Hypertension Pulmonaire de l'adulte et de l'enfant

Definitions et Classification

Gerald Simonneau

Centre de Référence de l'Hypertension Pulmonaire Sévère
Service de Pneumologie CHU de Bicêtre,
INSERM U999, Université Paris-Sud 11
Le Kremlin Bicêtre – France

UNIVERSITÉ PARIS SUD

Institute thématique Inserm
Institut national de la santé et de la recherche médicale

LabEx LERMIT

TORINO
DHU Thorax Innovation

Hôpitaux universitaires Paris-Sud

Definition of Pulmonary Hypertension (PH)

- PH is an Hemodynamic and pathophysiologic condition defined as mPAP ≥ 25mmHg at rest
- There is still not sufficient evidence to add an exercise criterion to this definition
- A resting mPAP of 8 to 20 mm Hg should be considered normal, based on available evidence.
- Patients with mPAP values between 21 and 24 mmHg should be carefully followed, particularly if they are at risk of developing PAH (e.g. CTD patients or family members of IPAH/HPAH patients).**The term "borderline PH" should not be used**

Hoeper MM, et al. J Am Coll Cardiol 2013.

Definitions of PH/PAH

- PVR (mPAP-mPAWP/CO) should be given in Wood units
- PVR should not be used in general PH definition
- but should be included in the hemodynamic definition of patients with Pulmonary Arterial Hypertension (PAH) as follows:

  mPAP ≥ 25 mmHg

  PAWP ≤ 15 mm Hg) and

  elevated PVR (> 3 WU).

Hôpitaux universitaires Paris-Sud

Definitions of PH due to Left Heart Disease

-**PH due to Left Heart Disease** is defined as:

mPAP ≥ 25 mmHg and PAWP>15mmHg

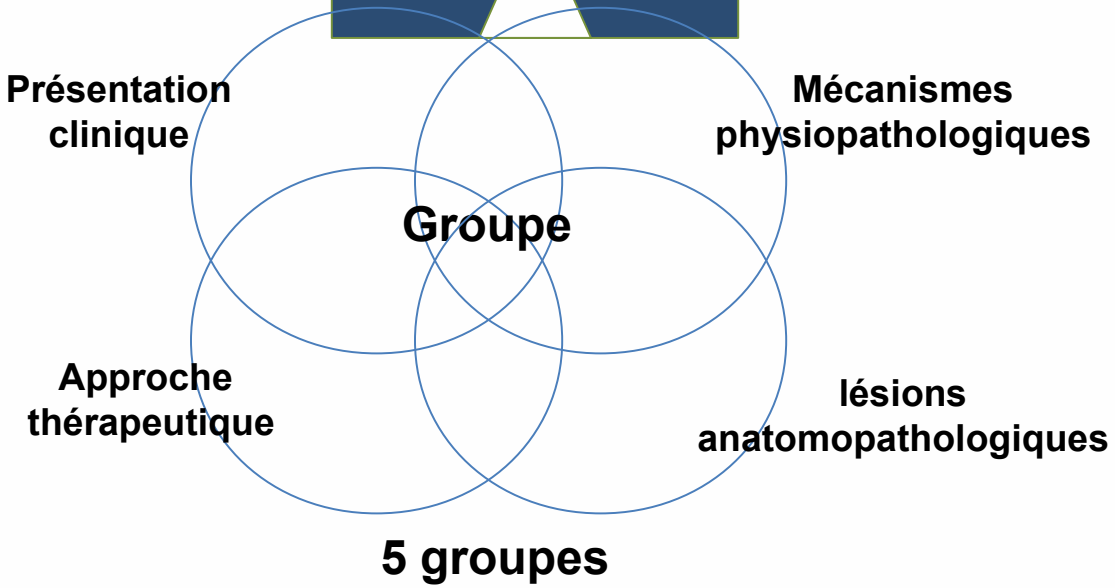
Sub-groups	PAWP	PAPd-PAWP
Isolated post capillary PH (IpcPH)	**> 15 mmHg**	**< 7 mmHg**
Combined post and precapillary PH (CpcPH)	**> 15 mmHg**	**≥ 7 mmHg**

Vachiéry JL *et al.* J Am Coll 2013.

1ère classification OMS en 1973

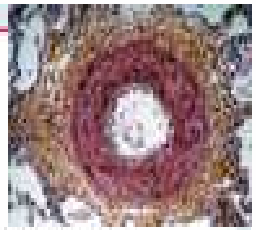
Hypertension pulmonaire primitive	Hypertension pulmonaire secondaire

classifications Evian 98, Venise 2003, Dana Point 2008



5 groupes

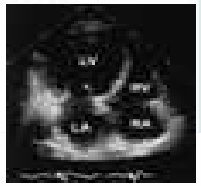
Clinical Classification of Pulmonary Hypertension



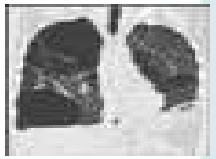
1 Pulmonary arterial hypertension (PAH)
- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2
  - 1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
  - 1.2.3 Unknown
- 1.3 Drugs and toxins induced
- 1.4 Associated with (APAH)
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
  - 1.4.6 Chronic haemolytic anaemia
- 1.5 Persistent pulmonary hypertension of the newborn

1' Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

2 Pulmonary hypertension due to left heart disease
- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease



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 abnormalities



4 Chronic thromboembolic pulmonary hype

5 PH with unclear and/or multifactorial mec
- 5.1 Haematological disorders: myeloproliferative disorders, splenectomy.
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Simonneau G, et al. J Am Coll Cardiol 2009.

Hôpitaux universitaires Paris-Sud

Classification Dana Point 2008

1. Hypertension artérielle pulmonaire

- **PAPm > 25 mmHg et Pcp < 15 mmHg**
- **Lésions plexiformes**
- **Traitements spécifiques de l'HTAP (voies de la PGI2,NO,Endotheline)**

1'. MVO et HCP

2. HTP associée à une cardiopathie gauche

- **PAPm > 25 mmHg et Pcp > 15 mmHg**
- **Traitement insuffisance cardiaque gauche**

3. HTP secondaire à une maladie respiratoire

- **PAPm > 25 mmHg et Pcp < 15 mmHg**
- **Oxygénothérapie**

4. HTP postembolique

- **PAPm > 25 mmHg et Pcp < 15 mmHg**
- **Endarteriectomie pulmonaire**

5. Autres

?

Simonneau G *et al*. J Am Coll Cardiol 2009.

