Pulmonary hypertension in parenchymal lung diseases

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PH in parenchymal lung diseases

- COPD
- Idiopathic interstitial pneumonia
- Combined emphysema fibrosis
- Sarcoidosis
- Histiocytosis X
- LAM

Table 1 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

*5th WSPH Nice 2013. Main modifications to the previous Dana Point classification are in bold.
BMPR = bone morphogenic protein receptor type II; CAV1 = caveolin-1; ENG = endoglin; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension.

Simonneau JACC 2013

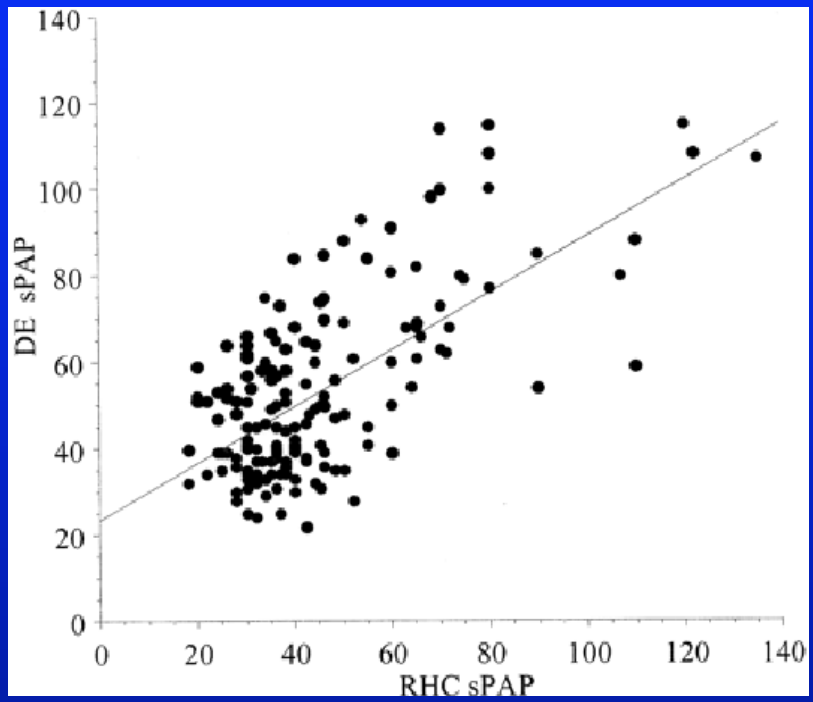
Definition of pulmonary hypertension (PH)

- mPAP ≥ 25 mmHg at rest

- The definition requires a precise measurement of mPAP= RHC

Evaluation of PAP in advanced pulmonary disease
Echodoppler or RHC?

- 374 pts, evaluated for LTx, COPD: 68%
- RHC and echo in all pts
- PH in 25% of pts
- Echo : PAPs measurable in 166 pts (44%)
- Good correlation between invasive PAPs and echo PAPs



Arcasoy et al, AJRCCM 2003

- Inaccuracy of echographic measurement (52% of the measurements are inaccurate)
- Echo for the diagnosis of PH (PAPs ≥45mmHg):
  - Sensitivity~ 85%
  - Specificity: 55%, PPV 52%
- Considerable overdiagnosis of PH with echo

Arcasoy et al, AJRCCM 2003

Mr TRA…, 60 year-old

- Diagnosis of COPD, under O_2 therapy since 2007
- Major dyspnea: 30 m on the flat, 1 flight of stairs
- Sat: 92% (3l/min), 84% RA
- FEV1: 2,26l, FEV1/FVC: 56%
- « Low » PAP on echocardiography
- RHC= PAPs: 50mmHg, PAPd:20 mmHg, PAPm:30 mmHg

Questions

- Can we confidently make the diagnosis of PH?
- Does this case represent an usual profile?

PH in COPD
Main characteristics

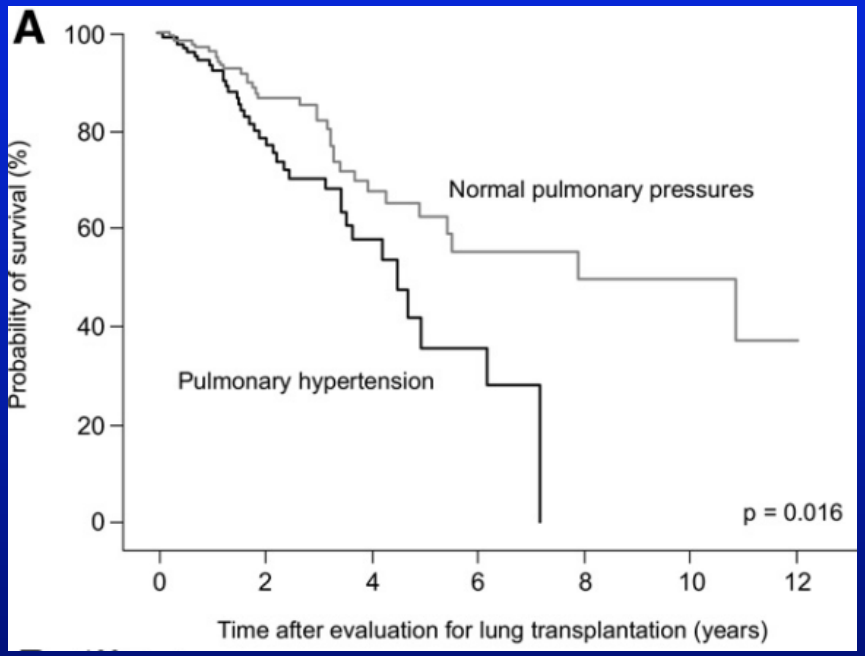
- PH is not constant
- Prevalence is variable (20-90%), depending on the severity of the airway obstruction
- mPAP is modestly elevated
  in general: 25 mmHg<mPAP<35 mmHg
- Conservation of cardiac output
- Marked elevation of mPAP during exacerbations followed by a return to baseline
- Statistical relation between mPAP and FEV_1/PaO_2

PH in COPD
Main characteristics

- On exercise: m PAP increases markedly in patients with resting PH
- 30 W exercise in pts with advanced COPD:
  - doubling of cardiac output
  - mPAP rises from 25-30 mmHg to 50-60 mmHg
  - PVR does not decrease during exercise

