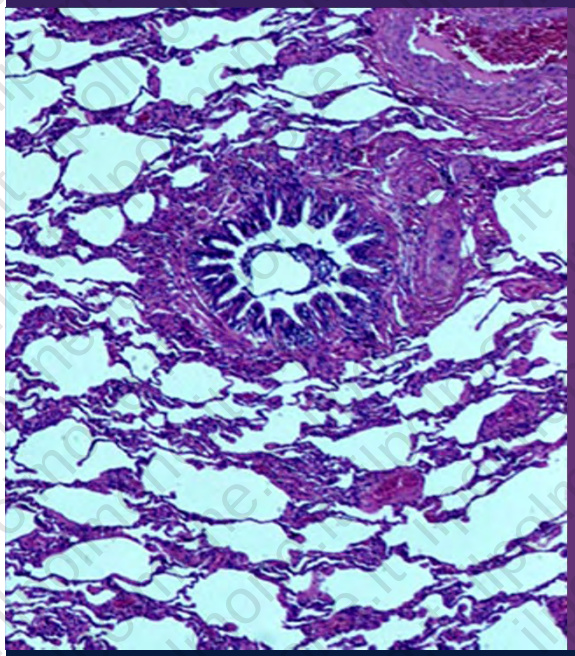

La Classificazione di Dana Point. Cosa cambia?

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U.O. di Pneumologia e UTIR
Servizio di Emodinamica e
Fisiopatologia Respiratoria
Ospedale San Giuseppe – Milano

19 Novembre 2010

Current Definition of PH

- PAPmean >25 mm Hg at rest
- PAPmean >30 mm Hg at exercise
- PAOP ≤15 mm Hg

2nd and 3rd PAH Symposium, Evian 1998 and Venice 2003

Limits of Current Definition

- 25 mm Hg at rest does not reflect the upper limit of normal
- 30 mm Hg during exercise is an arbitrary value

  not supported by published data

  healthy individuals can reach much higher values

Normal PA Pressure at Rest

- Normal PAPm at rest: 14 ± 3.3 mmHg,
- Upper limit of normal (mean ± 2 SD): 20.6 mmHg

Data provided by G Kovacs, H Olschewski

Proposal for New PH Definition

	PAPmean (mmHg) [1]
Upper limits of normal	20
Borderline PH	21-24
Manifest PH	≥ 25

New !

[1] Obtained during right heart catheterization

Hemodyamic definitions of pulmonary hypertension

Definition	Characteristics	Clinical group(s)[b]
Pulmonary hypertension (PH)	Mean PAP ≥25 mmHg	All
Pre-capillary PH	Mean PAP ≥25 mmHg PWP ≤15 mmHg CO normal or reduced[c]	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	Mean PAP ≥25 mmHg PWP >15 mmHg CO normal or reduced[c]	2. PH due to left heart disease
Passive	TPG ≤12 mmHg	
Reactive (out of proportion)	TPG >12 mmHg	

Geneva Diagnostic Classification (1st WS, 1973)

- Primary pulmonary hypertension (PPH)*
- Secondary pulmonary hypertension

* *Several subsets of patients with unexplained PH and associated conditions are included in this group (PPH):*

  - hepatic cirrhosis
  - primary Raynaud's phenomenon
  - diet pills
  - collagen disease without other systemic manifestations

Evian Meeting (2nd WS, 1998)
Venice Meeting (3rd WS, 2003)

A new classification was proposed:

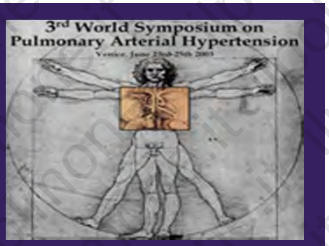
- *To individualize different categories of PH sharing*
  - similar pathophysiological mechanism
  - similar histological findings
  - similar clinical presentation
  - similar management

Rationale for a Clinical Classification of Pulmonary Hypertension

A clinical classification of various forms of pulmonary hypertension can be useful:

- in communicating about individual patients
- in standardizing diagnosis and treatment
- in conducting trials with homogeneous groups of patients
- in analyzing novel pathobiological abnormalities in well-characterized patient populations

Pulmonary Hypertension Diagnostic Classification (2003)



1. Pulmonary Arterial Hypertension

- Idiopathic PAH
- Familial PAH
- Associated with:
  - connective tissue diseases
  - congenital systemic to pulmonary shunts
  - portal hypertension
  - HIV infection
  - drugs and toxins
  - Others: thyroid, glycogen storage, or Gaucher disease; HHT; MPD; hemoglobinopathies; splenectomy
- PAH with venous or capillary involvement (PVOD, PCH)
- PPHN

2. PH with Left Heart Disease

- Atrial or ventricular
- Valvular

3. PH with Lung Diseases / Hypoxemia

- COPD
- Interstitial lung diseases
- Sleep-disordered breathing
- Chronic exposure to high altitude
- Developmental abnormalities

4. PH Due to Chronic Thrombotic and / or Embolic Disease

- TE obstruction of proximal PA
- TE obstruction of distal PA
- Non-thrombotic pulmonary embolism (tumor, parasitis, foreign material)

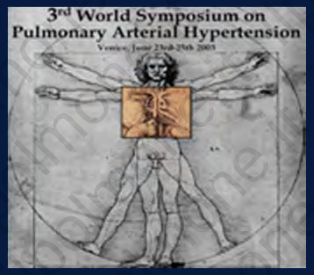
5. Miscellaneous

- Sarcoidosis, histiocytosis X, LAM, compression of PV (tumor adenopathy, fibrosing mediastinitis)

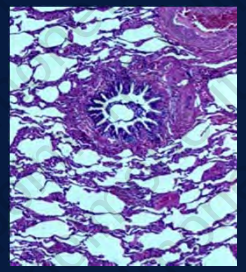
Over the last 5 years, FDA and EMEA have widely used the VENICE classification for the labeling of new approved drugs.

