Idiopathic pulmonary fibrosis: the disease process and supportive care

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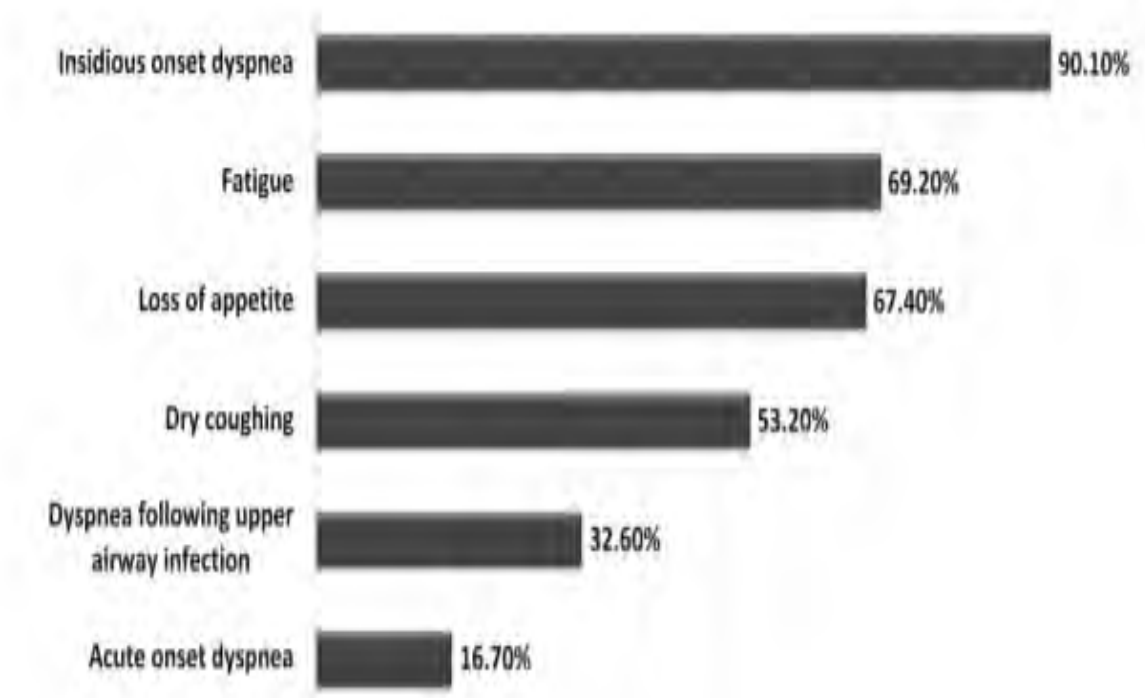
Our case

This patient is referred because of lung fibrosis. He is 69 years old, and has noticed a worsening in his breathing especially beginning in October such that he become short of breath walking up hill. He said he was diagnosed as having fibrotic lung disease at the VA 10 years ago and was followed by chest radiograph and was told he was stable. He did not have any PFTs done. He then saw his primary care physician recently because of this increased shortness of breath, underwent a cardiac evaluation which apparently was normal. It was found that he desaturated with exertion and this prompted further evaluation. Of note, he does have a mother who also has pulmonary fibrosis but she is 89 years old. He denies any rheumatic disease. There has been no joint pain but he does have reflux. He did have an episode of fractured ribs in the past.

He has been treated with back surgery in 2017, had nasal surgery in 1979. He underwent prior appendectomy and back surgery. He is retired, worked in the financial services.

Presenting symptoms in IPF



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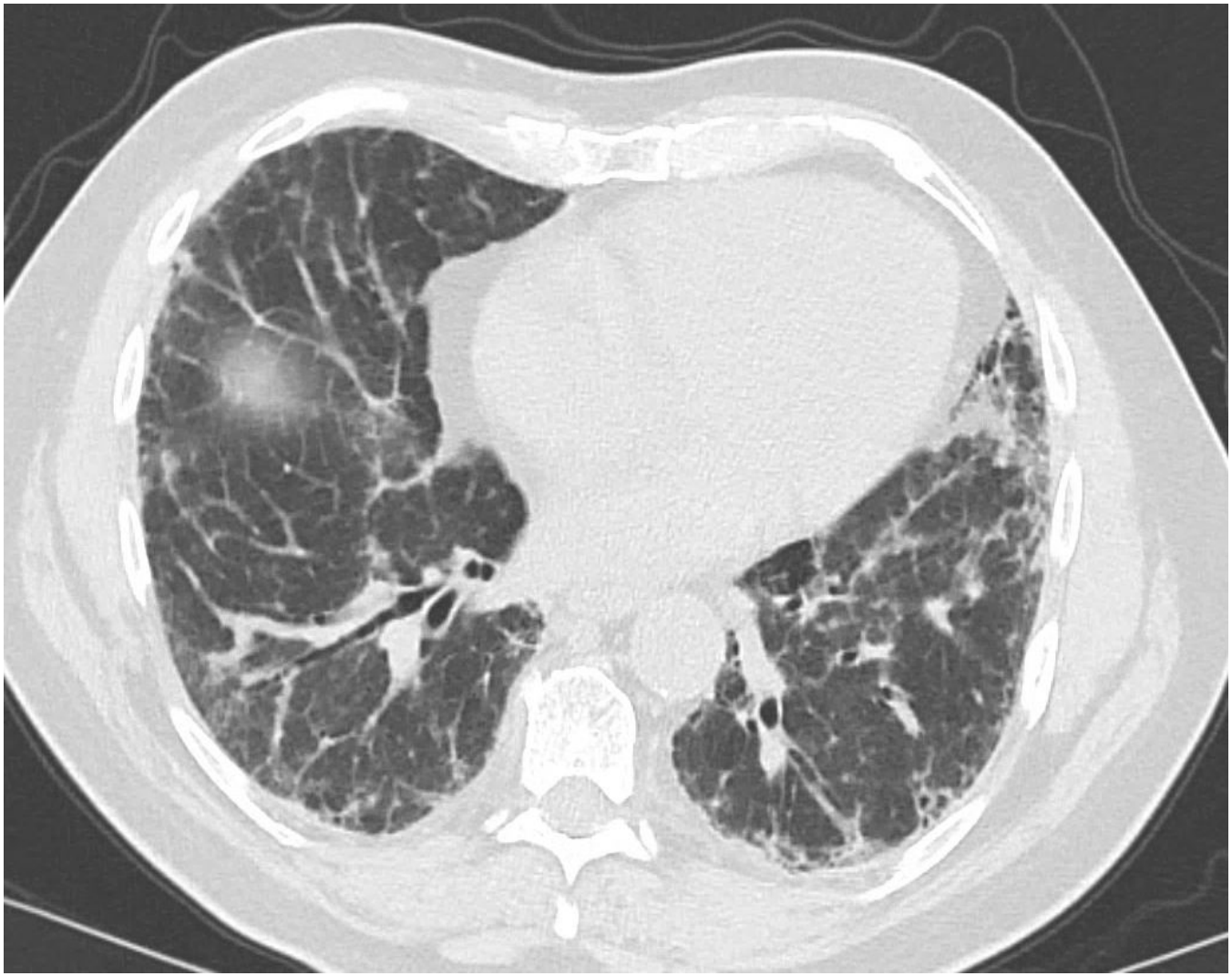
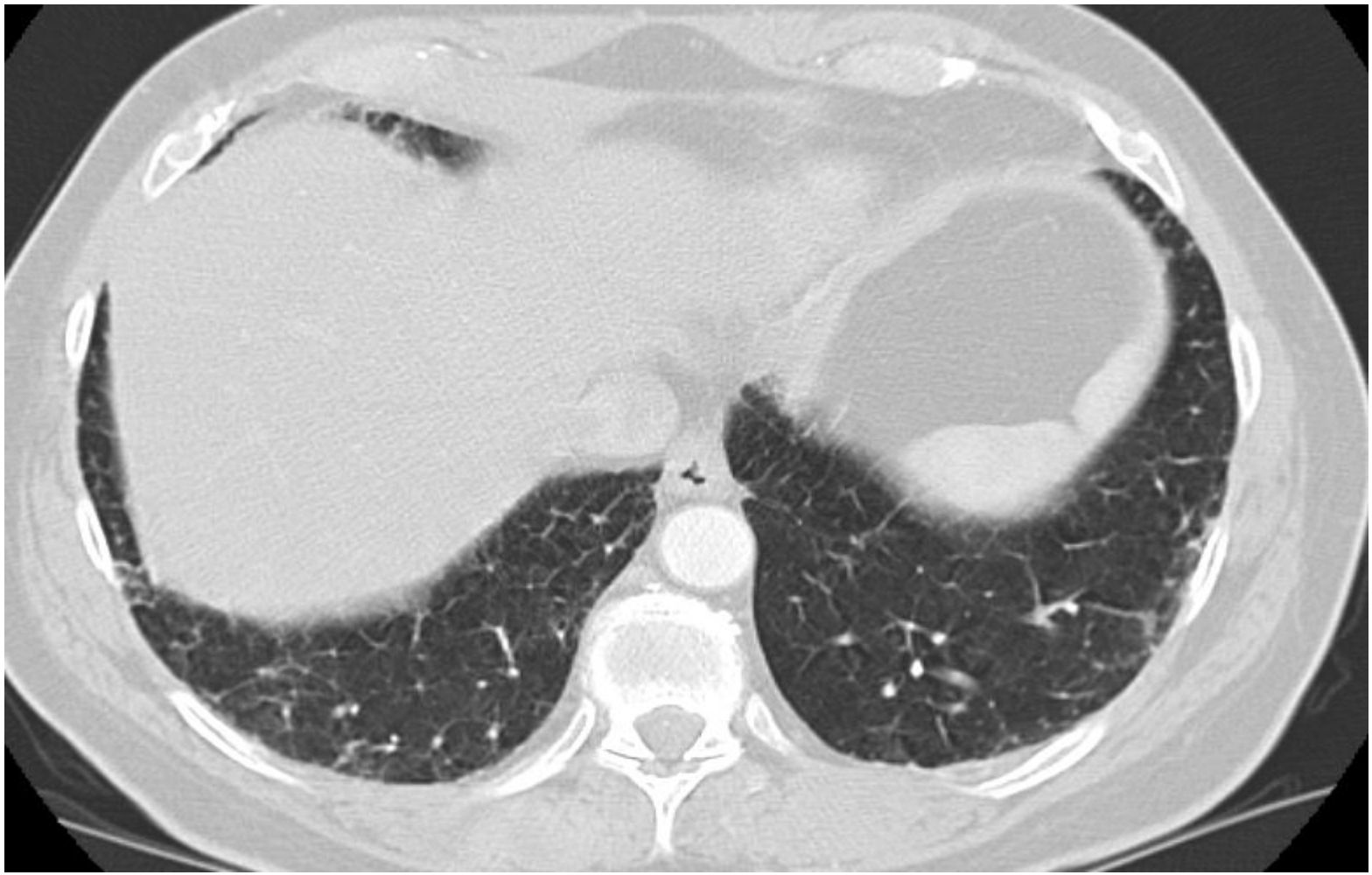
CT scan



Ct scan 2010



Features of CT in UIP

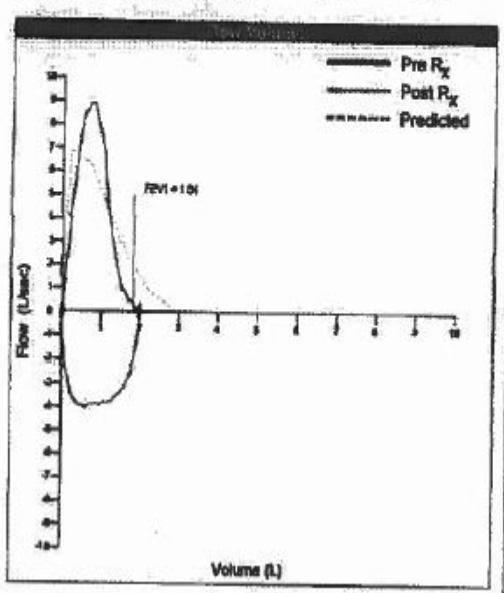
- Subpleural reticular shadows, basilar predominance
- Traction bronchiectasis
- Honeycombing
- Lack of adenopathy, pleural effusions, ground glass infiltrates, nodules

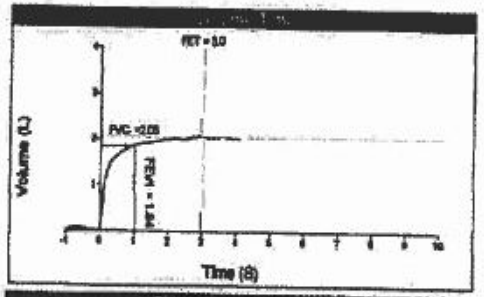
PFT evaluation

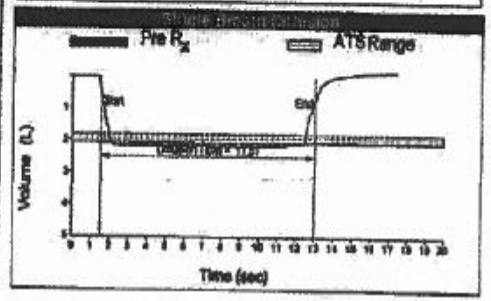
Spirometry		Predicted Mean	Lower Limit	Pre Bronchodilator Actual	% Pred
FVC	L	2.92	1.87	2.03	70
FEV.5	L	2.11	0.97	1.62	77
FEV_1	L	2.31	1.45	1.84	80
FEV_3	L	2.88	1.15	—	—
FEV_1 / FVC	%	79	72	91	115
FET	sec	—	—	2.95	—
FEF_{25}	L/s	6.31	2.55	8.37	133
FEF_{50}	L/s	3.08	0.95	7.17	233
FEF_{75}	L/s	0.98	—	1.06	108
FEF_{25-75}	L/s	2.42	0.63	3.17	131
PEFR	L/s	6.91	3.02	8.91	129
FIVC	L	2.92	1.87	2.06	71
PIFR	L/s	4.61	—	4.03	87
FIF50	L/s	—	—	3.88	—
MVV	L/m	110.1	53.3	87.8	80

Lung Volumes		Predicted Range Lower	Upper	Pre Bronchodilator Actual	% Pred
VC	L	1.87	3.97	2.11	72
ERV	L	—	2.37	0.84	92
IC	L	0.55	3.47	1.27	63
FRC	L	1.58	4.48	2.12	70
TLC	L	3.57	6.49	3.39	67
RV	L	1.36	2.87	1.28	61
RV/TLC	%	26	—	38	109