PH in COPD
Main characteristics

- Slowly evolutive (1mmHg/year)
- Predictive of hospitalisation for EA Kessler R , AJRCCM 2009
- Proven prognostic value Andersen K, JHLT 2012



Pulmonary hemodynamics in COPD

Oswald-Mamosser, Respiration 1991

- 151 pts, FEV_1 : 1200ml, mPAP: 17 $\pm$ 5 mmHg
- mPAP>20 mmHg in 20% of cases

SM Scharf AJRCCM 2002 (NETT study)

- 120 pts (FEV_1: 27% pred, DLCO: 26% pred)
- Results of RHC
  - mPAP: 26 $\pm$ 5 mmHg, CI: 2.9 l/min/m_2
  - PH in 90% of pts (>20mmHg)

PH in COPD

- Chronic hypoxia with vascular remodeling +++

- Acute hypoxia/pulmonary vasoconstriction
- Direct effect of smoking on the pulmonary vasculature
- Destruction of the capillary circulation in case of emphysema
- Increase of intrathoracic pressure
- Increase of alveolar pressure
- Hyperviscosity
- Comorbidities: thrombo embolic disease, OSA

PH in IPF
Main characteristics

- Inconstant
- Prevalence is variable depending on the stage of the disease
- mPAP is modestly elevated at rest
- Marked increase at exercise
- Statistical relation mPAP/PaO_2
- No relation found with lung volumes
- Proven prognostic impact

PH in IPF

- Weitzenblum Respiration 1983
  - 31 IPF pts, VC : 65% pred
  - studied by RHC at rest and exercise
  - mPAP : 21.7±7.8 mm Hg at rest
  - mPAP: 45.3±16.2 mm Hg at moderate exercise
  - mPAP>20 mm Hg : approximately 50% of pts

