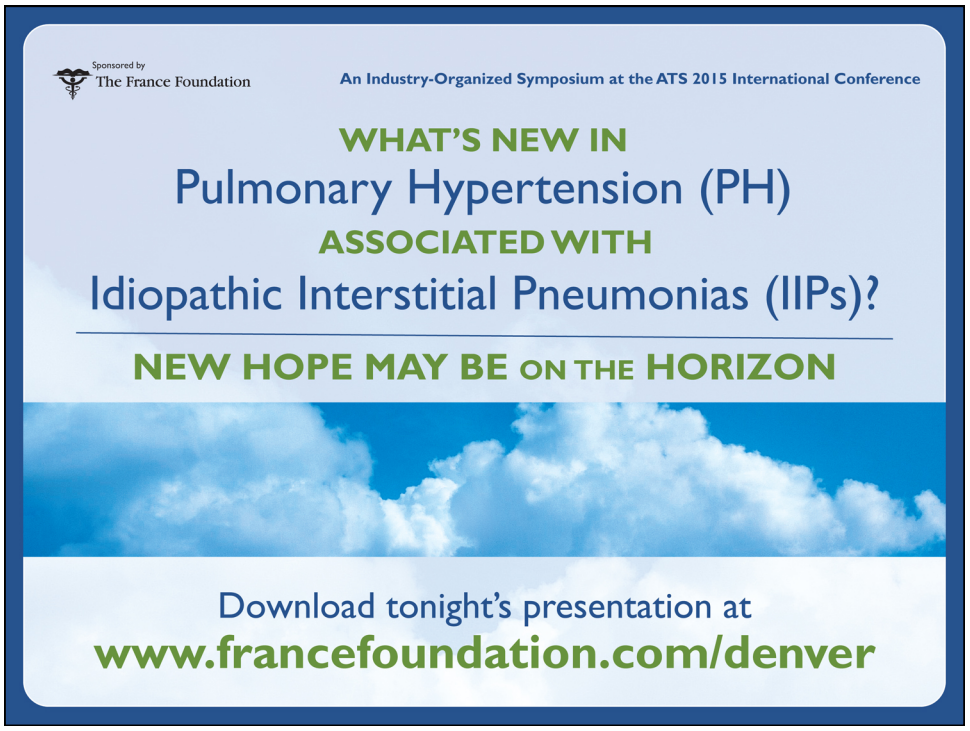
What's New in PH Associated with IIP? New Hope May be on the Horizon

May 17, 2015



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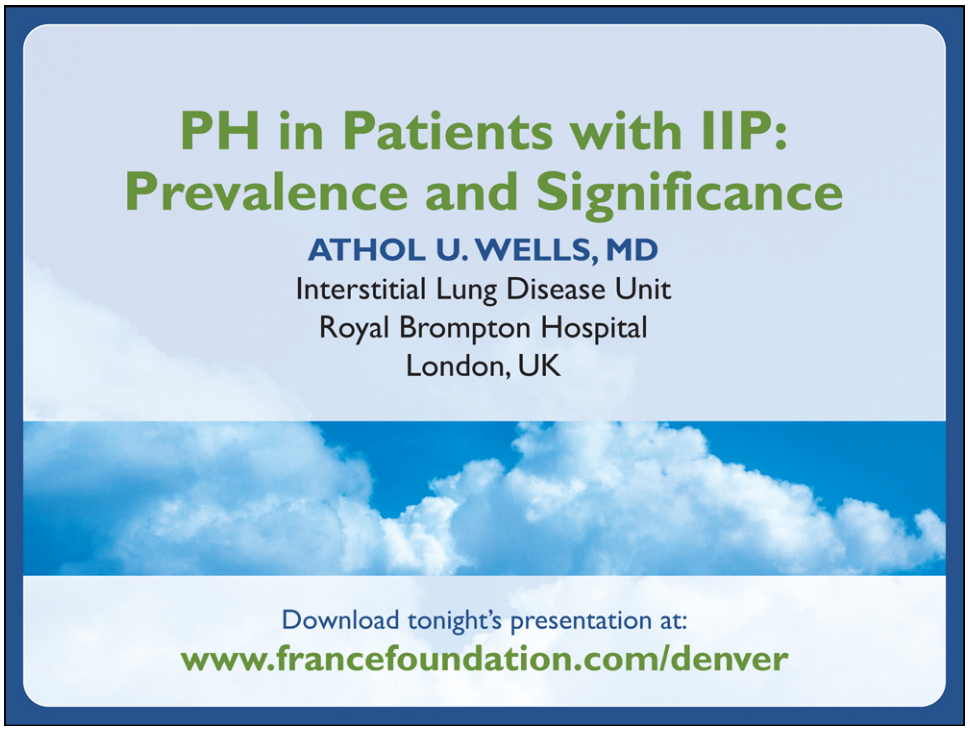
Agenda

6:30–6:45 PM	Gather and Dinner
6:45–7:00 PM	Welcome and Introductions ***Steven D. Nathan, MD (Chair)***
7:00–7:30 PM	PH in Patients with IIP: Prevalence and Significance ***Athol U. Wells, MD***
7:30–8:15 PM	Diagnosing PH in Patients with IIP: Recognizing the Need for Further Exploration ***Rajan Saggar, MD***
8:15–9:00 PM	Recent Trials in IIP-PH ***Steven D. Nathan, MD***
9:00 PM	Q&A

Educational Activity Learning Objectives

Upon completion of this activity, participants should be able to:

- Identify presenting signs and symptoms that may indicate the presence of PH in patients with IIP
- Explain key test results that can help to confirm PH diagnosis in patients with IIP
- Review data from studies evaluating treatments in patients IIP's



Difficulties in Defining Prevalence

- Selection bias a major constraint but plainly PH is not rare in ILD
- Prevalence in IPF from 32–85%, increasing with serial measurement; timing of investigation is crucial
- This problem is well illustrated in sarcoidosis

PH in Sarcoidosis

- Prospective study in 246 consecutive sarcoidosis patients: prevalence of PASP > 40mm on Doppler was **5.7%**
- Prevalence of PH (PASP > 40mm) was **49%** in 53 patients with chronic dyspnoea

Handa T, et al. *Chest.* 2006; 129:1246-52.
Baughman RP, et al. *Sarc Vasc Diffuse Lung Dis*. 2006; 23:108-16.

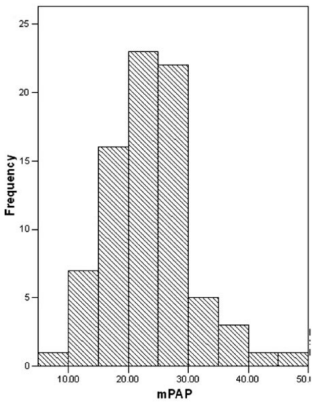
Most Data Apply to IPF

- The degree to which IPF data can be extrapolated to other fibrosing lung diseases is unclear
- However, the link between mortality and PH in IPF suggests that IPF data should be extrapolated with some caution

Prevalence and Outcomes of Pulmonary Arterial Hypertension in Advance Pulmonary Fibrosis

Characteristics	MAP ≤ 25 mm Hg (n = 54)	MAP > 25 mm Hg (n = 25)	p Value
Age, yr	56.2 ± 1.0	54.7 ± 3.8	0.27
Male gender, %	72.2	64.0	0.23
Supplemental oxygen, %	17.6	66.7	< 0.001
FVC, % predicted	52.5 ± 11.9	49.3 ± 11.0	0.13
TLC, % predicted	55.5 ± 10.7	57.8 ± 12.1	0.27
DLCO, % predicted	37.6 ± 11.3	31.1 ± 10.1	0.04
mPAP, mm Hg	19.1 ± 3.7	29.5 ± 3.3	n/a
RAP, mm Hg	4.3 ± 2.8	5.3 ± 3.5	0.14
Cardiac index, L/min/m^2	2.8 ± 0.4	3.2 ± 1.3	0.20
PAWP, mm Hg	8.4 ± 3.5	9.3 ± 3.5	0.22
Ejection fraction, %	61.5 ± 5.9	59.4 ± 5.0	0.12
Mortality rate, %	29.9	60.0	0.001
1-yr mortality rate, %	5.5	28.8	0.002

CONCLUSION: PAH is common in advanced cases of IPF and significantly impacts survival. A reduced DLCO, supplemental oxygen requirement, or poor 6-min walk performance should raise suspicion of the presence of underlying PAH. Identifying PAH might be an important adjunct in monitoring disease progression, triaging for transplantation, and guiding therapy.

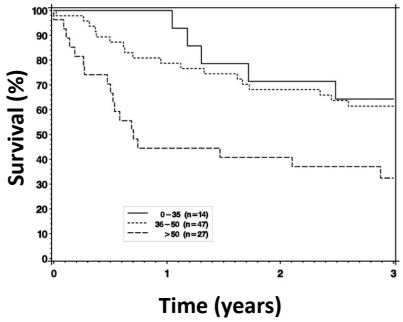


mPAP values. Histogram displaying the distribution of mPAPs among the cohort (values expressed in mm Hg). mPAP = mean pulmonary arterial pressure

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

Pulmonary Hypertension in Patients with Idiopathic Pulmonary Fibrosis

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%



CONCLUSION: In patients with IPF, PH correlates inversely with DLCO and has a significant adverse impact on survival, particularly with SPAP is > 50 mmHg

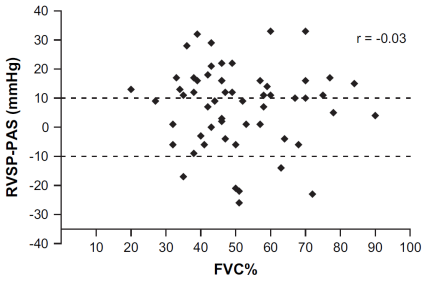
Nadrous HF, et al. *Chest*. 2005;128:2393-2399.

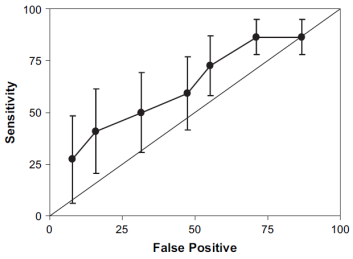
The Accuracy of Echocardiography

- 25% of 374 ILD patients referred for transplantation had PH (sPAP > 45 mmHg)
- TG_{ECHO} possible in 166 (44%)
- 48% misdiagnosed as having PH
- Overestimates PASP by 10 mmHg (52%)

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

Right Ventricular Systolic Pressure by Echocardiography as a Predictor of Pulmonary Hypertension in Idiopathic Pulmonary Fibrosis





$RVSP_{echo}$ (mmHg)	Diagnostic and 95% CI Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
$RVSP_{echo}$ > 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.

Combined Pulmonary Fibrosis and Emphysema: A Distinct Underrecognised Entity

Patients (all smokers) included 60 males and one female, with a mean age of 65 yrs. Dyspnoea on exertion was present in all patients. Basal crackles were found in 87% and finger clubbing in 43%. Pulmonary function tests were as follows (mean±SD): total lung capacity 88%±17, forced vital capacity (FVC) 88%±18, forced expiratory volume in one second (FEV_1) 80%±21 (% predicted), FEV_1/FVC 69%±13, carbon monoxide diffusion capacity of the lung 37%±16 (% predicted), carbon monoxide transfer coefficient 46%±19. Pulmonary hypertension was present in 47% of patients at diagnosis, and 55% during follow-up. Patients were followed for a mean of 2.1±2.8 yrs from diagnosis. Survival was 87.5% at 2 yrs and 54.6% at 5 yrs, with a median of 6.1 yrs. The presence of pulmonary hypertension at diagnosis was a critical determinant of prognosis.

Cottin V, et al. *Eur Respir J.* 2005;26:586-593.

Treatment of Idiopathic Pulmonary Fibrosis with Ambrisentan: A Parallel, Randomized Trial

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

Table 1. **Baseline Characteristics of Study Participants**

Characteristic	Placebo (n = 163)	Ambrisentan (n = 329)
Mean age (SD), *y*	66.1 (7.1)	65.8 (7.4)
Male, *n (%)*	111 (68.1)	244 (74.2)
White, *n (%)*	145 (89.0)	293 (89.1)
Smoking status, *n (%)*		
Never	53 (32.5)	105 (31.9)
Current	5 (3.1)	7 (2.1)
Former	104 (63.8)	217 (66.0)
Pulmonary hypertension, *n (%)**	16 (9.8)	32 (9.7)
Mean pulmonary arterial pressure (SD), *mm Hg*	20.6 (8.0)	20.3 (6.3)
SLB-confirmed diagnosis of IPF, *n (%)**	76 (46.6)	154 (46.8)
Mean disease duration (SD), *y*	0.9 (1.2)	1.1 (1.4)
Mean FVC (SD), *% predicted*	69.9 (13.8)	68.7 (13.1)
Mean hemoglobin-adjusted D_{LCO} (SD), *% predicted*	45.6 (13.3)	42.0 (13.8)
Mean CPI score (SD)	50.6 (10.4)	53.0 (10.5)
Mean 6MWD (SD), *m*	420.5 (121.4)	410.4 (118.7)
Mean SGRQ score (SD)	40.5 (21.1)	44.5 (21.6)
Mean TDI score (SD)	7.6 (2.5)	7.3 (2.4)

Raghu G, et al. *Ann Intern Med*. 2013;158:641-649.

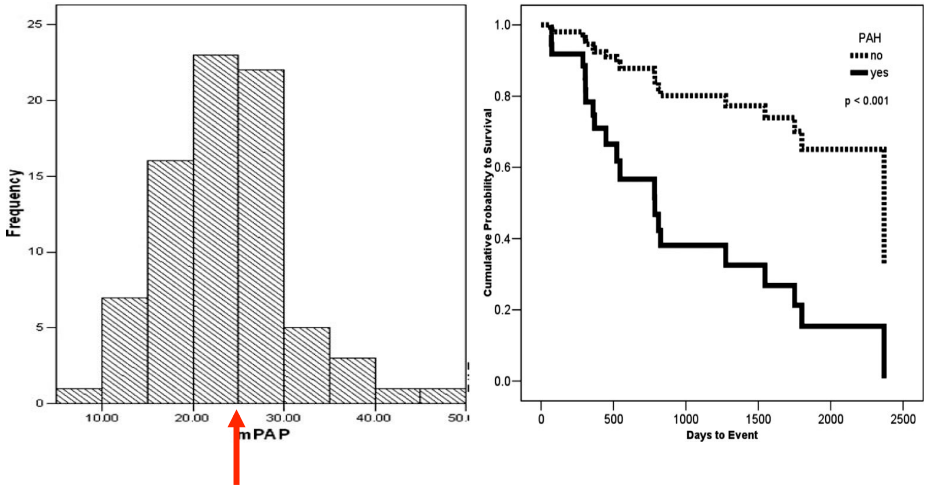
Prognostic Significance in IPF

PH as Predictor of Outcome

- Size of PA on CXR predicts mortality
- Systolic PAP (echo) correlates with survival
  sPAP > 50 median survival 0.7 years
  sPAP < 50 median survival > 4 years
- Transplant w/u patients with RHC data
  1 year mortality rate with PH 28.8%, without PH 5.5%

King TE, et al. *Am J Resp Crit Care Med*. 2001;164:1171-1181.
Nadrous HF, et al. *Chest*. 2005;128:2393-2399.
Lettieri C, et al. *Chest*. 2006;129:746-752.