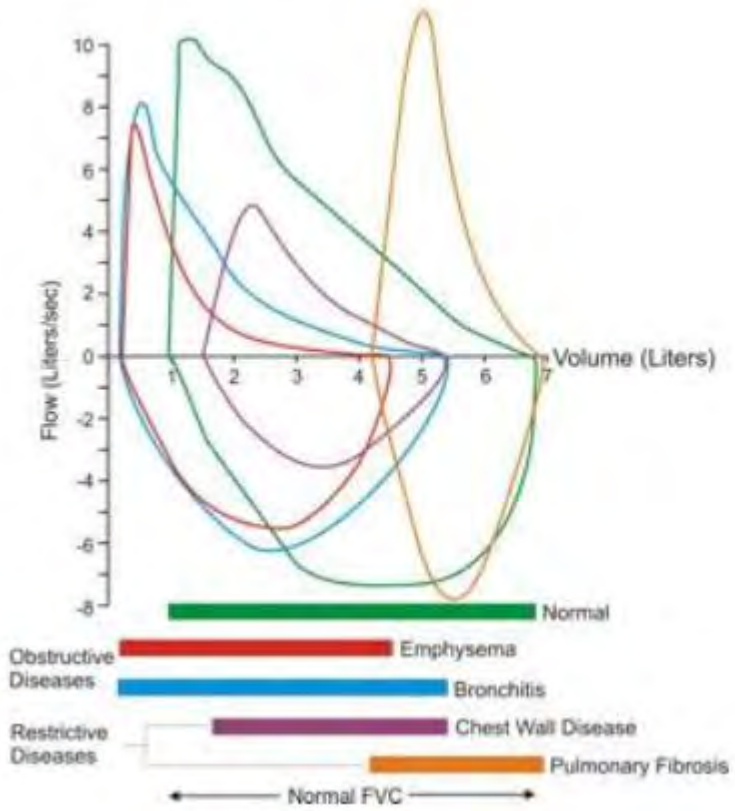
Diffusion		Predicted Range Lower	Upper	Pre Bronchodilator Actual	% Pred
DLCO	mL/min/mmHg	14.08	30.95	8.95	40
DLCO [Hb]	mL/min/mmHg	14.08	30.95	8.95	40
Hb	g/dl	12.0	16.0	—	—
VA [BTPS]	L	5.03	5.03	3.02	60
VI [BTPS]	L	—	—	2.13	—
DLCO/VA	mL/min/mmHg/L	3.71	5.26	2.96	56



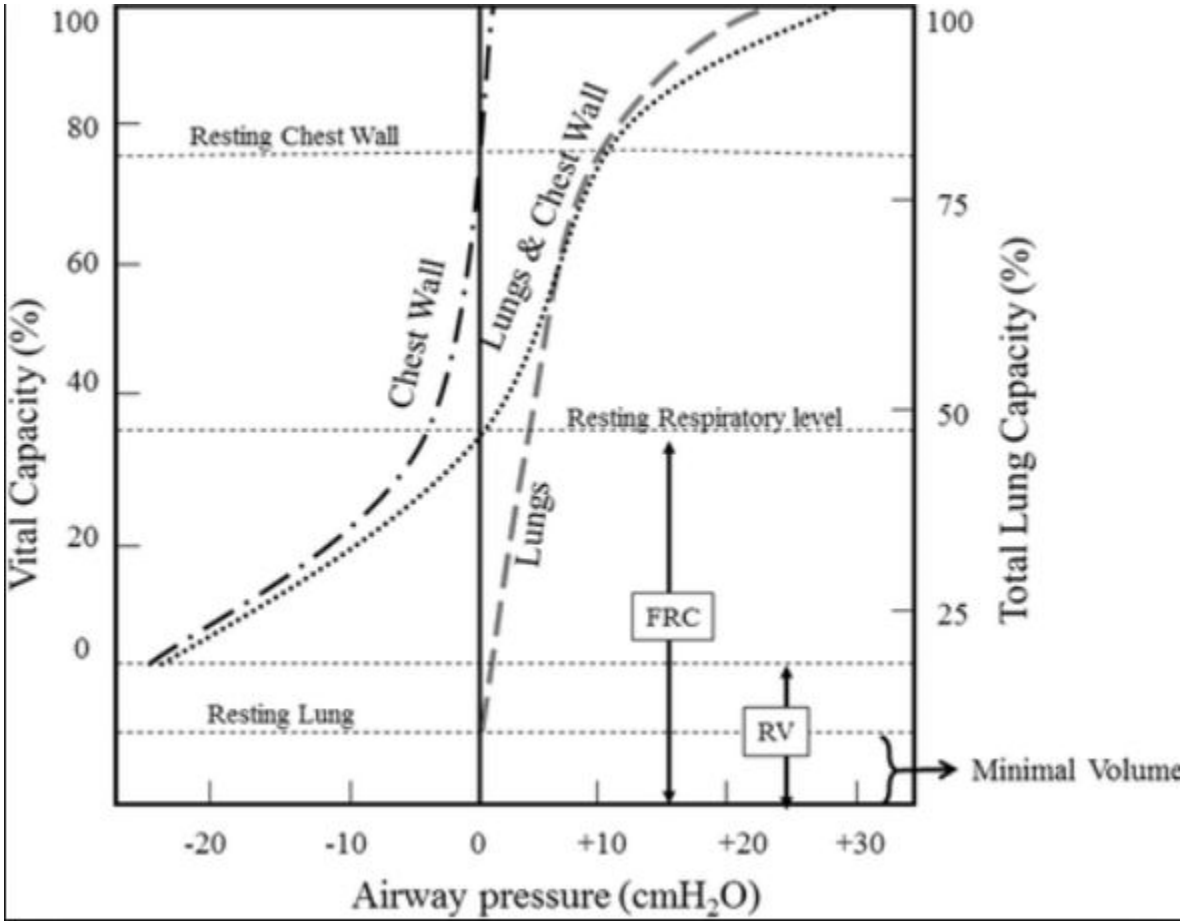




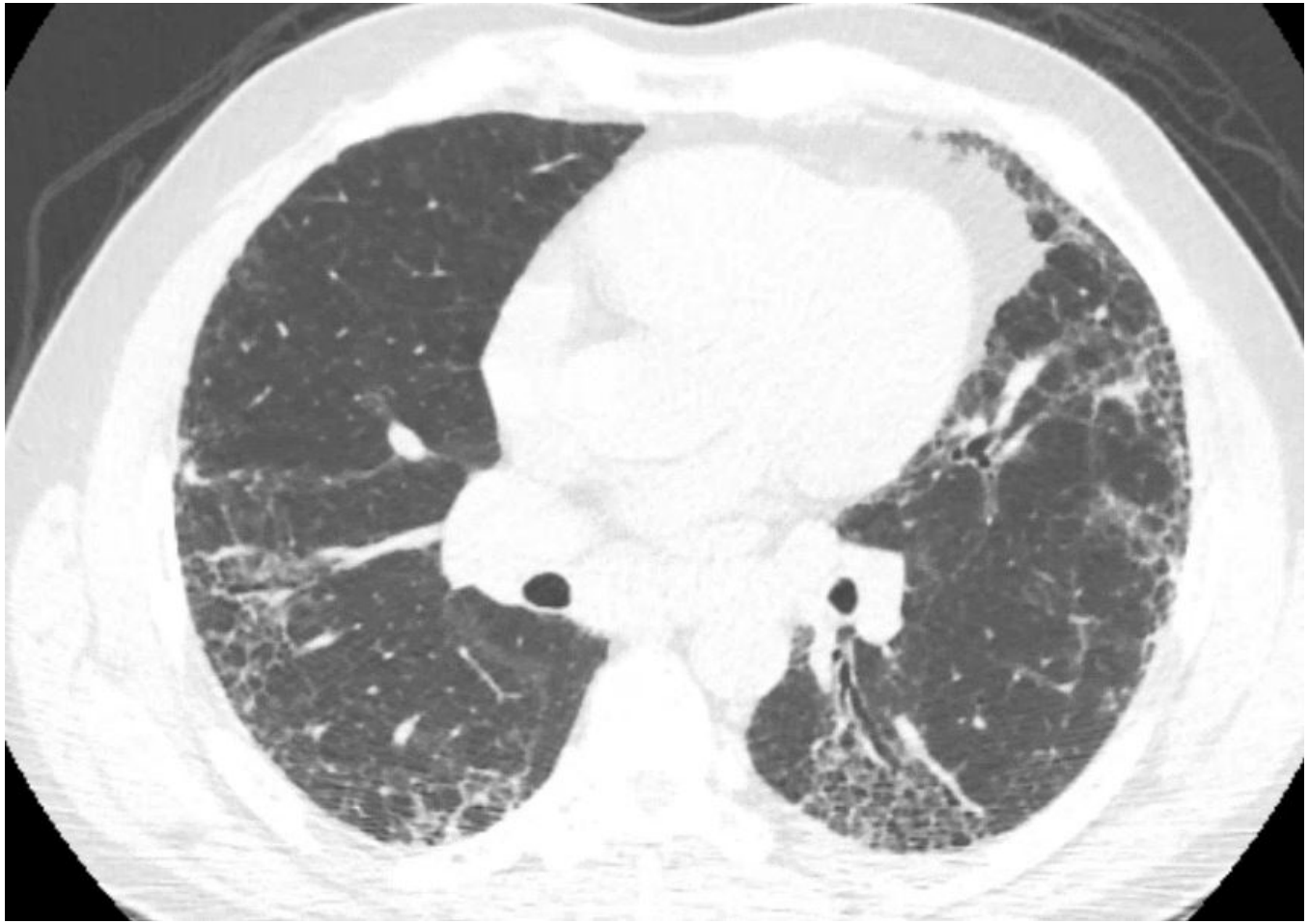
Lung mechanics vs gas exchange



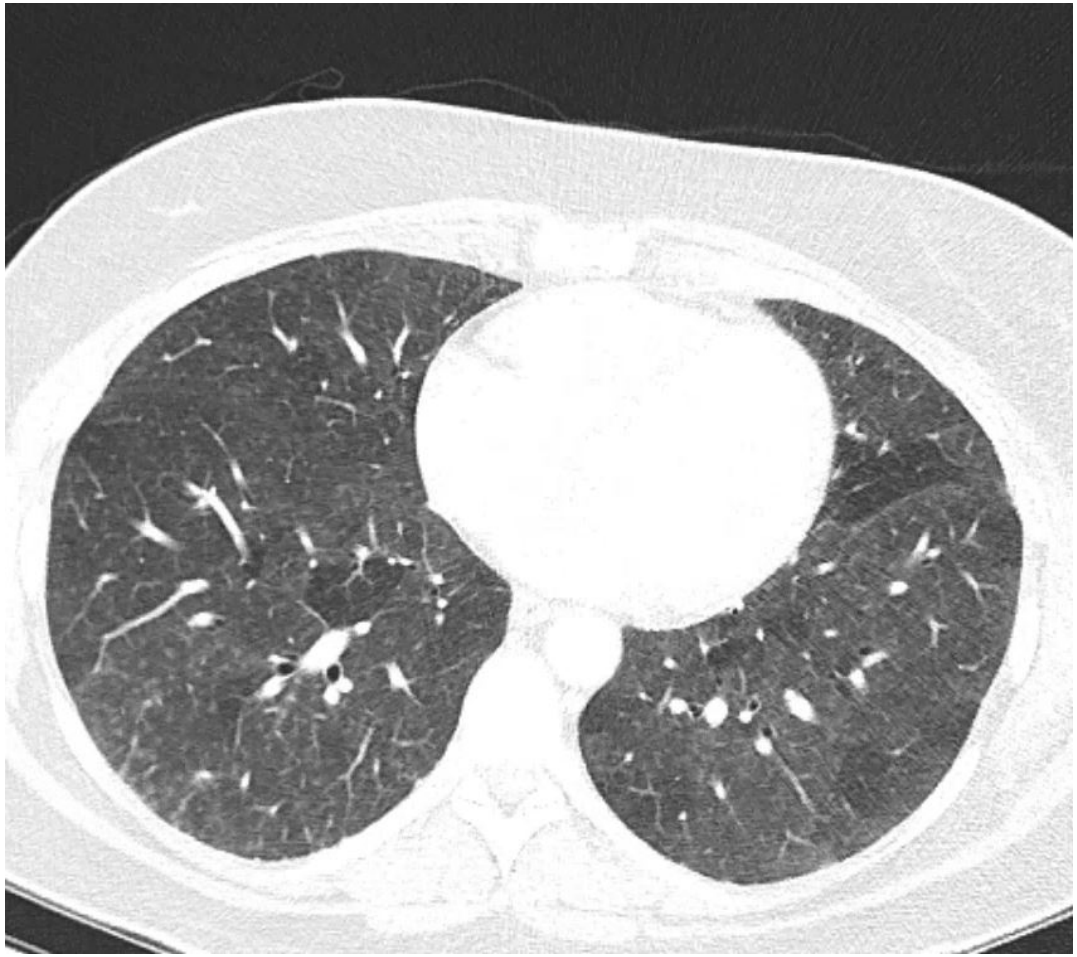
Determinates of lung volume



Diagnosis



Ground glass infiltrates and mosaicism
Not typical of IPF



IPF –the most common idiopathic interstitial pneumonia

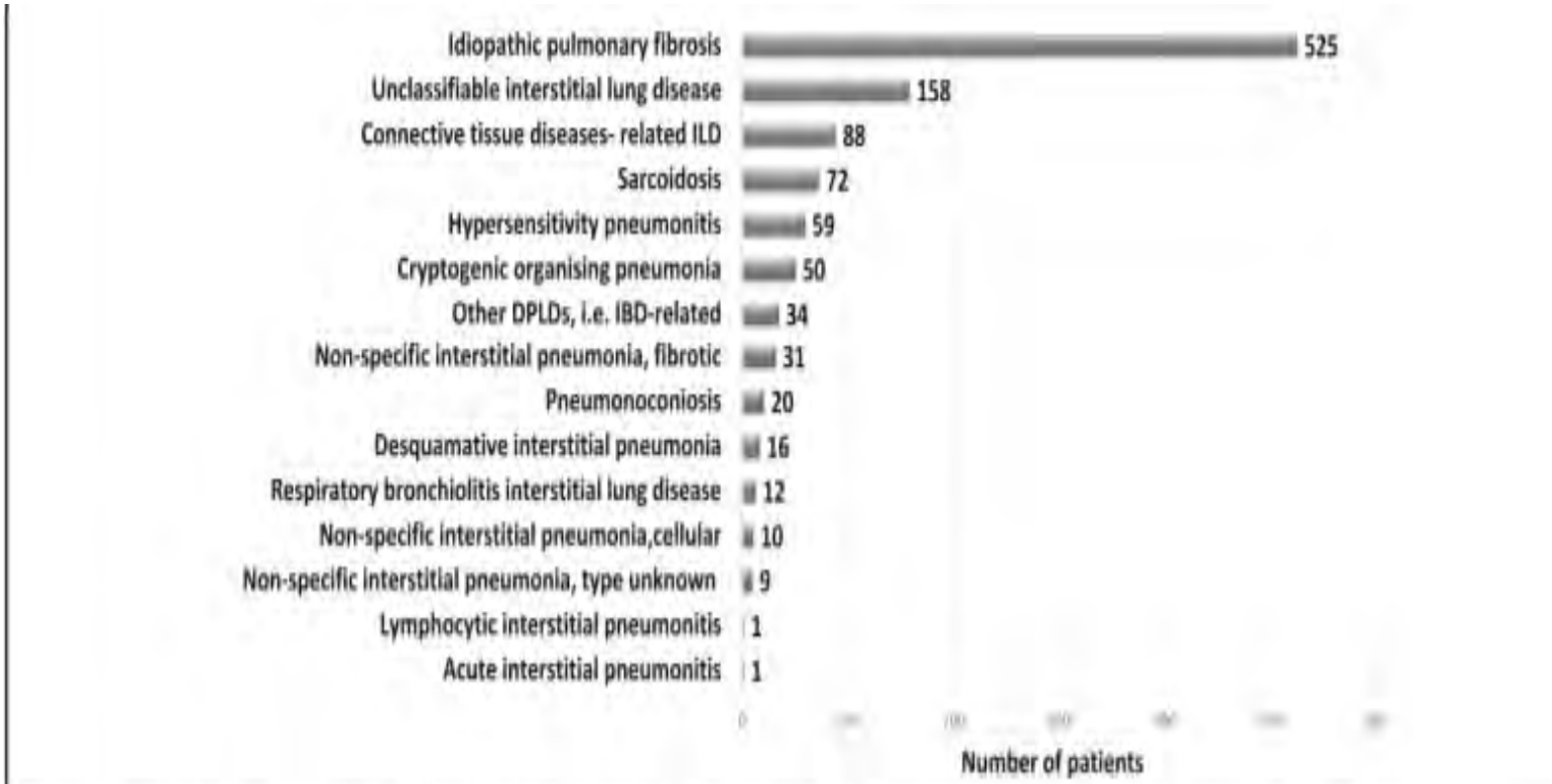


Fig. 1 Distribution and diversity of ILD diagnoses in the eurIPFreg cohort. Data are presented as patients numbers per diagnosis. IBD: inflammatory bowel diseases; DPLD: diffuse parenchymal lung diseases