PH in IPF
Patients referred for LTx

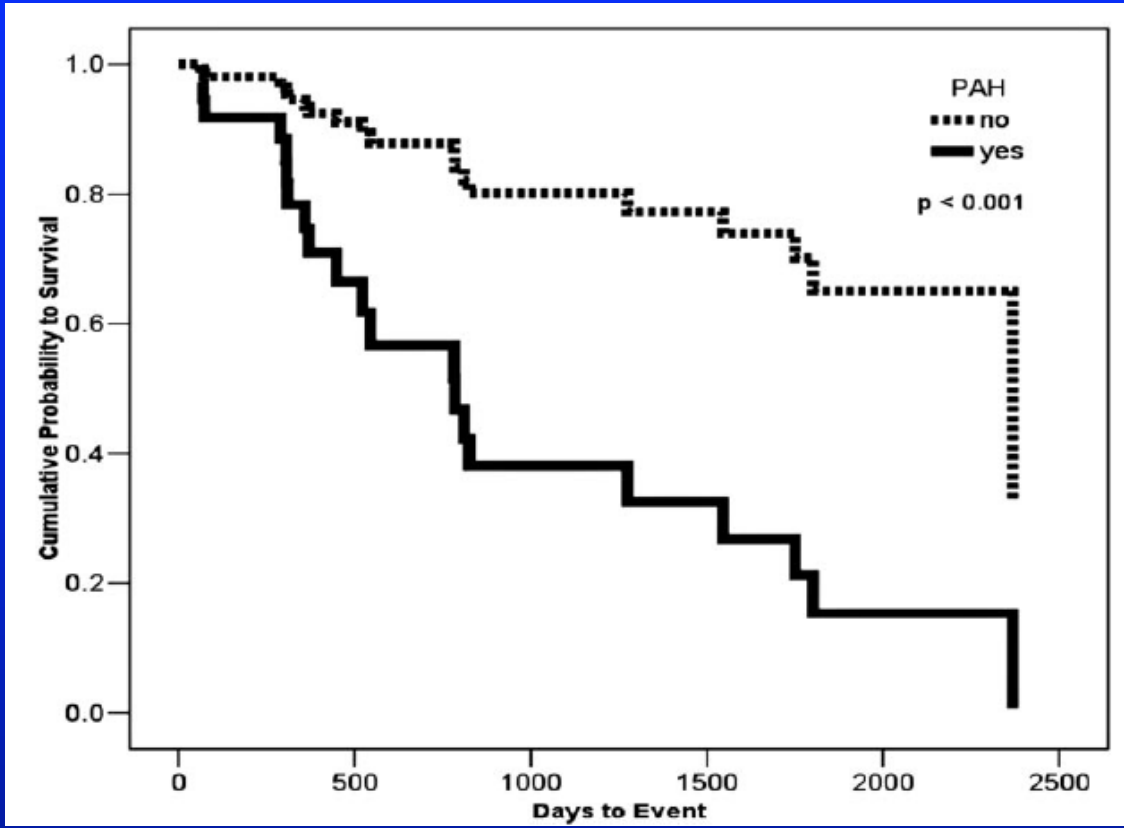
Personal data

- 48 IPF pts, VC: 39% pred,
- PAPm: 29.6±10.2 mmHg, PH in 61.7% of cases

Lettieri CJ, Chest 2006

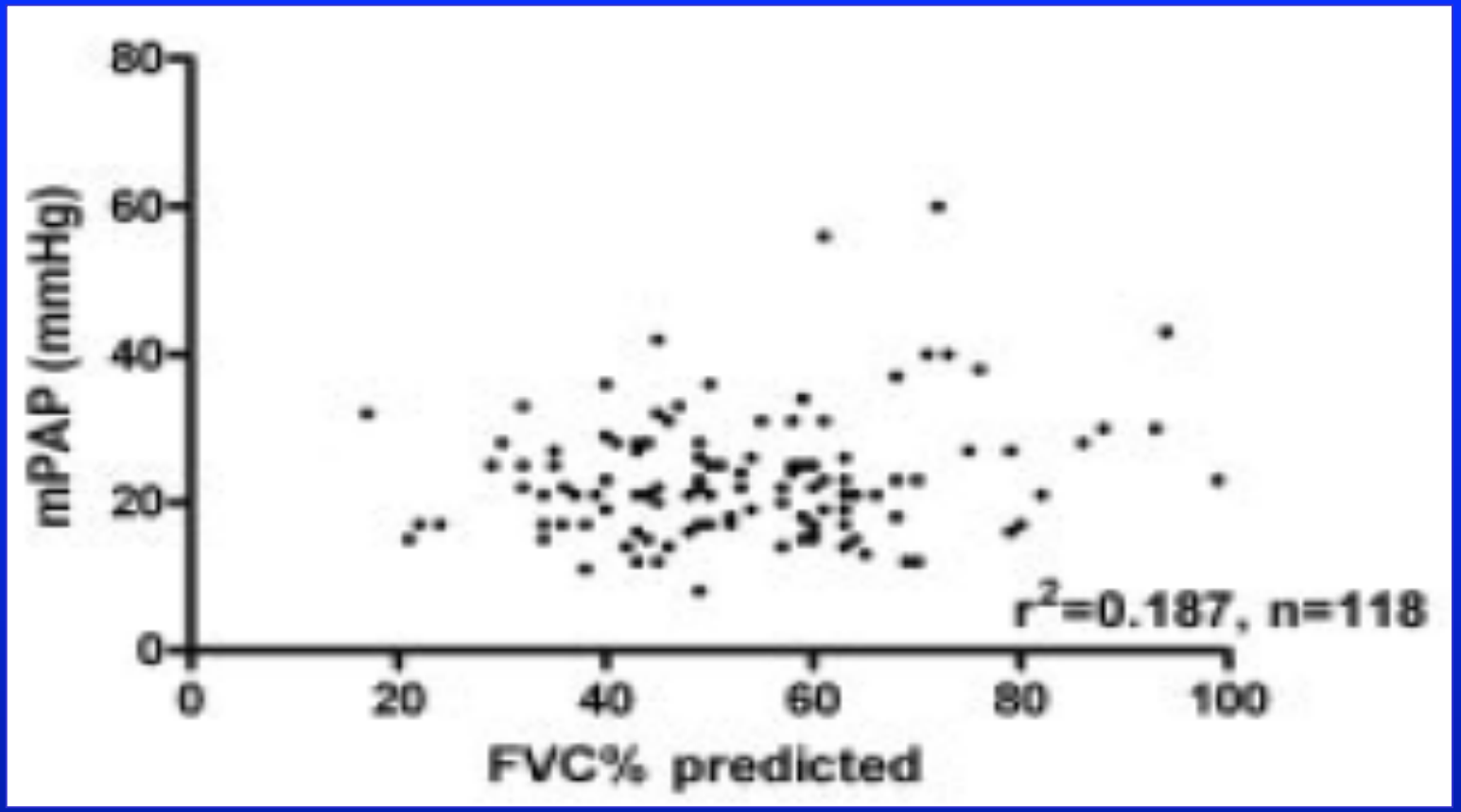
- 79 IPF pts, VC~50% pred
- mPAP:29.5±3.3 mmHg, PH in 32% of pts
- Relation between mPAP and DLCO/6MWT
- No relation between mPAP and lung volumes
- Clear impact of mPAP on survival

Pronostic impact of PH in IPF patients



1-yr mortality : 28% with PH, versus 5.5% without PH (p=0.002)

Lettieri CJ, *Chest* 2006;129:746



SD Nathan, Chest 2007

PH and risk of AE in IPF

- 55 IPF patients assessed for LTx (RHC)
- PAPm: 21±6.8 mmHg
- 27 experienced AE during follow-up
- PH at initial assessment= risk factor for AE (HR: 2.5, p= 0.026)

Judge EP et al. ERJ 2012; 40: 93

Pulmonary Hypertension in Chronic Lung Diseases

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Table 2 Management of PH in the Setting of Chronic Lung Disease

Underlying Lung Disease	mPAP <25 mm Hg at Rest	mPAP ≥25 and <35 mm Hg at Rest	mPAP ≥35 mm Hg at Rest*
COPD with FEV1 ≥60% of predicted IPF with FVC ≥70% of predicted CT: absence of or only very modest airway or parenchymal abnormalities	No PH No PAH treatment recommended	PH classification uncertain No data currently support treatment with PAH-approved drugs	PH classification uncertain: discrimination between PAH (group 1) with concomitant lung disease or PH caused by lung disease (group 3) Refer to a center with expertise in both PH and chronic lung disease
COPD with FEV1 <60% of predicted IPF with FVC <70% of predicted Combined pulmonary fibrosis and emphysema on CT	No PH No PAH treatment recommended	PH-COPD, PH-IPF, PH-CPFE No data currently support treatment with PAH-approved drugs	Severe PH-COPD, severe PH-IPF, severe PH-CPFE Refer to a center with expertise in both PH and chronic lung disease for individualized patient care because of poor prognosis; randomized controlled trials required

*Lower PA pressures may be clinically significant in COPD/DPLD patients with depressed cardiac index or right ventricular dysfunction.

CPFE = combined pulmonary fibrosis and emphysema; mPAP = mean pulmonary artery pressure; other abbreviations as in Table 1.

No treatment

Seeger W, JACC 2013

Bayer Terminates Phase II Study with Riociguat in Patients with Pulmonary Hypertension Associated with Idiopathic Interstitial Pneumonias

Communiqué de presse Mai 2016

Clinical observation

Some pts with COPD or IPF differ from the usual profile:

- much higher level of PAPm
- level mPAP sometimes disproportionate with the degree of bronchopulmonary involvement

COPD, 49 yrs, NYHA III

- FEV1: 70% pred, DLCO: 32% pred
- CT : centrolobular emphysema
- PaO_2: 58 mm Hg, PaCO2: 36 mm Hg (RA)
- SaO_2 (RA): from 91% to 83% on 6mWT
- mPAP: 39 mmHg, CI: 2.2 l/min/m^2 at rest

