Πνευμονική Υπέρταση
σε
Χρόνιες χρόνιες Αποφρακτικές Πνευμονοπάθειες

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Διακλινικό Ιατρείο Πνευμονικής Υπέρτασης
ΠΑΓΝΗ Κρήτη

Updated clinical classification of pulmonary hypertension (PH)

Simonneau G, Eur Respir J 12/2018

1 PAH
- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH (table 3)
- 1.4 PAH associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH long-term responders to calcium channel blockers (table 4)
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement (table 5)
- 1.7 Persistent PH of the newborn syndrome

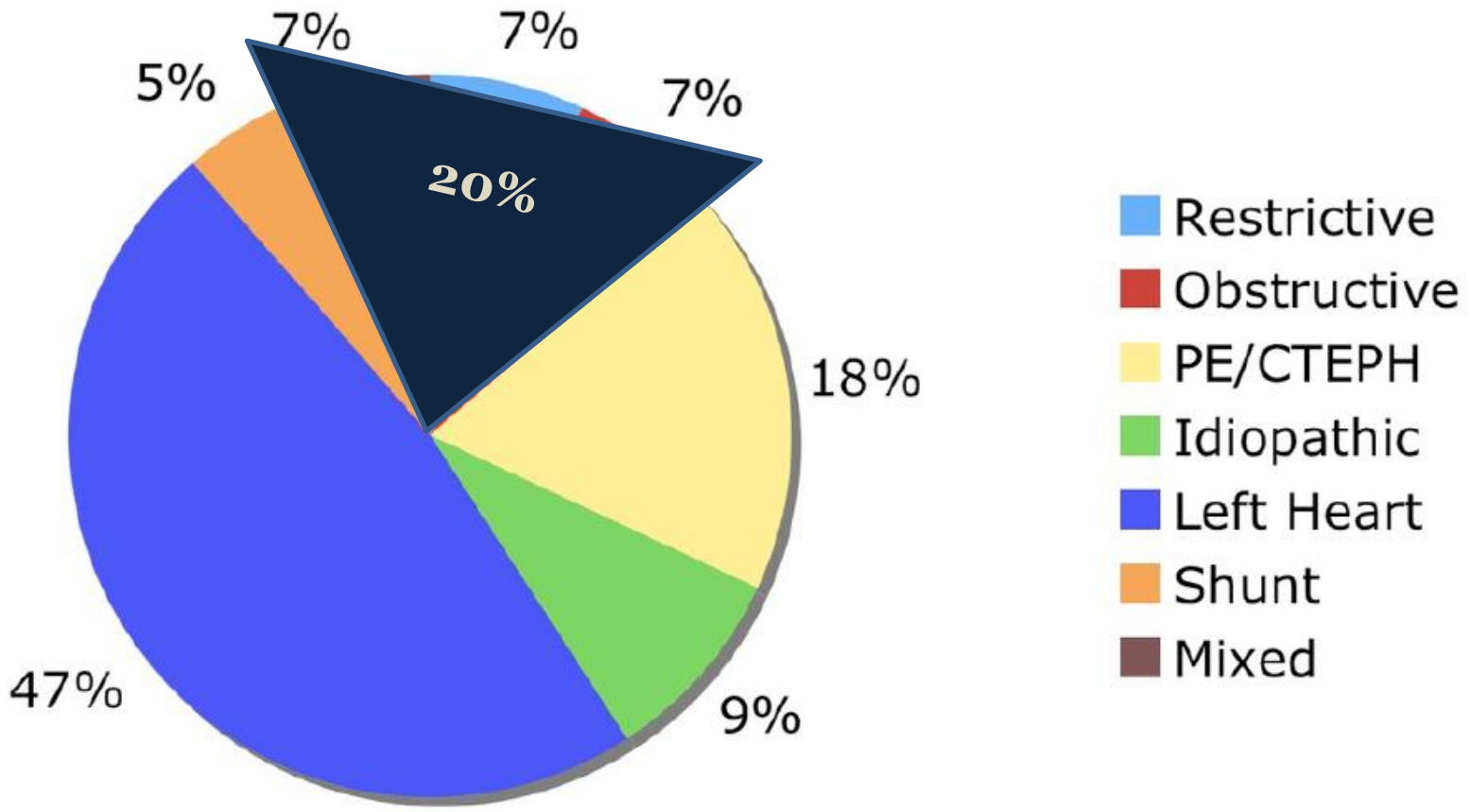
2 PH due to left heart disease
- 2.1 PH due to heart failure with preserved LVEF
- 2.2 PH due to heart failure with reduced LVEF
- 2.3 Valvular heart disease
- 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3 PH due to lung diseases and/or hypoxia
- 3.1 Obstructive lung disease
- 3.2 Restrictive lung disease
- 3.3 Other lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoxia without lung disease
- 3.5 Developmental lung disorders

4 PH due to pulmonary artery obstructions (table 6)
- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions

5 PH with unclear and/or multifactorial mechanisms (table 7)
- 5.1 Haematological disorders
- 5.2 Systemic and metabolic disorders
- 5.3 Others
- 5.4 Complex congenital heart disease

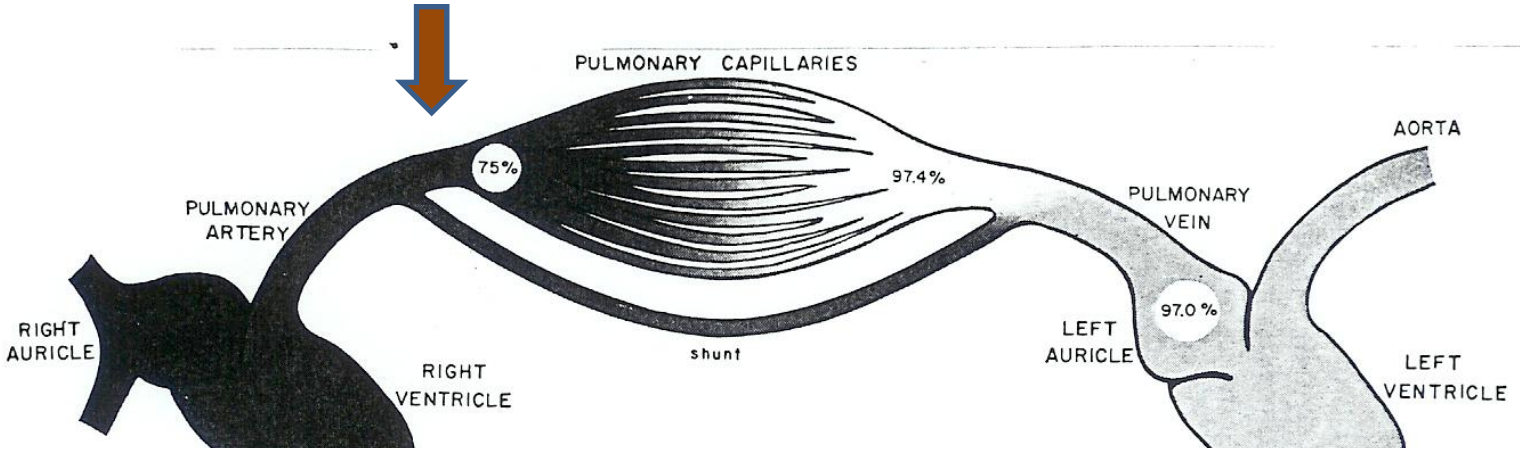
Κατανομή Πνευμονικής Υπέρτασης



Haemodynamic definitions of pulmonary hypertension (PH)

Proceedings of the 6th World Symposium on Pulmonary Hypertension

Simonneau G, Montani D, Celermajer DS, et al. Eur Respir J 12/2018



Definitions	Characteristics	Clinical groups
Pre-capillary PH	mPAP >20 mmHg PAWP ⩽15 mmHg PVR ⩾3 WU	1, 3, 4 and 5
Isolated post-capillary PH (IpcPH)	mPAP >20 mmHg PAWP >15 mmHg PVR <3 WU	2 and 5
Combined pre- and post-capillary PH (CpcPH)	mPAP >20 mmHg PAWP >15 mmHg PVR ⩾3 WU	2 and 5

Prevalence
20-91%

GOLD stage IV:
90% have mPAP >20 mmHg,
most ranging between 20 and 35 mmHg.

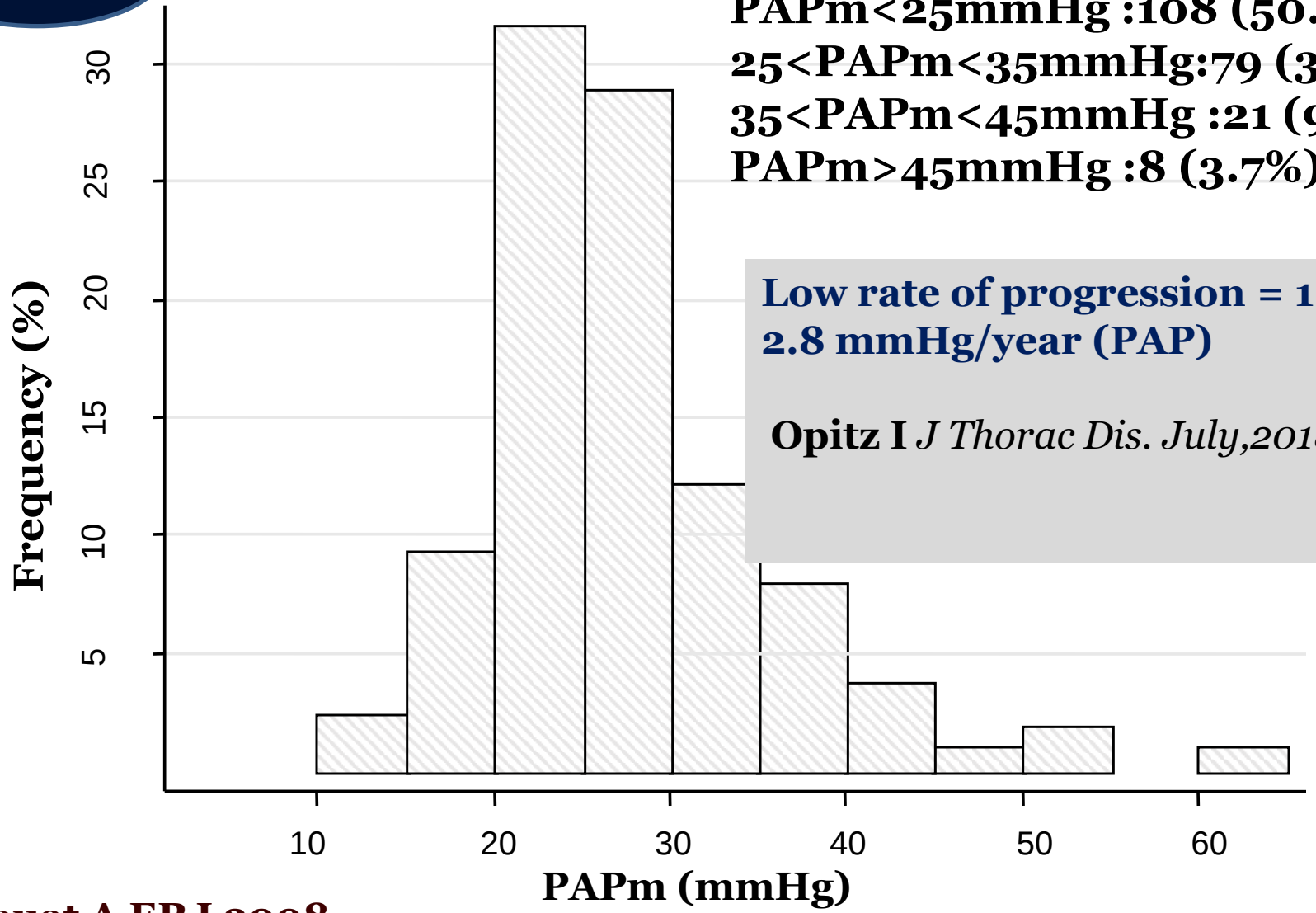
Prevalence and predictors associated with severe pulmonary hypertension in COPD

The results showed that there is an independent correlation between:
hypoxia, hypopnea and
compensatory metabolic alkalosis,
polycythemia,
left ventricular dysfunction,
emaciation, and cachectic with severe pulmonary hypertension.

The prevalence of severe PH in these patients was **13.7%.**

Distribution of PAPm

998 pts



PAPm<25mmHg :108 (50.2%)
25<PAPm<35mmHg:79 (36.7%)
35<PAPm<45mmHg :21 (9.8%)
PAPm>45mmHg :8 (3.7%)

Low rate of progression = 1.5-2.8 mmHg/year (PAP)

Opitz I *J Thorac Dis. July,2018;10*

Chaouat A ERJ 2008
Thabut, Chest 2005; 127: 1531

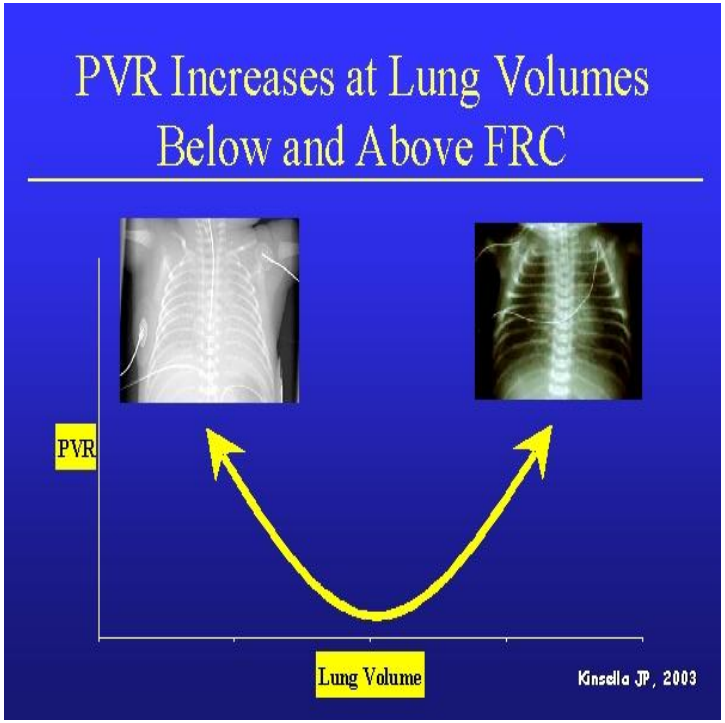
Pathophysiology

Singh I The American J of Med 2016

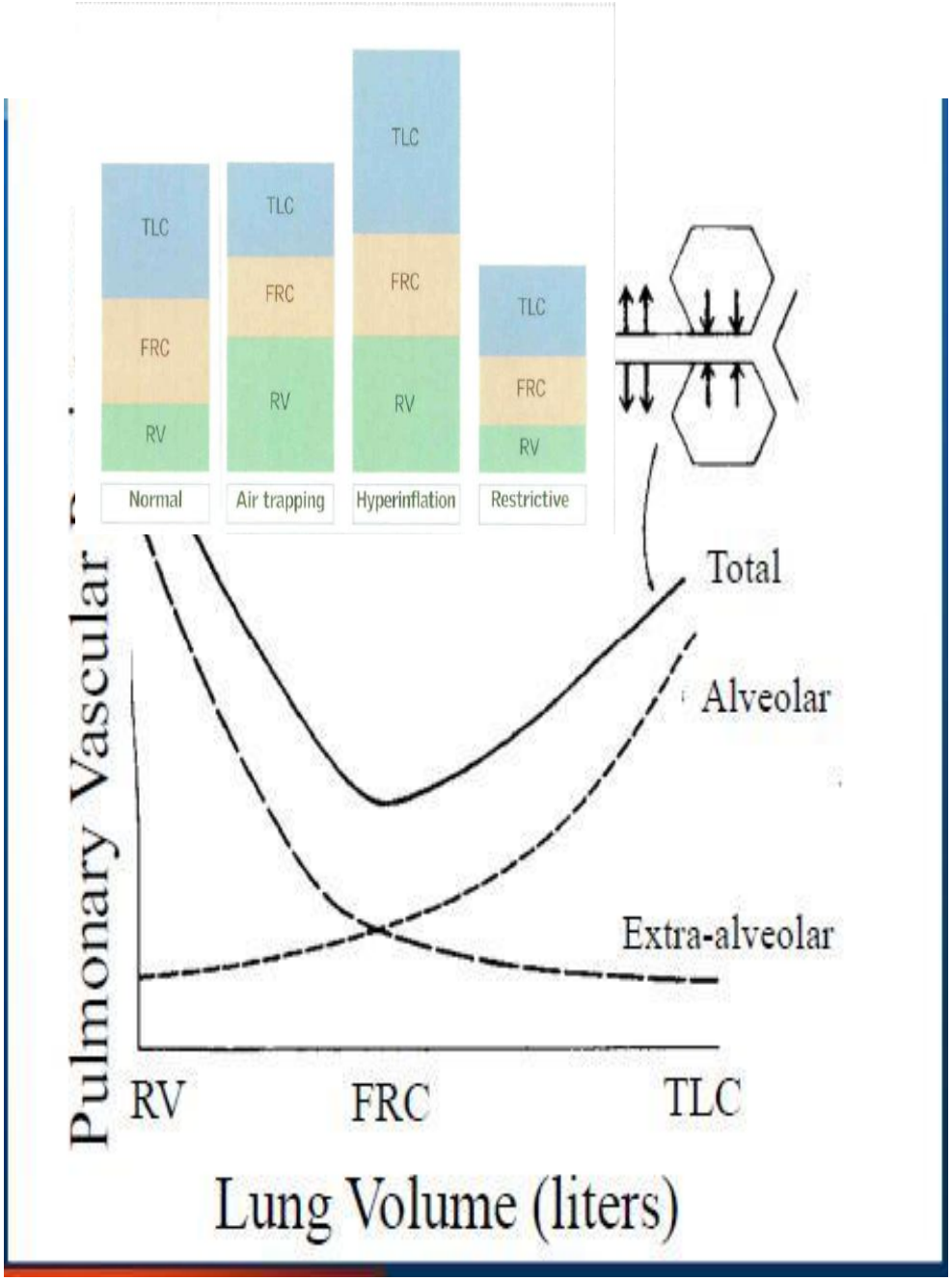
Passive Factors Influencing Pulmonary Vascular Resistance