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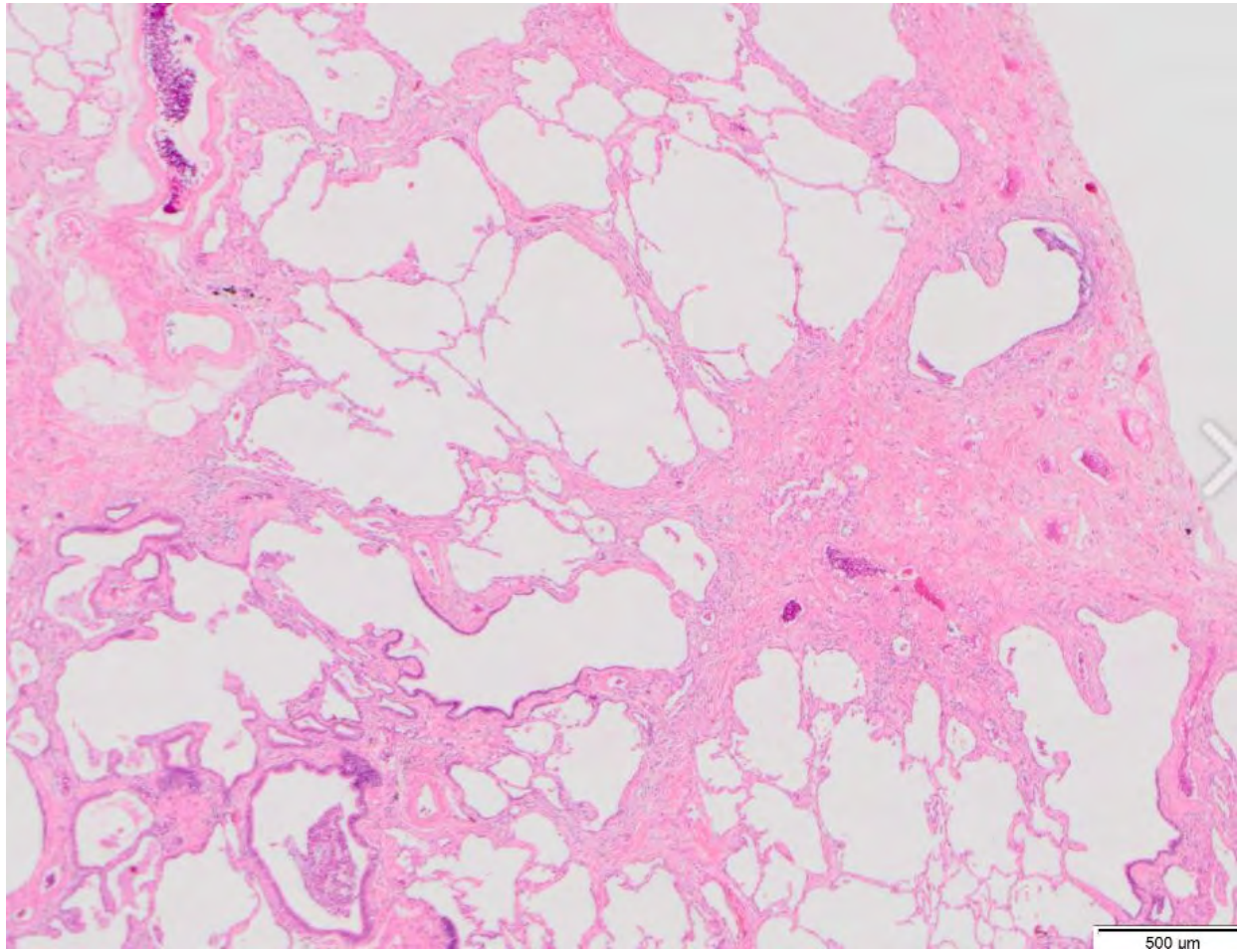
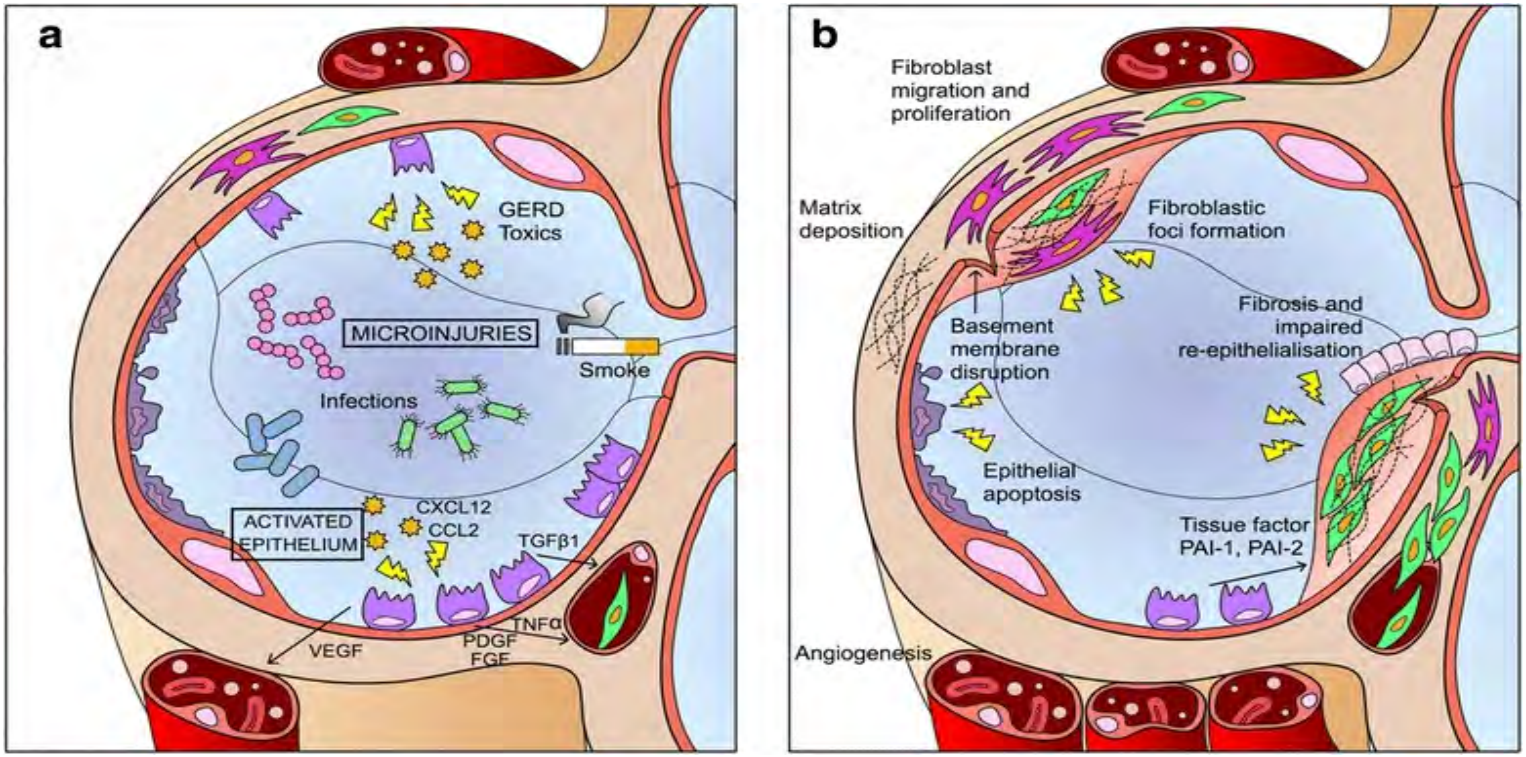
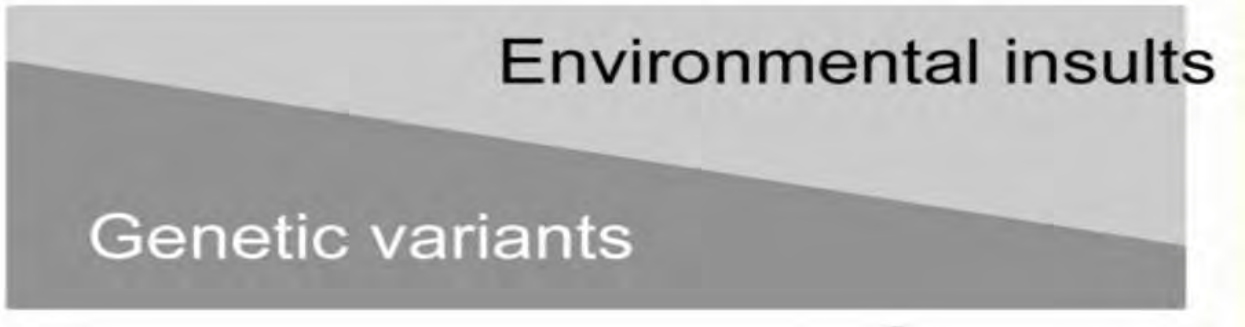
- Familial predominance
- Associated with environmental causes
- Increase incidence with aging
- Disease process imited to the lung alone
- Universally progressive
- Irreversible (maybe)
- Similar radiology and pathology in Rheumatoid arthritis, asbestosis (UIP pattern)
- Oxygen desaturation and restrictive lung picture
- Temporal heterogeneity on pathology

Pathology



Abnormal lung repair in IPF





Potential injurious factors

TABLE 1 Overt or occult environmental risk factors for idiopathic pulmonary fibrosis

	Risk factor
Intrinsic factors	Gastro-oesophageal reflux
	Microaspiration
	Microbiome
	Viral infection
Extrinsic factors	
Domestic/environmental	Tobacco smoke
	Wood fires
	Birds (including poultry, bird droppings, birdfeeders)
	Feather products (including feather duvets, comforter, pillows, jackets)
	Moulds (visible or unseen)
	Organic dusts
	Ventilation
	Hairspray
	Air pollution
Occupational[#]	Welding
	Farming/agriculture
	Hairdressing
	Dentists/dental technicians
	Metal dust
	Wood dust/paper mill factory workers
	Livestock, particularly birds
	Nuclear waste/radiation hazards
	Chemicals
	Aluminium, Corion®
	Stone cutting/sand/granite/silica
	Talc

[#]: these and other occupational exposures may be the cause of "occupational lung diseases" and thus not truly risk factors for patients diagnosed with idiopathic pulmonary fibrosis (IPF). Nevertheless, these may be occult if the patient otherwise diagnosed with IPF is not gainfully engaged with such environmental factors/exposures.

Genetic causes of IPF- role of abnormal mucous

Muc5b overexpression causes mucociliary dysfunction and enhances lung fibrosis in mice

Laura A. Hancock, Corinne E. Hennessy, George M. Solomon, Evgenia Dobrinskikh, Alani Estrella, Naoko Hara, David B. Hill, William J. Kissner, Matthew R. Markovetz, Diane E. Grove Villalon, Matthew E. Voss, Guillermo J. Tearney, Kate S. Carroll, Yunlong Shi, Marvin I. Schwarz, William R. Thelin, Steven M. Rowe, Ivana V. Yang, Christopher M. Evans & David A. Schwartz

Nature Communications **9**, Article number: 5363 (2018) | Download Citation

Idiopathic Pulmonary Fibrosis Is a Genetic Disease Involving Mucus and the Peripheral Airways

