# Πνευμονική Υπέρταση
## *σε*
## *Χρόνιες Πνευμονοπάθειες*

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## Updated Classification of Pulmonary Hypertension

1. Pulmonary arterial hypertension
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.2.1 BMPR2
   - 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
   - 1.2.3 Unknown
   - 1.3 Drug and toxin induced
   - 1.4 Associated with:
   - 1.4.1 Connective tissue disease
   - 1.4.2 HIV infection
   - 1.4.3 Portal hypertension
   - 1.4.4 Congenital heart diseases
   - 1.4.5 Schistosomiasis

1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1″. Persistent pulmonary hypertension of the newborn (PPHN)

2. Pulmonary hypertension due to left heart disease
   - 2.1 Left ventricular systolic dysfunction
   - 2.2 Left ventricular diastolic dysfunction
   - 2.3 Valvular disease
   - 2.4 Congenital/acquired left heart inflow/outflow 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

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   - 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   - 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   - 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

COPD and IPF
have been the archetype
and the source
of most
of the current knowledge
on this phenomenon

# Group 3. PH due to lung disease and/or hypo

- **Obstructive pulmonary disease**
  - COPD
  - Bronchiolitis obliterans
- **Interstitial Lung Diseases**
  - Idiopathic interstitial pneumonias
  - Chronic hypersensitivity pneumoni
  - Occupational lung disease
- **Other lung diseases with mixed restrictive/obstructive patettern**
  - Sarcoidosis
  - Combined pulmonary fibrosis and emphysema
  - Cystic fibrosis and non-cystic fibrosis bronchiectasis
  - Lymphangioleiomyomatosis
  - Other destructive lung disease
- **Alveolar Hypoxia without lung disease**
  - Sleep –disordered breathing
  - Chest wall abnormalities
  - Obesity hypoventilation syndromes
  - Other alveolar hypoventilation disorders
  - Chronic exposure to high altitude
- **Pediatrics**

**New**
**Nice 2018**

- The reported prevalence of PH in patients with COPD ranges from **25-91%**

**depends on the severity of the disease**
**3-85%**
Nathan Lancet 2017

Wide range due to differences in:
***Disease severity***
***PH definition***
***Diagnostic test***

# Pathophysiology

Singh I The American J of Med 2016

# Pathophysiology

## *PH in Chronic Lung Disease*

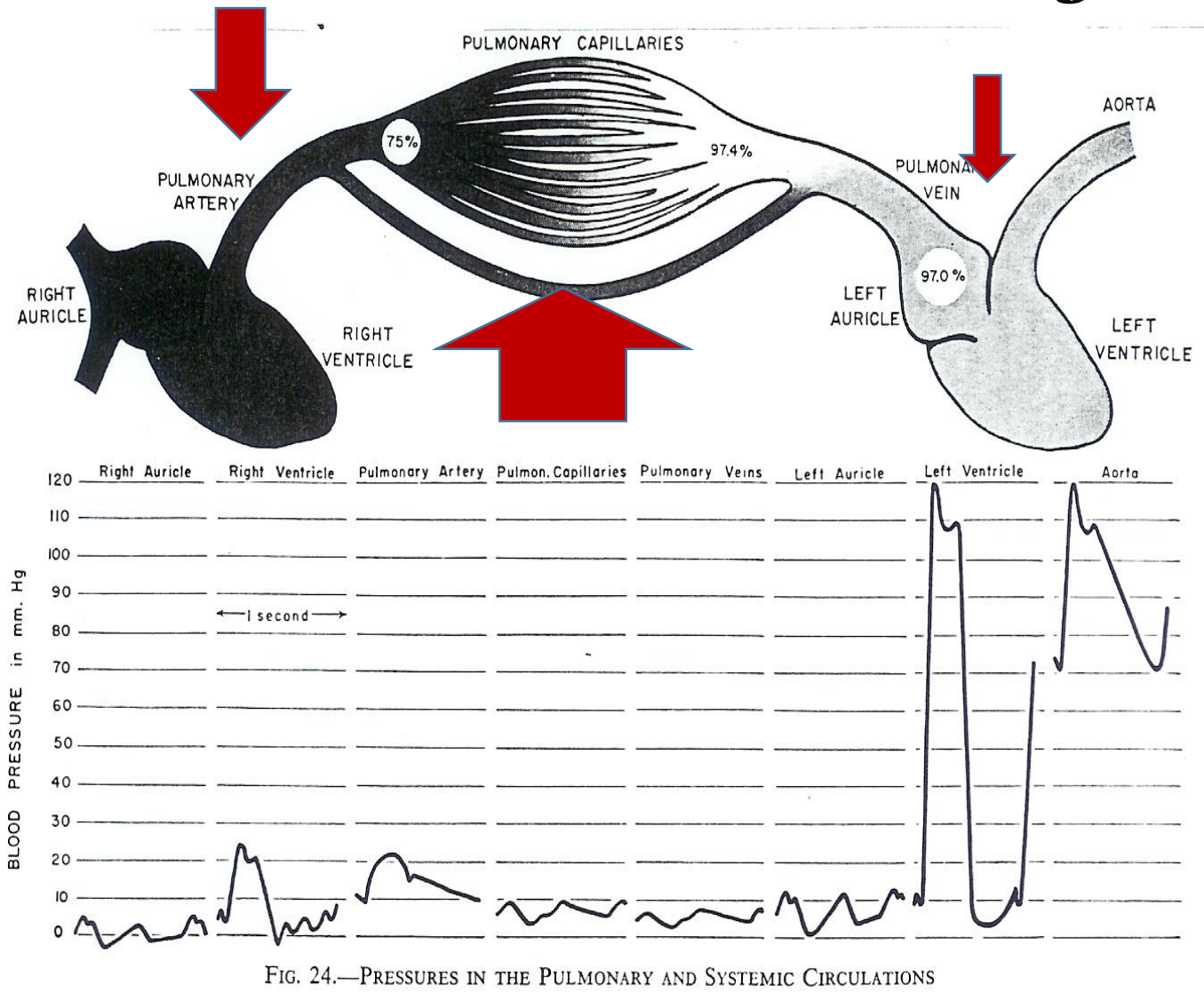
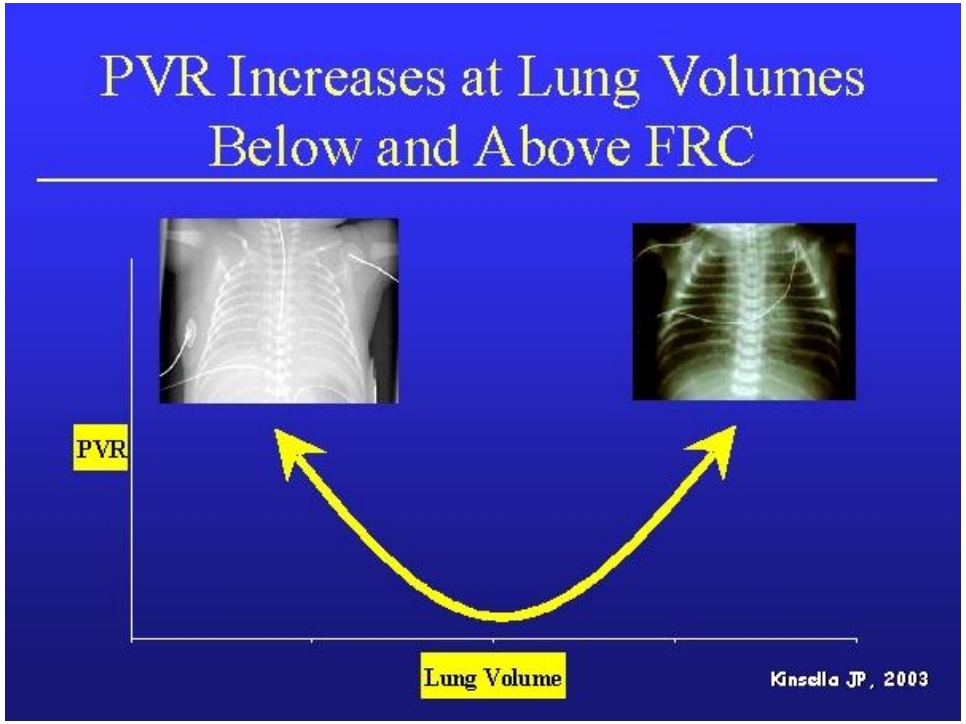



FIG. 24.—PRESSURES IN THE PULMONARY AND SYSTEMIC CIRCULATIONS

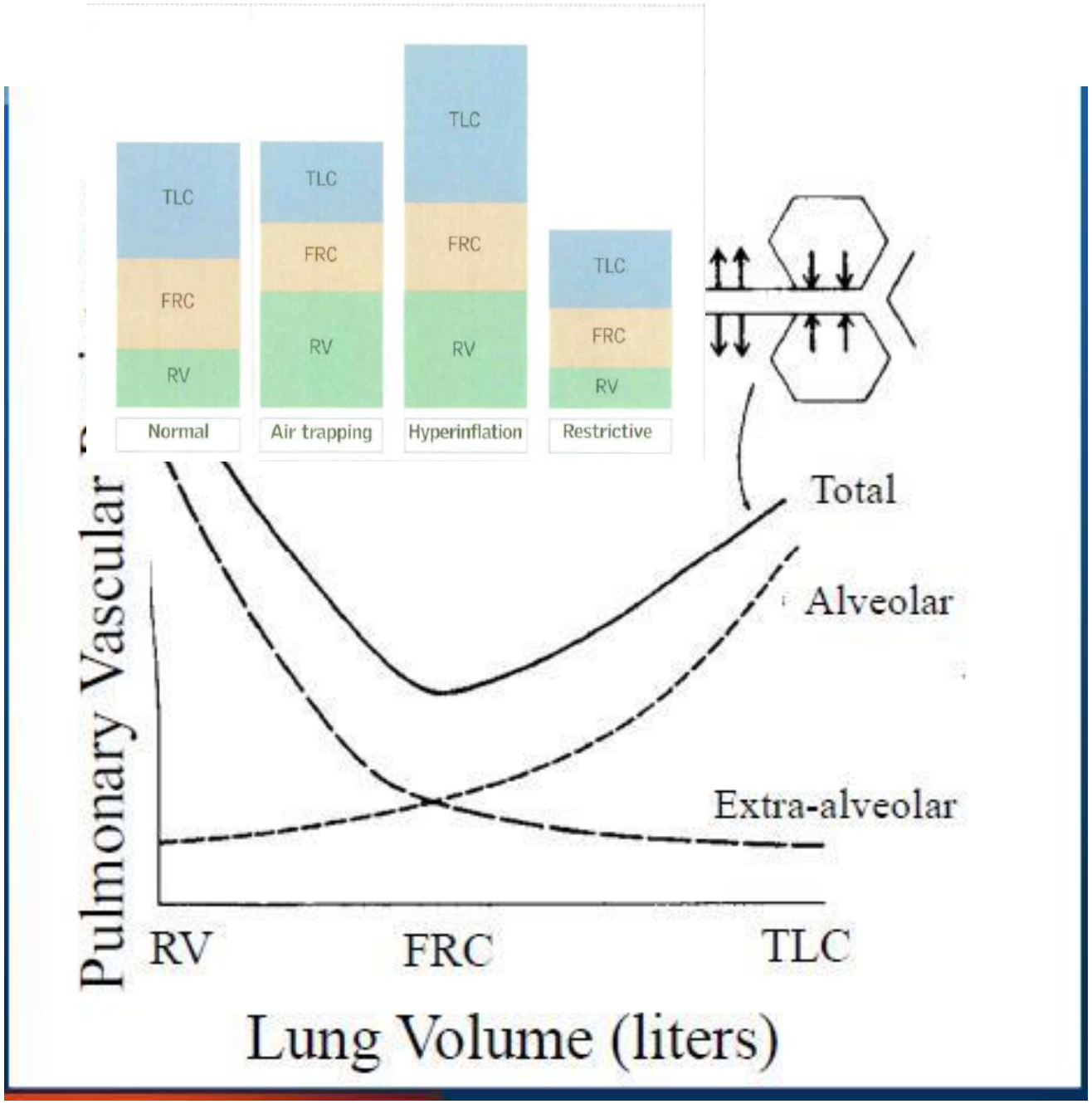
# Passive Factors Influencing Pulmonary Vascular Resistance

| Passive Factors | Effect on PVR | Mechanism of Increased PVR |
|---|---|---|
| Increased lung volume (above FRC) | Increases | Lengthening and compression of alveolar vessels |
| Decreased lung volume (below FRC) | Increases | Compression of extra-alveolar vessels |
| Increased pulmonary arterial pressure<br>Increased left atrial pressure<br>Increased pulmonary blood volume<br>Increased cardiac output | Decreases | Recruitment and distension of previously underperfused vessels |
| Gravity/body position | Decreases in gravity-dependent regions of the lungs | Hydrostatic effects leading to recruitment and distension of previously underperfused vessels |
| Increased blood viscosity | Increases | Viscosity directly increases resistance |
| Positive-pressure ventilation | Increases | Increased alveolar pressure with compression and lengthening of alveolar vessels<br>Increased intrapleural pressure with compression of extra-alveolar vessels<br>Reduces venous return resulting in decreased pulmonary blood flow and de-recruitment |