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 Increased left atrial pressure Increased pulmonary blood volume 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 Increased intrapleural pressure with compression of extra-alveolar vessels 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



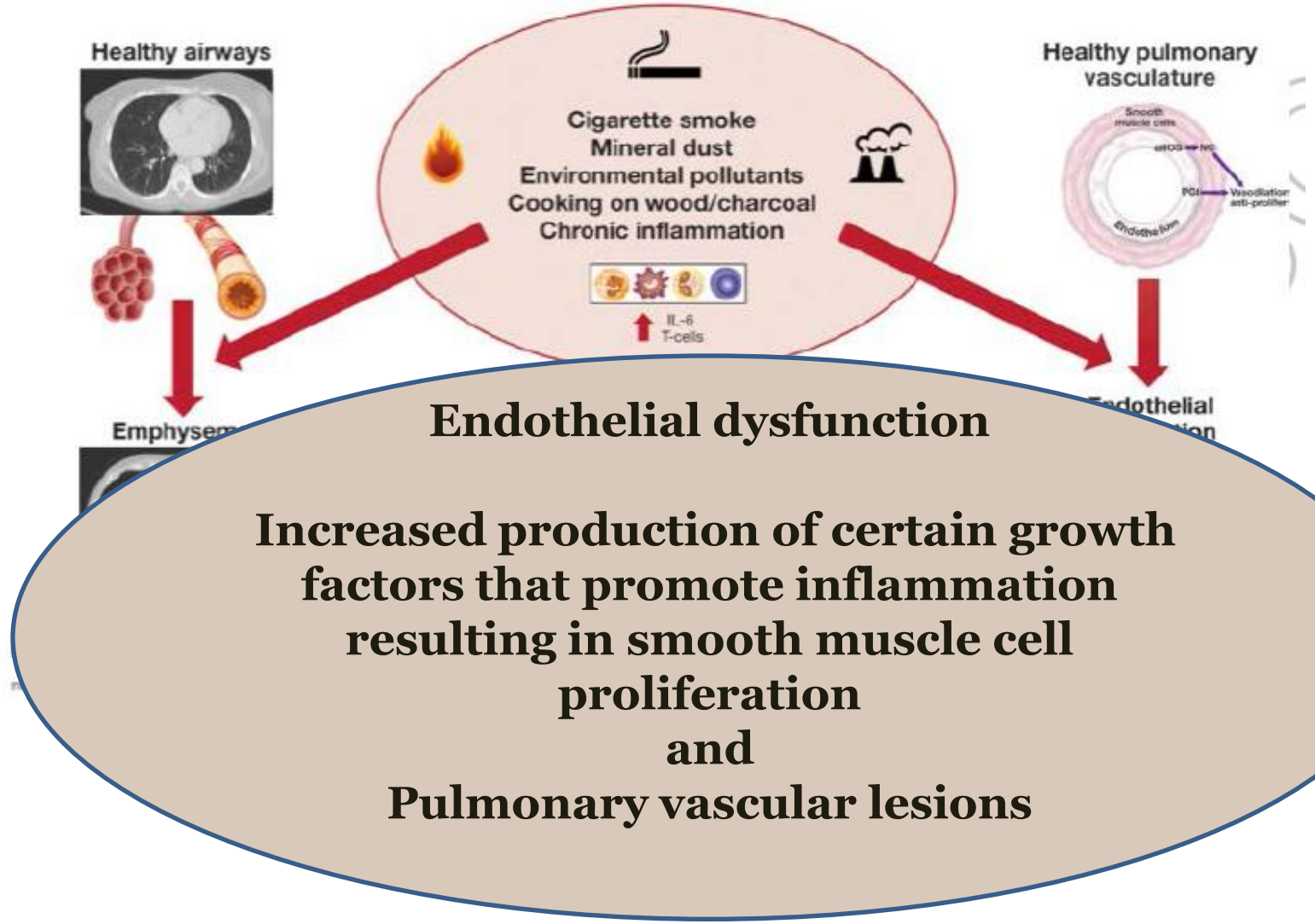
Factors contributing to elevation in PVR *in COPD*

Contributing Factors	Consequence
Expiratory airflow obstruction	Alveolar hyperinflation
Chronic hypoxia LL-genotype polymorphism of 5-HT Increased expression of ADORA2B Proliferation of bone marrow EPCs Cigarette smoking injury 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.

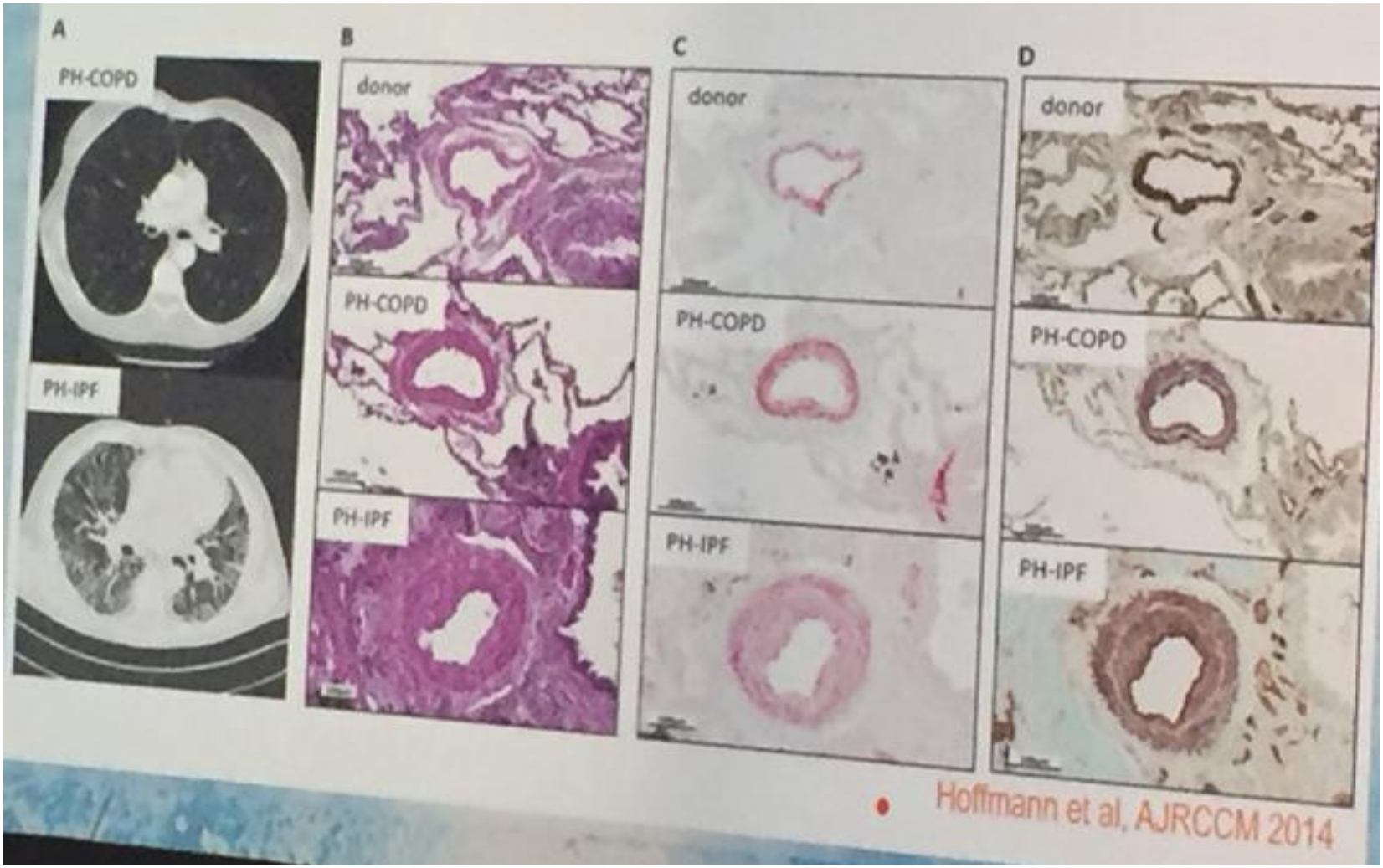
Active Factors that Increase PVR	Active Factors that Decrease PVR
Neural factors: • Sympathetic nervous system stimulation • Sympathomimetics: norepinephrine, epinephrine, and alpha-agonists	Neural factors: • Parasympathetic nervous system stimulation • Parasympathomimetics: acetylcholine • Sympathomimetic: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

Singh I The American J of Med 2016



J Grimminger Exper Rev in Res Med May 2016

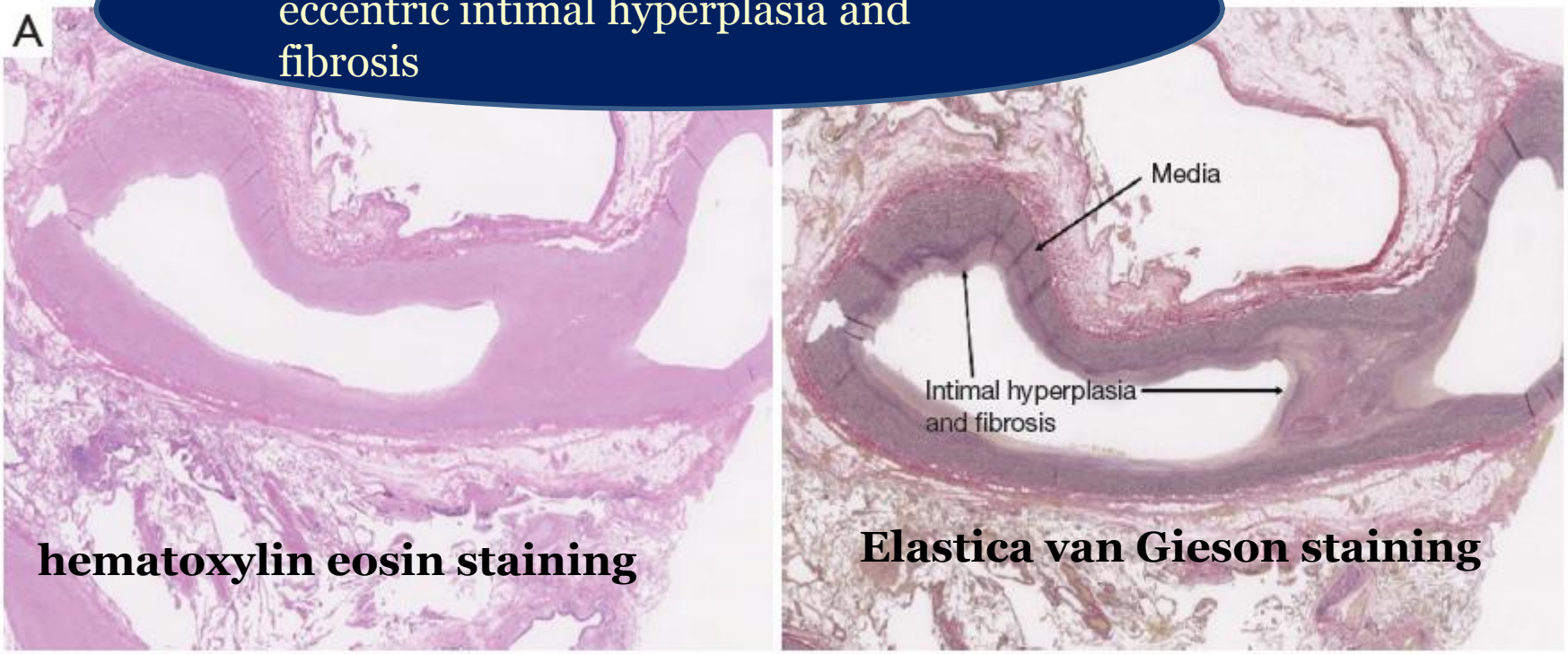
Similarities in vascular remodeling between PH-COPD and PAH?



Pulmonary hypertension in chronic obstructive pulmonary disease and emphysema patients

Vascular remodeling in an emphysema patient with PH

narrowing of the arterial lumen due to eccentric intimal hyperplasia and fibrosis

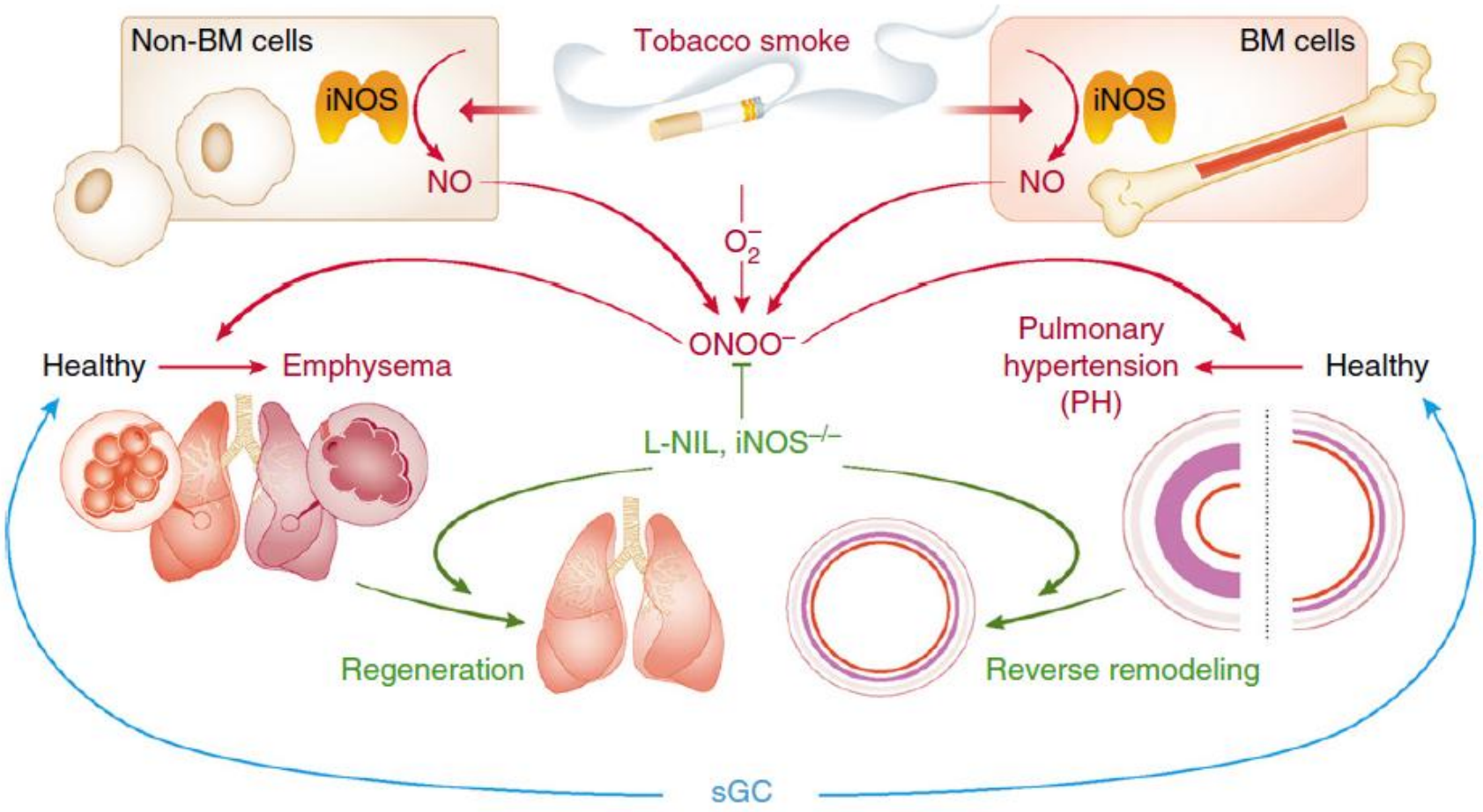


Courtesy of Dr. B. Vrugt, Institute of Pathology, University Hospital Zurich Switzerland.