David A. Schwartz

+ Author Affiliations

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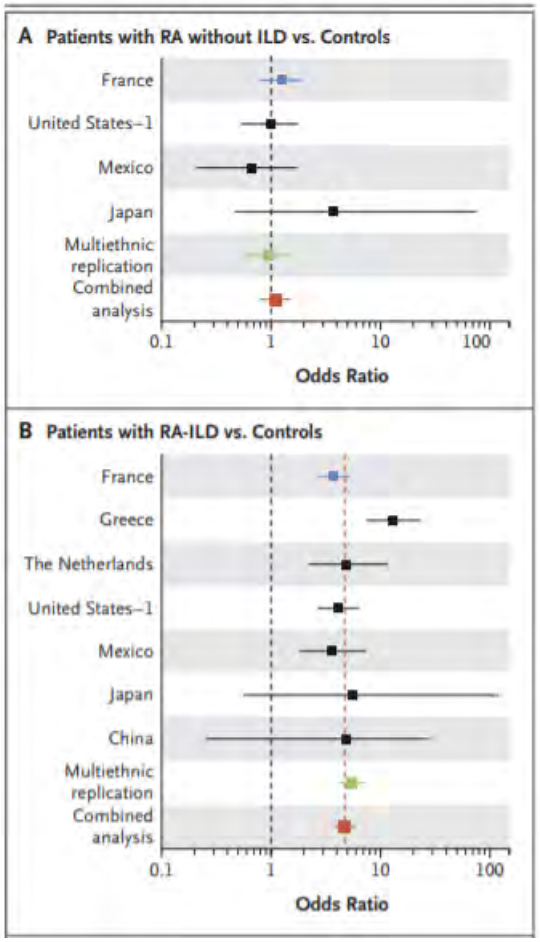
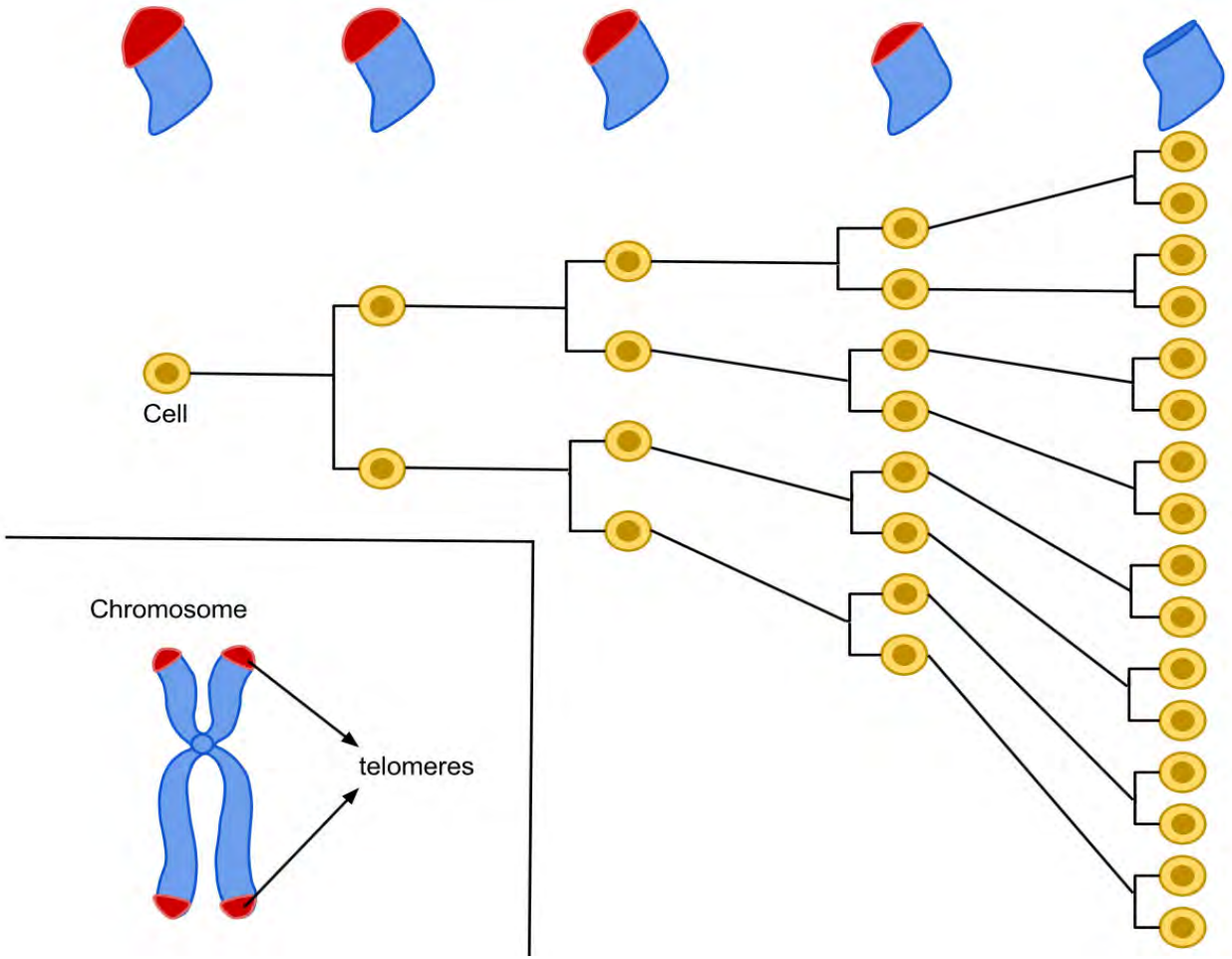
ORIGINAL ARTICLE

MUC5B Promoter Variant and Rheumatoid Arthritis with Interstitial Lung Disease



N Engl J Med 2018;379:2209-19.

Telomeres and aging

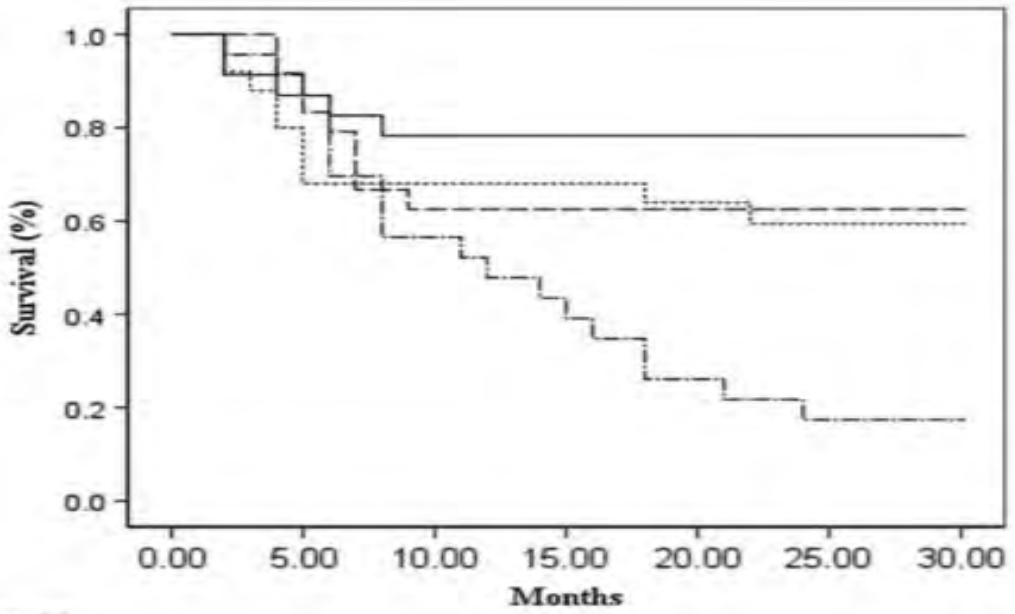


Cell division 50-70 x

Telomeres shorten with each division, until there are none remaining

This end stage is known as senescence and proves the concept that links the deterioration of telomeres and aging.

Telomere length vs survival in IPF



Number at risk				
Q1	23	13	6	0
Q2	24	16	15	6
Q3	24	15	15	9
Q4	23	18	18	18

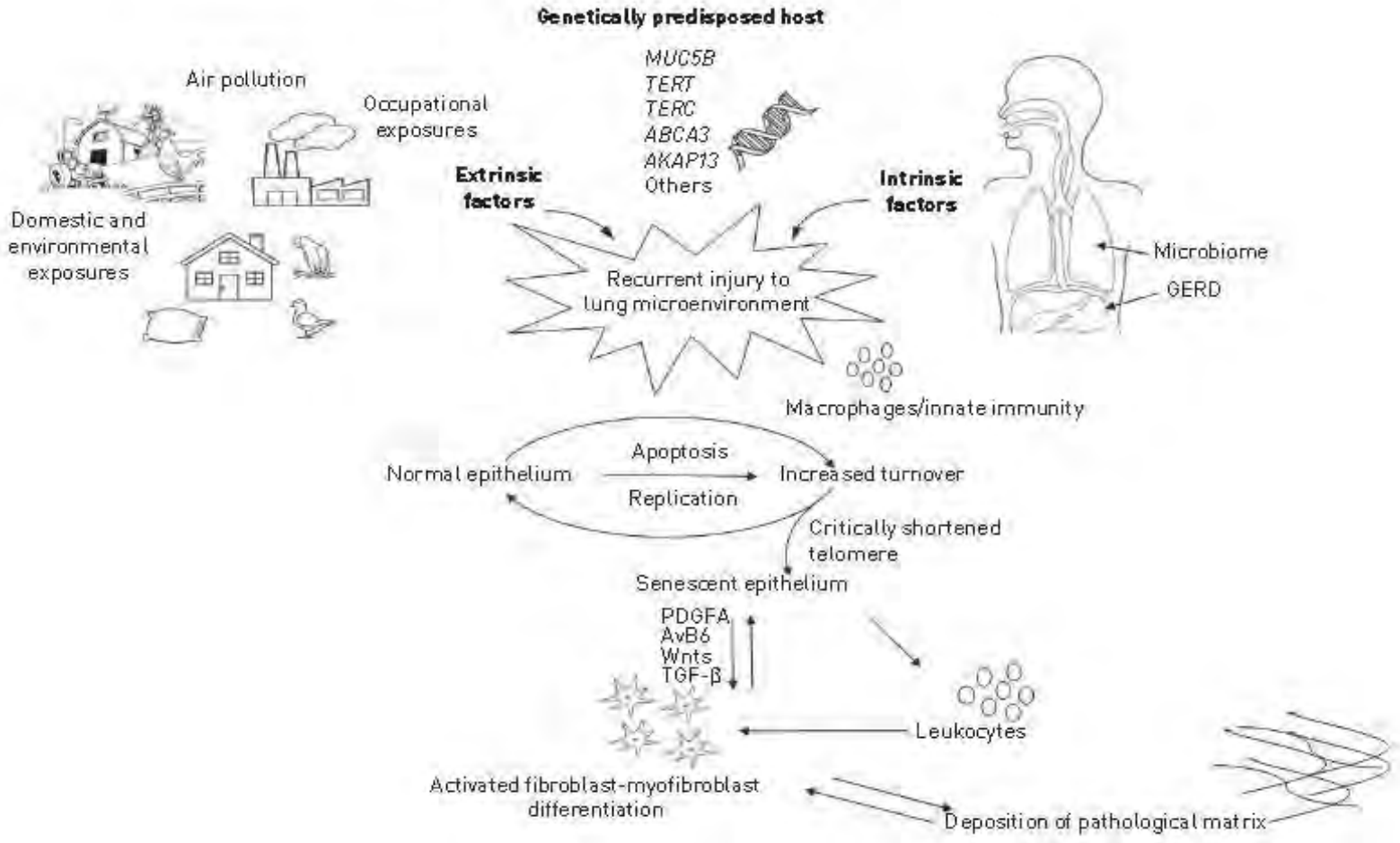
Figure 3 Survival time according to telomere length in patients with idiopathic pulmonary fibrosis (IPF). Survival time was estimated for patients with IPF, stratified by telomere length quartiles. (—) Q1; (- - -) Q2; (—) Q3; (—) Q4.

Jinghong, DAI Respirology (2015) 20, 947–952

Short telomere syndrome

- Premature graying
- Cryptogenic cirrhosis
- Bone marrow disease
- Family history of IPF

The disease process



Dyspnea from restriction

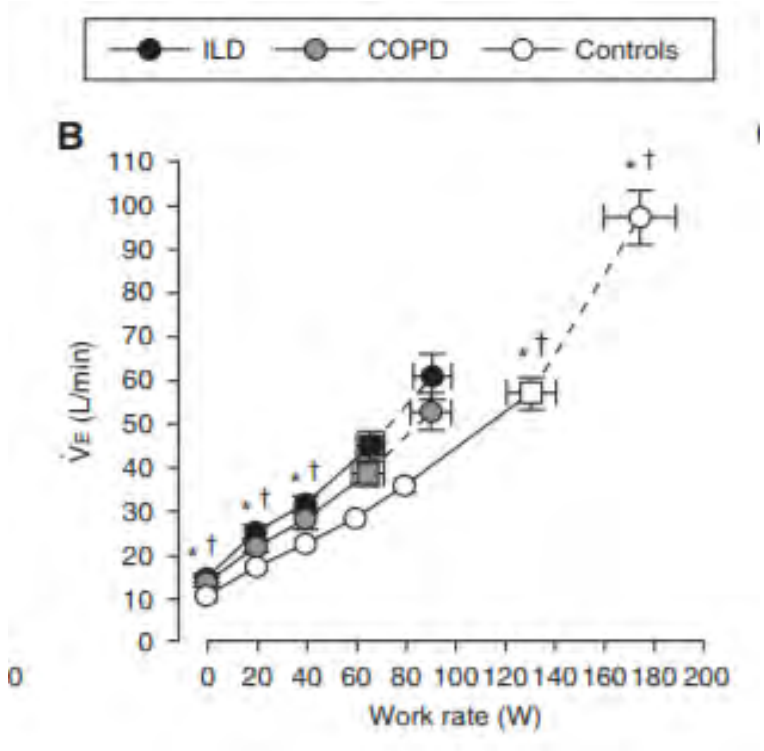
TABLE 1 Alterations of lung function tests in idiopathic pulmonary fibrosis (IPF)

	Mild IPF	Moderate to severe IPF
Spirometry		
FVC	Normal	Decreased
FEV1/FVC	Normal or increased	Normal or increased
Static lung volumes		
TLC	Normal	Decreased
FRC	Normal	Decreased
Blood gases at rest		
Pa_{O_2}	Normal	Decreased
Pa_{CO_2}	Normal	Decreased
Carbon monoxide transfer		
D_{LCO}	Decreased	Decreased
V_A	May be normal	Decreased
K_{CO}	May be normal	Decreased
Airways		
Cough reflex	Increased	Increased
Airway resistance	Decreased	Decreased
Pulmonary haemodynamics at rest		
PAP	May be increased	Frequently increased
PCWP	Normal	May be increased
Ventilatory drive		
$P_{0.1}$	May be normal	Increased
Ventilatory response to CO_2 rebreathing	Normal	Normal
Exercise physiology		
Peak V'_{O_2}	May be normal	Decreased
V_D/V_T	Increased	Increased
V'_E/V'_{CO_2}	Increased	Increased
PAP at exercise	Increased	Increased
$P_A a_{O_2}$ at exercise	Increased	Increased

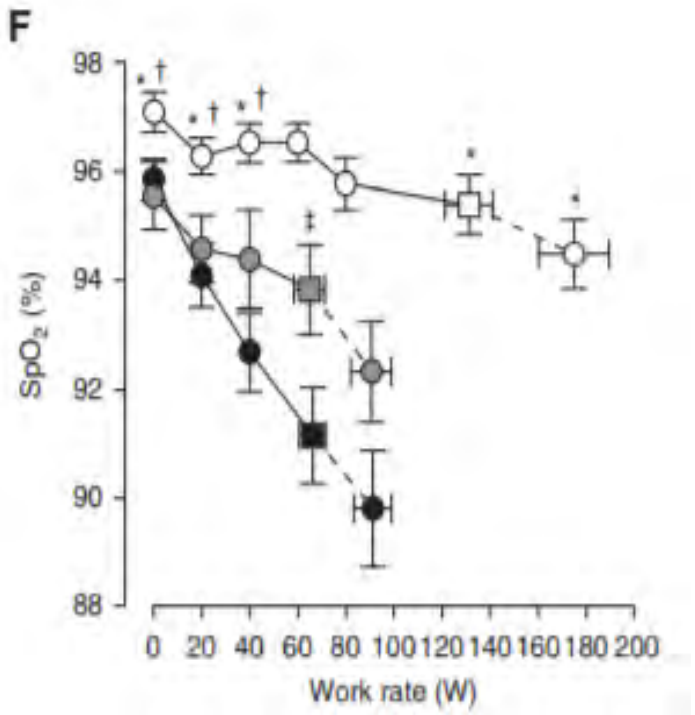
FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; TLC: total lung capacity; FRC: functional residual capacity; Pa_{O_2}: arterial oxygen tension; Pa_{CO_2}: arterial carbon dioxide tension; D_{LCO}: diffusing capacity of the lung for carbon monoxide; V_A: alveolar volume; K_{CO}: transfer constant of carbon monoxide; PAP: pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; $P_{0.1}$: 100 ms occlusion pressure; V'_{O_2}: oxygen uptake; V_D/V_T: ratio of dead space volume to tidal volume; V'_E/V'_{CO_2}: ratio of minute ventilation to carbon dioxide elimination; $P_A a_{O_2}$: alveolar–arterial oxygen tension difference.

