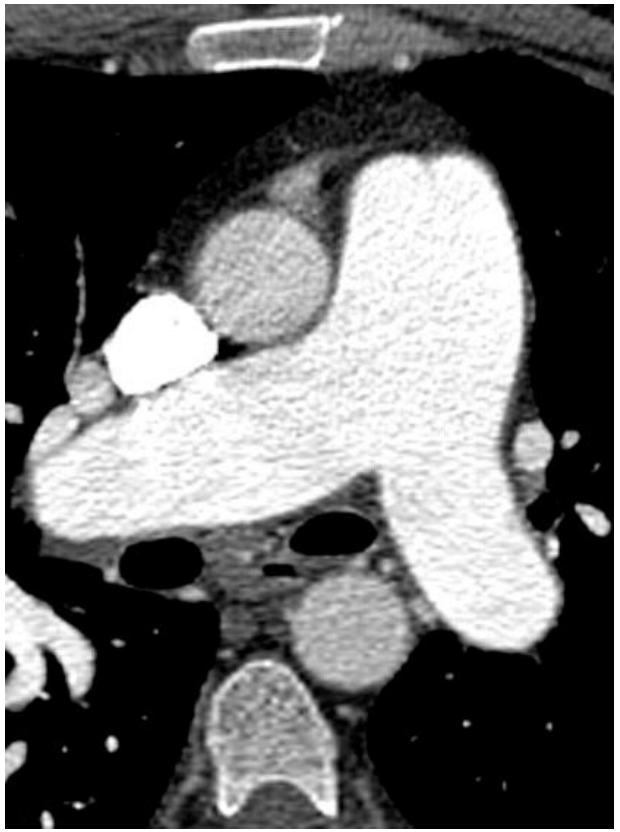
Πνευμονική Υπέρταση και IPF



2ο Πανελλήνιο Συνέδριο Πνευμονικής Υπέρτασης
17-06-18

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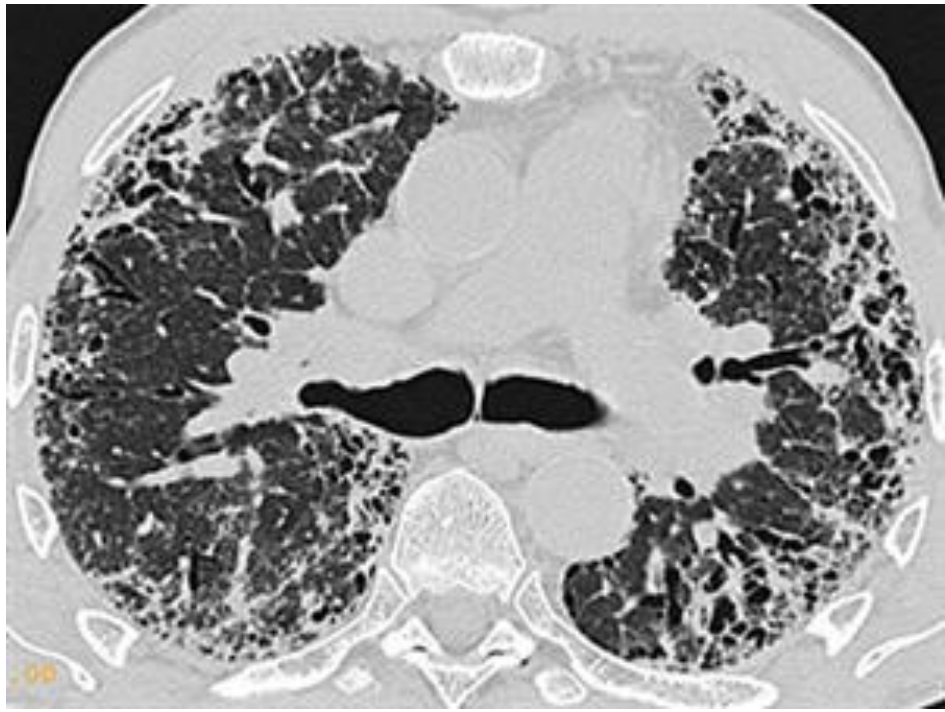

IPF and comorbidities

- IPF and emphysema – CPFE (30-60%)
- **IPF and Pulmonary Hypertension (10-80%)**
- IPF and Lung cancer (15%)
- IPF and GERD (80%)
- IPF and sleep apnea (6-10%)
- IPF and ischemic heart disease (30%)
- IPF and hypothyroidism (10%)
- IPF and depression (25%)

Raghu et al. Eur Respir J 2015. ;46: 1113-1130

Collard et al. Frontiers Med 2017 ;4: 123

Classification of PH-Nice 2013

1. Pulmonary arterial hypertension

1.1 Idiopathic PAH

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

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sion

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mia,

stiocytosis,

, Gaucher

tinitis,

chronic renal failure, segmental PH

tract obstruction and congenital cardiomyopathies

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

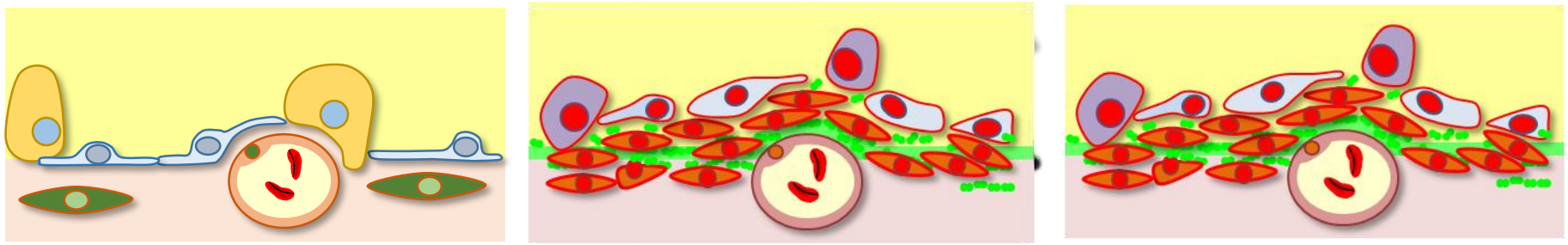
Simonneau G et al. J Am Coll Cardiol 2013;62:D34-41