Estimation of PAH prevalence in different subgroups

- Idiopathic
- Heritable
- Drugs and toxins (1/10,000)
- Associated with other diseases
  - Connective tissue diseases
    - Scleroderma (10%)
    - Other CTDs
  - HIV infection (0.5%)
  - Portal hypertension (1-2%)
  - Systemic-to-pulmonary shunts
  - Schistosomiasis (1%)
  - Chronic hemolytic anemia (1% in SCD)

Udated Clinical Classification

During the Nice Meeting(5th WSPH, 2013), the consensus was reach to maintain the general scheme of previous clinical classification. Main Modifications are :

- **Group 1**

-New genetics defects

-New Drugs inducing PAH

-PPHN moved to a specific subgroup 1''

-PAH associated with chronic hemolytic anemia moved from Group1 to group 5

-The wording of PAH associated with CHD has been slightly modified

- **In addition**, specific items related to pediatric PH have been added in order to create a comprehensive, common classification for both adults and children

Hôpitaux universitaires Paris-Sud

New Genetic predispositions

In Familial Cases of PAH:

- 80 % have BMPR2 mutation
- 5% of patients have rarer mutations of other genes:ALK1 (ACVRL1),ENG(Endoglin)
- About 15% of cases have no detectable mutation in currently known disease genes

Recently a new mutation have been identified

Mutation KCNK3* belongs to domain potassium channel family

*L. Ma et al. New Engl J Med 2013

Hôpitaux universitaires Paris-Sud

Niveau de risque	Définition	Médicaments et toxiques en cause
Certain	**Association basée sur l'apparition d'une épidémie ou sur les résultats d'une vaste étude épidémiologique multicentrique**	· **Aminorex** · **Fenfluramine** · **Dexfenfluramine** · **Huile de colza**
Probable	**Association basée sur les résultats d'une étude monocentrique cas-témoins ou sur plusieurs séries de cas**	· **Amphétamines,** · **Méthamphétamines** · **L-tryptophane**
Possible	**Médicaments aux mécanismes d'action similaires à ceux des catégories «certain» ou «probable» mais non encore étudiés**	· **Cocaïne** · **Phénylpropanolamine** · **Millepertuis** · **Agents de chimiothérapie** · **Inhibiteurs sélectifs de la recapture de la sérotonine** · **Pergolide**
Peu probable	**Association non confirmée par une étude épidémiologique**	· **Contraceptifs oraux** · **Oestrogènes** · **Tabac**

Benfluorex associated PAH

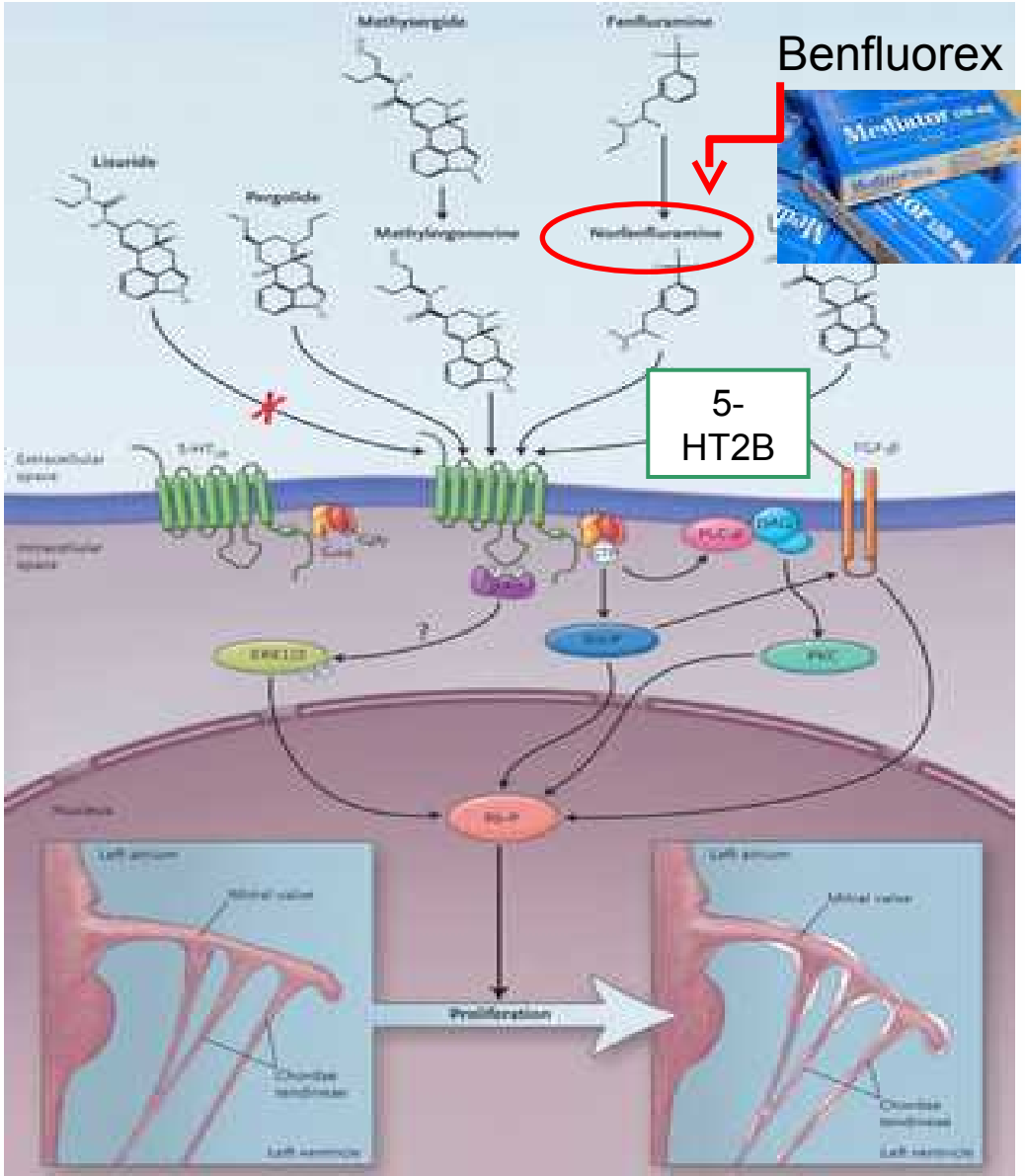
N Eng J Med 2007

FOCUS ON RESEARCH

Drugs and Valvular Heart Disease

Bryan L. Roth, M.D., Ph.D.