Dyspnea in COPD and IPF

Minute ventilation vs WR



Saturation vs WR



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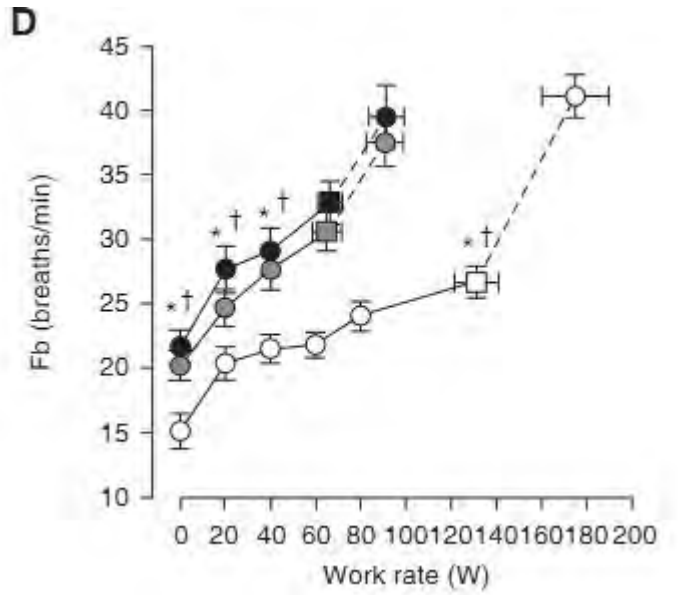
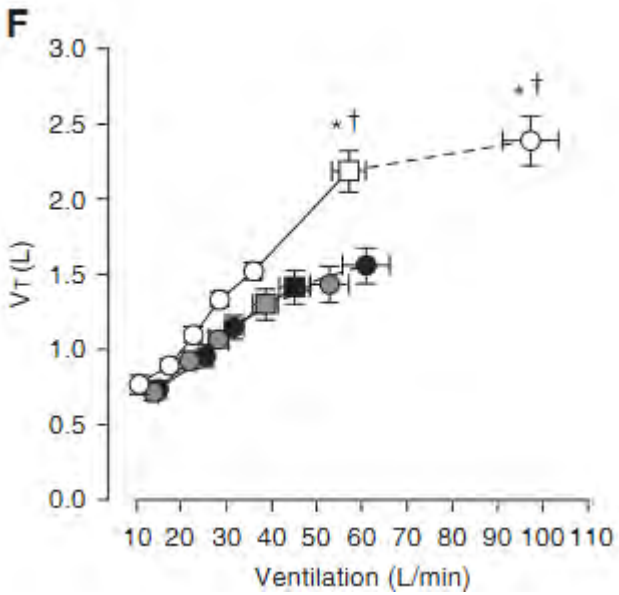
Respiratory Mechanics

Resp frequency vs work rate

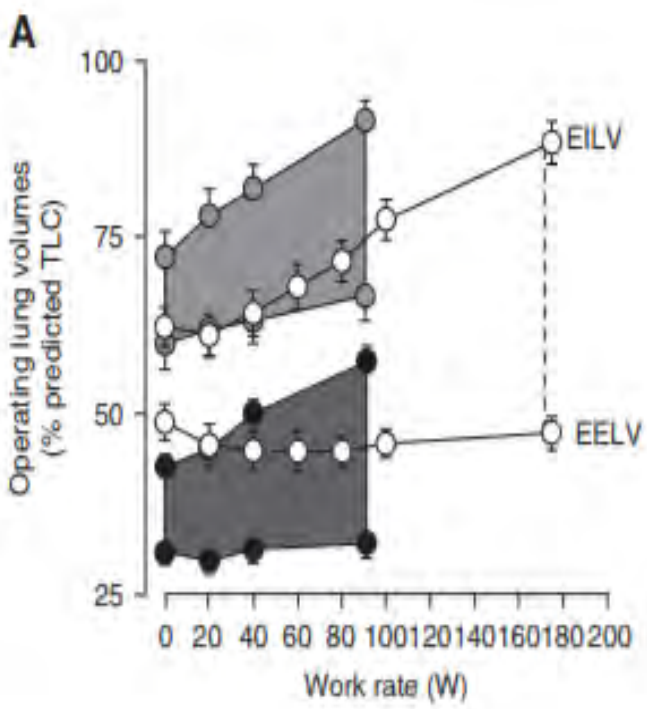


Tidal volume vs Ventilation

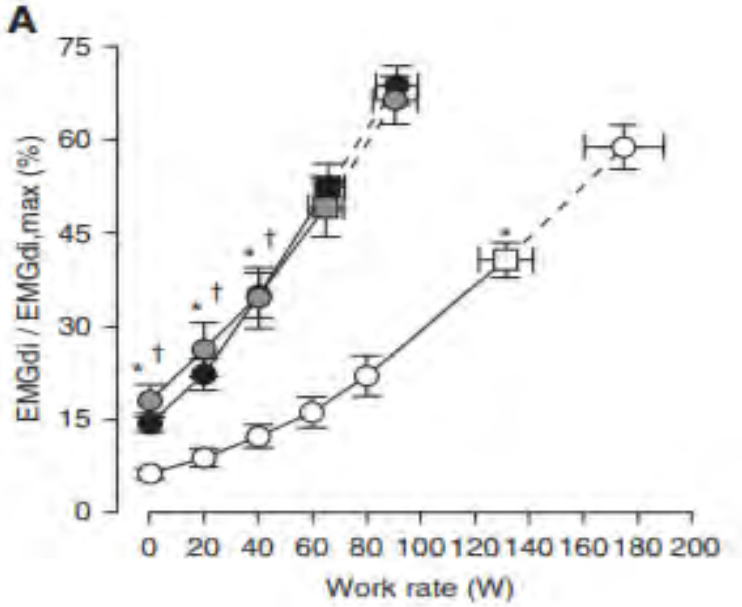


Effort to breathe

Lung volume changes with ex

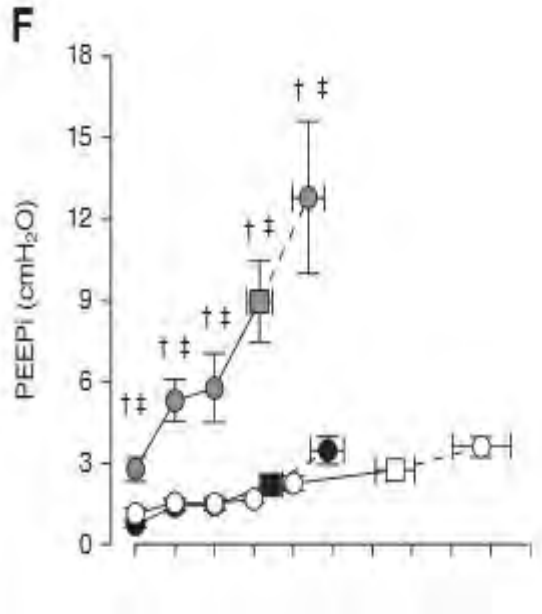


Diaphragm Stimulation vs WR

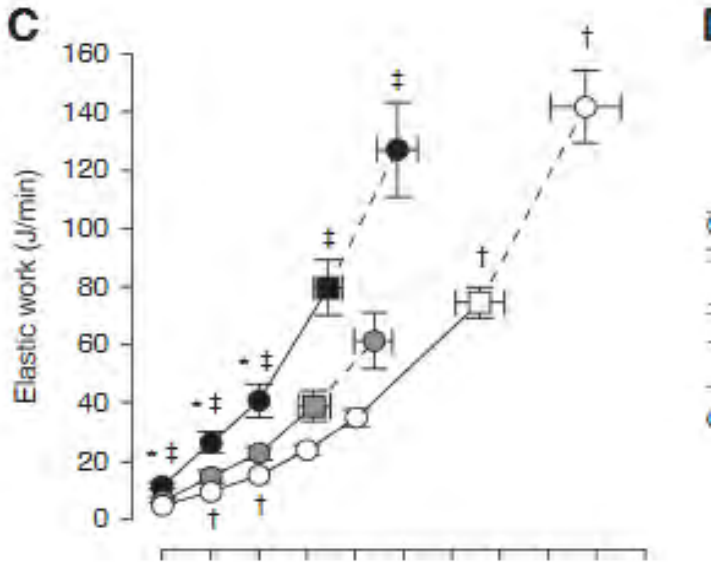


Work of Breathing

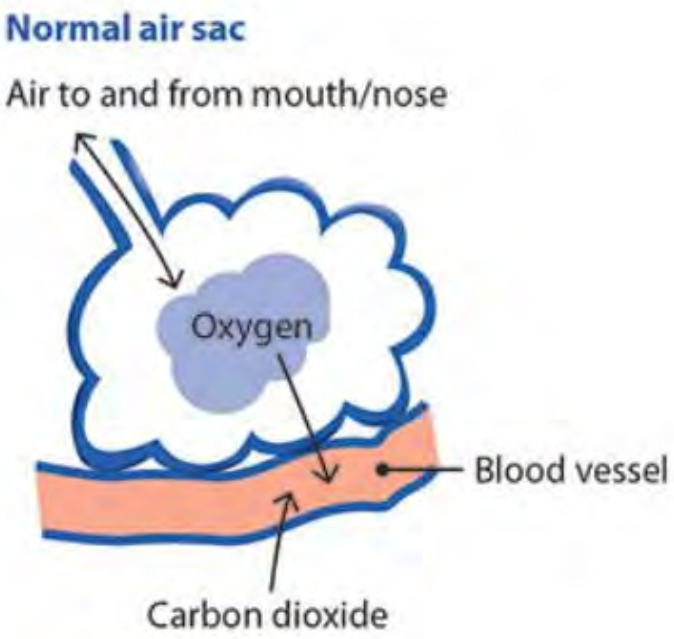
Intrinsic PEEP vs Work rate

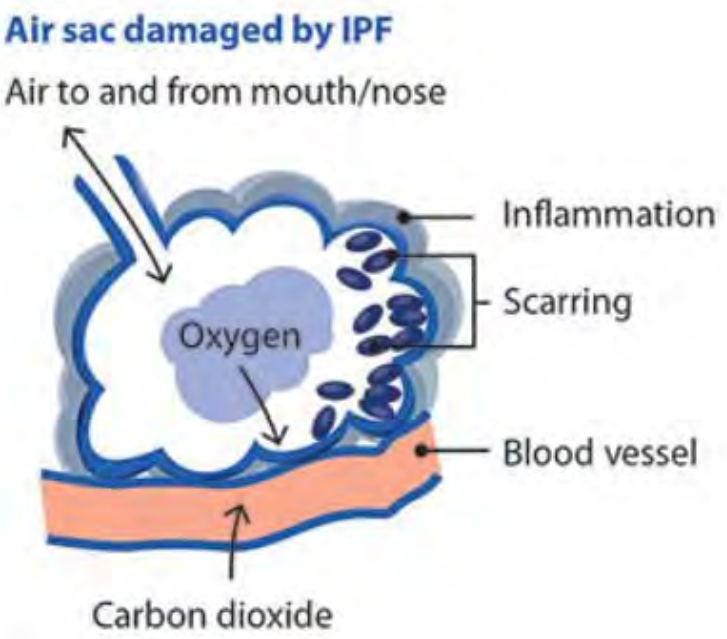


Elastic work vs work rate

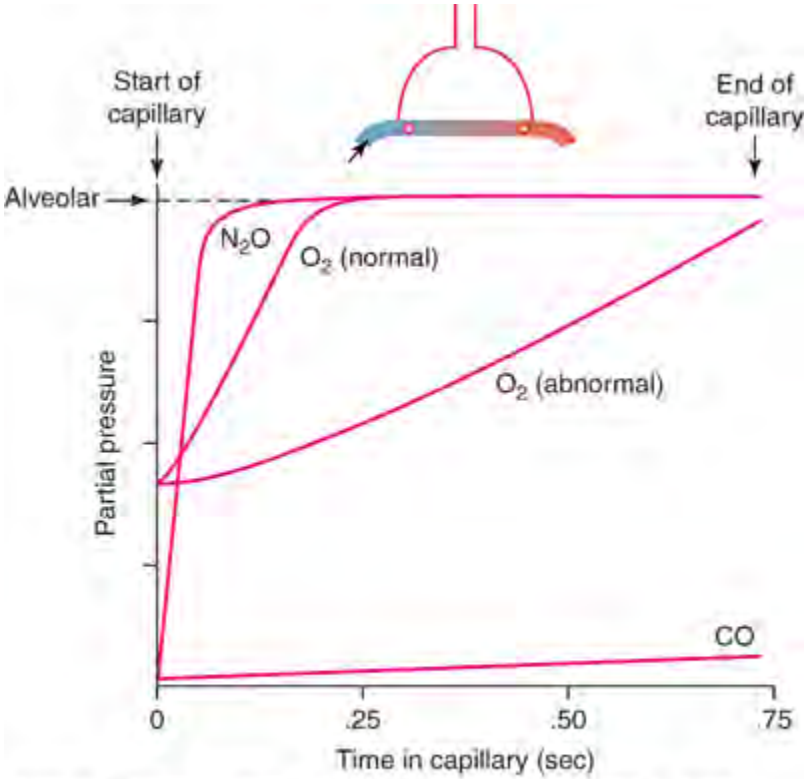


Diffusion capacity





Gas kinetics- CO vs O2



Source: Andrew J. Lechner, George M. Matuschak, David S. Brink: Respiratory: An Integrated Approach to Disease
www.accessmedicine.com

Pulmonary pressure vs FVC

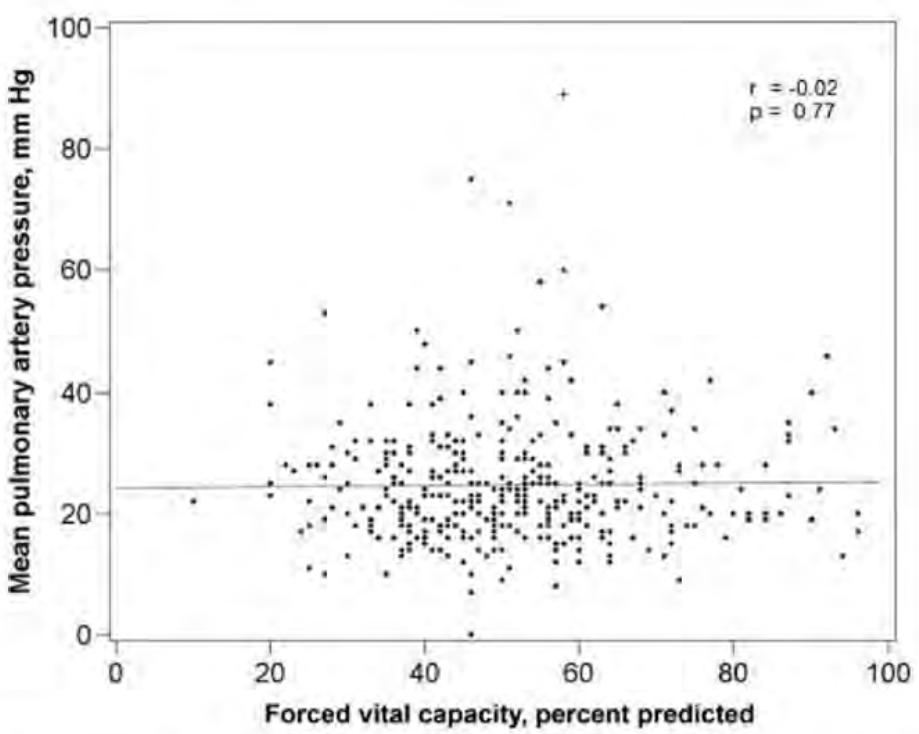


FIGURE 1. Scatter plot of FVC% vs mPAP in IPF patients listed for lung transplantation in the UNOS registry from 2004 to 2005 (n = 376) utilizing Pearson correlation coefficient (r). The regression line is shown.

