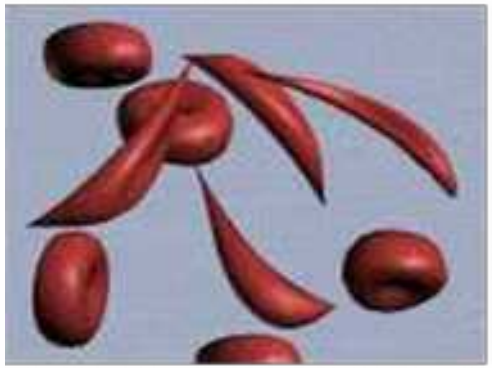
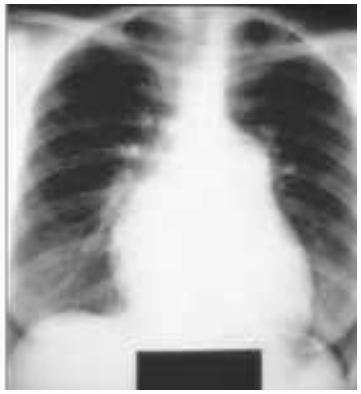
Hypertension pulmonaire et drépanocytose



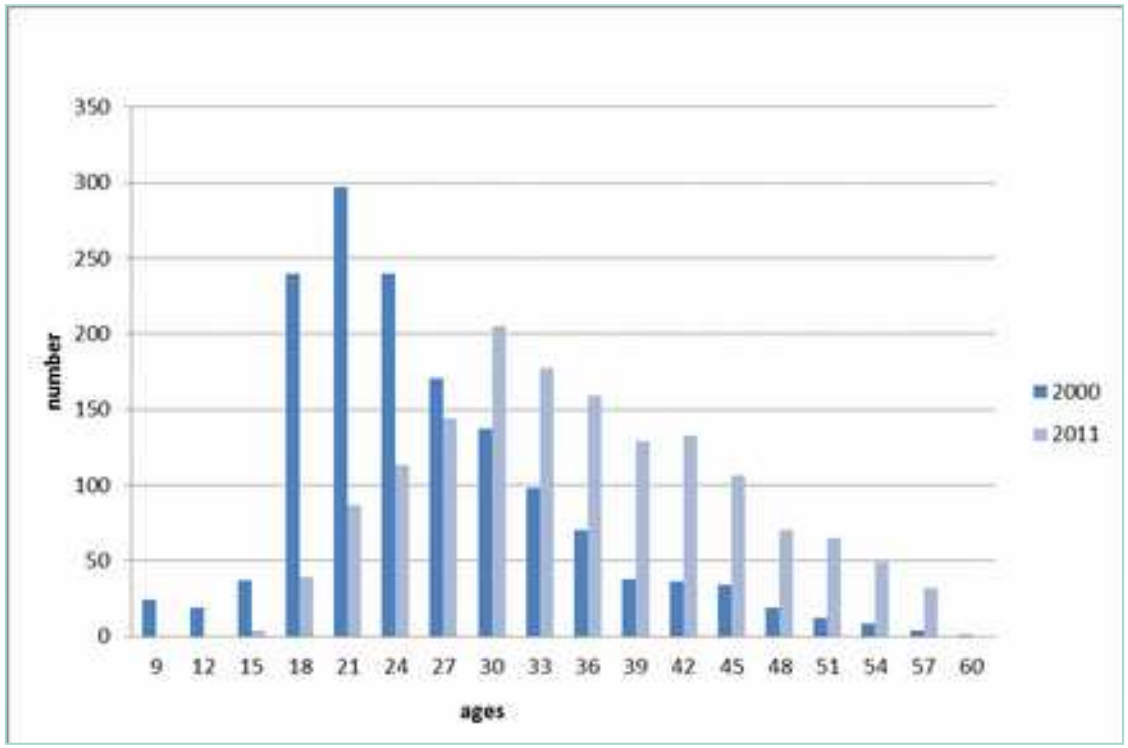


Dr Florence Parent
Centre de Référence de l'Hypertension Pulmonaire Sévère
Service de Pneumologie CHU de Bicêtre,
INSERM U999, Université Paris-Sud 11
Le Kremlin Bicêtre – France
Inserm U999. Université Paris-Sud

Hôpitaux universitaires Paris-Sud

Syndromes drépanocytaires majeurs

- SS, SC, Sbthal, SD Punjad, SO Arab
- Prévalence: 1 - 5 /10 000
  - 250 nouveaux cas / an en France métropolitaine
  - 250 000 nouveaux cas / an dans le monde
- Cohorte Hôpital Mondor: âge des patients suivis



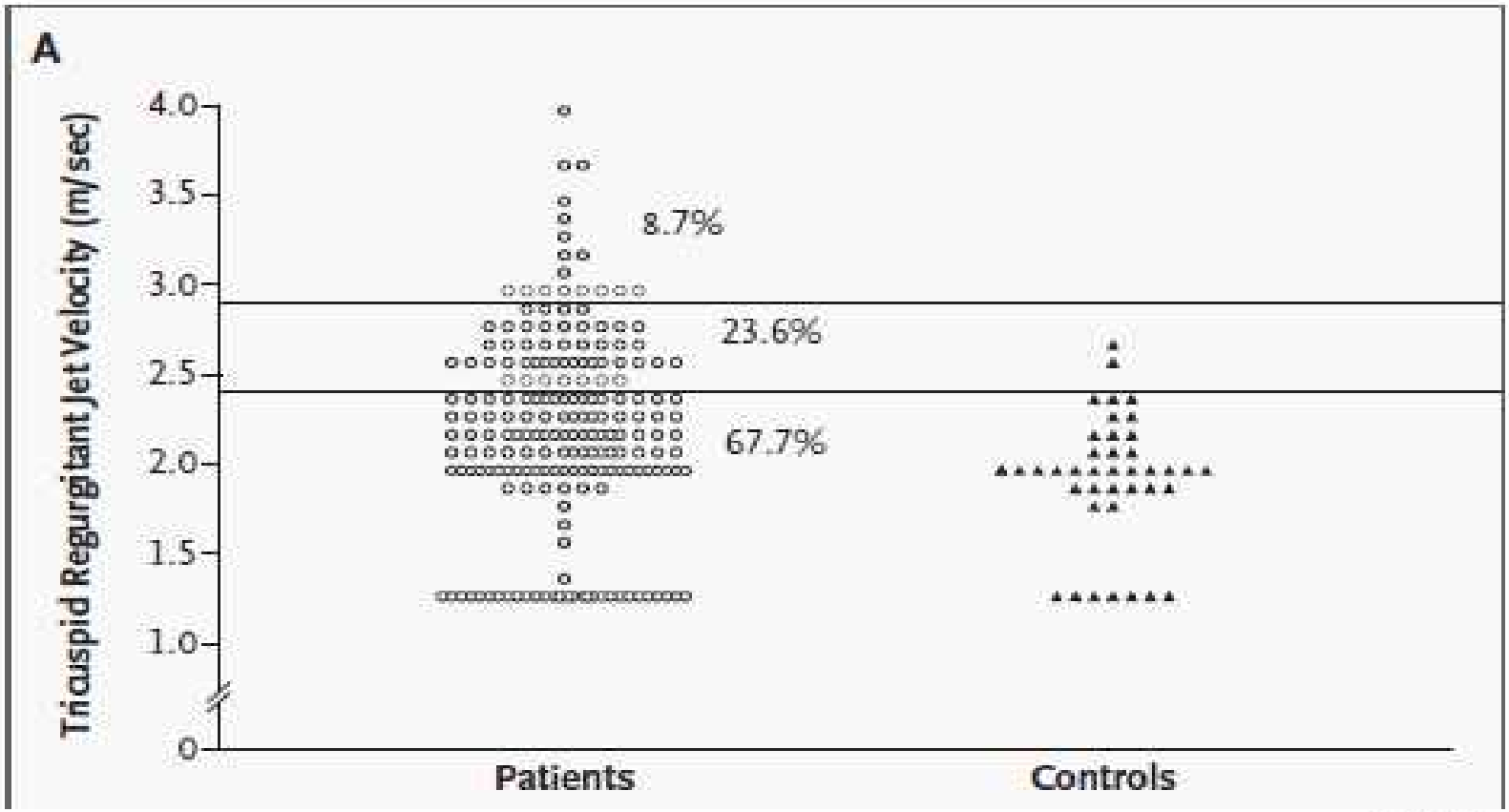
Hôpitaux universitaires Paris-Sud

HTP associée à la drépanocytose

- Prévalence, caractéristiques et pronostic
- Screening de l'HTP : à quels patients faut-il faire un cathétérisme cardiaque?
- Physiopathologie, classification et prise en charge

Pulmonary Hypertension as a Risk Factor for Death in Patients with Sickle Cell Disease

Mark T. Gladwin, M.D., Vandana Sachdev, M.D., Maria L. Jison, M.D., Yukitaka Shizukuda, M.D., Ph.D., Jonathan F. Plehn, M.D., Karin Minter, M.D., Bernice Brown, M.D., Wynona A. Coles, R.R.T., James S. Nichols, R.N., Inez Ernst, R.N., B.S.N., R.D.C.S., Lori A. Hunter, R.N., William C. Blackwelder, Ph.D., Alan N. Schechter, M.D., Griffin P. Rodgers, M.D., Oswaldo Castro, M.D., and Frederick P. Ognibene, M.D.



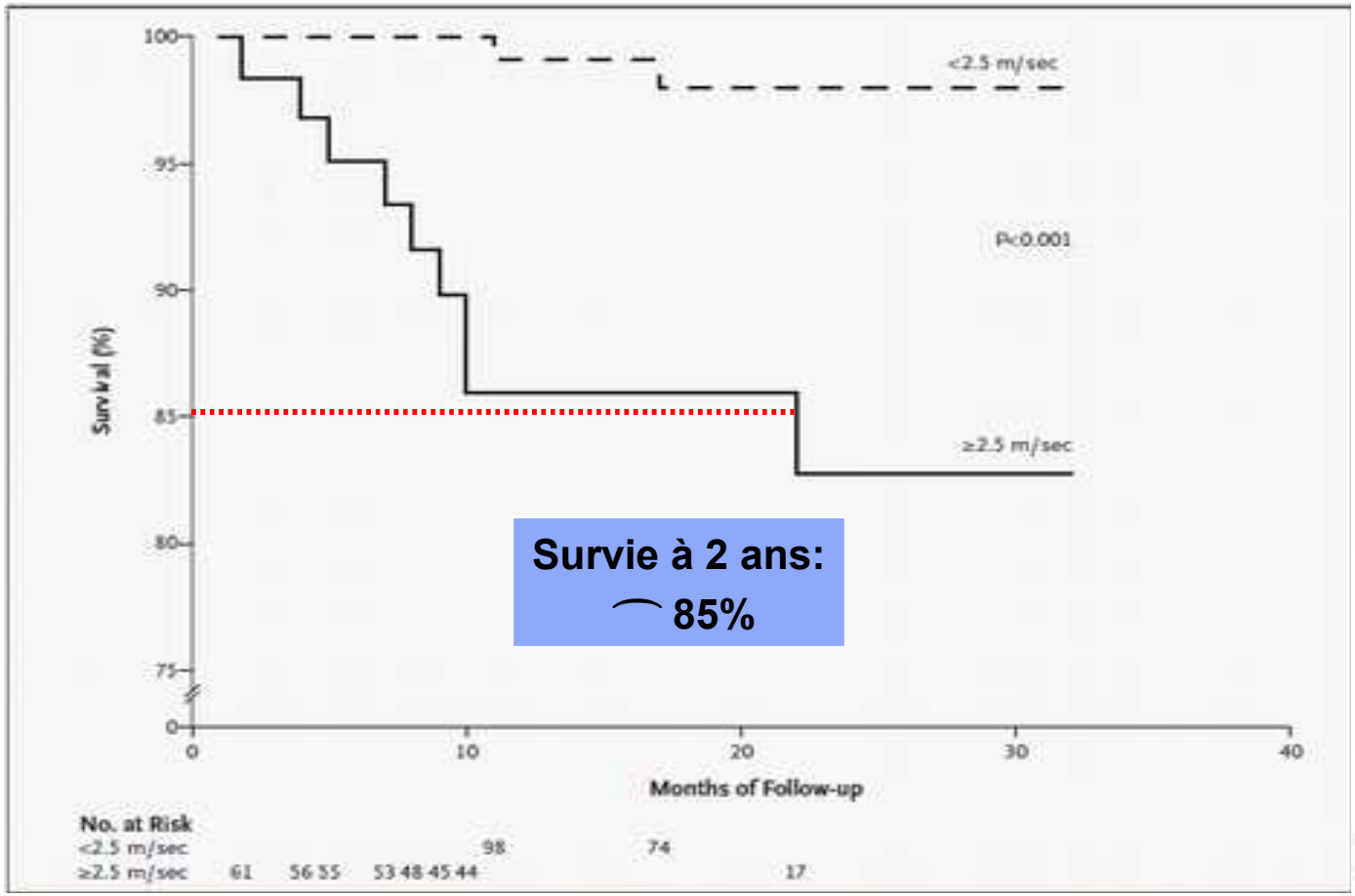
n=195

M Gladwin et al. New Engl J Med 2004

Hôpitaux universitaires Paris-Sud

Pulmonary Hypertension as a Risk Factor for Death in Patients with Sickle Cell Disease

Mark T. Gladwin, M.D., Vandana Sachdev, M.D., Maria L. Jison, M.D., Yukitaka Shizukuda, M.D., Ph.D., Jonathan F. Plehn, M.D., Karin Minter, M.D., Bernice Brown, M.D., Wynona A. Coles, R.R.T., James S. Nichols, R.N., Inez Ernst, R.N., B.S.N., R.D.C.S., Lori A. Hunter, R.N., William C. Blackwelder, Ph.D., Alan N. Schechter, M.D., Griffin P. Rodgers, M.D., Oswaldo Castro, M.D., and Frederick P. Ognibene, M.D.