Singh Inderjit AJM,2016(129)




Pulmonary Vascular Resistance = Pulmonary Driving Pressure/ Cardiac Output



# Factors contributing to elevation in PVR *in COPD*

| Contributing Factors | Consequence |
|---|---|
| Expiratory airflow obstruction | Alveolar hyperinflation |
| Chronic hypoxia<br>LL-genotype polymorphism of 5-HT<br>Increased expression of ADORA2B<br>Proliferation of bone marrow EPCs<br>Cigarette smoking injury<br>Airway and vascular wall inflammation | Pulmonary vascular remodeling |
| Hypoxia and acidosis | Reflexive pulmonary vascular constriction |
| Polycythemia | Increased blood viscosity |

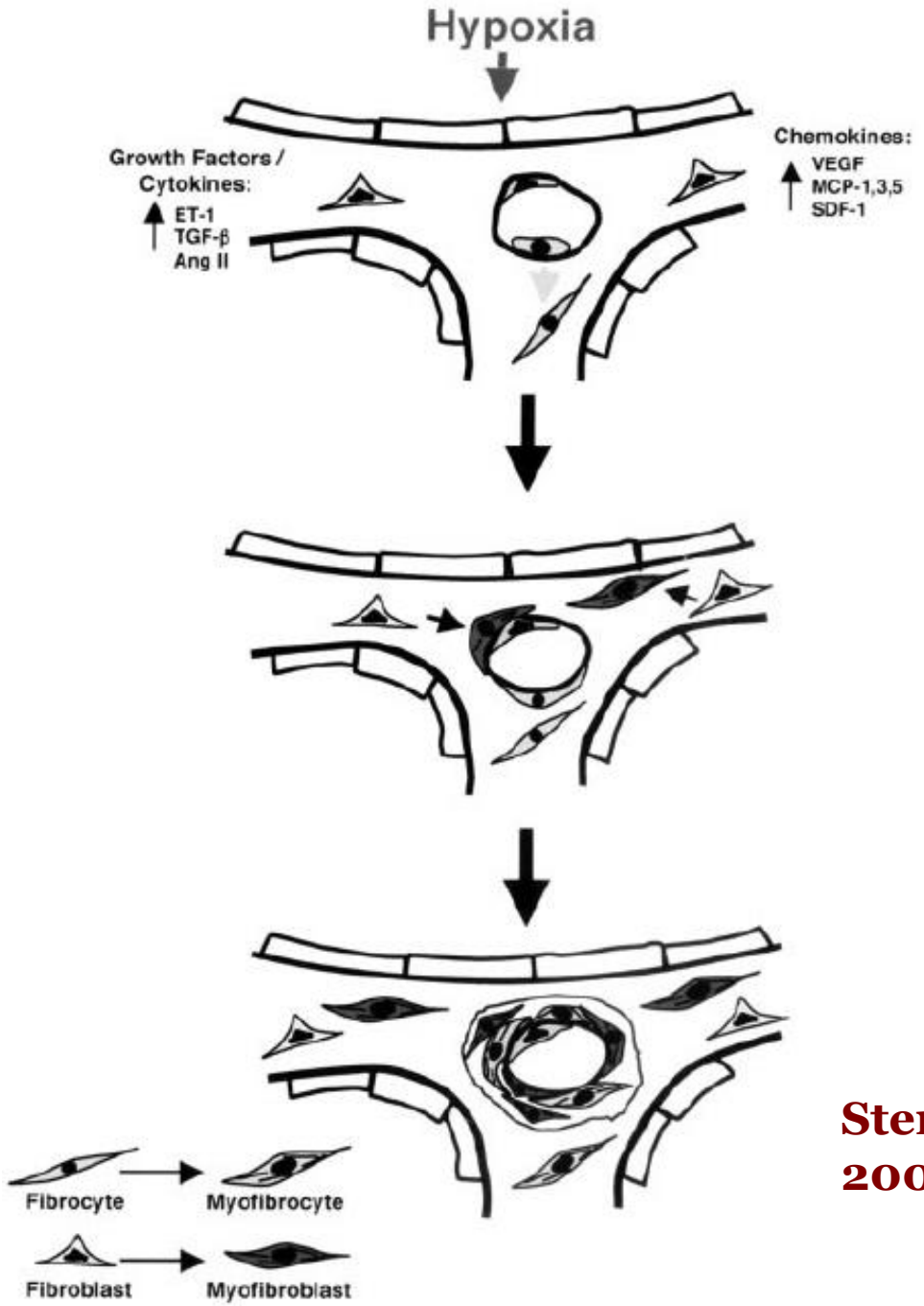
ADORA2B = adenosine A2B receptor; EPC = endothelial progenitor cell; 5-HT = serotonin.

Singh I The American J of Med 2016

# Active Factors Influencing Pulmonary Pressure *In Chronic Lung Disease*

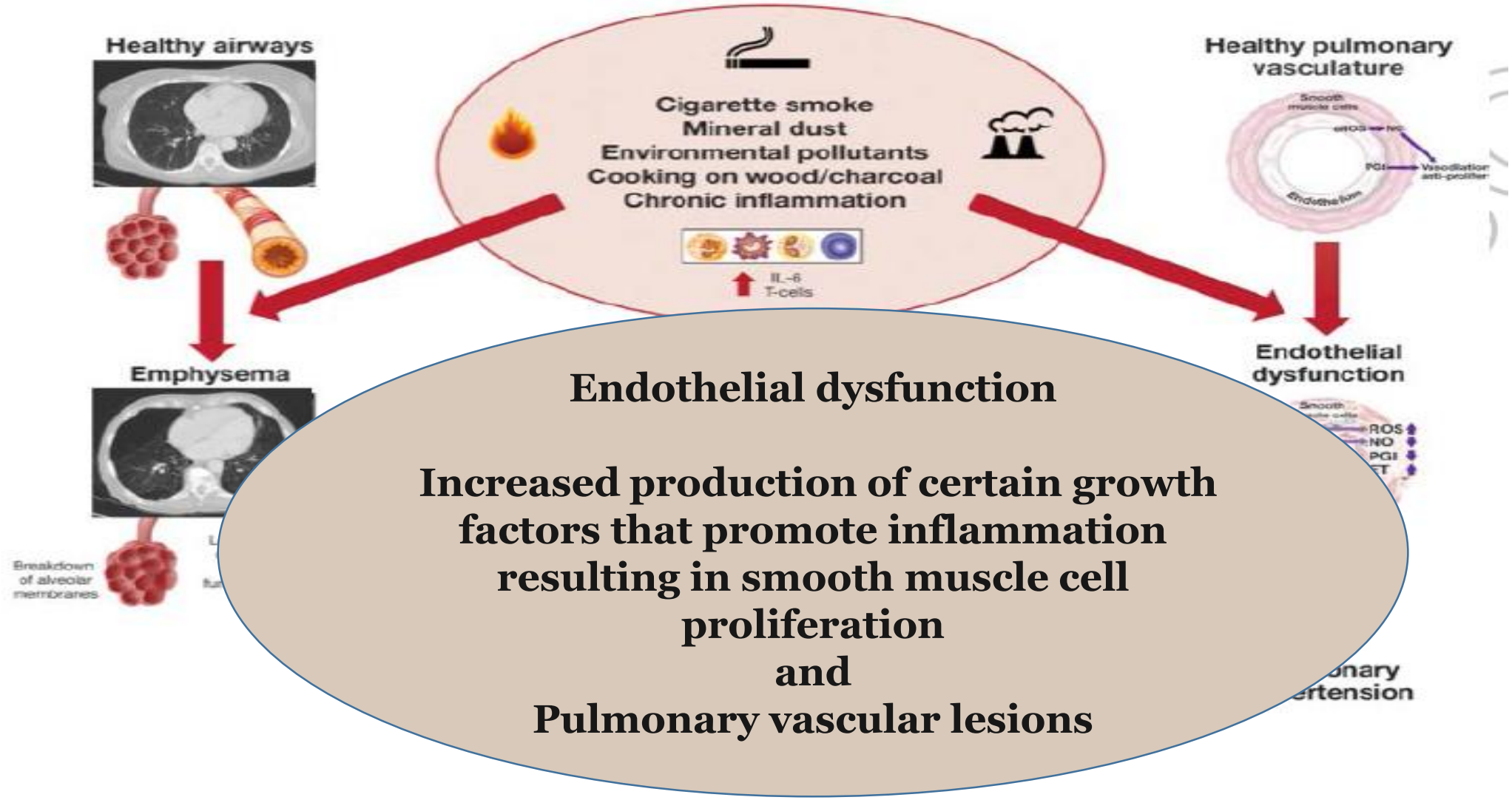
| Active Factors that Increase PVR | Active Factors that Decrease PVR |
|---|---|
| Neural factors:<br>• Sympathetic nervous system stimulation<br>• Sympathomimetics: norepinephrine, epinephrine, and alpha-agonists | Neural factors:<br>• Parasympathetic nervous system stimulation<br>• Parasympathomimetics: acetylcholine<br>• Sympathomimetic: beta-2-agonists |
| Gaseous factors:<br>• Alveolar hypoxia and hypercapnia | Gaseous factor:<br>• Nitric oxide |
| Other factors:<br>• Thromboxane<br>• Endothelin<br>• Angiotensin<br>• PG-$F_{2alpha}$ and PG-E2<br>• Low pH of mixed venous blood | Other factors:<br>• Prostacyclin<br>• Bradykinin<br>• PG-E1 |

Singh Inderjit AJM,2016(129)