PH as Predictor of Outcome



Advanced IPF, referred for transplant (n=79)
PH = mPAP > 25 mmHg

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

Pulmonary Hypertension in Patients with Idiopathic Pulmonary Fibrosis

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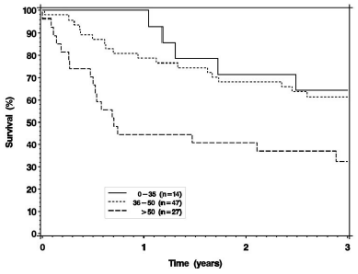


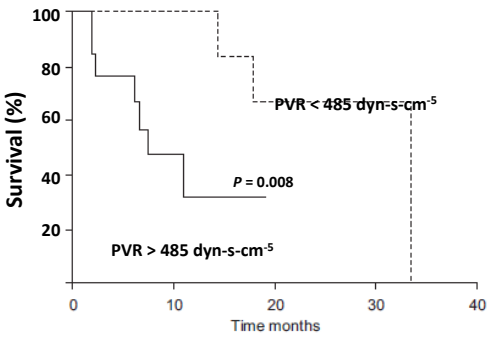
CONCLUSION: In patients with IPF, PH correlates inversely with DLCO and has a significant adverse impact on survival, particularly with SPAP is > 50 mm Hg

Nadrous HF, et al. *Chest*. 2005;128:2393-2399.

Pulmonary Hypertension in Patients with Combined Pulmonary Fibrosis and Emphysema Syndrome

TABLE 4 Univariate analysis relating survival to selected baseline variables

Variables	Hazard ratio	95% CI	p-value
Age yrs	1.04	0.97–1.11	0.297
NYHA class (II–III/IV)	2.25	0.86–5.87	0.096
$D_{L,CO}$ % pred	0.93	0.87–1.00	0.049
K_{CO} % pred	0.94	0.88–1.01	0.071
P_{a,O_2} kPa	0.80	0.35–1.84	0.604
6MWD m	0.99	0.99–1.00	0.157
S_{a,O_2} 6MWD %	0.97	0.91–1.04	0.444
f_C beats·min^{-1}	1.07	1.01–1.12	0.010
P_{ra} mmHg	0.99	0.84–1.17	0.904
Mean P_{pa} mmHg	1.07	1.00–1.14	0.049
CI L·min^{-1}·m^{-2}	0.23	0.05–1.02	0.054
PVR dyn·s·cm^{-5}	1.01	1.00–1.01	0.002
S_{v,O_2} %	1.02	0.95–1.10	0.513
Medical treatment of PH (yes/no)	1.32	0.39–4.93	0.656



Cottin V, et al. *Eur Respir J*. 2010;35:105-111.

Idiopathic Pulmonary Fibrosis and Emphysema Decreased Survival Associated with Severe Pulmonary Arterial Hypertension

Variables	Patients With IPF Alone (n = 70)	Patients With IPF and Emphysema (n = 31)	OR (95% CI)	p Value
Gender, No.			18 (2.7–773.7)	0.001
Male	49	30		
Female	30	1		
Age, yr	63 ± 10	67 ± 7		0.12
Smoking status			3.8 (1.36–11.6)	0.004
Yes	36	24		
No	40	7		
Pack-yrs	0 (0–78)	5 (0–60)		0.001
FVC, % predicted	58.7 ± 18	62.1 ± 15.6		0.37
FEV_1, % predicted	67.4 ± 20.3	69.9 ± 14.9		0.63
FEV_1/FVC ratio	92.6 ± 10.9	90.5 ± 8.5		0.33
$Paco_2$,* mm Hg	50.3 ± 8.9	48.7 ± 8.2		0.39
Spo_2, %				
At rest	88.2 ± 3.7	87.1 ± 3.6		0.16
During exercise	74.8 ± 5.9	71.0 ± 6.9		0.01
Change	13.5 ± 4.6	16.3 ± 6.7		0.04
eSPAP, mm Hg	56.7 ± 15.3	82.3 ± 20.2		0.0001
PAH				
eSPAP > 50 mm Hg	39/68 (58)	26/29 (90)	6.2 (1.6–34.7)	0.0025
eSPAP > 75 mm Hg	8/68 (11.7)	21/29 (72)	19 (5.8–68.7)	< 0.0001
Fibrotic HRCT scan	1.55 ± 0.38	1.75 ± 0.36		0.015

The survival rate in patients with IPF and emphysema was significantly lower compared with those with IPF without emphysematous changes ($p = 0.01$ [log-rank test]) [Fig 2]. This result did not change when the patients with unknown vital status were excluded. Other variables associated with lower survival rate were the presence of eSPAP > 75 mm Hg ($p < 0.04$ [log-rank test]) and FVC < 50% predicted ($p < 0.005$ [log-rank test]). The results of the univar-

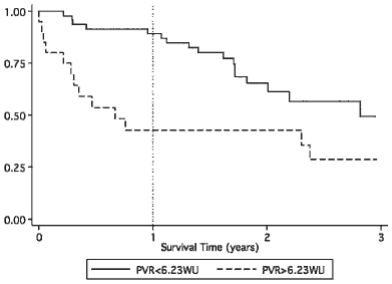
CONCLUSIONS: IPF patients with emphysema exhibited higher mortality compared with those with IPF without emphysema. This dire prognosis seems to be at least partially associated with the development of severe pulmonary arterial hypertension.

Mejia M, et al. *Chest*. 2009;136:10-15.

Pulmonary Vascular Resistance Predicts Early Mortality in Patients with Diffuse Fibrotic Lung Disease and Suspected Pulmonary Hypertension

Table 4 Predictors of overall survival (mortality as determined by Cox's proportional hazards regression)

	HR (95% CI)	p Value
Right heart catheterisation		
PVR	1.13 (1.05 to 1.22)	0.001*
PVR index	1.07 (1.03 to 1.12)	0.003*
mPAP	1.02 (0.99 to 1.05)	0.25
mRAP	0.96 (0.87 to 1.05)	0.32
mLAP	0.94 (0.88 to 1.00)	0.05
Cardiac output	0.86 (0.63 to 1.18)	0.34
Cardiac index	0.69 (0.36 to 1.33)	0.27
Echocardiography		
RV dilation	1.92 (0.93 to 3.98)	0.08
RV dysfunction	1.72 (0.84 to 3.53)	0.14
RVSP	1.00 (0.98 to 1.02)	0.81
Pulmonary function		
T_{LCO} %	0.94 (0.91 to 0.98)	0.001
K_{CO} %	0.98 (0.96 to 0.99)	0.03
FVC %	0.98 (0.96 to 0.99)	0.02
Composite physiological index	1.06 (1.03 to 1.10)	<0.0001†
Pao_2	0.73 (0.60 to 0.89)	0.002
Clinical		
Male gender	2.10 (0.96 to 4.57)	0.06
Age	1.01 (0.98 to 1.04)	0.47
IPF diagnosis	3.33 (1.58 to 7.00)	0.001
WHO class	1.85 (1.19 to 2.88)	0.006



Corte TJ, et al. *Thorax*. 2009;64:883-888.

Echocardiographic and Hemodynamic Predictors of Mortality in Idiopathic Pulmonary Fibrosis

CONCLUSIONS: Right-sided heart size and right ventricular dysfunction measured by echocardiography and higher pulmonary vascular resistance by invasive hemodynamic assessment predict mortality in patients with IPF evaluated for lung transplantation.

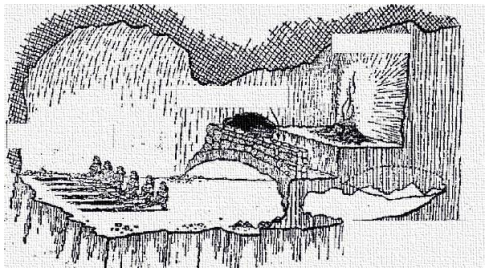
	Unadjusted Model			Adjusted Model[a]			Censored at Lung Transplantation[b]		
Variable	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
RAP, for 1 mm Hg increase	.9	.9-1.0	.34	.9	.9-1.0	.48	1.0	.9-1.1	.74
mPAP, for 10 mm Hg increase	1.3	1.0-1.7	.06	1.3	1.0-1.8	.06	2.4	1.4-3.9	.001
PVR, for 1-WU increase	1.3	1.1-1.4	<.001	1.3	1.1-1.5	.001	1.4	1.2-1.7	<.001
CO, for 1 L/min decrease	1.1	.9-1.4	.31	1.2	.9-1.5	.23	1.4	.9-2.0	.10
SV, for 10 mL decrease	1.1	1.0-1.2	.18	1.1	.9-1.3	.19	1.2	.9-1.5	.09
PCWP, for 1 mm Hg increase	.99	.9-1.0	.75	1.0	1.0-1.1	.96	1.0	.9-1.1	.46

	Unadjusted Model			Adjusted Model[a]			Censored at Lung Transplantation[b]		
Variable	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
RV:LV	3.8	1.5-9.7	.006	4.5	1.7-11.9	.003	5.6	1.6-19.8	.008
TAPSE < 1.6 cm	2.0	1.0-3.7	.05	1.9	1.0-3.7	.06	1.5	.7-3.5	.31
TAPSE (continuous)	.7	.4-1.2	.22	.8	.5-1.5	.56	.8	.3-2.1	.60
Moderate to severe RA dilation	2.4	1.2-4.7	.009	2.9	1.4-5.9	.004	3.0	1.2-7.8	.02
Moderate to severe RV dilation	2.6	1.4-4.6	.001	2.7	1.4-5.4	.004	3.2	1.4-7.8	.008
Moderate to severe RV dysfunction	4.9	2.5-9.6	<.001	5.5	2.6-11.5	<.001	7.5	2.7-20.8	<.001
RVSP, for 5 mm Hg increase	1.1	1.1-1.2	<.001	1.2	1.1-1.3	<.001	1.2	1.1-1.4	.002
RVOT VTI	.9	.9-1.0	.16	.9	.9-1.0	.17	.8	.7-1.0	.01
RVOT AT	1.0	.9-1.0	.46	1.0	.9-1.0	.64	1.0	.9-1.0	.11
Notching of RVOT	1.4	.8-2.3	.27	1.4	.8-2.4	.25	2.4	1.0-5.4	.05

Rivera-Lebron BN, et al. *Chest*. 2013;144:564-570.

Given the prognostic significance of PH in ILD, what can be concluded on the prognostic significance of PH markers?

PH Markers: Shadows on the Wall of Plato's Cave…



- Echocardiography
- Desaturation on exercise
- Serum BNP
- Enlarged PA on HRCT
- Resting PFT:
  - High FVC/DLco
  - Low Kco
  - Low pO2/DLco

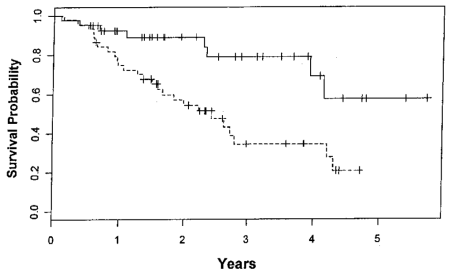
6MWT Desaturation

- 6MWT 366m (PH-) vs 144m (PH+)
- O_2 nadir 88% (PH-) vs 80% (PH+)
- Hypothesis: that desaturation below 88% on 6MWT reflects either fixed PH or **pulmonary hypertension on exercise**

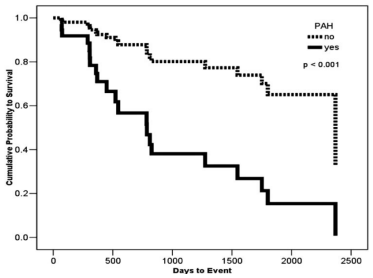
Lettieri CJ, et al. *Chest*. 2006;129:746-752.
Kawut SM, et al. *Respir Med*. 2005;99:1431-1439.

Concordance Between 6MWT and Pulmonary Hypertension

6MWT



PH



Lama VN, et al. *Am J Respir Crit Care Med*. 2003;168:1084-90.
Lettieri CJ, et al. *Chest.* 2006;126:746-752.

BNP Levels in Advanced IPF (n = 39)

- PH in over 25%; BNP increased in 20/39
- BNP increases correlated with increased mPAP, reduced 6MWT & cardiac output
- PFT did not correlate with BNP or distinguish between PH and non-PH
- BNP 33.3pg/mL a cut-off for mPAP > 35 mm (ROC area under curve = 96%)

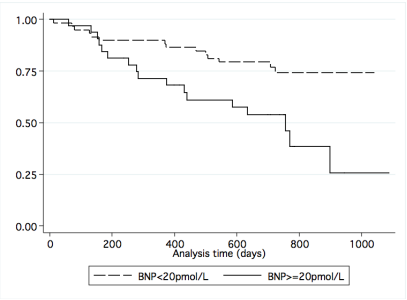
Leuchte HH, et al. *Am J Respir Crit Care Med*. 2006; 170:360-365.

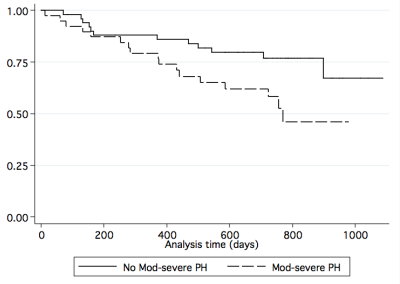
Serum BNP Across ILDs

- Serum BNP levels evaluated against survival in 90 patients with a mixture of ILDs
- Prognostic value of BNP compared with pulmonary function tests and echocardiography
- 28 (31%) died, 20 ± 9 months follow-up
- *A priori* thresholds – BNP 4, 20 pmol/L; ECHO RVSP 40, 50 mmHg

Corte TJ, *et al*. *Eur Resp J*. 2010:36;819-25.

Vascular Markers: BNP in ILD





- Higher BNP concentrations were associated with increased mortality independent of age, gender and pulmonary function
- Patients with BNP ≥ 20pmol/L had a 14-fold increase in mortality over patients with BNP < 4 pmol/L independent of age, gender and pulmonary function. (HR 13.92; 95% CI 1.52, 128.79; *P* = 0.02)

Corte TJ, *et al*. *Eur Resp J*. 2010:36;819-25.

Pulmonary Function Tests

- Disproportionate reduction in gas transfer (DLco), as judged by Kco or FVC/DLco
- Prognostic significance of FVC/DLco not evaluated in a large IPF cohort
- FVC/DLco requires measurement of VA, Kco and FVC
- Kco (Dlco/VA) used for decades as a marker of vasculopathy and has the key advantage of being a single measure

Pulmonary Function Vascular Index Predicts Prognosis in Idiopathic Interstitial Pneumonia

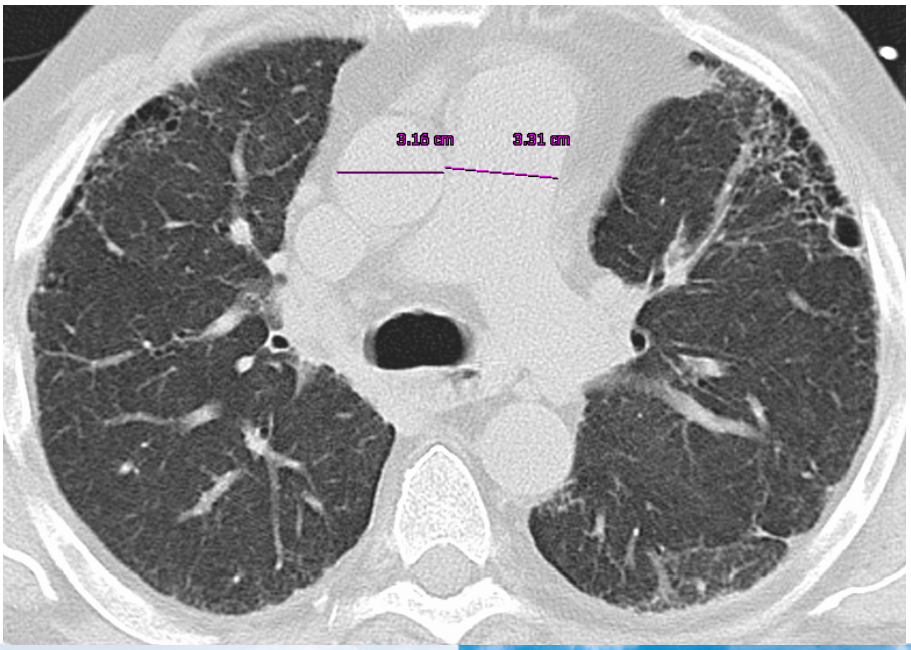
SUMMARY: In patients with IIP, baseline Kco (diffusing capacity adjusted for VA) and 6-month decline in Kco are both associated with increased early and overall mortality and, in a subgroup of patients with follow-up echocardiography, are associated with the development of pulmonary hypertension at follow-up.