- Fenfluramine is metabolized into norfenfluramine.
- Norfenfluramine is an agonist of serotonin receptor 5-HT2B
- Activation of 5-HT2B receptor is a key step in initiating valvular heart disease and PAH

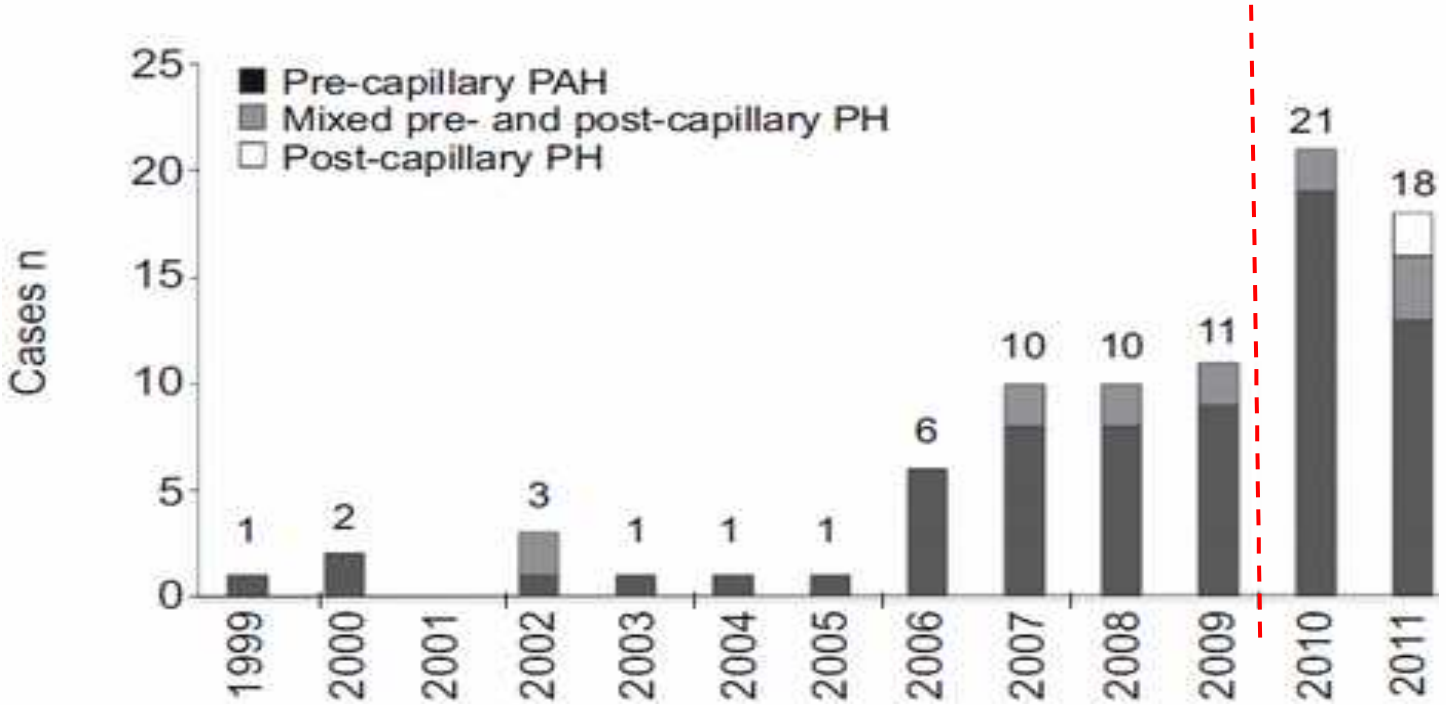


HTAP associée au benfluorex

Laurent Savale, Marie-Camille Chaumais, Vincent Cottin, Emmanuel Bergot, Irène Frachon, Grégoire Prevot, Christophe Pison, Claire Dromer, Patrice Poubeau, Nicolas Lamblin, Gilbert Habib, Martine Reynaud-Gaubert, Arnaud Bourdin, Olivier Sanchez, Pascale Tubert-Bitter, Xavier Jaïs, David Montani, Olivier Sitbon, Gérald Simonneau and Marc Humbert

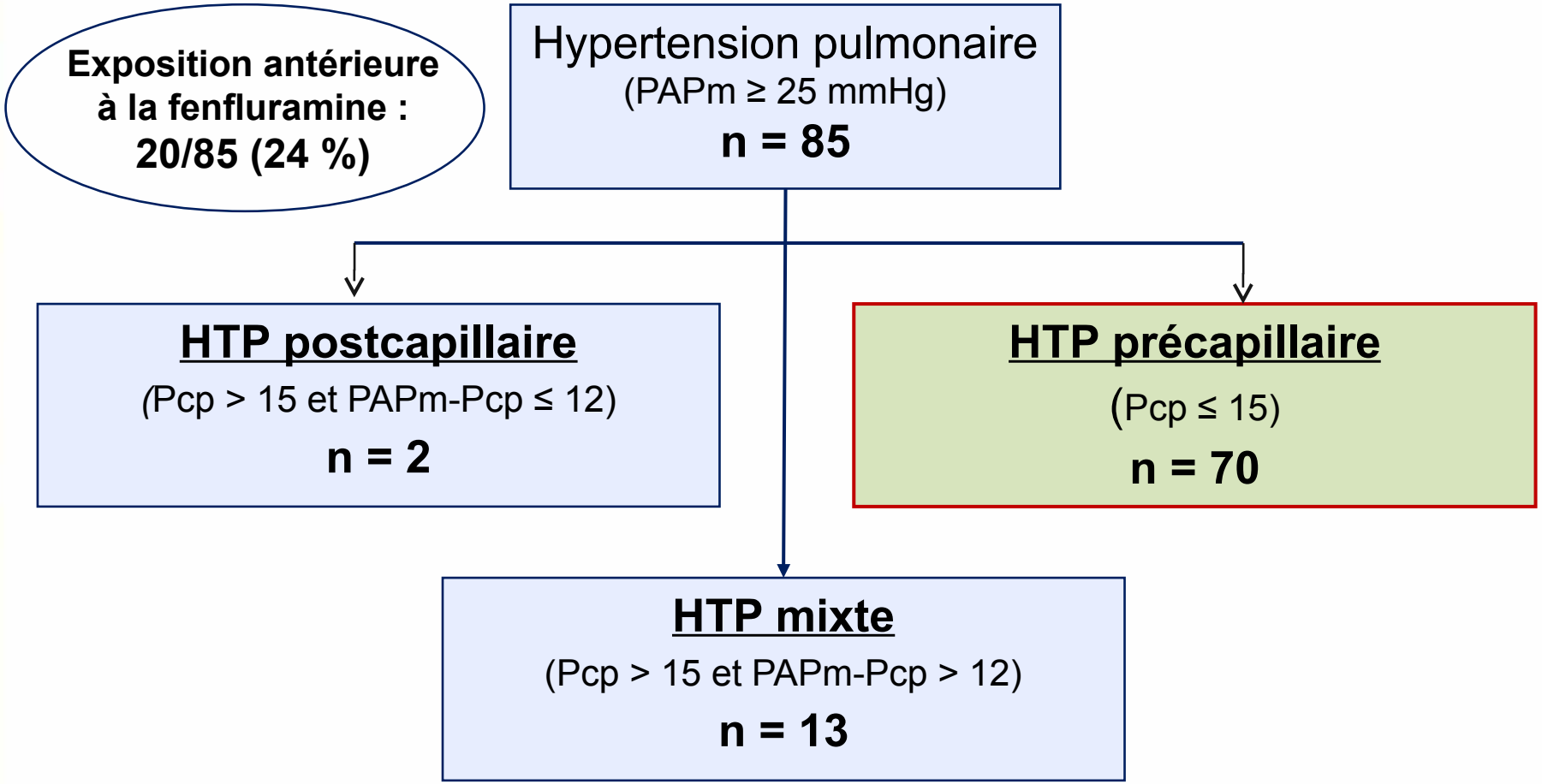
ERJ 2012

Retrait du benfluorex en France



Boutet K *et al.* Eur Respir J 2009.
Savale L *et al.* Eur Respir J 2012.

