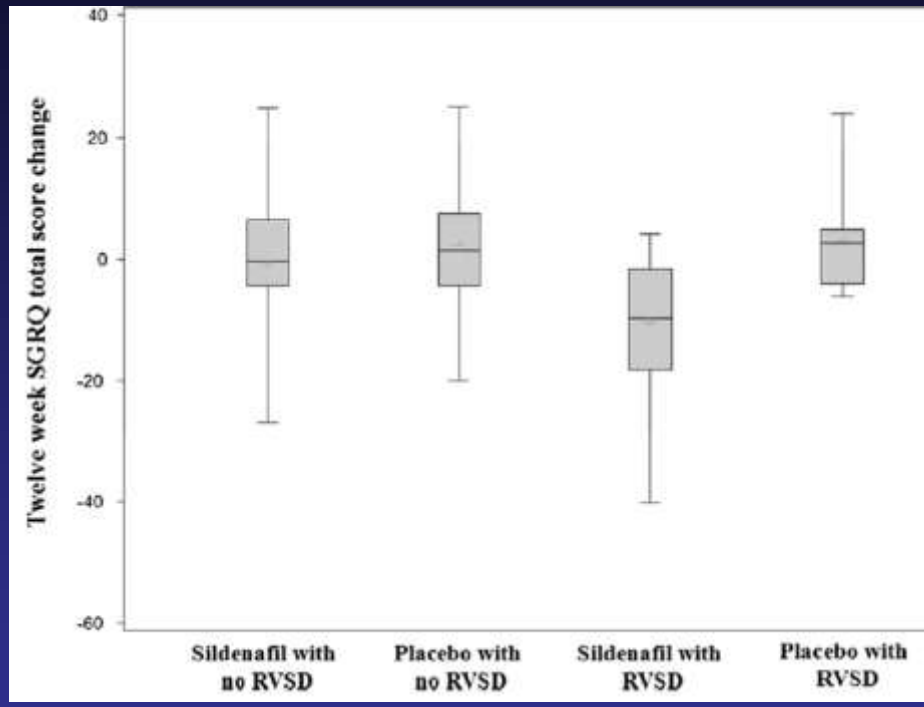
- Multivariable linear regression models estimated the relationship between RV abnormality, sildenafil treatment, and changes in 6MWD,
- St. George's Respiratory Questionnaire (SGRQ), the EuroQol instrument, and SF-36 Health Survey (SF-36) from enrollment to 12 weeks.