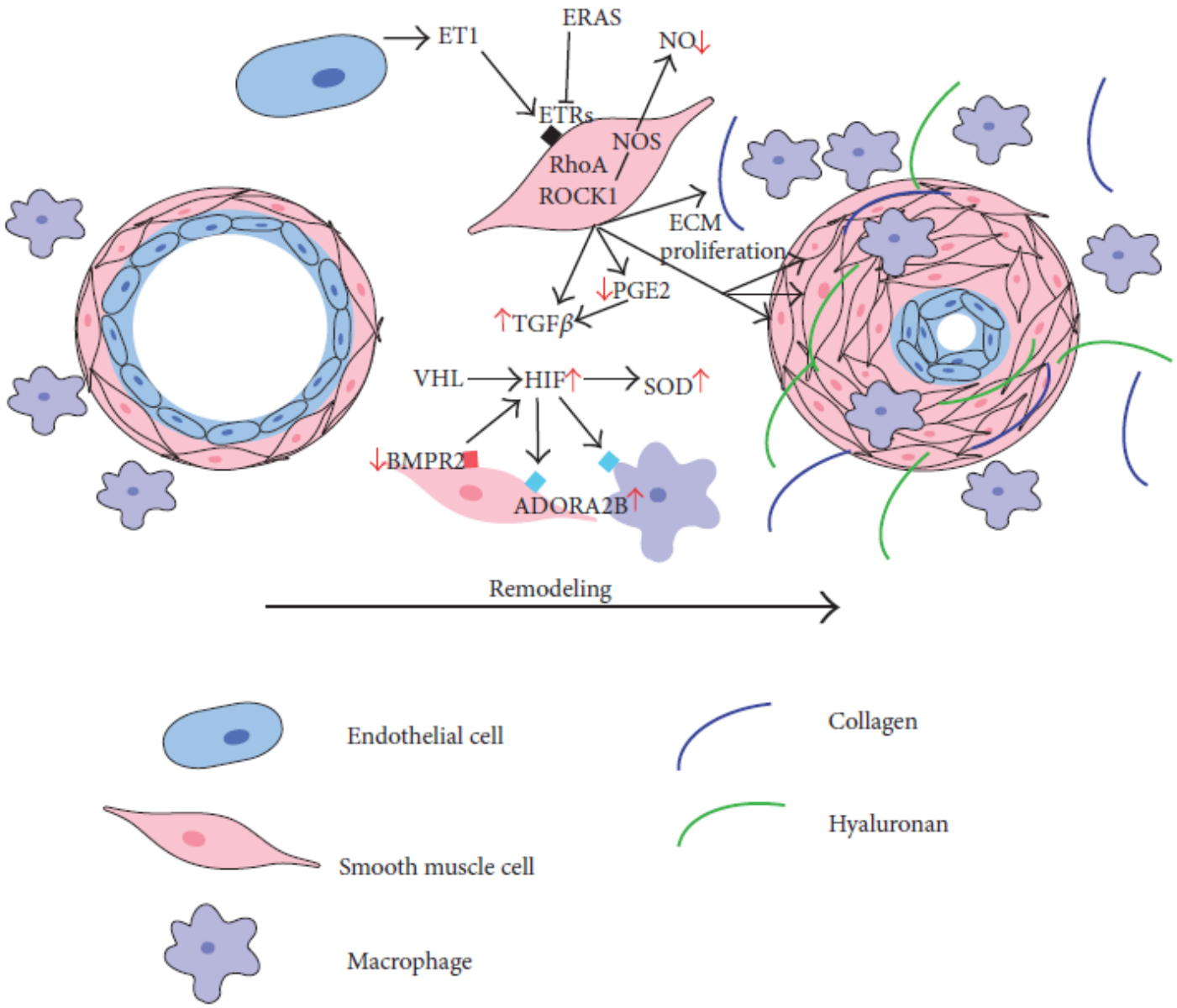


**Stenmark KR Circul Resear 2006;99:675**



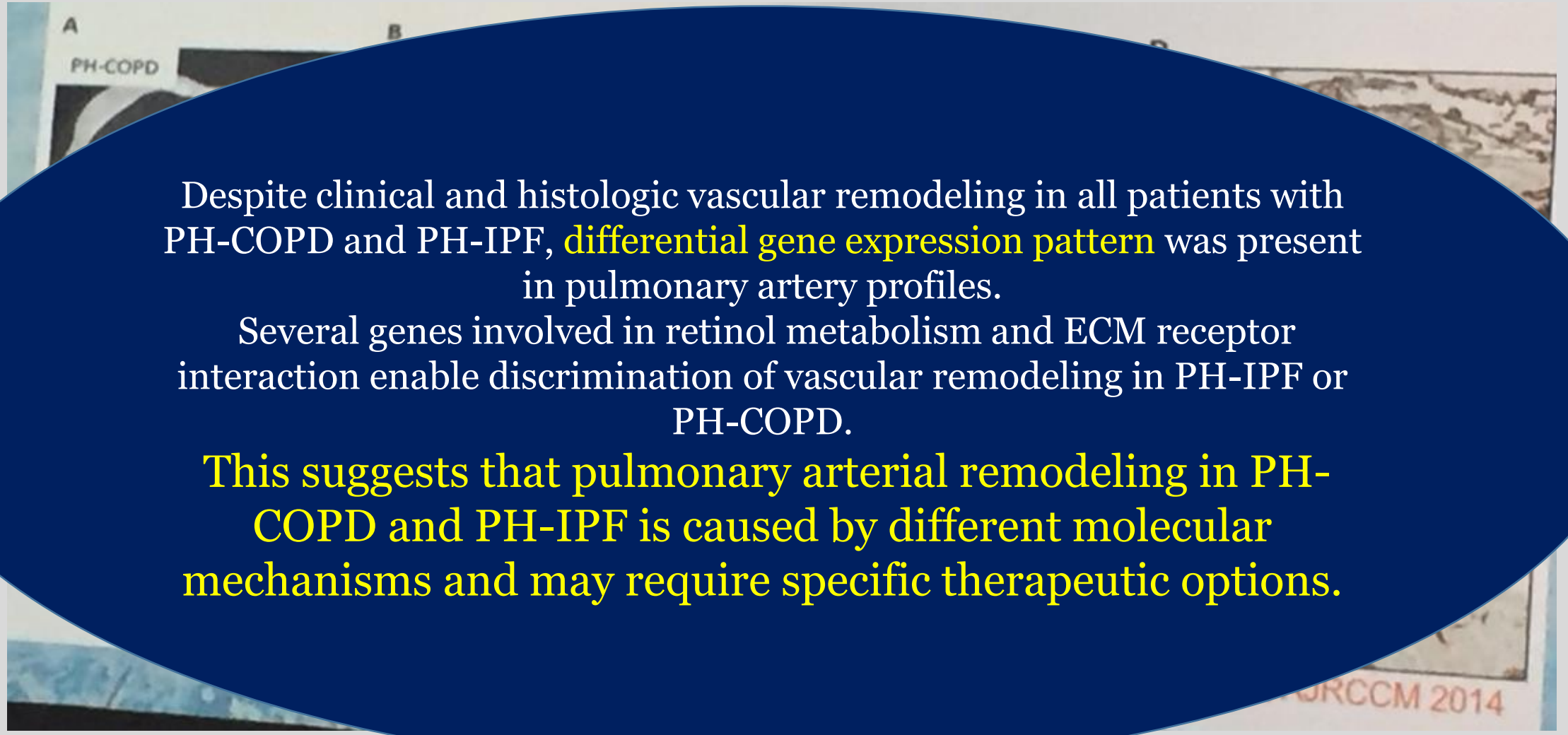

J Grimminger Exper Rev in Res Med May 2016

Cellular processes and mediators involved in the pathogenesis of PH associated with lung fibrosis.




**Scott DC CRJ 2017**

# Similarities in vascular remodeling between PH-COPD and PH-IPF ?




Despite clinical and histologic vascular remodeling in all patients with PH-COPD and PH-IPF, differential gene expression pattern was present in pulmonary artery profiles.

Several genes involved in retinol metabolism and ECM receptor interaction enable discrimination of vascular remodeling in PH-IPF or PH-COPD.

This suggests that pulmonary arterial remodeling in PH-COPD and PH-IPF is caused by different molecular mechanisms and may require specific therapeutic options.

# Assessment /Definition

Current (2015)
Haemodynamic classification
of Pulmonary Hypertension
due to
Lung diseases

| | Right heart catheterisation |
|---|---|
| COPD/ILD without PH | Mean PAP <25 mm Hg |
| COPD/ILD with PH | Mean PAP ≥25 mm Hg, but <35 mm Hg |
| COPD/ILD with severe PH | Mean PAP >35 mm Hg, or ≥25 mm Hg with low cardiac output (CI <2.5 l/min/m$^2$) |

COPD = chronic obstructive pulmonary disease; ILD = interstiti lung disease; PAP = pulmonary arterial pressure; PH = pulmonary hypertension

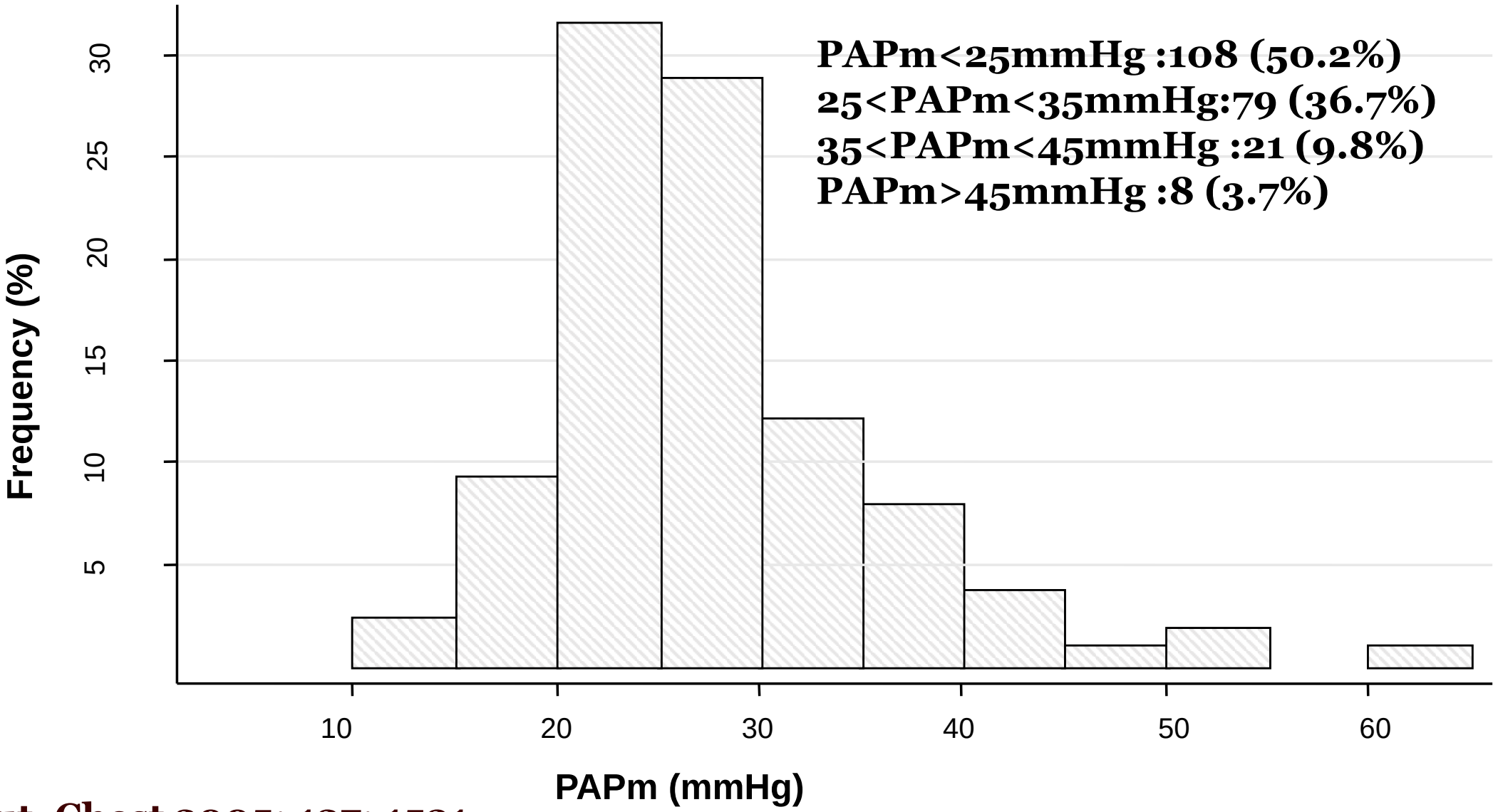
Includes a minority of pts
mPAP>35 mmHg → ↓ DLCO, rest PaO2,
lower exercise capacity
decline PaO2 at exercise independent of PFTs

# 2018 classification

- Chronic lung disease (CLD) without PH **(mPAP<20mmHg)**
- CLD with PH>/= 20mmHg and PVR>/= 3WU, with supplemental O2 if needed)
  - Stick to the standard definition
  - RHC needed to assessment of CO and PAOP
- CLD with severe PH (mPAP>/=35mmH
  - Rationale:
    - at this level hemodynamics contribute to exercise limitation
    - minor subpopulation with 'vascular phenotype' (in COPD <3%)
    - optimal target population in future RCT addressing PH in chronic lung disease

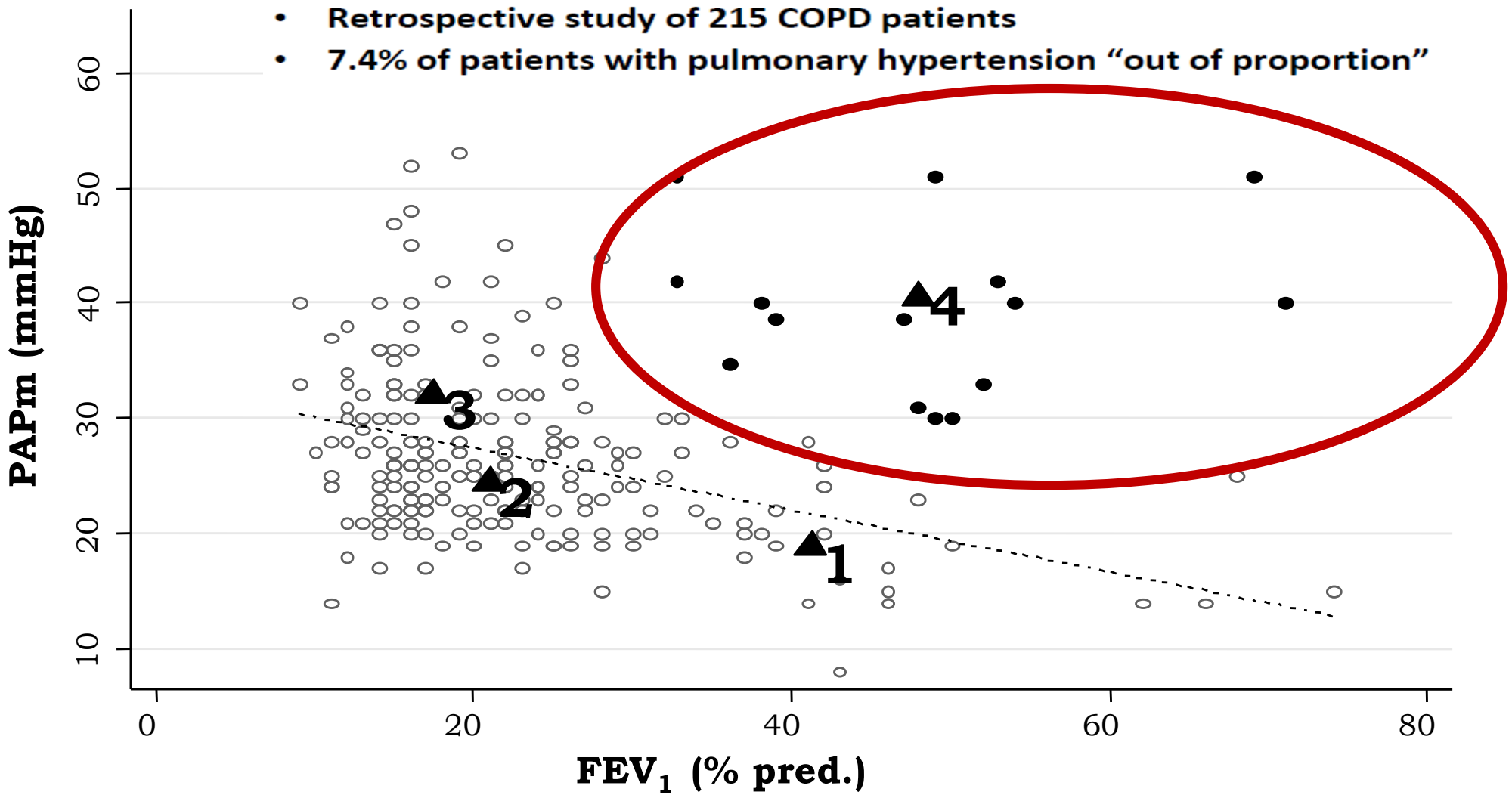
**Lower PA clinically significant in COPD/DPLD If ↓CI or RV dysfunction**