Questionnaire on the Clinical Classification for Pulmonary Hypertension

42 ANSWERS

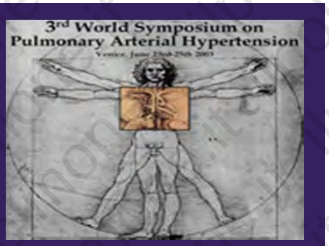


1. *The VENICE classification (2003) is:*
   - a) confusing and not useful 0%
   - b) clear and useful 33%
   - c) imperfect needing changes 67%



2. *During the Dana Point 4TH WS, we need to:*
   - a) maintain the classification unchanged 23%
   - b) propose mild modifications 63%
   - c) propose major modifications 14%
   - d) totally abandon the VENICE classification 0%

Pulmonary Hypertension Diagnostic Classification (2003)



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Critical Issue

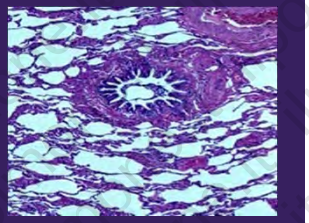
- Detection of mutations in IPAH patients (25%) means that family members have increased risk for PAH
- In terms of genetic mutation, the distinction between idiopathic and familial PAH is arbitrary.

Proposed Classification - 2008

Heritable pulmonary arterial hypertension (HPAH)

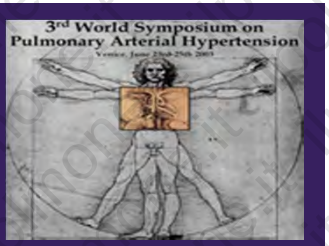
- Includes PAH patients with a family history (with or without identified mutations) or IPAH patients with mutations
- Does not mandate genetic tests
- Permits identification of risk for family members

Proposed Classification – 2008



1. Pulmonary arterial hypertension (PAH)
   - 1.1 Isolated pulmonary vascular disease
     - 1.1.1 Idiopathic (IPAH)
     - 1.1.2 Heritable (HPAH)
       - 1.1.2.1 BMPR2 mutations (familial 70% or isolated 11-40%)
       - 1.1.2.2 ALK1 or endoglin mutations (with or without HHT)
       - 1.1.2.3 Undefined
     - 1.1.3 Drugs and toxins

Pulmonary Hypertension Diagnostic Classification (2003)



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5. Miscellaneous

- Sarcoidosis, histiocytosis X, LAM, compression of PV (tumor adenopathy, fibrosing mediastinitis)

Schistosomiasis Prevalence

- 200 million people infected
- 120 million – symptomatic disease
- 4 to 8% develop periportal fibrosis
- 6.3 to 13.5% of patients with hepatosplenic disease may develop PH (current definition)
- *65 patients with hepatosplenic disease:*
  - *18.1% echo prevalence of PH*
  - *6.1% PAH*

Ross, 2002
Figueiredo, 2003
ATS - Dias, 2008

Schistosomiasis

Pathogenesis

- Embolic obstruction
- Egg impactation may act as a trigger:
  - oxidative stress
  - inflammation
  - endothelial dysfunction
- Portal hypertension

Schistosomiasis

- Same clinical presentation as IPAH
- Plexiform lesions observed in pathological studies
- Proposed reclassification as a sub-category of PAH

Chronic Hemolytic Anemias

(sickle cell disease, thalassemia, PNH,spherocytosis, stomatocytosis, microangiopathic hemolytic anemia)

- 20%-40% prevalence in sickle cell and thalassemia[1-3]
- PAH with plexiform lesions on pathological studies
- NO consumption

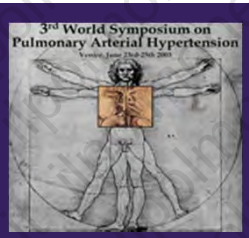
1. Simmons et al. *Arch Intern Med.* 1988;148:1526.
2. Sutton et al. *Am J Cardiol.* 1994;74:626.
3. Castro. *Hematol Oncol Clin North Am.* 1996;10:1289.
4. Reiter et al. Nat Med. 2002; 1383:89
5. Gladwin et al Nat Med 2003; 496-500.