Disproportionate (severe) PH

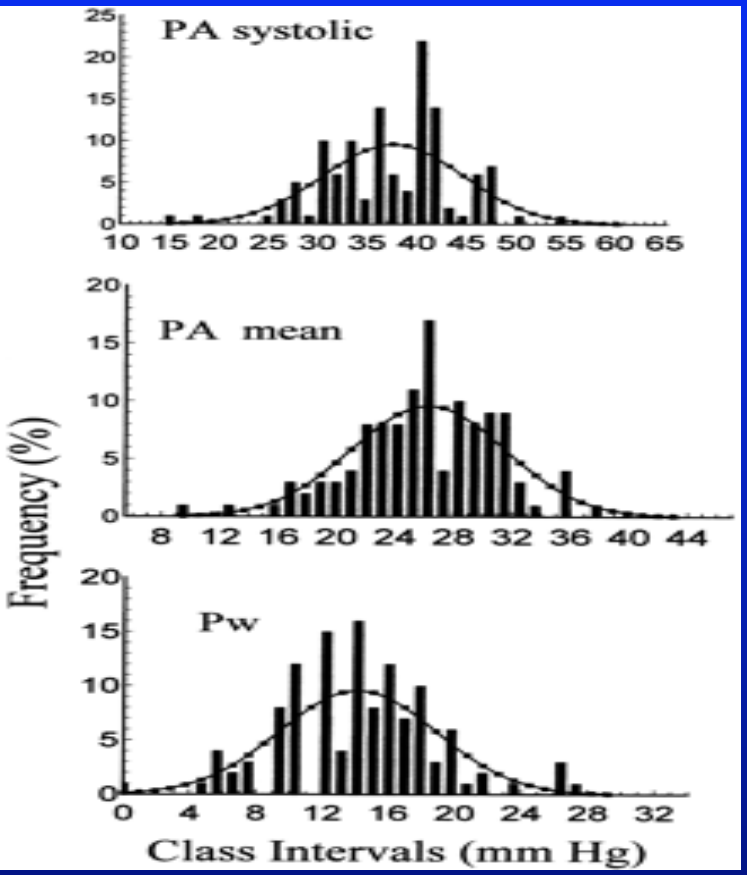
Simple clinical definition

- Association of parenchymal lung disease and PH, with a mPAP level above the usual values
- Proposed threshold: mPAP≥35 mmHg at rest
- Severe PH (Nice 2013) : PAPm≥35 mmHg or PAPm≥25 with CI<2l/min/m^2
- Should we consider the pulmonary hemodynamic profile at exercise?

COPD, 71 yrs, NHYA III, O_2 for 3 yrs

- FEV1: 66% pred, DLCO: 32% pred
- PaO_2: 51 mmHg, $PaCO_2$: 34 mmHg (RA)
- SaO_2: from 87% to 64% on 6MWT
- mPAP:32 mmg Hg at rest
- mPAP: 55 mm Hg for a 10W exercise without rise in cardiac output
- Specific TT ?

Severe PH-COPD



- 120 pts from the NETT
- 20 mmHg<PAPm <35 mmHg: 86%
- PAPm>35mmHg:5%

SM Scharf AJRCCM 2002; 166:314

215 COPD patients :
169 males/46 females

123 patients evaluated
before Lung Volume Reduction Surgery

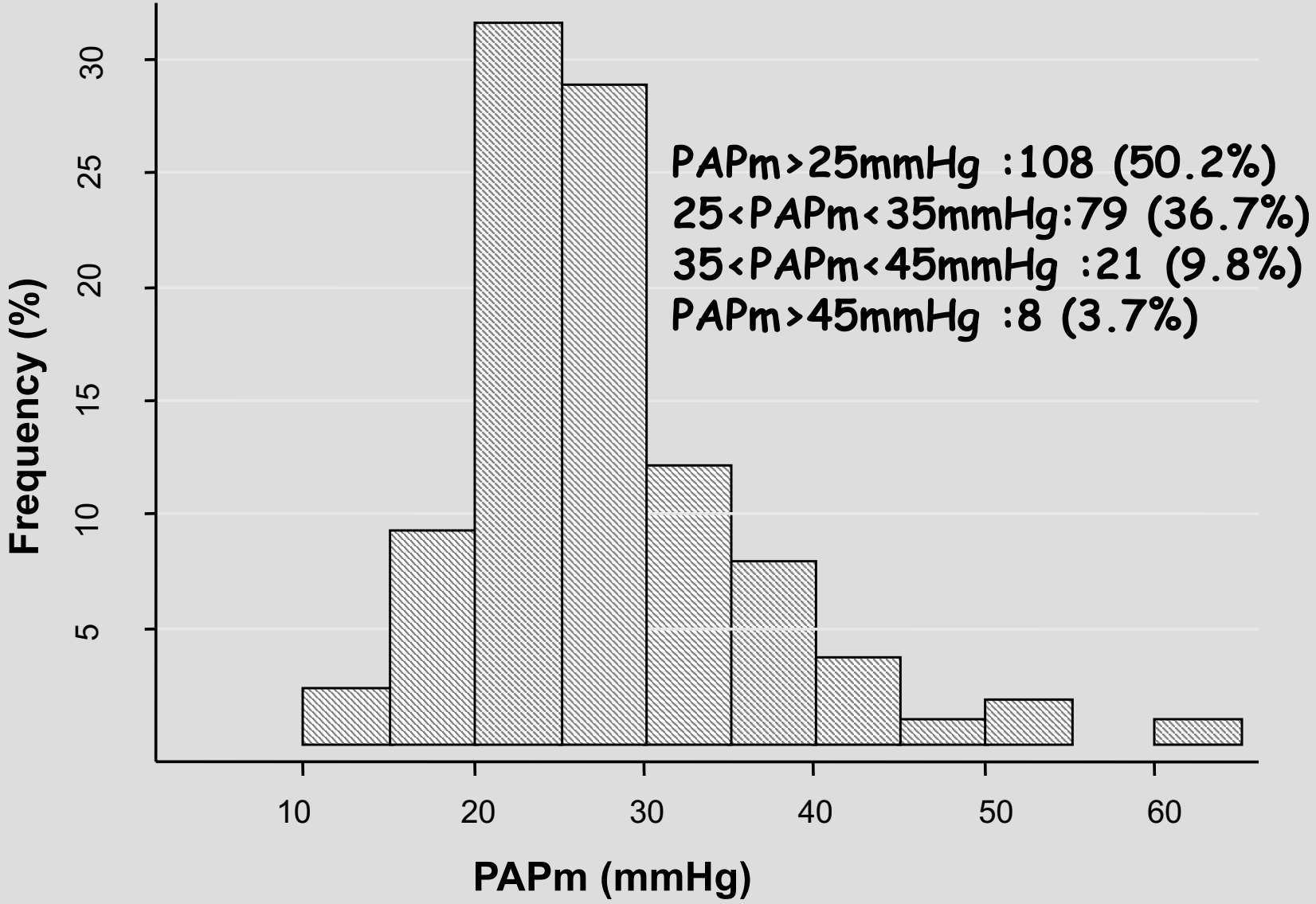
FEV_1 (% pred) : 27.9 ± 12.9
mPAP: 25.4 ± 7.6
PaO_2 : 66.2 ± 12.5
$PaCO_2$: 40.6 ± 6.6