# Distribution of PAPm



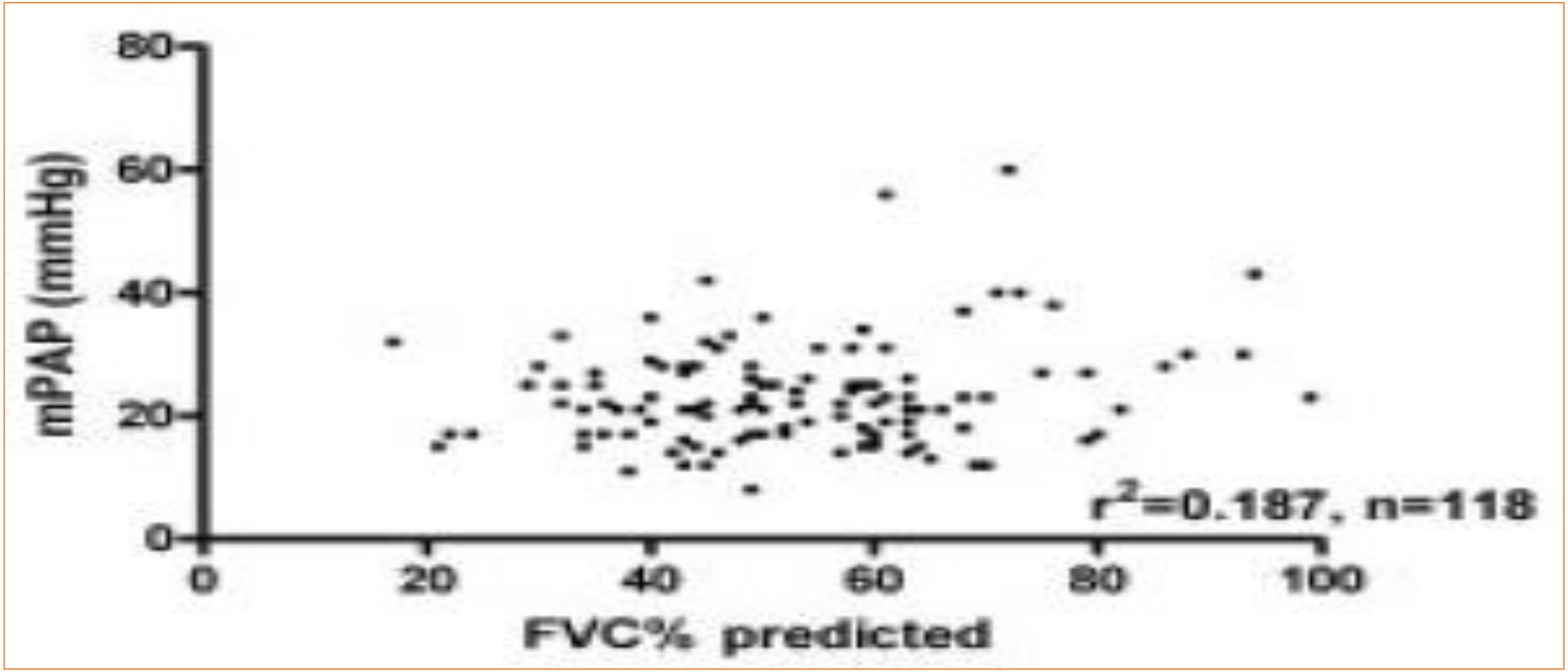

Thabut, Chest 2005; 127: 1531

# COPD and Pulmonary Hypertension




*Thabut, Chest 2005; 127: 1531*

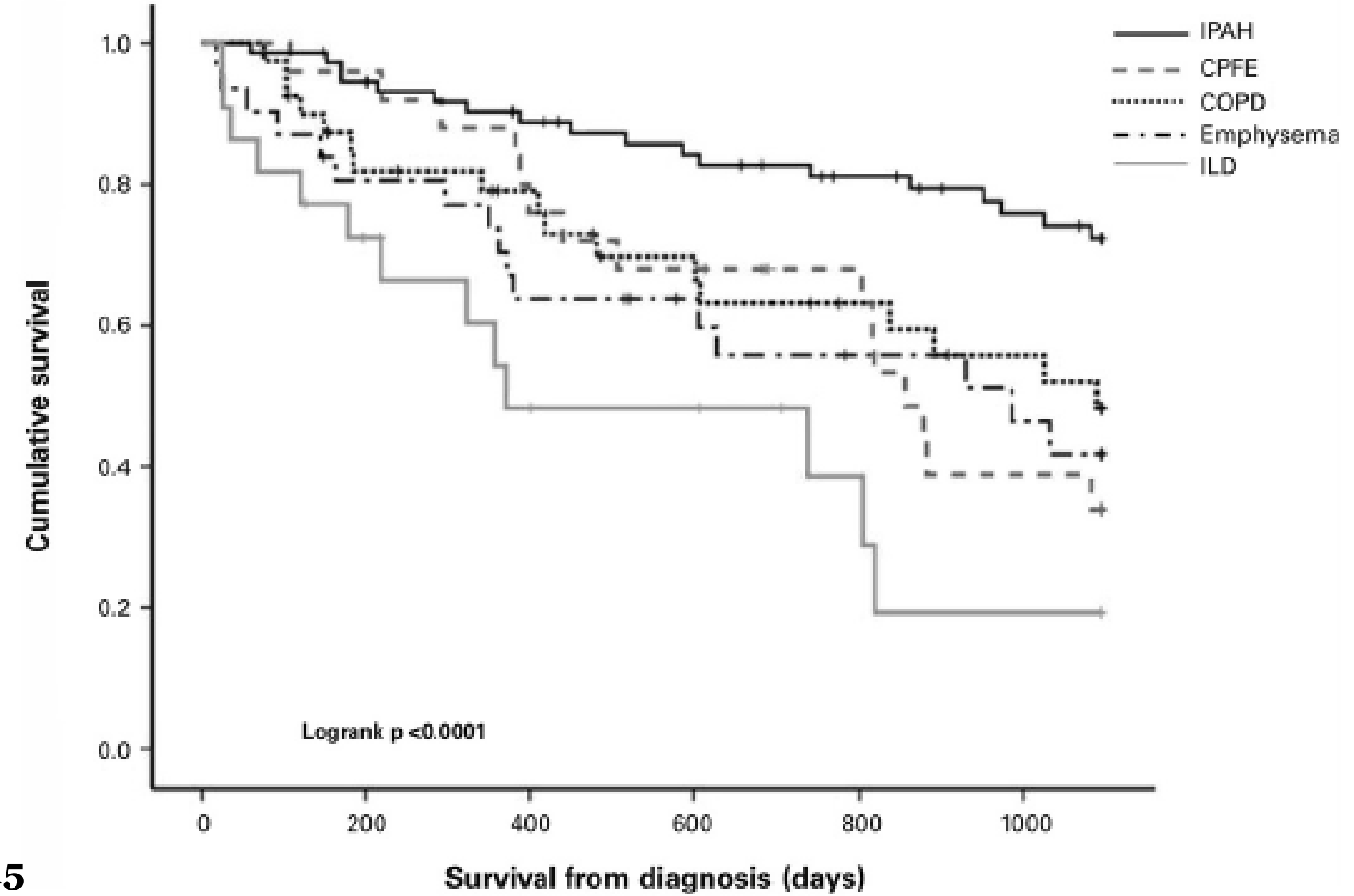
# ILD and Pulmonary Hypertension




SD Nathan, Chest 2007

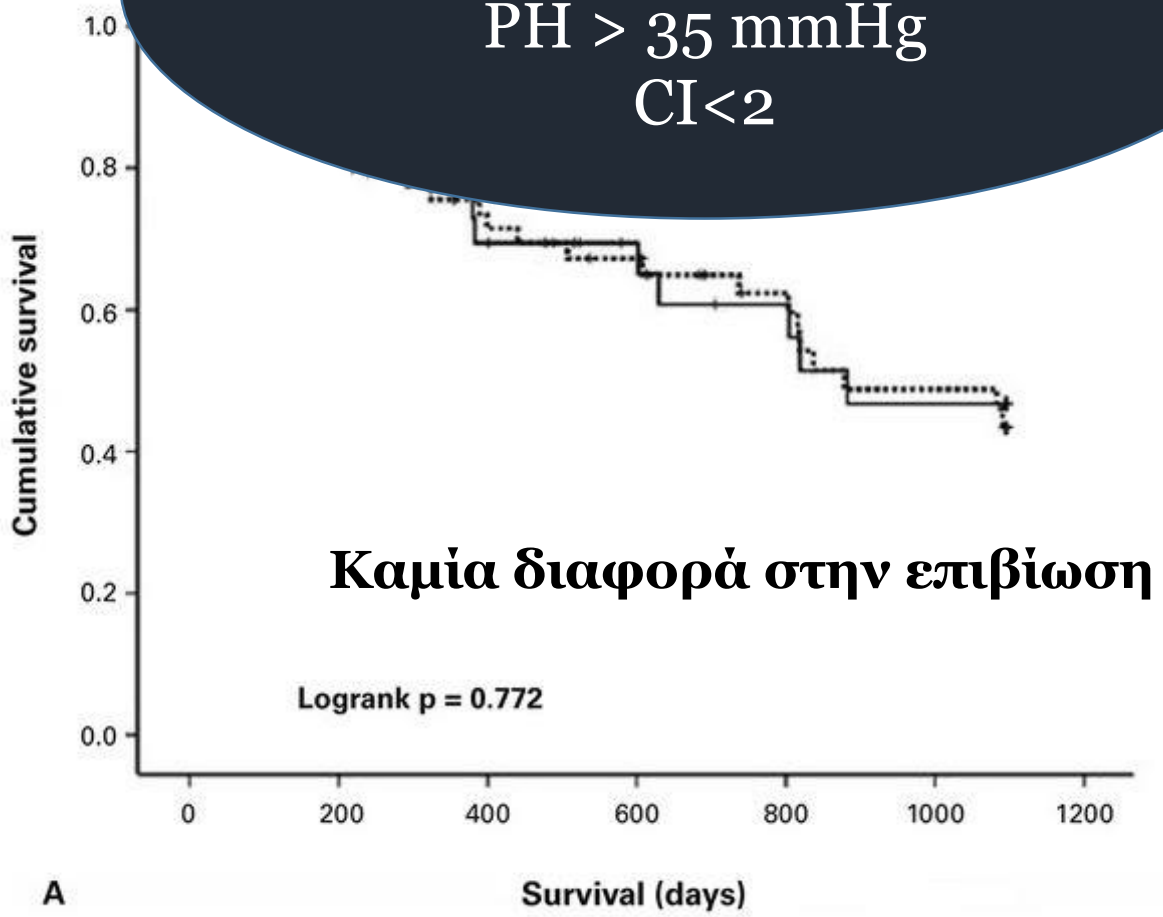
# PH and Chronic Lung Disease

## *So What*

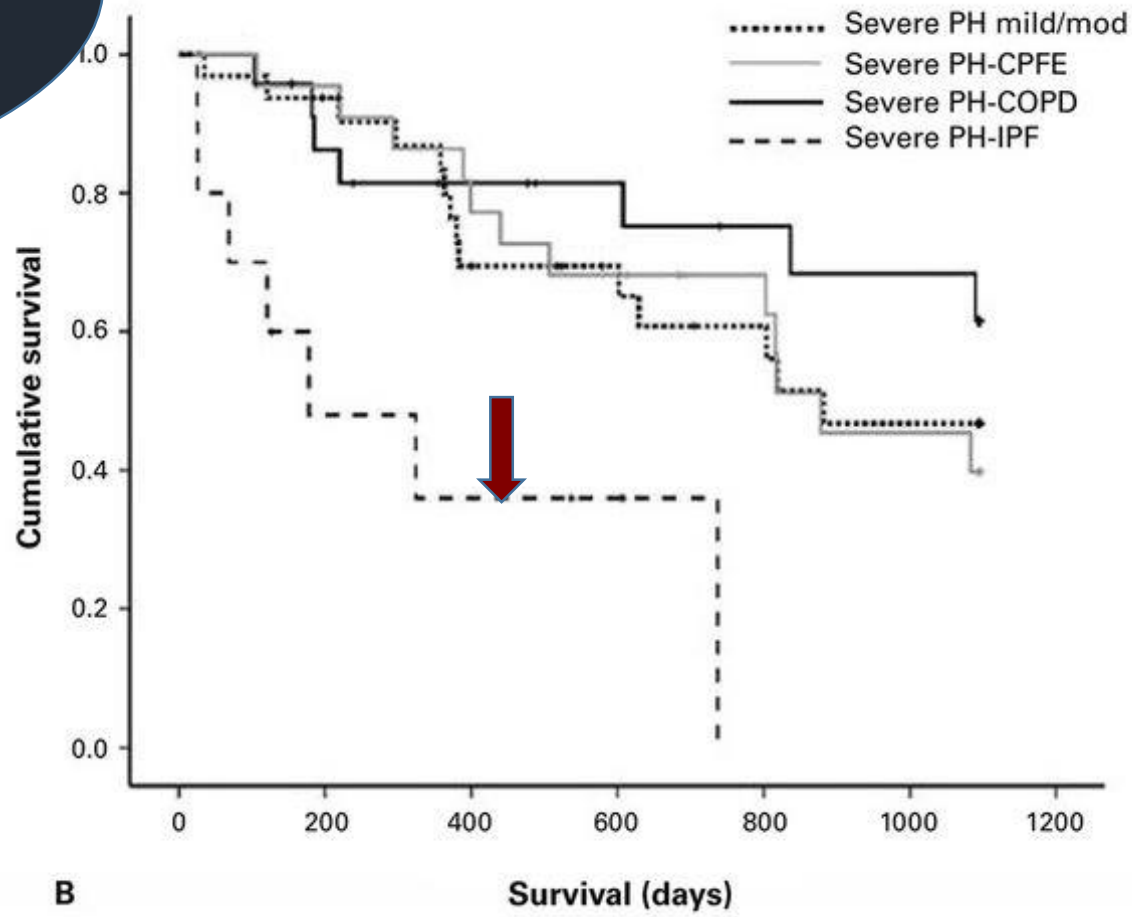



**Bruise ERJ 2015**

Ήπια πνευμονική νόσος
FEV1 >60% / Σοβαρή Νόσο
PH > 35 mmHg
CI<2

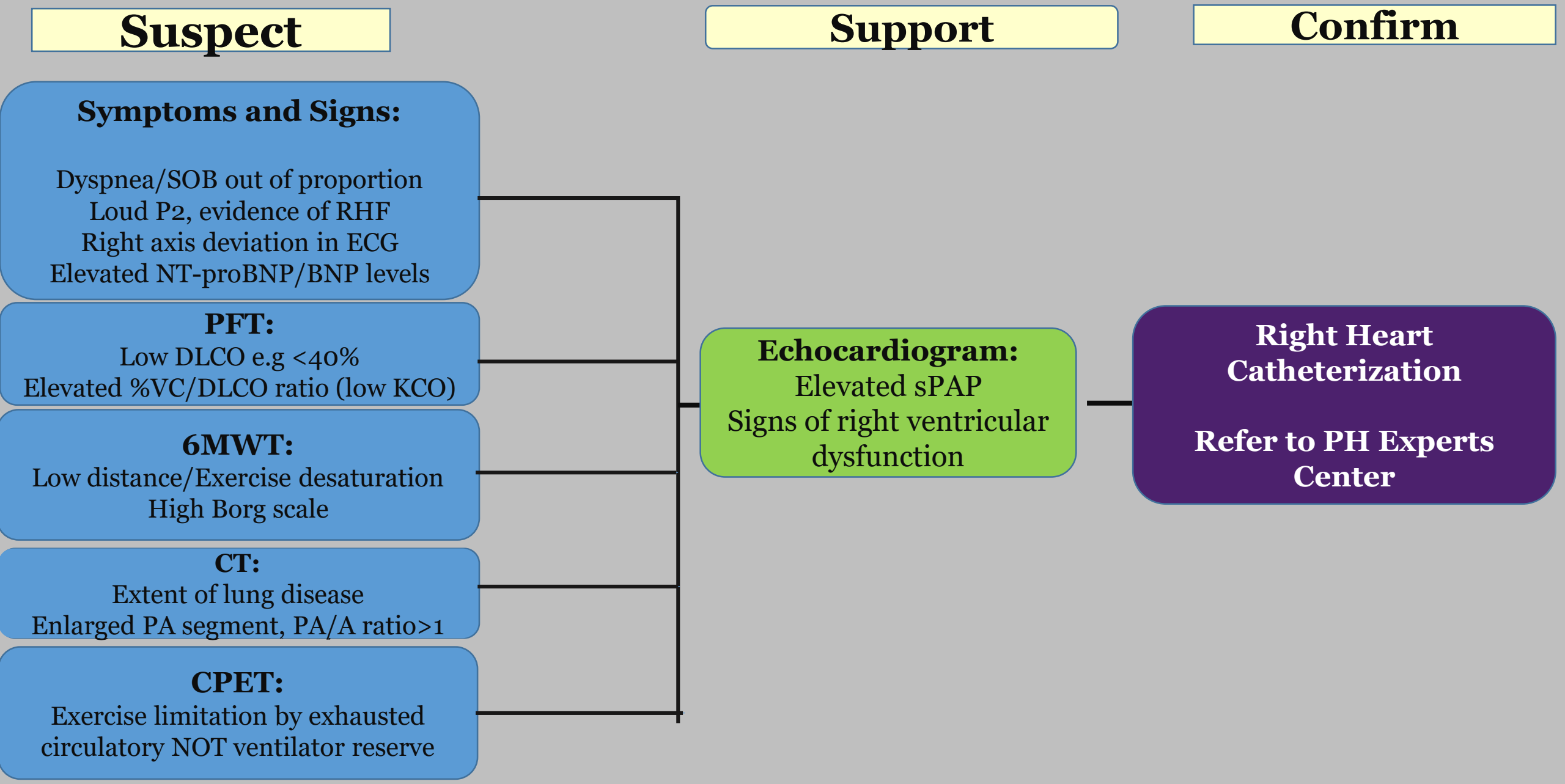



**Καμία διαφορά στην επιβίωση**




Funke M, OD Schoch 2016 Swiss Med Wkly

# Algorithm for Diagnosis of PH in Known Lung Disease



| Criteria favoring group 1 (PAH) | Testing | Criteria favoring group 3 (PH due to lung disease) |
|---|---|---|
| **Extent of lung disease** | | |
| Normal or mildly impaired:<br>FEV1>50% pred. (COPD)<br>FVC >70% pred. (IPF)<br>Low diffusion capacity in relation to obstructive /restrictive changes | Pulmonary function testing | Moderate to very severe impairment:<br>- FEV1<60%pred.(COPD)<br>- FVC <70% pred.(IPF)<br>- Diffusion capacity "corresponds" to obstructive /restrictive changes |
| Absence of or only modest airway or parenchymal abnormalities | High resolution CT scan ** | Characteristic airway and/or parenchymal abnormalities |
| **Hemodynamic profile** | | |
| Moderate to severe pH | Right heart catheterization | Mild to moderate PH |
| **Ancillary Testing** | | |
| Present | Further PAH risk factors (as e.g HIV, connective tissue disease, BMPR2 mutations, …) | Absent |
| Features of exhausted circulatory reserve<br>-Preserved breathing reserve<br>-Reduced oxygen pulse<br>-Low CO/VO2 slope<br>-Mixed venous oxygen saturation at lower limit<br>-No change or decrease in PaCO2 during exercise | Cardiopulmonary exercise test ***<br>(particulary relevant in COPD) | Features of exhausted ventilatory reserve<br>- Reduced breathing reserve<br>-Normal oxygen pulse<br>-Normal CO/VO2 slope<br>-Mixed venous oxygen saturation above lower limit<br>- Increase in PaCO2 during exercise |

**Predominal Hemodynamic profile**

**Predominant obstructive/restrictive profile**

**2015**
Recommendations for Pulmonary Hypertension due to Lung disease

# Management

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| Echocardiography is recommended for the non-invasive diagnostic assessment of suspected PH in patients with lung disease | I | C |
| Referral to an expert centre is recommended[d] in patients with echocardiographic signs of severe PH and/or severe right ventricular dysfunction | I | C |