Table 1 Baseline parameters

Baseline parameters	Study subjects ($n = 192$) n	Mean ± SD
Pulmonary function		
DL_{CO} (% predicted)	192	40.7 ± 14.4
K_{CO} (% predicted)	192	73.0 ± 19.6
TLC (% predicted)	188	66.8 ± 17.4
FEV_1 (% predicted)	185	71.7 ± 21.1
FVC (% predicted)	185	71.5 ± 23.1
SaO_2 (%)†	158	94.3 ± 3.5
PaO_2 (kPa)†	158	9.7 ± 1.6
$PaCO_2$ (kPa; $n = 154$)†	158	5.2 ± 0.6
Composite physiologic index	185	50.7 ± 13.6
Echocardiography		
RVSP (mmHg)	116	38 ± 13
Pulmonary acceleration time (ms)	120	113 ± 29
Fractional shortening (%)	163	38 ± 8

	Early mortality Odds ratio (95% CI)	*P*-value	Overall mortality Hazard ratio (95% CI)	*P*-value
Pulmonary function—baseline				
K_{CO} % predicted	0.98 (0.96, 1.00)	0.09‡	0.99 (0.98, 0.999)	<0.05†‡
K_{CO} % ≤ 50%	4.11 (1.52, 11.10)	0.005†‡	2.39 (1.32, 4.33)	0.004†‡
DL_{CO} % predicted	0.94 (0.91, 0.97)	0.001†	0.96 (0.95, 0.97)	<0.0001†
FVC% predicted	0.99 (0.97, 1.00)	NS	0.98 (0.97, 0.99)	0.001†
CPI	1.06 (1.02, 1.10)	0.003†	1.04 (1.03, 1.07)	<0.0001†
PaO_2 (kPa)	0.62 (0.47, 0.82)	0.001†	0.68 (0.59, 0.79)	<0.0001†

Corte TJ, et al. *Respirology*. 2012;17:674-680.



PH Prevalence in IPF: Summary

- Prevalence critically dependent on nature of population. Echocardiography overstates prevalence
- High prevalence in severe IPF
- High prevalence in CPFE
- However, prevalence of 9% in mild to moderate IPF in one study.

Prognostic Significance: Summary

- Severe PH a malignant prognostic determinant in IPF overall, in advanced disease and in CPFE
- At RHC, PVR seems to provide the most prognostic value
- Prognostic significance robust when echocardiographic markers are evaluated
- Other markers of pulmonary vasculopathy (BNP, 6MWT desaturation, Kco, enlarged PA on HRCT also malignant determinants

Diagnosing PH in Patients with IIP: Recognizing the Need for Further Exploration

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Download tonight's presentation at:
www.francefoundation.com/denver

Learning Objectives

- Identify presenting signs and symptoms that may indicate the presence of PH in a patient with an IIP
- Explain key test results that can help to confirm a PH diagnosis

Clinic OCT 2008

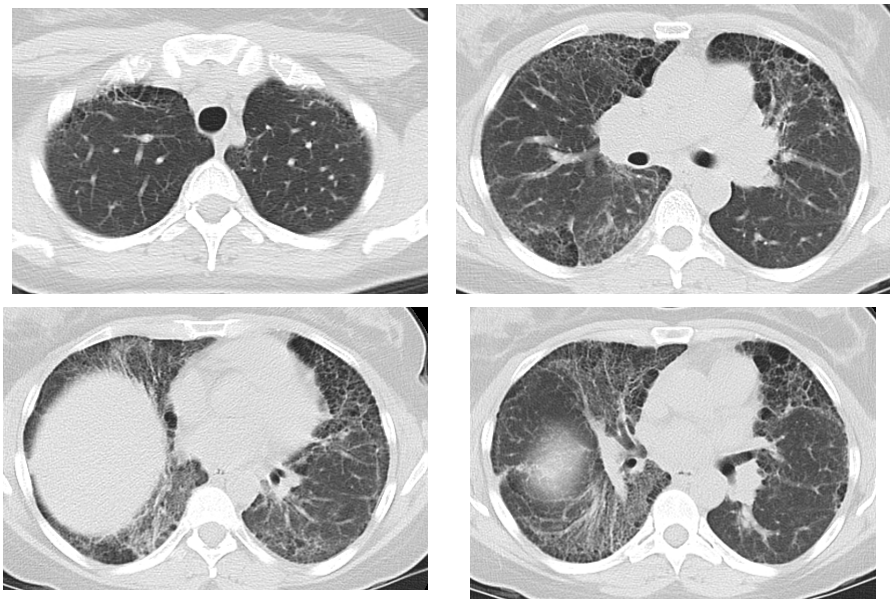
- 41-year-old African American female with slowly progressive DOE initially seen January 2001
- Serial CTD panels negative
- ILD on CT chest
- Surgical lung biopsy in 2004 showed nonspecific interstitial pneumonitis (NSIP)
- Treated with azathioprine and prednisone
- Remained stable despite severe restrictive physiology
- Cursory LTx evaluations through the years

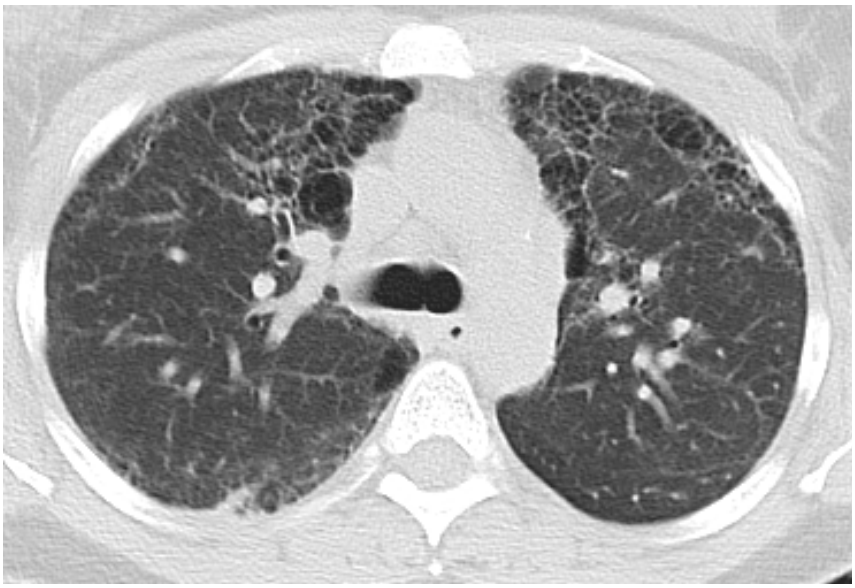
PFT and 6MWT

Jan 2006	
FVC	1.33 (38%)
FEV1	1.15 (39%)
FEV1/FVC	86%
Dlco	4.2 (15%)
TLC	2.07 (41%)

Oct 2008	Room Air	Supplemental Oxygen (2L/min)
SpO2 rest	98	100
SpO2 nadir	79	90
Distance	74 m (1:50 secs)	270 m

CT Chest DEC 2008





Echo Oct 2008

LEFT VENTRICLE: Size was normal. Normal ejection fraction 65 %

LEFT ATRIUM: Size was normal

RIGHT VENTRICLE: The ventricle was slightly dilated. Systolic function was normal. Wall thickness was normal

PULMONARY ARTERY: Estimated peak pressure was estimated 35 mmHg

TRICUSPID VALVE: Mild regurgitation

RIGHT ATRIUM: The atrium was normal

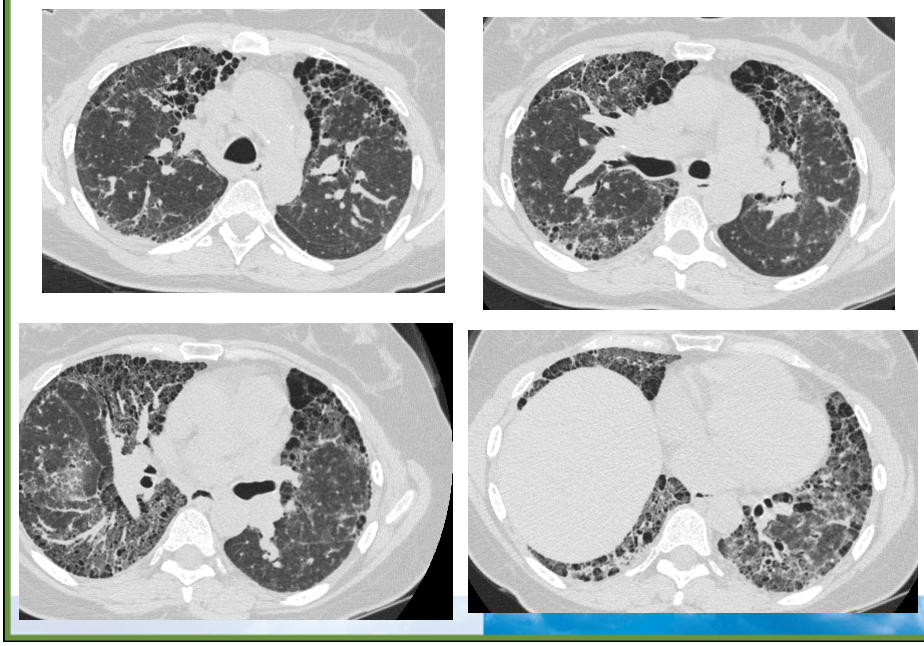
Right Heart Catheterization

	July 2005	DEC 2009
RA	6 mmHg	3 mmHg
RV	33/4 mmHg	48/5 mmHg
PA	33/11 (mean 22 mmHg)	47/14 (mean 28) mmHg
PAWP	6 mmHg	6 mmHg
CO/CI (TD)	4.2/2.45	3.6/2.1
PVR	3.8	6.1

Clinical Course

- A PDE-5 inhibitor was prescribed, but the patient didn't tolerate this (headaches)
- Continued with slowly progressive symptoms
- Reluctant to consider lung transplantation
- SOB with minimal activity including dressing and showering
- Supplemental oxygen needs continued to increase at 5-6 L/min and up to 10 liters with exercise
- Azathioprine switched to mycophenolate

CT FEB 2013



Clinic Testing June 2013

PFTs	JUNE 2013	FEB 2013
FVC	1.03 (35%)	1.23 (42%)
FEV1	0.92 (39%)	0.92 (39%)
FEV1/FVC	89	75%

6MWT	JUNE 2013
Oxygen	10L
Rest SpO2	98
SpO2 nadir	76
Distance	134 m
Rest pulse	91
Max pulse	109
Pulse rate recovery	5
Borg	6

Echo July 2013

LEFT VENTRICLE: Size was normal. Normal ejection fraction 60 % to 65 %. There was flattening of the septum during systole

LEFT ATRIUM: Size was normal

RIGHT VENTRICLE: The ventricle was markedly dilated. Systolic function was normal. Wall thickness was normal

PULMONARY ARTERY: Estimated peak pressure was at least 85 mmHg

TRICUSPID VALVE: Moderate regurgitation

RIGHT ATRIUM: The atrium was markedly dilated

RHC Was Repeated…

	July 2005	DEC 2009	July 2013
RA	6 mmHg	3 mmHg	5
RV	33/4 mmHg	48/5 mmHg	
PA	33/11 (22 mmHg)	47/14 (28) mmHg	86/43 (55)
PAWP	6 mmHg	6 mmHg	7 mmHg
CO/CI (TD)	4.2/2.45	3.6/2.1	2.37/1.4
PVR	3.8	6.1	20

Current Recommendations for Active Listing for Lung Transplantation for ILD

- Decline in FVC ≥10% during 6 months of follow-up (note: a 5% decline is associated with a poorer prognosis and may warrant listing).
- Decline in DLCO ≥15% during 6 months of follow-up.
- Desaturation to <88% or distance <250 m on 6-minute-walk test or >50 m decline in 6-minute-walk distance over a 6-month period.
- Pulmonary hypertension on right heart catheterization or 2-dimensional echocardiography.
- Hospitalization because of respiratory decline, pneumothorax, or acute exacerbation.

Weill D, et al. *J Heart Lung Transplant*. 2015;34:1-15.

Definition of PH-IPF

- mPAP < 25mmHg defines the absence of PH
- mPAP ≥ 25mmHg defines PH
- Severe PH in IPF either:
  - mPAP ≥ 25mmHg with low cardiac index (<2 L/min/m^2)
  - mPAP ≥ 35mmHg
- Several comorbidities to rule out: OSA, CAD, LVDD, and/or PE

Seeger W, et al. *J Am Coll Cardiol*. 2013;62(25S):D109-D116.
Mermigkis C, et al. *Sleep Breath*. 2010;14:387-390.
Nathan SD, et al. *Respir Med*. 2010;104:1035-1041.

Diagnostics in Consideration of PH in IPF

- H&P
- PFT
- CT Chest
- 6MWT
  - Distance
  - Desaturation
  - Pulse rate recovery
- BNP
- CPET
- Echocardiography
- RHC

PH-IPF Is Associated with DLCO% but Not FVC%

- Prospective study incident IPF (n = 70) with RHC and PFT
  - Baseline: room air; FVC% 76 ± 22; DLCO% 45 ± 15; mPAP 16 ± 5)
  - Prevalence of PH was 8.1%
  - mPAP inversely correlated with paO_2 and DLCO% ($r < 0.5$), but not FVC%

Hamada K, et al. *Chest*. 2007;131:650-56.

PH-IPF Is also Associated with Oxygenation at Rest & Exertion

- Retrospective study incident IPF (n=101)
  - Prevalence PH 14.9% (only 4 cases mPAP>35)
  - Baseline: room air
    - FVC% 70+/-20
    - DLCO 48+/-19
    - mPAP 19.2+/-6.5
    - 6MWD 527+/-154

Variables	MPAP ≤20 mm Hg (n = 66)	MPAP >20 mm Hg (n = 35)	p value
Sex (M/F)	53/13	32/3	0.145
Age, years	66.6 ± 7.0	63.2 ± 8.3	0.027
BMI	23.1 ± 3.8	24.1 ± 4.6	0.24
Smoking status current/former/never	7/40/19	1/31/3	0.014
FVC, % predicted	71.5 ± 19.7	67.7 ± 20.9	0.373
DLCO, % predicted	52.5 ± 20.5	38.4 ± 13.1	<0.001
Pa_{O_2}, mm Hg	83.5 ± 10.0	72.8 ± 12.6	<0.001
MMRC	1.3 ± 0.9	1.9 ± 0.9	0.004
6MWD, m	561.2 ± 150.0	461.2 ± 141.8	0.002
Lowest SpO_2, %	83.8 ± 9.1	75.1 ± 10.6	<0.001
PVRI, $dyn \cdot s \cdot cm^{-5} \cdot m^2$	225.9 ± 90.7	397.4 ± 177.5	<0.001
Cardiac index, $l \cdot min^{-1} \cdot m^{-2}$	3.14 ± 0.54	3.06 ± 0.7	0.518
PCWP, mm Hg	6.8 ± 3.3	10.2 ± 3.2	<0.001

Data are presented as means ± SD or numbers. n = 101 except for DLCO (n = 96).

Kimura M, et al. *Respiration*. 2013;(85):456-63.