CHEST 2007; 131:650–656

Predicting pulmonary hypertension

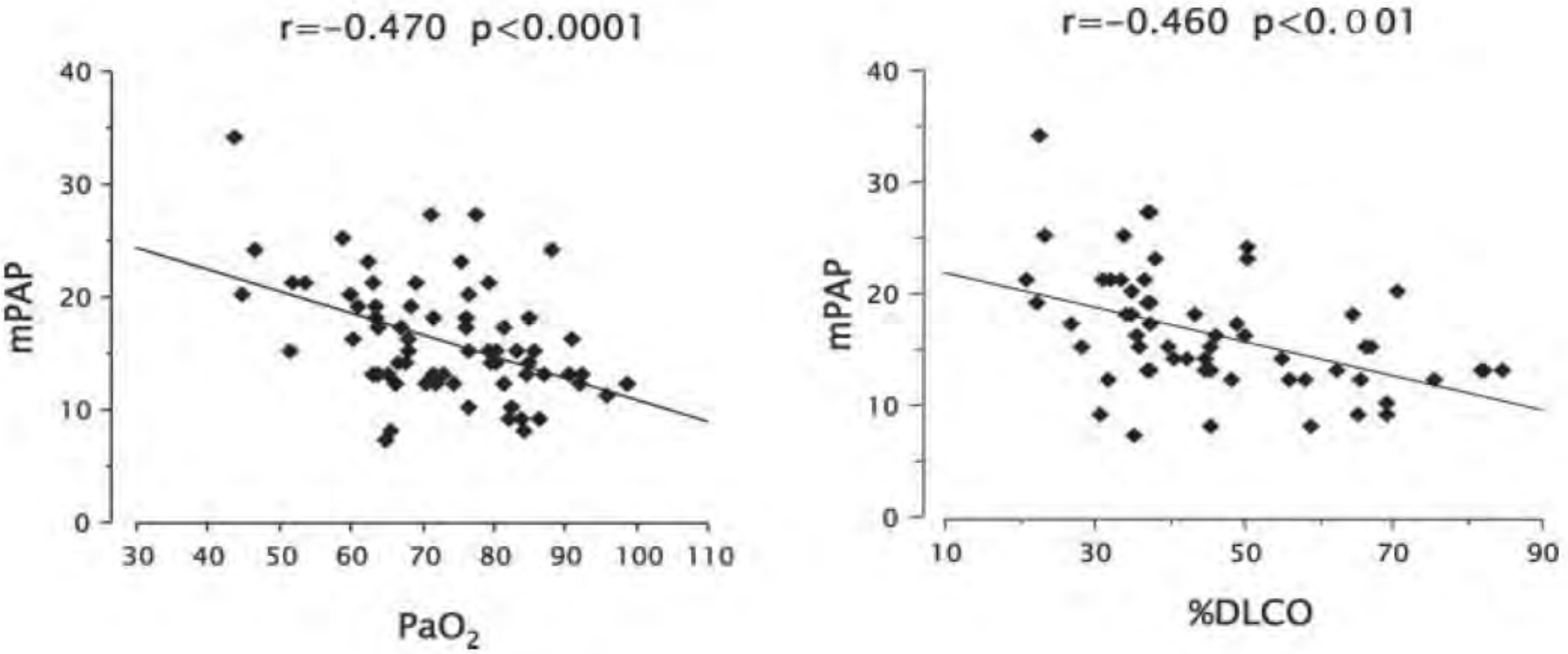


FIGURE 1. Correlations of mPAP with Pao_2 (*left*) and %DLCO (*right*). Both correlations are fairly loose, suggesting that the mechanism and development of PAH associated with ILD stem from multiple causes.

GAP staging and mortality

Figure 2. **The GAP Index and staging system.**

	Predictor	Points
G	Gender	
	Female	0
	Male	1
A	Age, y	
	<60	0
	61–65	1
	>65	2
P	Physiology	
	FVC, *% predicted*	
	>75	0
	50–75	1
	<50	2
	Dlco, *% predicted*	
	>55	0
	36–55	1
	<35	2
	Cannot perform	3
	Total Possible Points	8

Stage	I	II	III
Points	0–3	4–5	6–8
Mortality			
1-y	5.6	16.2	39.2
2-y	10.9	29.9	62.1
3-y	16.3	42.1	76.8

Effect of DlCO and PAP on survival

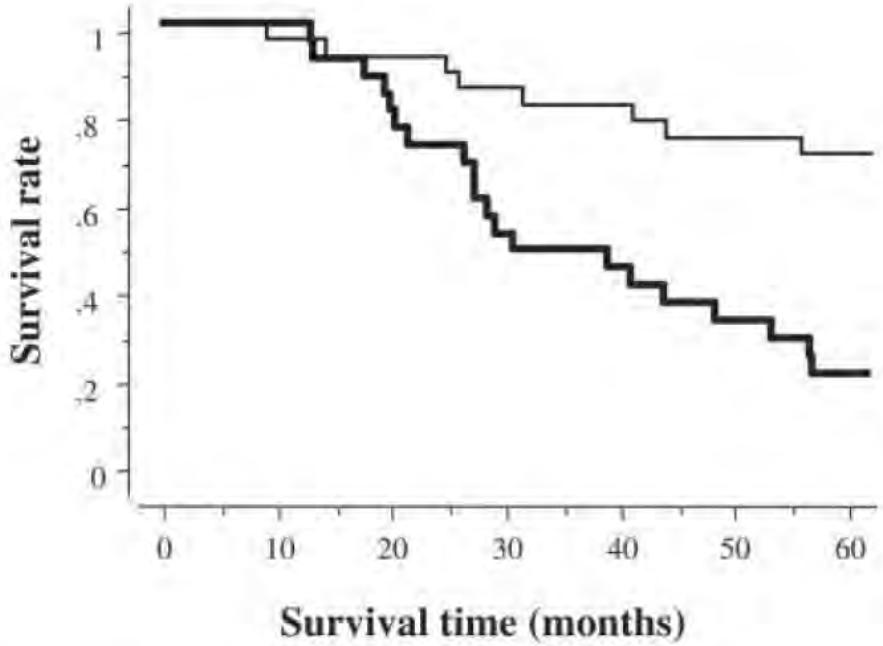


FIGURE 3. Five-year survival rates of patients grouped by DLCO status. Thin line, preserved-DLCO group (%DLCO ≥ 40, n = 27); bold line, low-DLCO group (%DLCO < 40, n = 25).

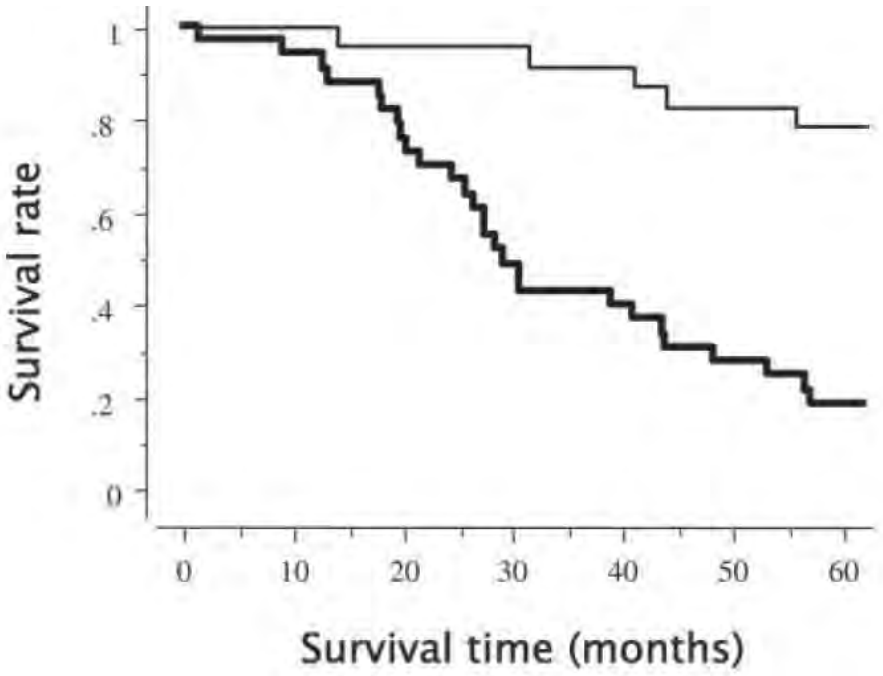


FIGURE 4. Five-year survival rates of patients grouped by PAP and DLCO status. Thin line, group 1 (normal PAP and preserved DLCO, n = 23); bold line, group 2 (high PAP and/or low DLCO, n = 31).

CHEST / 131/3/ MARCH, 2007

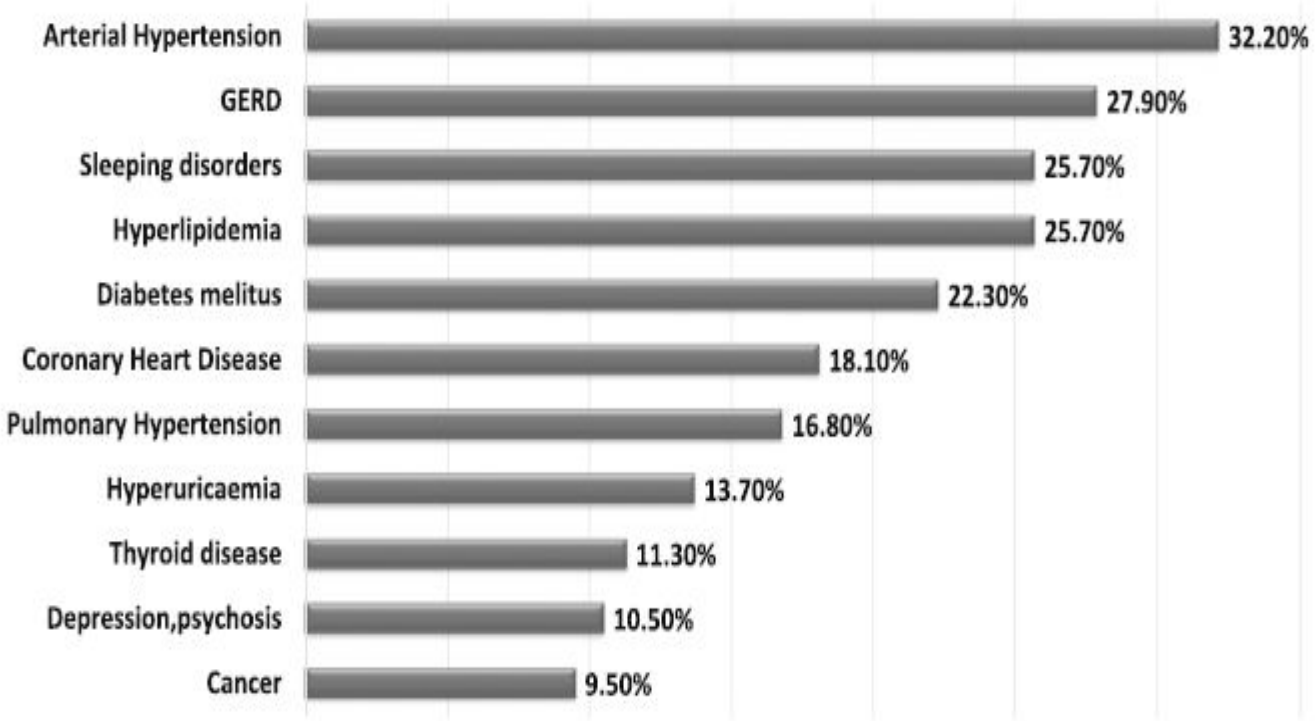
Supportive treatment in IPF

Sufficient supplemental oxygen in a convenient means to provide it.