HTAP associée au benfluorex



Savale L *et al.* Eur Respir J 2012

HTAP associée au Dasatinib

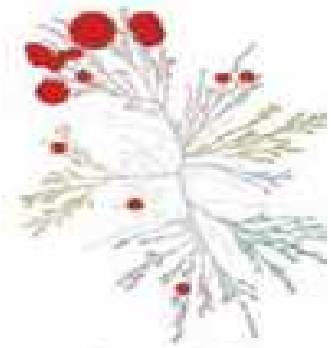
- **Imatinib : traitement de première ligne dans la LMC**
- **Réponse cytogénétique incomplète dans plus de 20 % des cas sous Imatinib**
- **Meilleur taux de réponse complète sous Dasatinib chez les patients résistants à l'Imatinib**

Imatinib

PDGFR

c-kit

Bcr-Abl



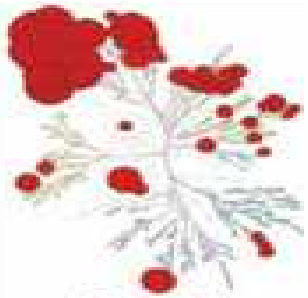
Dasatinib

PDGFR

c-kit

Bcr-Abl

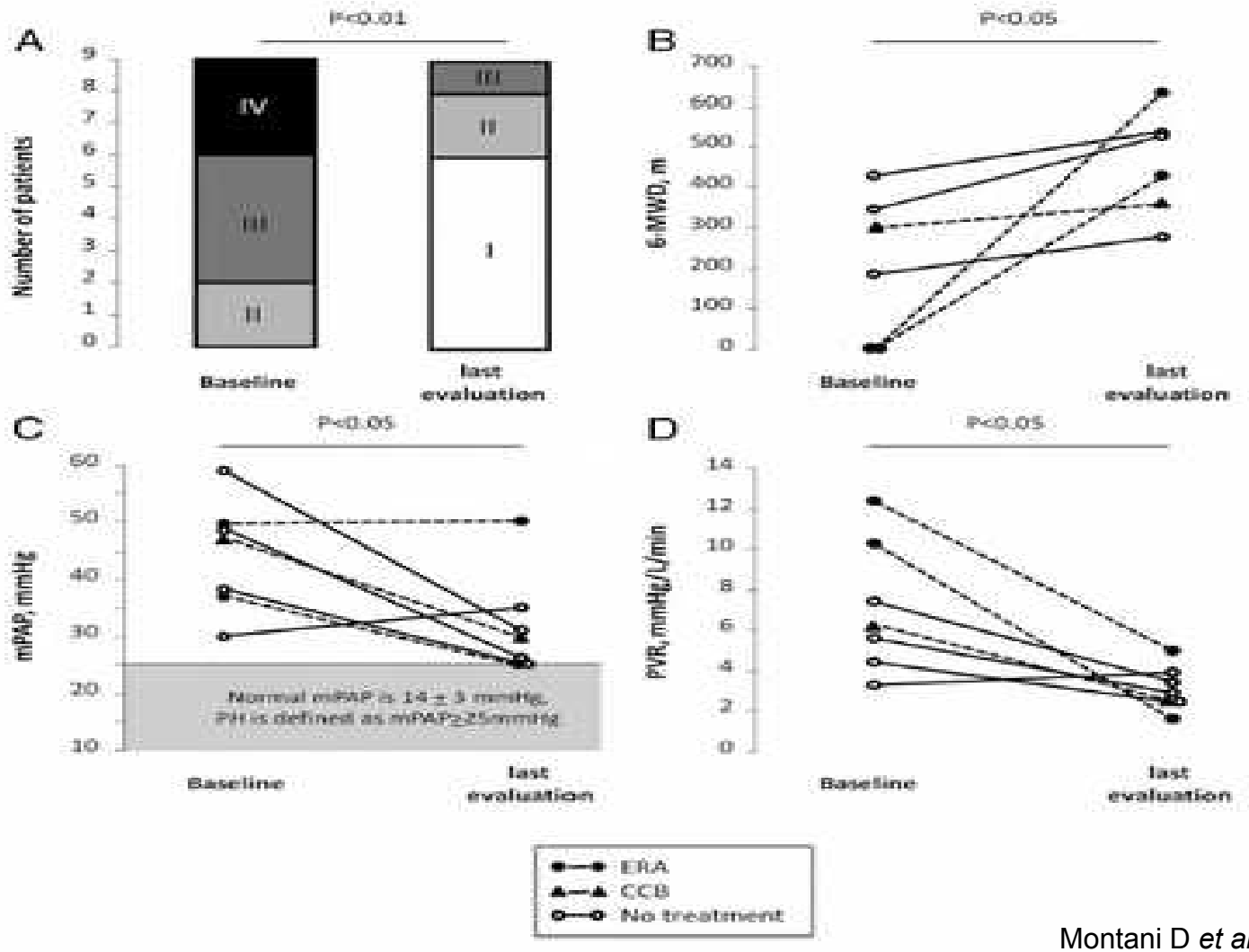
Src



Hoeper m *et al.* Circulation 2013.

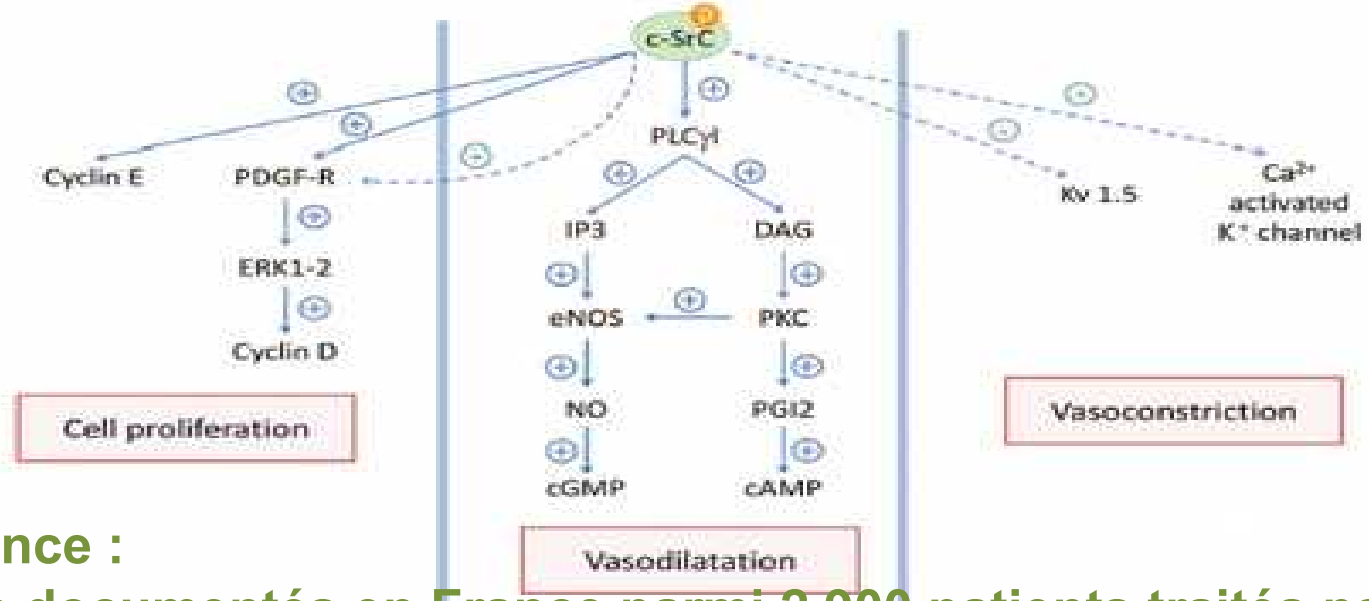
Rasheed W *et al*. Leuk Res 2009.