| The optimal treatment of the underlying lung disease, including long-term $O_2$ therapy in patients with chronic hypoxaemia, is recommended in patients with PH due to lung diseases | I | C |
| Referral to PH expert center should be considered for patients with signs of severe PH/severe RV failure for individual-based treatment | IIa | C |
| RHC is not recommended for suspected PH in patients with lung disease, unless therapeutic consequences are to be expected (e.g. lung transplantation, alternative diagnoses such as PAH or CTEPH, potential enrolment in a clinical trial) | III | C |
| The use of drugs approved for PAH is not recommended in patients with PH due to lung diseases | III | C |

# Right Heart Catheterization in Chronic Lung disease

**Nice 2018**

- RHC remains the **gold standard** for the diagnosis of PH

-*suspicion of underlying PH does not always mandate RHC*

-RHC **should be performed** in patients with chronic lung disease

1. Evaluation for lung transplantation
2. Suspicion of left ventricular systolic/diastolic dysfunction
3. Severe PH is suspected and further therapy or inclusion in clinical trials or registries are being considered.

-RHC **may be considered:**

1. Clinical worsening, progressive exercise limitation and/or gas exchange abnormalities are disproportionate to ventilatory impairment.
2. When an accurate prognostic assessment is deemed sufficiently important

Technique: averaging of pressure values over several respiratory cycles.

**2015**
Recommendations for Pulmonary Hypertension due to

2018
Treatment of PH in Lung Diseases
Evidence for appropriate benefit to risk ratio of PAH approved drugs??

General
1. Treatment of underlying disease
2. No established vascular therapy except for LTOT in COPD
3. Rational for use PAH approved therapy?

*- PH contributes to limitation of exercise capacity*
*- PH contributes to shortage of life expectancy?*
*- Vascular abnormalities contribute to bronchial/parenchymal disease progression*

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| Echocardiography is recommended for the non-invasive diagnostic assessment of suspected PH in patients with lung disease | I | C |
| Referral to an expert centre is recommended[d] in patients with echocardiographic signs of severe PH and/or severe right ventricular dysfunction | I | C |
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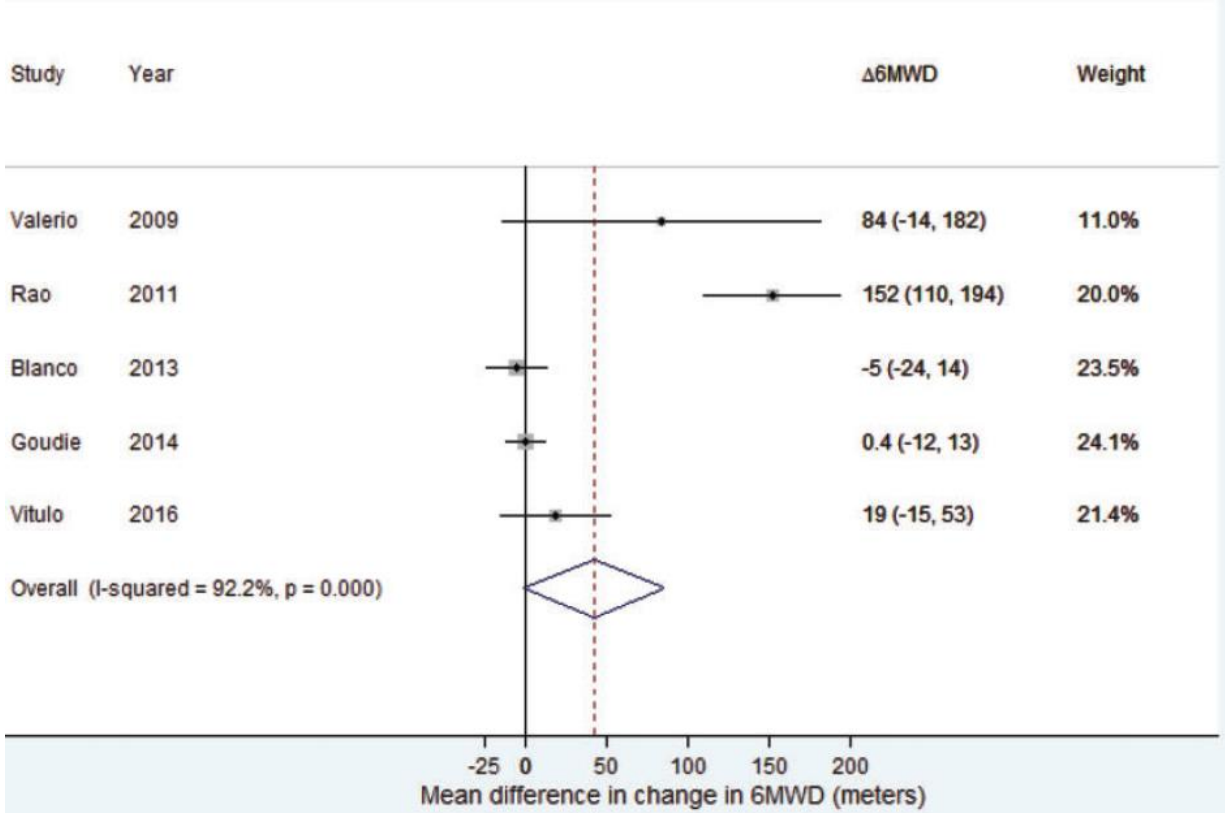
| The use of drugs approved for PAH is not recommended in patients with PH due to lung diseases | III | C |