Chest 2013; 143 (6): 1699-1708

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



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

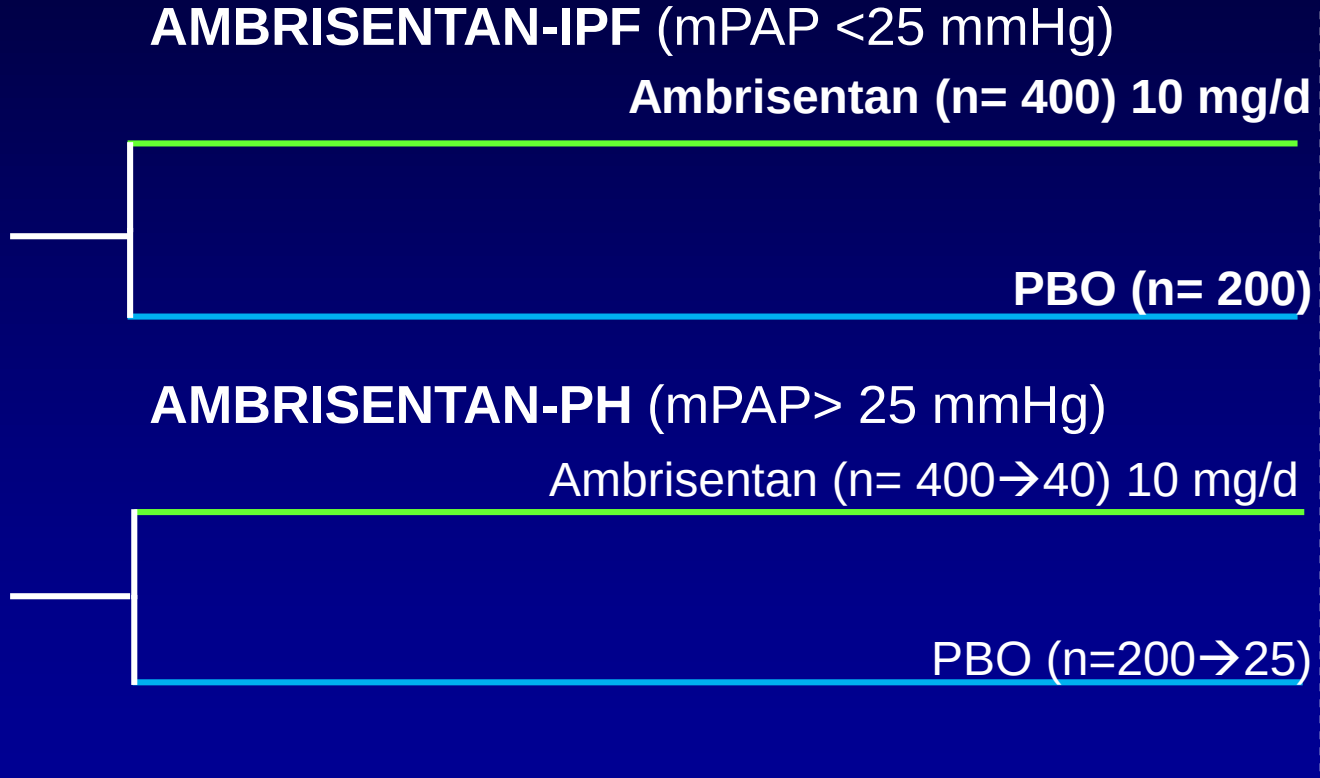


Change in SGRQ total score at 12 weeks by treatment and presence or RVSD

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 mean PAP >25 mm Hg

Second, the 6-MWD, 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; 145: 1087

Out-of-proportion pulmonary hypertension

A paradigm for rare diseases

Out-of-proportion PH is a gray area of medicine that needs further clarification on some issues.

First of all, we need to clarify whether a mean PAP of 35 mm Hg is the adequate value to define this category of patients, or whether another cutoff should be selected.

Secondly, we need to clarify if we should consider only patients with minor pulmonary function abnormalities and moderate to severe PH as potential candidates for PH therapies.

Harari S. Chest, 2012; 145: 1087

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

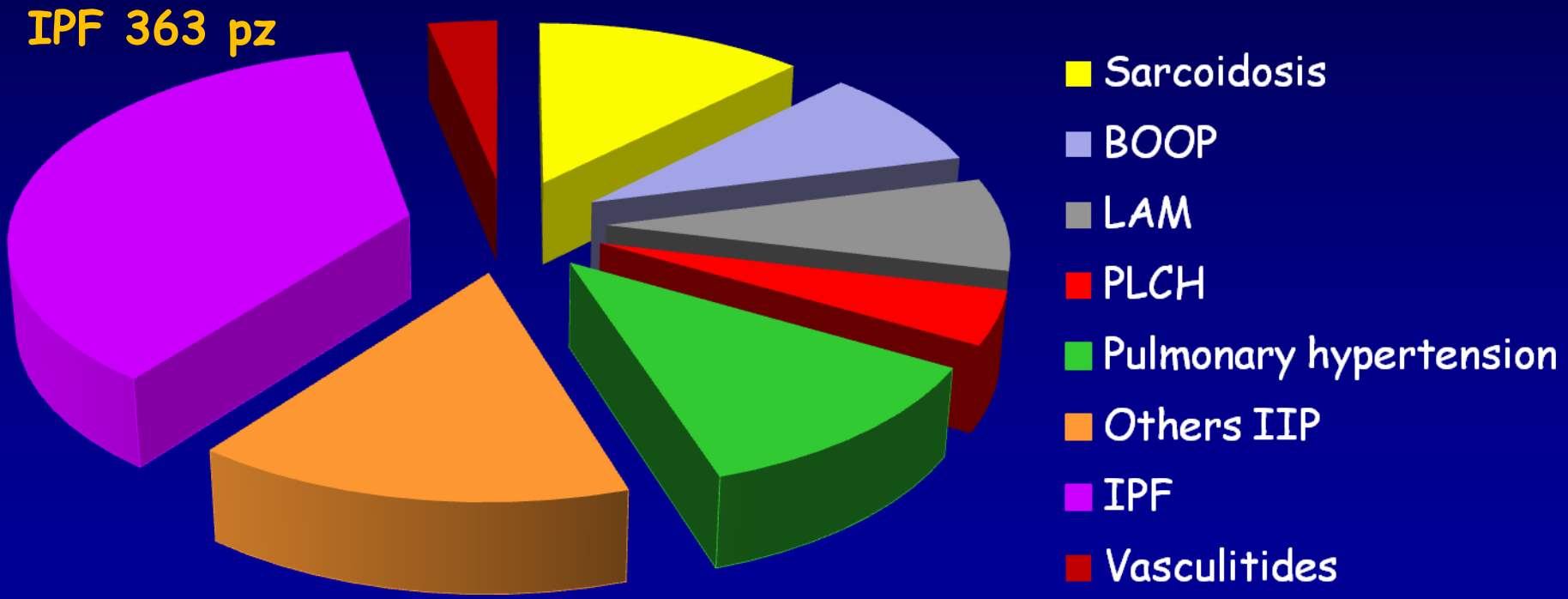
Intervention: patients received oral riociguat (1.0–2.5 mg three times daily) for 12 weeks (n=22), followed by an ongoing long-term extension (interim analysis at 12 months) in those eligible (n=15)