Are there any mechanistic commonalities?
Balance of pulmonary hemodynamics and fibrotic lung remodeling

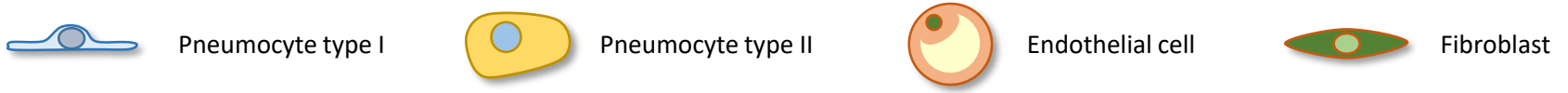
IPF pathogenesis

Alveolar physiological state → **Usual Interstitial Pneumonia Lesion**

Recurring microinjuries → Epithelial cells apoptosis → Epithelial & fibroblast activation → Matrix remodeling → Cell proliferation and migration



PH=Adaptation? – Hypoxic vasoconstriction – Destruction of pulmonary vascular bed?
Ventilatory impairment does not correlate with Hemodynamic Impairment



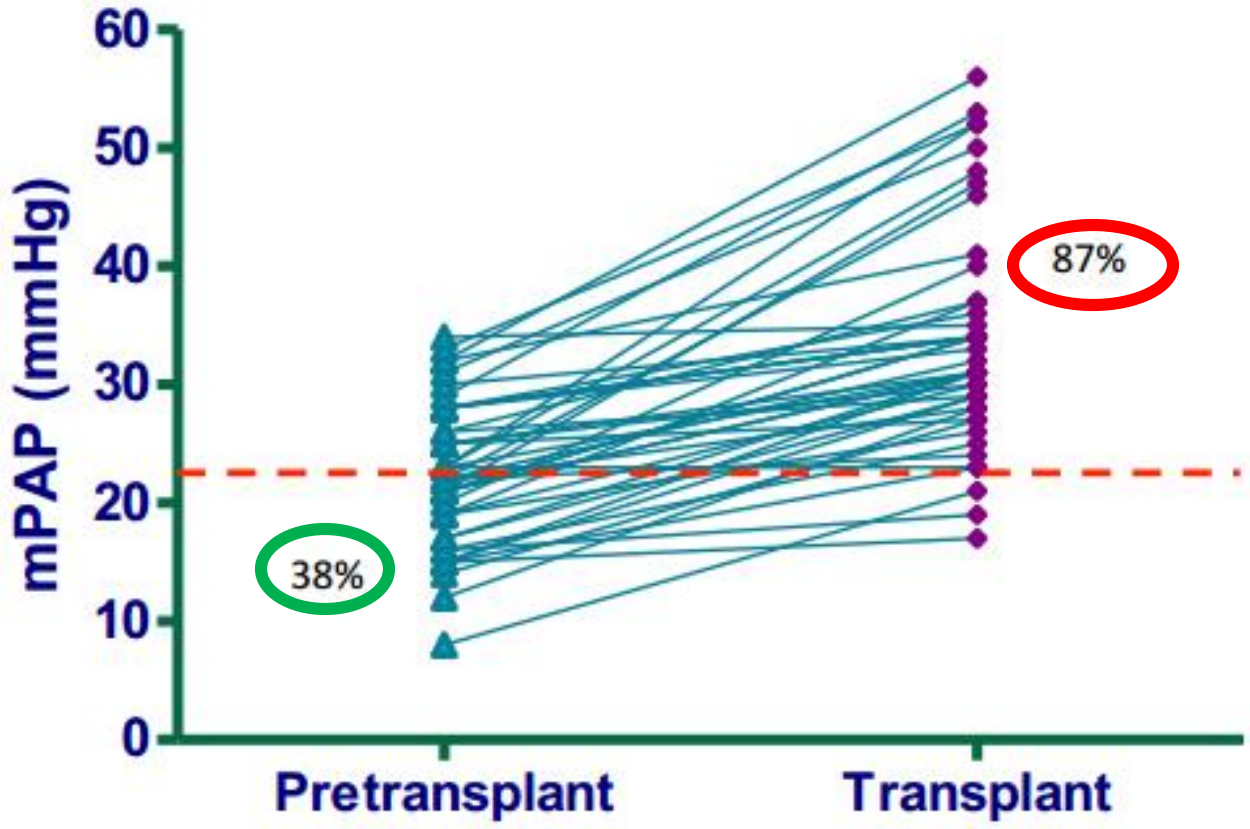
Is PH prevalent in IPF patients?

Author	Year	Patients	Diagnosis	Threshold	Prevalence (%)
Leuchte et al	2004	28	RHC	mPAP>35 mmHg	21.4
Nadrous et al potential for substantial selection bias	2005	88	Echo	sPAP>35 mmHg sPAP>50 mmHg	84 31
Lettieri et al Referred for transplantation	2006	79	RHC	mPAP>25 mmHg	31.6
Hamada et al Initial presentation-pro	2007	70	RHC	mPAP>25 mmHg	8.1
Nathan et al.	2008	118	RHC	mPAP>40 mmHg	40.7
Song et al	2009	131	Echo	mPAP>40 mmHg	25.2
Minai et al abstract	2009	148	RHC	mPAP>25 mmHg mPAP>40 mmHg	46 14
Kimura et al* Initial presentation-retro	2013	101	RHC	mPAP>25 mmHg	15
Raghu	2015	488	RHC	mPAP>25 mmHg	14

1. Disease stage
2. Diagnostic modality
3. mPAP threshold

Does PH affect IPF survival?