92 patients evaluated
before Lung Transplantation

FEV_1 (% pred) : 18.5 ± 9.5
mPAP: 27.8 ± 7.3
PaO_2 : 55.4 ± 12.2
$PaCO_2$: 50.1 ± 10.0

Thabut, Chest 2005; 127: 1531

Distribution of PAPm



Thabut, Chest 2005; 127: 1531

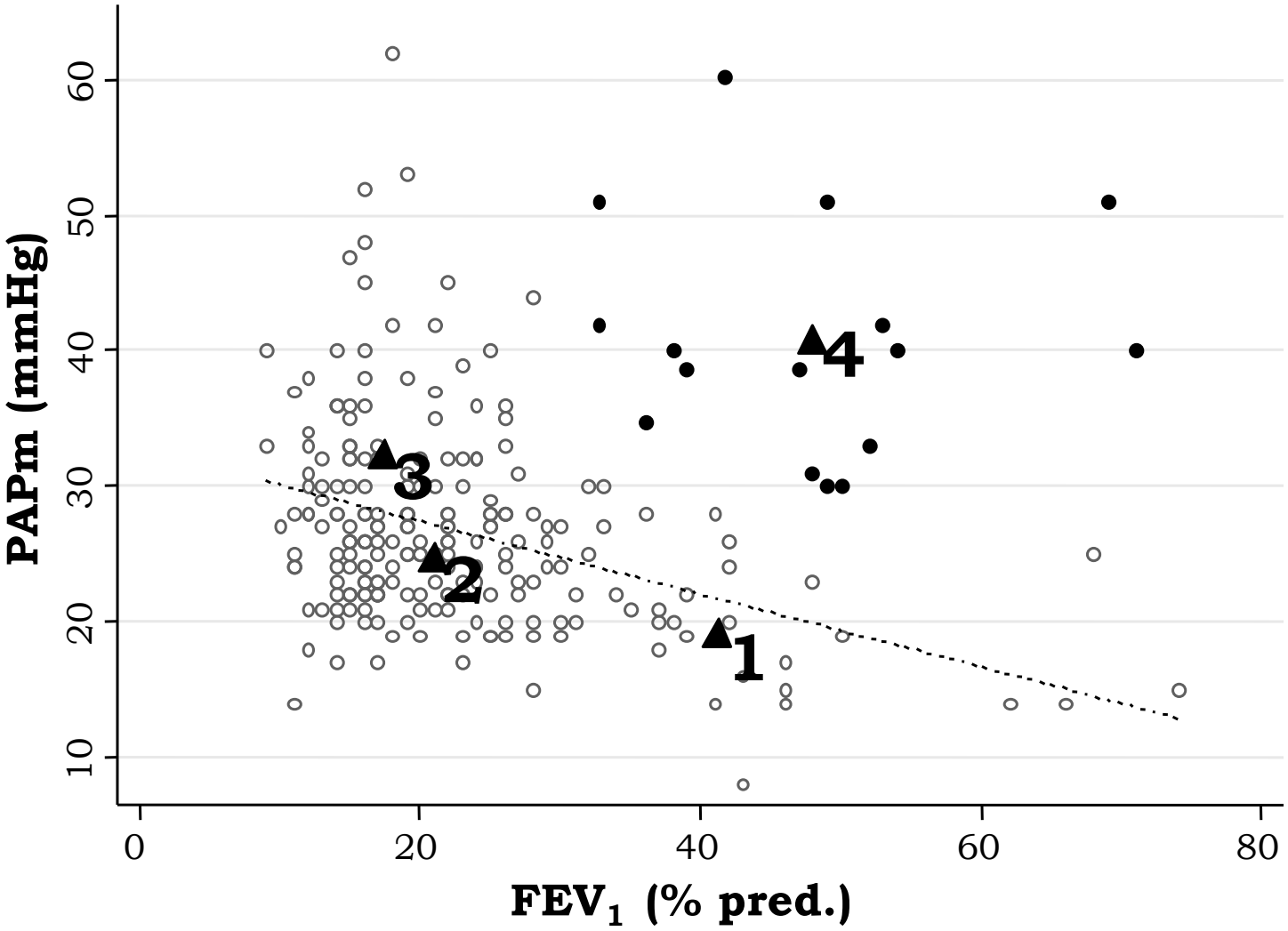
Cluster analysis

According to hemodynamic, spirometric measurements and arterial blood gases, 4 groups were determined by cluster analysis :

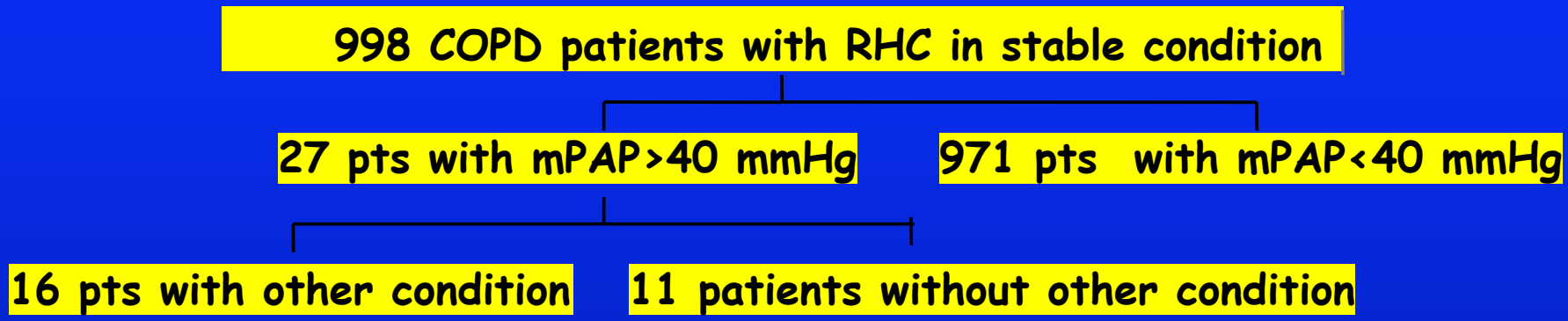
- Group 1 (n=30): FEV1: 41.5%, mPAP: 19mmHg, PaO2: 80mmHg
  All Patients assessed before LVRS
- Group 2 (n=106): FEV1: 20.3%, mPAP: 24.5mmHg, PaO2: 65mmHg
  Patients assessed for LVRS (66%) or before lung transplantation (33%)
- Group 3 (n=63): FEV1 : 17%, mPAP: 31.3mmHg PaO2:48 mmHg
  All patients assessed before lung transplantation
- Group 4 (n=16) FEV1: 48.5%, mPAP: 40 mmHg, PaO2: 46.2 mmHg, PaCO2: 39 mmHg
  Patients assessed either before LVRS or lung transplantation