Considerations

- Weight
- Pulsed vs continuous flow
- Maximum flow rate
- Durability
- Cost
- Use in airplanes or altitude (travel)

Co-morbidities in IPF



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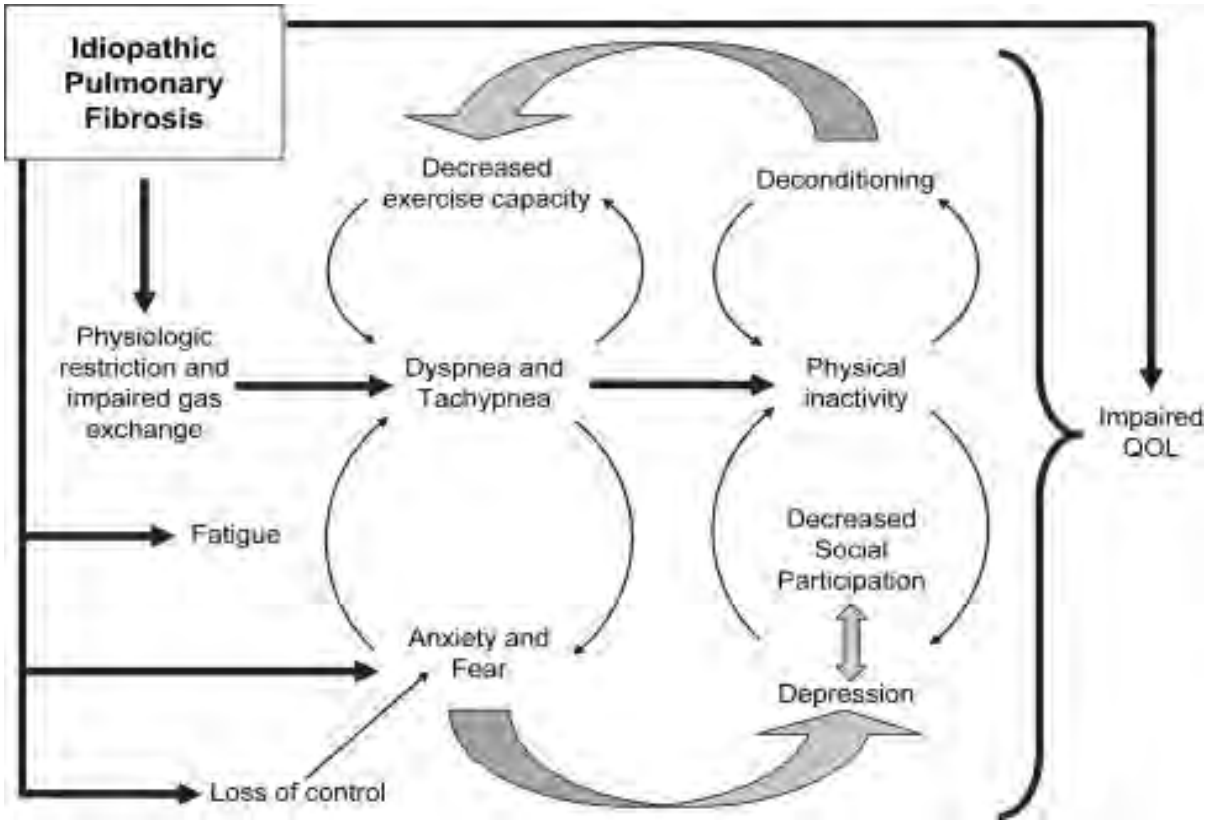
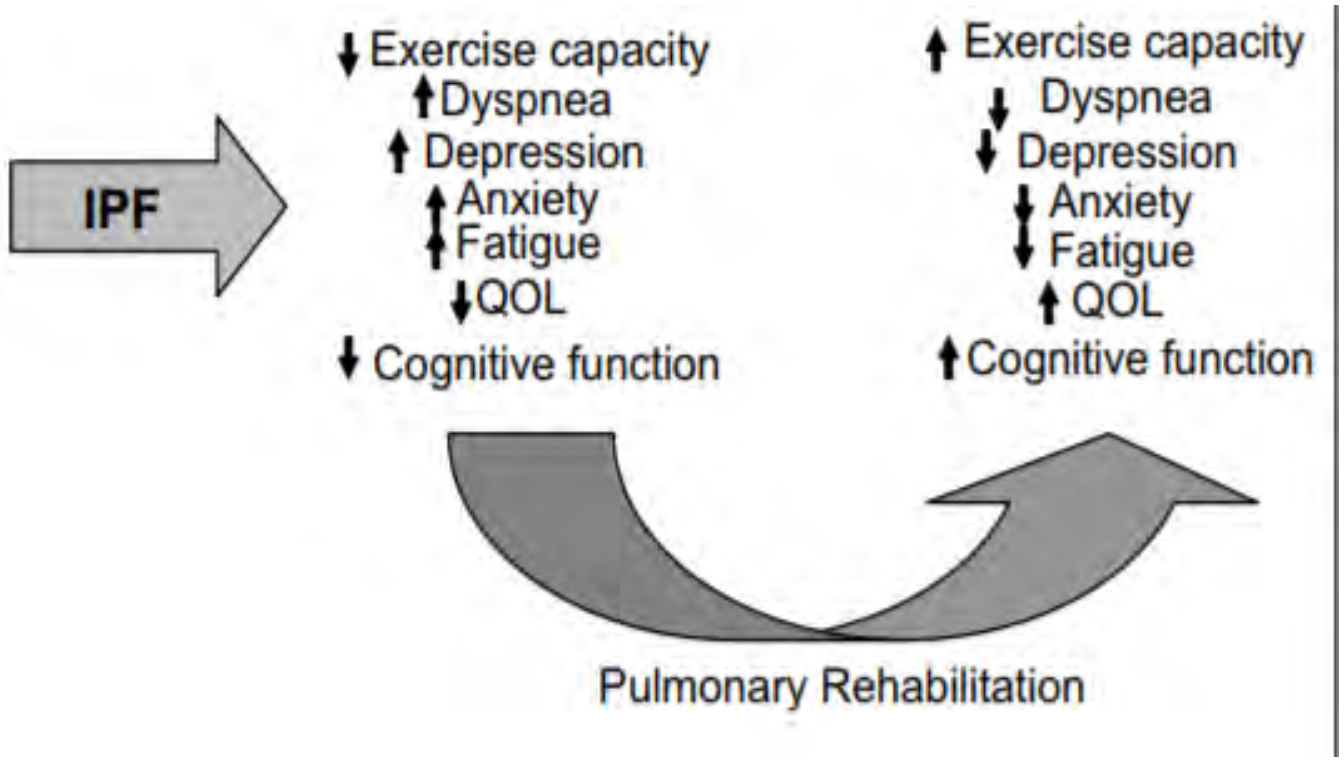
IPF=Isolation and deconditioning



Goals of rehabilitation



Effect of rehabilitation on exercise tolerance

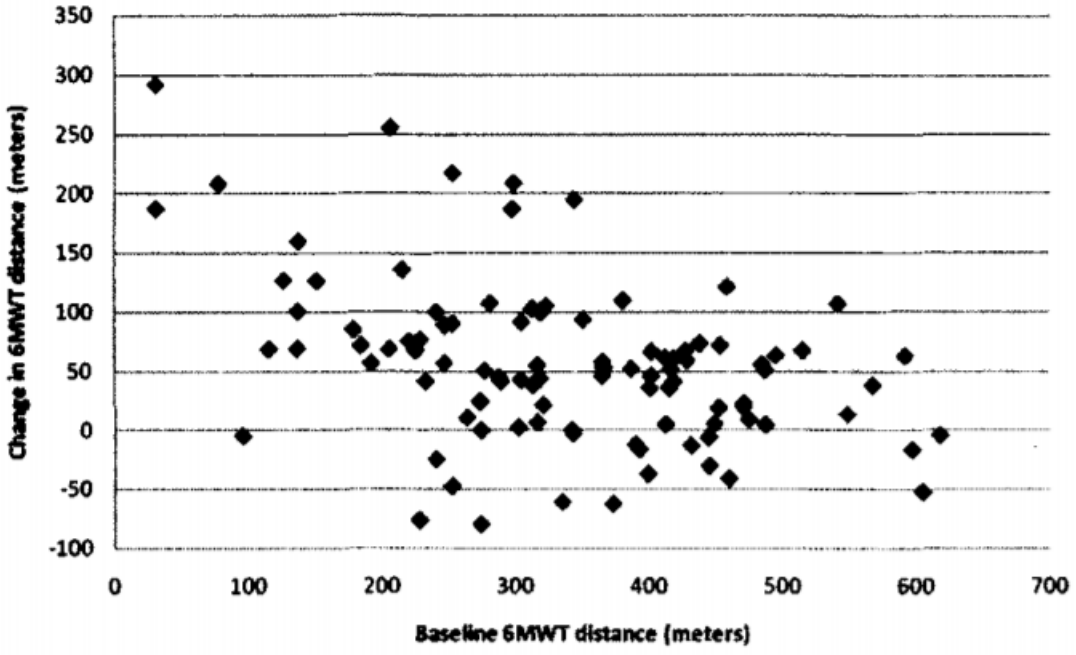


FIGURE 1. Relationship of baseline 6-min walk distance to change in 6-min walk distance after PR.

CHEST 2009; 135:442-447

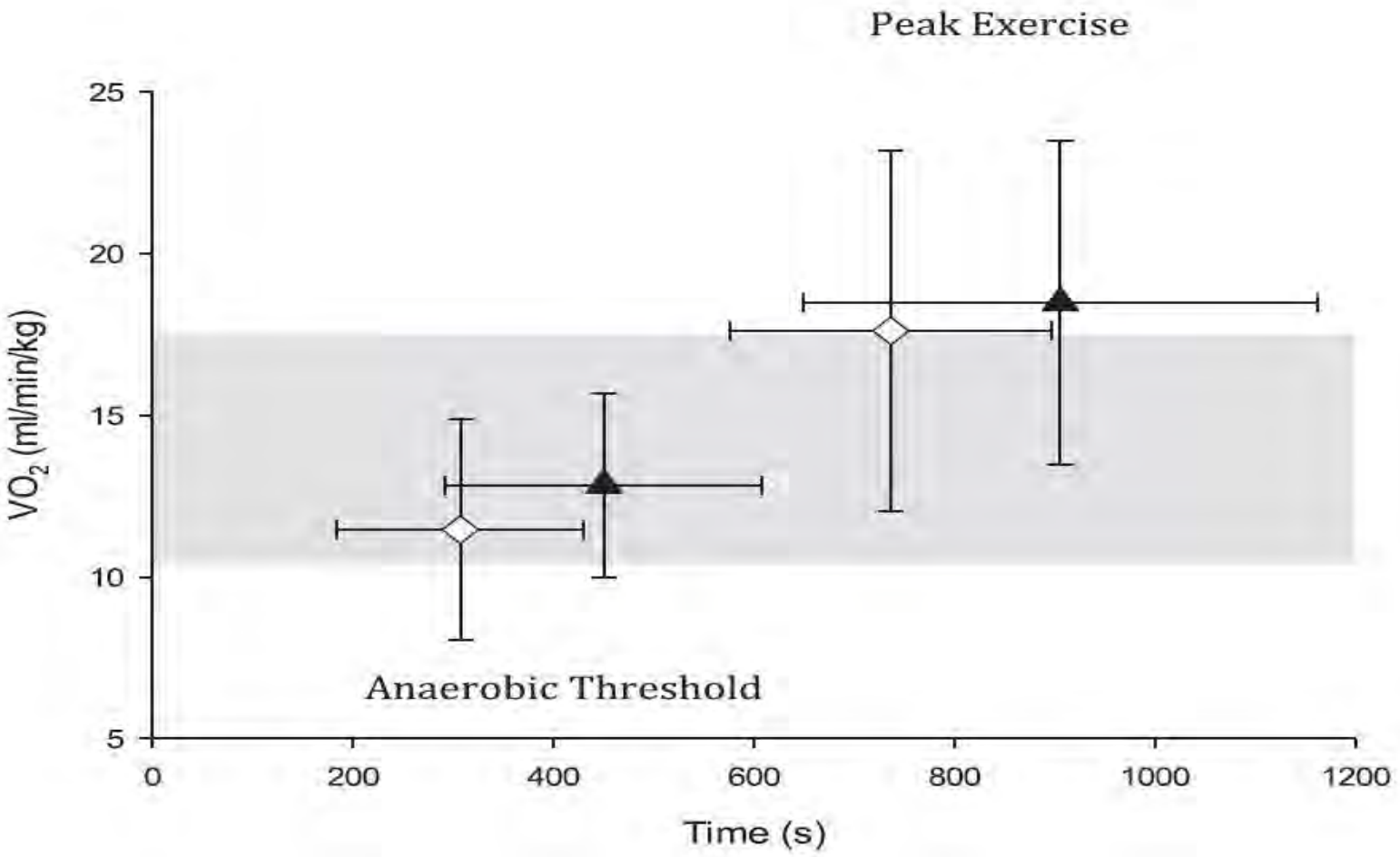
Table 2—*Change in Dyspnea, 6-Min Walk Distance, and Depression After PR

Variables	Baseline	After PR	Change	p Value
Borg score (n = 99)	3.6 (2.0)	2.7 (1.7)	− 1.0 (1.7)	< 0.0001
UCSD questionnaire (n = 29)	57.4 (25)	49.1 (25)	− 8.3 (14)	0.005
6MWT distance, m (n = 99)	335 (131)	391 (118)	56 (69)	< 0.0001
6MWT distance, % change (n = 99)			14 (2, 33)†	0.002
CES-D score (n = 27)	15.7 (8)	13.6 (8)	− 2.2 (5)	0.046

*Values expressed are mean (SD) unless otherwise noted.

†Median (25th percentile, 75th percentile).