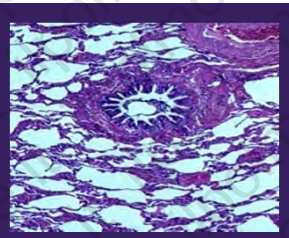
Proposal for an Updated Classification (2008)

1. Pulmonary Arterial Hypertension

- Idiopathic PAH
- Heritable (BMPR2, ALK1, endoglin, unknown)
- Associated with drugs and toxins
- Associated with other diseases:
  - connective tissue diseases*‡
  - HIV infection
  - portal hypertension*
  - systemic to pulmonary shunts
  - schistosomiasis†
  - chronic hemolytic anemias*
- PPHN

*These subcategories share a high prevalence of left heart disease
†Most frequently related to portal hypertension
‡Contribution of coexistent lung fibrosis should be considered





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- Idiopathic PAH
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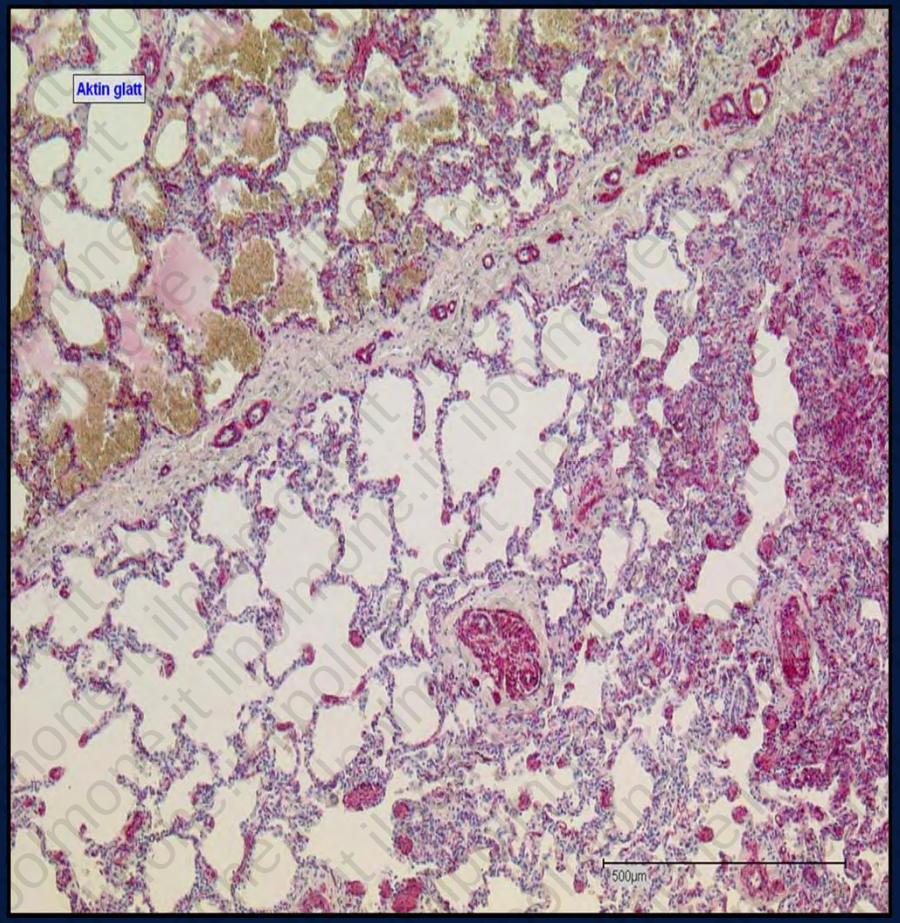
  - BMPR2
  - ALK1, endoglin (with or without HHT)
  - unknown
- Drugs and toxins induced
- Associated with:
  - connective tissue diseases
  - systemic to pulmonary shunts
  - portal hypertension
  - HIV infection
  - schistosomiasis
  - chronic hemolytic anemia