PH-IPF (Pre Lung Tx Setting) No Correlation with FVC%

	N	FVC%	DL_{CO}%	mPAP (mmHg)	Patients with PH	%
FVC range						
> 70%	16	80.4	43.2	29.7	10	62.5
60-69%	26	63.1	41.1	22.1	7	26.9
50-59%	23	54.6	31.1	23.2	10	43.5
40-49%	31	44.8	32.5	22.9	13	41.9
< 40%	22	32.0	22.1	21.6	8	36.4
DL_{CO} range						
> 50%	16	60.9	61.3	24.0	5	31.3
40-49%	15	66.4	44.6	22.0	4	26.7
30-39%	32	55.4	34.6	21.2	9	28.1
20-29%	26	52.7	24.5	25.6	14	53.8
< 20%	13	43.7	13.7	27.2	8	61.5

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

Performance Characteristics of PFTs and 6MW Alone and in Combination with the RVSP for the Detection of PH-IPF

Sensitivity 50; Specificity 68

		RVSP Excluded*	RVSP (mmHg) >30	RVSP (mmHg) >40	RVSP (mmHg) >50	RVSP (mmHg) >60
DL_{CO}%	< 30	62.5 / 66.7	36.8 / 78.9	30.0 / 86.0	25.0 / 91.5	17.4 / 98.0
	< 40	87.5 / 23.1	66.7 / 46.7	52.6 / 68.6	31.6 / 82.1	18.2 / 97.6
	< 50	95.8 / 10.3	77.8 / 32.1	63.2 / 63.6	36.8 / 81.1	22.7 / 97.4
Spo2 rest	< 95	90.9 / 50.0	63.6 / 57.1	54.5 / 60.7	36.4 / 78.6	18.2 / 100
	< 90	9.1 / 88.9	5.9 / 93.0	5.9 / 93.0	5.9 / 100	5.9 / 100
SpO2 exercise	< 85	100 / 61.9	45.5 / 83.3	41.7 / 89.5	23.1 / 94.7	14.3 / 97.6
	< 80	56.1 / 72.2	8.3 / 97.4	7.7 / 100	7.1 / 100	6.7 / 100
6MW Distance (meters)	< 100	53.3 / 88.9	28.6 / 97.1	25.0 / 97.6	16.7 / 97.8	9.5 / 98.0
	< 200	80.0 / 61.1	53.8 / 80.0	40.0 / 86.5	17.6 / 97.6	10.0 / 97.9
	< 300	86.7 / 52.8	61.5 / 75.0	46.7 / 82.9	23.5 / 94.9	10.0 / 97.9

*sensitivity/specificity

For Predicting PH: DLCO > FVC/DLCO > FVC

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

PH in IPF: Associated with Shorter Distance and Worse Desaturation

	mPAP ≤ 25 mm Hg (N = 10)	mPAP > 25 mm Hg (N = 24)	*P* value
6MWD (m)	**366 ± 82**	**144 ± 66**	< 0.001
SpO_2 nadir (%)	**88 ± 4**	**80 ± 4**	< 0.001

Lettieri CJ, et al. *Chest*. 2006;129:746-742.

UNOS Registry Finds PH-IPF Overall Sicker than IPF Without PH

- UNOS data (pre-LAS) over 9.5 years; >2500 IPF patients
  - PH prevalence ~46%
  - Severe PH (mPAP > 40) 9%
- %FEV1 and %FVC was different between (+)PH and (–)PH groups but not clinically significant
- Factors distinguishing mild to moderate PH from no PH: need for O_2, PAWP, FEV1%
- Factors distinguishing severe PH from no PH included: age, AA, need for oxygen, PAWP, pCO_2

Shorr AF, et al. *Eur Resp J*. 2007;30:715-21.

The Need for Oxygen at Rest and Severe Loss of Diffusing Capacity Predicts PH-IPF

- Retrospective IPF pre-transplant cohort (n=79)
- Prevalence of PH-IPF 31.6%
- Need for supplemental oxygen (paO_2 < 55 and/or resting SpO_2 RA < 88%) *and* %DLco < 40% were > 10x more likely to have PH-IPF
- All PFT parameters (other than %DLco) did *not* distinguish the PH-IPF patient

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

Validated Regression Equation with Strong NPV/PPV

$$\text{MPAP} = -11.9 + 0.272 \times \text{Spo}_2 + 0.0659 \times (100 - \text{Spo}_2)^2 + 3.06 \times (\text{percentage of predicted FVC/percentage of predicted DLCO})$$

Table 2—*Performance Characteristics of the Method in Establishing or Excluding a Diagnosis of PH Defined as MPAP From RHC > 25 mm Hg*

Criterion	Sensitivity (95% CI), %*	Specificity (95% CI), %*	PPV (95% CI), %*	NPV (95% CI), %*
Formula-predicted MPAP > 19 mm Hg	100 (66–100)	25 (13–41)	39 (13–41)	100 (66–100)
Formula-predicted MPAP > 21 mm Hg				
Validation	95 (74–99)	58 (41–73)	51 (35–70)	96 (78–100)
Derivation, %†	100	40	50	100
Formula-predicted MPAP > 25 mm Hg				
Validation	63 (38–84)	85 (70–94)	67 (36–86)	83 (63–89)
Derivation, %†	71	81	71	81
Formula-predicted MPAP > 35 mm Hg	21 (6–46)	100 (91–100)	100 (22–99)	73 (60–82)

*PH was considered to be present when MPAP by RHC was > 25 mm Hg.

- Formula derived mPAP > 25 correlated with oxygen saturation, PaO_2, and Echo-RVSP[2]

Zisman DA, et al. *Chest*. 2008;133:640-645.
Ghanem MK, et al. *Ann Thorac Med*. 2009;4:187-196.

Echocardiographic RVSP ≥ 45 mmHg Is Not Specific for PH-ILD (N = 106; Pre-lung Transplant)

PH Prevalence 20%

Patient Group	Finding	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
ILD	sPAP	85% (68–95%)	17% (5–39%)	60% (44–74%)	44% (14–79%)
	RV findings	76% (61–87%)	53% (40–67%)	57% (43–69%)	74% (58–86%)

RV findings are defined as the presence of RV dilation, hypertrophy, or systolic dysfunction.

- Strong correlation between Echo RVSP (*where available*) and RHC RVSP
- Estimation of Echo RVSP in only 54% of ILD cohort; patients with an available RVSP estimation were more likely to have RHC proven PH (p<. 0001)
- Accuracy of Echo RVSP was 37% in the ILD cohort and decreased further as the Echo RVSP increased beyond 45mmHg

Arcasoy SM, et al. *Am J Respir Crit Care Med*. 2003;167:735-740.

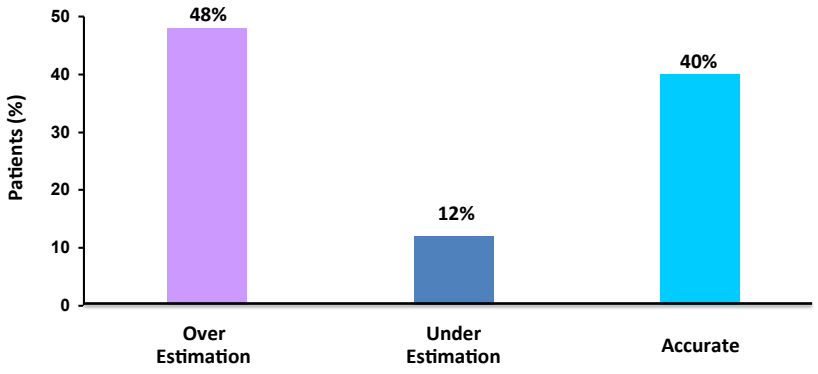
Echocardiographic RVSP Is Superior to 6MWD, DSP, Resting Spo2 in Detecting PH-IPF

- Single center retrospective study: 131 IPF pre-lung transplant; 58 with eligible data
- PH-IPF (n=25); IPF without PH (33)
- PH prevalence 43%

	RVSP (%)	6-Min Walk Distance (%)	Distance-Saturation Product (%)	S_{pO_2} (%)
Sensitivity	72	48	64	44
Specificity	66	67	57	76
Positive predictive value	62	36	53	58
Negative predictive value	76	63	32	64

Modrykamien AM, et al. *Respiratory Care*. 2010;55(5):584-588.

Echocardiography Does Not Accurately Predict PH in IPF



N = 110, idiopathic pulmonary fibrosis patients with both ECHO and RHC
Comparison of RVSP by ECHO to PASP by RHC
***** RVSP only reported in 54.5% of cohort; 1/3 of this subgroup had +PH by RHC*****

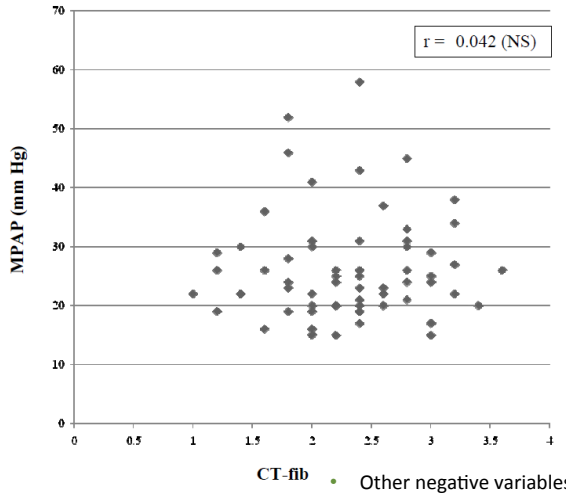
Nathan SD, et al. *Respir Med.* 2008;102:1305-1310.

Brain Natriuretic Peptide (BNP)

- 39 patients (*28 IPF*) underwent RHC, 6MW, PFT (Baseline %FVC 45 ± 2.7; %DLCO 27.8 ± 2.5)
- Normal BNP(n = 16) (≤ 18pg/mL) versus elevated BNP(n = 12) correlated with mPAP (r = 0.74), CO (r = -0.57), and PVR (r = 0.8)
- BNP inversely correlated with 6MW (r = -0.40)
- BNP did NOT correlate with PFT parameters
- *BNP does not allow diagnosis of latent or mild PH and elevated BNP may normalize in 'compensated' PH-IPF*[2]

Leuchte HH, et al. *Am J Resp Crit Care Med*. 2004;170:360-365.
[2]Behr J, et al. *Eur Resp J*. 2008;31:1357-67.

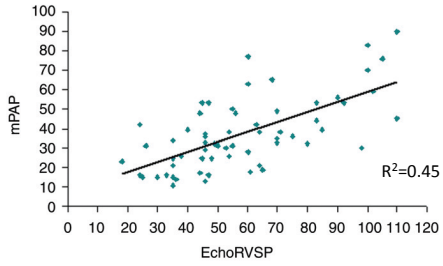
No Relationship Between CT-fib and Measured mPAP in IPF



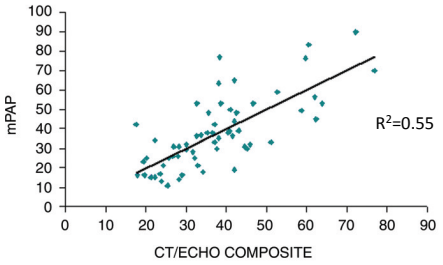
- Other negative variables: main PA diameter (MPA); MPA/Aortic diameter; MPA/BSA
- PA diameter increased in both groups (both > than other control populations)

Zisman DA, et al. *Chest*. 2007;132:773-779.
Kazerooni EA, et al. *AJR*. 1997;169:977-983.

Detection of Pulmonary Hypertension with Multidetector CT and Echocardiography Alone and in Combination



mPAP = dPA/dAA x 23.6 + RVSP x 0.34 – 8.3



Devaraj A, et al. *Radiology*. 2010;254:609-616.

When to Suspect PH in IPF

- PFTs
  - DL_{CO}< 40%
- 6MWT
  - Distance
  - SpO_2 nadir
  - Pulse rate recovery
- BNP
- Echocardiography

Cardiopulmonary Exercise Testing May Have a Diagnostic Role in PH-IPF

- IPF(+PH; RVSP > 50mmHg), compared to IPF(-PH), has the following CPX profile:
  - Decreased maximum work
  - Decreased VO_2max
  - Decreased O_2 pulse
  - Decreased anaerobic threshold
- Strongest correlation of sPAP with VE/VCO_2 at anaerobic threshold
- VE vs. VCO_2 $slope_{pred}$ cutoff >152% was the strongest CPX predictor of PH (*median mPAP 34*); superior to any PFT parameter

Boutou AK, et al *Respirology*. 2011;16:451-458.
Glaser S, et al. *Respir Med*. 2009;103:317-324.
Glaser S, et al. *PLoS One*. 2013;8(6):e65643.

ORIGINAL ARTICLE

Heart rate recovery after six-minute walk test predicts pulmonary hypertension in patients with idiopathic pulmonary fibrosis

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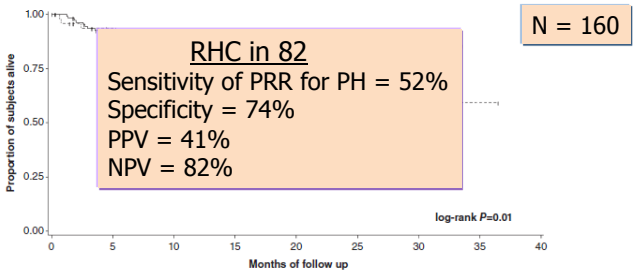
[1]*Interstitial Lung Disease Program and Autoimmune Lung Center, National Jewish Health, Denver, Colorado, and* [2]*Advanced Lung Disease and Transplant Program, Inova Fairfax Hospital, Falls Church, Virginia, USA*



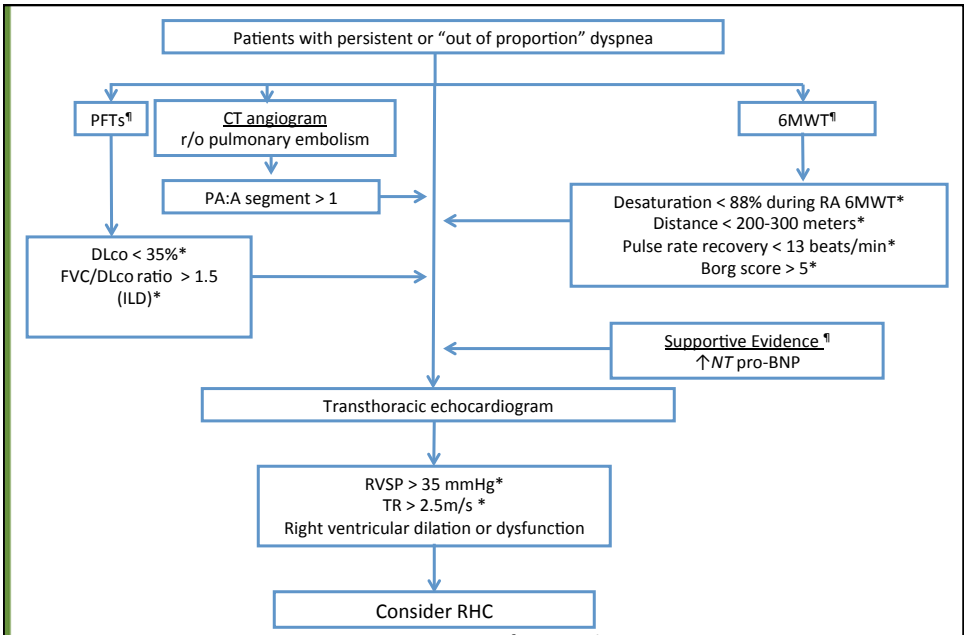
N = 160

RHC in 82
Sensitivity of PRR for PH = 52%
Specificity = 74%
PPV = 41%
NPV = 82%

Swigris JJ, et al. *Respirology*. 2011;16:439-445.

PH in Lung Disease: When to Suspect?

History	Physical Examination	PFTs	6MWT	Imaging	Blood tests	Echo
SOB that is "disproportionate" to the extent of ILD	Loud P2	DLco < 40%	Distance<200 meters	Ratio of PA to aorta diameter > 1 on CT of the chest	Elevated pro-ntBNP or BNP	Elevated RVSP
	Signs of right heart failure	FVC%/DLCO% ratio > 1.5	Desaturation<88% on room air			Dilated RV/RA
			Pulse rate recovery < 13 beats/minute following 6MWT			RV dysfunction



¶ Assessment of parameters are complimentary and should be made in parallel
* All of these thresholds have not been validated as indicators of PH in DPLD and represent the opinion of the authors

Nathan SD, et al. *Respir Med.* 2008;102:1305-1310.
Swigris JJ, et al. *Respirology*. 2011;16:439-445.