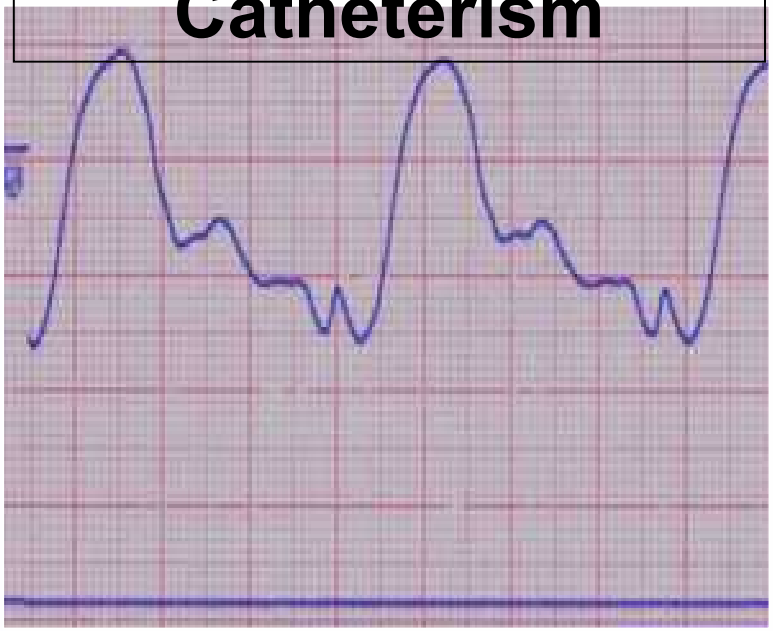
Survie à 2 ans:
≃ 85%

M Gladwin et al. New Engl J Med 2004

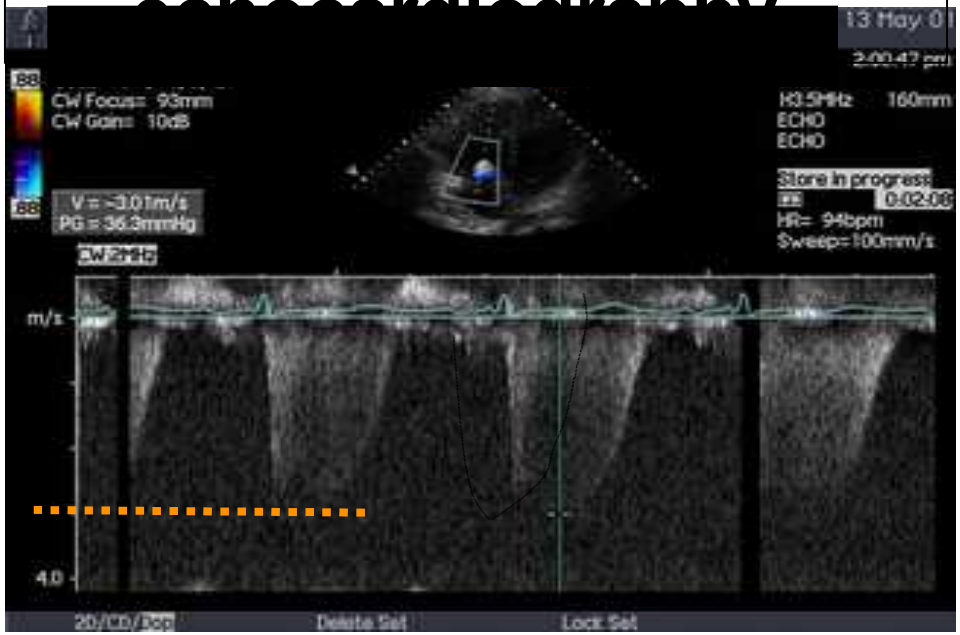
Hôpitaux universitaires Paris-Sud

Measurement of Pulmonary arterial pressure

Right Heart Catheterism



Doppler



Gold Standard Tool

Mean PAP > 25 mmHg

Estimation from TRJV

Systolic PAP =

(TRJV max)²+

RAP(estimated)

Hôpitaux universitaires Paris-Sud

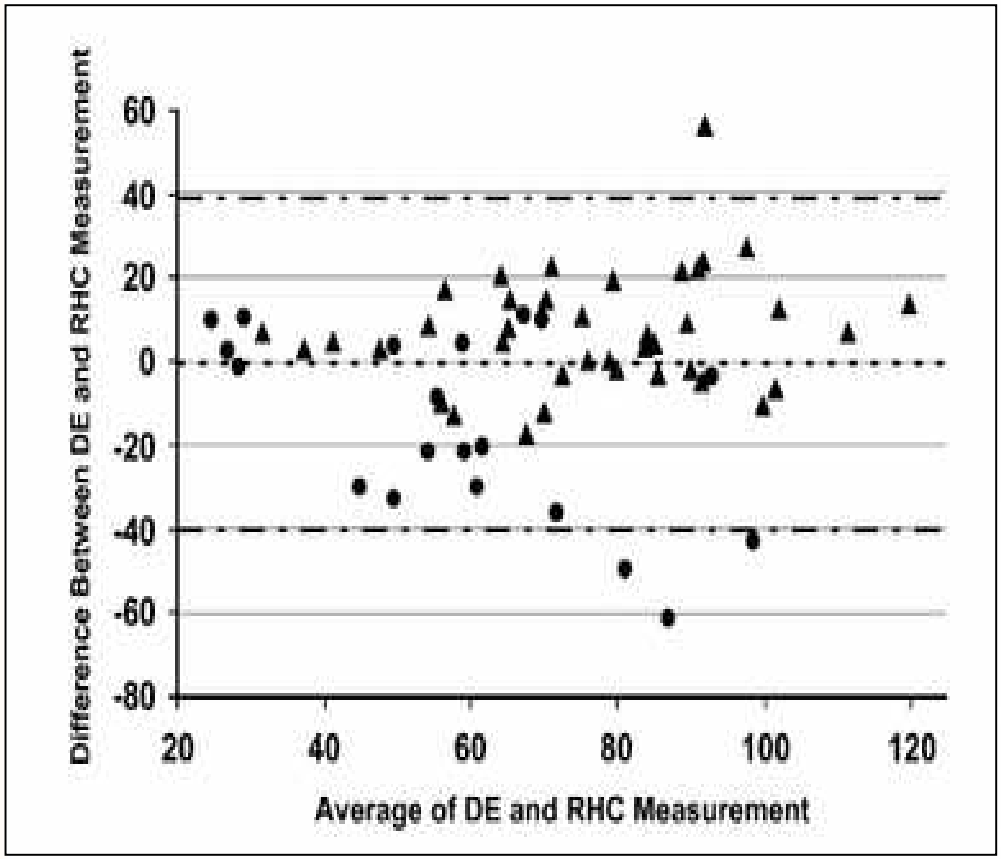
Correlation between RH catheterization and echocardiography

Accuracy of Doppler Echocardiography in the Hemodynamic Assessment of Pulmonary Hypertension

Micah R. Fisher[1]*, Paul R. Forfia[2]†, Elzbieta Chamera[2], Traci Housten-Harris[1], Hunter C. Champion[2], Reda E. Girgis[1], Mary C. Corretti[2], and Paul M. Hassoun[1]

Am J Respir Crit Care Med 2009

[1]Division of Pulmonary and Critical Care Medicine; [2]Division of Cardiology, Department of Medicine, Johns Hopkins University, Baltimore, Maryland



Doppler Echocardiography was inaccurate in 48% of cases (D greater than ~ 10 mmHg)

Over and under-estimation occured with a similar frequency (16% vs15%)

Hôpitaux universitaires Paris-Sud

Definitions of PH/PAH

- **Pulmonary Hypertension(PH)** is an Hemodynamic and pathological condition defined as mPAP ≥ 25mmHg at rest
  - **Pre-capillary PH** : (PAWP ≤ 15 mm Hg)
  - **Post-capillary PH** : (PAWP >15 mm Hg)

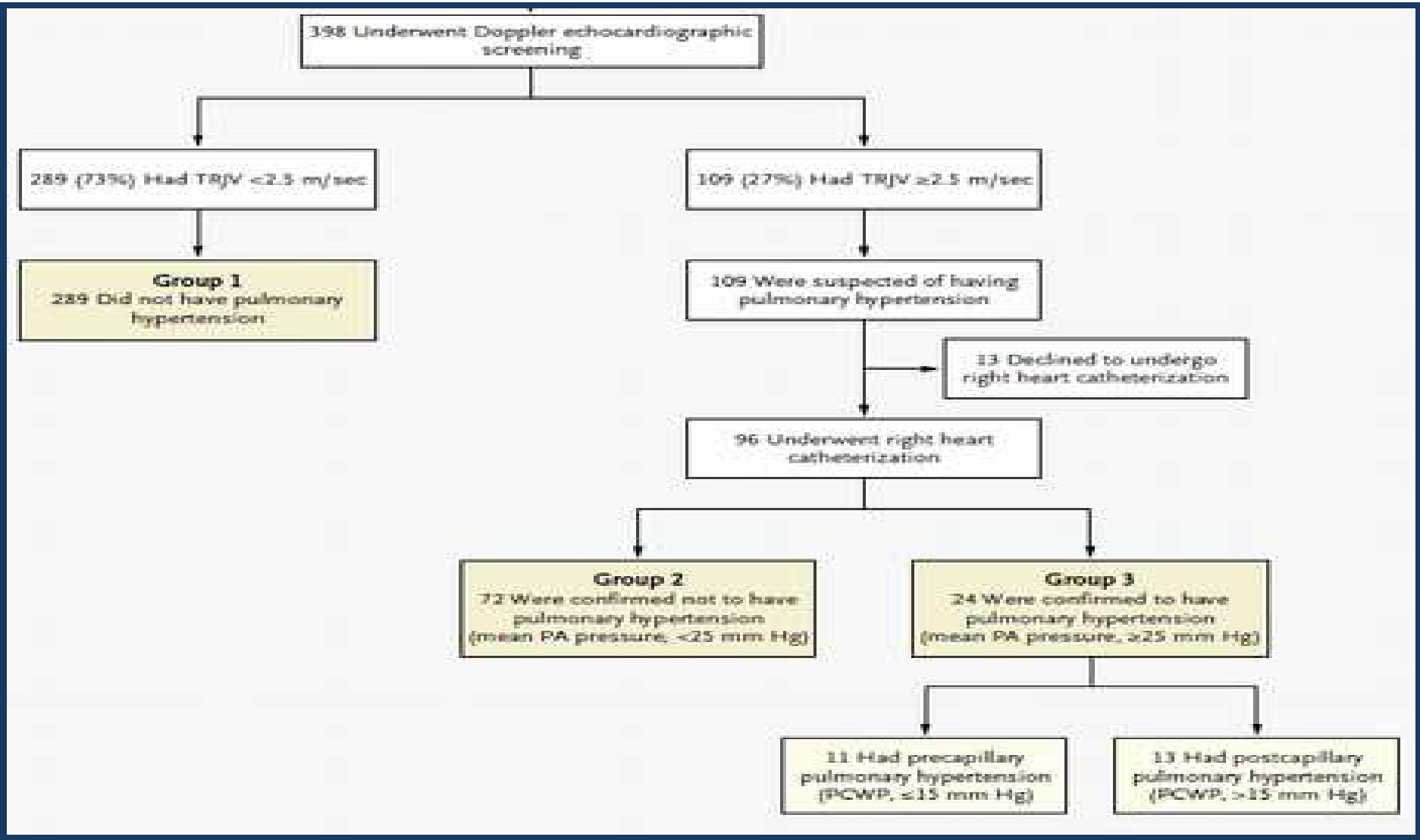
- Pulmonary vascular resistance PVR (mPAP-PAWP/CO) is not be used in general PH definition

- But is included in the hemodynamic definition of **PAH** (Group1) as follows: mPAP ≥ 25 mmHg, PAWP ≤ 15 mm Hg and elevated PVR > 3 WU (240 dynes.s.cm-5)

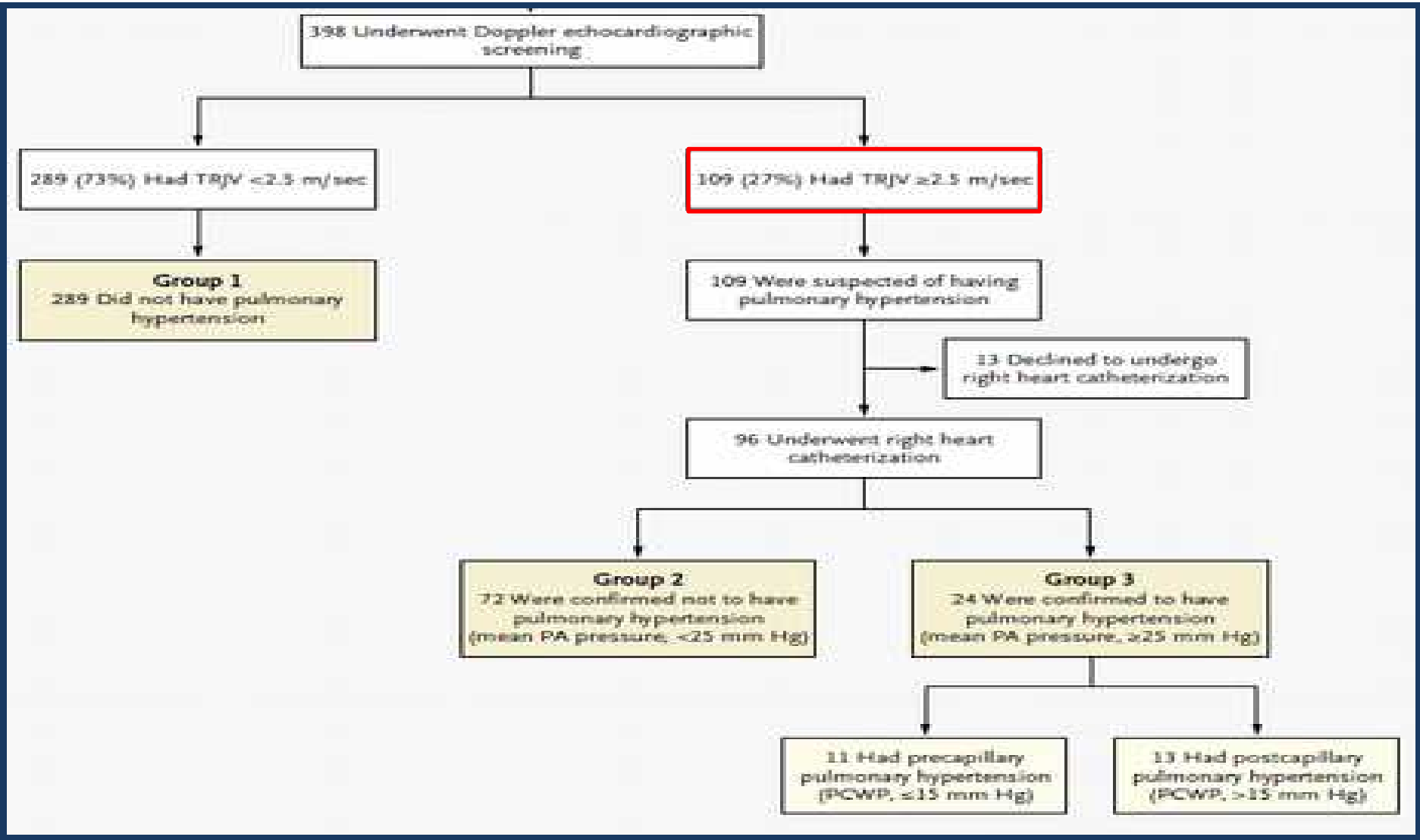
Hoeper MM, et al. J Am Coll Cardiol 2013