Thabut, Chest 2005; 127: 1531

Cluster analysis



Severe PH in COPD



Chaouat AJRCCM 2005; 172:189

Severe PH in COPD

The Strasbourg experience

Characteristics of the 11 pts

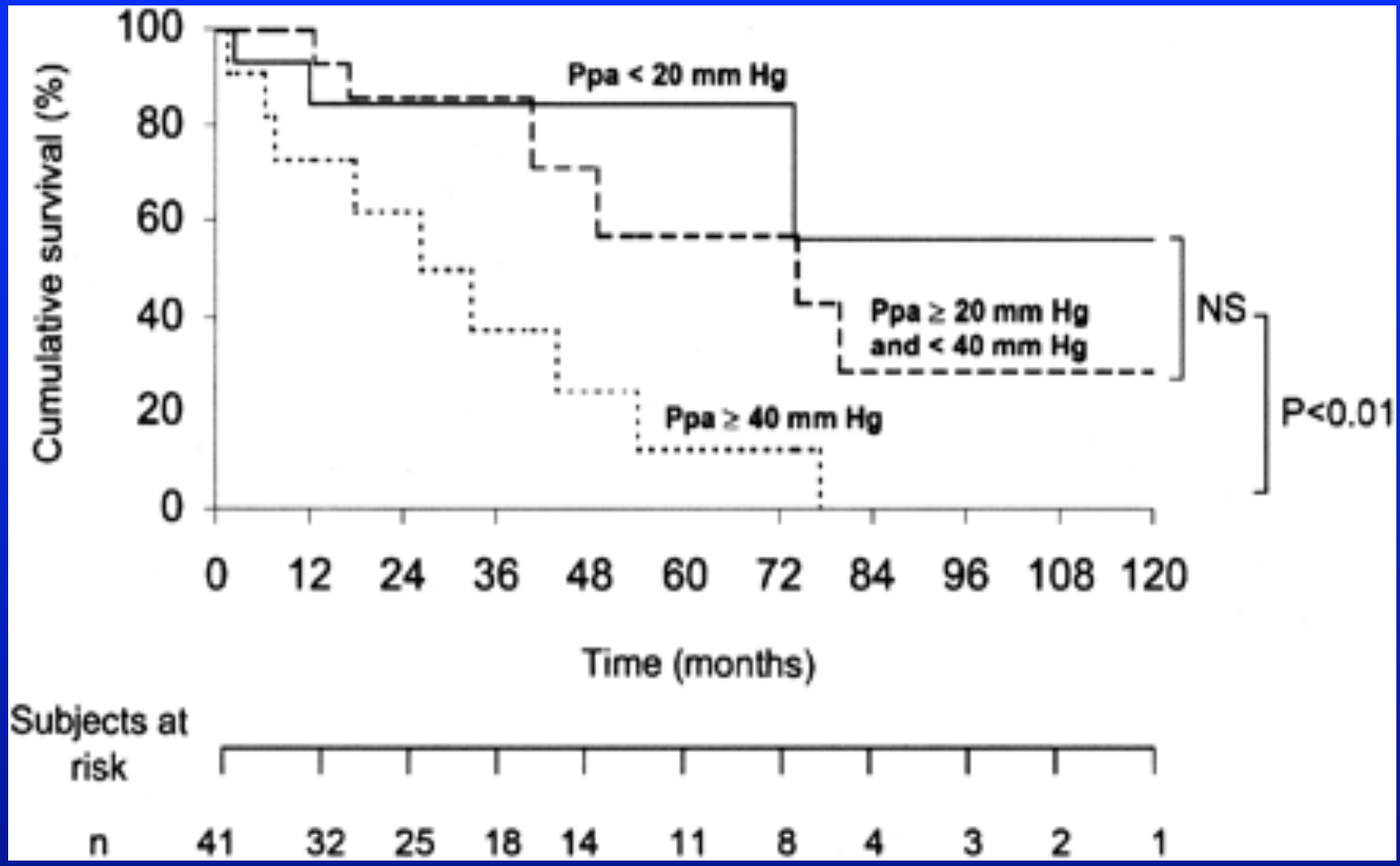
- FEV1: 50% pred (44-57), dyspnea: 4 (3-5)
- PaO_2: 46 mmHg (35-62), $PaCO_2$: 32 mmHg (26-37)
- mPAP: 48 mmHg (42-54), CI: 2.25 l/min/m^2 (1.23-2.48)

Significant difference with a control group of COPD pts

- PaO2, PaCO2, DLCO
- dyspnea grade
- FEV1
- Survival

A Chaouat AJRCCM 2005; 172:189

Severe PH-COPD
The Strasbourg experience



Chaouat AJRCCM 2005; 172:189

Severe PH in COPD

- Some COPD pts present with a predominant pulmonary vascular disease and a probable circulatory limitation
- Particular profile (clinical presentation, prognosis, PFT, hemodynamics, blood gas results)
- Potential candidates for specific treatments
- Genetic susceptibility?
- Fortuitous association COPD/PAH or direct role of COPD in the genesis of PH?