Natural course = Progression



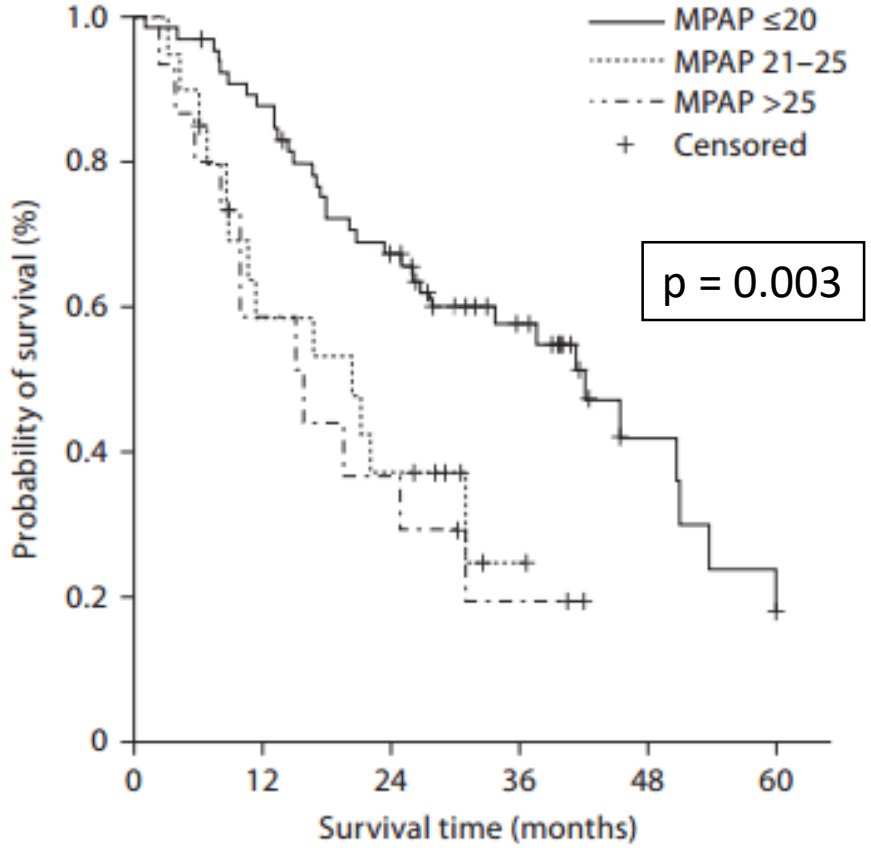
Nathan SD, et al. Respir Med. 2008;102:1305-1310.

Negative prognostic factor irrespective of disease severity

Initial Presentation

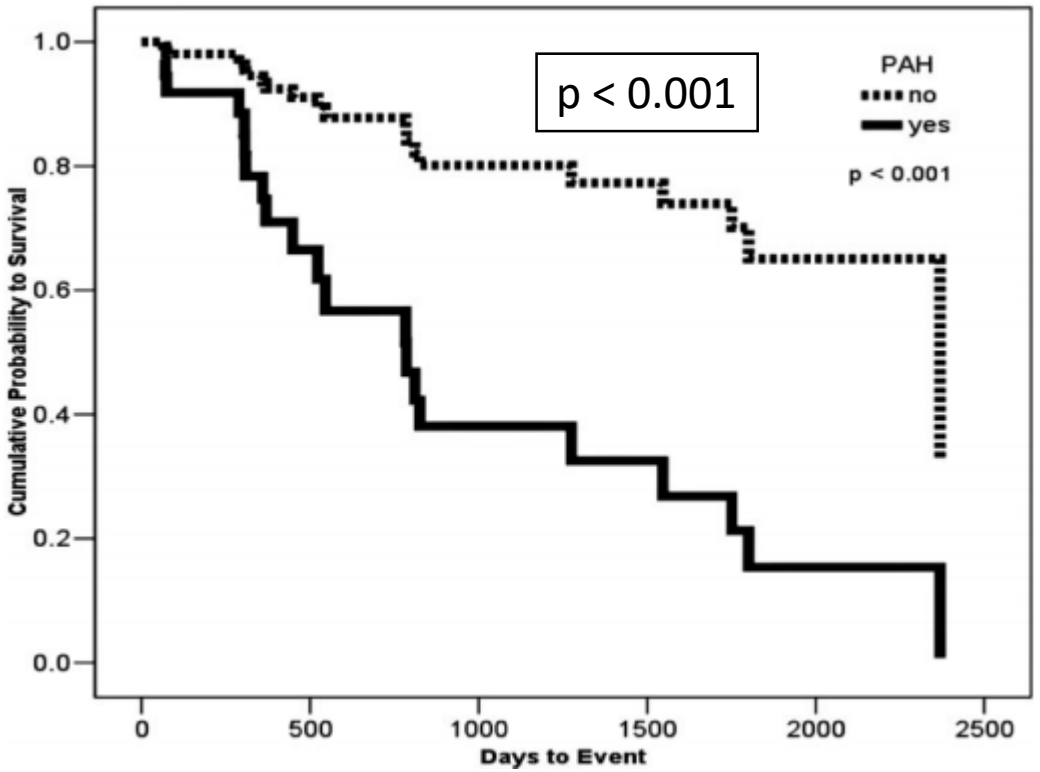
1 yr mortality w/o PH = 5%
1 yr mortality w PH = 35%

Advanced disease – Pre-lung Tx



Number at risk						
MPAP ≤20	66	57	41	22	7	4
MPAP 21–25	20	11	7	1	0	0
MPAP >25	15	8	5	2	0	0