Hôpitaux universitaires Paris-Sud

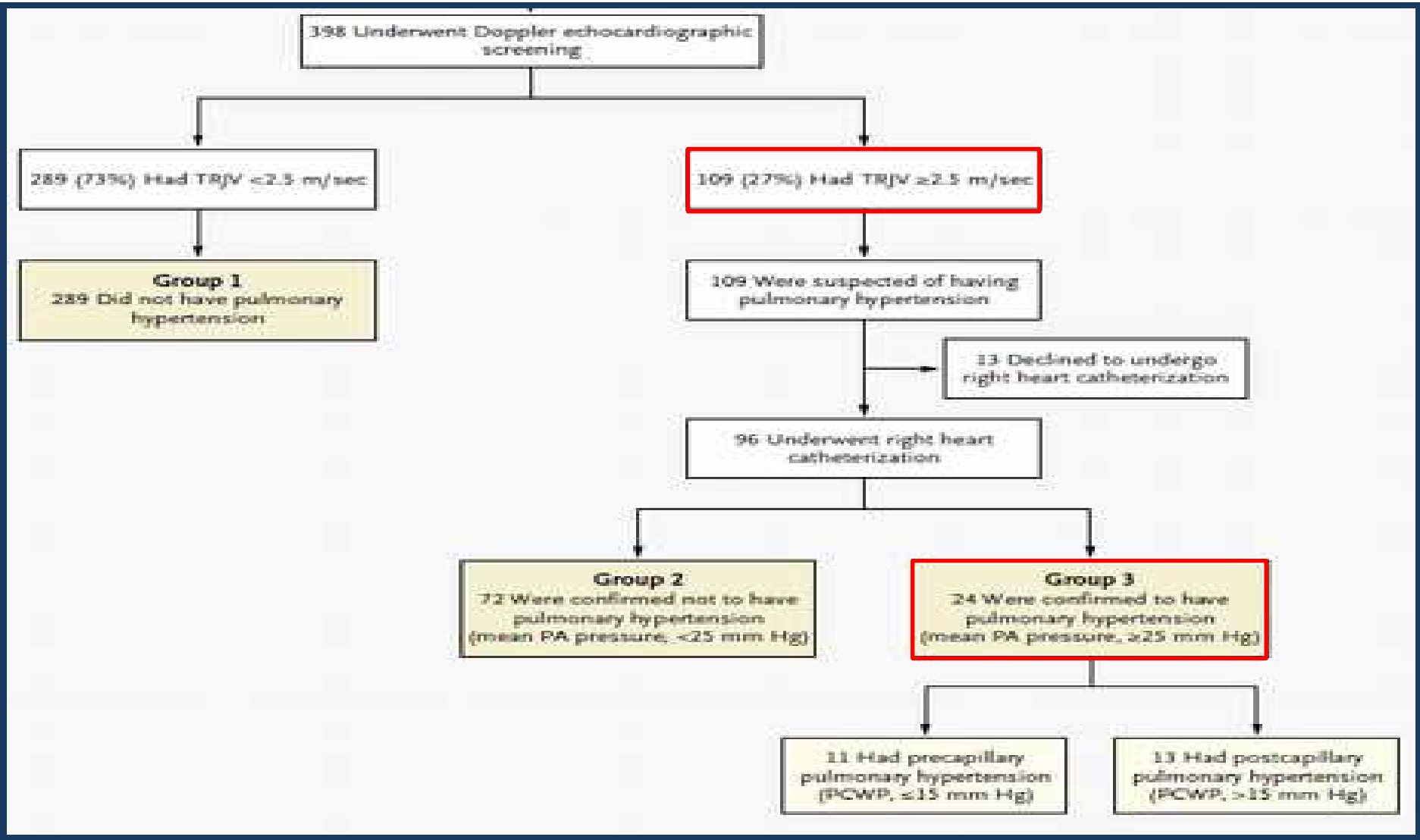
A Hemodynamic Study of Pulmonary Hypertension in Sickle Cell Disease



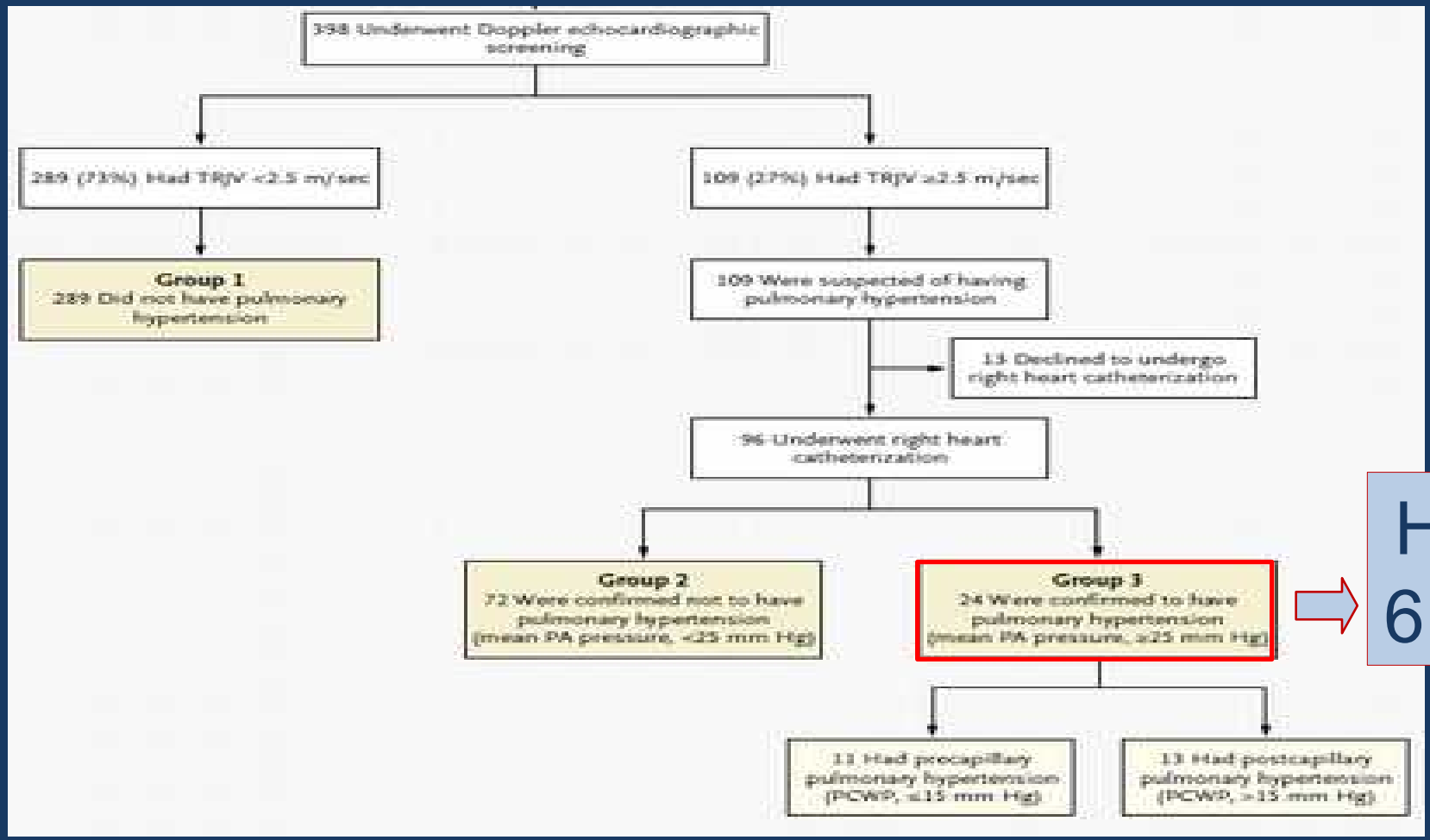
A Hemodynamic Study of Pulmonary Hypertension in Sickle Cell Disease



A Hemodynamic Study of Pulmonary Hypertension in Sickle Cell Disease

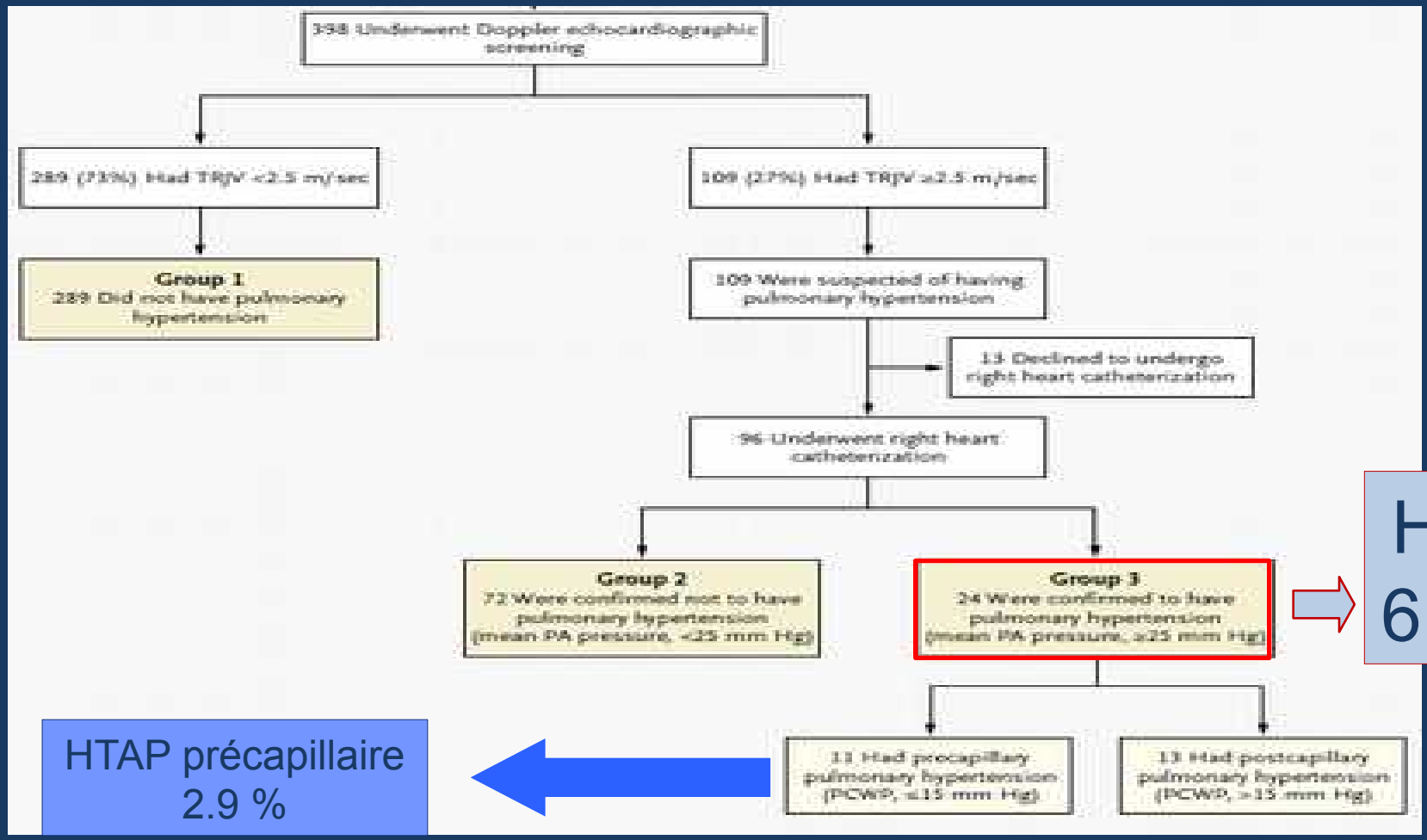


A Hemodynamic Study of Pulmonary Hypertension in Sickle Cell Disease



HTP
6.2%

A Hemodynamic Study of Pulmonary Hypertension in Sickle Cell Disease



HTP
6.2%

HTAP précapillaire
2.9 %

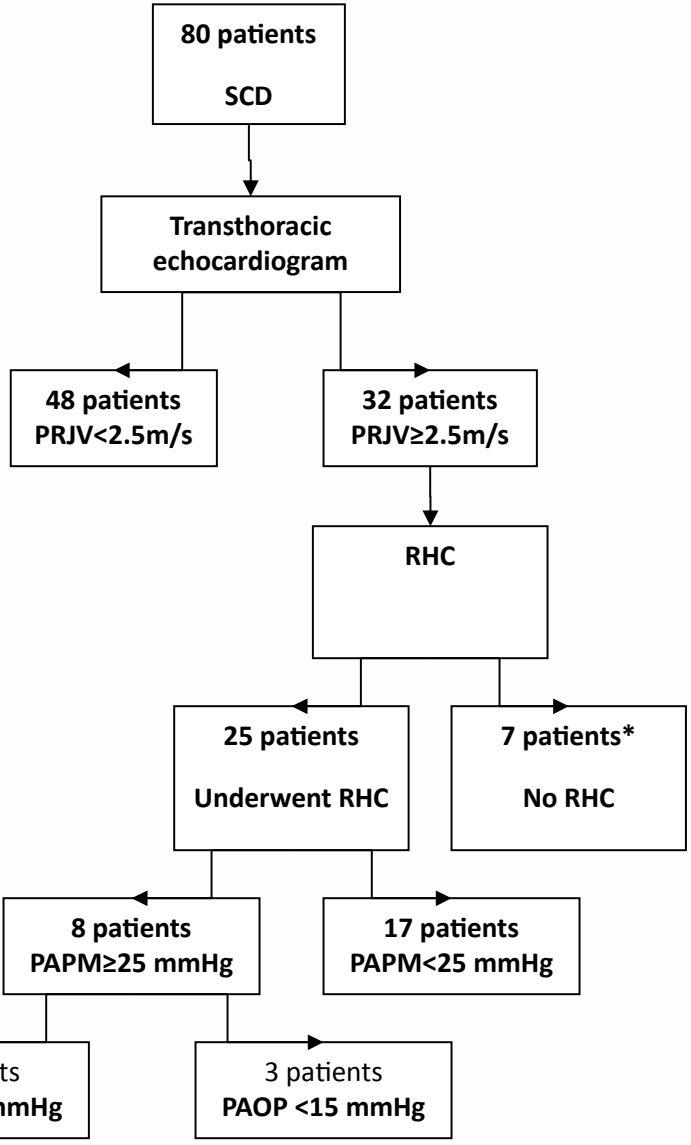
Hemodynamics in different PH Subgroups

	Precapillary Pulmonary Hypertension (N=11)	Postcapillary Pulmonary Hypertension (N=13)
Patients who were evaluated (% of all study patients)	3	3
Tricuspid regurgitant jet velocity (m/sec)	3.1±0.5	3.0±0.4
Mean pulmonary arterial pressure (mm Hg)	28±4	32±7
Pulmonary arterial systolic pressure (mm Hg)	43±7	45±8
Pulmonary arterial diastolic pressure (mm Hg)	15±5	22±6
Right atrial pressure (mm Hg)	5±2	13±5
Pulmonary-capillary wedge pressure (mm Hg)	10±3	21±5
Cardiac output (liter/min)	8.2±16	9.1±2.1
Pulmonary vascular resistance (dyn·sec·cm^{-5})	178±55	104±26