1' Pulmonary veno occlusive disease and pulmonary capillary hemangiomatosis

Proposal:
To Keep PVOD and PCH in a Same Subgroup

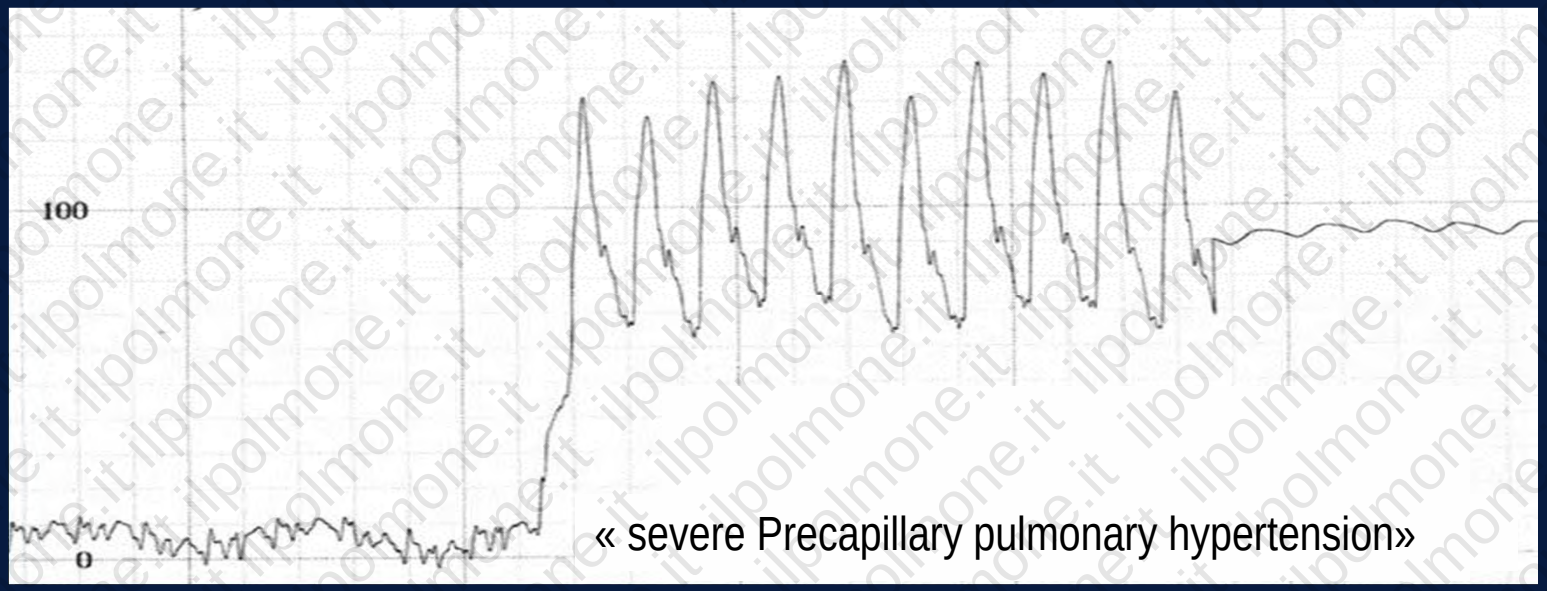


- A recent clinicopathological study from 35 patients diagnosed as either PVOD or PCH suggest these 2 entities are frequently associated (80%).
- These authors consider that PCH could be an angioproliferative process frequently associated with PVOD.
- In addition, PVOD and PCH are clinically indistinguishable.

S Lantuejoul et al. Am J Surg Pathol 2006

Proposal: To Place PVOD / PCH in a Separate Group Distinct from PAH

- They present some similarities with PAH
- PVOD and PCH share with PAH same risk factors: scleroderma, familial cases, BMPR2 mutation, HIV infection, anorexigens intake



« severe Precapillary pulmonary hypertension»

However, phenotype is quite different!!

Proposal: To Place PVOD / PCH in a Separate Group Distinct from PAH

Clinical Presentation Is Quite Different from PAH

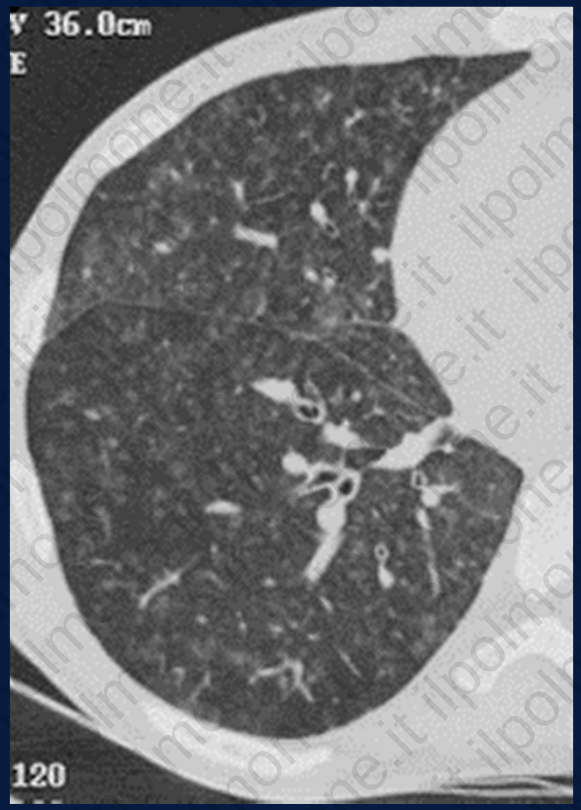
- Clinically: crackles, clubbing
- Chest X ray: kerley B lines
- Lung function test: normal lung volume, DLCO significantly reduced (< 55%), lower resting pO2, lower nadir SpO2 during 6MWT
- BAL: presence of iron-laden macrophages