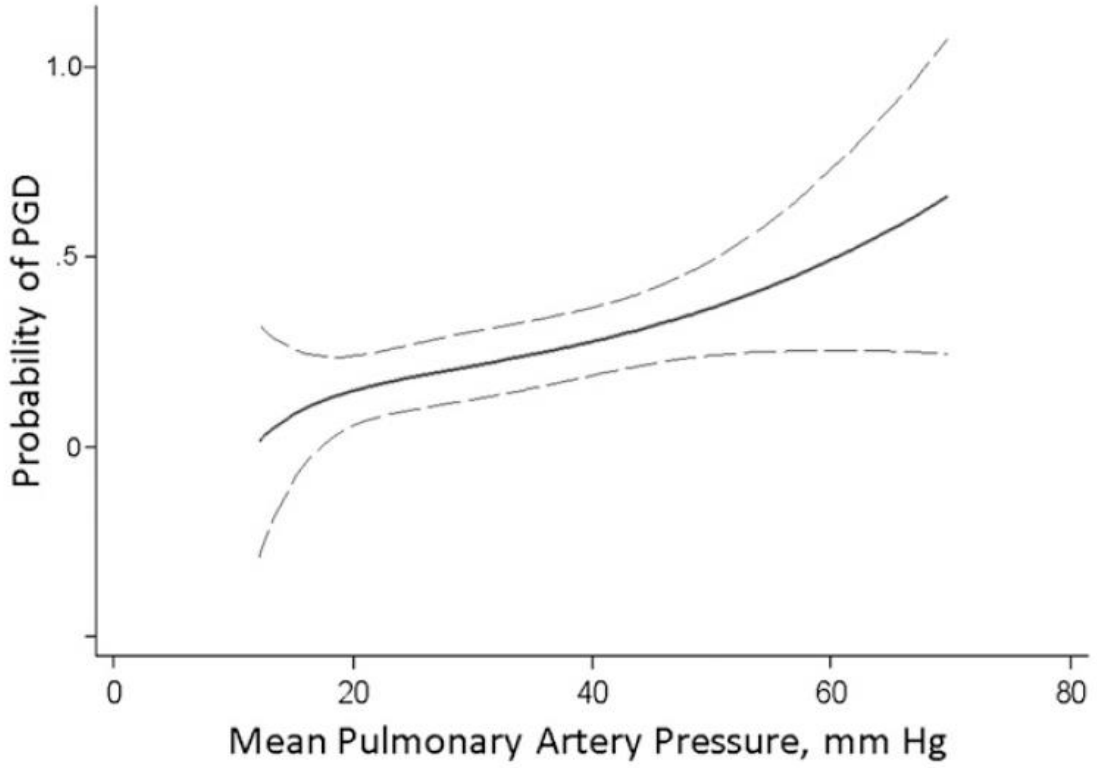
Kimura M et al. Respiration 2013;85:456-63



Lettieri C, et al. Chest 2006; 126:746-752

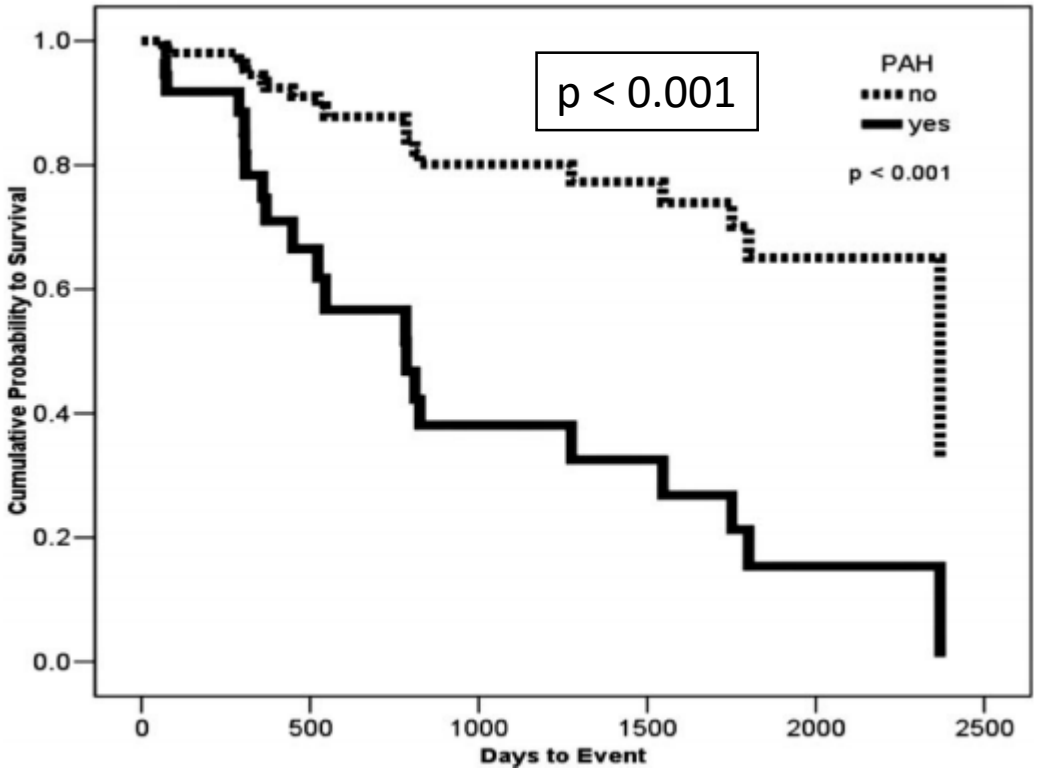
Negative prognostic factor for Lung Tx and QoL