Parent et al, New Engl J Med, 2011

Hôpitaux universitaires Paris-Sud

Sickle Cell Disease
Hemodynamics



Prevalence of PH: 10%

Fonseca, ERJ, 2012

Hemodynamic results in the French and US cohorts

	n	mPAP (mm Hg)	Pcwp (mm Hg)	CO (l / mn)	PVR (dyn.sec.cm-5)
French* Cohort	24	30 ~ 6	16 ~ 7	8.7 ~ 1.9	138 ~ 58
US** Cohort	18	34 ~ 11	17 ~ 5	10.2 ~ 3	148 ~ 111

**Gladwin *et al.* N Engl J Med. 2004

*Parent et al, New Engl J Med, 2011

Hôpitaux universitaires Paris-Sud

Hemodynamic results in the French and US cohorts

	n	mPAP (mm Hg)	Pcwp (mm Hg)	CO (L/min)	PVR (dyn.sec.cm-5)
French* Cohort	24	30 ~ 6	16 ~ 7	8.7 ~ 1.9	138 ~ 58
US** Cohort	18	34 ~ 11	17 ~ 5	10.2 ~ 3	148 ~ 111
US*** Cohort	55	32 ~ 12	16 ~ 5	8.4 ~ 2.5	227 ~ 149

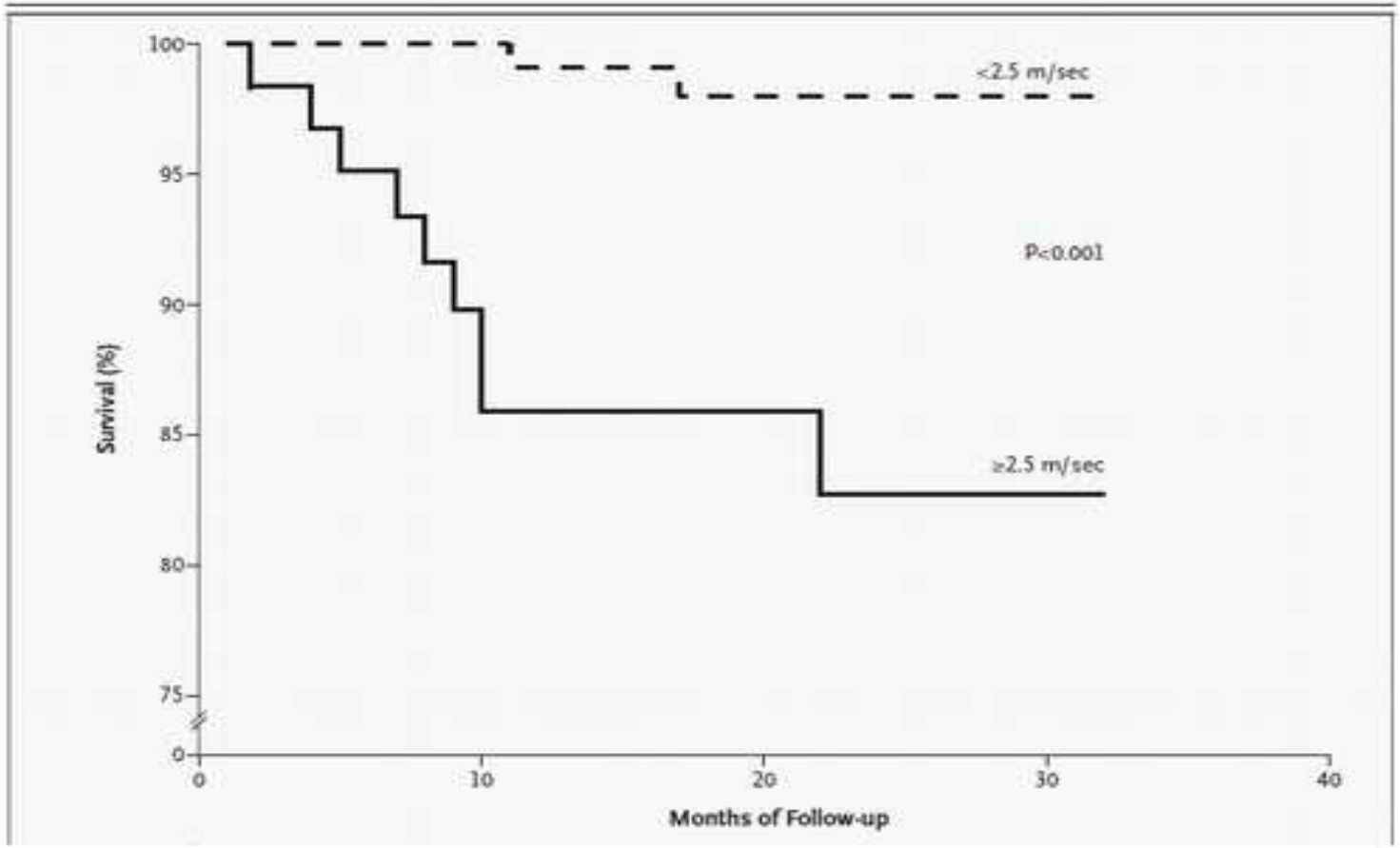
*Parent et al, New Engl J Med, 2011
**Gladwin *et al.* N Engl J Med. 2004
***Mehari et al, AJRCCM, 2013