Isabelle Opitz, Silvia Ulrich *J Thorac Dis. July,2018;10*

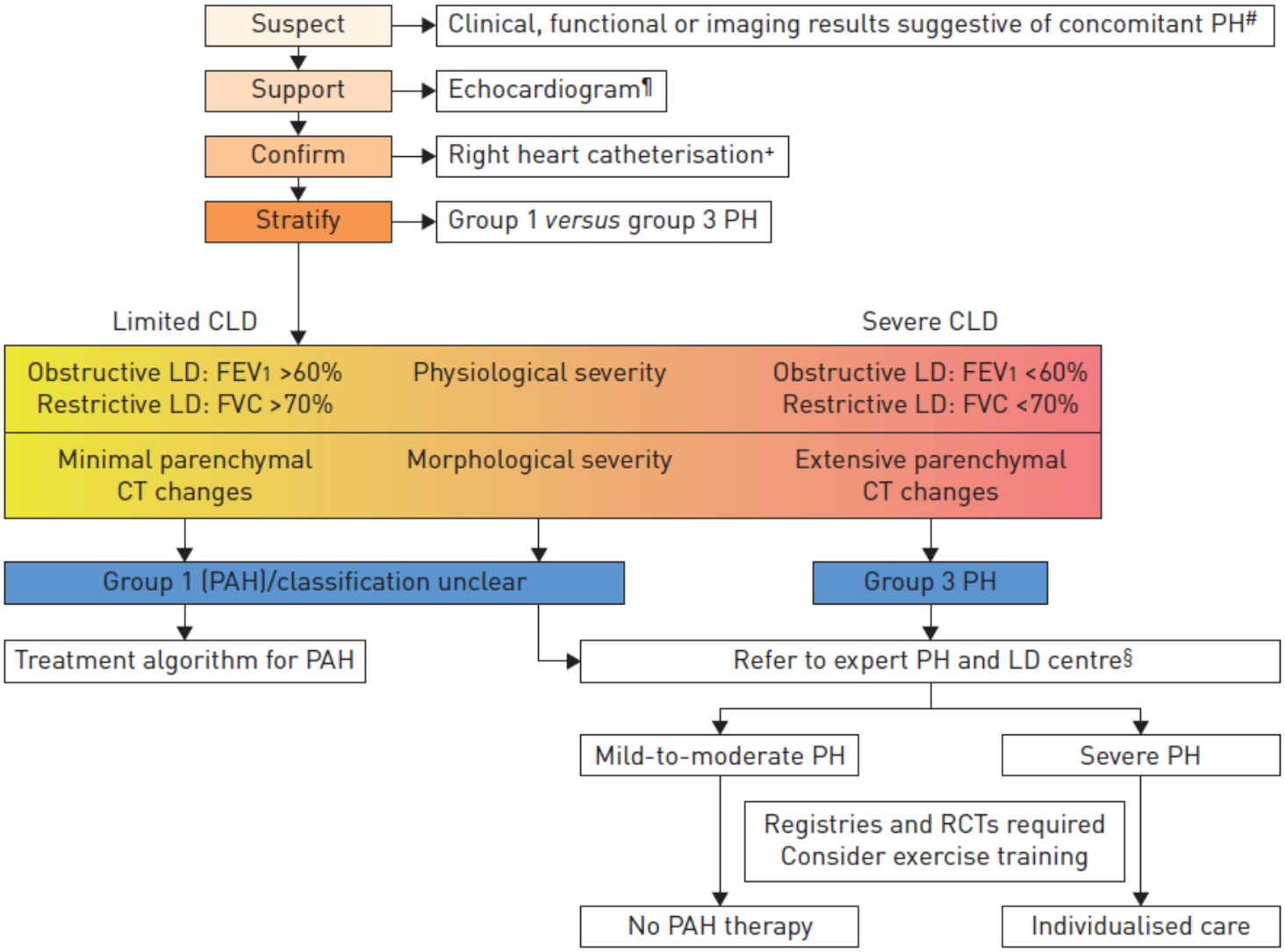
Chronic Obstructive Pulmonary Disease and Pulmonary Vascular Disease

A Comorbidity?



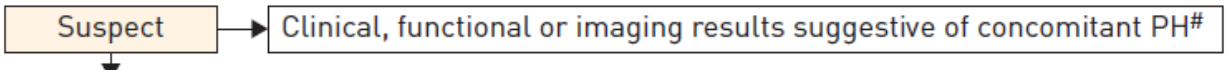
STATE OF THE ART Norbert Weissmann Annals ATS December 2018