Lung Tx



Fang M et al. Chest 2011;139 (4) :782-87

QoI



Lettieri C, et al. Chest 2006; 126:746-752

When to suspect PH in IPF

- **History**

✓Dyspnea disproportionate to the extent of IPF

- **Physical examination**

✓Symptoms and signs of right heart failure

- **Blood tests**

✓Elevated BNP, pro-BNP

- **Pulmonary function test**

✓DLco<40%

✓FVC%/DLco%>1.5

- **6 Minute Walk Test**

✓Distance <200m

✓SpO2<88%

✓Pulse rate recovery <13 beats/min

- **HRCT**

✓Ratio of PA/AA>1

- **Echocardiography**

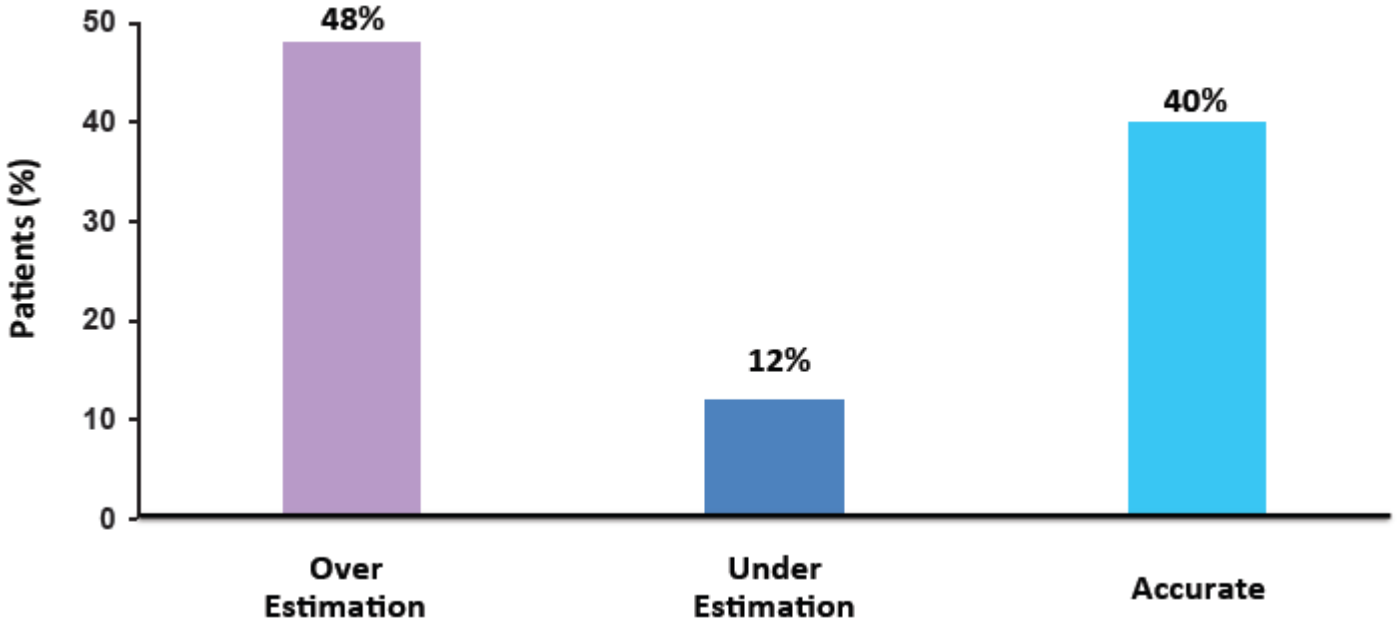
✓Elevated RVSP

✓RV/PA dilation

✓RV dysfunction

Do not forget to screen for other IPF or age-related comorbidities linked with PH (OSA, diastolic dysfunction, Thromboembolic disease)

Diagnostic accuracy of Echo



- ✓ 110 IPF patients examined by ECHO and RHC
- ✓ $RVSP_{ECHO}$ vs $PASP_{RHC}$

35% of IPF pts have emphysema!!
Poor acoustic window - Hyperinflation

Nathan SD, et al. Respir Med. 2008;102:1305-1310

Arcasoy SM, et al. Am J Respir Crit Care Med. 2003;167:735-40

Echo yield is decreased as PH progresses

$RVSP_{echo}$ (mmHg)	Diagnostic and 95% CI		Positive Predictive Value	Negative Predictive Value
	Sensitivity	Specificity		
$RVSP_{echo}$ > 30	86.4 (69.8-95.0)	13.2 (3.3-30.9)	34.4	64.8
$RVSP_{echo}$ > 35	86.4 (69.8-95.0)	28.9 (14.1-47.8)	39.0	80.1
$RVSP_{echo}$ > 40	72.7 (51.6-87.1)	44.7 (26.7-63.0)	40.9	75.7
$RVSP_{echo}$ > 45	59.1 (38.7-76.8)	52.6 (33.5-69.8)	39.6	70.9
$RVSP_{echo}$ > 50	50.0 (30.7-69.3)	68.4 (48.3-82.9)	45.5	72.0
$RVSP_{echo}$ > 55	40.9 (23.2-61.3)	84.2 (60.4-91.6)	57.7	73.0
$RVSP_{echo}$ > 60	27.3 (12.9-48.4)	92.1 (73.9-98.9)	64.5	70.6