Hôpitaux universitaires Paris-Sud

Pronostic in Patients with PH associated with SCD

US cohort

Mean Follow-up 18 months
Overall rate of Death 5.3 %



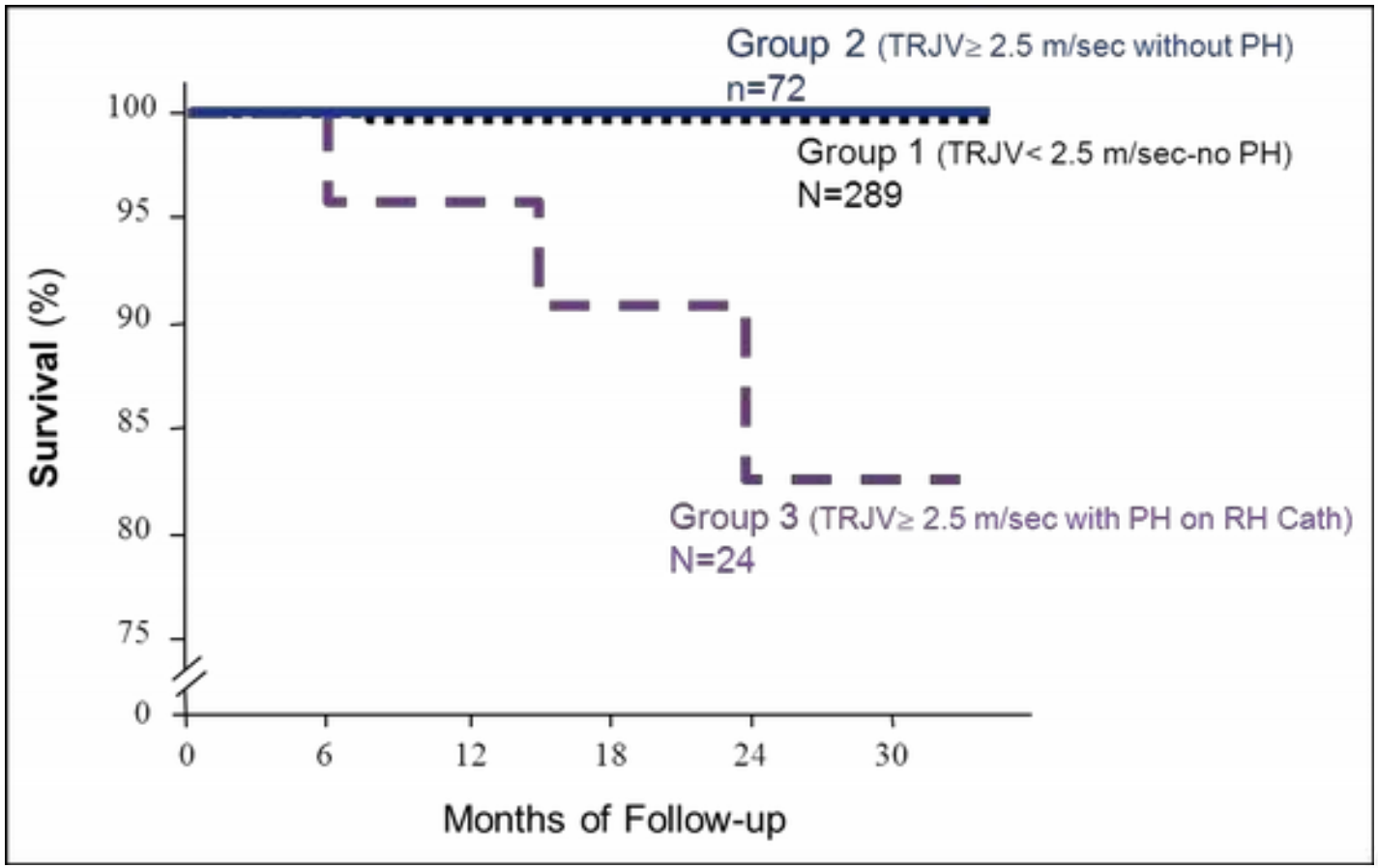
M Gladwin et al. New Engl J Med 2004

Hôpitaux universitaires Paris-Sud

Pronostic in Patients with PH associated with SCD

French cohort

Mean Follow-up 26 months: overall rate of death 2.0 %



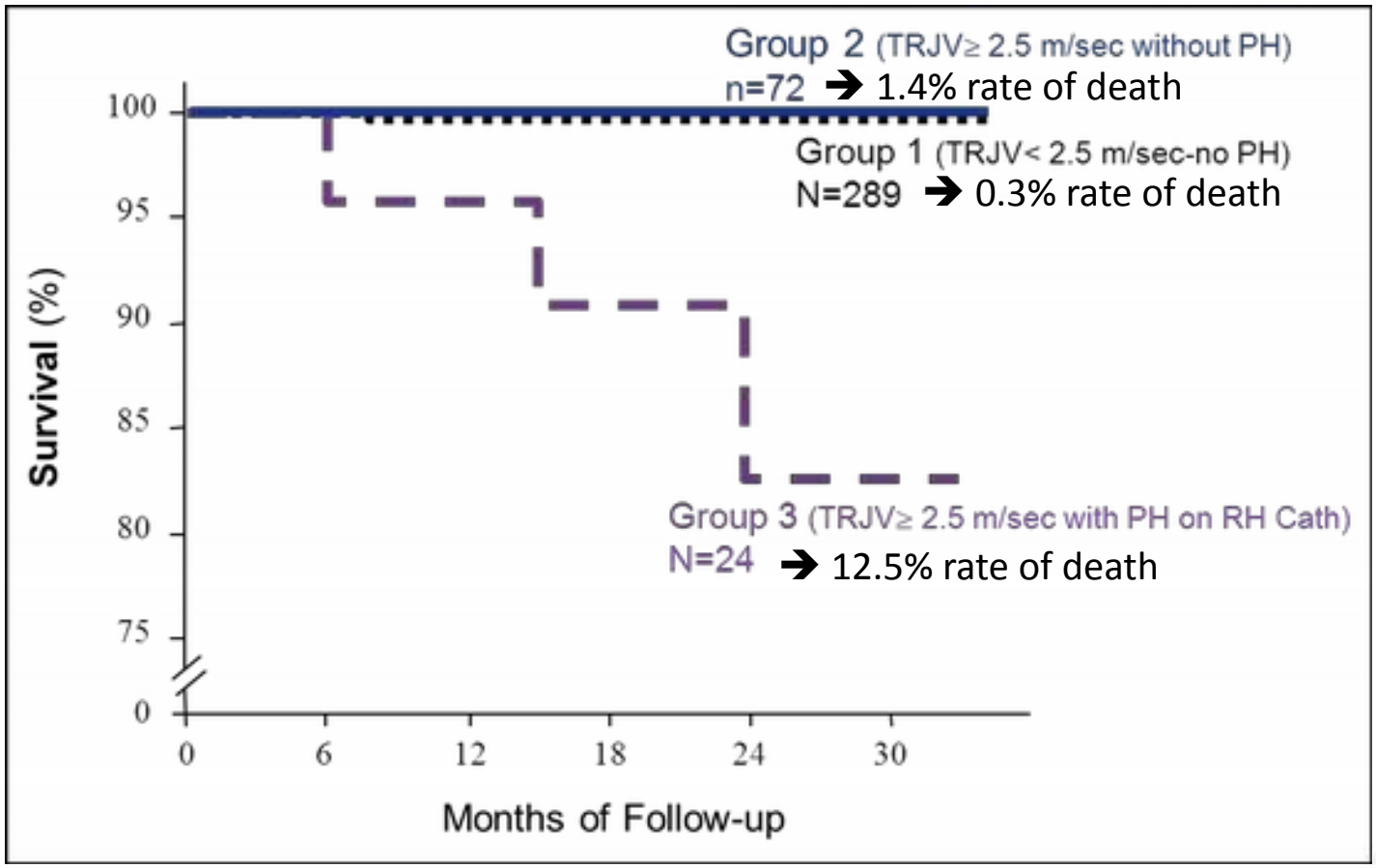
F Parent et al, New Engl J Med, 2011

Hôpitaux universitaires Paris-Sud

Pronostic in Patients with PH associated with SCD

French cohort

Mean Follow-up 26 months: overall rate of death 2.0 %

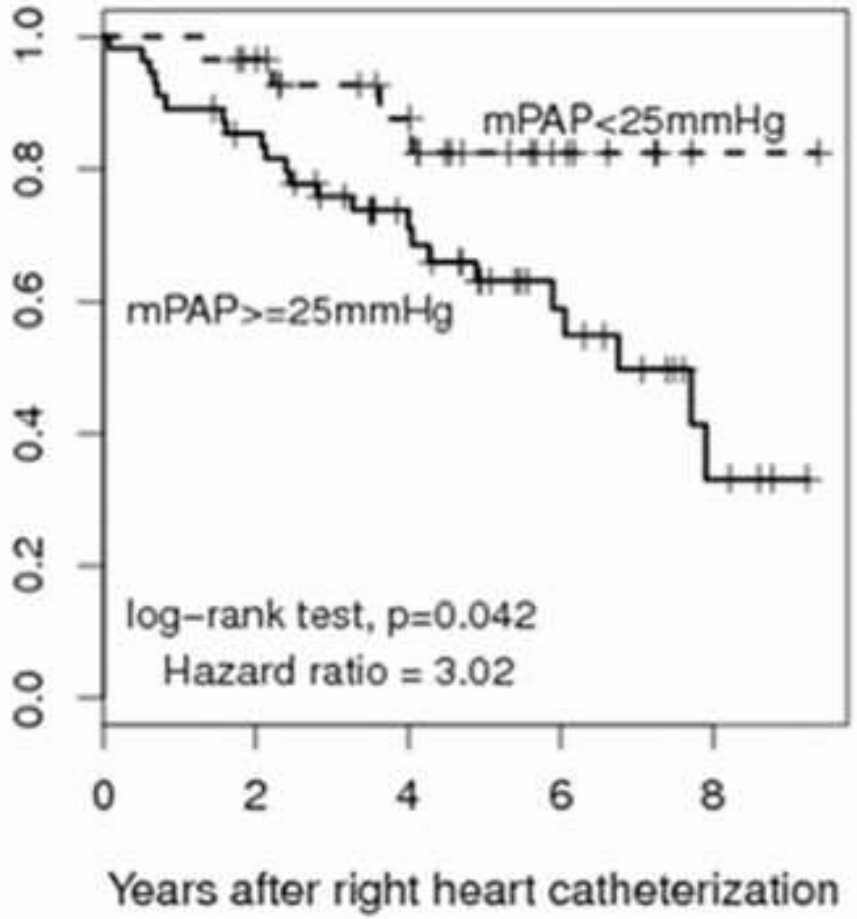


F Parent et al, New Engl J Med, 2011

Hôpitaux universitaires Paris-Sud

Pronostic in Patients with PH associated with SCD

US cohort: 84 SCD with RHC



Mehari et al. AJRCCM 2013; 187: 840-7

Hôpitaux universitaires Paris-Sud

CHARACTERISTICS OF PATIENTS

Characteristics	French Cohort** N=385	US Cohort* N=195
Age *(yr)*	34 ~ 10	36 ~ 12
Female sex *(%)*	60%	58%
History of ACS *(%)*	34%	83%
History of stroke *(%)*	5%	15%
Systolic blood pressure *(mmHg)*	118 ~ 16	122 ~ 18
Hemogobin SS Hemogobin SC Hemogobin S-thalassemia	98.5% 0% 1.5%	69% 18% 12%
Hydroxyurea therapy *(%)*		
Blood transfusion	36%	42%

*

Hôpitaux universitaires Paris-Sud

Causes of Death in SCD French Cohort

Characteristic	*Patient 1*	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*
	*TRJV<2.5m/s**	*TRJV≥2.5m/s*	*TRJV≥2.5m/s*	*TRJV≥2.5m/s*	*TRJV≥ 2.5m/s*
	Group 1	**Group 2**		**Group 3**	
Age (yr)	37	40	58	58	56
TRJV (m/s)	2.3	2.8	2.5	2.7	4.0
mPAP (mmHg)	NA	14	36	31	25
RAP (mmHg)	NA	5	19	5	5
PCWP (mmHg)	NA	9	26	10	6
CO (L/min)	NA	5.9	8.5	7.9	8.1
PVR (dyn.s.cm^{-5})	NA	68	94	213	188
Cause of death	Vaso-occlusive crisis	Sudden death at 37 weeks of pregnancy	Acute chest syndrome	Acute chest syndrome	Progressive right heart failure

Parent et al, New Engl J Med, 2011 (Supplement)

Paris-Sud

Echocardiography for screening PH in SCD

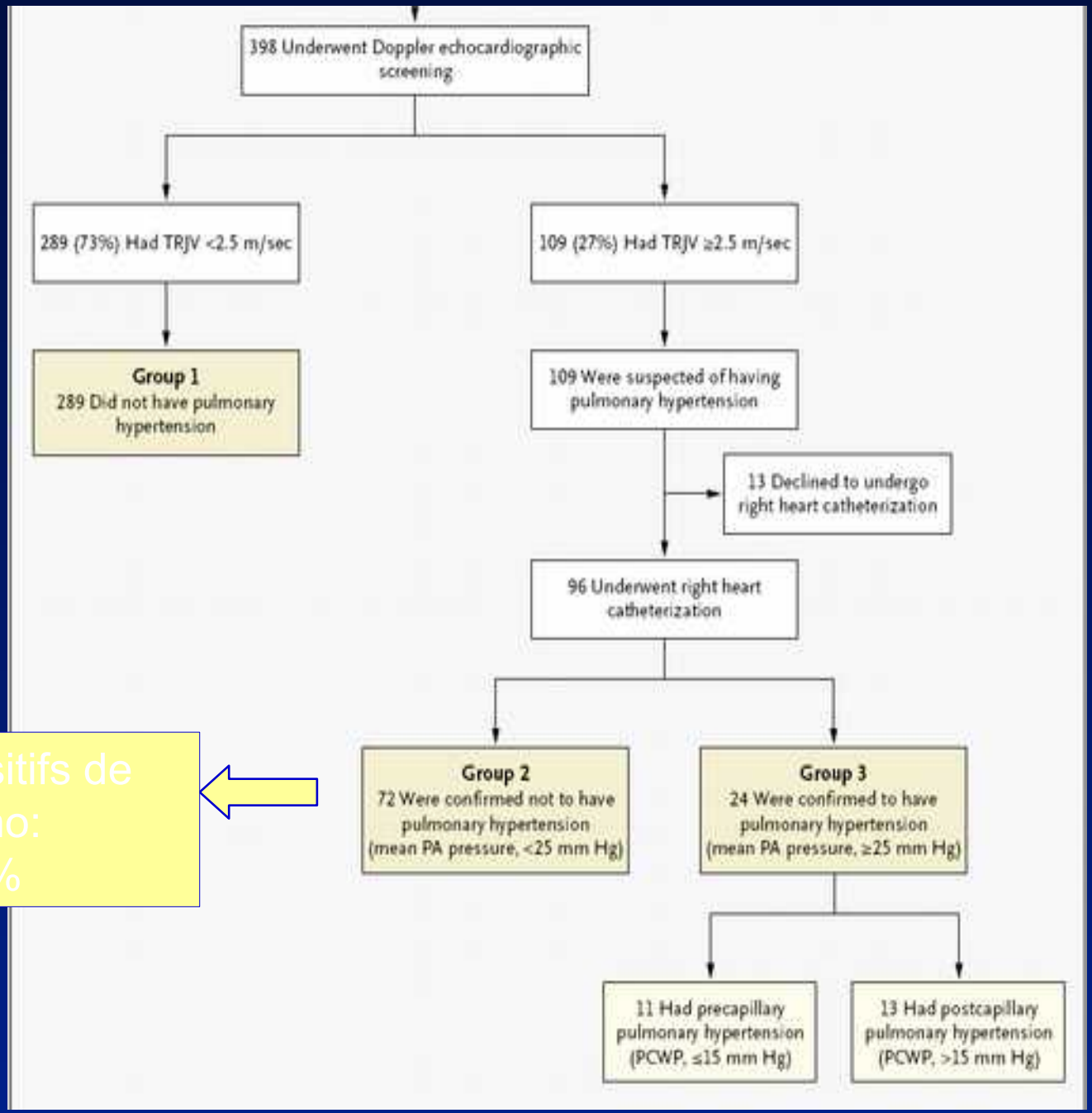
- It is clear, from out data* that in asymptomatic patients with SCD, echocardiography (TRJV) used as a single tool to select patients who should undergo RHC is not ideal, regardless of the cut-off value of TRJV

- Limitations of echocardiography alone for screening PH, have been also recently shown in a population of asymptomatic SSc patients (Detect sudy**)

Parent F et al, New Engl J Med, 2011 *

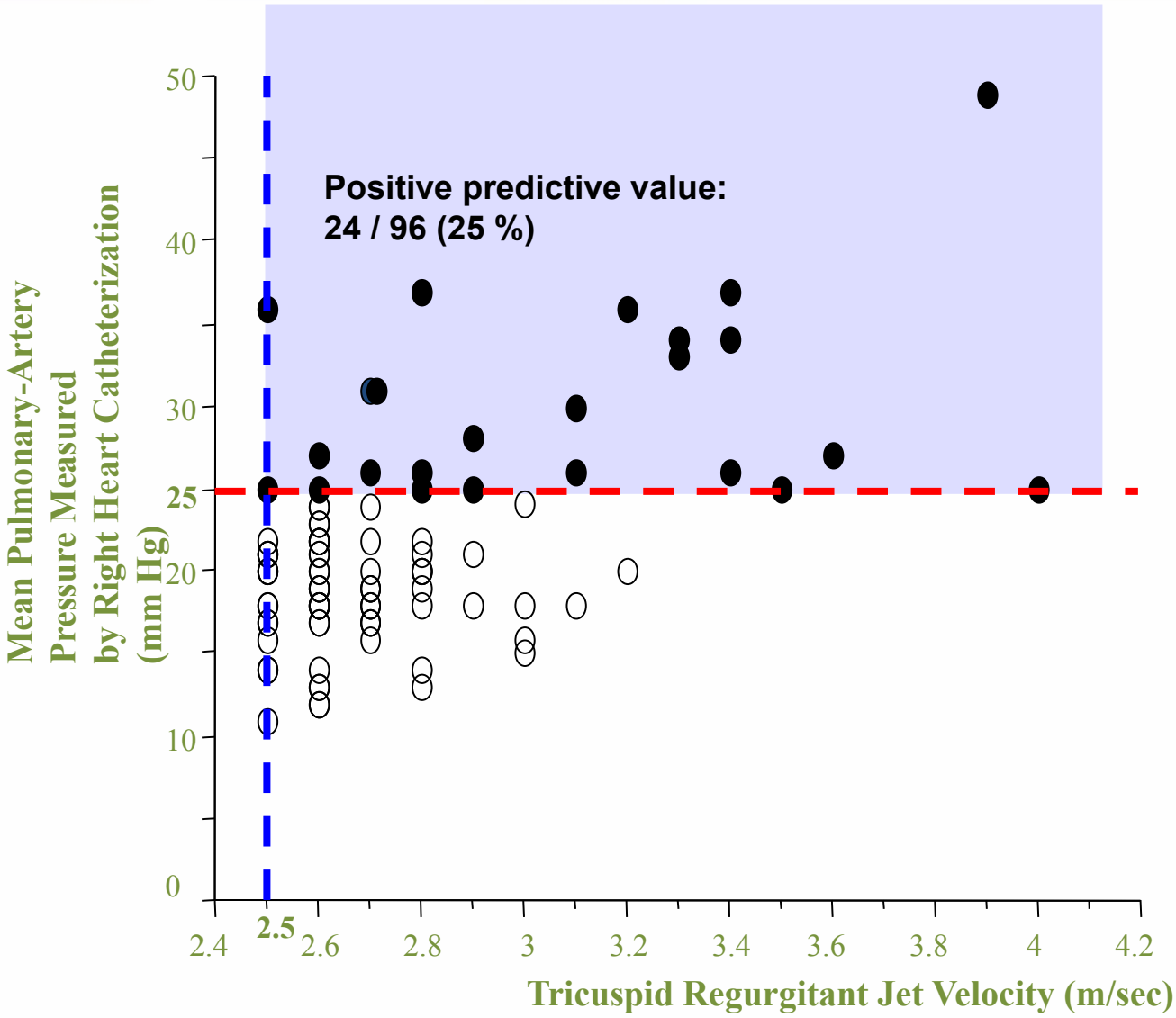
Coghlan JG et al, Ann Rheum Dis, 2014**

Hôpitaux universitaires Paris-Sud



Faux positifs de l'écho: 75%

Echocardiography for screening PH in SCD

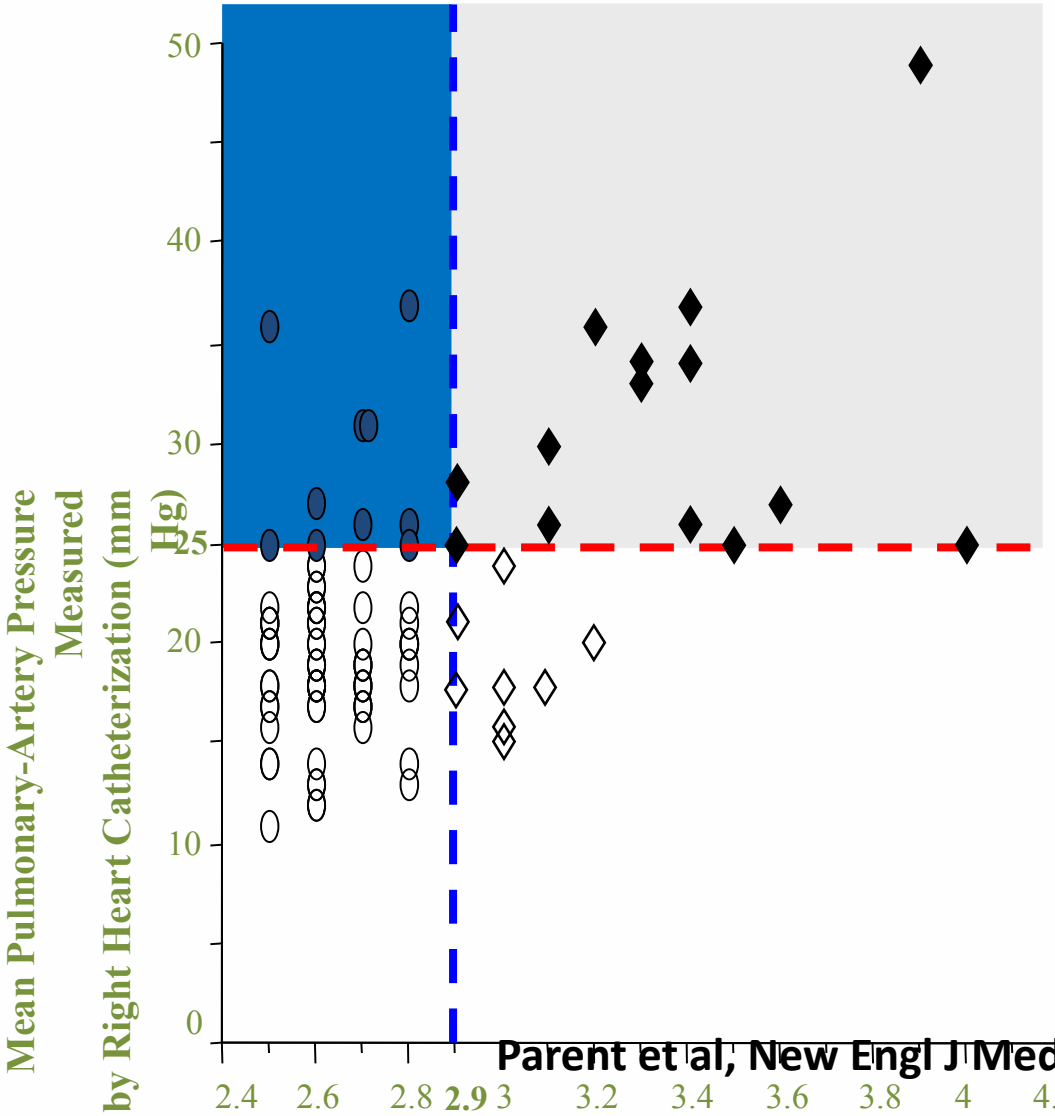


Parent et al, New Engl J Med, 2011

Echocardiography for screening PH in SCD

False negative: at least 42% 10/24

Positive predictive value: 14 / 22 (64 %)