Detection of PH in CLD



Steven D. Nathan:Eur Respir J 2019; 53

Detection of PH in CLD



Symptoms

1. Dyspnea
2. Loud P2
3. Signs of RHF, NT-proBNP

Pulmonary function tests

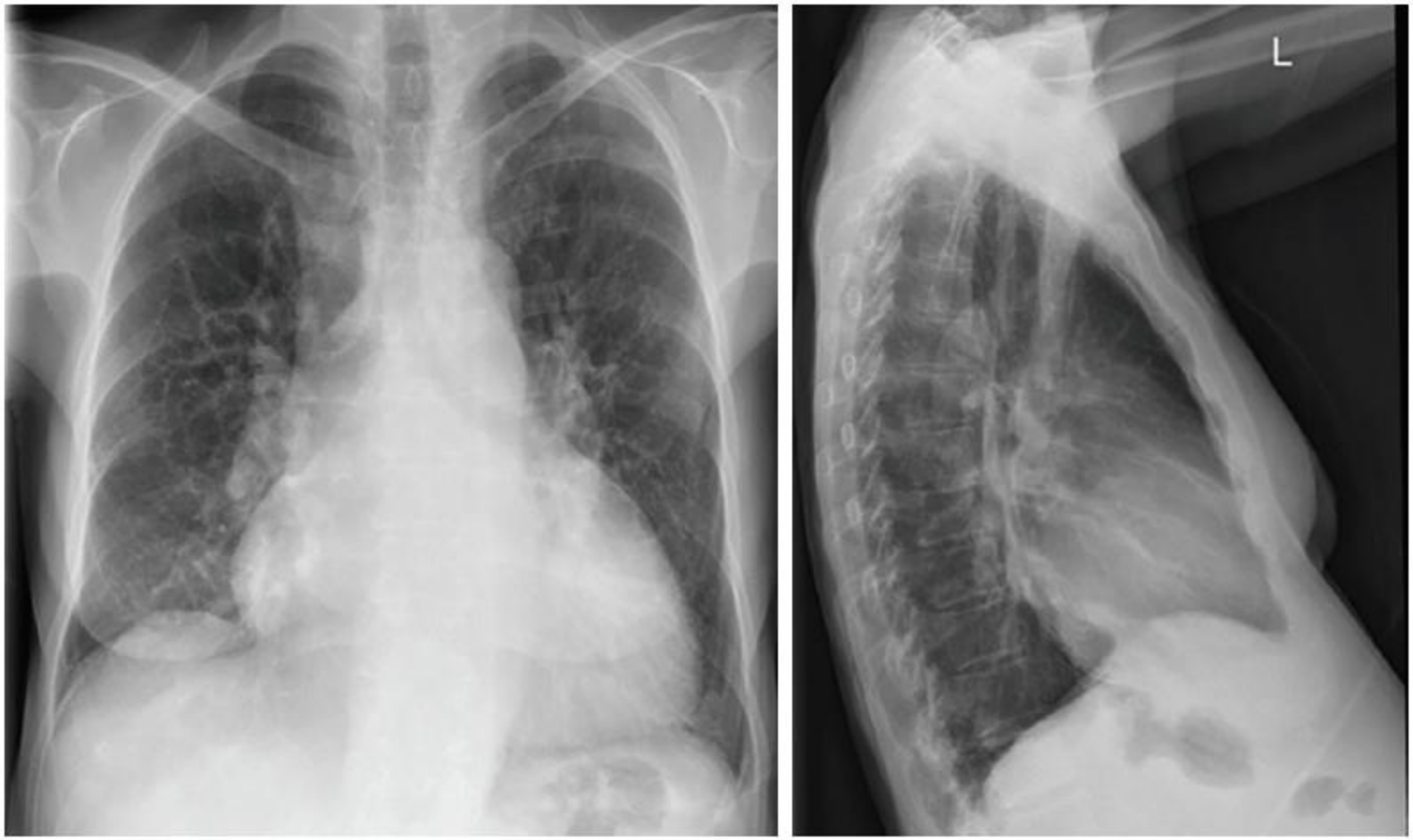
1. DLCO<50% pred
2. Elevated %FVC/%DLCO

Exercise test findings

Imaging findings

Steven D. Nathan:Eur Respir J 2019; 53

Chest radiography AP and lateral

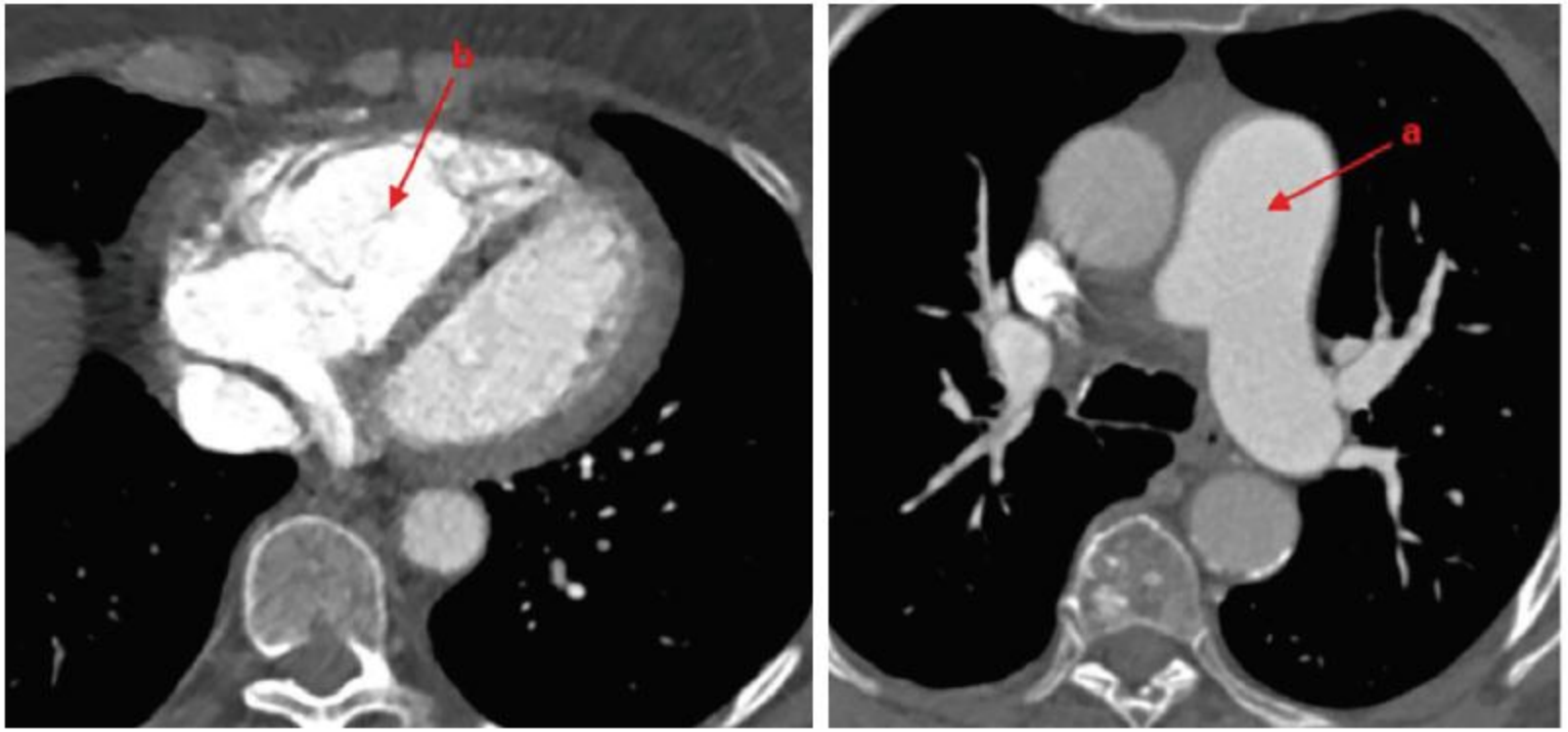


Isabelle Opitz, Silvia Ulrich *J Thorac Dis. July,2018;10*

CT systemic vascular characteristics

a. enlargement of central pulmonary vessel

b. enlargement and hypertrophy of RV



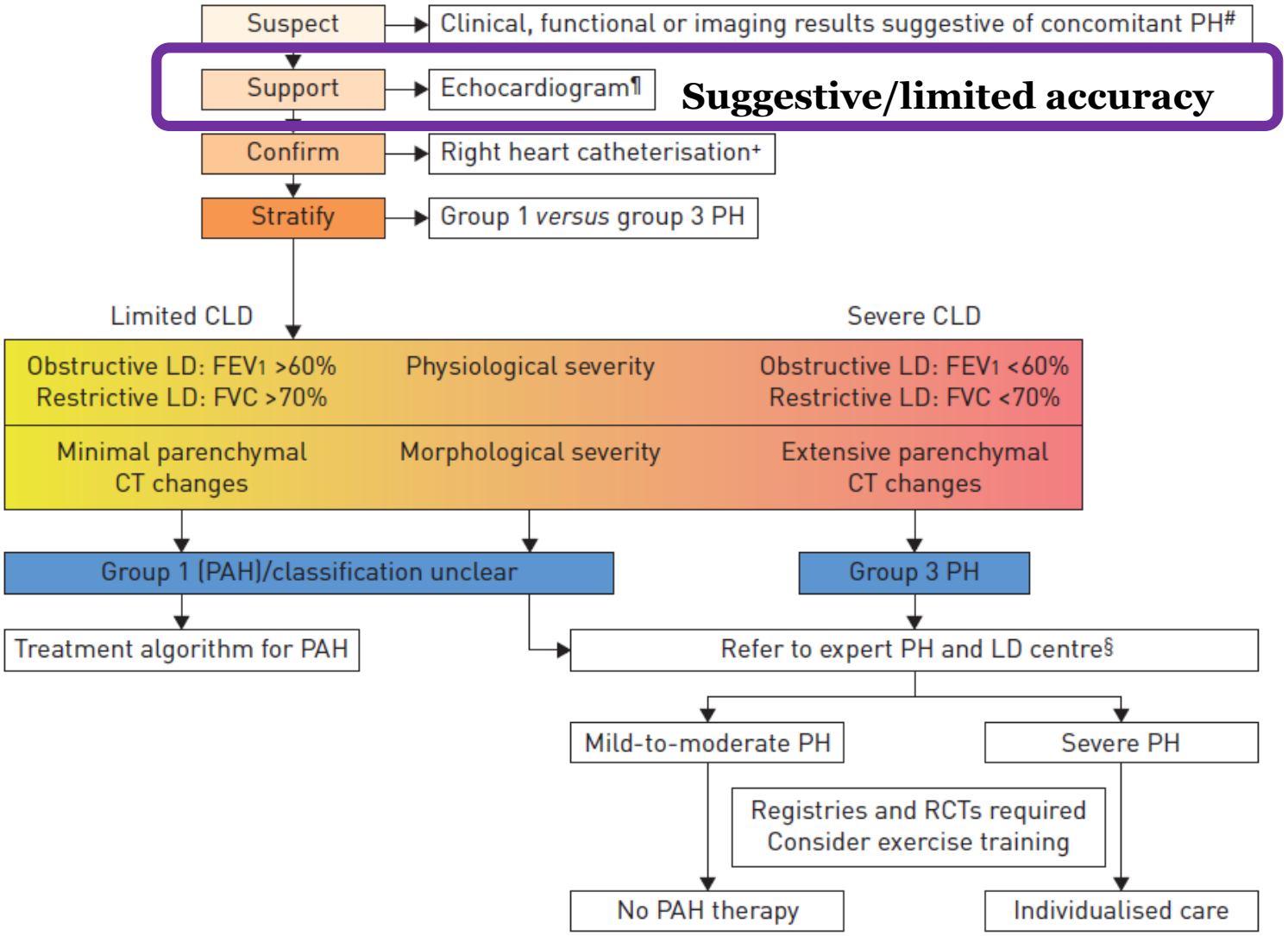
Pulmonary artery / aorta >1

Sensitivity = 70%

Specificity = 92%

Isabelle Opitz, Silvia Ulrich *J Thorac Dis. July,2018;10*

Detection of PH in CLD



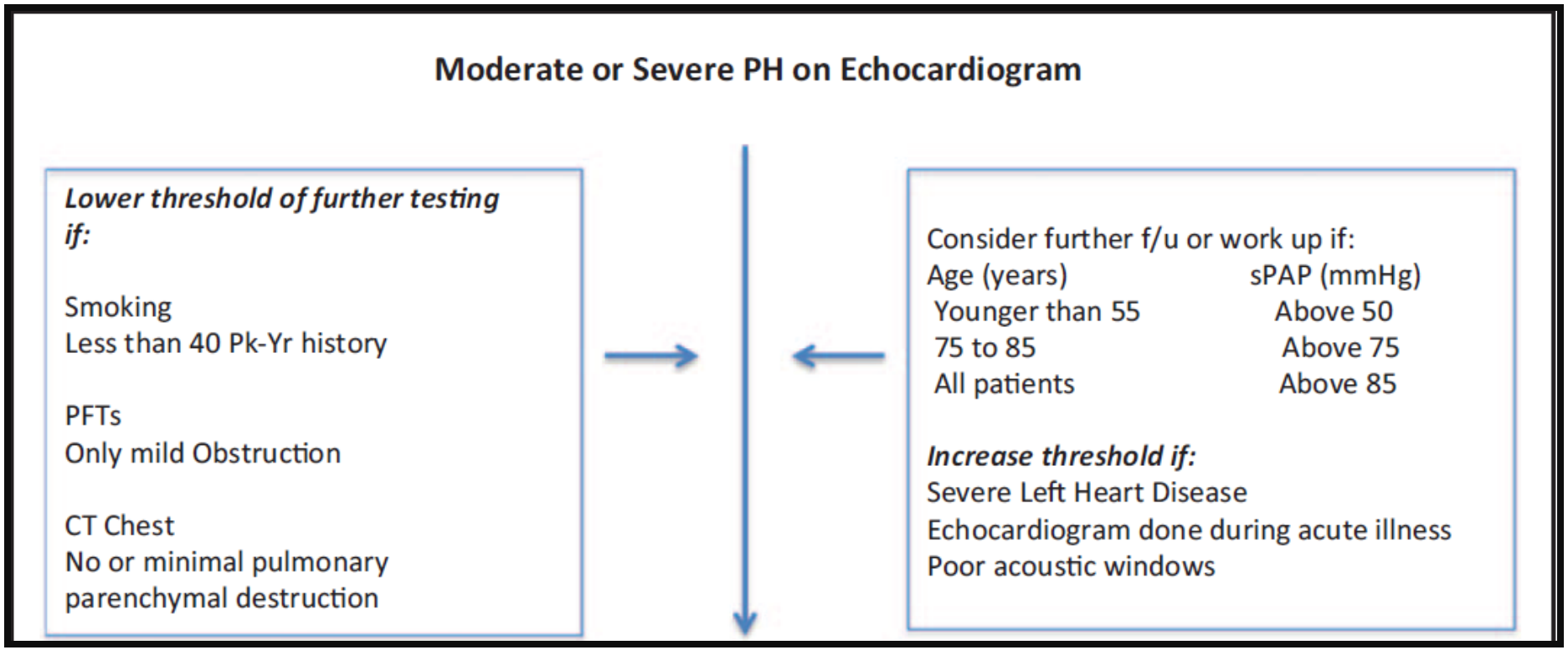
Steven D. Nathan:Eur Respir J 2019; 53

Ηχωκαρδιογραφική εκτίμηση Πνευμονικής Υπέρτασης σε ασθενείς με σοβαρή Πνευμονική νόσο

Patient Group/Finding	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
All patients*				
sPAP	85 (73 to 93)	55 (45 to 64)	52 (41 to 62)	87 (76 to 94)
RV findings†	82 (73 to 89)	57 (51 to 62)	39 (32 to 46)	90 (85 to 94)
OLD				
sPAP	76 (50 to 93)	65 (54 to 75)	32 (18 to 48)	93 (83 to 98)
RV findings	84 (67 to 95)	56 (49 to 62)	22 (15 to 30)	96 (91 to 99)
ILD				
sPAP	85 (68 to 95)	17 (5 to 39)	60 (44 to 74)	44 (14 to 79)
RV findings	76 (61 to 87)	53 (40 to 67)	57 (43 to 69)	74 (58 to 86)

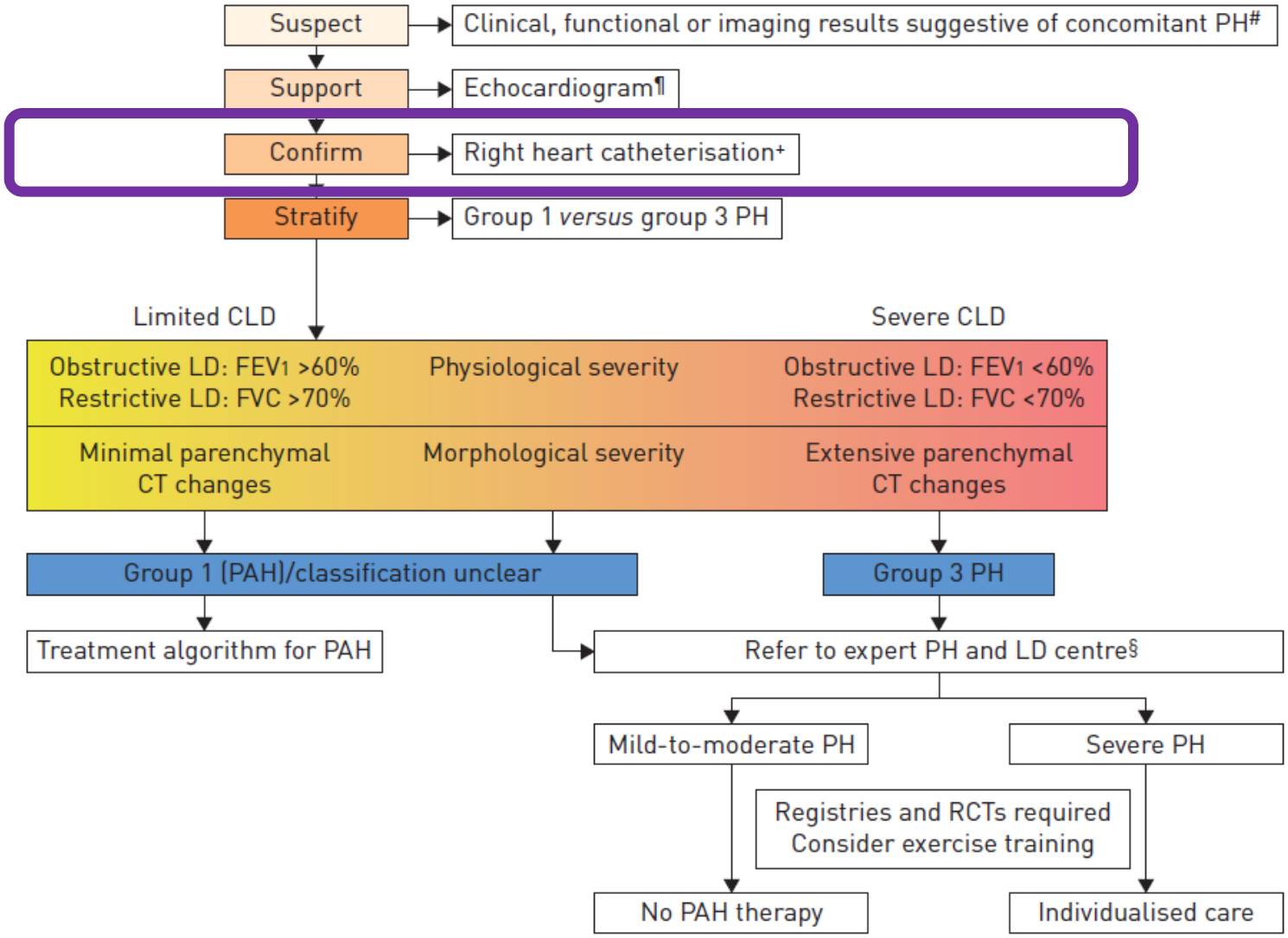
PPV indicates positive predictive value; NPV, negative predictive value; sPAP, systolic pulmonary artery pressure; RV, right ventricular; OLD, obstructive lung disease; and ILD, interstitial lung disease.

Arcasoy SM AJRCCM 2013 167: 735-40



K Chatterjee: Curr Opin Pulm Med 2017

Detection of PH in CLD



Steven D. Nathan:Eur Respir J 2019; 53

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

Definition for PH in the context of CLD-PH

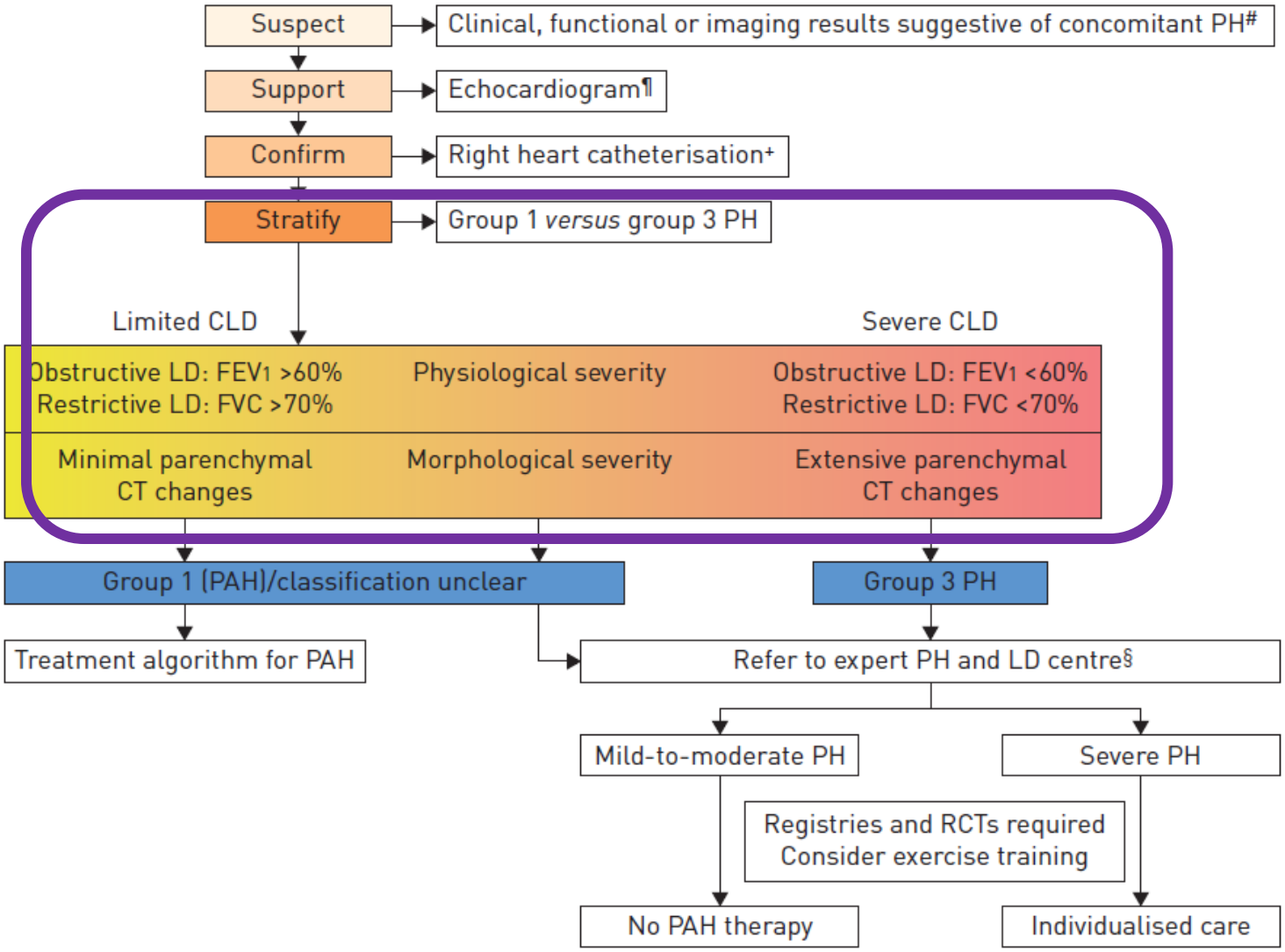
1) CLD *without* PH (mPAP <21 mmHg, or mPAP 21–24 mmHg with pulmonary vascular resistance (PVR) <3 Wood Units (WU)).
2) CLD *with* PH (mPAP 21–24 mmHg with PVR ⩾3 WU, or mPAP 25–34 mmHg) (CLD-PH).
3) CLD *with severe* PH (mPAP ⩾35 mmHg, or mPAP ⩾25 mmHg with low cardiac index (<2.0 $L \cdot min^{-1} \cdot m^{-2}$)) (CLD-severe PH).

Technique: averaging of pressure values over several respiratory cycles.

A floating average over several breaths (without a breath hold) is suggested for measurement of mean pressures, including the pulmonary capillary wedge pressure

SD. Nathan:Eur Respir J 2019; 53

Detection of PH in CLD



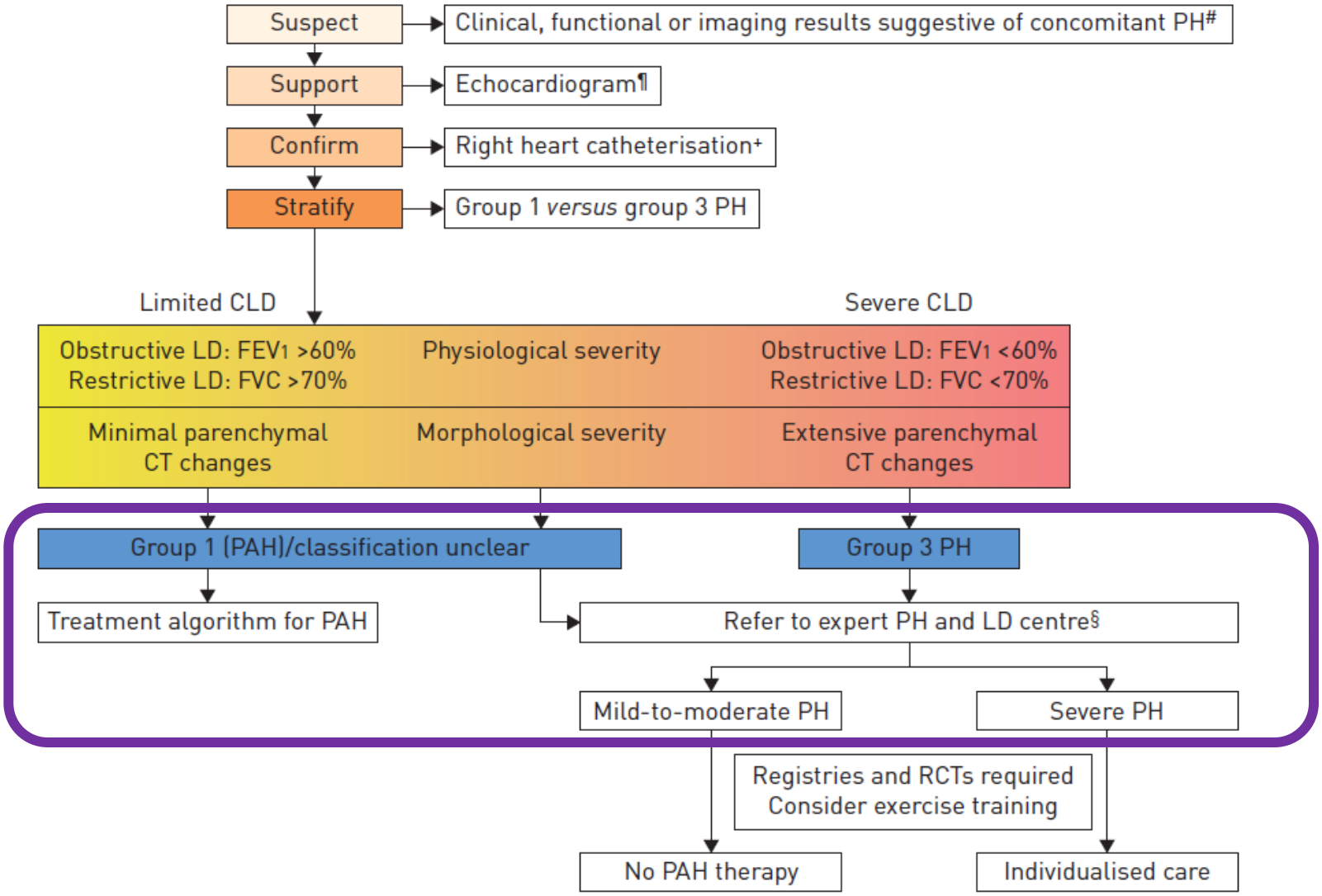
Steven D. Nathan:Eur Respir J 2019; 53

Criteria favouring group 1 versus group 3 pulmonary hypertension (PH)