Detection of severe PH-COPD

- When RHC is done systematically
  (LTx, LVRS, routine)
- Systematic echocardiographic assessment
  - if PVR $\geq$ 3.5 m/s : RHC
  - if PVR < 3.5 m/s or non interpretable : RHC in case of discrepancy between severity of the COPD and:
    - Dyspnea
    - Desaturation on exercise
    - Hypoxemia
    - DLCO

H Mal Curr Opin Pulm Med 2007

Characteristics of Severe Pulmonary Hypertension Associated with COPD in a French Multicenter Study

G.Dauriat [1], V.Cottin[2] , M.Reynaud-gaubert[3] , O.Sitbon[4] , D.Montani[4] , B.lamia[5] , M.Canuet[6], I.Frachon[7] , C.Pison[8] , A.Bourdin[9] , E.bergot[10] , A.chaouat[11] ,C.Viacroze[12] , A.Kanaragatnam [13] , Y.Costa[13] , G.Thabut[14], H.Mal[1]

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Introduction

Pulmonary hypertension (PH) is commonly observed in chronic obstructive pulmonary disease (COPD) with a mean pulmonary artery pressure (mPAP) usually below 35 mmHg.

A small proportion of COPD patients present with severe PH, defined by a mPAP above or egal 35 mmHg.

The prevalence of severe PH associated with COPD is estimated to be between 1 and 5%. Little is known on the characteristics of COPD patients with severe PH.

Objective

The aim of the study is to provide a description of this subgroup of patients.

Methods

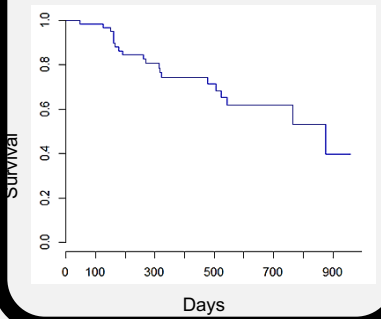
We prospectively included and followed in a national registry all patients with COPD and mPAP ≥ 35 mmHg measured by right heart catheterization.

We excluded the files of patients with pulmonary artery wedge pressure (PAWP) above 16 mmHg.
From January 2013 to September 2015, 68 patients were included in this registry.

Patients characteristics

Age (years)	66 +/- 8
Female (%)	22
Smoking habbit	
Current smoker (%)	13
Ex smoker (%)	82
Pack/year	52 +/- 27

Survival rate



Functional characteristics

FEV1 (% pred)	48 +/- 18
FEV1 post BD(% pred)	53 +/-20
FEV1/FVC (%)	47
TLC (% pred)	111 +/- 21
TLCO (% pred)	25 +/- 11
KCO (% tpred)	34 +/- 18
PaO_2 room air (mmHg)	53 +/- 13
$PaCO_2$ room air (mmHg)	38 +/- 8
Gold 1 (%)	9
Gold 2 (%)	38
Gold 3 (%)	34
Gold 4 (%)	19
COPD assessment test (CAT)	18 +/- 7
BODE index	5.1 +/- 2.2

RAP (mmHg)	9 +/- 5
PAPm (mmHg)	43 +/- 8
PAWP (mmHg)	12 +/- 4
CO (l/min)	5.5 +/- 1,6
CI (l/min)	3.1 +/- 0.9
PVR (WU)	6 +/- 2.8

Results

We analyzed the characteristics of the first 68 patients of this cohort collected in 12 french centers.

There were 9 prevalent cases and 59 incident cases.

The diagnosis of PH was obtained on the average 4 years after the diagnosis of COPD.

PFT showed a moderate obstructive pattern with a mean FEV1 at 53±20% of predicted and a low TLCO at 25±11% of predicted.

Almost all patients had emphysema lesions on CT scan.

All patients were hypoxemic on room air without hypercapnia.

Hemodynamic profile showed severe pulmonary vascular disease with a mPAP at 43+8 mmHg with a low PAWP =12+ 4 mmHg.

Among the 68 patients, 22 had comorbid conditions that may have affected the level of PAP (12 sleep apnea syndrom, 9 venous thrombo-embolic disease, 1 left ventricular dysfonction).

Out of the 68 pts, 51 patients received antiproliferative therapy. .

The median survival of this cohort was 877 days after the diagnosis of severe PH.

Conclusions

The results of this prospective cohort show that this subgroup of COPD patients is characterized by moderate level of airway obstruction, marked hypoxemia, low TLCO and high level of mPAP.

The patients presenting with this entity have a poor prognosis, the mortality being higher than expected in COPD patients with this level of airway obstruction.

Severe PH in pts with advanced IPF, evaluated for LTx

AF Shorr, ERJ 2007

- 3457 IPF pts listed in the UNOS registry
- 2525 had RHC
- 46% had PH
- 9 % had severe PH (mPAP>40 mmHg)

Beaujon Hospital, personal data

- 48 IPF pts listed for LTx
- 25 mmHg<mPAP<35 mmHg: 46.8%
- Severe PH~15% of pts
  - 35 mmHg<mPAP<45 mmHg: 8.5%
  - mPAP>45 mmHg: 6.4%

Severe PH in IPF

- Subgroup of pts with severe PH
- Prevalence is not precisely known
- Impact on prognosis?
- Implication in the acute exacerbation?
- Benefit of a specific treatment?

Management of severe group 3 PH

Table 2 Management of PH in the Setting of Chronic Lung Disease

Underlying Lung Disease	mPAP <25 mm Hg at Rest	mPAP ≥25 and <35 mm Hg at Rest	mPAP ≥35 mm Hg at Rest*
COPD with FEV1 ≥60% of predicted IPF with FVC ≥70% of predicted CT: absence of or only very modest airway or parenchymal abnormalities	No PH No PAH treatment recommended	PH classification uncertain No data currently support treatment with PAH-approved drugs	PH classification uncertain: discrimination between PAH (group 1) with concomitant lung disease or PH caused by lung disease (group 3) Refer to a center with expertise in both PH and chronic lung disease
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*Lower PA pressures may be clinically significant in COPD/DPLD patients with depressed cardiac index or right ventricular dysfunction.

CPFE = combined pulmonary fibrosis and emphysema; mPAP = mean pulmonary artery pressure; other abbreviations as in Table 1.