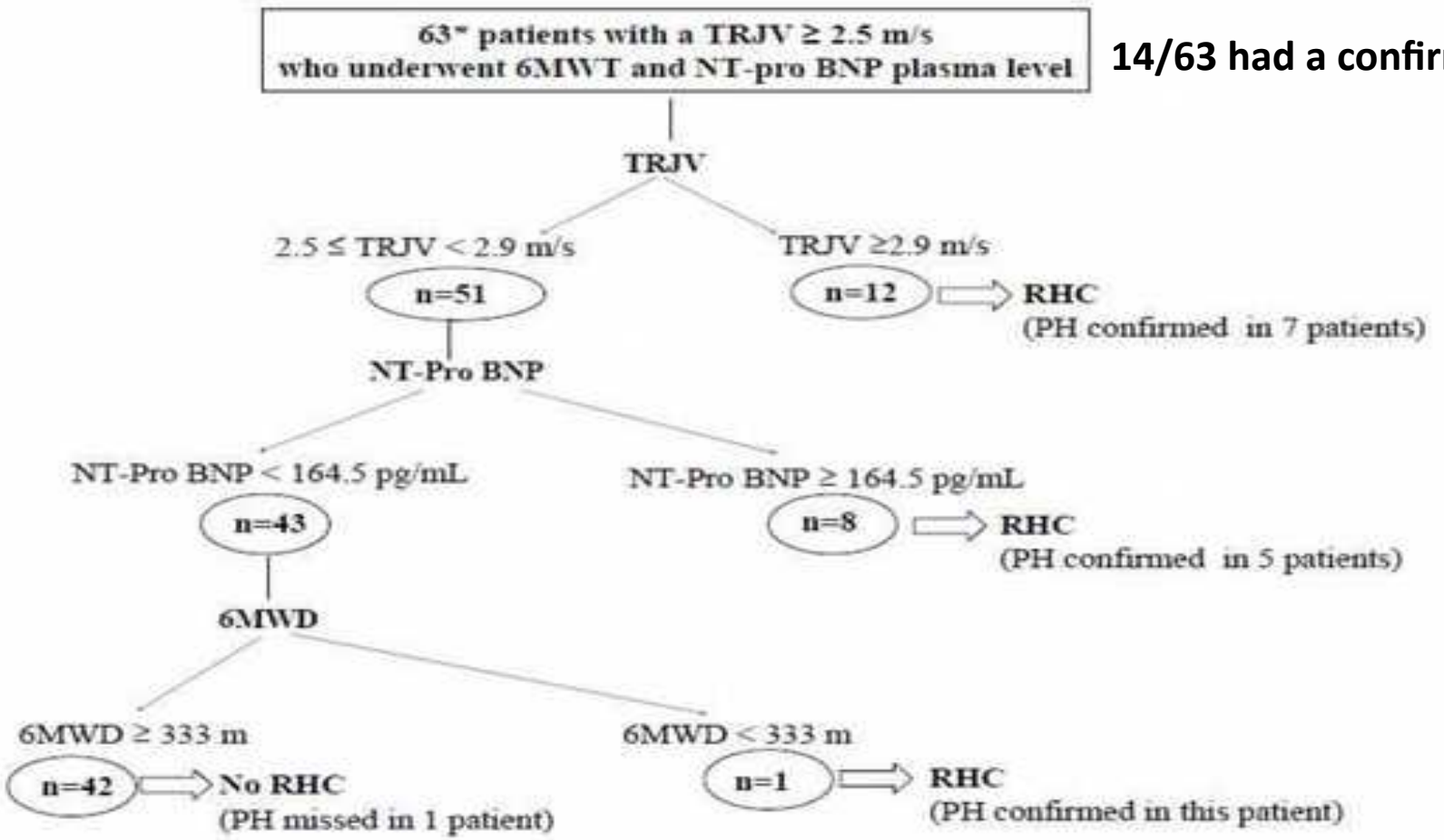


Parent et al, New Engl J Med, 2011

Characteristic	TRV < 2.5 m.s-1 *N=289*	*P value*	TRV ≅ 2.5 m.s-1 without PH *N=72*	*P value*	TRV ≅ 2.5 m.s-1 with PH *N=24*
Age *(yr)*	33 ± 9	***0.03***	36 ± 11	***<0.001***	45 ± 10
Female sex *(%)*	32%	***0.11***	51%	***0.10***	71%
NYHA I/II *(%)* NYHA III *(%)*	94.5 5.5	***0.4***	93.1 6.9	***0.0001***	62.5 37.5
Systolic blood pressure *(mm Hg)*	116 ± 16	***0.03***	121 ± 14	***0.31***	124 ± 15
6MWD *(m)*	520 ± 88	***0.49***	527 ± 62	***<0.0001***	404 ± 94
PaO2 *(mmHg)*	87 ± 11	***0.38***	86 ± 11	***0.04***	80 ± 12
Urea *(mmol/l)*	3.3 ± 1.4	***0.26***	3.7 ± 2.2	***0.17***	5.0 ± 4.2
LDH *(U/L)*	466 ± 224	***0.32***	501 ± 274	***0.009***	901 ± 606
Bilirubin: total *(mmol/l)* direct *(mmol/l)*	58 ± 44 11 ± 8	***0.6*** ***0.9***	62 ± 86 11 ± 6	***0.9*** ***0.02***	60 ± 35 16 ± 15
NT–proBNP *(pg/ml)*	121 ± 185	***0.44***	107 ± 101	***<0.0001***	1020 ± 2153

Characteristic	TRV < 2.5 m.s-1 *N=289*	*P value*	TRV ≅ 2.5 m.s-1 without PH *N=72*	*P value*	TRV ≅ 2.5 m.s-1 with PH *N=24*
Age *(yr)*	33 ± 9	***0.03***	36 ± 11	***<0.001***	45 ± 10
Female sex *(%)*	32%	***0.11***	51%	***0.10***	71%
NYHA I/II *(%)* NYHA III *(%)*	94.5 5.5	***0.4***	93.1 6.9	***0.0001***	62.5 37.5
Systolic blood pressure *(mm Hg)*	116 ± 16	***0.03***	121 ± 14	***0.31***	124 ± 15
6MWD *(m)*	520 ± 88	***0.49***	527 ± 62	***<0.0001***	404 ± 94
PaO2 *(mmHg)*	87 ± 11	***0.38***	86 ± 11	***0.04***	80 ± 12
Urea *(mmol/l)*	3.3 ± 1.4	***0.26***	3.7 ± 2.2	***0.17***	5.0 ± 4.2
LDH *(U/L)*	466 ± 224	***0.32***	501 ± 274	***0.009***	901 ± 606
Bilirubin: total *(mmol/l)* direct *(mmol/l)*	58 ± 44 11 ± 8	***0.6*** ***0.9***	62 ± 86 11 ± 6	***0.9*** ***0.02***	60 ± 35 16 ± 15
NT–proBNP *(pg/ml)*	121 ± 185	***0.44***	107 ± 101	***<0.0001***	1020 ± 2153

A non parametric and regression tree (CART) analysis combining TRJV and two markers of PH NT-pro BNP & 6' WD



14/63 had a confirmed PH

- only 21 RHC instead of 63
- Positive predictive value of CART model 62 % (13 / 21)
- False negative of CART model ~7% (1 / 14)

Parent et al, New Engl J Med, 2011

Precapillary PH associated with SCD
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)

Classification of Pulmonary Hypertension

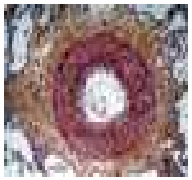
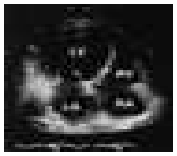
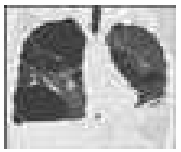
- ***During the most recent world meetings on PH, a clinical classification was proposed to individualize different categories of PH sharing***

  - similar pathophysiological mechanism
  - similar histological findings
  - similar clinical presentation
  - similar management

Evian Meeting (2nd WS, 1998)
Venice Meeting (3rd WS, 2003)
Dana Point Meeting (4th WS, 2008)
Nice Meeting(5th WS, 2013)

Hôpitaux universitaires Paris-Sud

Clinical classification of Pulmonary Hypertension

Category	Characteristics
Group 1 **Pulmonary Arterial Hypertension**	  
Group 2 **PH due to Left Heart diseases** **proliferation**	 **mild medial & intimal**
Group 3 **PH due to Lung Diseases** **proliferation**	 **mild medial & intimal**
Group 4 **Chronic Thromboembolic PH**	
Group 5 **PH with unclear or multifactorial mechanisms**	

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

Hôpitaux universitaires Paris-Sud

Drépanocytose:mécanismes de l'HTP pré-capillaire

- **Augmentation du débit cardiaque en rapport avec l'anémie chronique**
- Thrombose au niveau des artères pulmonaires (asplénisme, thrombocytose, état d'hypercoagulabilité)
- Modification de la rhéologie sanguine (hyperviscosité) entrainant une élévation des RVP
- Dysfonction endothéliale entrainant un remodelage des AP de petit calibre (< 500 µ) comme dans l'HTAP.

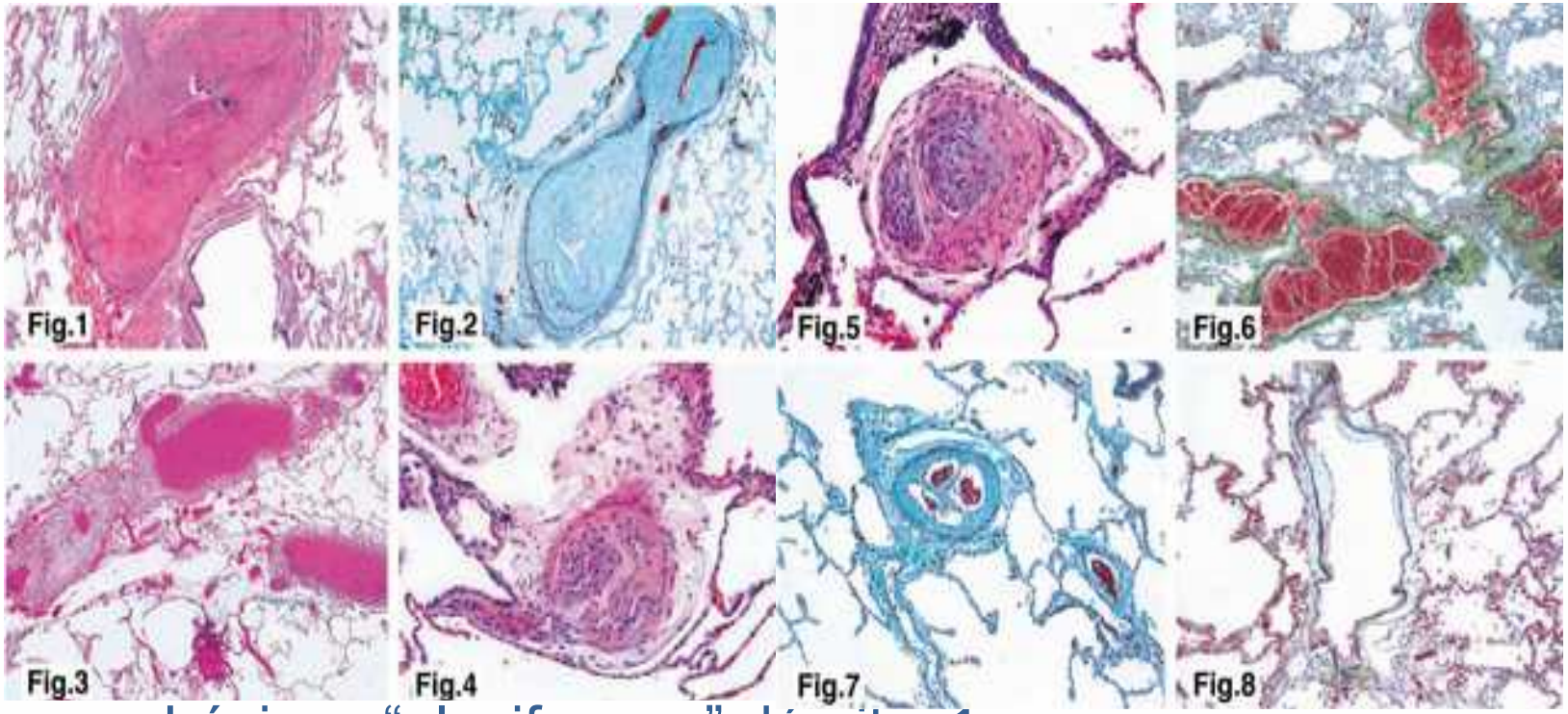
Hôpitaux universitaires Paris-Sud

Drépanocytose:mécanismes de l'HTP pré-capillaire

- **Augmentation du débit cardiaque en rapport avec l'anémie chronique**
- **Thrombose au niveau des artères pulmonaires (asplénisme, thrombocytose, état d'hypercoagulabilité)**
- Modification de la rhéologie sanguine (hyperviscosité) entrainant une élévation des RVP
- Dysfonction endothéliale entrainant un remodelage des AP de petit calibre (< 500 µ) comme dans l'HTAP.