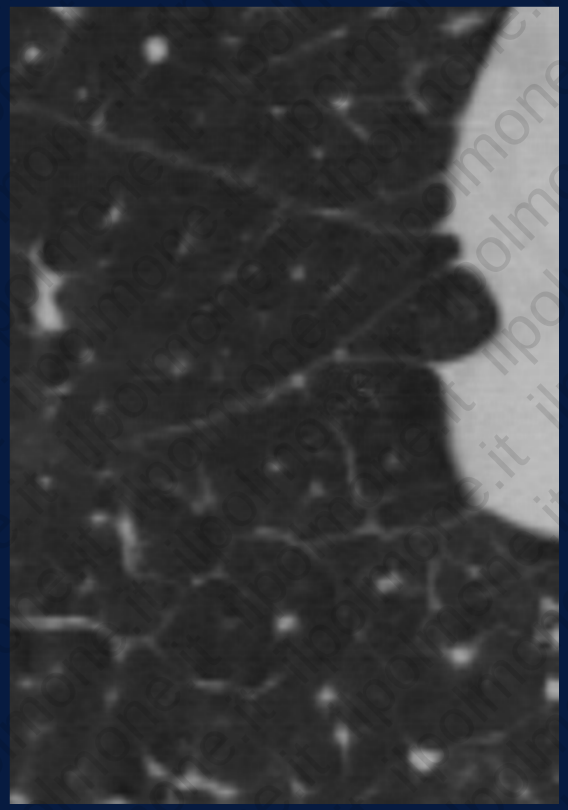
Prognosis Different Too

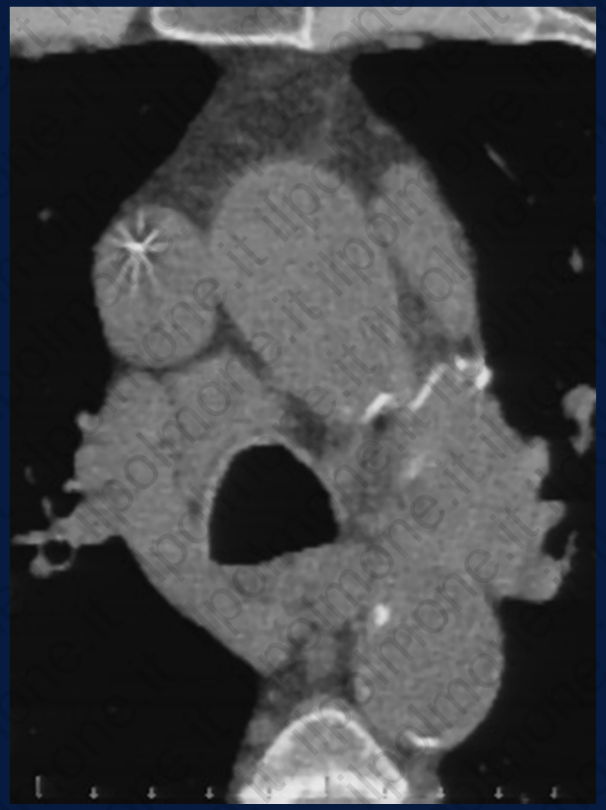
- Worse prognosis
- Specific PAH therapy (prostanoids, PDE-5 inhibitors, ERA have to be used with great caution due the risk of pulmonary edema)