Summary

- Suspect PH in patients with ILD when:
  - Dyspnea is disproportionate to extent of ILD
  - Loud P2, signs of right heart failure
  - DLco < 40%
  - Reduced 6MWT, desaturation < 88% on room air, pulse rate recovery < 13 bpm
  - PA:A segment > 1 on chest CT
  - Elevated pro-ntBNP/BNP
- Echocardiography is a good screening tool, but does not accurately predict PH in IPF
- Right heart catheterization is the diagnostic gold standard for PH in IPF

Recent Trials in IIP-PH

STEVEN D. NATHAN, MD
Medical Director, Lung Transplant Program
Director, Advanced Lung Disease Program
Inova Fairfax Hospital
Falls Church, Virginia

Download tonight's presentation at:
www.francefoundation.com/denver

Off-Label Disclosures

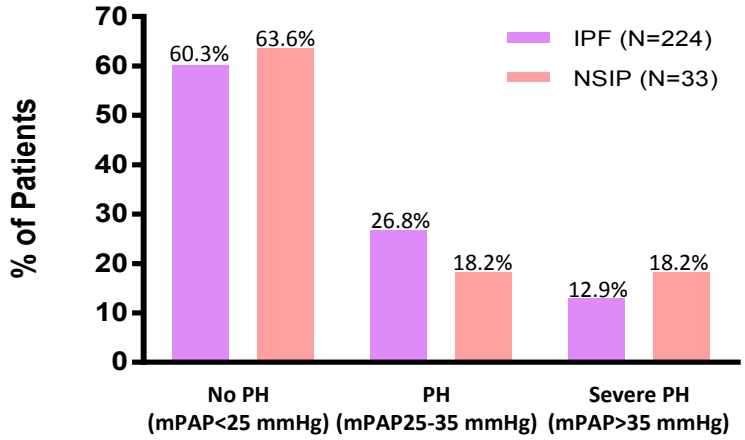
Disclaimer: My presentation may include mention of "off-label" use of the following for PH in lung disease:

- Sildenafil
- Tadalafil
- Bosentan
- Ambrisentan
- Inhaled Iloprost
- Treprostinil
- Epoprostenol
- Macitentan
- Riociguat

Learning Objective

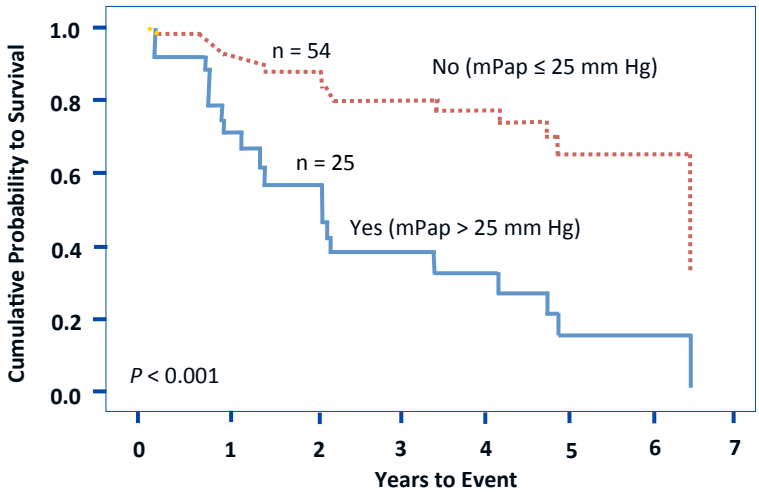
- Review data from studies evaluating treatments for PH in patients with IIPs/IPF

Distribution of mPAP in Patients with IIP



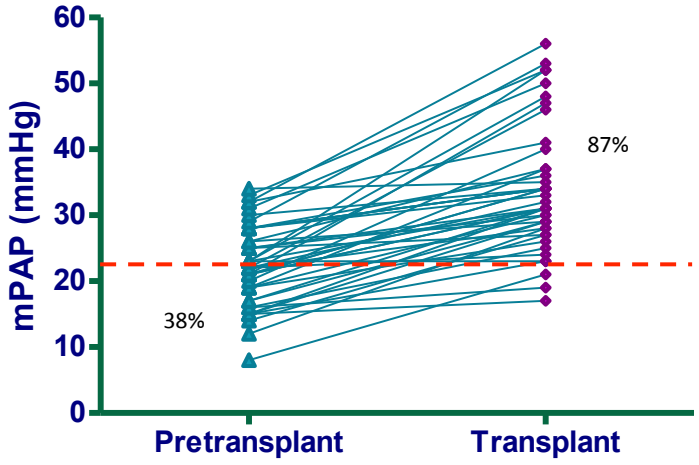
Inova Fairfax data: August 2013

Mean Pulmonary Artery Pressure: Prognostic Value in IPF



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

PH Progression in IPF



Nathan SD, et al. *Respiration*. 2008;76:288-294.

PH in IPF: Impact on 6MWT

	mPAP ≤ 25 mm Hg (N = 24)	mPAP > 25 mm Hg (N = 10)	*P*-value
6MWD (m)	366 ± 82	144 ± 66	< 0.001
SpO_2 nadir (%)	88 ± 4	80 ± 4	< 0.001

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

Acute Exacerbations and PH

Eur Respir J 2012; 40: 93–100
DOI: 10.1183/09031936.00115511
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Acute exacerbations and pulmonary hypertension in advanced idiopathic pulmonary fibrosis

Eoin P. Judge*,#, Aurelie Fabre¶, Huzaifa I. Adamali*,# and Jim J. Egan*,#

ABSTRACT: The aim of this study was to evaluate the risk factors for and outcomes of acute exacerbations in patients with advanced idiopathic pulmonary fibrosis (IPF), and to examine the relationship between disease severity and neovascularisation in explanted IPF lung tissue.

55 IPF patients assessed for lung transplantation were divided into acute (n=27) and non-acute exacerbation (n=28) groups. Haemodynamic data was collected at baseline, at the time of acute exacerbation and at lung transplantation. Histological analysis and CD31 immunostaining to quantify microvessel density (MVD) was performed on the explanted lung tissue of 13 transplanted patients.

Acute exacerbations were associated with increased mortality (p=0.0015). Pulmonary hypertension (PH) at baseline and acute exacerbations were associated with poor survival (p<0.01). PH at baseline was associated with a significant risk of acute exacerbations (HR 2.217, p=0.041). Neovascularisation (MVD) was significantly increased in areas of cellular fibrosis and significantly decreased in areas of honeycombing. There was a significant inverse correlation between mean pulmonary artery pressure and MVD in areas of honeycombing.

Acute exacerbations were associated with significantly increased mortality in patients with advanced IPF. PH was associated with the subsequent development of an acute exacerbation and with poor survival. Neovascularisation was significantly decreased in areas of honeycombing, and was significantly inversely correlated with mean pulmonary arterial pressure in areas of honeycombing.

Judge EP, et al. *Eur Respir J*. 2012;40:93-100.

What we know…

- PH commonly complicates the course of the IIPs
- PH associated with
  - Worsened survival
  - Reduced functional status
  - ? AE's

What we think we know…

- The etiology
- How to diagnose PH

What we don't know…

- Is PH the driver of outcomes or…
- …a surrogate of other "badness?"
- What is "disproportionate" PH?

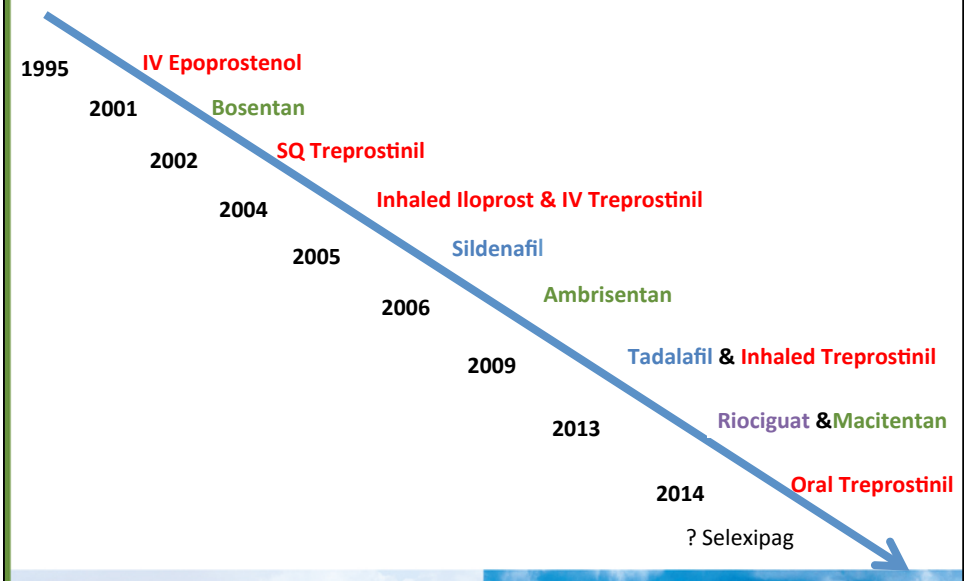
What we don't know, but shouldn't be too scared to ask…

- Should we treat PH?
- Does it affect functional status?
- Survival?
- More harm than good?

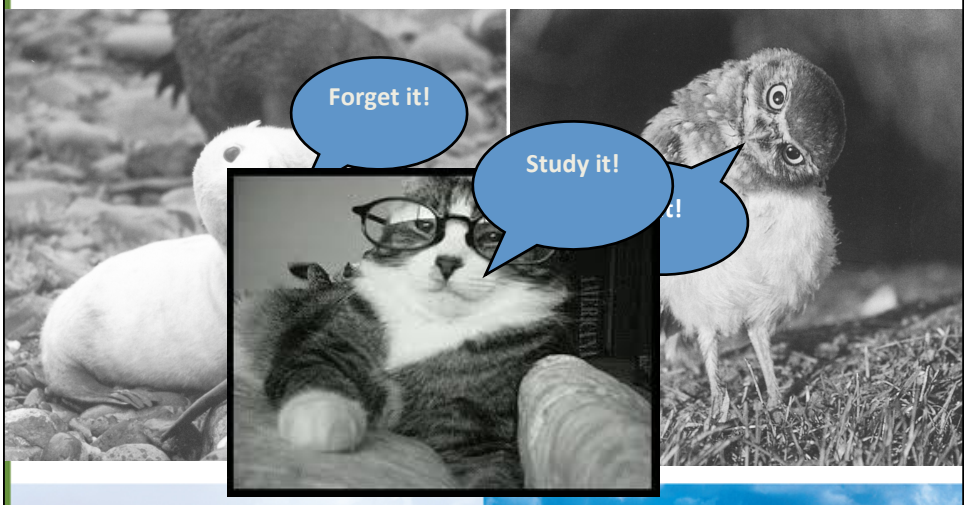
PH in Pulmonary Fibrosis: The Low Hanging Fruit

- Treat the underlying condition
- Comorbidities
  - -Diastolic heart failure
    - IPF – 10-18%
    - Sarcoidosis –19%
  - -Hypoxia/nocturnal desaturation
  - -Obstructive sleep apnea
  - -Pulmonary embolism

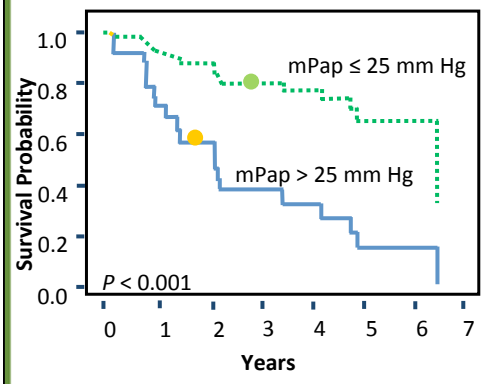
Drug Approvals in PAH

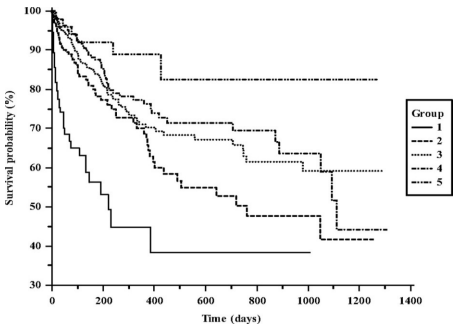


Should We Treat with PH-directed Therapies?



IPF Prognosis…
Can it be Altered by Targeting Prognostic Indicators?



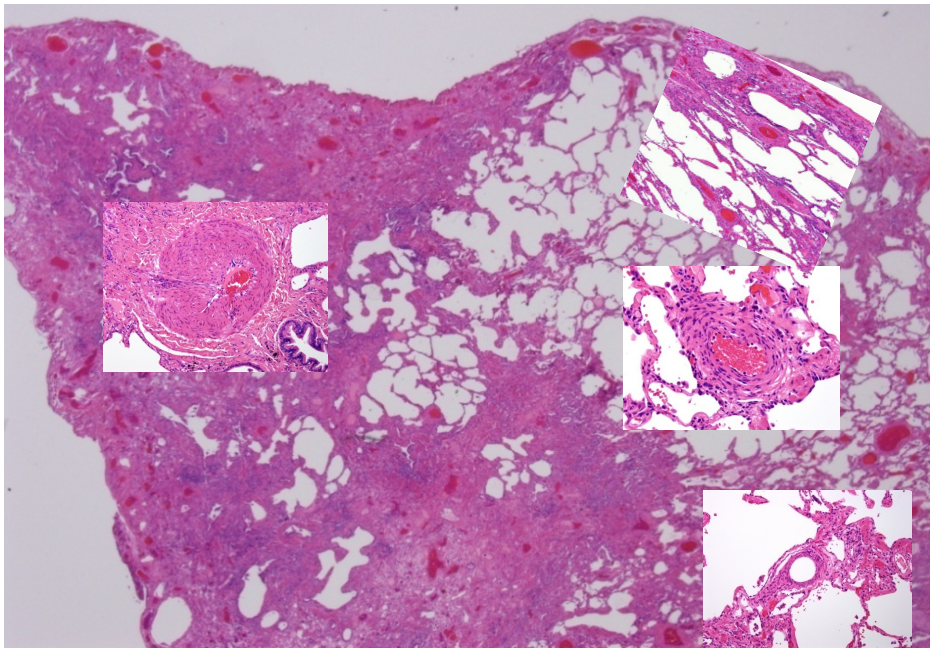


Serum Albumin (g/dL)
Gr.1: 1.7–3.3
Gr. 2: 3.7–3.7
Gr. 3: 3.8–4.1
Gr. 4: 4.2–4.5
Gr. 5: 4.6–5.3

Lettieri CJ, et al. *Chest*. 2006;129:746-752.
Zisman DA, et al. *Chest*. 2009;135:929-935.