Hôpitaux universitaires Paris-Sud

Intégré au Groupe 1 dans la classification Dana point

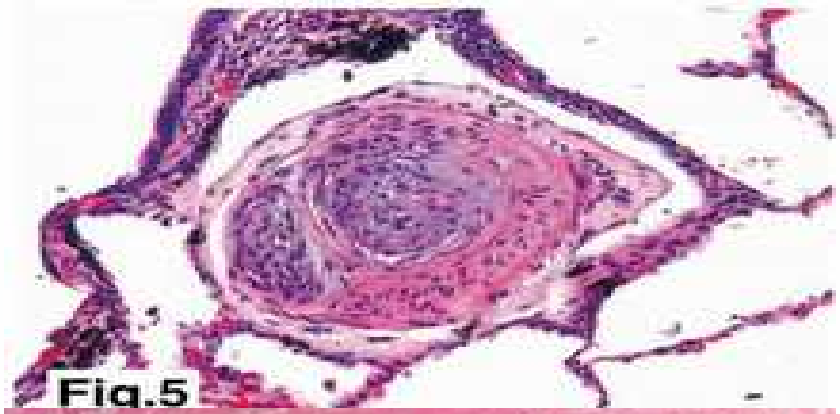


- Lésions “plexiformes” décrites1
- Incidence élevée? 2
- Impact sur la survie2

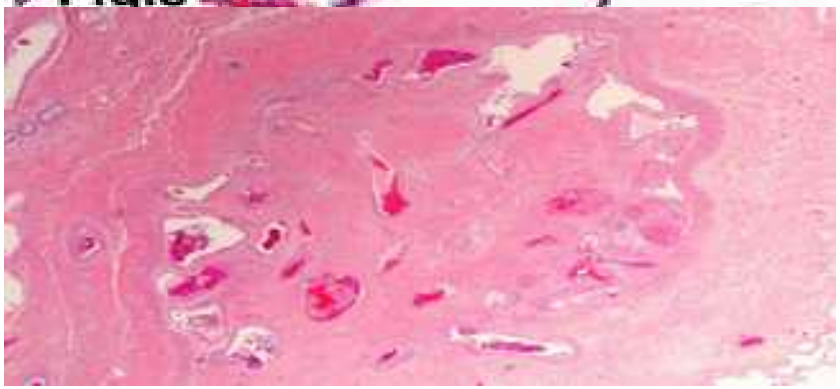
Mais ….

1Haque *et al.* Human Pathology 2002
2Gladwin *et al*, NEJM 2003

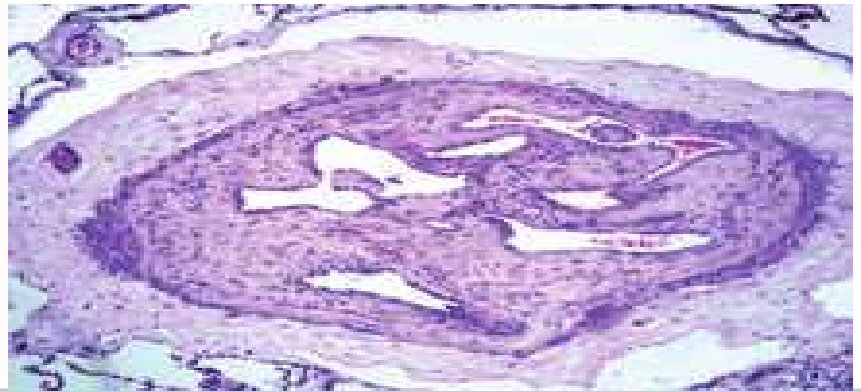
Distal thrombotic obstructions of pulmonary arteries with partial recanalization



Haque et al,
Human Pathology, 2002
Lésions "plexiformes"décrites ?



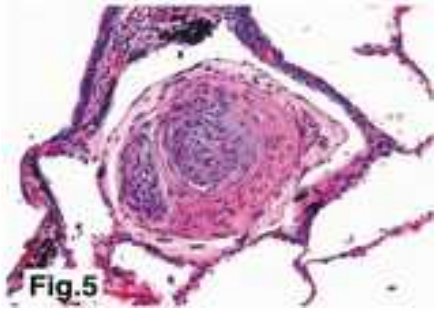
R Souza et al,
Unpublished data



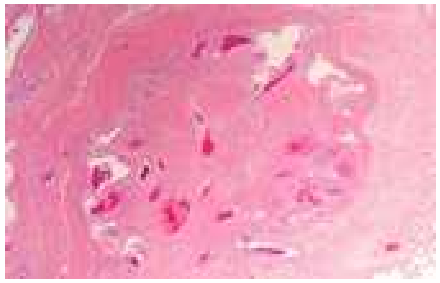
Graham et al,
Am J Forens Med Path, 2007

Hôpitaux universitaires Paris-Sud

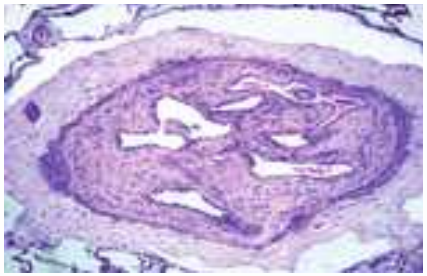
HTP et drépanocytose : lésions histologiques



Haque *et al.* Human Pathology 2002.



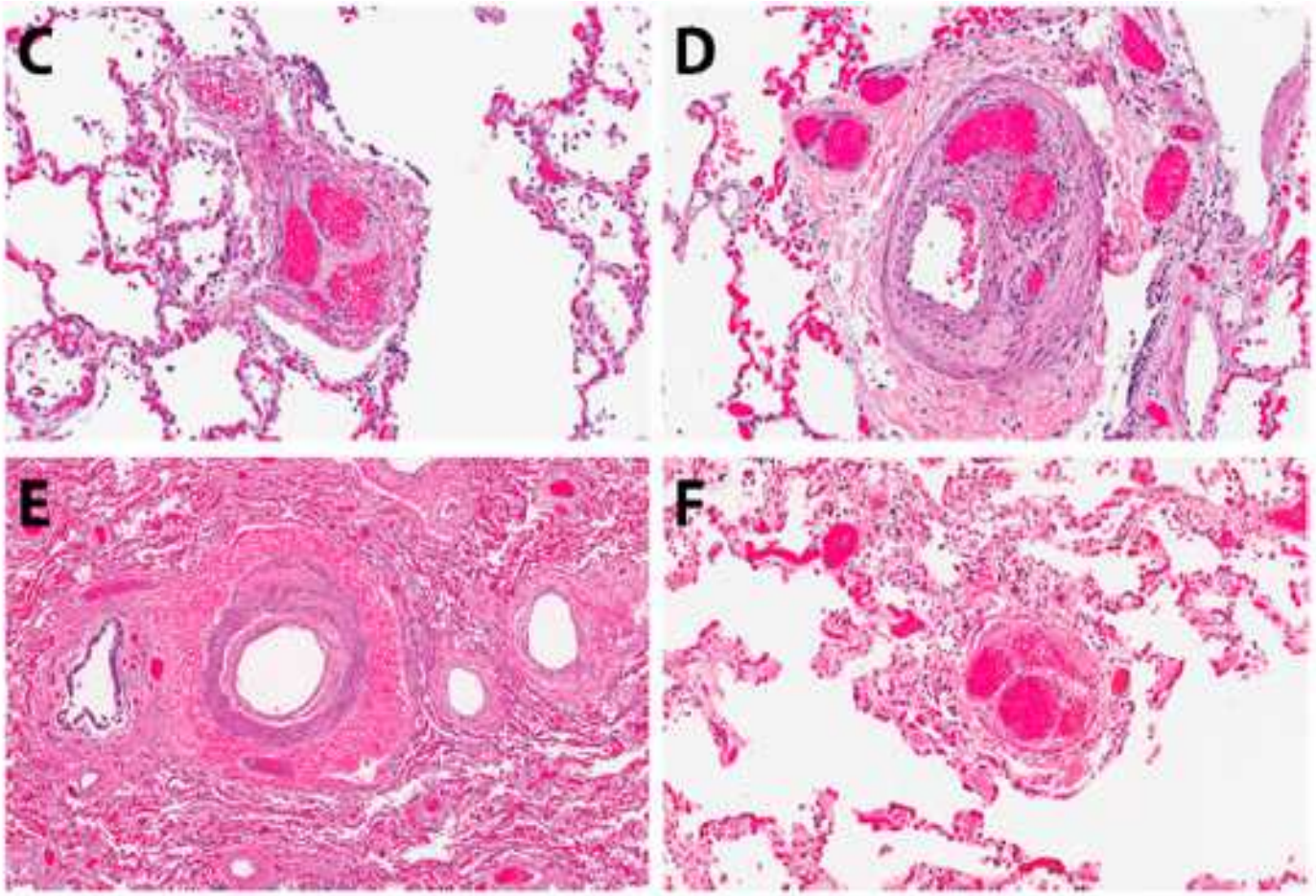
Rasse *et al.* ERS congress 2013.



Graham *et al.* Am J Forens Med Path 2007.

Pas de lésions plexiformes mais:
- obstruction thrombotique distale avec recanalisation partielle
- Epaississement de l'intima et de la media
- Hémangiomatose capillaire

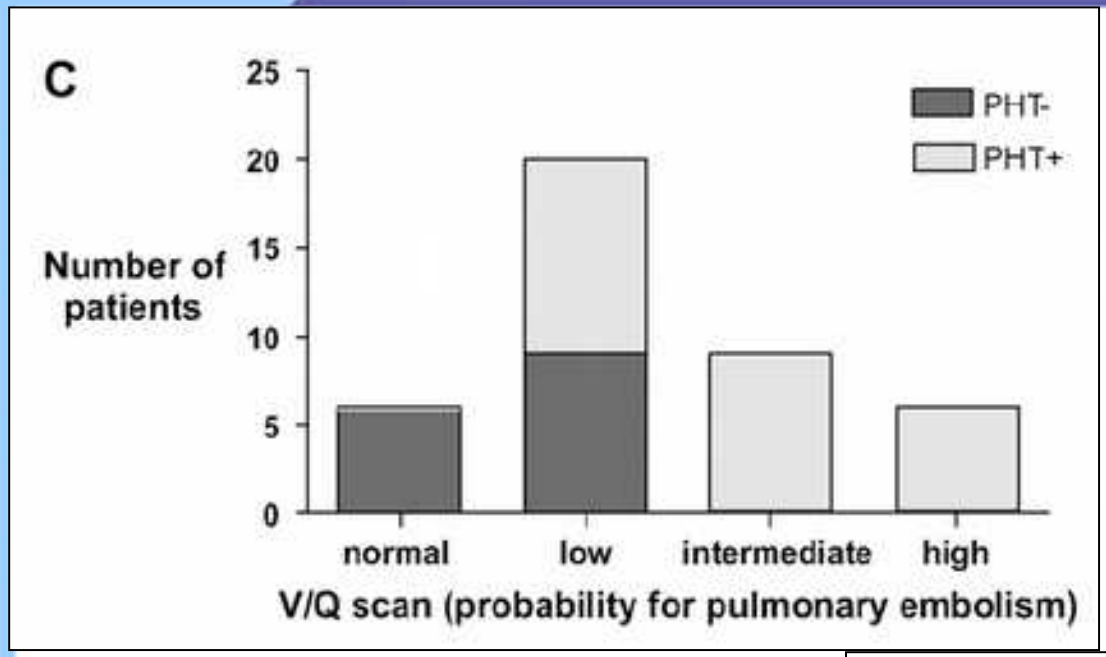
Distal thrombotic obstructions of pulmonary arteries with partial recanalization



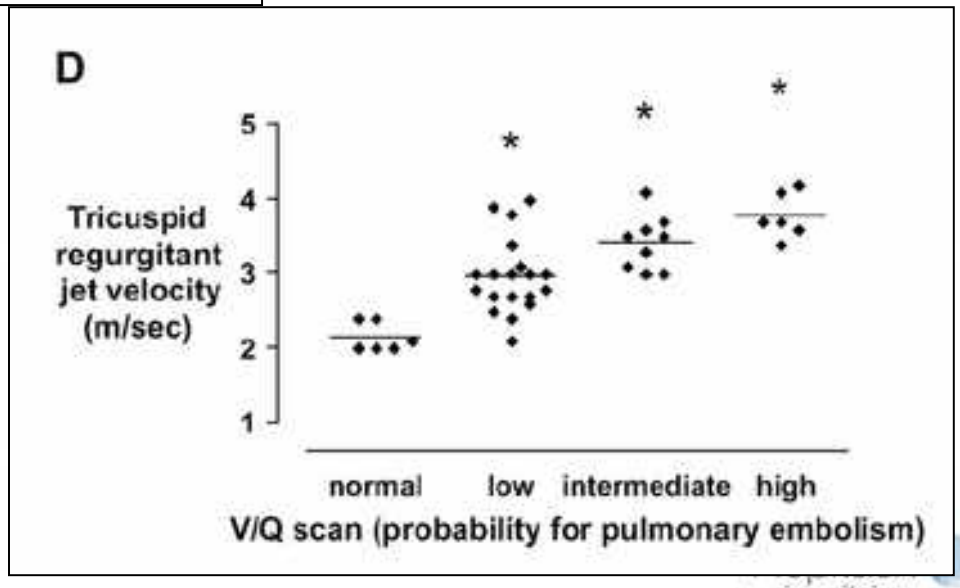
A Mehari et al Am j Respir Crit Care Med 2013