Criteria favouring group 1 (PAH)	Testing	Criteria favouring group 3 (PH due to lung disease)
	Extent of lung disease	
Normal or mildly impaired: • FEV_1 >60% pred (COPD) • FVC >70% pred (IPF) • Low diffusion capacity in relation to obstructive/restrictive changes	Pulmonary function testing	Moderate to very severely impaired: • FEV_1 <60% pred (COPD) • FVC <70% pred (IPF) • 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
	Haemodynamic profile	
Moderate-to-severe PH	Right heart catheterisation Echocardiogram	Mild-to-moderate PH
	Ancillary testing	
Present	Further PAH risk factors (*e.g.* HIV, connective tissue disease, *BMPR2* mutations, *etc.*)	Absent
Features of exhausted circulatory reserve: • Preserved breathing reserve • Reduced oxygen pulse • Low $CO/\dot{V}O_2$ slope • Mixed venous oxygen saturation at lower limit • No change or decrease in P_{aCO_2} during exercise	Cardiopulmonary exercise test+ (P_{aCO_2} particularly relevant in COPD)	Features of exhausted ventilatory reserve: • Reduced breathing reserve • Normal oxygen pulse • Normal $CO/\dot{V}O_2$ slope • Mixed venous oxygen saturation above lower limit • Increase in P_{aCO_2} during exercise
Predominant haemodynamic profile		Predominant obstructive/restrictive profile

Steven D. Nathan:Eur Respir J 2019; 53

Detection of PH in CLD



Steven D. Nathan:Eur Respir J 2019; 53

2018/19

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

Recommendations	Class[a]	Level[b]
chocardiography is recommended for e non-invasive diagnostic assessment suspected PH in patients with lung sease	I	C
eferral to an expert centre is commended[d] in patients with chocardiographic signs of severe PH d/or sev right ventricular nction	I	C
e optimal treatment of the underlying g disease, including long-term O_2 erapy in patients with chronic poxaemia, is recommended in tients with PH due to lung diseases	I	C
eferral to PH expert center should be nsidered for patients with signs of vere PH/severe RV failure for dividual-based treatment	IIa	C
HC is not recommended for suspected H in patients with lung disease, unless erapeutic consequences are to be pected (e.g. lung transplantation, ternative diagnoses such as PAH or TEPH, potential enrolment in a clinical al)	III	C
he 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

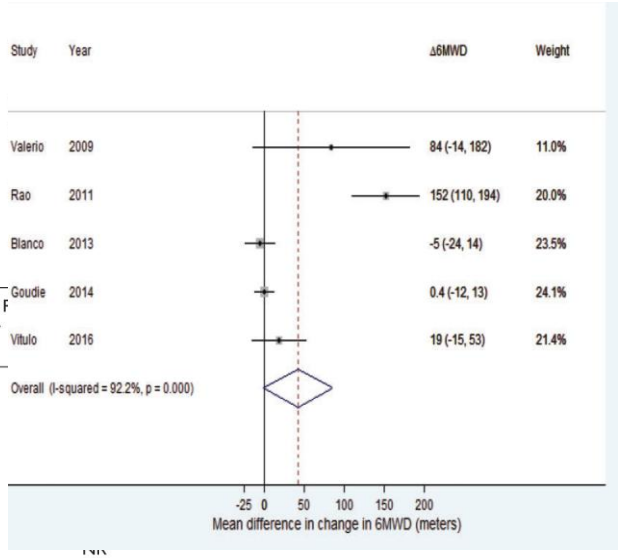
Chronic use of PAH-specific therapy in World Health Organization Group III Pulmonary Hypertension: a systematic review and meta-analysis

Kurt W. Prins, Sue Duval, Jeremy Markowitz, …

First Published March 24, 2017

Author	Symptomatic assessment	Treated-placebo difference	Post treatment	*P* value	Oxygenation assessment	Treated-placebo difference	Post treatment	*P* value
COPD-PH								
Blanco	St. George's Respiratory Questionnaire	1.3 (–3.5 –6.9)	–	0.526	Arterial oxygen tension (mmHg)			
Rao	NR	NR	NR	NR	NR			
Valerio	St. George's Respiratory Questionnaire	NR	C: 43 ± 13 T: 46 ± 13	NS	Arterial oxygen tension (mmHg)			
Goudie	St. George's Respiratory Questionnaire	–2.64 (–6.53 – 1.15)	NR	0.17	NR			
Vitulo	QoL	9.85 (9.07–10.63)	–	0.04	Arterial oxygen tension (mmHg)			

Author	PA Pressure Baseline (mm Hg)	Post Treatment Pressure (mm Hg)	*p*-value	PVR Baseline (dynes s/cm^5 or Wood Units)	Post Treatment P (dynes s/cm^5 or Wood Units)
COPD-PH					
Blanco	P: 26 (26,27), *n* = 5 T: 31 (29,33), *n* = 9	NR	NR	NR	NR
Rao	P: 48 ± 13 (PASP) T: 53 ± 12 (PASP)	P: 44 ± 12 T: 41 ± 8	0.025 (pre/post treatment)	NR	NR
Valerio	P: 36 ± 5 9 (mPAP) T: 37 ± 5 (mPAP)	P: 38 ± 7 (mPAP) T: 31 ± 6 (mPAP)	0.002 (pre/post treatment)	P: 420 ± 170 T: 442 ± 192	P: 435 ± 189 T: 250 ± 170
Goudie	P: 30.8 ± 6.8 (mPAP) T: 30.1 ± 5.2 (mPAP)	P: 30.8 ± 7.5 (mPAP) T: 26.6 ± 5.2 (mPAP)	0.025 (mean difference between groups)	NR	NR
Vitulo	P: 39.1 ± 2.9 (mPAP) T: 39.3 ± 2.1 (mPAP)	P: 36.7 ± 2.9 (mPAP) T: 35.5 ± 2.3 (mPAP)	NS (difference in change)	P: 6.3 ± 0.8 T: 7.01 ± 0.6	P: 6.4 ± .08 T: 5.72 ± 0.6



0.04 (difference in change of PVR)

Assessment of symptomatic burden and oxygenation changes.

Hemodynamic effects of PAH-specific therapy.

Exersice capacity (6MWD)

COPD pts : studies included > 20 pts

Outcome

1. Effect on pulmonary hemodynamics
    1. Long-term use of PAH-targeted therapy improves pulmonary haemodynamics in COPD patients with PH, as shown in two different meta-analyses.
    2. Beneficial haemodynamic effects with long-term PAH therapy, assessed by RHC, have been demonstrated with both sildenafil and bosentan

2. Effect on exercise tolerance, symptoms and quality of life
    1. The effect of PAH-t[illegible] patients with COPD-PH is less

Taken together, the available studies
do not provide clear evidence that the effect of PAH-targeted therapy on pulmonary haemodynamics in COPD-PH translates into an improvement in exercise tolerance and symptoms.

3. Effects on oxygenation
    1. Evidence for a long-term benefit of PH therapy in COPD-PH is heterogeneous
        1. deterioration of gas exchange with the long-term use of bosentan or sildenafil
        2. no change was observed in others using sildenafil or tadalafil and rarely resulted in treatment withdrawal
    2. Reduction in oxygenation related to pulmonary vasodilation might be compensated for by an increased CO that may maintain or even improve tissue oxygen delivery, especially with exercise

2018/19

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

4. 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]
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Clinical relevance