HTAP associée au Dasatinib



Montani D *et al.* Circulation 2012.

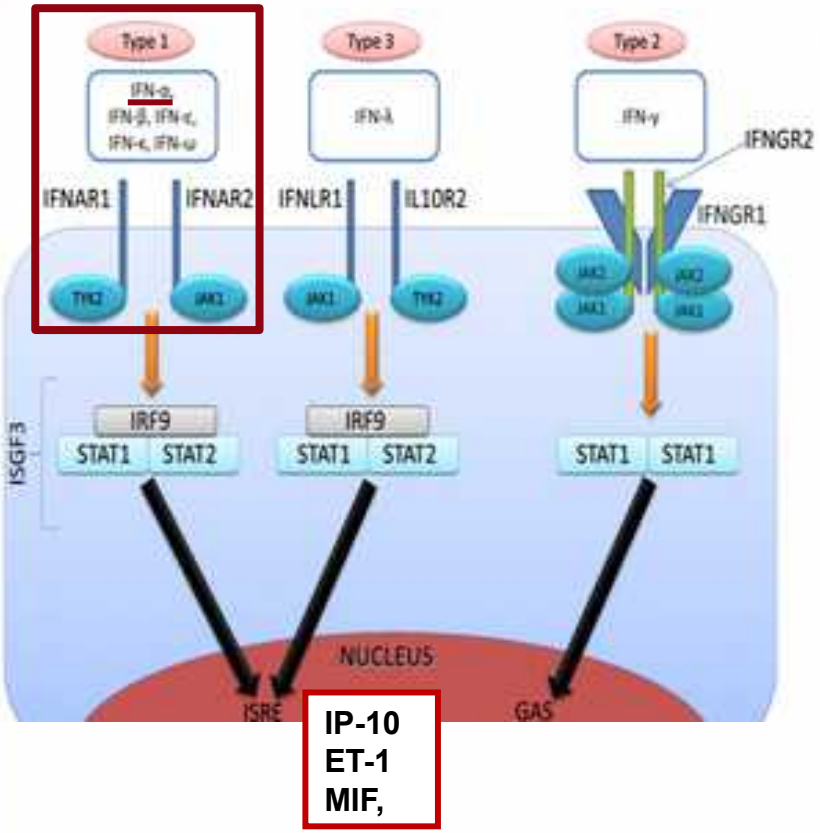
- **Mécanisme : voie de signalisation Src**



- **Incidence :**
  20 cas documentés en France parmi 2 900 patients traités par Dasatinib pour LMC : estimation de l'incidence minimum à 0,5 % (1 per 10 000 pour les dérivés de la fenfluramine)

*Montani D *et al.* Poster at the 5th WS Nice 2013.

HTAP associée à l'interféron



IP-10
ET-1
MIF,

ANTIVIRAL ACTIVITY

- **3 Classes d'interférons : Type I, Type II, Type III**
- **Activité antivirale, antiproliférative, anticytotoxique et antitumorale**
- **Interféron-α et Interféron-β activent le relargage d'ET-1 par les cellules vasculaires pulmonaires**
- **11 cas d'HTAP chez des patients traités par Interféron-α ** et Interféron-β*** ont été rapportés**

Fruehauf, Annals of hematology 2001.
Al-Zahrani, Leukemia & Lymphoma 2003.
Anderson, American journal of hematology 2003.
Jochmann, Cardiovascular ultrasound 2005.
Ledinek, Multiple sclerosis 2009.
Al-Dhillon, Digestive Diseases and Sciences 2010.
Caravita, Cardiology 2011.

HTAP associée à l'interféron

- Analyse rétrospective des patients du centre de référence HTAP
- 53 patients avec ATCD d'exposition à l'IFN
- 48 patients exposés à l'Interféron-α pour hépatite chronique. FdR associé chez la plupart (HTPo et/ou HIV)
- 5 patients exposés à l'Interféron-β pour SEP
- Délai entre début exposition interférons et diagnostic HTAP ~ 3 ans

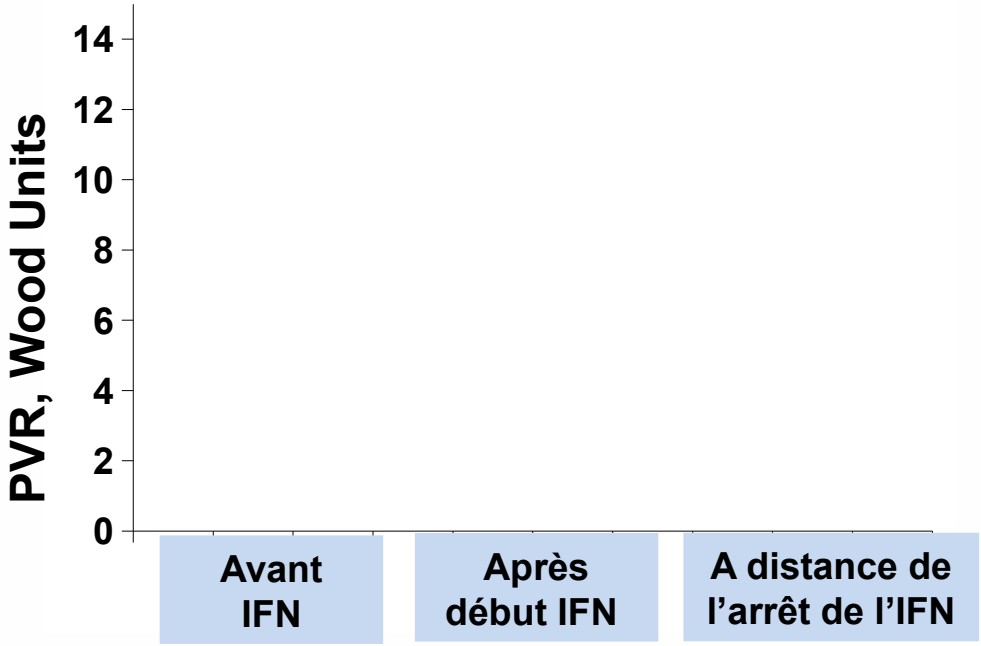
53 patients identifiés (1998 - 2012)	
Age, years	46 ± 6
Sex ratio (M / F)	32 / 21
IFN indication	
HCV infection,	48
Multiple sclerosis,	5
NYHA I, II / III, IV %	29 / 71
6MWD, m	366 ± 144
Hemodynamics	
Pcwp mmHg	8 ± 4
Mean PAP mmHg	48 ± 13
CO, l/min	5.7 ± 1.8
PVR, Wood units	8.6 ± 7.6

Savale L *et al.* Poster at ERS congress 2013.