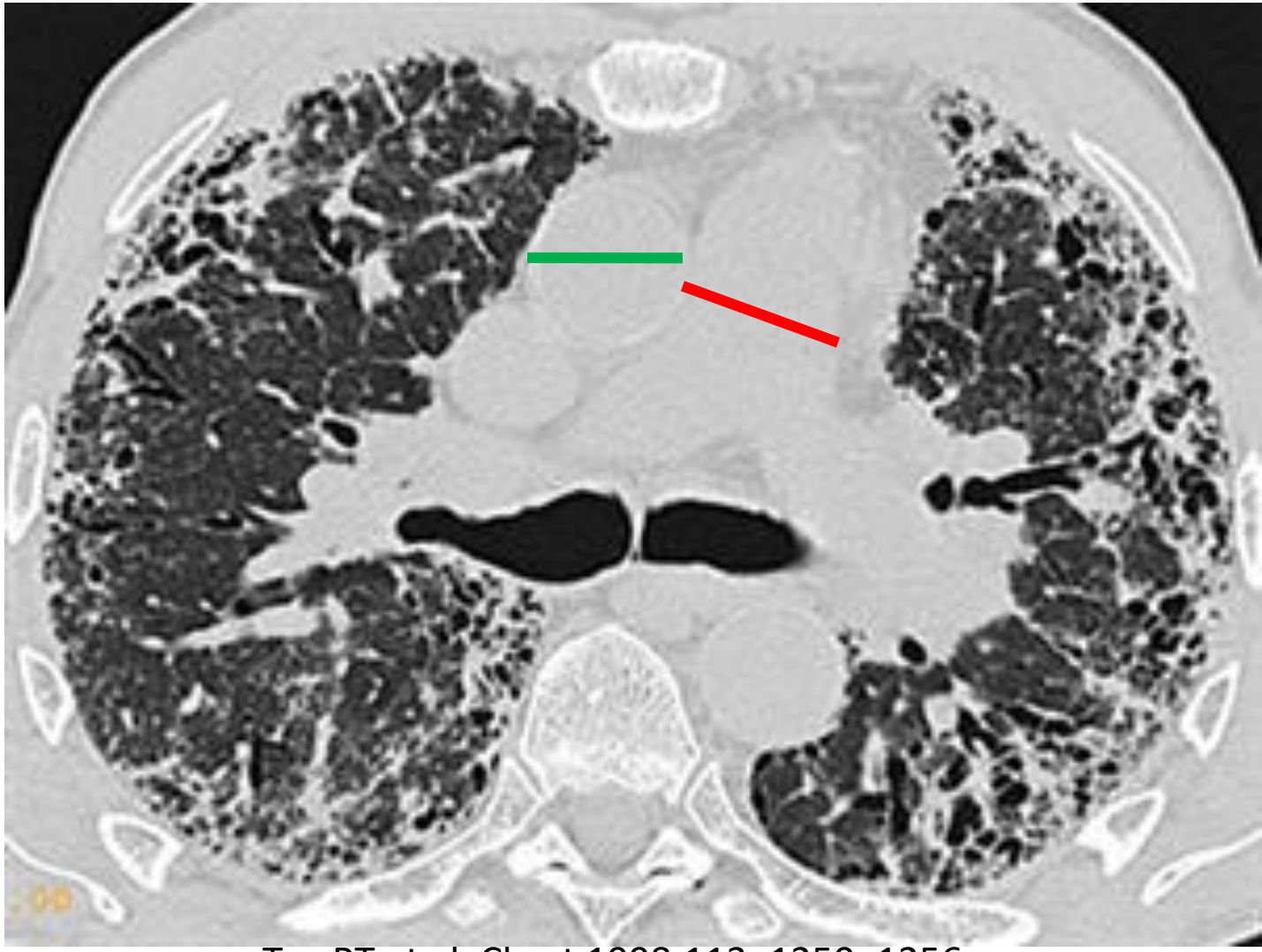
Nathan SD, et al. Respir Med. 2008;102:1305-1310

CT yield for PH diagnosis

- Pulmonary artery diameter ≥29 mm:

✓Positive predictive value: 97%

- In patients with pulmonary fibrosis, the PA dilates in the absence of PH.
- **dAA/dPA>1 is a more reliable indicator of PH**



Tan RT et al. Chest 1998;113: 1250–1256
Devaraj A. Radiology 2008;249:1042–1049

Role of Brain Natriuretic Peptide (BNP)

- 39 patients (28 IPF) underwent RHC, 6MWT, PFT
- Normal BNP (≤18pg/mL, n=16,) versus elevated BNP (n=12)
- Significant correlation with:
- mPAP (r=0.74)
- CO (r=-0.57)
- PVR (r=0.8)
- 6MWT (r=-0.40)
- No correlation with PFT parameters

Prognostic Usefulness only!!!Limited use……

Leuchte HH et al. Am J Respir Crit Care Med 2004;170:360–365

Special considerations

Disproportionate PH – Group 1 or 3?

One size (RVSP-mPAP, CI, PVR, sPAP) might not fit all!!!

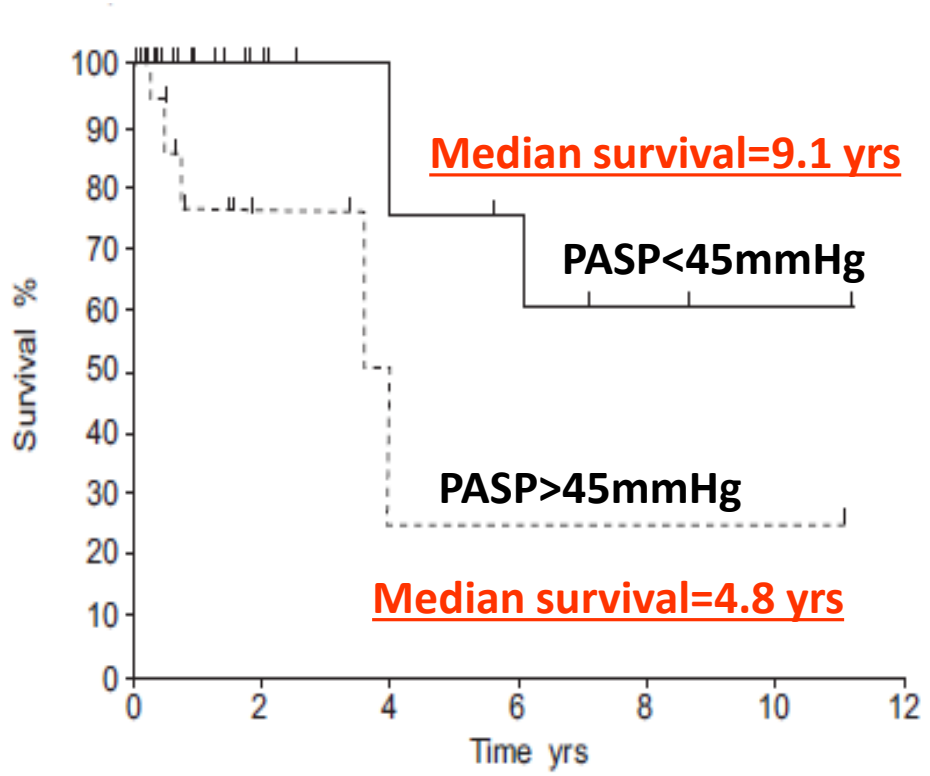
Criteria Favoring Group 1 (PAH)	Parameter	Criteria Favoring Group 3 (PH Due to Lung Disease)
Normal or mildly impaired	Ventilatory function	Moderate to very severe impairment
FEV1 >60% predicted (COPD)		FEV1 <60% predicted (COPD)
FVC >70% predicted (IPF)		FVC <70% predicted (IPF)
Absence of or only modest airway or parenchymal abnormalities	High-resolution CT scan*	Characteristic airway and/or parenchymal abnormalities
Features of exhausted circulatory reserve		Features of exhausted ventilator reserve
Preserved breathing reserve		Reduced breathing reserve
Reduced oxygen pulse		Normal oxygen pulse
Low Co/Vo_2 slope		Normal Co/Vo_2 slope
Mixed venous oxygen saturation at lower limit		Mixed venous oxygen saturation above lower limit
No change or decrease in $PaCo_2$ during exercise		Increase in $PaCo_2$ during exercise