Effect of PH on Prognosis

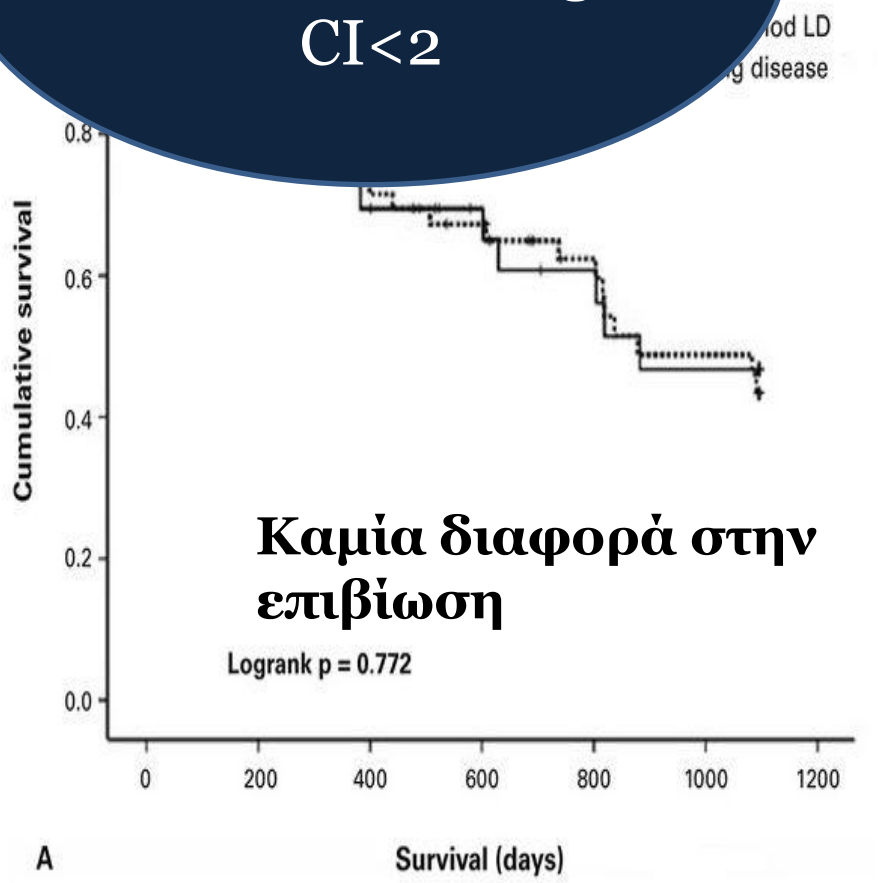
AND

Quality of life

Ήπια πνευμονική νόσος
FEV1 >60% / Σοβαρή Νόσο

PH > 35 mmHg

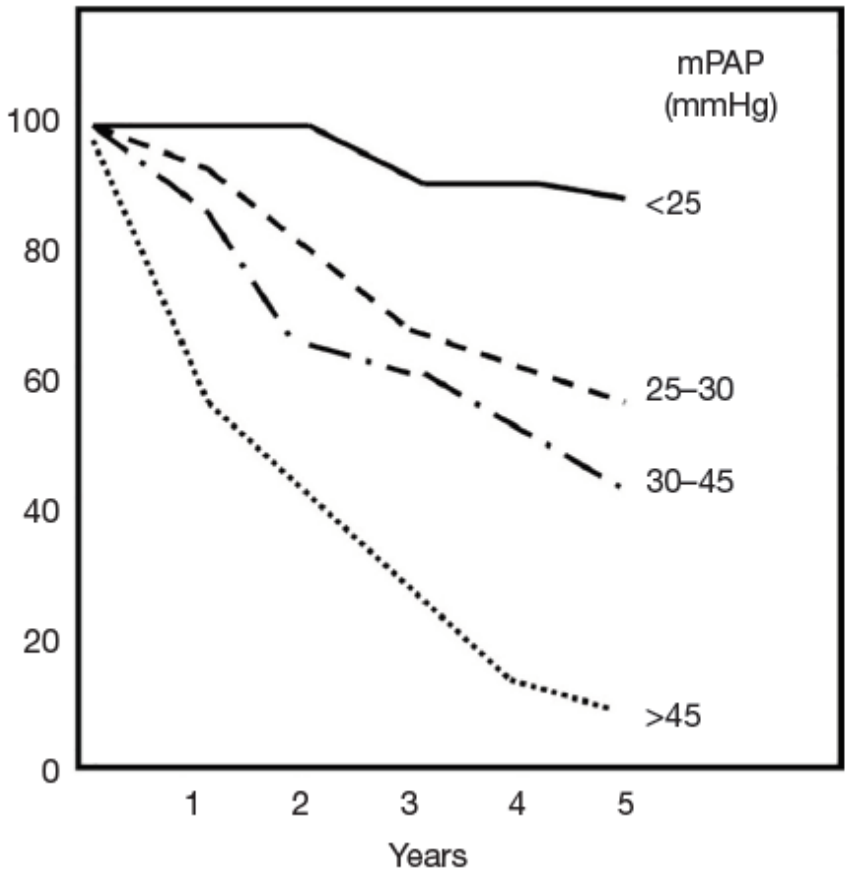
CI<2



Καμία διαφορά στην επιβίωση

Logrank p = 0.772

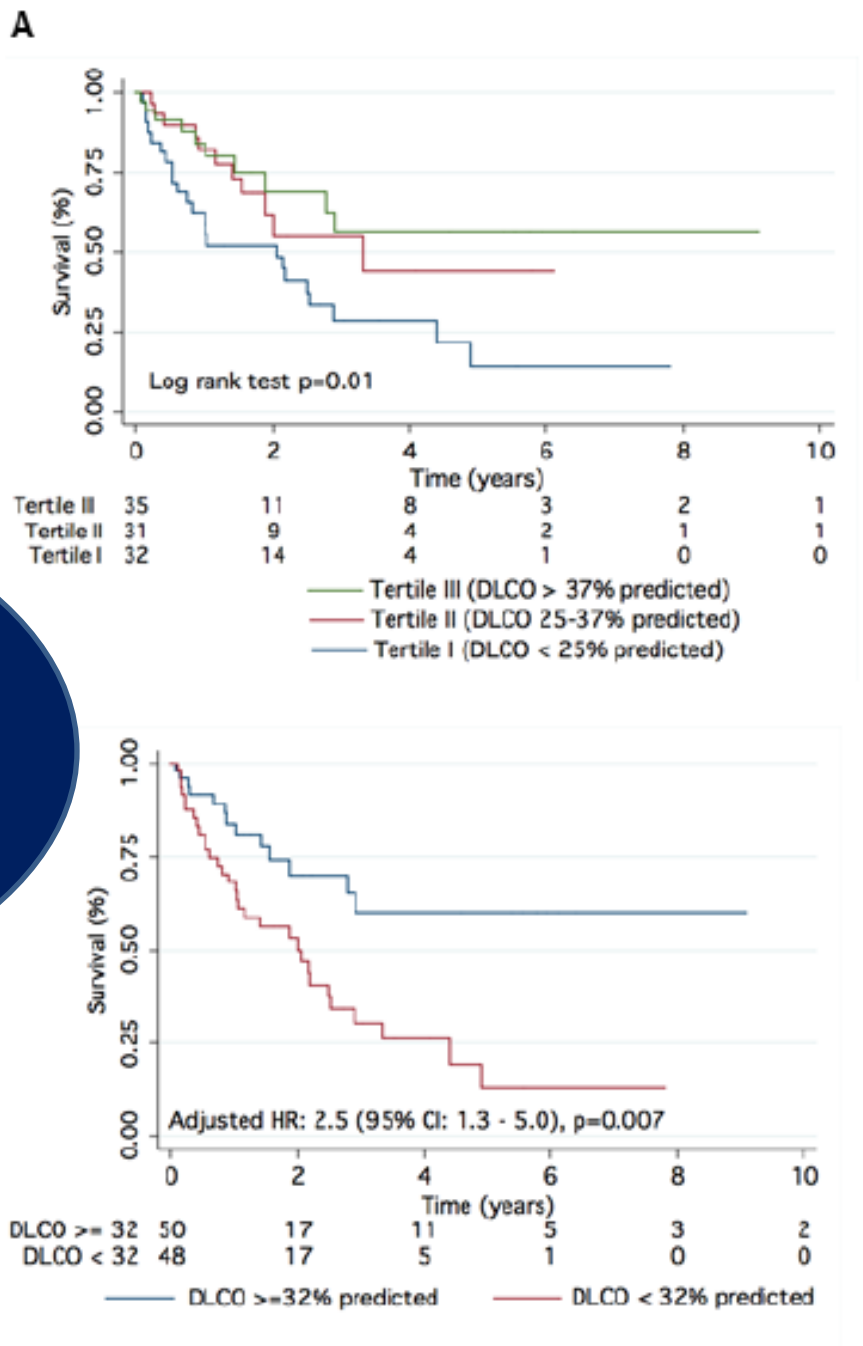
Funke M, 2016 Swiss Med Wkly

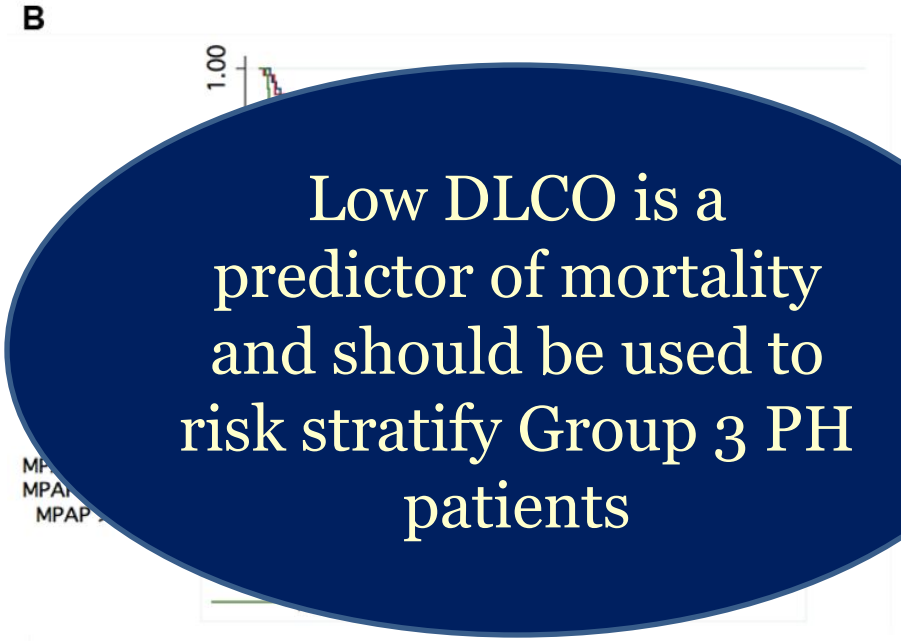


I Opitz, *J Thorac Dis. July,2018;10*

Survival in Pulmonary Hypertension due to Chronic Lung Disease:

Infuence of Low Diffusion Capacity of the Lungs for Carbon Monoxide





Low DLCO is a predictor of mortality and should be used to risk stratify Group 3 PH patients

Rose L, Journal of Heart and Lung Transplantation 11/2018

Clinical relevance

Effect of PH on Prognosis

AND

Quality of life

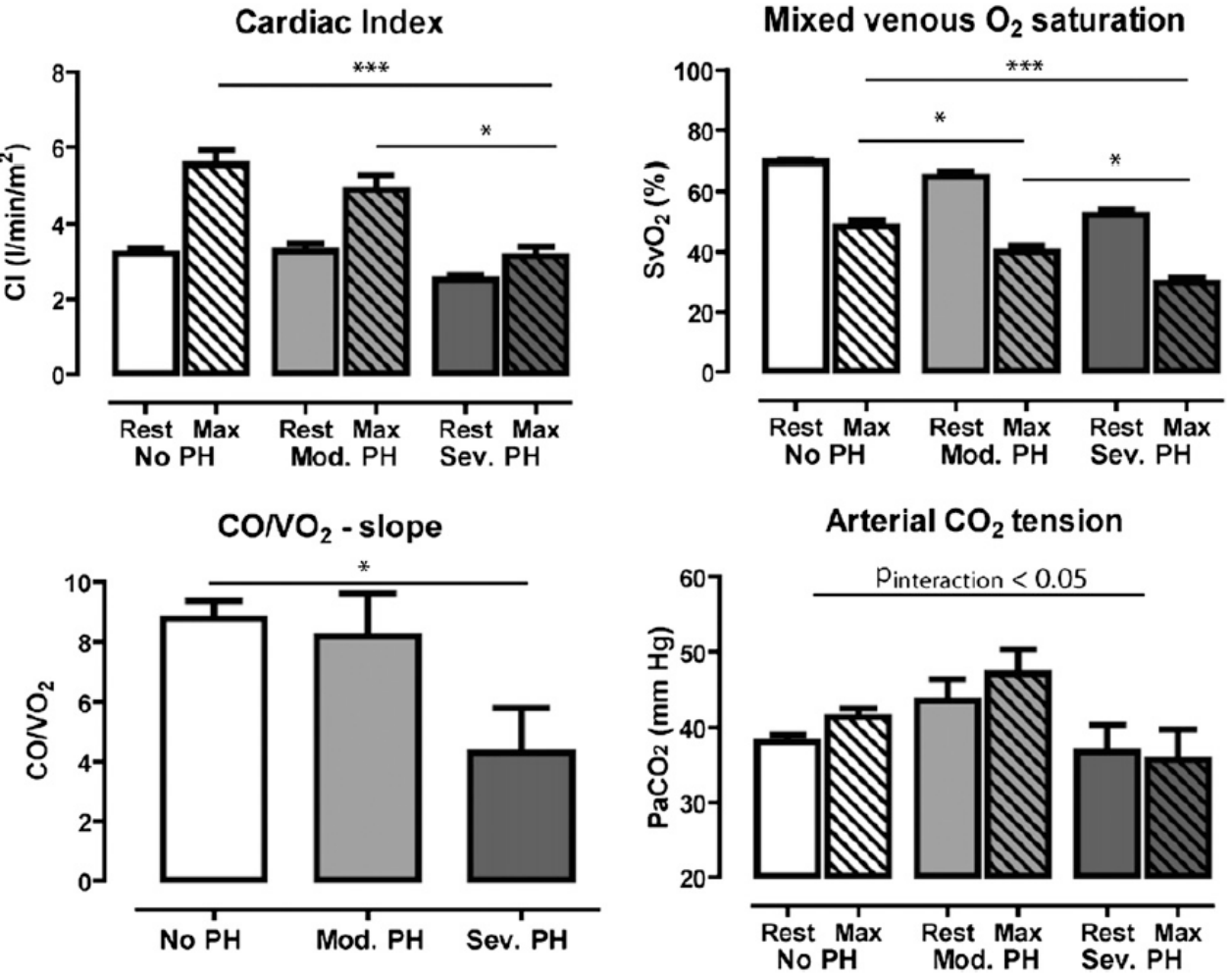
Pulmonary hypertension at exercise in COPD:

does it matter?

Robert Naeije, Bart G. Boerrigter

Ventilatory and cardiocirculatory exercise profiles in COPD: the role of pulmonary hypertension.

COPD pts
GOLD II – IV
no PH (Mpap< 25 mm Hg)
moderate PH (mPAP= 25-39 mm Hg), and
severe PH (mPAP> 40 mm Hg)

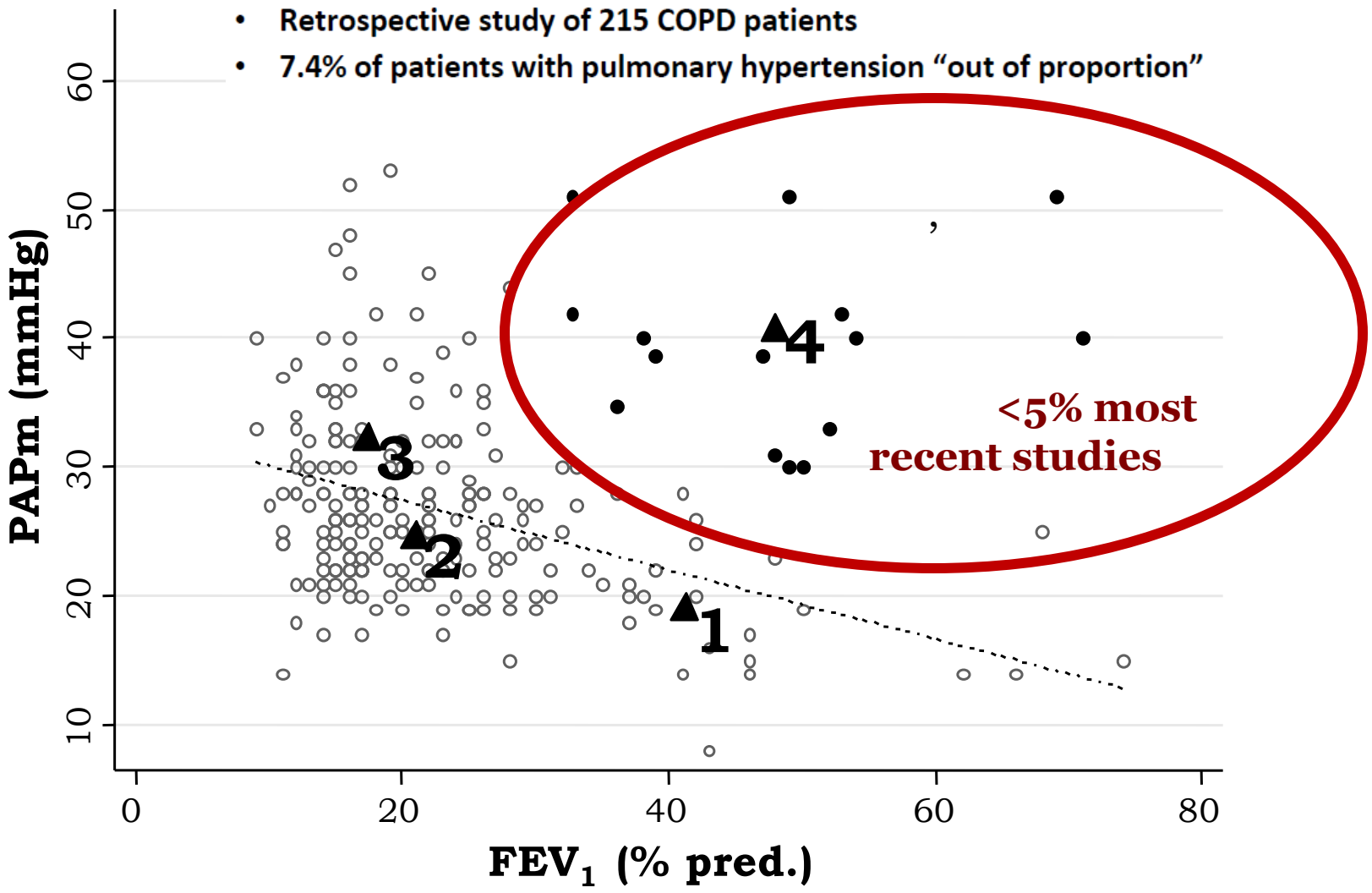


PH-induced circulatory limitation to exercise in patients with COPD and an mPAP of 40 mm Hg.

In patients with COPD without or with moderate PH, the exercise profile indicates a circulatory reserve and a predominantly ventilatory limitation to exercise

Boerrigter BG . Chest. 2012 Nov;142(5).

COPD and Pulmonary Hypertension



Thabut, Chest 2005; 127: 1531

Pulmonary hypertension at exercise in COPD: does it matter?

Robert Naeije, Bart G. Boerrigter

- The right ventricle limits exercise capacity only in COPD patients with “out of proportion pulmonary hypertension”:
  - Preserved ventilatory reserve
  - Hypocapnia, hypoxaemia and
  - Very low mixed venous oxygenation at maximal exercise
- Only these patients might be candidates for trials of targeted therapies with drugs shown efficacious in PAH.

Japan: 5.3 million patients with COPD / 50,000 COPD patients with PH

'Early Cor-pulmonale'

"pulmonary vascular COPD phenotype"
'Early Cor-pulmonale'

less severe airflow limitation,
hypoxaemia,
very low diffusing capacity of the lung for carbon monoxide (DLCO),
normo- or hypocapnia and
a cardiovascular exercise limitation profile

Nathan S 2019 Proceedings

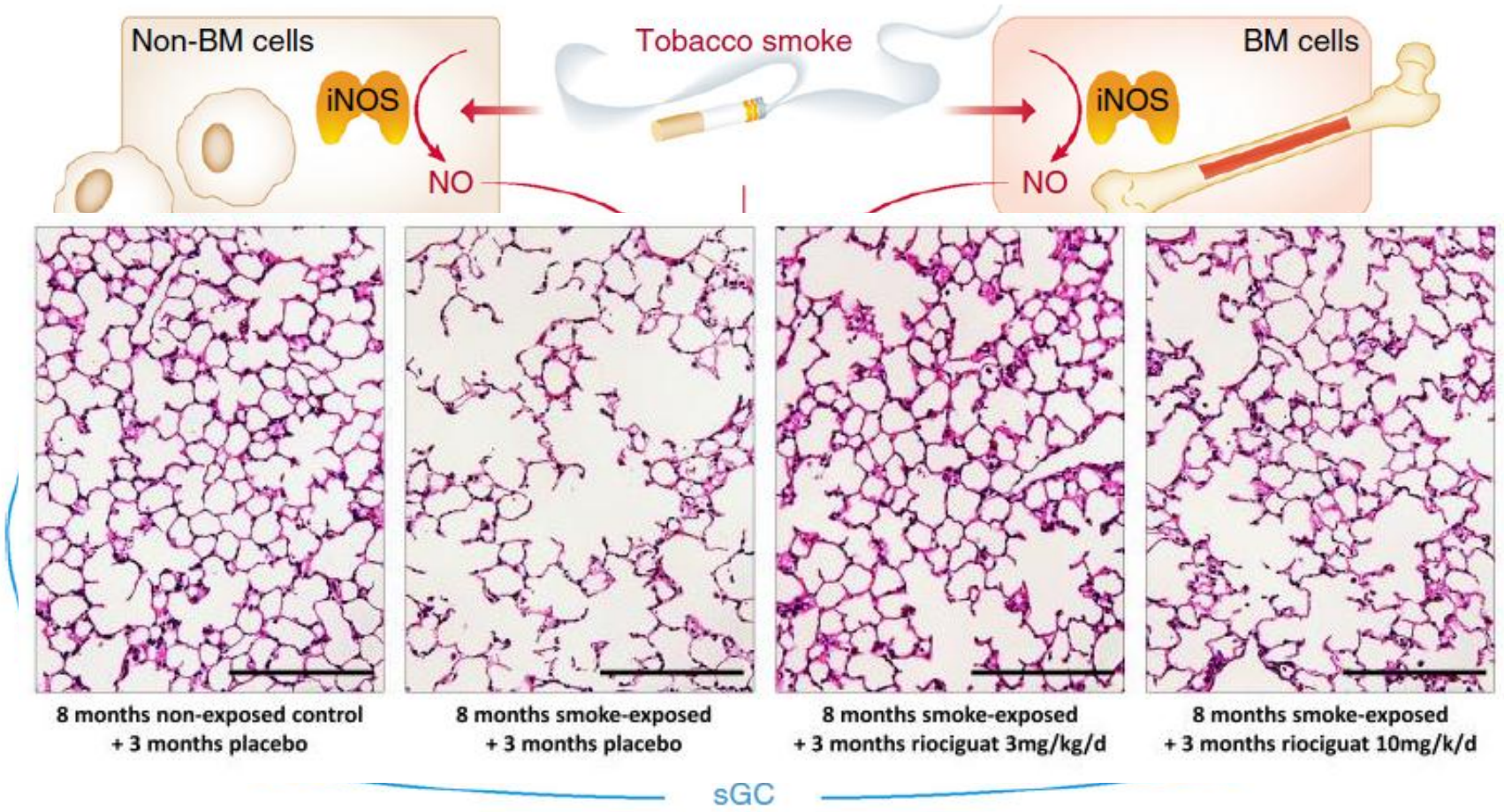
•Pulm

Any Future for New Therapies?

Seiichiro Sakao: J Resp Inves March 2019.03

Chronic Obstructive Pulmonary Disease and Pulmonary Vascular Disease

A Comorbidity?



STATE OF THE ART Norbert Weissmann Annals ATS December 2018

Riociguat for treatment of pulmonary hypertension in COPD – a translational study

- It has been suggested that patients with circulatory, but not ventilatory limitation during exercise might profit most from vasoactive treatment of PH.
- However, large clinical trials are missing to answer the question which patients profit most from therapy.