HTAP associée à l'interféron

- **16 patients exposés ou ré-exposés à l'interféron après le diagnostic d'HTA**
  - **Suivi disponible chez 12 d'entre eux**

At diagnosis	n = 16
Age, years	45 ± 6
Sex ratio (M / F)	14 / 2
NYHA II / III	14 / 2
6MWD	443 ± 40
Hemodynamic	
RAP, mmHg	5 ± 3
Pcwp, mmHg	7 ± 3
Mean PAP, mmHg	42 ±11
CO, l/min	6.5 ±1.4
PVR, Wood units	6 ± 2.4

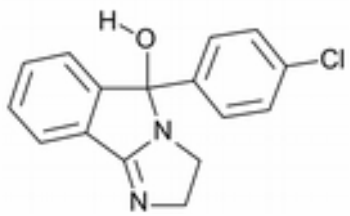


➔ **Etude cas-contrôle ?**

Savale L *et al.* Poster at ERS congress 2013.

HTAP associée aux dérivés de l'amphétamine

- **Methylphenydate**
  - Indication : hyperactivité de l'enfance
  - Inhibiteur de la recapture de la dopamine et de la norepinéphrine (effet amphétamine-like)
  - 1 cas d'HTAP décrit
- **Phentermine + topiramate (QsymiaTM)**
  - Approuvé par la FDA en 2012 mais rejeté par l'AEM
- **Mazindol**
  - Effet amphetamine-like
  - Traitement de la narcolepsie et de l'obésité
  - Un cas d'HTAP partiellement reversible
- **Ropirinole**
  - Effet amphetamine-like
  - Traitement des jambes sans repos



HTAP associée aux IRS durant la grossesse

- **HTAP persistante du nouveau né : 2 / 1000 naissances**

- **7 études ont évalué le lien entre exposition aux IRS durant la grossesse et HTAP du nouveau né :**
  2 études négatives / 5 études positives

	Etudes	OR (IC 95%)
Chambers CD *et al.* NEJM 2006	377 cas 836 contrôles	6,1 (2,2 - 16,8)
Kieler H *et al.* BMJ 2012	Cohorte de 30 000 femmes exposées dont 11 000 après 20 S.A.	2,1 (1,5 - 3) (> 20 S.A.)

- **Association entre exposition aux IRS dans la population générale et HTAP non démontrée**

Update on drugs inducing PH

Definite	Possible
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine
Dexfenfluramine	St. John's Wort
Toxic rapeseed oil	Chemotherapeutic agents
Benfluorex **Serotonine Reuptake Inhibitors**	**Interferon type I** **Amphetamines-like**
Likely	**Unlikely**
Amphetamines	Oral contraceptives
Tryptophan	Estrogen
Methamphetamines	Cigarette smoking
Dasatinib	

Precapillary PH associated with Sickle Cell Disease
In Which Group?

The classification of pre-capillary PH associated with SCD has evolved during the successive world meetings, revealing uncertainties in potential causes and mechanisms

Evian meeting(1998) → Group 4(CTEPH)

Venice meeting(2003)
Dana point meeting(2008) → Group 1(PAH)

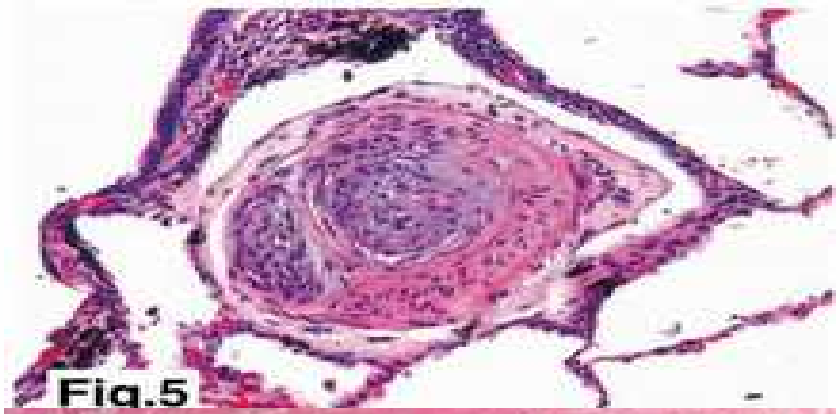
Nice meeting(2013) → Group 5(multifactorial)

PAH due to Sickle Cell Disease moved from Group 1 to Group 5

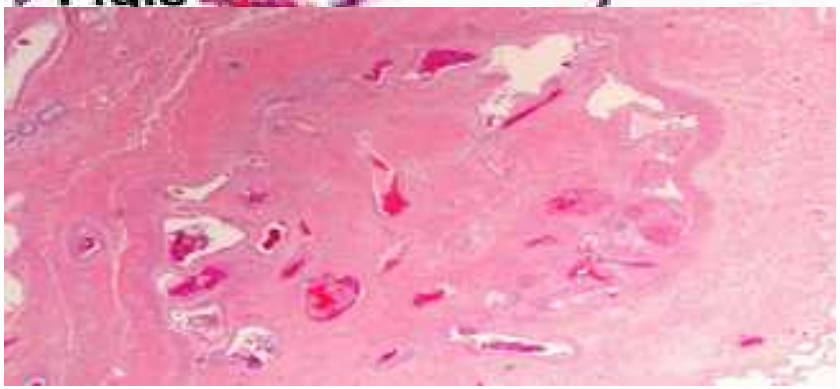
To belong to Group 1 (PAH), different subgroups have to share with IPAH:

- similar histological findings
- similar hemodynamic characteristics
- similar management

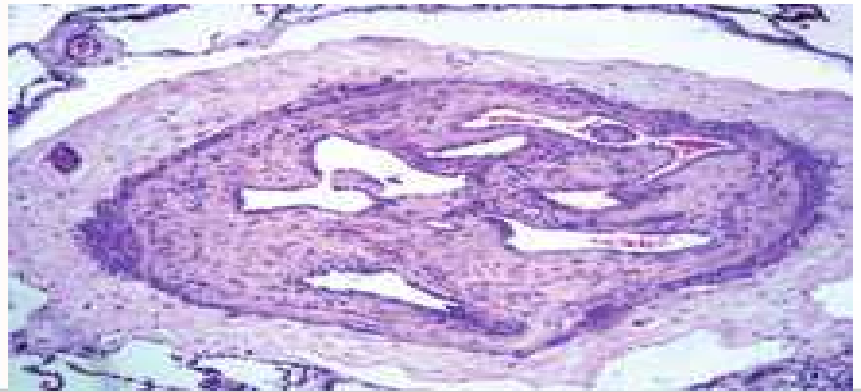
Distal thrombotic obstructions of pulmonary arteries with partial recanalization