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.

Pulmonary rare diseases

Ospedale San Giuseppe Experience (2001- 2012)

Tot. 996 patients



RHC and 6MWD in IPF

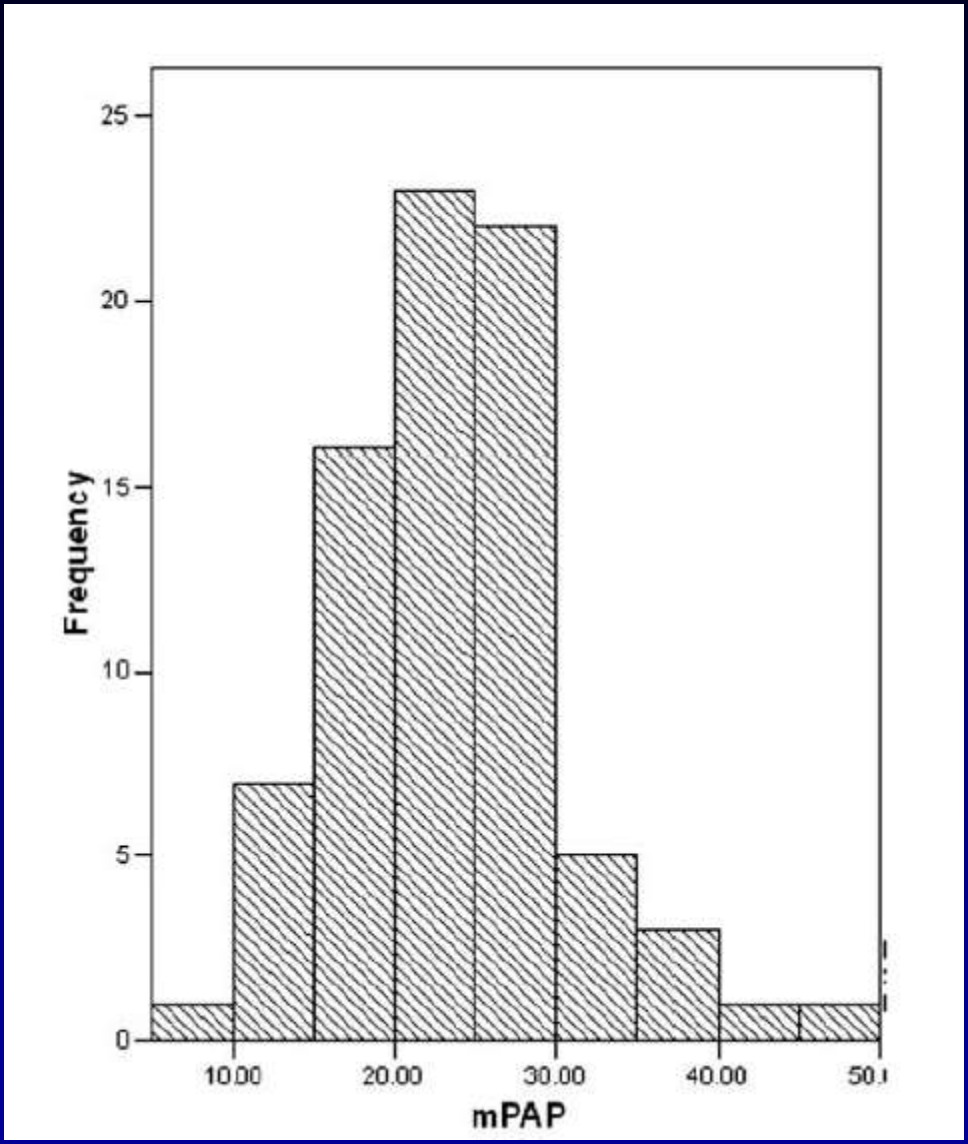
Variables	MAP ≤ 25 mmHg (n= 17)	MAP > 25 mmHg (n= 13)	MAP > 35 mmHg (n= 4)	P value
MPAP, mmHg	19.4 ± 3.6	32.4 ± 6	40,5 ± 2,6	NA
6MWT distance, m	222.0 ± 118.5	222.3 ± 118.5	203.7 ± 128.3	>0.1
FVC, %	51.6 ± 13.8*	63.8 ± 16*	56.0 ± 6.7	<0.05
FEV1, %	58.3 ± 16.3	65.8 ± 18.8	55.2 ± 3.7	>0.05
DLCO, %	31.4 ± 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. Sarcoidosis in press