- Moreover, an approach addressing both, vascular and alveolar remodeling, as well as bronchial obstruction would be desirable. In this regard, it has been shown recently in animal models of smoke-induced emphysema that treatment with activators of the nitric oxide/cyclic guanoside monophosphate (NO-cGMP) pathway can reduce PH and emphysema when applied in a preventive approach.
  - NO activates the soluble guanylate cyclase (sGC) to produce cGMP that activates cGMP-dependent protein kinases that can modulate:
    - **apoptosis, proliferation, migration, and extracellular matrix protein expression**

Pichl A: *Eur Respir J 2019; in press*

Riociguat for treatment of pulmonary hypertension in COPD – a translational study

	Pre-Treatment	Post-Treatment (4-7 month after start of riociguat	Post-Treatment (21-29 months after start of riociguat)
Blood gases			
pO_2 (mmHg)	67 ± 6	74 ± 4 (p=0.939)	75 ± 9 (p=0.927)
pCO_2 (mmHg)	38 ± 7	39 ± 3 (p=0.997)	40 ± 4 (p=0.990)
O_2-suppl. (l/min)	2.00 ± 2.00	2.00 ± 2.00 (p=1.000)	2.00 ± 2.00 (p=1.000)
Lung function parameters			
Rtot%	225 ± 17	174 ± 37* (p=0.039)	240 ± 55 (p=0.737) # (p=0.005)
FEV1%	56 ± 3	63 ± 7 (p=0.956)	59 ± 3 (p=0.997)
FEV1/VC%	59 ± 3	60 ± 5 (p=0.999)	52 ± 3 (p=0.945)
RV/TLC%	56 ± 3	53 ± 5 (p=0.973)	52 ± 6 (p=0.954)
DLCO/SB%	31 ± 8	40 ± 10 (p=0.895)	41 ± 11 (p=0.888)
Echocardiographic parameters			
sPAP (mmHg)	69 ± 6	63 ± 5 (p=0.943)	61 ± 10 (p=0.920)
TAPSE (mm)	16 ± 2	18 ± 3 (p=0.998)	20 ± 2 (p=0.986)

Conclusion

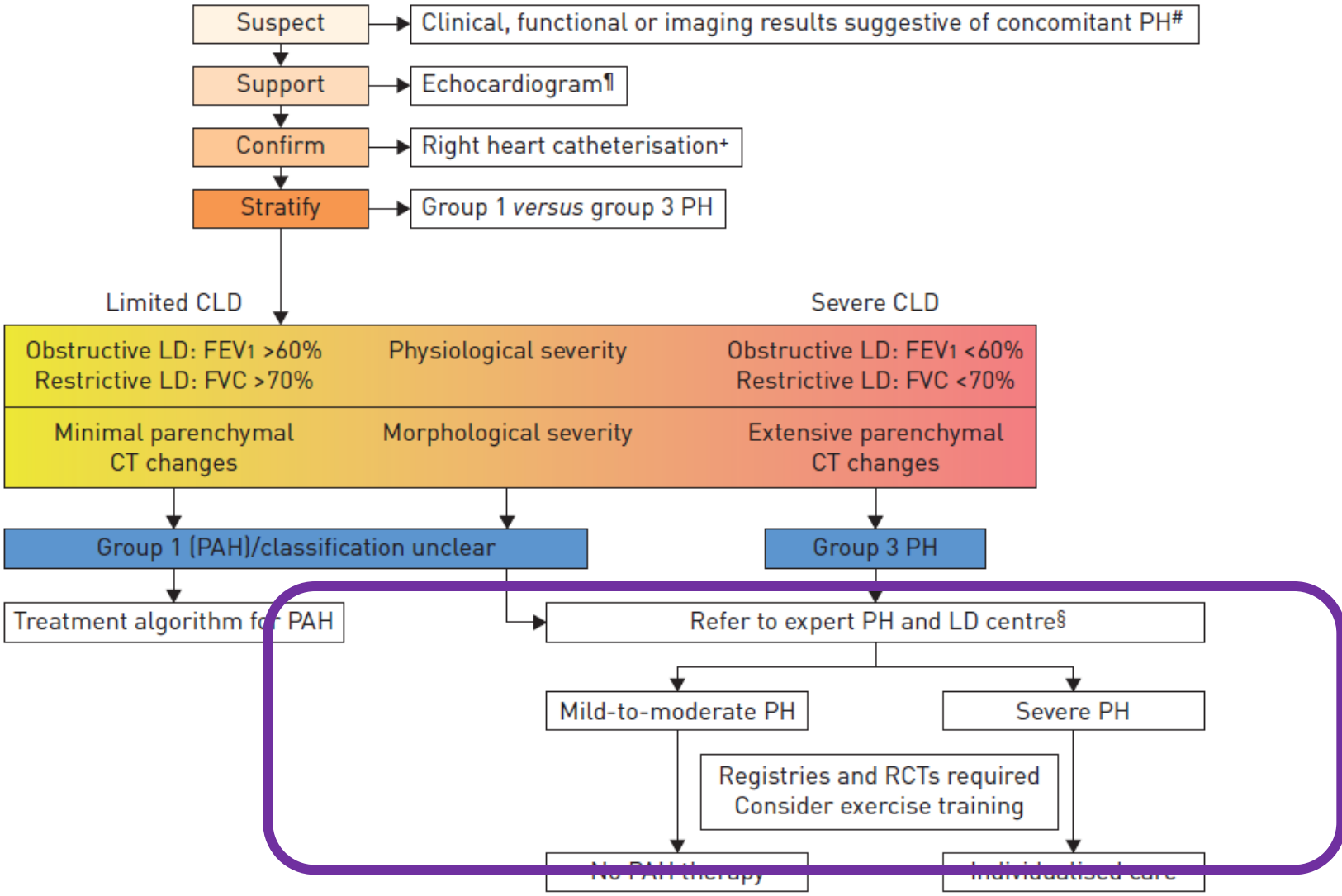
- **'Severe pulmonary hypertension' is replacing the term 'out of proportion'**

Trials, decisions
on
individualized patient care
should be made in the context of
expert centers

associated PH.

- life-preserving measures should only be considered as a bridge to transplantation. Patients in any of

Detection of PH in CLD



Steven D. Nathan:Eur Respir J 2019; 53

Japan: 5.3 million patients with COPD / 50,000 COPD patients with PH

“pulmonary vascular COPD phenotype”
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Nathan S 2019 Proceedings

•Pulm

Any Future for New Therapies?

Seiichiro Sakao: J Resp Inves March 2019.03

Conclusion

- **'Severe pulmonary hypertension' is replacing the term 'out of proportion' pulmonary hypertension in hypoxic pulmonary diseases.**

- **'Severe pulmonary hypertension' is defined as mPAP at least 35 mmHg or CI less than 2.0 l/min/m2 on RHC.**

- **'Severe pulmonary hypertension' is quite rare (1–3% of severe COPD patients) in obstructive lung diseases.**
- **Currently, there are no conclusive data to support or completely reject the possibility of use of specific PAH therapies in COPD patients, especially with mild-to moderate pulmonary hypertension.**

- **Patients with mild-to-moderate COPD by PFTs and CT chest, and evidence of severe pulmonary hypertension by RHC, may be treated with specific PAH therapies similar to WHO group-I PAH guidelines.**

Conclusion

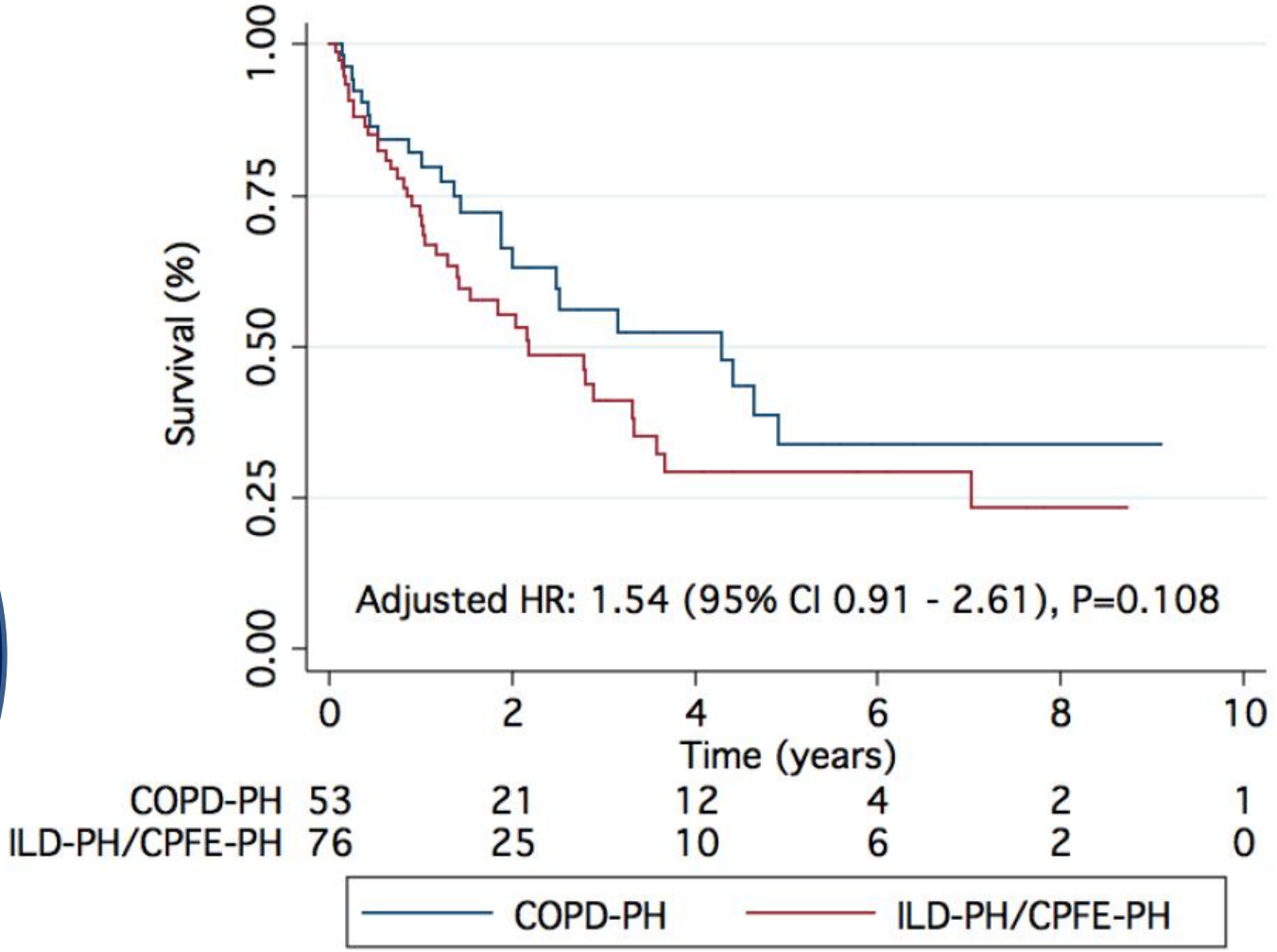
- Although preliminary evidence suggests that currently available vasoactive medications may have a benefit in COPD-PH patients with mPAP ⩾35 mmHg, further studies are required before PAH therapies can be recommended.
  - ***Therefore, these patients should be a target population for larger prospective studies***.
- This does not preclude COPD patients with lower mPAP being enrolled in future studies, especially if the cardiac index is low or PVR is significantly elevated.

Steven D. Nathan:Eur Respir J 2019; 53

Survival in Pulmonary Hypertension due to Chronic Lung Disease:

Infuence of Low Diffusion Capacity of the Lungs for Carbon Monoxide

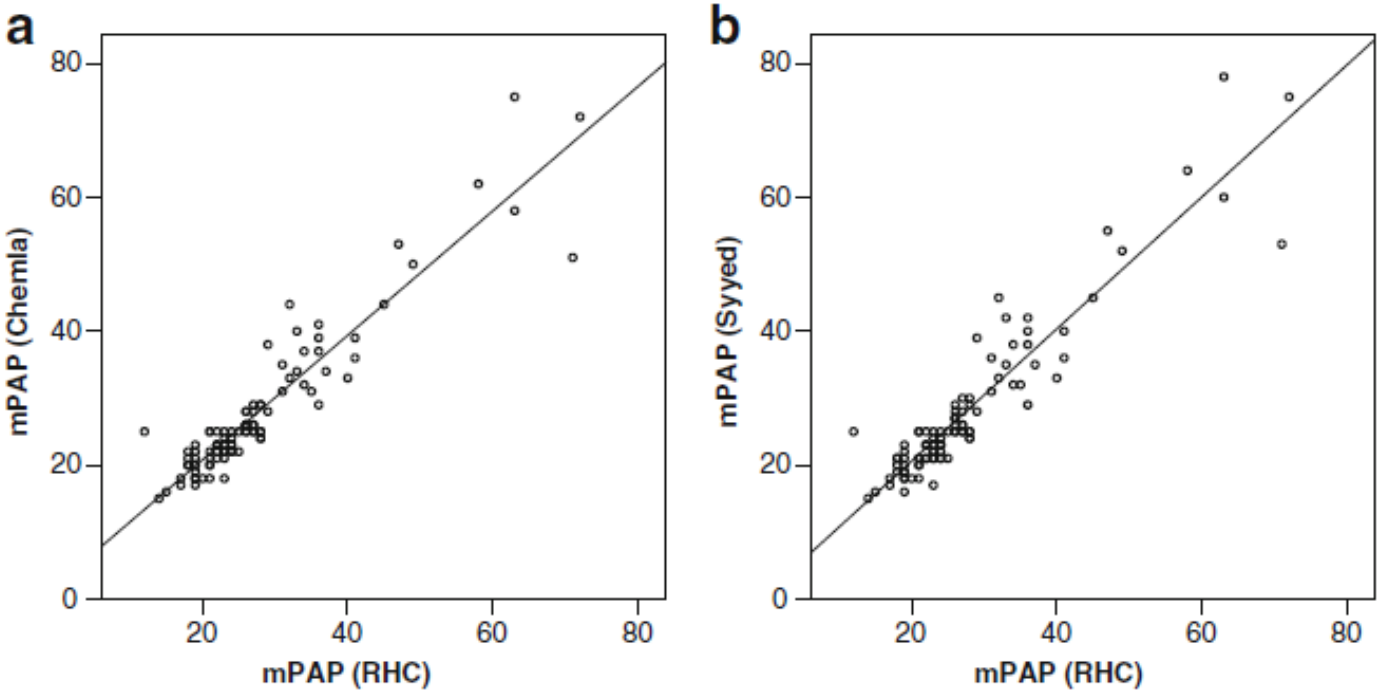
There is reduced survival in ILD-PH as compared to COPD-PH



Rose L, Journal of Heart and Lung Transplantation 11/2018

Correlation between RHC-measured mPAP and echocardiographic-estimated mPAP

using the Chemla formula (a) and the Syyed formula (b)