Sometimes, in patients with mild ventilatory impairment and severe PH, the distinction between group 3 and group 1 PH is elusive and represents a diagnostic dilemma

Seeger W, et al. J Am Coll Cardiol 2013;62:D109–16
ERS/ESC guidelines. Eur Heart J. 2015

CPFE and PH

Prevalence: 28-80% by echo, 68% by RHC (mPAP> 35 mmHg)



Cottin et al. Eur Respir J. 2010;35(2):105-11 Sugino K et al. Respirology. 2014;19(2):239-45 Mejıa M, et al. Chest 2009; 136: 10

Therapeutic approaches

Target the PH or IPF? or both?

A Controlled Trial of Sildenafil in Advanced Idiopathic Pulmonary Fibrosis

N Engl J Med 2010;363:620-8.

- **180 patients with advanced IPF – 1 year sildenafil (60 mgr) vs placebo**
- **No effect in primary end-point (6-MWD) – Negative study!!!!!!**
- **Positive secondary end-points (QoL, Dyspnea, DLCO)**

Major Clinical trials in Patients with IPF-PH

Therapy	Study	Year	Study population	Duration	Primary end point	Result
Bosentan	BUILD-1	2008	IPF-158 (1/1)	52 weeks	6MWD	Negative
Bosentan	BUILD-3	2011	IPF-616 (2/1)	52 weeks	Time to IPF worsening or death	Negative
Bosentan	B-PHIT	2014	Fibrotic IIP-60 (2/1)	16 weeks	Decrease in PVRi≥20%	Negative
Macitentan	MUSIC	2013	IPF-178 (2/1)	52 weeks	%change in FVC	Negative
Ambrisentan	ARTEMIS	2013	IPF-492 (75%) (2/1)	n/a	Time to IPF disease progression	Early termination
Sildenafil	STEP	2010	Adv. IPF-180 (1/1)	12 weeks	6MWD≥20%	Negative
Riociguat	RISE-IIP	2017	Major IIPs	26 weeks	6MWD	Early termination

Do not dilate remodeled vessels!!

Worsens V/Q mismatch w/o CO improvement

Management of PH in IPF

- **Best supportive care**

✓LTOT to maintain arterial oxygen saturation> 90%

✓Diuretics

- **Referral for lung transplantation**
- **Enroll in clinical trials!!**

What lies in the future?

Need for treatment

Imatinib in Pulmonary Arterial Hypertension Patients with Inadequate Response to Established Therapy

Hossein A. Ghofrani[1], Nicholas W. Morrell[2], Marius M. Hoeper[3], Horst Olschewski[4], Andrew J. Peacock[5], Robyn J. Barst[6], Shelley Shapiro[7], Heiko Golpon[3], Mark Toshner[2], Friedrich Grimminger[1], and Steve Pascoe[8]

Am J Respir Crit Care Med Vol 182. pp 1171–1177, 2010
Originally Published in Press as DOI: 10.1164/rccm.201001-0123OC on June 25, 2010

- 24 week – 59 patients
- 29% dropout!!!!!
- No effect in 6MWD – Decrease in PVR – Increase in CO

Conclusions: These data from a Phase II study are consistent with imatinib being well tolerated in patients with PAH, and provide proof of concept for further studies evaluating its safety, tolerability, and efficacy in PAH.

FEATURED ARTICLES

Long-term safety and efficacy of imatinib in pulmonary arterial hypertension

- **Extension trial – 204 weeks -144 patients**
- **93% drop outs!!!**
- **6 hematomas – 17 deaths!!!**