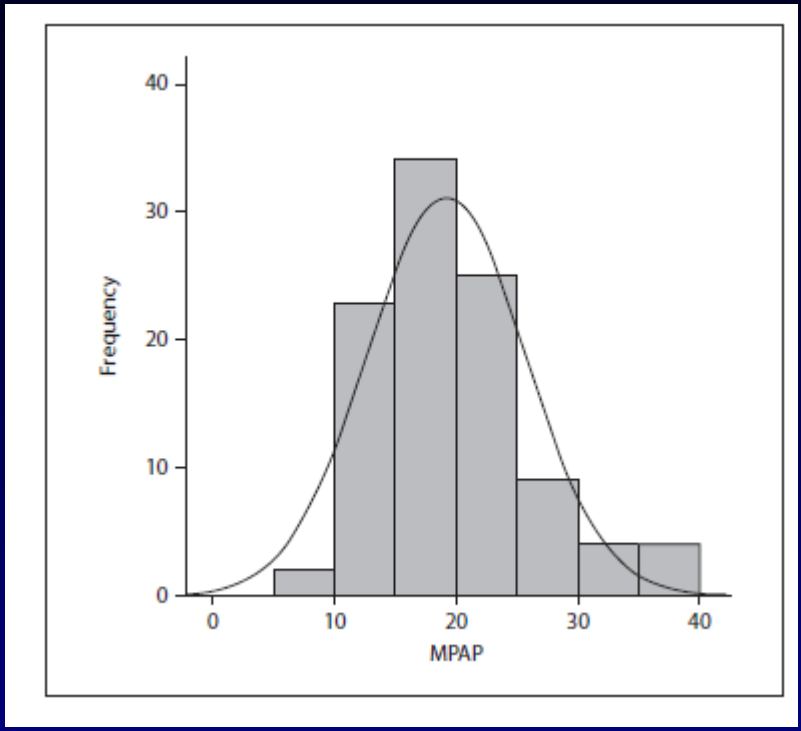
Our data suggest that meters walked during 6MWT are not statistically different in IPF patients with - without PH or with out of proportion PH.

6MWD should not be used as surrogate end point in clinical study in IPF-PH pts.

Harari S. Sarcoidosis in press



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



Kimura M et al. Respiration 2012

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 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

1-yr survival was 60%.

Higher pulmonary vascular resistance, higher heart rate, lower cardiac index and lower carbon monoxide diffusion transfer were associated with shorter survival.

Conclusion: Patients with CPFE and PH confirmed by RHC have a dismal prognosis despite moderately altered lung volumes and flows and moderately severe haemodynamic parameters.

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 the present study 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.

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Echocardiography is recommended as a screening tool for the assessment of PH due to lung diseases	I	C
RHC is recommended for a definite diagnosis of PH due to lung diseases	I	C
The optimal treatment of the underlying lung disease including long-term O2 therapy in patients with chronic hypoxaemia is recommended in patients with PH due to lung diseases	I	C
Patients with "out of proportion" PH due to lung diseases should be enrolled in RCTs targeting PAH specific drugs	IIa	C
The use of PAH-specific drug therapy is not recommended in patients with PH due to lung diseases	III	C

Eur Respir J 2009; 34:1219

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Eur Respir J 2009; 34:1219

The Question: *PH in IPF what to do: ERA, PDE5 inhibitors or palliation?*

The Answer: *Palliation- oxygen therapy, diuretics, etc.. We need well designed clinical trial to evaluate response to therapy of selected IPF population of patients*