Caveats to Empiric Therapy

- Worsening oxygenation
- PVOD
  - IPF
  - Sarcoidosis
  - Drug/Radiation-induced fibrosis
  - Scleroderma
- Occult heart failure



What's New in PH Associated with IIP? New Hope May be on the Horizon

May 17, 2015

Lung Disease	Investigator	Year	Study Design	Subject Number	Therapy	Results	Comments
ILD	Olschewski	1999	Open-label	8	Nitric oxide, Epo IV and inhaled	Inhaled prostanoids improved gas exchange	
ILD	Ghofrani	2002	Open-label	16	Sildenafil or Epo	Sildenafil ↑V/Q matching and ↑oxygenation	Prostacyclin worsened V/Q matching
IPF	Krowka	2007	RCT	51	Inhaled Iloprost	no differences 6MWT, NYHA class, Dyspnea score, exercise O_2 sat	
IPF	Gunther	2007	Open-label	12	Bosentan	No worsening of gas exchange	
IPF	Collard	2007	Open-label	14	Sildenafil	57% improved 6MWT by ≥ 20%	Median follow-up of 91 days
ILD	Minai	2008	Retrospective	19	Epo(n=10) Bosentan(n=9)	79% with↑6MWT > 50 m	
ILD	Chapman	2009	Retrospective	5	Sildenafil	Improved 6MWT	Decreased mPAP 2-12 months
IPF	Zisman	2010	RCT	180	Sildenafil	Failed to improve 6MWT by ≥ 20%	Improved oxygen saturation and QOL

Lung Disease	Investigator	Year	Study Design	Subject Number	Therapy	Results	Comments
IPF	Jackson	2010	RCT	29	Sildenafil	No difference in 6MWT or Borg score	
ILD	Corte	2010	Retrospective	15	Sildenafil	Improved 6MWT and lower BNP	
ILD	Badesch	2011	Open-label	21	Ambrisentan	6MWT distance ↓; BNP ↓	Studied mixed PH population
IPF	Raghu	2013	RCT	492	Ambrisentan	Terminated early: lack of efficacy in time to clinical worsening	32 patients with PH: no change in time to disease progression
ILD	Hoeper	2013	Open-label	22	Riociguat	Improved CO and PVR but not mPAP	O2 sat↓, mixed-venous ↑
ILD	Zimmerman	2014	Open-label, observational	10	Sildenafil(n=5) Tadalafil(n=5)	↑CO and ↓PVR	No change in 6MWT or BNP
ILD	Corte	2014	RCT	60	Bosentan	Unchanged:hemo's, symptoms, FC	RHC confirmed PH
ILD	Saggar	2014	Open-label	15	Treprostinil	Improved hemo's without hypoxemia	All had mPAP ≥ 35 mmHg

Active Study of Inhaled Iloprost

Parameter	Iloprost	Placebo	*P*-value
Number	26	25	
Class II/III	12/14	7/16	
Supplemental O_2	18 (69%)	22 (88%)	
Baseline 6MWD (mean)	262 m	224 m	
Week 12 6MWD	219	238	
Change in 6MWD	-31	+10	0.16

Krowka MJ, et al. *Chest*. 2007;132:633S.

Step Study: ? Proof of Concept

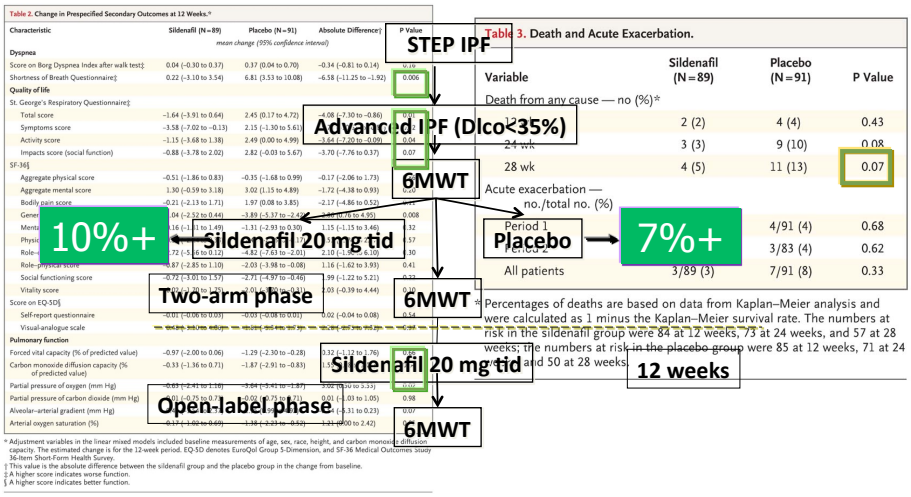


Table 3. Death and Acute Exacerbation.

Variable	Sildenafil (N=89)	Placebo (N=91)	P Value
Death from any cause — no (%)*			
12 wk	2 (2)	4 (4)	0.43
24 wk	3 (3)	9 (10)	0.08
28 wk	4 (5)	11 (13)	0.07
Acute exacerbation — no./total no. (%)			
Period 1	4/91 (4)	4/91 (4)	0.68
Period 2	3/83 (4)	3/83 (4)	0.62
All patients	7/91 (8)	7/91 (8)	0.33

* Percentages of deaths are based on data from Kaplan–Meier analysis and were calculated as 1 minus the Kaplan–Meier survival rate. The numbers at risk in the sildenafil group were 84 at 12 weeks, 73 at 24 weeks, and 57 at 28 weeks; the numbers at risk in the placebo group were 85 at 12 weeks, 71 at 24 weeks, and 50 at 28 weeks.

The Idiopathic Pulmonary Fibrosis Clinical Research Network.
N Engl J Med. 2010; 363:620-628.

Riociguat for Interstitial Lung Disease and Pulmonary Hypertension: A Pilot Trial

- Multicenter, open label, uncontrolled study
- N = 22
- Oral riociguat (1.0-2.5 mg, 3 times/day)
- 12 weeks plus 12-month extension
- Primary endpoint: safety and tolerability
- Secondary endpoints included hemodynamic changes and 6MWD

Key Findings

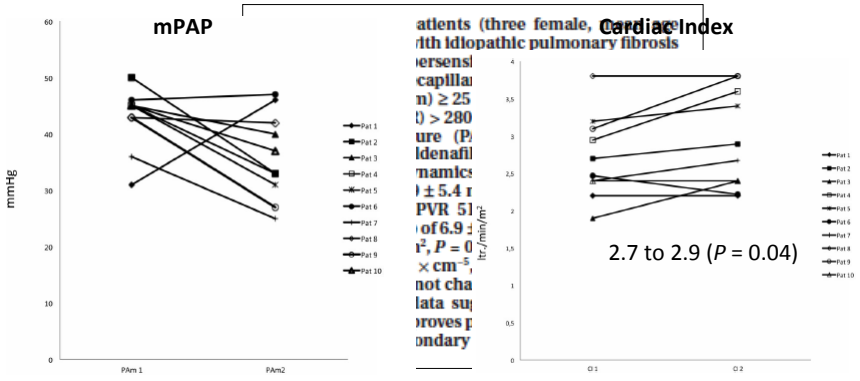
Safety (n = 22)
- **AEs:** dyspnea, peripheral edema (27%), dyspepsia, headache, feeling hot (14%), hypotension (5%)
- **SAEs** (possibly drug related)**:** syncope, respiratory disorder, respiratory failure (n = 1), pancytopenia (n = 2), dyspnea (n = 3)

Efficacy
1. **6MWD,** +25 m
2. **Hemodynamics**
   - **Cardiac index**: +0.7 L/min^{-1}·m^{-2} (+25%)
   - **PVR**: -120 dyn·s·cm^{-5} (-19%)
   - **PAP**: no change (+1 mmHg)

The results of this pilot trial indicate that riociguat appears to be well tolerated by the majority of patients with PH-ILD. It is associated with a substantial increase in cardiac output and reductions in SVR and PVR and may have the potential to improve exercise capacity in some patients

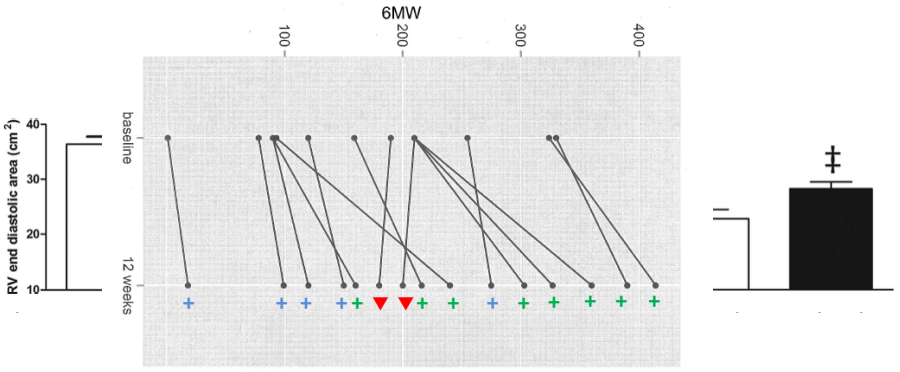
Hoeper MM, et al. *Eur Respir J*. 2013;41:853-860.

Hemodynamic Changes in Pulmonary Hypertension in Patients with ILD Treated with PDE-5 Inhibitors



Zimmermann GS, et al. *Respirology*. 2014;19;700-706.

Changes in right heart haemodynamics and echocardiographic function in an advanced phenotype of pulmonary hypertension and right heart dysfunction associated with pulmonary fibrosis



Conclusions PH-targeted therapy may improve right heart haemodynamics and echocardiographic function without affecting systemic oxygen saturation in an advanced PH phenotype associated with RV dysfunction in the setting of PF.

+ = Improved by ≥ 57 m
+ = Improved by ≥ 17 m
▼= Declined by 10 m

Saggar R, et al. *Thorax*. 2014;69:123-129.

Bosentan in Pulmonary Hypertension Associated with Fibrotic Idiopathic Interstitial Pneumonia

Abstract

Rationale: Pulmonary hypertension (PH) associated with fibrotic idiopathic interstitial pneumonia (IIP; idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia) confers important additional morbidity and mortality.

Objectives: To evaluate the safety and clinical efficacy of the dual endothelin-1 receptor antagonist bosentan in this patient group.

Methods: In a randomized, double-blind, placebo-controlled study, 60 patients with fibrotic IIP and right heart catheter confirmed PH were randomized 2:1 to bosentan (n = 40) or placebo (n = 20). The primary study endpoint was a fall from baseline pulmonary vascular resistance index (PVRi) of 20% or more over 16 weeks.

Measurements and Main Results: Sixty patients (42 men; mean age, 66.6 ± 9.2 yr), with a mean pulmonary artery pressure of 36.0 (± 8.9) mm Hg, PVRi 13.0 (± 6.7) Wood Units/m^2 and reduced cardiac index of 2.21 (± 0.5) L/min/m^2 were recruited to the study. Accounting for deaths and withdrawals, paired right heart catheter data were available for analysis in 39 patients (bosentan = 25, placebo = 14). No difference in the primary outcome was detected, with seven (28.0%) patients receiving bosentan, and four (28.6%) receiving placebo achieving a reduction in PVRi of greater than or equal to 20% (P = 0.97) at 16 weeks. There was no change in functional capacity or symptoms between the two groups at 16 weeks, nor any difference in rates of serious adverse events or deaths (three deaths in each group).

Conclusions: This study shows no difference in invasive pulmonary hemodynamics, functional capacity, or symptoms between the bosentan and placebo groups over 16 weeks. Our data do not support the use of the dual endothelin-1 receptor antagonist, bosentan, in patients with PH and fibrotic IIP.
Clinical trial registered with www.clinicaltrials.gov (NCT 00637065).

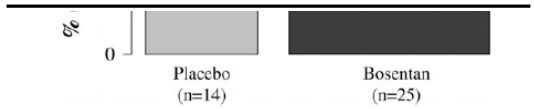
Keywords: hypertension, pulmonary; interstitial lung diseases; clinical trial

Corte T, et al. *Am J Respir Crit Care Med*. 2014;190:208-217.

BPHIT Study: No Efficacy Signal

Table 2. Change in Prespecified Outcomes at 16 Weeks

	Bosentan (*n* = 25)	Placebo (*n* = 14)	*P* Value
Δ PVR index	−1.1 (3.9)	0.8 (4.2)	0.19
Δ mPAP, mm Hg	−1.3 (5.6)	0.2 (7.4)	0.43
Δ mRAP, mm Hg	−1.7 (5.5)	−0.8 (5.2)	0.74
Δ Cardiac index, L/min/m^2	0.1 (0.5)	−0.1 (0.4)	0.31
Δ SpO_2, %	−0.76 (4.0)	−0.57 (3.9)	0.74
Δ 6MWD, m	−25.9 (56.7)	−53.1 (66.9)	0.42
Δ 6MWT, dyspnea pre	0.8 (1.4)	1.1 (2.0)	0.98
Δ 6MWT, dyspnea post	−0.04 (2.3)	0.0 (1.2)	0.51
Δ 6MWT, fatigue pre	0.4 (2.9)	0.4 (1.7)	0.71
Δ 6MWT, fatigue post	0.2 (3.7)	−1.8 (1.8)	0.12
Δ CAMPHOR, symptom score	0.0 (4.5)	0.4 (3.5)	0.92
Δ CAMPHOR, activities score	1.2 (3.8)	0.9 (4.5)	0.94
Δ CAMPHOR, QOL score	0.2 (4.3)	0.3 (3.8)	0.96
Δ D_{LCO}, % predicted	−3.2 (6.9)	−2.1 (4.9)	0.96
Δ Kco, % predicted	−5.8 (8.9)	−0.2 (14.5)	0.54
Δ FVC, % predicted	−0.9 (6.8)	−2.6 (23.2)	0.96
Δ CPI	2.0 (5.2)	0.4 (6.0)	0.95
Δ BNP, pg/ml	13.0 (90.5)	21.0 (50.4)	0.32
Δ TAPSE, mm	1.8 (4.4)	1.4 (4.7)	0.56
Δ RV inlet size, mm	0.4 (0.8)	−0.1 (0.6)	0.12



Corte T, et al. *Am J Respir Crit Care Med.* 2014;190:208-217.

How to Design Studies of Rx for Pulmonary Hypertension in Association with Pulmonary Fibrosis

Inova Advanced Lung Disease
& Transplant Progra

Study Design: Many Moving Parts to Get it Right!