# Therapeutic trials focusing on PH-COPD

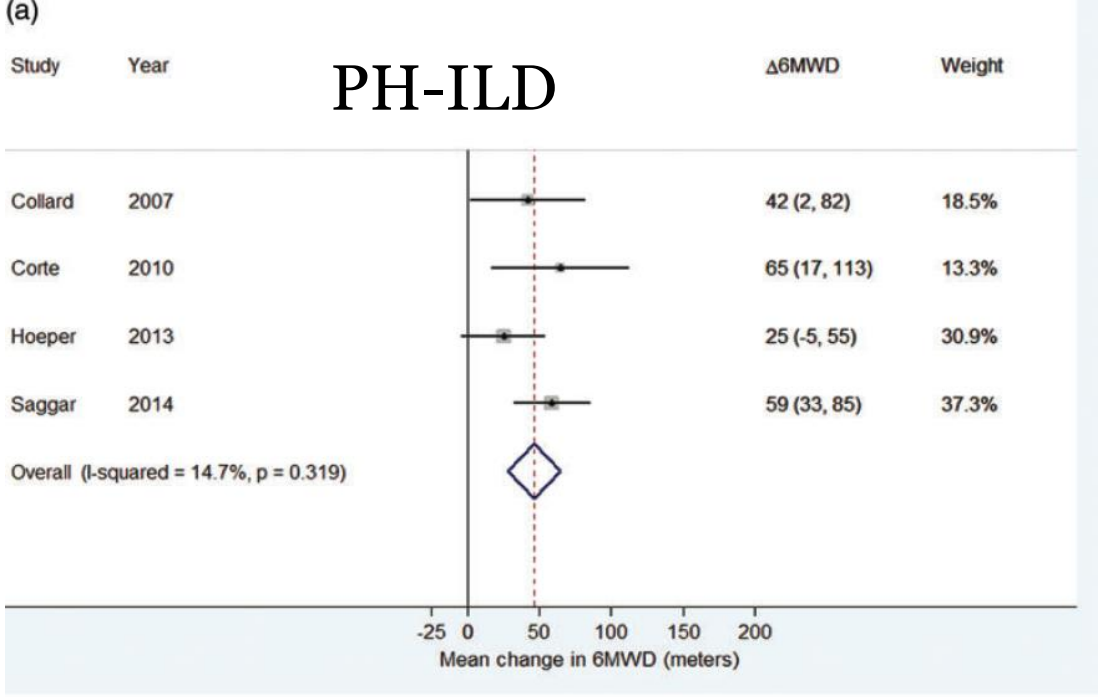
*Meta-analysis: Chen et al, J Thorac Dis 2015*
*Meta-analysis: Prins et al Pulm Circ 2017*

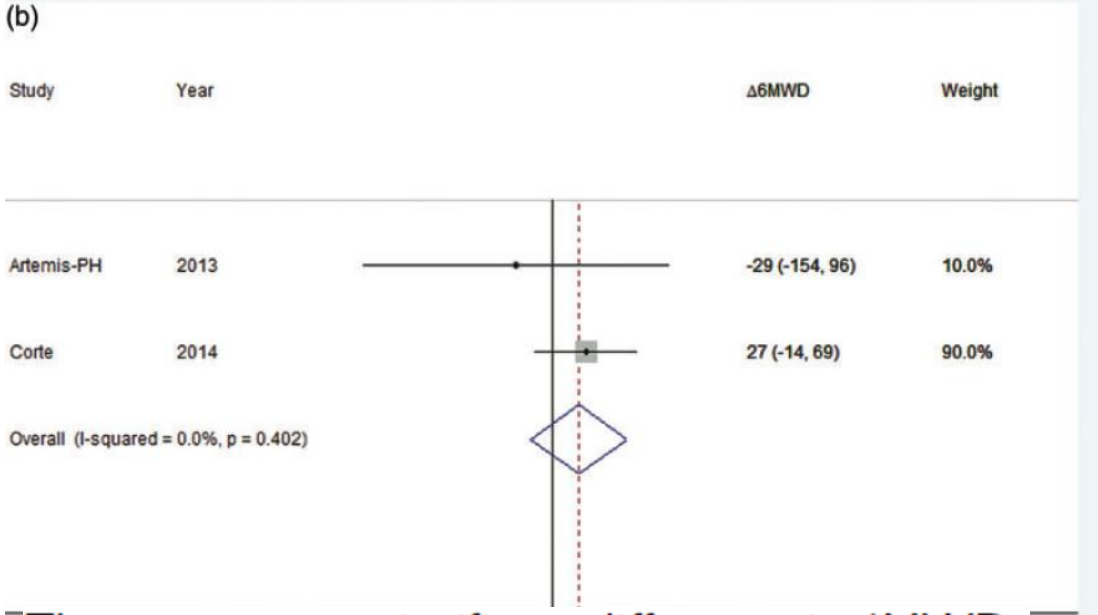
# Prins K 2017




COPD-PH. PAH-specific therapy did not significantly increase walking distance

## PH-ILD




There was not a significant difference in 6MWD

# PAH targeted therapy in COPD

***2 meta-analysis and recent small trials***

- Βελτίωση αιμοδυναμικών παραμέτρων ιδιαίτερα σε σοβαρή PH-COPD (mPAP>35mmHg)
- Preliminary evidence that may translate into improvement of exercise tolerance and quality of life, in particular in severe PH-COPD
- Gas exchange may initially deteriorate with minor relevance upon long term use
  - Differences between inhalative and systemic route of application
- Large RCTs are missing-should focus be on the ‘vascular phenotype COPD’ (mPAP>35mmHg, circulatory exercise limitation)
- This does not preclude to focus on COPD patients with lower mPAP being enrolled in future studies

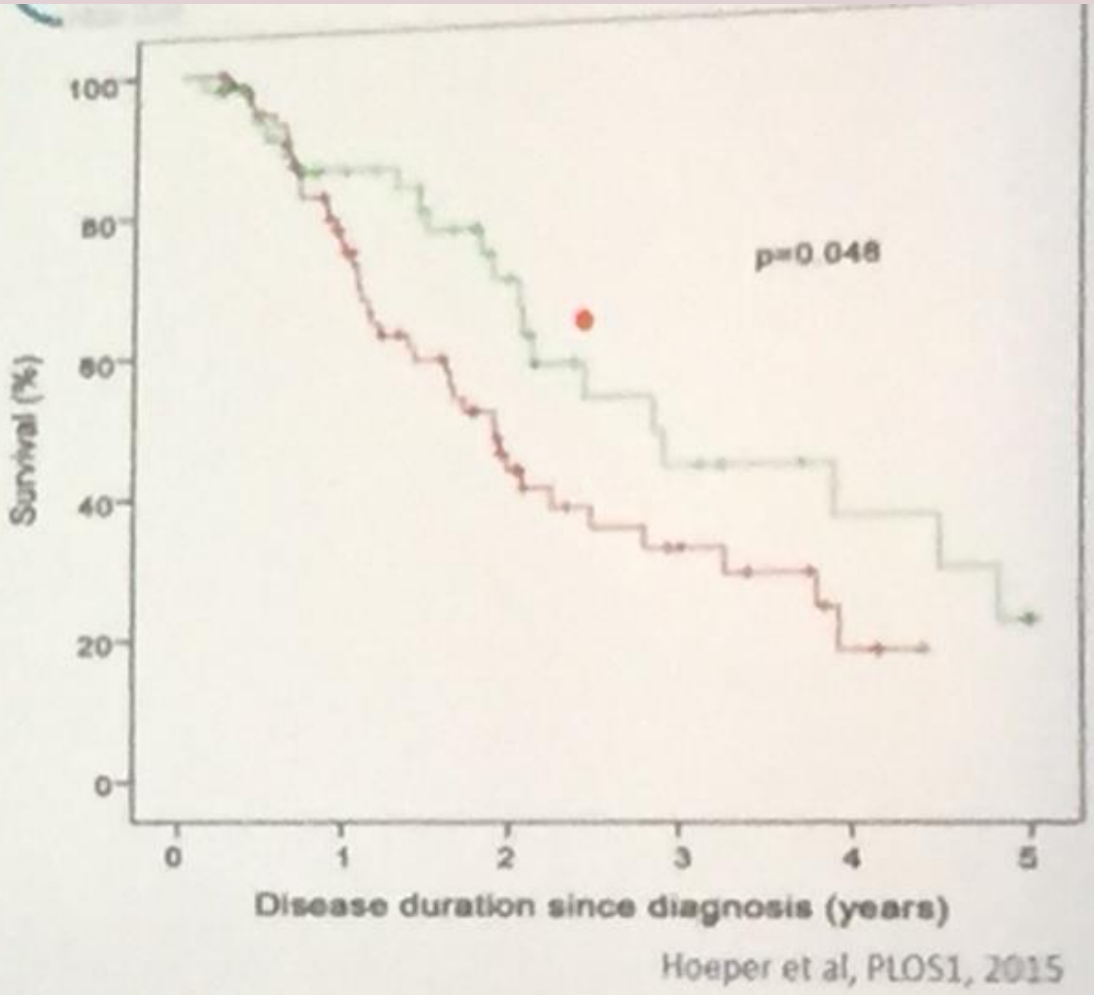
# Studies of PH-associated IPF

With

Targeted therapy

| | Disease type | Study design | Number of patients | Therapy | Outcomes | Notes | Findings |
|---|---|---|---|---|---|---|---|
| Olschewski et al (1999)[23] | Lung fibrosis | Open-label | Eight total, one with IPF | Inhaled NO and epoprostenol; intravenous epoprostenol | Inhaled prostanoids increased gas exchange | .. | Positive |
| Ghofrani et al (2002)[24] | ILD | Open-label | 16 total, seven with IPF | Sildenafil or epoprostenol | Sildenafil increased V/Q mismatch and oxygenation saturation; epoprostenol worsened V/Q | .. | Positive |
| Krowka et al (2007)[25] | IPF | RCT | 51 | Inhaled iloprost | No differences for 6MWT, NYHA functional class, dyspnoea score, and exercise oxygen saturation | Abstract only | Negative |
| Gunther et al (2007)[26] | IPF | Open-label | 12 | Bosentan | No worsening of gas exchange | .. | Equivocal |
| Collard et al (2007)[27] | IPF | Open-label | 14 | Sildenafil | 57% had improved 6MWT by ≥20% | .. | Positive |
| Minai et al (2008)[28] | ILD | Retrospective | 19 total, eight with IPF | Epoprostenol (n=10) and bosentan (n=9) | 79% had improved 6MWT by >50 m | .. | Positive |
| Zisman et al (2010)[29] | IPF | RCT | 180 | Sildenafil | No increase in 6MWT by ≥20%, but QOL and oxygen saturation increased | .. | Equivocal |
| Jackson et al (2010)[30] | IPF | RCT | 29 | Sildenafil | No difference in 6MWT or Borg Dyspnea Scale | .. | Negative |
| Raghu et al (2013)[31] | IPF | RCT | 492 | Ambrisentan | Terminated early because of an absence of efficacy in TTCW | .. | Negative |
| Hoeper et al (2013)[32] | ILD | Open-label | 22 total, 13 with IPF | Riociguat | Increased cardiac output and decreased PVR; no decrease in mPAP | .. | Positive |
| Zimmerman et al (2014)[33] | ILD | Open-label, observational | Ten total, six with IPF | Sildenafil (n=5) and tadalafil (n=5) | Increased cardiac output and decreased PVR; no change in 6MWT and BNP | .. | Equivocal |
| Corte et al (2014)[34] | ILD | RCT | 60 total, 46 with IPF | Bosentan | Unchanged haemodynamics, symptoms, and NYHA functional class | .. | Negative |
| Saggar et al (2014)[35] | ILD | Open-label | 15 total, eight with IPF | Treprostinil | Improved haemodynamics without hypoxaemia | .. | Positive |
| Raghu et al (2015)[36] | IPF | RCT | 117 | Ambrisentan | Unchanged haemodynamics | .. | Negative |
| Hoeper et al (2015)[37] | ILD | Retrospective registry review | 151 total, 113 with IPF | Various drugs | Improved 6MWT and NYHA functional class | Poor survival in ILD-PH | Positive |
| RISE-IIP (NCT02138825) | IPF | RCT | 147 | Riociguat | Terminated early for harm | To be published | Negative |

# COMPERA Registry: response to sildenafil in PH-IIP




Hoeper et al, PLOS1, 2015

Stratification by clinical response at first follow-up defined of onset of sildenafil treatment:

6 MWD + >/= 20 m

or

NYHA class+ 1

Total number: 121

"Response": 48

"No response": 73

# Overall conclusion IIP-PH

- No evidence for the use of ERAs in IIP-PH with ambrisentan contraindicated in IPF.
- Riociguat is contraindicates in PIIP-PH.
- The data on the use of sildenafil and prostanoid therapy in IIP-PH is too limited for any current recommendation, but further RCT's are encouraged