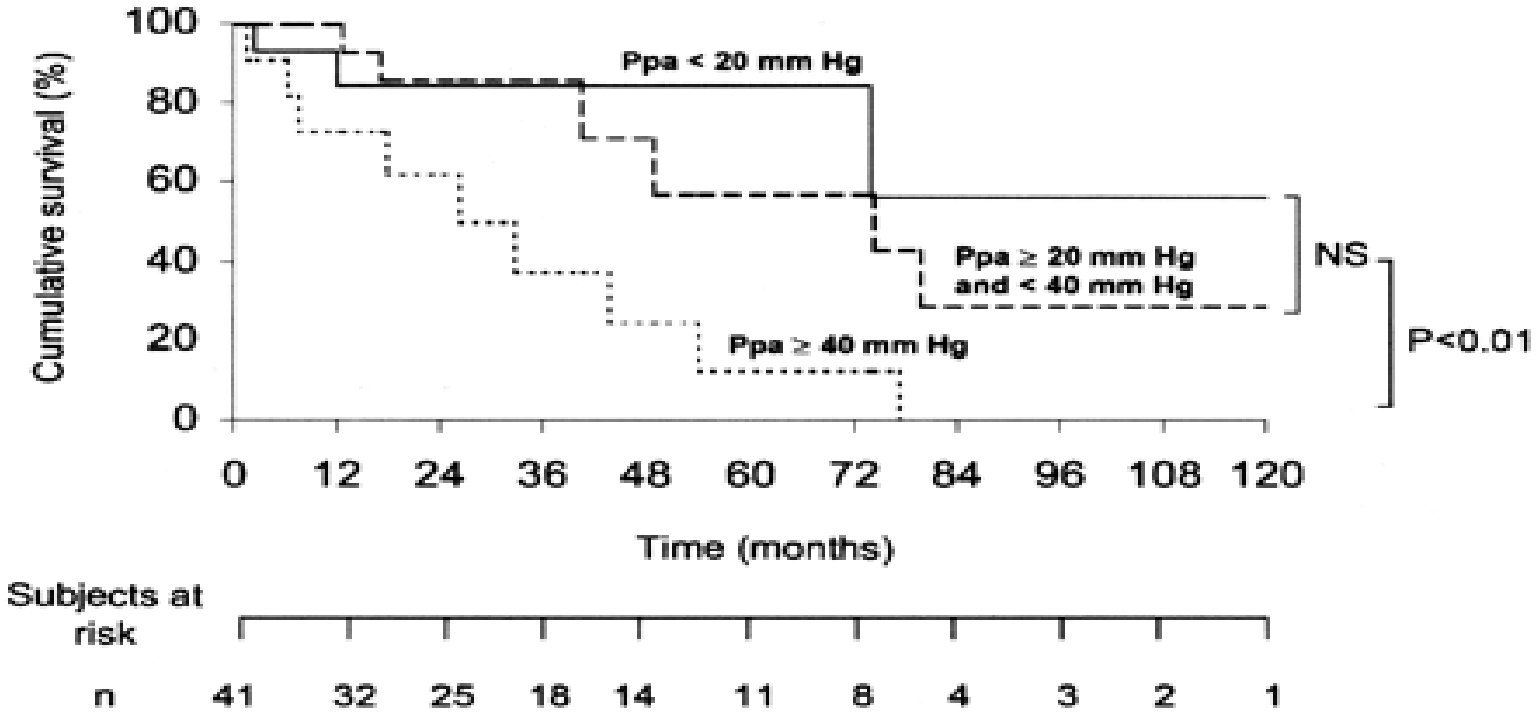


It has been suggested that both
Chemla formula (mPAP = sPAP × 0.61 + 2 mmHg)
and
Syyed formula (mPAP = sPAP × 0.65 + 0.55 mmHg) might accurately estimate the mPAP

Cottini et al. Critical Care (2017) 21:115

Disproportionate PH

Strasbourg group



Chaouat AJRCCM 2005; 172:189

2018 classification

- Chronic lung disease (CLD) with[illegible] **Hg)**
- CLD with PH>/= 20mmHg an[illegible]ental O2 if needed)
  - Stick to the standard definitio[illegible]
  - RHC needed to assessment of C[illegible]
- CLD with severe PH (mPAP>/=35mmHg[illegible]ental O2)
  - 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

Chronic obstructive pulmonary disease and the early stage of cor pulmonale:
A perspective in treatment with pulmonary arterial hypertension approved drugs

Στο ρεβ αρχίζει αναφερονατσ 2 μελετεες

Summary of studies identified for systematic review and meta-analysis

Author	PH definition	Treatment	Dose	Duration	Placebo (n)	Treated (n)	Mean age (years)	Sex M:F
COPD-PH								
Blanco	Echo estimated PA systolic >34 mmHg or RHC mPAP ≥ 25 mmHg	Sildenafil	20 mg TID	3 months	27	24	P: 65 ± 8 T: 66 ± 8	P: 26:5 T: 28:1
Rao	Echo estimated PA systolic pressure >40 mmHg	Sildenafil	20 mg TID	12 weeks	18	15	P: 63.6 ± 6.7 T: 60.7 ± 8.5	NR
Valerio	RHC mPAP ≥ 25 mmHg	Bosentan	125 mg BID	18 months	16	16	P: 65 ± 10 T: 66 ± 9	P: 12:4 T: 13:3
Goudie	Echo estimated PA systolic pressure >30 mmHg or PA-AT < 120 ms	Tadalafil	10 mg daily	12 weeks	57	56	P: 70 ± 7 T: 68 ± 8	P: 40: 20 T: 42:18
Vitulo	RHC mPAP ≥ 35 mmHg if FEV_1 ≥30% after bronchodilator or mPAP ≥ 30 mmHg if FEV_1 >30% after bronchodilator	Sildenafil	20 mg TID	16 weeks	10	18	P: 64.1 ± 11 T: 66.4 ± 6.5	P: 8:2 T: 13:5

PAH-specific therapy in World Health Organization Group III Pulmonary Hypertension: a systematic review and meta-analysis

Kurt W. Prins Sue Duval Jeremy Markowitz

Seiichiro Sakao: J Resp Inves March 2019.03

Chronic obstructive pulmonary disease and the early stage of cor pulmonale: A perspective in treatment with pulmonary arterial hypertension approved drugs

The off-label use of PAH-approved drugs

The Nippon COPD Epidemiology Study showed that there are approximately 5.3 million patients with COPD in Japan [20], and the prevalence of PH is reported to be 1.1% [21], suggesting that there are approximately 50,000 COPD patients with PH in Japan. In an actual clinical setting, there are several patients in whom PAH-approved drugs are used because of Japanese universal health insurance.

However, there is concern about the present situation regarding the off-label use of PAHapproved drugs without evidentiary support. Actually, there are some cases in which PAH-approved drugs are likely to be effective for COPD with PH. Thus, there is an urgent need for a prospective study aiming to distinguish the cases in which such treatment can be effective in a clinical setting.

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

COPD-PH

CPET: contribution of pulmonary vascular disease for dyspnea and activity limitation.

- Parameters suggesting inadequate intrapulmonary gas exchange.
- Oxy-hemoglobin desaturation.
- Hyper-circulatory and hyper-ventilatory response due to elevated inspiratory neural drive.
- Decrease maximum oxygen consumption (VO_2 max).
- Variable combination of fatigue and dyspnea as limiting symptoms.

K Chatterjee: Curr Opin Pulm Med 2017

Moderate or Severe PH on Echocardiogram

Lower threshold of further testing if:

Smoking
Less than 40 Pk-Yr history

PFTs
Only mild Obstruction

CT Chest
No or minimal pulmonary parenchymal destruction

Consider further f/u or work up if:

Age (years)	sPAP (mmHg)
Younger than 55	Above 50
75 to 85	Above 75
All patients	Above 85

Increase threshold if:
Severe Left Heart Disease
Echocardiogram done during acute illness
Poor acoustic windows

Does patient has known left heart disease or current Echocardiogram shows predominant left heart disease, e.g..

- Low LVEF
- AS, MS, AR, MR
- Left atrial dilation more than right atrial dilation

Does patient has known condition or risk factors for WHO Group I PAH, e.g..

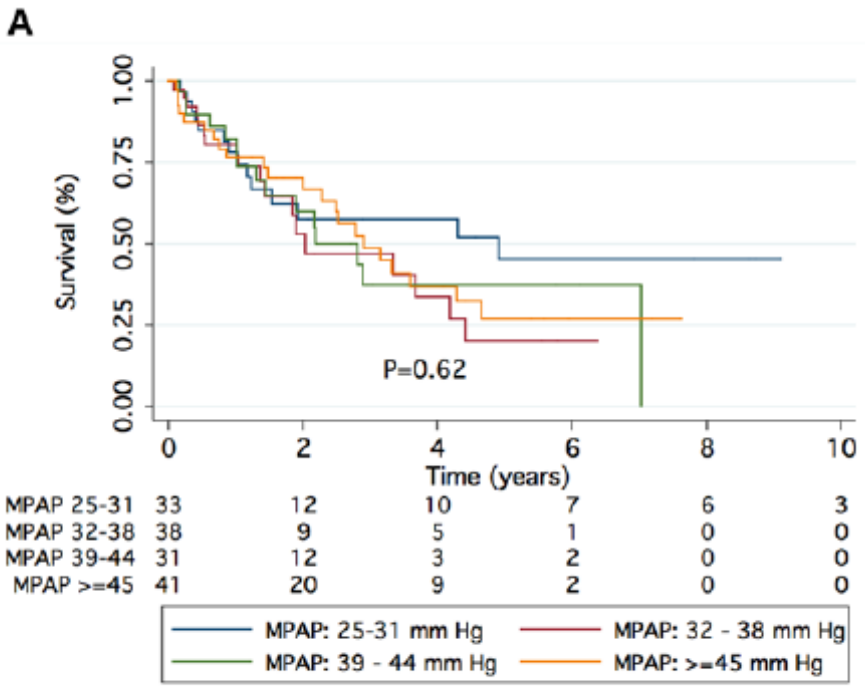
- Connective Tissue Disorder
- Family History of PAH
- Cirrhosis or Portal Hypertension
- HIV / AIDS
- Delayed ASD / VSD closure
- Cocaine, Amphetamines use

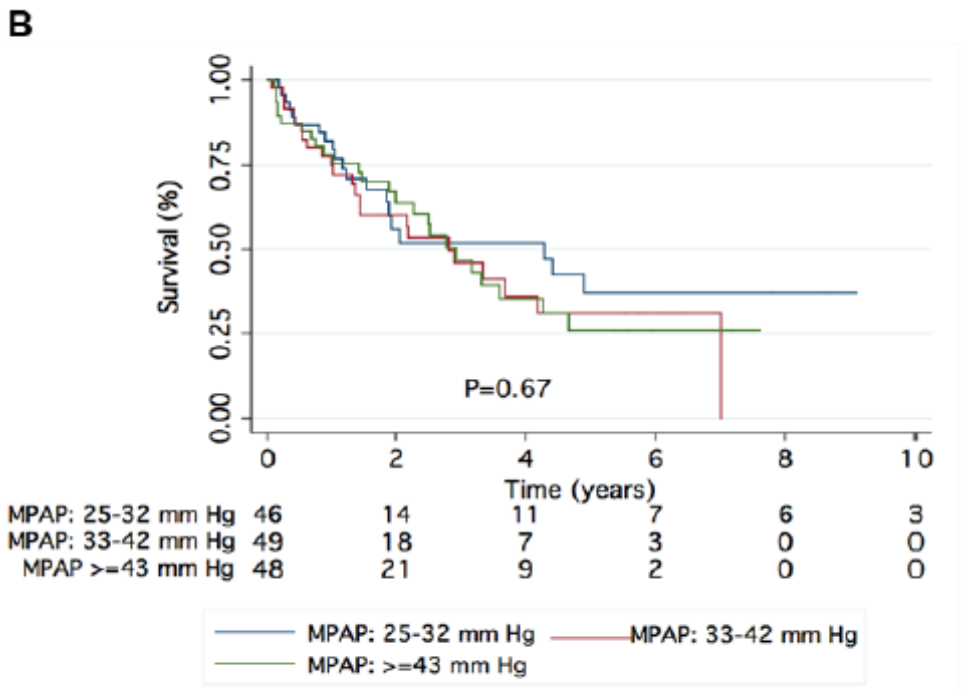
Does patient has known condition or risk factors for WHO Group IV PAH, e.g..

- Intermediate or high probability V/Q scan
- H/O PE, DVT

Decision to perform Right Heart Catheterization and Consideration for Specific PAH Therapies

Survival in Pulmonary Hypertension due to Chronic Lung Disease



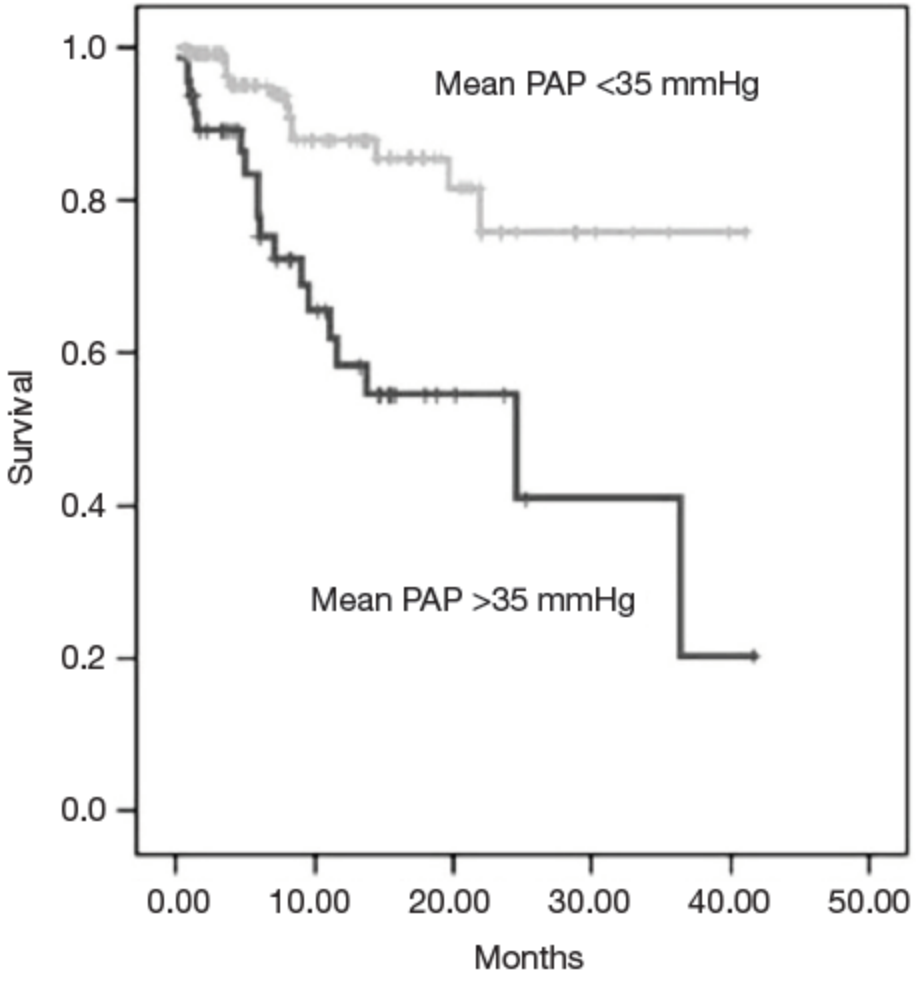


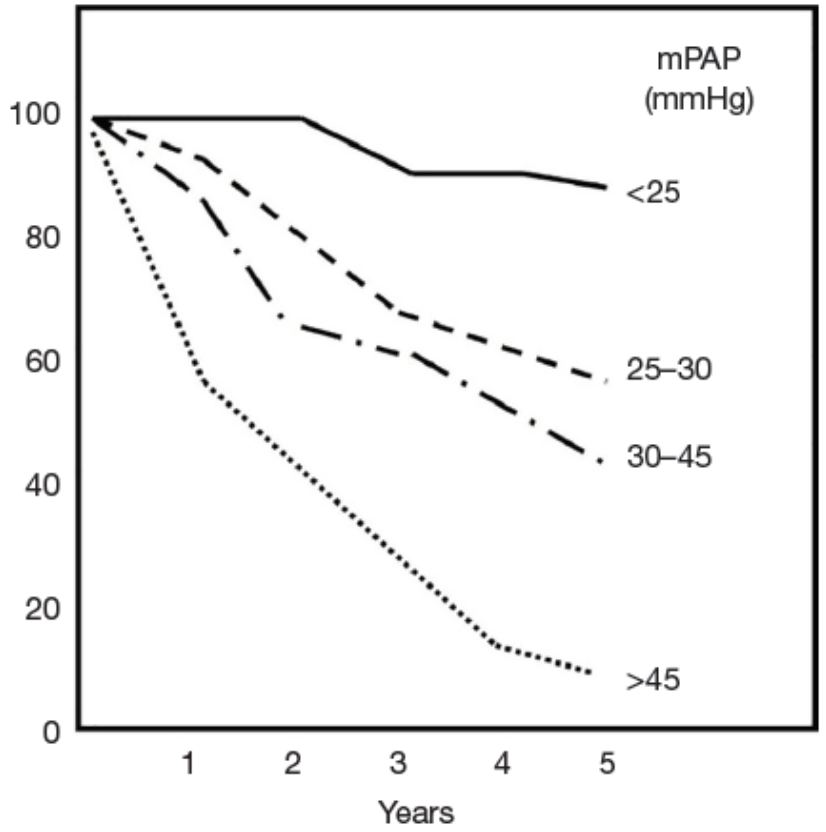
There was no difference in survival when Group 3 PH cohort was divided in tertiles and quartiles of mPAP.

Rose L, Journal of Heart and Lung Transplantation 11/2018

Effect of mPAP on survival in patients with COPD according to severity of mPAP increase

Note the marked negative effect on survival as PH becomes severe





Isabelle Opitz, Silvia Ulrich *J Thorac Dis. July,2018;10*

PAH targeted therapy in COPD

2 meta-analysis and recent small trials

- Improving of hemodynamics in severe 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**