A drug that works — and is well tolerated

The right dose, frequency — and route of administration

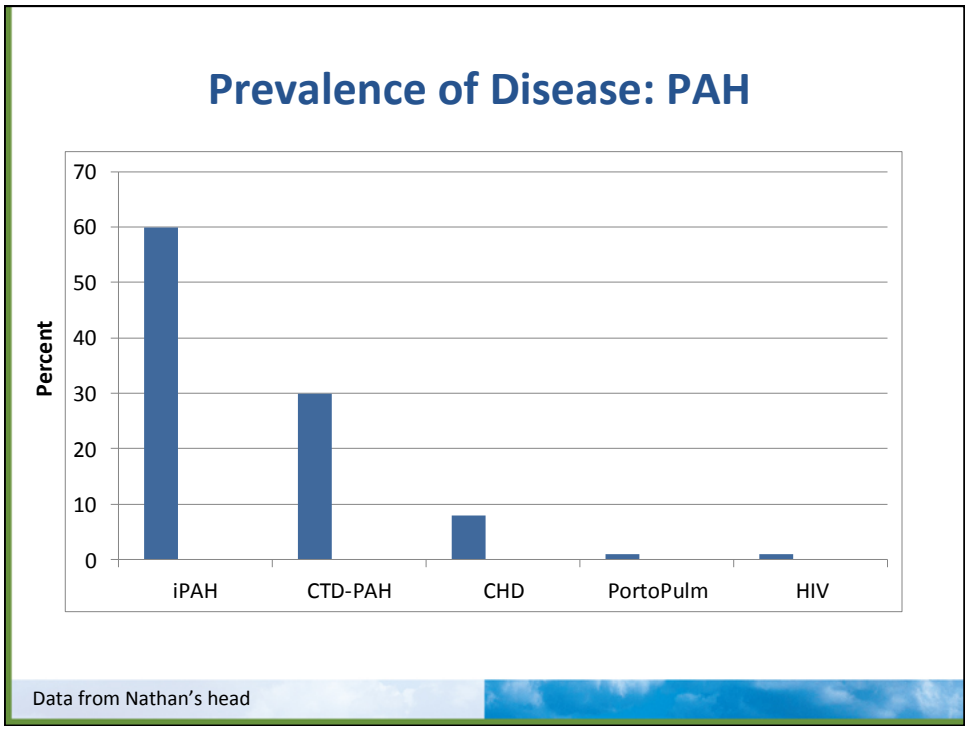
The right patient population — that is likely to be retained

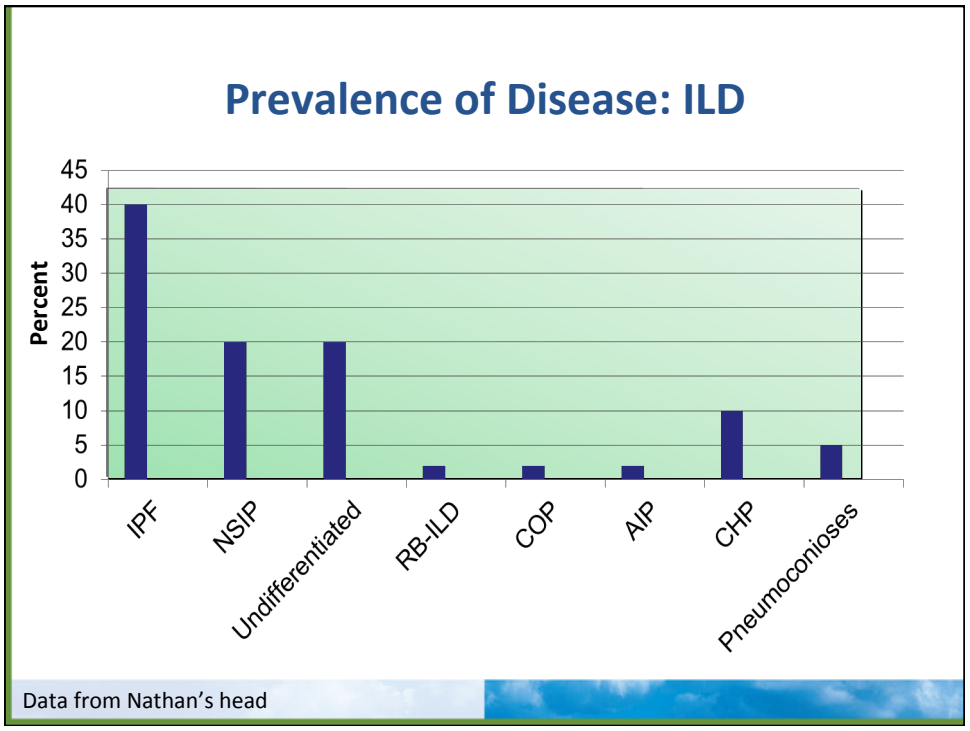
Disease stage, phenotype

The right duration — the right endpoint(s)

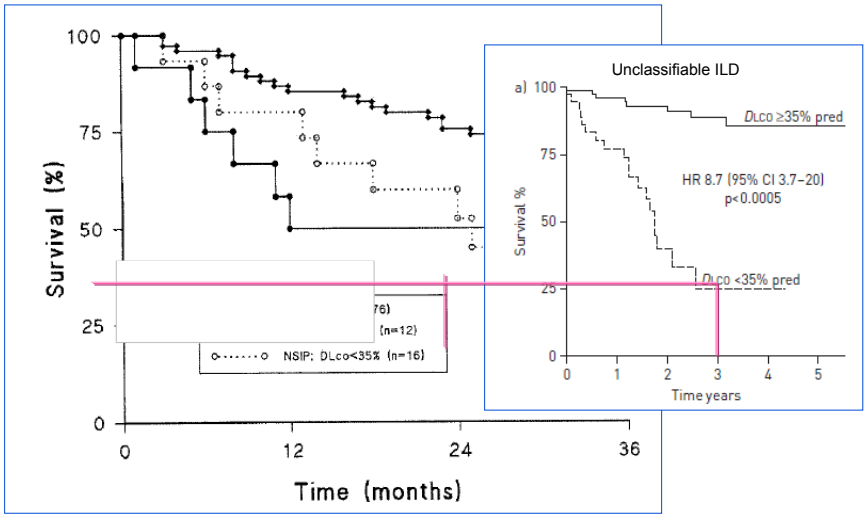
Important Inclusionary Criteria: *Choosing the "best" patient phenotype*

- Likely to respond to therapy
  - How to define this?
- Balance of amount of parenchymal lung disease versus severity of pulmonary vascular disease
- Casting a wide enough net
  - Distinct entity vs distinct group of entities


Prevalence of Disease: PAH
Percent
70
60
50
40
30
20
10
0
iPAH
CTD-PAH
CHD
PortoPulm
HIV
Data from Nathan's head


Prevalence of Disease: ILD
Percent
45
40
35
30
25
20
15
10
5
0
IPF
NSIP
Undifferentiated
RB-ILD
COP
AIP
CHP
Pneumoconioses
Data from Nathan's head

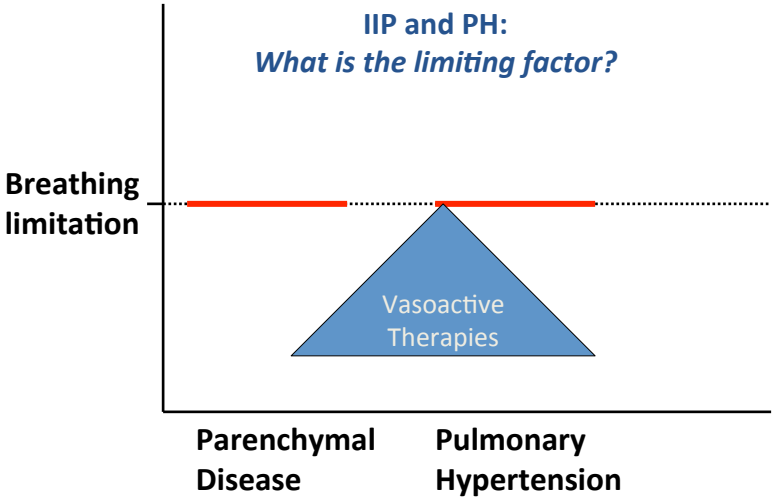
Pulmonary Fibrosis: A Final Common Path?



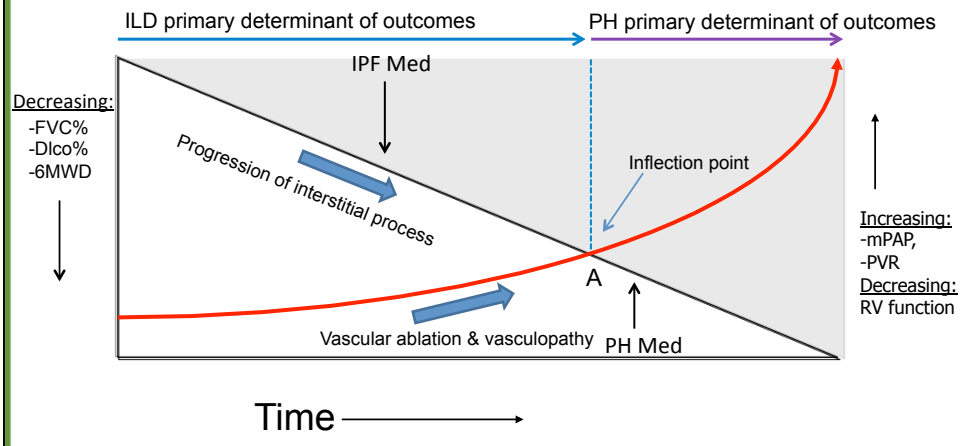
Laatsi PI, et al. *Am J Respir Crit Care Med*. 2003;168:531-537
Ryerson CJ, et al. *Eur Respir J*. 2013;42:750-757.

Choosing the Patient Population to Demonstrate Efficacy

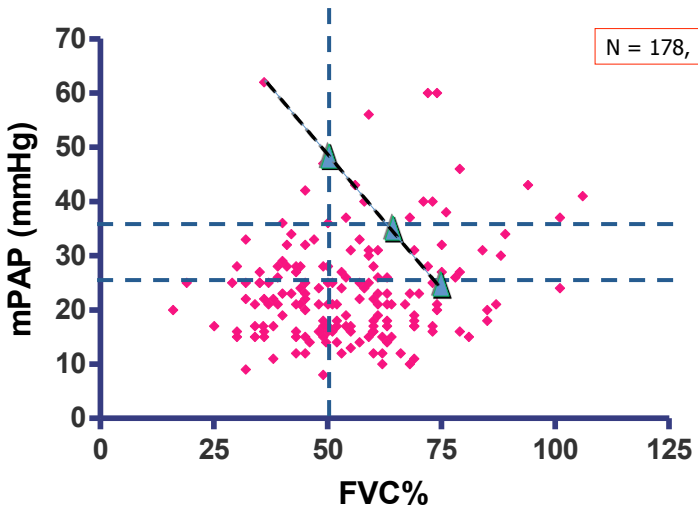
IIP and PH:
What is the limiting factor?

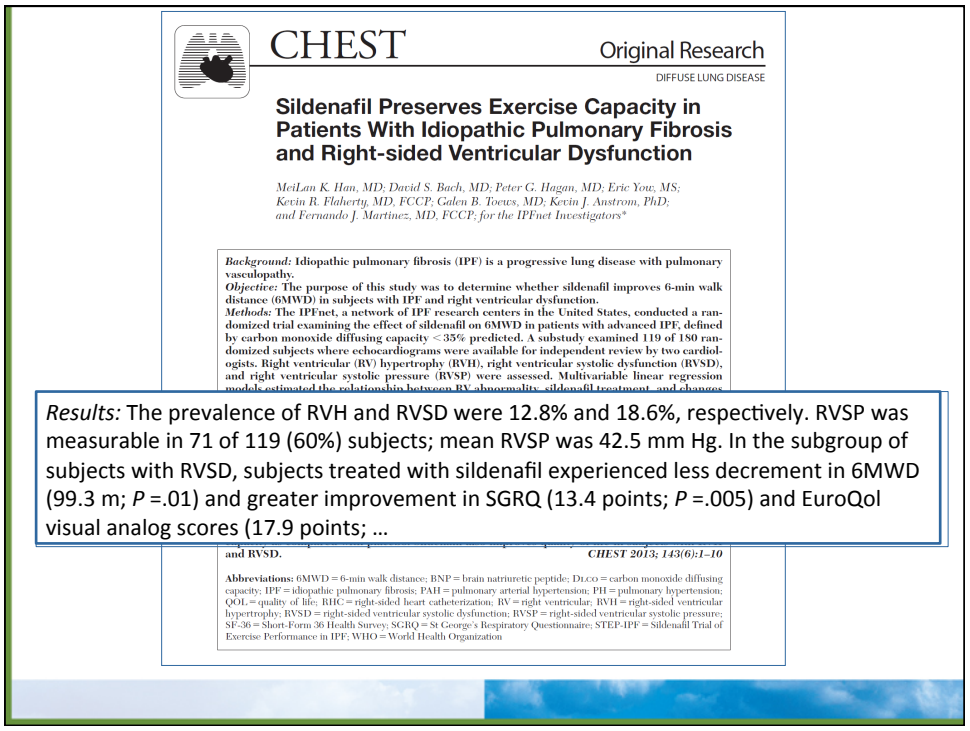


ILD with PH: What Drives Outcomes?
ILD with PH: What of Therapy?



IPF: Which Patient Group Should be Targeted?





CHEST Original Research

DIFFUSE LUNG DISEASE

Sildenafil Preserves Exercise Capacity in Patients With Idiopathic Pulmonary Fibrosis and Right-sided Ventricular Dysfunction

*MeiLan K. Han, MD; David S. Bach, MD; Peter G. Hagan, MD; Eric Yow, MS; Kevin R. Flaherty, MD, FCCP; Galen B. Toews, MD; Kevin J. Anstrom, PhD; and Fernando J. Martinez, MD, FCCP; for the IPFnet Investigators**

Background: **Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease with pulmonary vasculopathy.**
Objective: **The purpose of this study was to determine whether sildenafil improves 6-min walk distance (6MWD) in subjects with IPF and right ventricular dysfunction.**
Methods: **The IPFnet, a network of IPF research centers in the United States, conducted a randomized trial examining the effect of sildenafil on 6MWD in patients with advanced IPF, defined by carbon monoxide diffusing capacity < 35% predicted. A substudy examined 119 of 180 randomized subjects where echocardiograms were available for independent review by two cardiologists. Right ventricular (RV) 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**

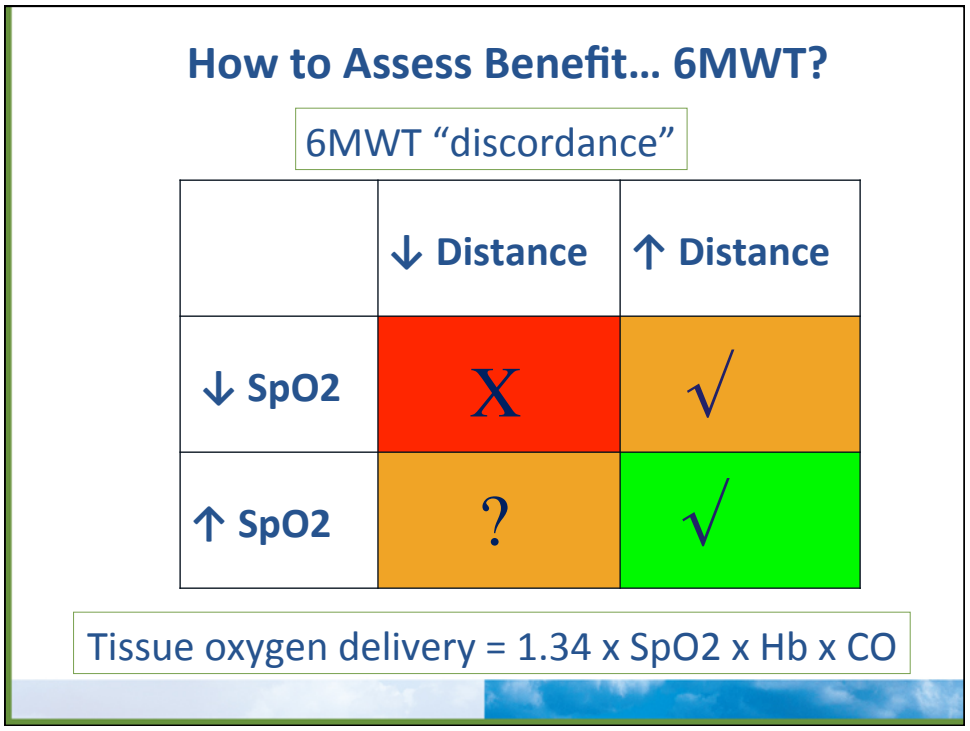
Results: The prevalence of RVH and RVSD were 12.8% and 18.6%, respectively. RVSP was measurable in 71 of 119 (60%) subjects; mean RVSP was 42.5 mm Hg. In the subgroup of subjects with RVSD, subjects treated with sildenafil experienced less decrement in 6MWD (99.3 m; *P* =.01) and greater improvement in SGRQ (13.4 points; *P* =.005) and EuroQol visual analog scores (17.9 points; …

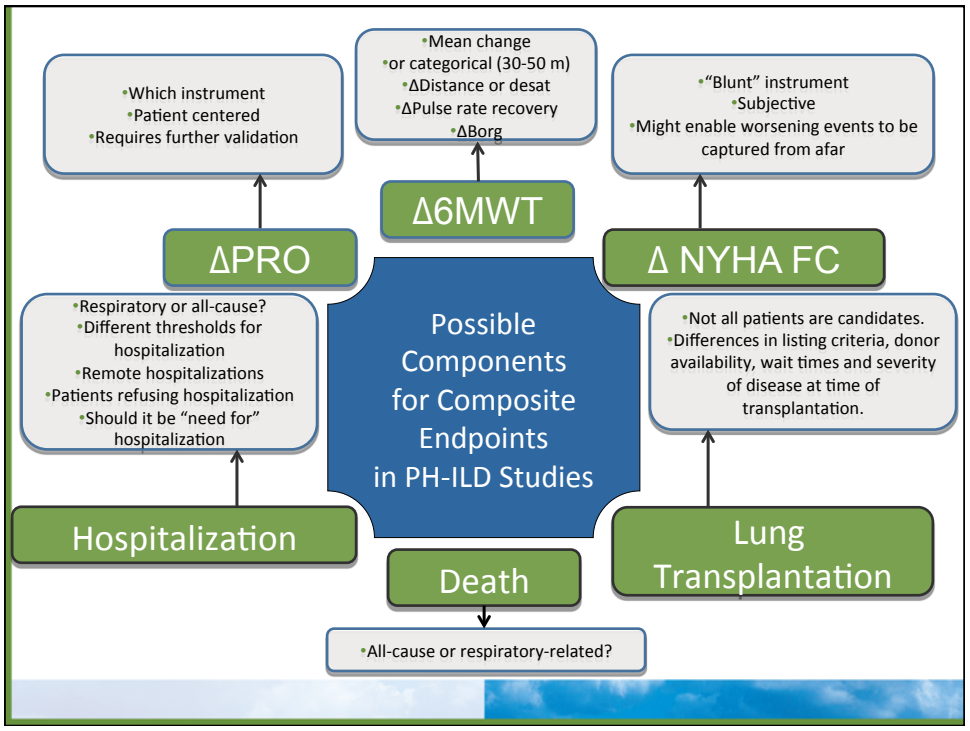
and RVSD. ***CHEST 2013; 143(6):1–10***

Abbreviations: 6MWD = 6-min walk distance; BNP = brain natriuretic peptide; DLCO = carbon monoxide diffusing capacity; IPF = idiopathic pulmonary fibrosis; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; QOL = quality of life; RHC = right-sided heart catheterization; RV = right ventricular; RVH = right-sided ventricular hypertrophy; RVSD = right-sided ventricular systolic dysfunction; RVSP = right-sided ventricular systolic pressure; SF-36 = Short-Form 36 Health Survey; SGRQ = St George's Respiratory Questionnaire; STEP-IPF = Sildenafil Trial of Exercise Performance in IPF; WHO = World Health Organization

Choosing the Best Endpoint: What Does PH Effect?