# Group 3. PH due to lung disease and/or hypo

New
Nice 2018

- **Obstructive pulmonary disease**
  - COPD
  - Bronchiolitis obliterans
- **Interstitial Lung Diseases**
  - Idiopathic interstitial pneumonias
  - Chronic hypersensitivity pneumonitis
  - Occupational lung disease
- **Other lung diseases with mixed restrictive/obstructive patettern**
  - Sarcoidosis
  - Combined pulmonary fibrosis and emphysema
  - Cystic fibrosis and non-cystic fibrosis bronchiectasis
  - Lymphangioleiomyomatosis
  - Other destructive lung disease
- **Alveolar Hypoxia without lung disease**
  - Sleep –disordered breathing
  - Chest wall abnormalities
  - Obesity hypoventilation syndromes
  - Other alveolar hypoventilation disorders
  - Chronic exposure to high altitude
- **Pediatrics**

# Combined Pulmonary Fibrosis and Emphysema *(CPFE)*

- 30% - 50% of pt
  - Severe
    lun

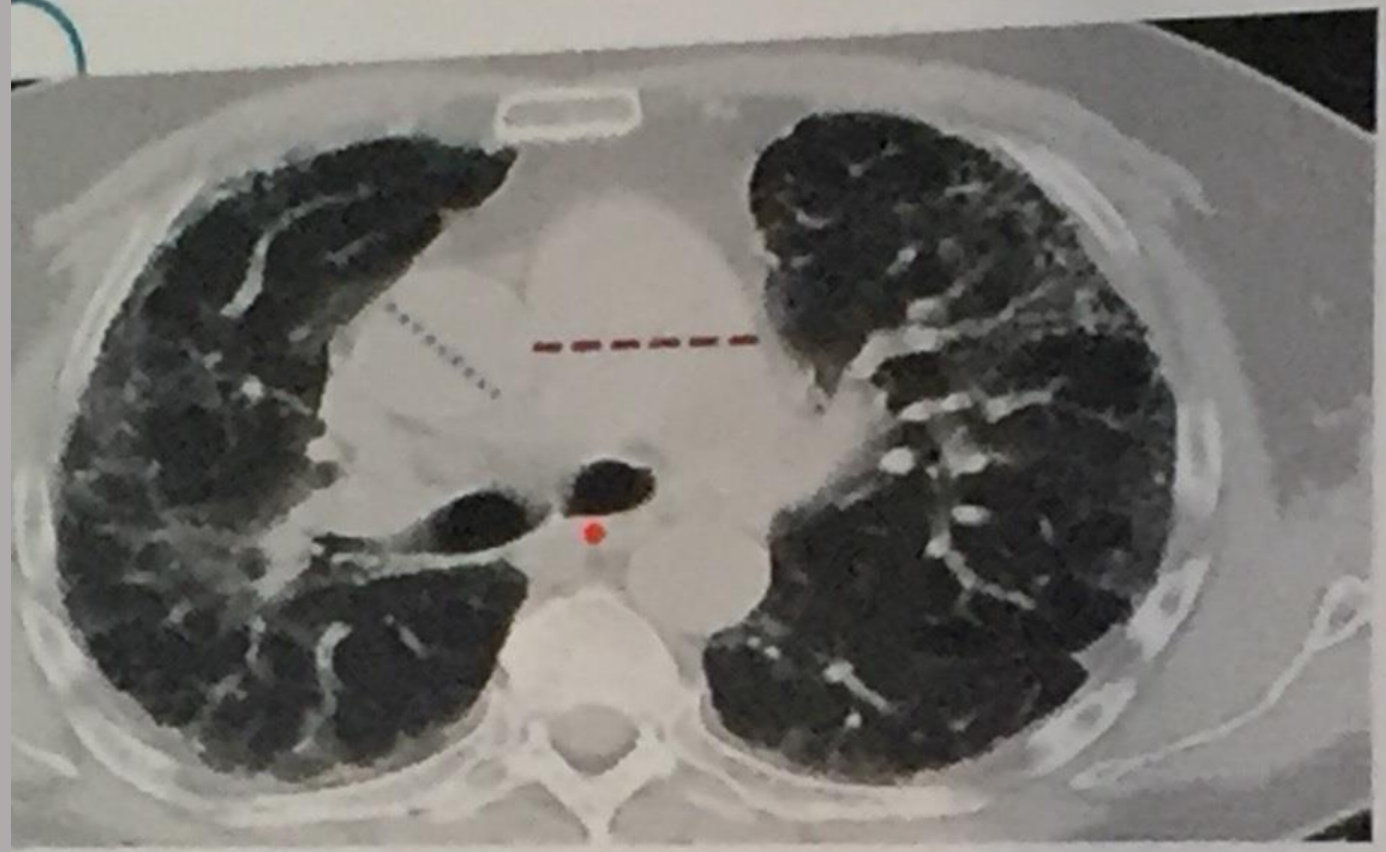
**RHC:**

mPAP >35% mm Hg in 68% of patients
mPAP >40% mm Hg in 48% of patients

And
The CI was the most accurate prognostic determinant

**Cottin ERJ 2010**

# PH in sarcoidosis



Among 373 patients awaiting TX in advanced sarcoidosis, 74% have PH

(Shorr et al, Chest 2003)

# Studies in PH sarcoidosis

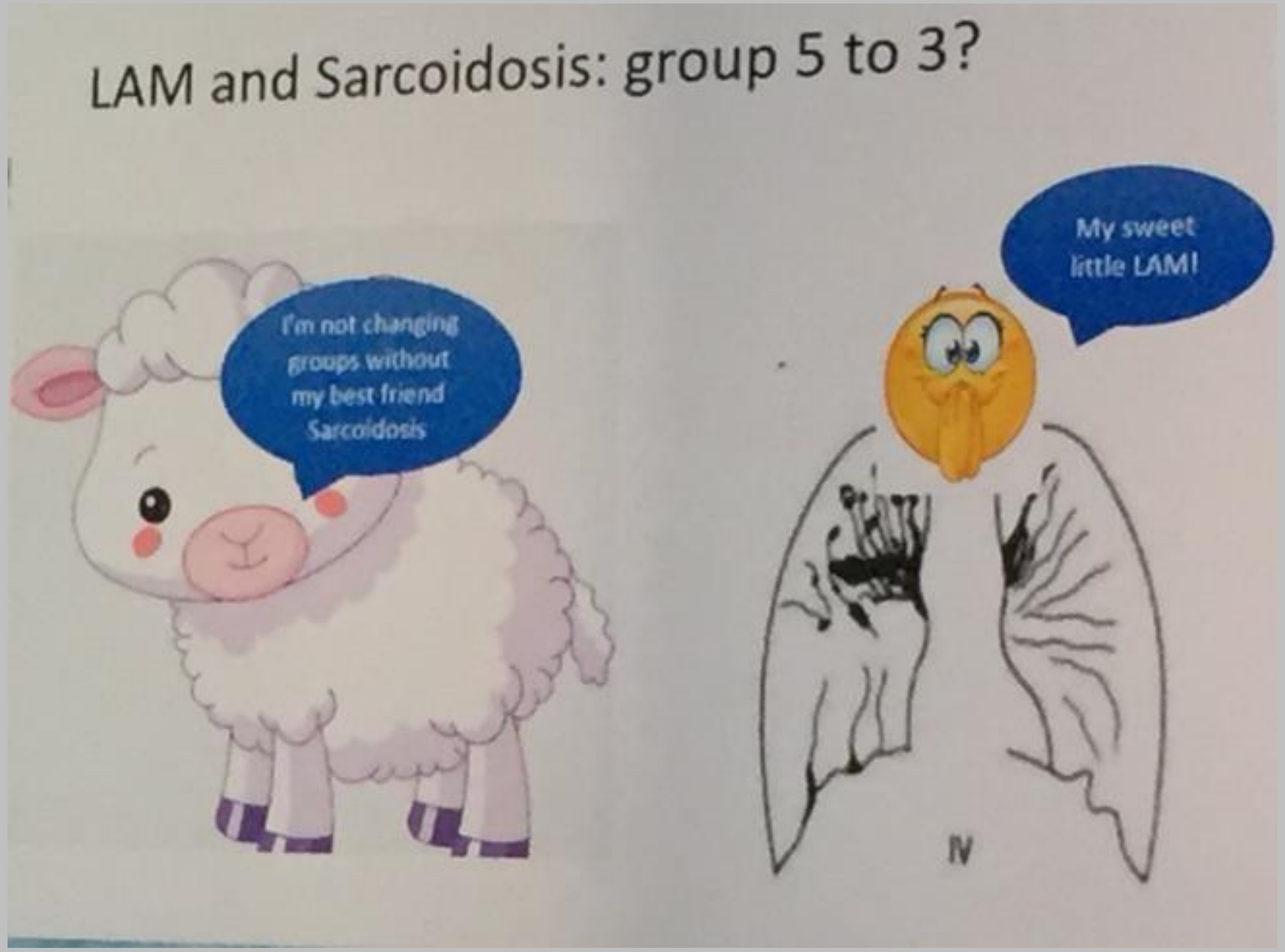
| | Type of Study/Number | Therapy | Outcomes |
|---|---|---|---|
| Preston et al. | Prospective observational (8) | Inhaled NO (5), Inhaled NO with IV EPO (1), CCBs (2) | Short term 20% decrease in PVR and mPAP; Long term ↑in 6MWT |
| Baughman et al. | Prospective open label 16 week trial (32) | Inhaled iloprost (16) | 8/16 patients showed ↓mPAP/PVR, 3/16 improvement in 6MWT |
| Fisher et al. | Retrospective case series (7) | IV Epo (6), SQ treprostinil (1) | Improved NYHA Class |
| Barnett et al. | Retrospective case series (22) | Initial: IV Epo, bosentan, sildenafil | Improved 6MWT, NYHA Class<br>↓mPAP and PVR in 12 patients |
| Millman et al. | Retrospective chart review (12) | Sildenafil (12) | ↓mPAP/PVR, ↑cardiac output, no Δ 6MWT |
| Culver et al. | Retrospective chart review (7) | Bosentan (3), bosentan and IV Epo (4) | ↓mPAP at 6-18 months in half the patients |
| Baughman et al. | Retrospective chart review (5) | Bosentan (5) | ↓mPAP from 58mmHg to 36mmHg in 3/5 patients at 4 months |
| Judson et al. | RCT 12 weeks study (26) | Ambrisentan | No Δ 6MWT<br>9 patients discontinued study |
| Baughman et al | RCT 16 weeks (35) | Bosentan | ↓mPAP and PVR, no Δ 6MWT |
| Keir et al | Retrospective (33) | Sild=29, bos=3 | 6MWT +13 m, ↓BNP, ↑TAPSE |

# Does Sarcoidosis belong in group 5 or Group 3?

- **Case for group 5**
  1. "Uncertain" as to the etiology
  2. ?PH responds better to treatment than other group 3 conditions?

- **Case for group 3:**
  1. In the vast majority of cases it's a predominant lung disease
  2. Virtual all cases with severe PH have parenchymal lung changes
  3. In these lungs, the remodeling morphology of the lung vessels is similar to other lung diseases, not characterized by predominant granuloma formation
  4. Does it "sit better" with blood dyscrasias and renal failure ☹ or with other lung diseases ☺ ?
  5. Goal of classification Task Force is eventually to eliminate group 5

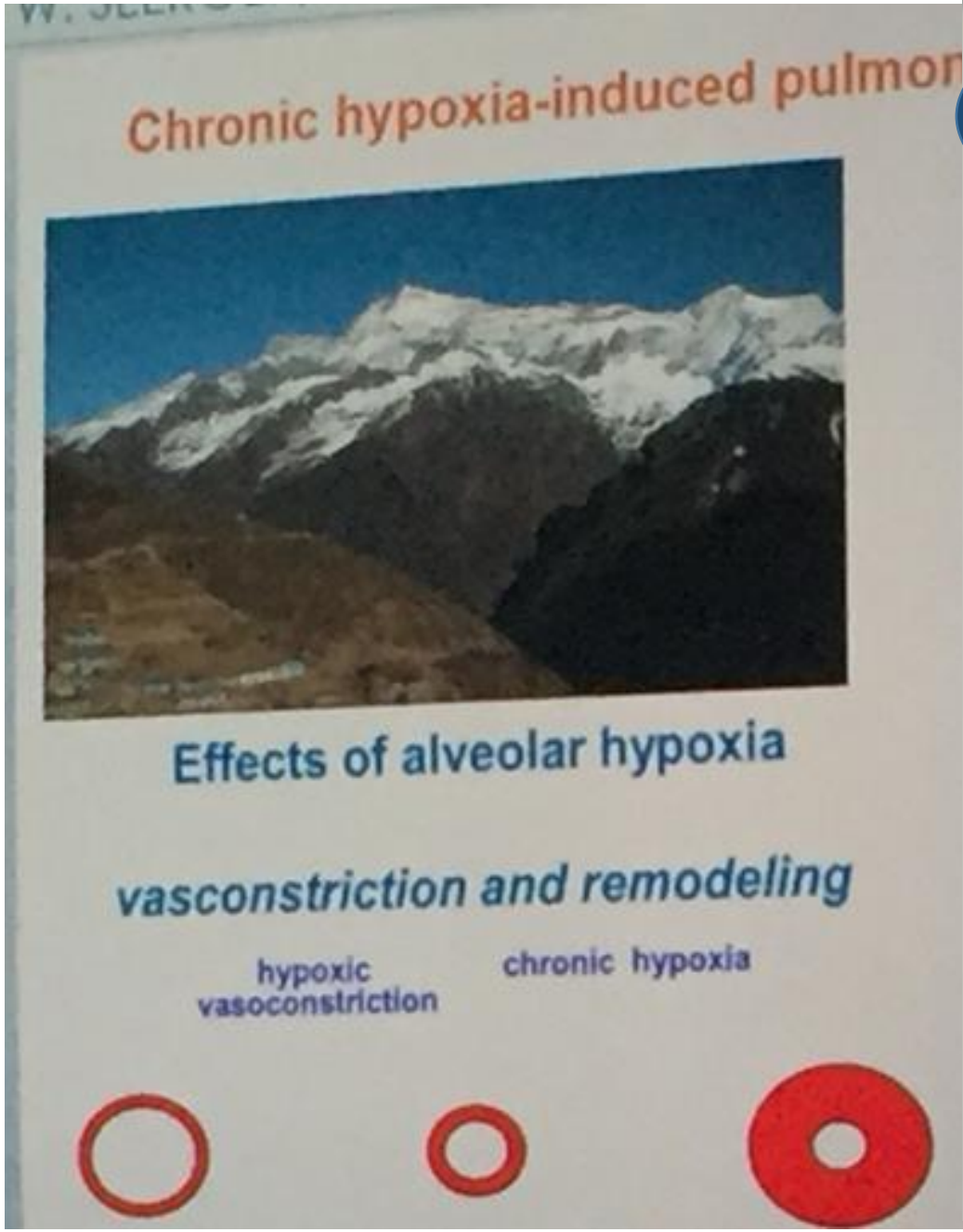
# LAM and Sarcoidosis: group 5 to 3?