CT Scan Findings PVOD / PCH

- Ground-glass opacities, septal lines, and mediastinal lymph nodes hypertrophy



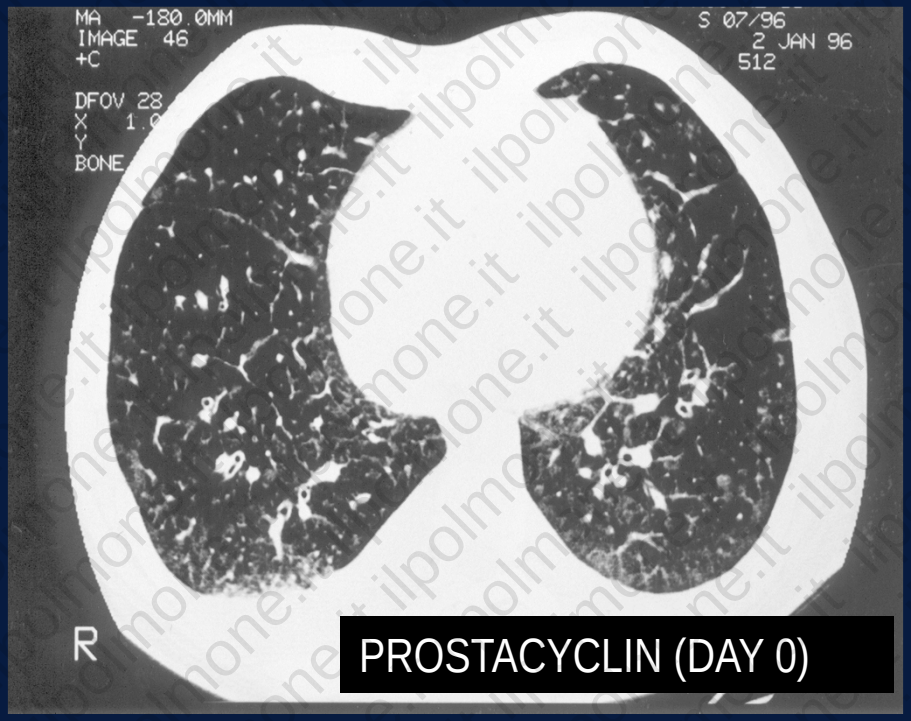




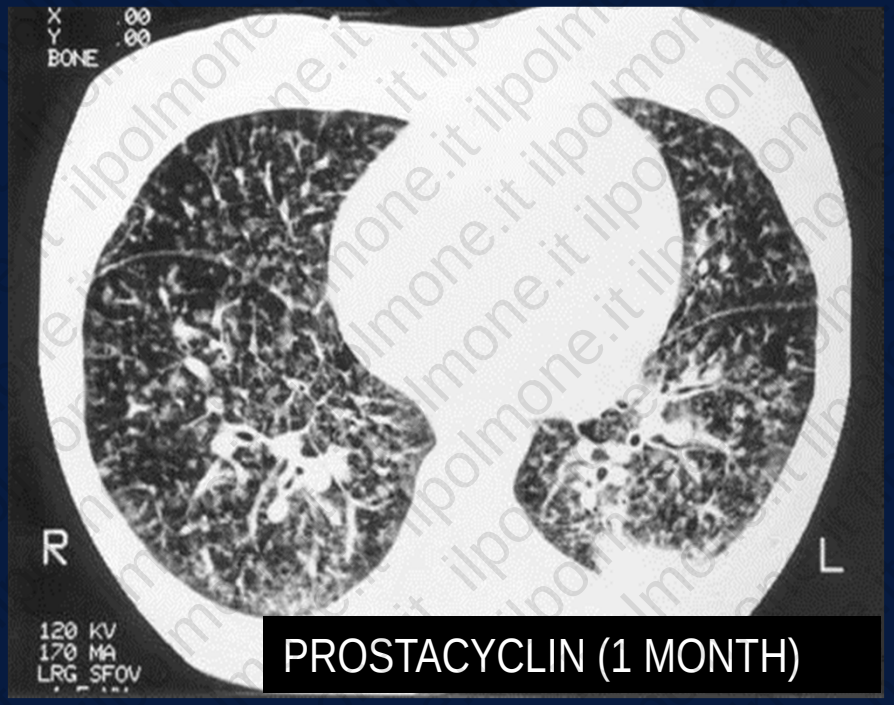
Resten et al.AJR 2004

PVOD / PCH

The diagnosis needs to be made before initiation of specific vasodilator therapy because of the risk of drug-induced severe pulmonary edema

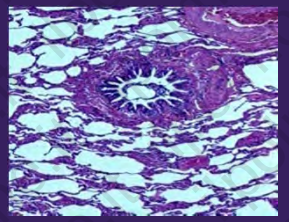


PROSTACYCLIN (DAY 0)



PROSTACYCLIN (1 MONTH)

Humbert et al. Am J Respir Crit Care Med 1998
Resten et al. Radiology 2002



2. PH with Left Heart Disease

- Atrial or ventricular
- Valvular

3. PH with Lung Diseases / Hypoxemia

- COPD
- Interstitial lung disease
- Sleep-disordered breathing
- Chronic exposure to high altitude
- Developmental abnormalities

2. Pulmonary hypertension due to left heart disease

- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease

3. Pulmonary hypertension due to lung diseases and / or hypoxia

- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Other pulmonary diseases with mixed restrictive and obstructive pattern*
- Sleep-disordered breathing
- Chronic exposure to high altitude
- Developmental abnormalities

Cottin et al.ERJ, 2005*

PH due to lung diseases/hypoxia

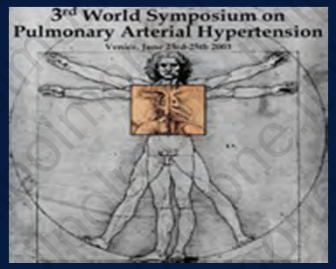
- PAPm 25-35 mmHg (>50%)
- Mechanisms
  - hypoxic vasoconstriction
  - mechanical stress of hyperinflated lungs
  - loss of capillaries
  - inflammation
  - toxic effects of sigarette smoke
  - trombosis in situ
  - secondary polycythaemia

Notion of « out of proportion PH » in chronic respiratory disease - hypoxia

- Prevalence of COPD with « out of proportion PH » defined as PAPm > 40 mmHg and moderately severe lung function abnormalities with low-normal $PaCO_2$: around 1 % of COPD, or 10-20 per million (= prevalence of PAH)*
- Prevalence of out of proportion PH probably similar in other components of third category WHO classification
- If suspected (clinical picture, echo, BNP), PH should be confirmed by RHC – severe PH (Ppa > 35 mmHg) should be referred to expert center
- Such patients should be treated in setting of clinical trials

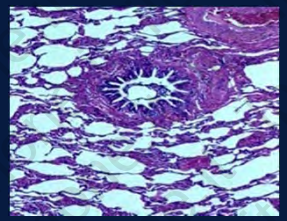
Chaouat et al.AJRCCM, 2005*

4. PH due to Chronic Thrombotic and / or Embolic Disease



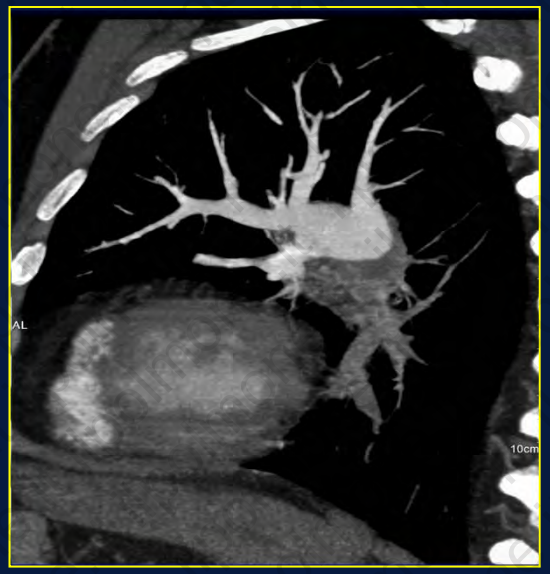
- *Thromboembolic obstruction of proximal PA*
- *Thromboembolic obstruction of distal PA*
- *Non-thrombotic pulmonary embolism (tumor, parasitis, foreign bodies)*