Improvement in exercise fatigue with intensive exercise

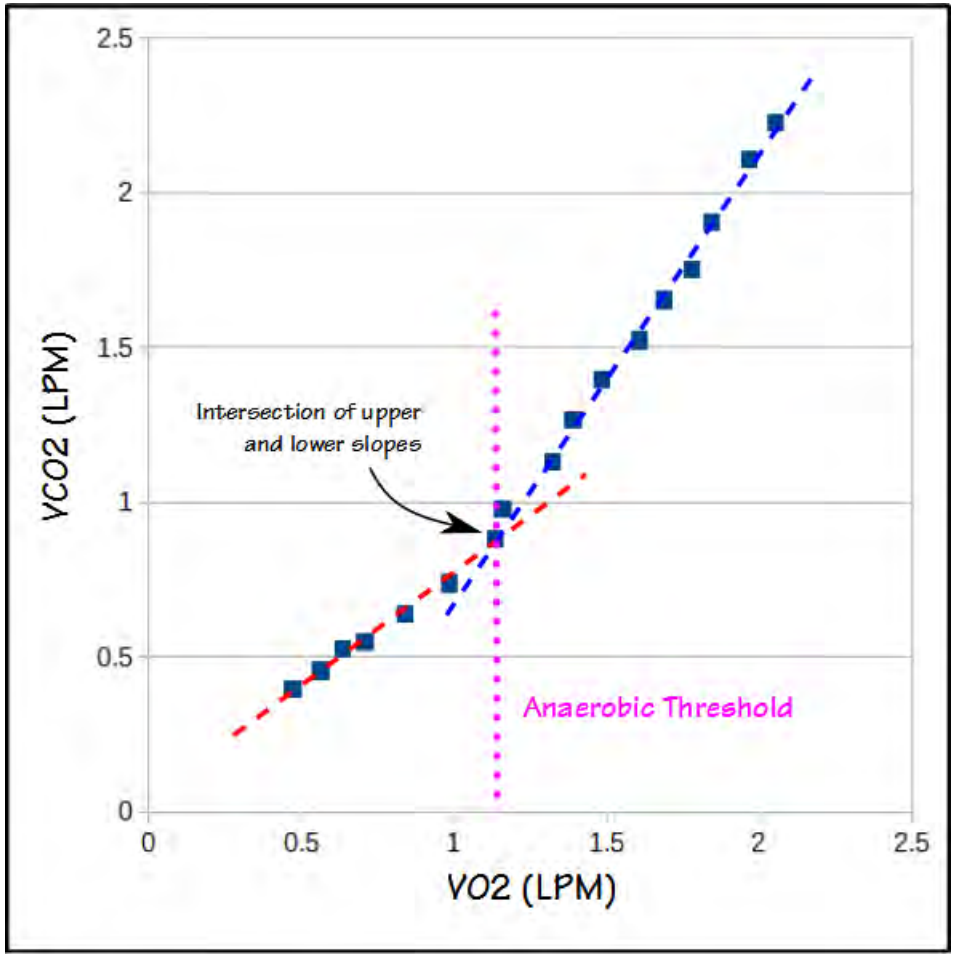


Respiratory Medicine (2015) 109, 517e525

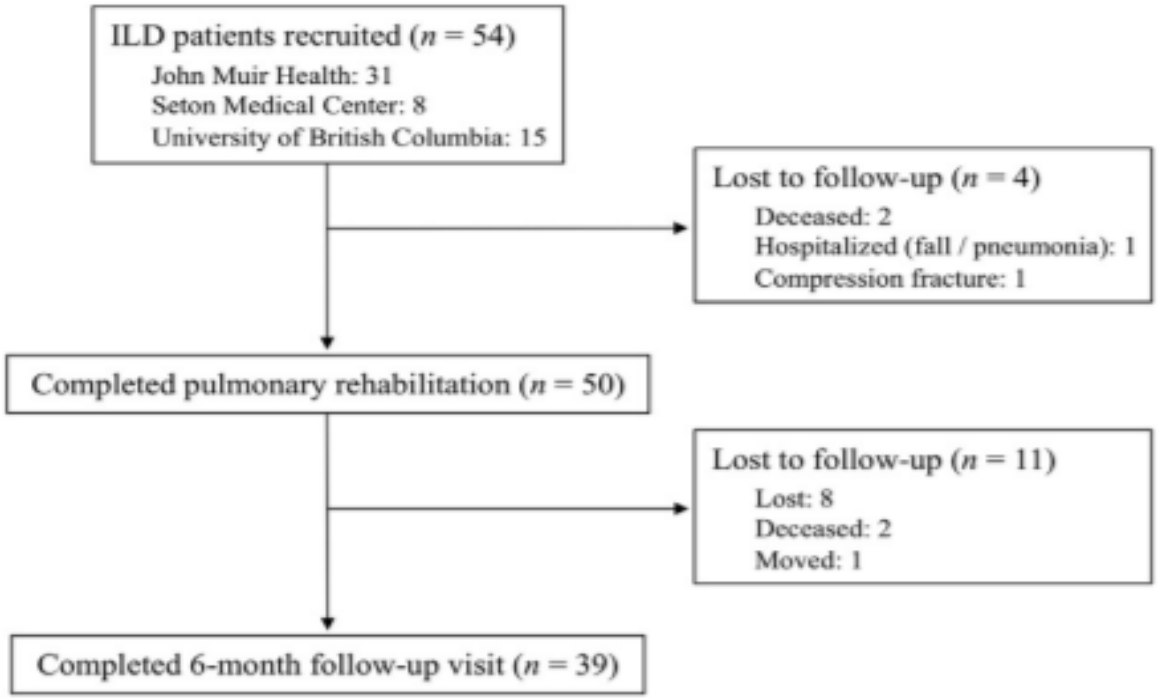
Cochrane Review 2014

Pulmonary rehabilitation seems to be safe for people with ILD. Improvements in functional exercise capacity, dyspnoea and quality of life are seen immediately following pulmonary rehabilitation, with benefits also evident in IPF. Because of inadequate reporting of methods and small numbers of included participants, the quality of evidence was low to moderate. Little evidence was available regarding longer-term effects of pulmonary rehabilitation.

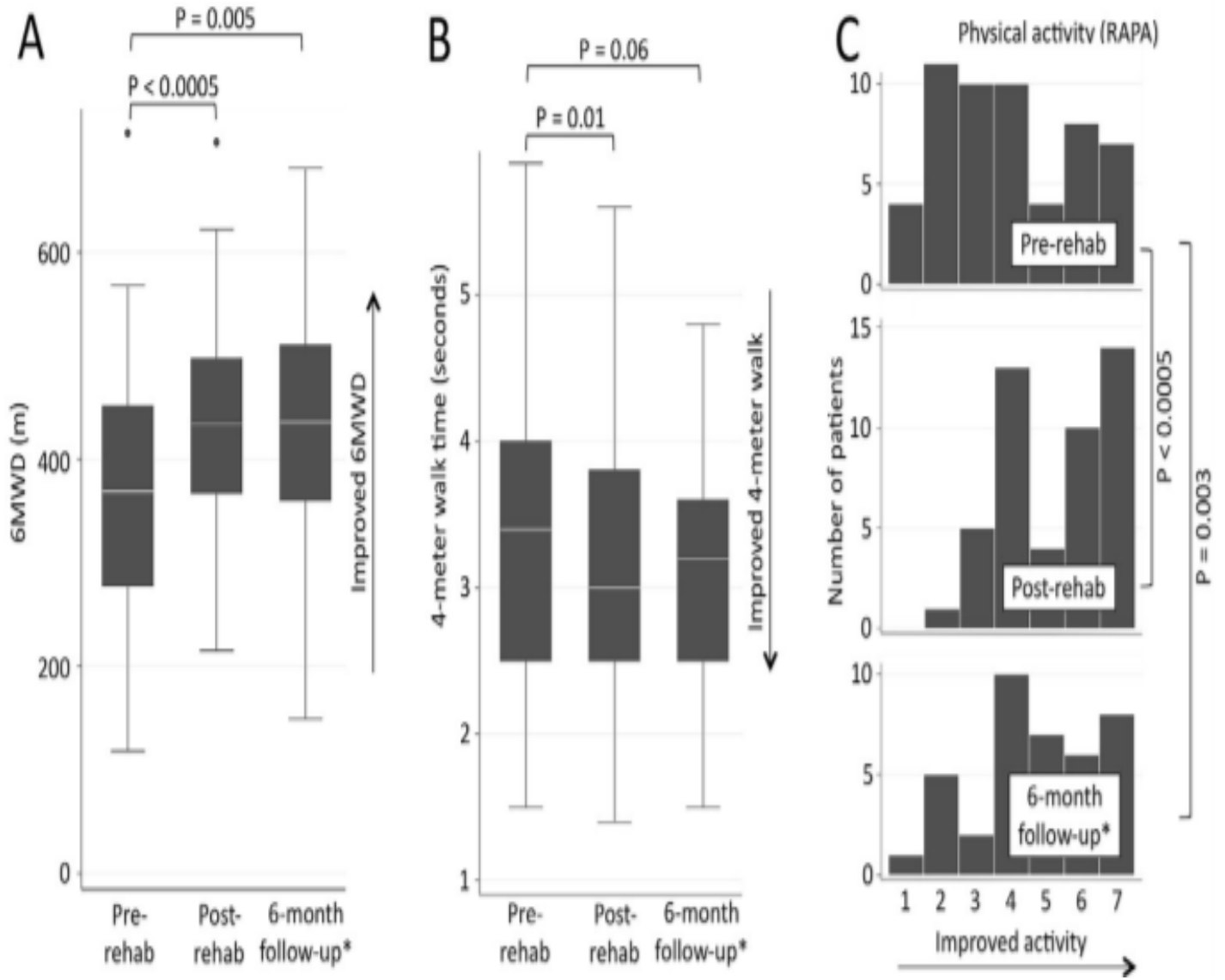
Anaerobic threshold- so what

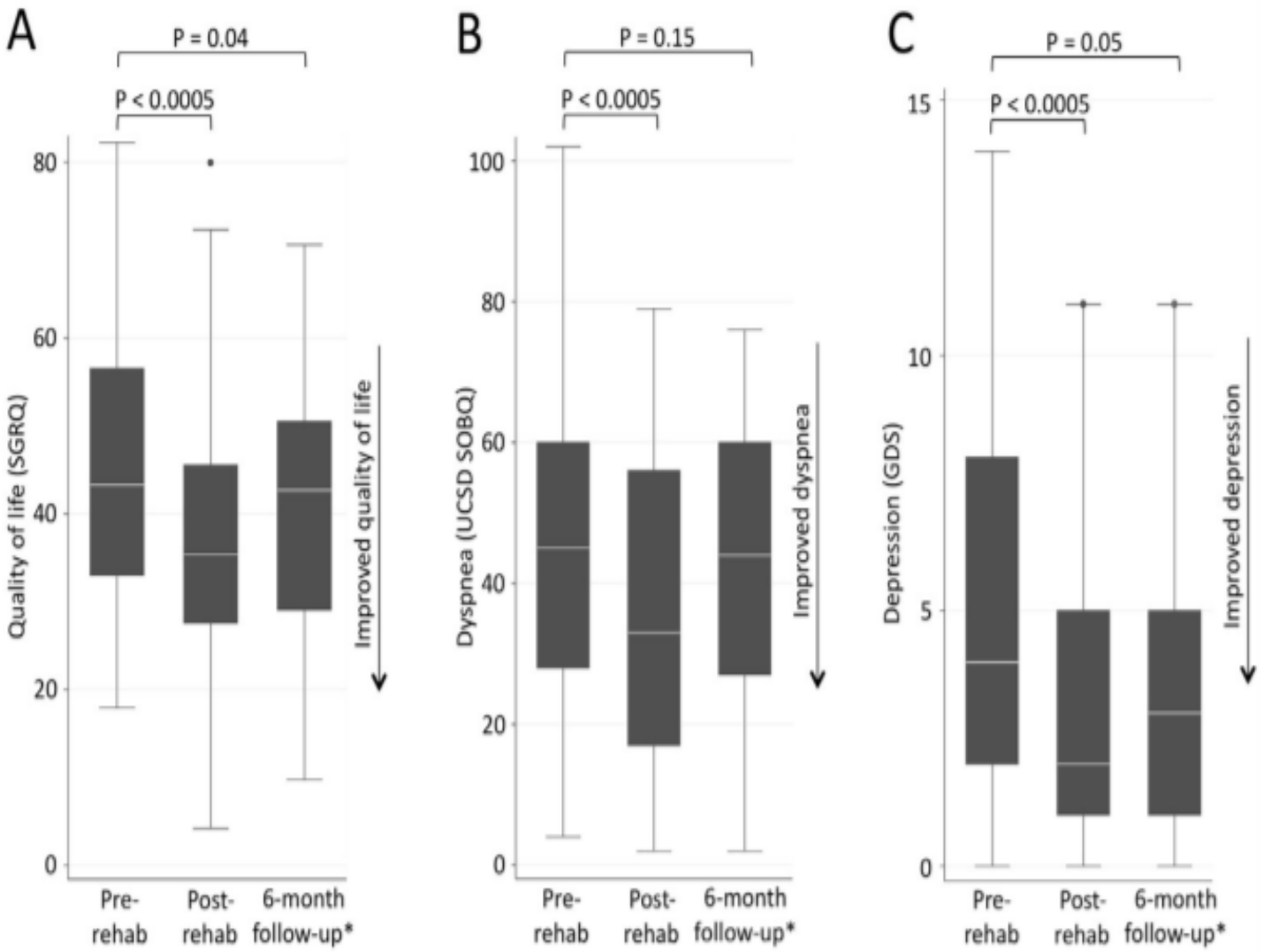


Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: A prospective cohort study



Respiratory Medicine (2014) 108, 203e210


A
P = 0.005
P < 0.0005
6MWD (m)
600
400
200
0
Improved 6MWD
Pre-rehab
Post-rehab
6-month follow-up*
B
P = 0.06
P = 0.01
4-meter walk time (seconds)
5
4
3
2
1
Improved 4-meter walk
Pre-rehab
Post-rehab
6-month follow-up*
C
Physical activity (RAPA)
Number of patients
Pre-rehab
Post-rehab
6-month follow-up*
P < 0.0005
P = 0.003
1 2 3 4 5 6 7
Improved activity


A
P = 0.04
P < 0.0005
Quality of life (SGRQ)
Improved quality of life
0
20
40
60
80
Pre-rehab
Post-rehab
6-month follow-up*
B
P = 0.15
P < 0.0005
Dyspnea (UCSD SOBQ)
Improved dyspnea
0
20
40
60
80
100
Pre-rehab
Post-rehab
6-month follow-up*
C
P = 0.05
P < 0.0005
Depression (GDS)
Improved depression
0
5
10
15
Pre-rehab
Post-rehab
6-month follow-up*

Why rehabilitation?

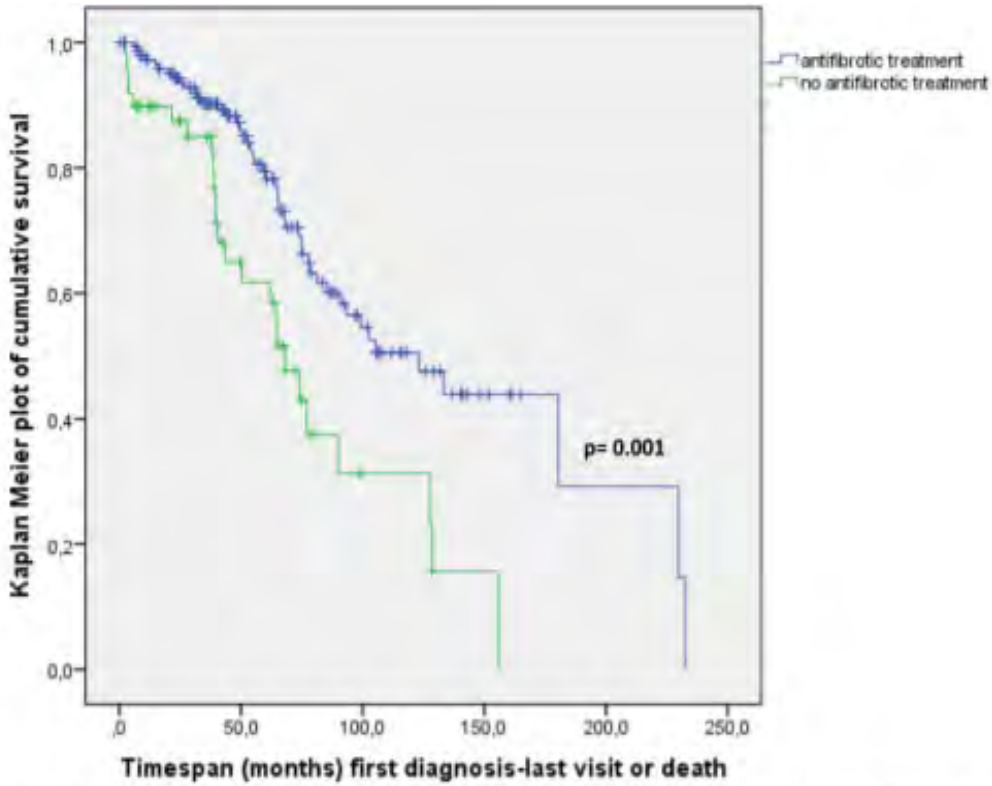


Fig. 6 Overall survival of IPF patients upon first diagnosis depending on treatment. Given are Kaplan-Meier curves for cumulative survival, based on definite outcome data (survival status definitely known as per end of 2016) and on last visit data. A statistically significant difference in survival was encountered between patients receiving anti-fibrotic treatment and those not receiving antifibrotics, significance level p was 0.001. Within the group of patients receiving antifibrotic treatment, 83% of patients received pirfenidone and 17% received nintedanib

Guenther et al. Respiratory Research (2018) 19:141

COPD and/or IPF?

- Shorter lifespan
- Pulmonary rehabilitation improves lung function
- Pursed lip breathing has an important role in relieving shortness of breath
- Genetic factors play an important identifiable role
- Medical management prevent disease progression
- Pulmonary hypertension can aggravate dyspnea on exertion
- Muscle function is adversely affected