# Group 3. PH due to lung disease and/or hypo

New
Nice 2018

- **Obstructive pulmonary disease**
  - COPD
  - Bronchiolitis obliterans
- **Interstitial Lung Diseases**
  - Idiopathic interstitial pneumonias
  - Chronic hypersensitivity pneumonitis
  - Occupational lung disease
- **Other lung diseases with mixed restrictive/obstructive patettern**
  - Sarcoidosis
  - Combined pulmonary fibrosis and emphysema
  - Cystic fibrosis and non-cystic fibrosis bronchiectasis
  - Lymphangioleiomyomatosis
  - Other destructive lung disease
- **Alveolar Hypoxia without lung disease**
  - Sleep –disordered breathing
  - Chest wall abnormalities
  - Obesity hypoventilation syndromes
  - Other alveolar hypoventilation disorders
  - Chronic exposure to high altitude
- **Pediatrics**




**Definition of High-Altitude PH by the International Society of Mountain Medicine resting mPAP>30mmHg**

## Reversibility –Treatment

High –altitude PH **is reversible** upon re-exposure to normoxia /see-level

Sildenafil / Bosentan

## Conclusion

Model disease not well known

RCTs missing

# Hypoventilation Syndromes

- What do they have in common?

  *Alveolar hypoxia causing HPV, assumed to be the main driver of PH*

- Without lung parenchymal damage

  *Obesity hypoventilation syndrome*

  *Kyphoscoliosis*

  *Neuro/ Mascular dysfunction*

- With lung parenchymal damage

  *COPD*

  *Combined obstructive/restrictive diseases*

# Effect of NIV on Obesity Hypoventilation Syndrome-induced PH

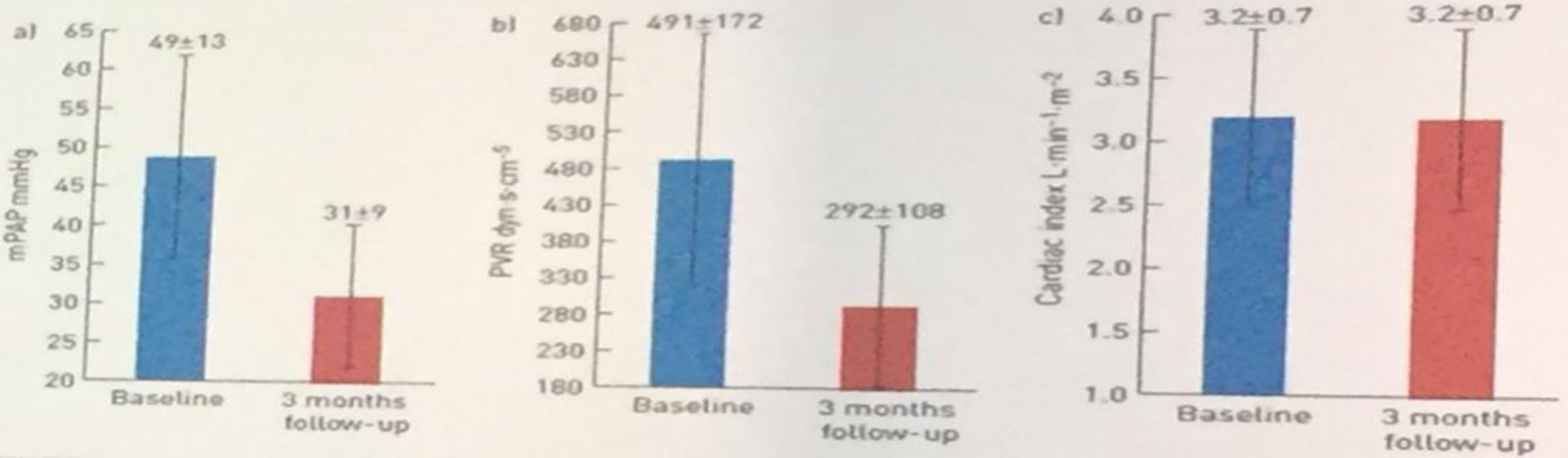
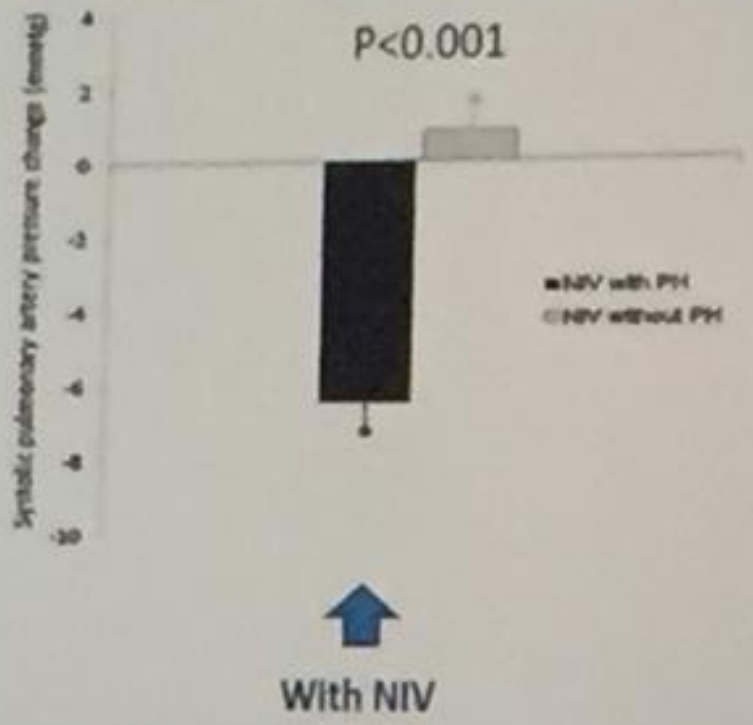



FIGURE 4 Changes in haemodynamic parameters after 3 months of noninvasive positive-pressure ventilation. a) Change in mean pulmonary artery pressure (mPAP), n=16; p<0.001. b) pulmonary vascular resistance (PVR), n=16; p<0.001. c) Change in cardiac index, n=15; p=0.807.

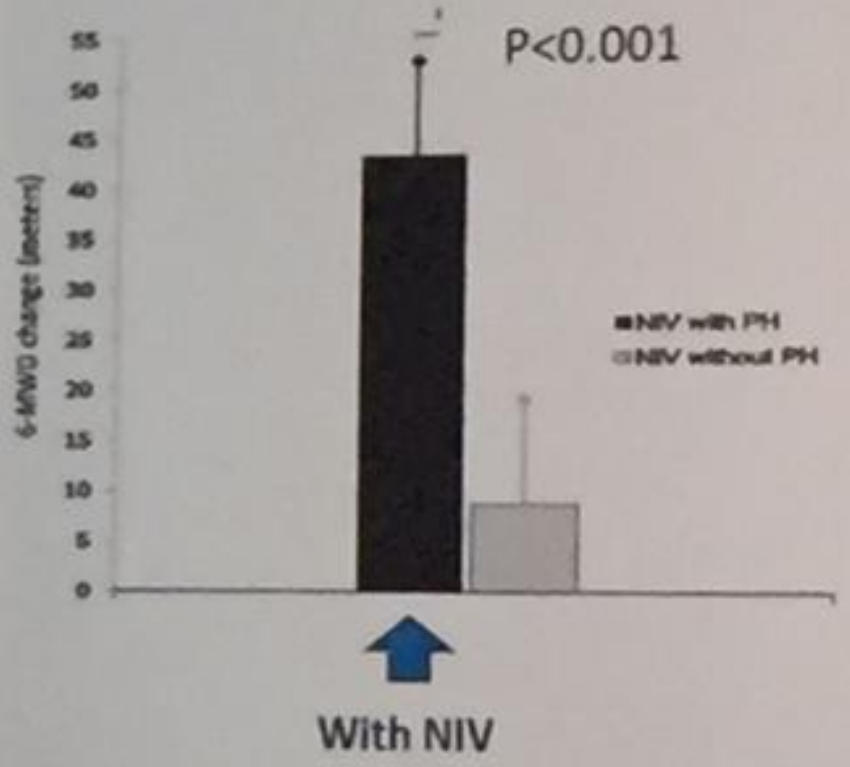
Held et al. ERJ 2014; 43:156-165

# Effect of NIV on echocardiographic measures of PH in obesity hypoventilation syndrome

## sPAP change




## 6mwd change




Coral et al. Thorax 2017, 64 patients with NIV versus 67 control patients; follow up period = xxx months?

# Conclusion

- Hypoventilation syndrome patients should be treated with NIV
- NIV reduces mPAP/PVR in hypoventilation syndrome patients with PH
- The extent to which the improvement of pulmonary hemodynamics contributes to the beneficial effect of NIV in hypoventilation syndrome patients is unclear
- NIV improves mortality in hypercapnic COPD patients, but link to PH is unclear

# Recommendations for Pulmonary Hypertension due to Lung disease

2018
Treatment of PH in Lung Diseases
Evidence for appropriate benefit to risk ratio of PAH approved drugs??

General
1. Treatment of underlying disease
2. No established vascular therapy except for LTOT in COPD
3. Rational for use PAH approved therapy?

*- PH contributes to limitation of exercise capacity*
*- PH contributes to shortage of life expectancy?*
*- Vascular abnormalities contribute to bronchial/parenchymal disease progression*

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| Echocardiography is recommended for the non-invasive diagnostic assessment of suspected PH in patients with lung disease | I | C |
| Referral to an expert centre is recommended[d] in patients with echocardiographic signs of severe PH and/or severe right ventricular dysfunction | I | C |
| The optimal treatment of the underlying lung disease, including long-term $O_2$ therapy in patients with chronic hypoxaemia, is recommended in patients with PH due to lung diseases | I | C |
| Referral to PH expert center should be considered for patients with signs of severe PH/severe RV failure for individual-based treatment | IIa | C |
| RHC is not recommended for suspected PH in patients with lung disease, unless therapeutic consequences are to be expected (e.g. lung transplantation, alternative diagnoses such as PAH or CTEPH, potential enrolment in a clinical trial) | III | C |
| The use of drugs approved for PAH is not recommended in patients with PH due to lung diseases | III | C |

# Effects of rehab in PH-chronic lung disease

- **Evidence from 3 studies that rehab improves exercise capacity in CLD-PH**

- ***No adverse effect reported in these studies***

- Further studies needed:
  - *Reproducible in larger trials with focus on PH-chronic lung disease?*
  - *Differences between various underlying lung diseases?*
  - *Long-term effects?*
  - *Impact on survival?*

**Dowman LM Thorax 2017**
**Oki Y Int J Chr Ob Pul Dis 2016**

# PH management in the setting of chronic lung disease

**Limited**

**Obstructive LD ; FEV1 > 60%**
**Restrictive LD ; FVC > 70%**

**Physiologic severity**

**Severe**

**Obstructive LD ; FEV1 < 60%**
**Restrictive LD ; FVC < 70%**

**Minimal parenchymal CT changes**

**Morphologic severity**

**Extensive parenchymal CT changes**

**Discern between Group 1 and Group 3 PH**

**Group 3 PH**

**Refer to Expert PH & Lung disease Unit**

**PH severity**

**Group 1 PH**

**Treatment algorithm for PAH**

**Mild to moderate PH m PAP 25-34 mm Hg**

**No evidence for targeted PAH therapy Registries and further RCTs required , consider exercise training**

**Severe PH m PAP > 35 mm Hg / Cl < 2 L / min m2**

**Individualized patient care due to very poor prognosis , registries and RCTs required**