- Survival
- Functional status
  - 6MWT
  - Functional class
- QOL
  - PROs
- AE's
- Hospitalization
- Transplantation


How to Assess Benefit… 6MWT?
6MWT "discordance"
↓ Distance
↑ Distance
↓ SpO2
X
√
↑ SpO2
?
√
Tissue oxygen delivery = 1.34 x SpO2 x Hb x CO


•Mean change
•or categorical (30-50 m)
•ΔDistance or desat
•ΔPulse rate recovery
•ΔBorg
•Which instrument
•Patient centered
•Requires further validation
•"Blunt" instrument
•Subjective
•Might enable worsening events to be captured from afar
Δ6MWT
ΔPRO
Δ NYHA FC
•Respiratory or all-cause?
•Different thresholds for hospitalization
•Remote hospitalizations
•Patients refusing hospitalization
•Should it be "need for" hospitalization
Possible Components for Composite Endpoints in PH-ILD Studies
•Not all patients are candidates.
•Differences in listing criteria, donor availability, wait times and severity of disease at time of transplantation.
Hospitalization
Death
Lung Transplantation
•All-cause or respiratory-related?

RISE-IIP Study

- **Diagnosed with a major idiopathic interstitial pneumonia**
- **Major Inclusion criteria**
  - FVC ≥ 45%
  - 6MWD ≥ 150 m and ≤ 450 m
  - PH confirmed by RHC with mPAP ≥ 25 mmHg and PCWP ≤15 mmHg at rest
  - Systolic blood pressure ≥ 95 mmHg and no signs or symptoms of hypotension
  - WHO functional class II-IV disease
- **Major Exclusion criteria**
  - Known significant left heart disease: symptomatic coronary artery disease or LVEF < 45%
  - Active state of hemoptysis or pulmonary hemorrhage
  - Difference > 15% between the eligibility and the baseline 6MWD
  - FEV_1/FVC < 0.65 after bronchodilator administration
  - Approved IPF drug initiated within 3 months prior to screening

NCT02138825. https://www.clinicaltrials.gov/ct2/show/NCT02138825. Accessed Mar 2015.

RISE-IIP Efficacy Endpoints

Primary efficacy variables

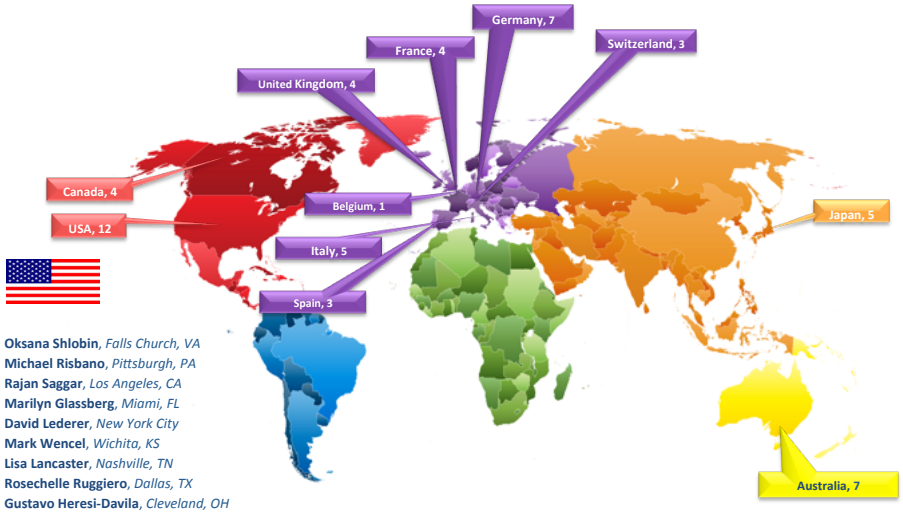
- Mean change in 6MWD from baseline to week 26

Secondary efficacy variables

- Time to clinical worsening as evidenced by the first of any of the following four events
  - All-cause mortality
  - Need for hospitalization due to worsening cardiopulmonary status, attributable to progression of disease (including but not limited to increased shortness of breath or increased leg swelling)
  - 15% decrease in 6MWD from baseline
  - Worsening of WHO functional class

NCT02138825. https://www.clinicaltrials.gov/ct2/show/NCT02138825. Accessed Mar 2015.

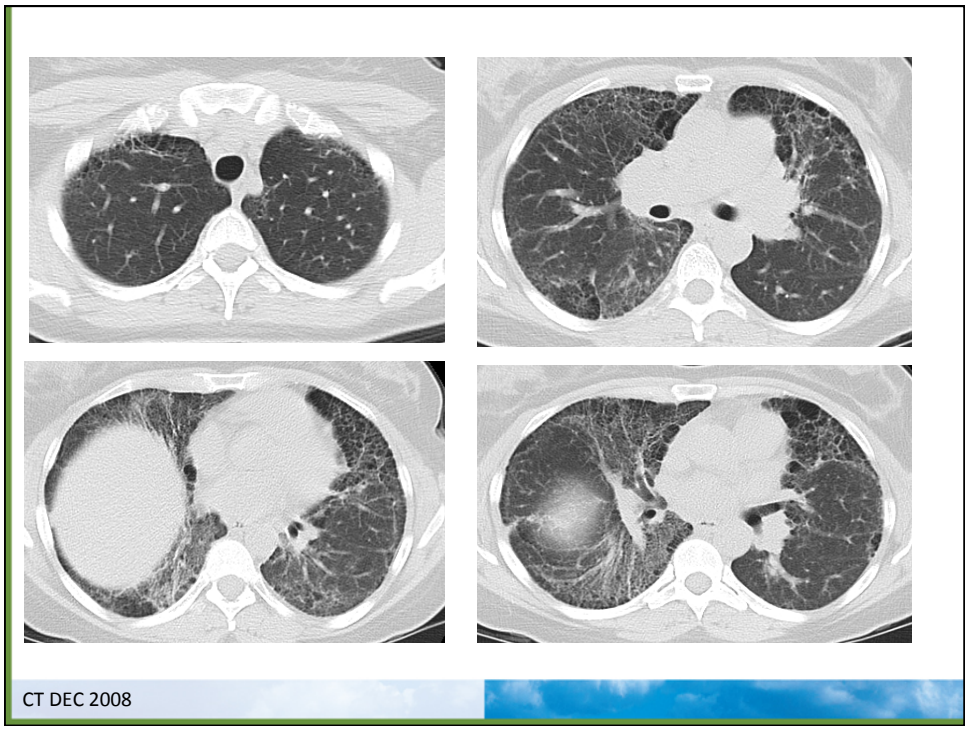
RISE-IIP: Participating Countries and Sites

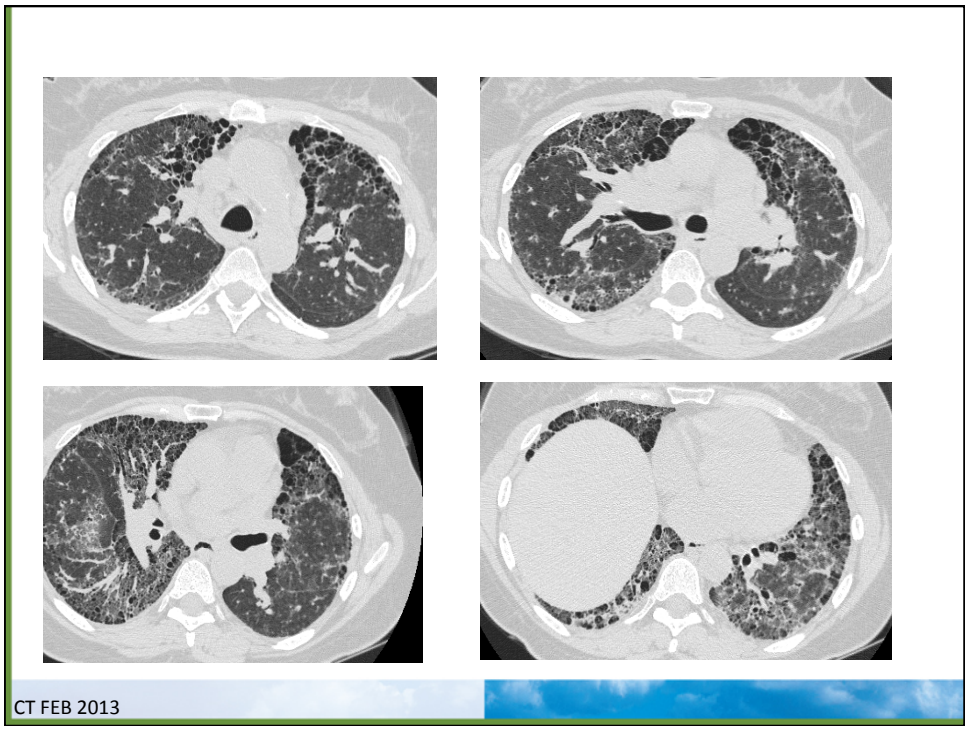


Oksana Shlobin, *Falls Church, VA*
Michael Risbano, *Pittsburgh, PA*
Rajan Saggar, *Los Angeles, CA*
Marilyn Glassberg, *Miami, FL*
David Lederer, *New York City*
Mark Wencel, *Wichita, KS*
Lisa Lancaster, *Nashville, TN*
Rosechelle Ruggiero, *Dallas, TX*
Gustavo Heresi-Davila, *Cleveland, OH*
Lake Morrison, *Durham, NC*
Todd Bull, *Aurora, CO*
Jeffrey Golden, *San Francisco, CA*

NCT02138825. https://www.clinicaltrials.gov/ct2/show/NCT02138825. Accessed Mar 2015.

Case Continuation …


CT DEC 2008


CT FEB 2013

Right Heart Catheterization

	July 2005
RA	6 mmHg
RV	33/4 mmHg
PA	33/11 (22 mmHg)
PAWP	6 mmHg
CO/CI (TD)	4.2/2.45
PVR	3.8

Which of the following is the most appropriate management strategy for this patient's pulmonary vascular disease?

A. Do nothing
B. Treat with off-label PAH medication to prevent development of PH
C. Refer to ILD Program for management
D. Refer to PH Program for management

RHC was Repeated

	July 2005	Dec 2009
RA	6 mmHg	3 mmHg
RV	33/4 mmHg	48/5 mmHg
PA	33/11 (22 mmHg)	47/14 (28) mmHg
PAWP	6 mmHg	6 mmHg
CO/CI (TD)	4.2/2.45	3.6/2.1
PVR	3.8	6.1

Which of the following is the most appropriate management strategy for this patient's pulmonary vascular disease?

A. Do nothing
B. Treat with off-label PAH medication to prevent progression of PH
C. Refer to ILD Program for management
D. Refer to PH Program for management
E. Repeat RHC in a year
F. Refer for enrollment in clinical trial

RHC was Repeated … Again

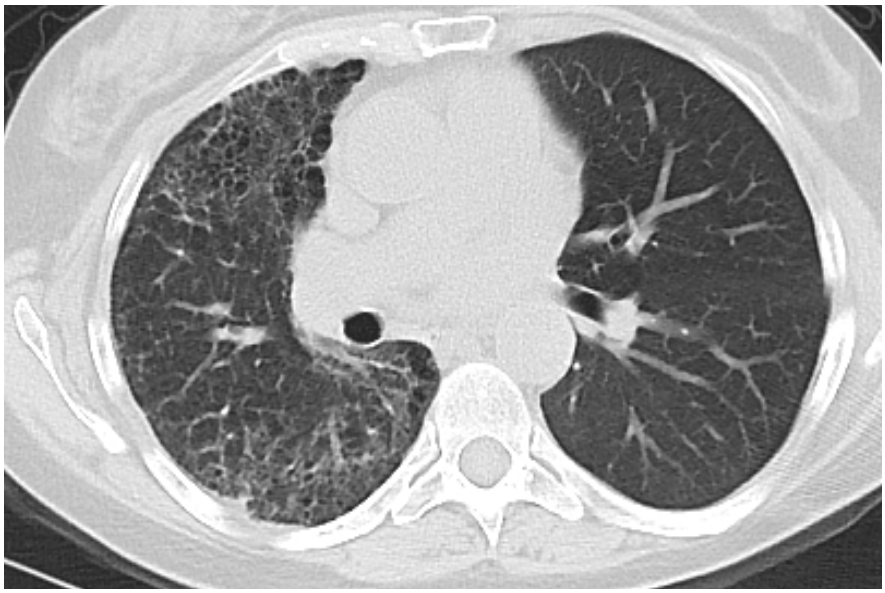
	July 2005	Dec 2009	July 2013
RA	6 mmHg	3 mmHg	5 mmHg
RV	33/4 mmHg	48/5 mmHg	
PA	33/11 (22 mmHg)	47/14 (28mmHg)	86/43 (55 mmHg)
PAWP	6 mmHg	6 mmHg	7 mmHg
CO/CI (TD)	4.2/2.45	3.6/2.1	2.37/1.4
PVR	3.8	6.1	20

Which of the following is the most appropriate management strategy for this patient's pulmonary vascular disease?

A. Do nothing
B. Treat with off-label PDE-5 inhibitor
C. Treat with off-label ERA
D. Treat with off-label parenteral prostanoid
E. Refer to PH Program for management
F. Refer for enrollment in clinical trial

Clinical Course

- IV prostanoid started
- Oxygenation improved with IV therapy; Oxymizer 10L/min with 100% NRB to recover from activity
- Prostanoid infusion increased to 20ng/kg/min
- Lung transplant evaluation completed in-house
- Listed for transplant for single or bilateral lung, first available with LAS of 95
- Received left single lung transplant 7 days later



CT post LTx Dec 2013

The Future

- Better phenotyping of IIP patients
  - Define patients at risk or with PH
  - Is the concept of disproportionate PH valid?
- Define the role of screening
  - When and how…and how often?
- Is PH a viable therapeutic target?
- Studies of therapy are