Seeger W, JACC 2013

Specific TT of severe PH/IPF and COPD

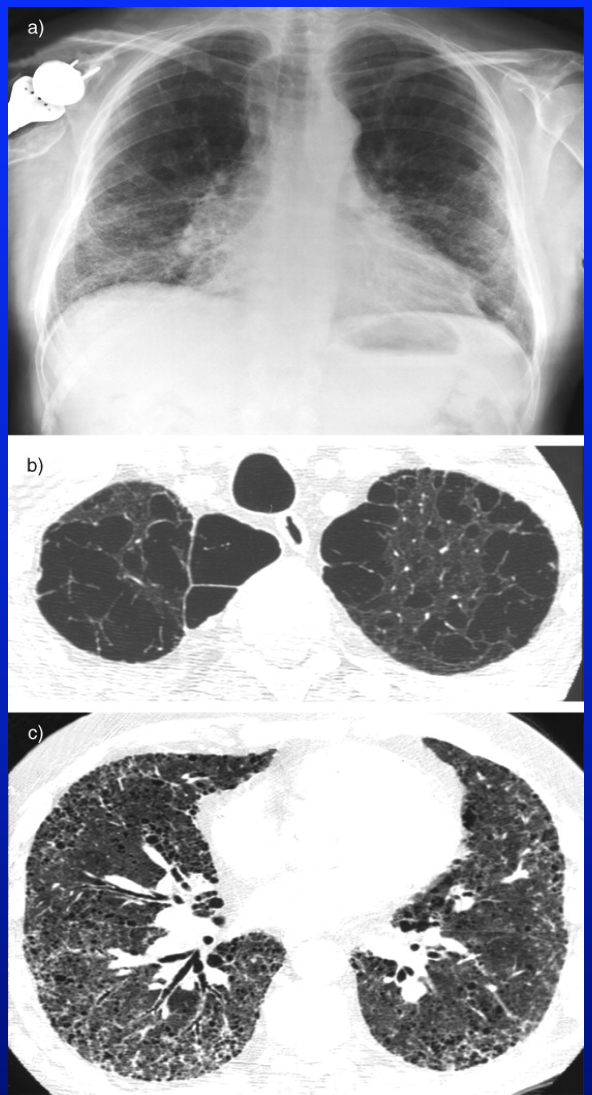
- Bosentan or sildenafil
- Encouraging results
- Short series
  - Duration
  - Number of pts included
- Larger series are required

B Madden Vascular Pharmacol 2006
S Alp, Pulm Pharmacol&Therap, 2005
Wilkens , AJRCCM 2005, 2, A195
Sulica AJRCCM 2005, 2, A 204
Collard, Chest 2007
Vitulo P, JHLT 2016

Combined fibrosis and emphysema

- 61 pts, PH (echo) present in:
  - 47 % at diagnosis
  - 55% during follow-up
- 40 pts with RHC:

  PAPm: 40 mmHg, ≥35 mmHg: 68%
- PH: critical determinant of prognosis



Cottin et al. Eur Resp J 2005
Cottin et al. Eur Resp J 2009

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Seeger W, JACC 2013

PH in sarcoidosis
Main characteristics

- PH is a rare complication of sarcoidosis
- Not uncommon in advanced disease
- Frequent in pts listed for LTx
- When present, PH is often severe

Shorr AF, Eur Resp J 2005

- 363 pts listed for LTx
- PH: 74% of pts
- mPAP≥40mmHg: n=131 (36%)

PH in sarcoidosis

Main characteristics

- Clear prognostic impact at least in pts on waiting list for LTx

  Arcasoy Chest 2001, Shorr Chest 2003

- The majority of cases are observed in pts with stage IV
  - 15/22 cases (68%) Nunes Thorax 2005
  - 23/38 cases (60%) Sulica Chest 2005
- No relation between hemodynamics and lung volumes in stage IV
- Cases are also observed in stage 0, I, II, III

PH in sarcoidosis

- Mechanism:
  - Lung fibrosis
  - Vasculopathy (granuloma, VOD)
  - Compression by adenopathies
  - Mediastinal fibrosis
  - Pulmonary embolism
- Small-size open studies have reported encouraging results with bosentan, sildenafil, epoprostenol

PH in histiocytosis X

- PH is uncommon in pulmonary Langerhans' cell histiocytosis (PLCH)
- In advanced forms of the disease
  - PH is very frequent
  - When present, PH is most often severe

PH in histiocytosis X

The A. Béclère experience

- 21 pts with advanced PLCH referred for LTx
- All of them had severe PH
- mPAP: 59 ± 4 mm Hg (range 36-74 mmHg)
- No correlation between mPAP and PFT
- Pathological findings (n = 12) : intrinsic proliferative vasculopathy involving both small to medium-sized arteries and septal veins. VOD in 1/3 of pts

Fartoukh M. et al. AJRCCM 2000

Histiocytosis X

- 39 pts who had LTx for PLCH at 7 centers in France
- PH (PAPm>25 mmHg): 92% of cases
- PAPm≥35 mmHg: 72.5% of cases

G Dauriat et al, Transplantation 2006

LAM

Lung Transplantation for Lymphangioleiomyomatosis: The French Experience

Martine Reynaud-Gaubert,[1,10] Jean-François Mornex,[2] Hervé Mal,[3] Michèle Treilhaud,[4] Claire Dromer,[5] Sébastien Quétant,[6] François Leroy-Ladurie,[7] Romain Guillemain,[8] François Philit,[2] Gaëlle Dauriat,[3] Dominique Grenet,[9] and Marc Stern[9]

Transplantation 2008

44 pts who underwent LTx in France
PH in 45% of pts
Mean PAP: 33±8.3 mmHg

Pulmonary hypertension in lymphangioleiomyomatosis: characteristics in 20 patients

Vincent Cottin, Sergio Harari, Marc Humbert, Hervé Mal, Peter Dorfmüller, Xavier Jaïs, Martine Reynaud-Gaubert, Grégoire Prevot, Romain Lazor, Camille Taillé, Jacques Lacronique, Sabrina Zeghmar, Gérald Simonneau, Jean-François Cordier and the Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P)

Eur Respir J 2012

20 LAM pts with PH
Mean PAP: 32±6 mmHg, CI: 3.5±1.1L/min/m^2
Mean PAP>35 mmHg: 20%

Eur Respir J 2012; 40: 630–640
DOI: 10.1183/09031936.00093111

Conclusions

- Renewal of interest on the pulmonary circulation in parenchymal diseases
- Better description of the hemodynamic profile of the pts
- Identification of subgroups of pts with a predominant vascular disease which could be a target for a specific treatment
- The so called « vasodilator » treatment is not recommended at the present time

Pulmonary Hypertension in Chronic Lung Diseases

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Seeger W, JACC 2013