Haque et al
,Human Pathology, 2002



R Souza et al
Unpublished data

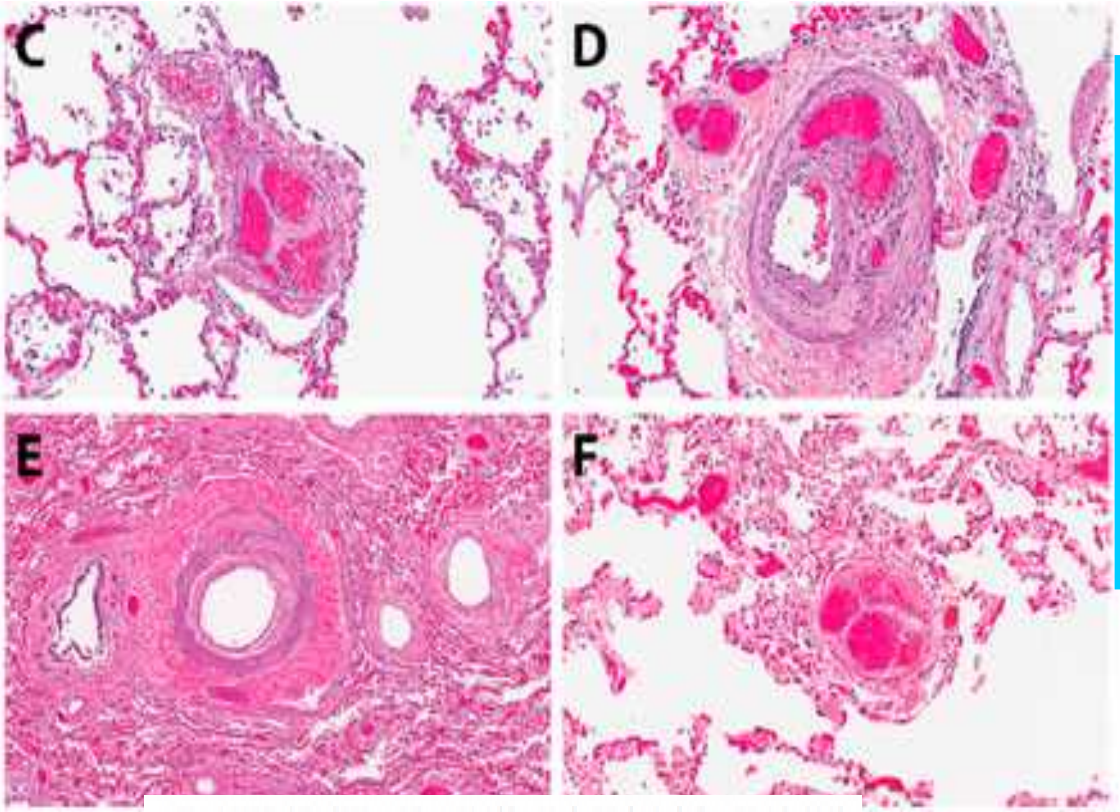


Graham et al
,Am J Forens Med Path, 2007

hôpitaux universitaires Paris-Sud

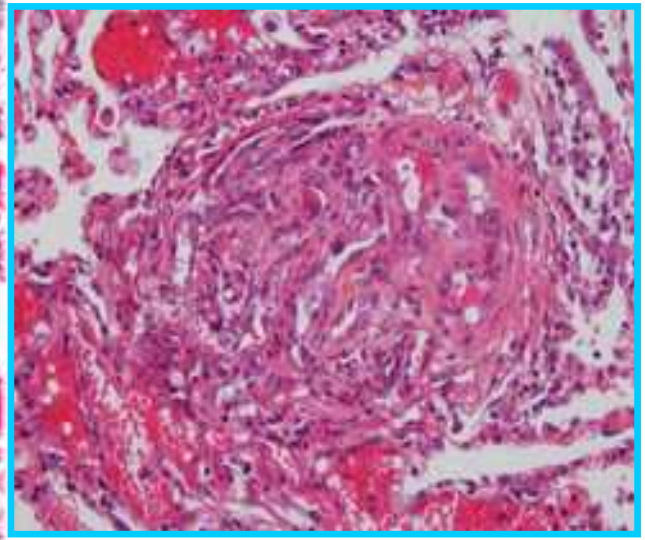
Hemodynamic Predictors of Mortality in Adults with Sickle Cell Disease

Alem Mehari[1,2*], Shoaib Alam[1*], Xin Tian[3], Michael J. Cuttica[4], Christopher F. Barnett[5], George Miles[6], Dihua Xu[3], Catherine Seamon[7], Patricia Adams-Graves[8], Oswaldo L. Castro[1,2], Caterina P. Minniti[7], Vandana Sachdev[1], James G. Taylor VI[7], Gregory J. Kato[7†], and Roberto F. Machado[9†]