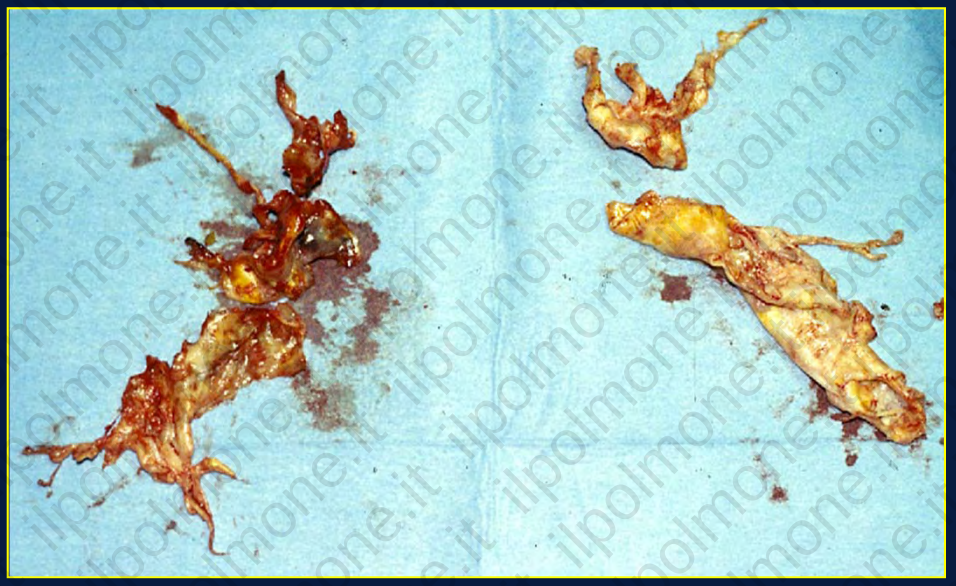
4. Chronic Thromboembolic Pulmonary Hypertension*



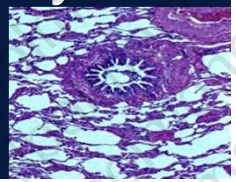
Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

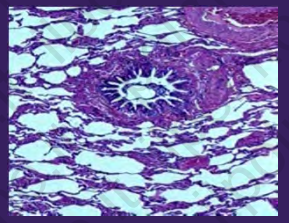
- The diagnosis of CTEPH is generally easily made by the combination of V/Q scan, spiral CT scan and angiography





- When the patient is not operable, he can benefit from specific PAH therapy. However these drugs need further evaluation by RCTs in this setting





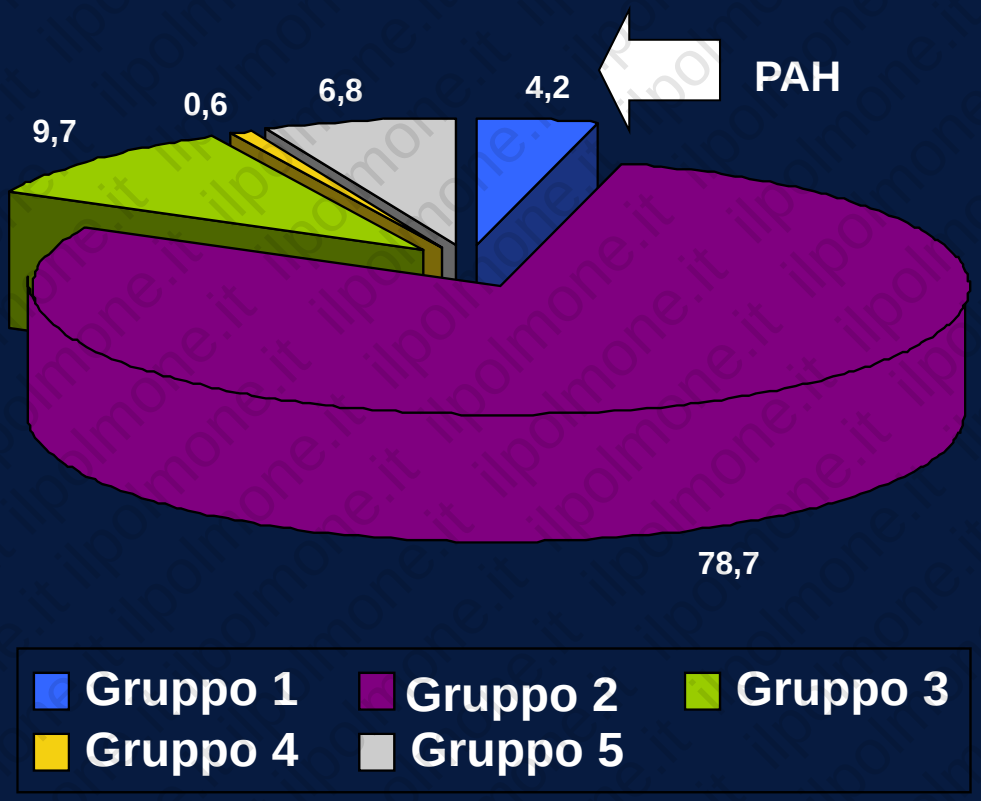
5. Miscellaneous

- Sarcoidosis, histiocytosis X , LAM, compression of pulmonary vessels (tumor adenopathy, fibrosing mediastinitis)