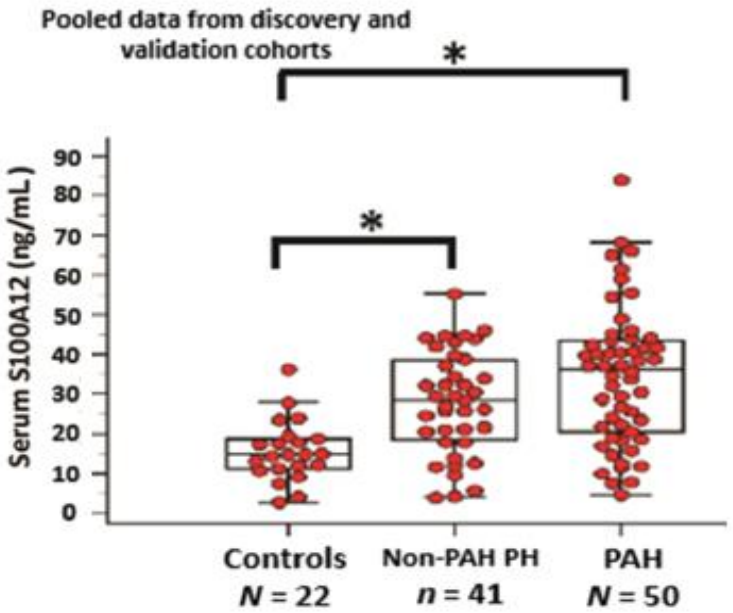
CONCLUSIONS: Severe adverse events, significant side effects, and a high discontinuation rate limit the utility of imatinib in the treatment of PAH. These risks outweigh any possible improvements in hemodynamics and walk distance seen in those patients able to remain on drug. The off-label use of this compound in PAH is discouraged.

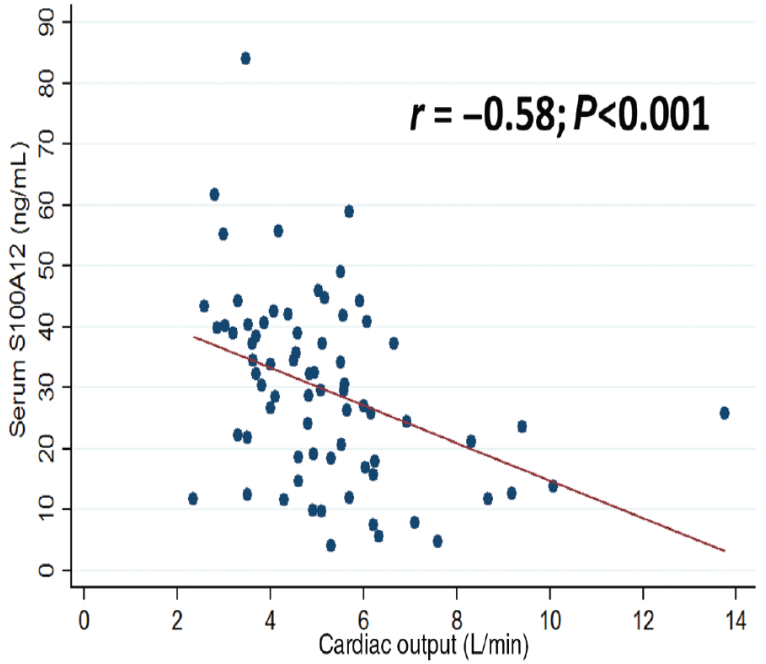
J Heart Lung Transplant 2015;34:1366–1375

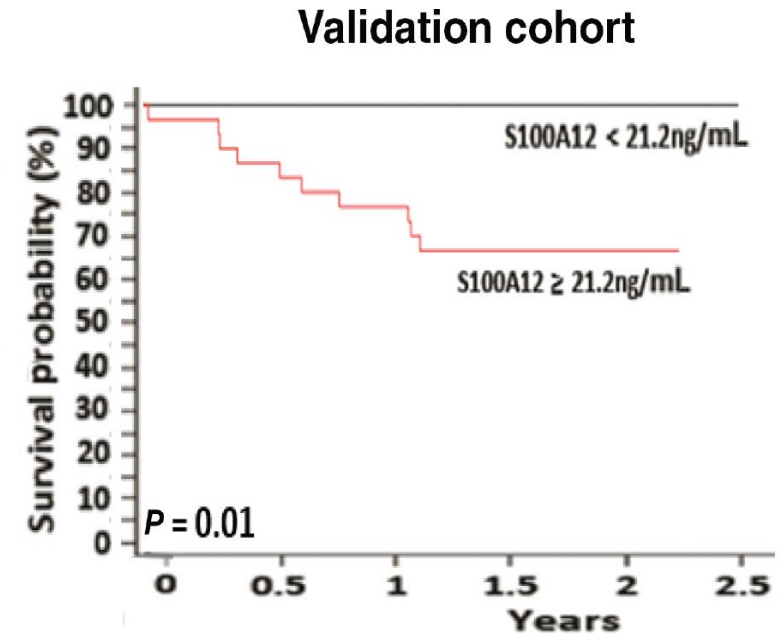
Need for biomarkers

S100A12 as a marker of worse cardiac output and mortality in pulmonary hypertension

Argyrios TZOUVELEKIS,[1] Jose D. HERAZO-MAYA,[1] Changwan RYU,[1] Jen-Hwa CHU,[1] Yingze ZHANG,[2] Kevin F. GIBSON,[2] Percy K. ADONTENG-BOATENG,[1] Qin LI,[1] Hongyi PAN,[1] Benjamin CHERRY,[1] Ferhaan AHMAD,[3] Hubert J. FORD,[4] Erica L. HERZOG,[1] Naftali KAMINSKI[1] AND Wassim H. FARES[1]







Take home messages

- **RHC is the gold standard diagnostic modality – Select patients on U/S**
- **Negative prognosticator**
- **Suspect PH when: "disproportionate" dyspnea+ LOW DLCO, 6MWD< 200m, dPA/DAA>1**
- ✓**No approved vasoactive therapy– DO NO HARM!!!!! – BEST SUPPORTIVE CARE – Pirfenidone and Nintedanib trials??**
- **Identify and exclude patients with worse V/Q mismatches**

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

Pulmonary hypertension in patients with interstitial lung disease

Theodoros Karampitsakos[a], Argyrios Tzouvelekis[b,c], Serafeim Chrysikos[a], Demosthenes Bouros[b], Iraklis Tsangaris[d], Wassim H. Fares[e,*]