Am J Respir Crit Care Med Vol 187, Iss. 8, pp 840–847, Apr 15, 2013

plexiform lesionsin PAH



With the courtesy of
P.Dorfmuller
Paris-Sud University

Hôpitaux universitaires Paris-Sud

Sickle Cell DiseasePathology

TABLE 1. Demographic Pathologic Data

Case no.	Age/sex	SCS/HbE	PH grade	Plex lesion	Pulm. edema	Heart wt (g)	RV (cm)	RV dil/ hyper	LV (cm)	PP/Echo	Spleen	Cirrhosis /hemchr	Cause of death
1	27/M	S 97.8%	3	−	+	480	0.3	+/−	1.5	normal/mild TR	0	+	SD
2	64/F	S 97.3%	4	+	−	420	0.2	+/−	1.5	41-46 sys/TR + PR	0	+/+	SD
3	33/M	S 96.7%	4	+	−	760	0.4	+/+	1.6	TR	0	+/+	SD
4	28/M	S 96.4%	4	+	+	560	0.7	+/+	NA	74/36/TR	0	−	SC crises
5	54/F	S 95.7%	4	+	−	500	0.8	+/+	2.2	H/o PH	0	+/+	GI bleed
6	47/M	S 92.9%	2	−	+	600	1.0	+/+	NA	normal/mild TR	0	+	SD
7	50/F	S 92.7%	4	+	−	510	0.5	+/−	1.8	Increased left atrial pr	0	+/+	SC crises, sepsis
8	40/M	S 90%	4	+	+	500	0.6	+/+	1.8	77/34/ mod TR	0	+/+	DIC
9	39/M	S 83%	4	+	+	520	0.4	+/+	1.5	78-82 sys/TR	0	+/+	SD
10	28/M	S 81.3%	3	−	+	560	0.4	+/−	1.1	ND	0	+	SC crises
11	19/F	S 53%	3	−	+	360	0.6	+/+	1.7	51-56/TR	0	+/+	Renal failure
12	41/M	S 42%	3	−	+	280	0.3	−/−	1.3	ND	500	−	SD
13	34/F	S 40%	4	+	−	430	0.2	+/−	1.2	ND/mild TR	550	+/+	SC crises
14	77/F	S 37%	4	+	+	390	0.3	+/−	1.4	55/35/TR	0	−	Sepsis
15	62/F	S 31%	4	+	+	720	0.6	+/−	NA	ND	230	−	Ovarian CA
16	40/M	S 23%	2	−	+	480	0.25	+/−	1.7	ND	330	−	Sepsis
17	19/M	+/ND	4	+	+	420	NA	NA	1.5	ND	150	−	SD
18	39/M	+/ND	4	+	+	540	0.4	+/−	1.5	ND	0	+	Cirrhosis
19	33/M	+/ND	1	−	+	580	0.3	+/−	1.4	ND	220	−	SD (PE)
20	41/F	+/ND	2	−	+	368	0.2	+/−	1.4	ND	188	−	Sepsis

Abbreviations: SCS, sickle cell screen; HbE, hemoglobin electrophoresis; Plex lesion, plexiform lesion wt, weight; RV dil/hypert, right ventricular dilatation/hypertrophy (in g); PP/Echo, pulmonary pressure/echocardiogram; TR, tricuspid regurgitation; PR, pulmonary regurgitation; ND, not done; Spleen 0, autosplenectomy; SD, sudden death; PE, Pulmonary embolism: DIC, disseminated intravascular coagulopathy.

Haque,Human Pathology, 2002

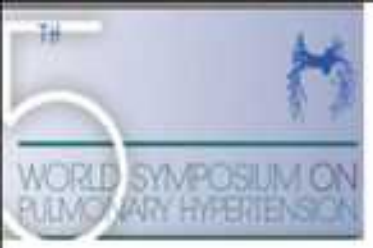
Hôpitaux universitaires Paris-Sud

PH in Sickle Cell disease

Hemodynamic findings

	IPAH1 (n=288)	CTD-PAH1 (n=157)	PoPH1 (n=127)	CHD-PAH1 (n=35)	HIV-PAH2 (n=59)	Precap. PH in SCD3 (n=11)
RAP, mmHg	8 ± 5	7 ± 5	8 ± 6	7 ± 5	8 ± 5	**5 ± 2**
mPAP, mmHg	49 ± 13	41 ± 9	47 ± 12	51 ± 16	49 ± 10	**28 ± 4**
PCWP, mmHg	9 ± 4	8 ± 4	9 ± 4	8 ± 4	9 ± 5	**10 ± 3**
Cardiac Index, L/min/m²	2.4 ± 0.8	2.8 ± 0.9	3.0 ± 1.0	3.0 ± 1.0	2.9 ± 0.7	**5.8 ± 1.3**
PVR, dyn.sec.cm-5	831 ± 461	649 ± 379	611 ± 311	753 ± 370	737 ± 328	**178 ± 55**

1. **Sitbon O, *et al*. *ESC & ERS 2011*.**
2. **Degano B, *et al. Eur Respir J* 2009 .**
3. **Parent F, *et al. New Engl J Med* 2011.**



PH in Sickle Cell disease

Effects of PAH drugs

- The walk-PHaSST study was a double-bind placebo controlled trial of 16 weeks to test safety and efficacy of sildenafil in PAH patients with SCD

- The NIH stopped the study,due to safety concerns when 33 patients had completed the trial

- sildenafil treated patients experienced more frequently sickle cell pain crisis (35%) compared to placebo-treated patients (14%).

Machado Ret al Blood, 2011

- Furthermore,there was no evidence of treatment-related

Mechanisms of pre-capillary PH in SCD

- **High Cardiac output resulting from anemia**
- **Pulmonary arteries thrombosis (asplenia, thrombocytosis, hypercoagulate state**)
- Alteration of blood rheology (hyperviscosity) leading to increase PVR
- Endothelial dysfunction leading to major remodeling of of small PA (< 500 µ)?

The classification of PAH-CHD has been modified

Table 3 Updated Clinical Classification of Pulmonary Arterial Hypertension Associated With Congenital Heart Disease*

1. Eisenmenger syndrome

   Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of pulmonary vascular resistance (PVR) and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis and multiple organ involvement are usually present.

New addition

2. Left-to-right shunts
   - Correctable†
   - Noncorrectable

   Include moderate to large defects; PVR is mildly to moderately increased systemic-to-pulmonary shunting is still prevalent, whereas cyanosis is not a feature.

3. Pulmonary arterial hypertension (PAH) with coincidental congenital heart disease

   Marked elevation in PVR in the presence of small cardiac defects, which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. To close the defects in contraindicated.

4. Post-operative PAH

   Congenital heart disease is repaired but PAH either persists immediately after surgery or recurs/develops months or years after surgery in the absence of significant postoperative hemodynamic lesions. The clinical phenotype is often aggressive.

Simonneau G, et al. J Am Coll Cardiol 2013.

Defect correction criteria in presence of PAH

Criteria for closing cardiac shunts in PAH patients with congenital heart defects

PVRI	PVR	Correction
< 4 Wood units.m2	(< 2.3)	Yes
> 8 Wood units.m2	(> 4.6)	No
4-8 Wood units.m2	(2.3-4.6)	Individual patient evaluation in tertiary centers

Simonneau G, et al. J Am Coll Cardiol 2013;

33

Updated Classification of PH

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 Drugs and toxins 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''. Persistant Pulmonary Hypertension of Newborn

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

5.Pulmonary Hypertension with Unclear Multifactorial Mechanisms

- 5.1 Hematologic disorders:chronic hemolytic anemias myeloproliferative disorders splenectomy,
- 5.2 Systemic disorders, Sarcoidosis, pulmonary Langerhans cell histiocytosis, Lymphangioleiomyomatosis, neurofibromatosis, vasculatis
- 5.3 Metabolic disorders: Glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others:tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Simonneau G *et al.* J Am Coll Cardiol 2013

Conclusion

La classification de l'HTP évolue en fonction connaissances épidémiologiques, cliniques et physiopathologiques.

- **Durant les 5 dernières année[illegible]ouv[illegible]ogues ont été identifiées comme facteurs de risque possibles, probables ou définitifs d'HTAP**
- **De nouvelles prédispositions ou mutations génétiques ont été identifiées**
- **Les données récentes cliniques, épidémiologiques et anatomopathologiques sur l'HTP liée à la drépanocytose motivent un changement de classification (groupe1 ➔ groupe 5)**
- **Mise en commun de la classification adulte et pédiatrique des HTAP associées à une cardiopathie congénitale**