5. PH with Unclear or Multifactorial Mechanisms

- Hematologic disorders: myeloproliferative disorders, splenectomy
- Systemic disorders: vasculitis, sarcoidosis, pulmonary Langerhans cell histiocytosis, neurofibromatosis
- Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- Congenital heart disease (other than systemic to pulmonary shunt)
- Others: obstruction by tumors, fibrosing mediastinitis, chronic renal failure on dialysis, others

Epidemiology



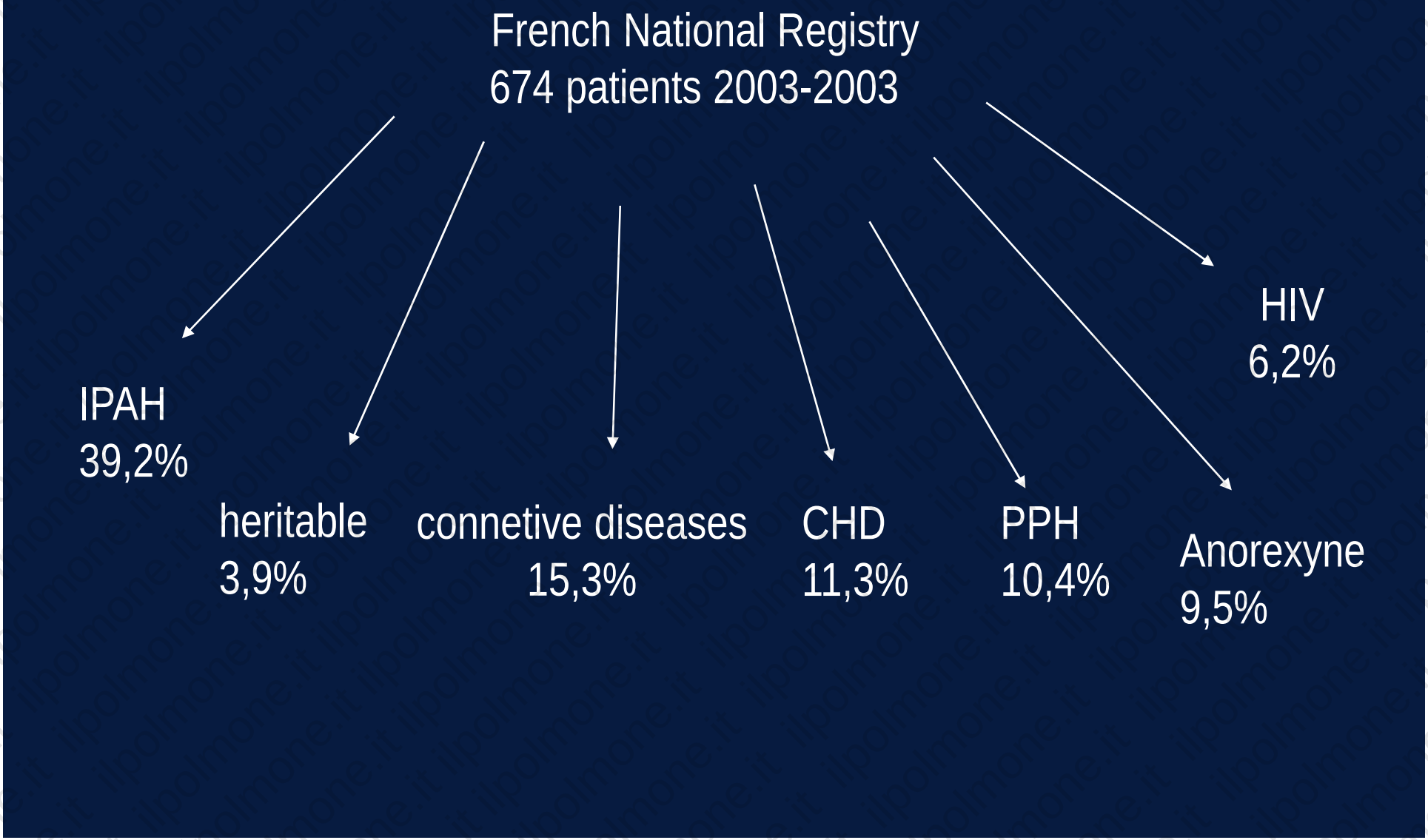
AMERICAN JOURNAL OF Respiratory and Critical Care Medicine

Analisi della prevalenza dell'Ipertensione Polmonare (PH) (definita quantitativamente con PAP >40 mmHg) in 4579 pazienti.

Prevalenza complessiva del 10.5%.

Gabbay et al., *Am J Resp Crit Care Med* 2007; 175:A713

Epidemiology



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  - systemic to pulmonary shunts
  - schistosomiasis
  - chronic hemolytic anemia
- PPHN

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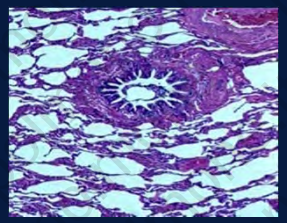
- Diatolic dysfunction
- Valvular disease



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Grazie !