Hôpitaux universitaires Paris-Sud

V/Q Scan is frequently abnormal in Patients with SCD



PH+: n = 26
PH-: n=17



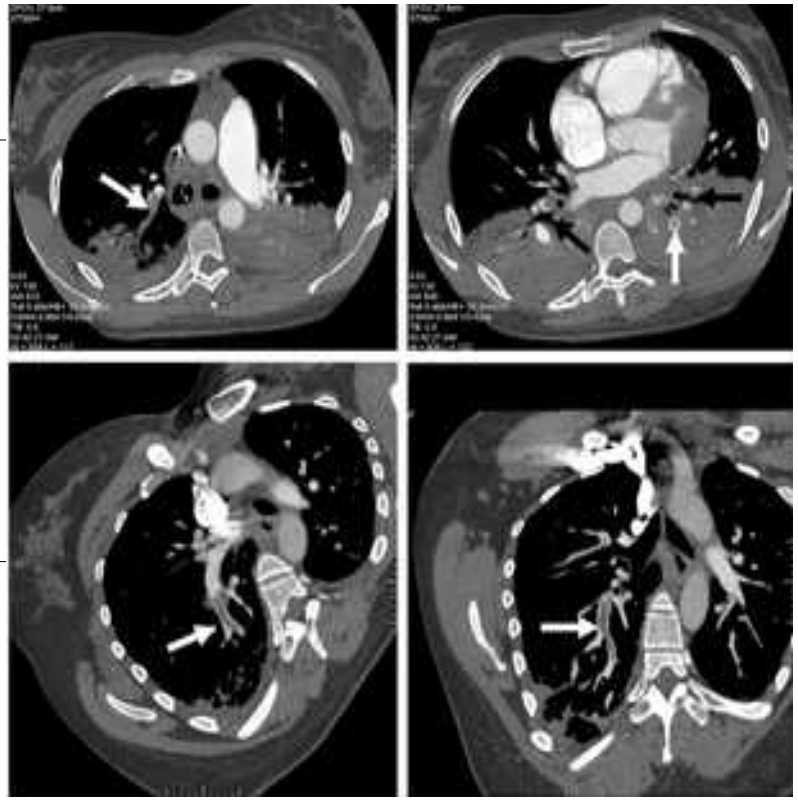
A Anthi et al. Am J Respir Crit Care Med 2007

universitaires Paris-Sud

Pulmonary Artery Thrombosis during Acute Chest Syndrome in Sickle Cell Disease

Armand Mekontso Dessap[1,2,3], Jean-François Deux[2,4], Nour Abidi[1], Cécile Lavenu-Bombled[2,5], Giovanna Melica[6], Bertrand Renaud[2,7], Bertrand Godeau[2,8], Serge Adnot[2,9], Laurent Brochard[1,2,3], Christian Brun-Buisson[1,2], Frederic Galacteros[2,10], Alain Rahmouni[2,4], Anoosha Habibi[10*], and Bernard Maitre[2,11*]

- 125 pts consécutifs / 144 STA
- 103 angioscanners pulmonaires (121 STA)
- Prévalence EP: 17% [10-23%]



Am J Respir Crit Care Med 2011

Hôpitaux universitaires Paris-Sud

Pulmonary Hypertension and Cor Pulmonale during Severe Acute Chest Syndrome in Sickle Cell Disease

Armand Mekontso Dessap[1,2], Rusel Leon[1], Anoosha Habibi[3], Ruben Nzouakou[3], Françoise Roudot-Thoraval[4], Serge Adnot[2], Bertrand Godeau[5], Frederic Galacteros[3], Christian Brun-Buisson[1], Laurent Brochard[1,2], and Bernard Maitre[2,6]

Am J Respir Crit Care Med 2008

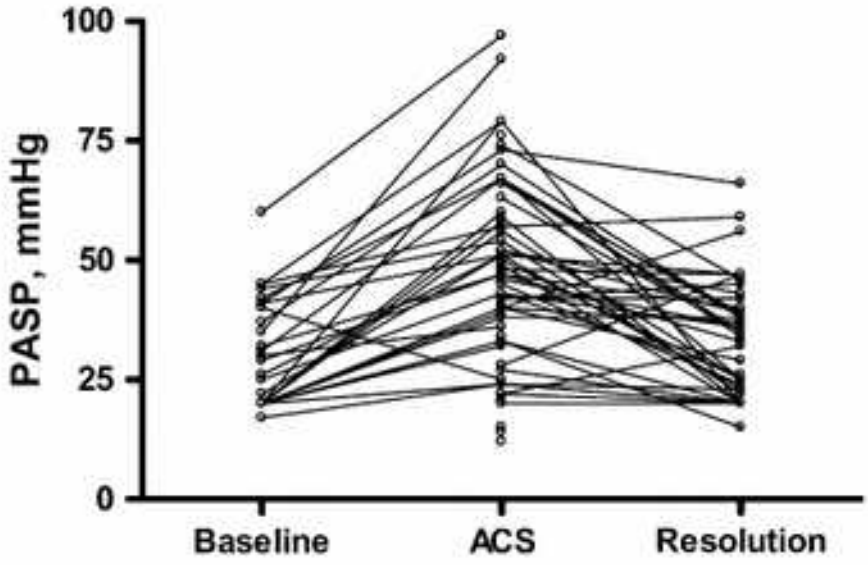


Figure 1. Pulmonary artery systolic pressure (PASP) at baseline (n = 29), during severe acute chest syndrome (ACS) (n = 84), and after its resolution (n = 44). PASP was estimated from tricuspid regurgitant jet velocity.

Hôpitaux universitaires Paris-Sud

Hypertension pulmonaire et STA

Dessap AM et al. Am J Respir Crit Care Med 2007

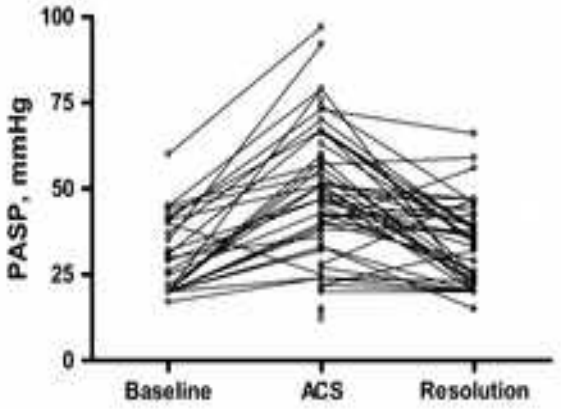


Figure 1. Pulmonary artery systolic pressure (PASP) at baseline (n = 29), during severe acute chest syndrome (ACS) (n = 84), and after its resolution (n = 44). PASP was estimated from tricuspid regurgitant jet velocity.

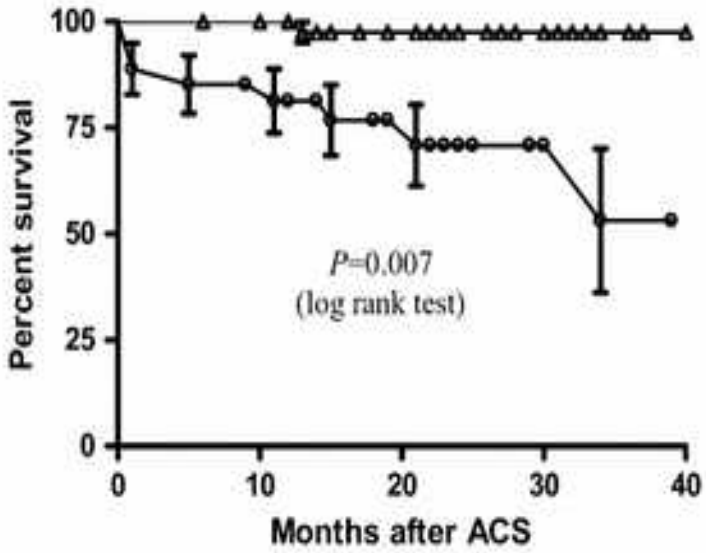


Figure 4. Kaplan-Meier long-term survival curves according to tricuspid regurgitant jet velocity (TRV) during severe acute chest syndrome (ACS). *Triangles*, TRV < 3 m/second during all episodes (n = 43, deaths = 1); *circles*, TRV ≥ 3 m/second during at least one episode (n = 27, deaths = 8).

Hôpitaux universitaires Paris-Sud

Successful Pulmonary Thromboendarterectomy in Two Patients with Sickle Cell Disease

GORDON L. YUNG, RICHARD N. CHANNICK, PETER F. FEDULLO, WILLIAM R. AUGER, KIM M. KERR, STUART W. JAMIESON, DAVID P. KAPELANSKI, and KENNETH M. MOSER†

Division of Pulmonary and Critical Care Medicine, Department of Medicine, and Division of Cardiothoracic Surgery, Department of Surgery, University of California at San Diego, San Diego, California

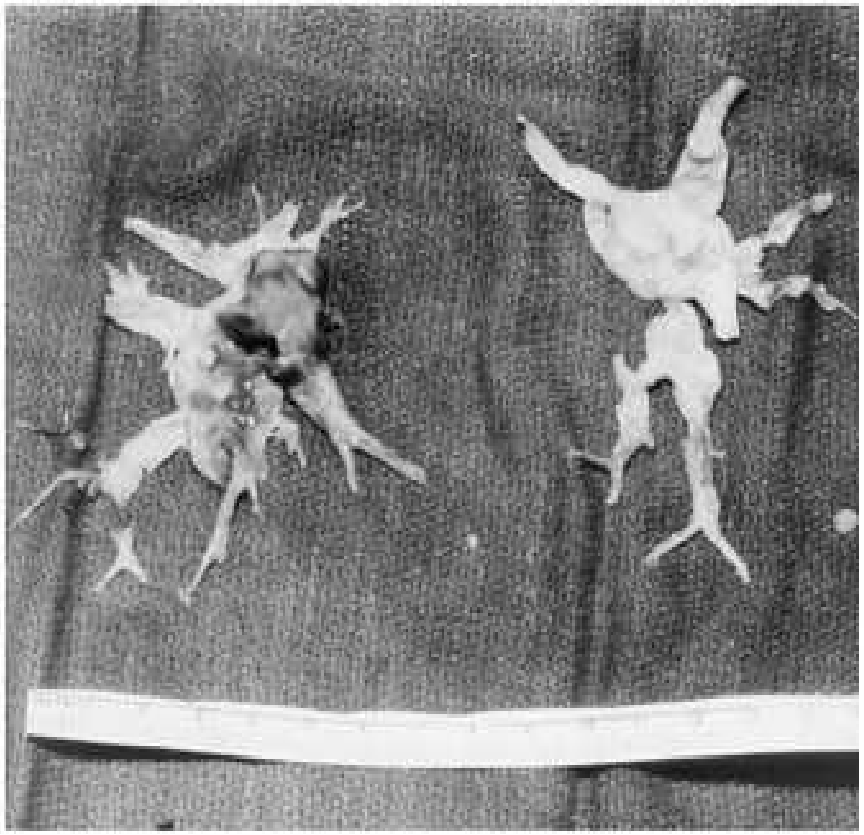


Figure 1. Organized thrombi removed from patient in Case 1.

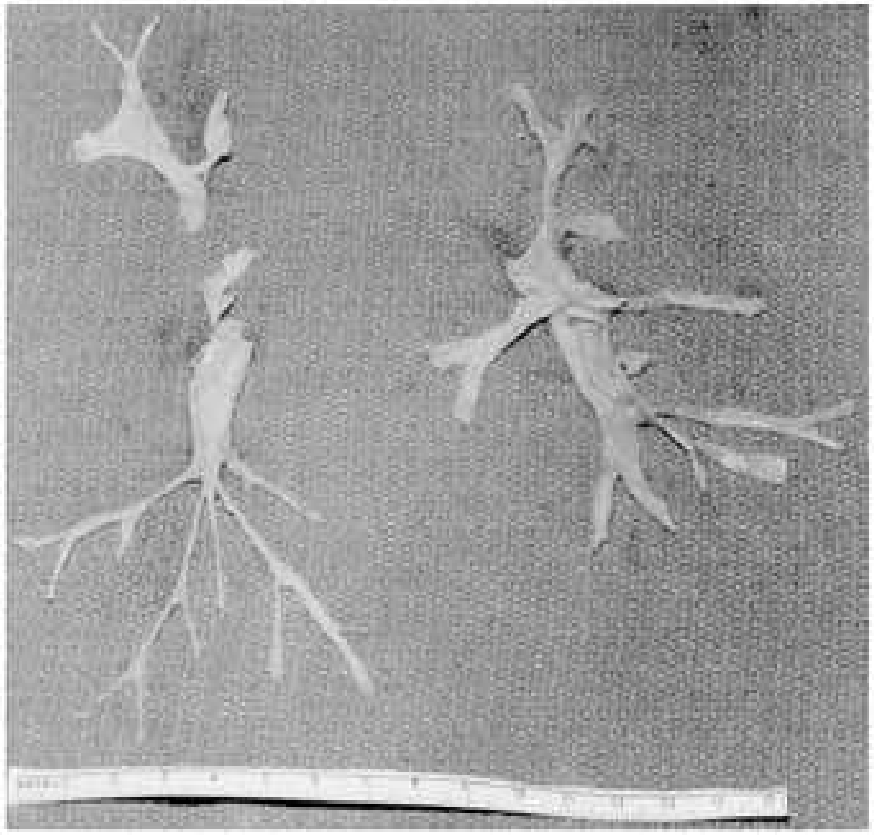


Figure 2. Organized thrombi removed from patient in Case 2.

L Gordon et al. Am j Respir Crit care Med 1998

Hôpitaux universitaires Paris-Sud

Drépanocytose:mécanismes de l'HTP pré-capillaire

- Augmentation du débit cardiaque en rapport avec l'anémie chronique
- Thrombose au niveau des artères pulmonaires (asplénisme, thrombocytose, état d'hypercoagulabilité)
- **Modification de la rhéologie sanguine (hyperviscosité) entrainant une élévation des RVP**
- Dysfonction endothéliale entrainant un remodelage des AP de petit calibre (< 500 µ) comme dans l'HTAP.

Hôpitaux universitaires Paris-Sud

bjh correspondence

Regular automated red cell exchange transfusion in the management of pulmonary hypertension in sickle cell disease

- Report on 2 patients with symptomatic PH (TRJV 3.6 m/s and 4.0 m/s respectively) treated with ARCET
- There was a rapid clinical and echocardiographic improvement and a decrease of NT-pro BNP
- The observed benefit, when a lower Hb S level is achieved, suggests it may exist in these patients a degree of reversibility of Pulmonary Hypertension

D Tsitsikas et al, Br J Haematol 2014 (Letter)

Benefit on pulmonary circulation of a lower Hb S level

Clinical Case

- A 54 year-old man Born in French West Indies Suffering from severe SCD (Hb SS)
- Multiple episodes of Acute Vaso-occlusive pain
- Three episodes of Acute Chest Syndrome leading to ICU admission
- No other history of cardio-pulmonary disease
- Treatment: Hyroxyurea for several years and chronic blood transfusion

Hôpitaux universitaires Paris-Sud

Effects of ARCET: A clinical case with RHC evaluation

	June 10	October 10	March 11	July 11
NYHA FC	III	II	III	II
6MWD, *m*	300	350	240	370
mPAP, *mmHg*	34	28	42	29
mPCWP *mmHg*	8	4	6	7
CO *L/min*	6.4	7.0	5.1	6.6
PVR, *dyn.s.cm-5*	320	272	558	265
BNP, *pg/ml*	500	100	850	120
Hemogl. g/dl	9.6 Hb S 39 %	9.2 Hb S 32 %	8.9 Hb S 54 %	9.8 Hb S 24 %
Treatment	–	Sildenafil	Sildenafil	Sildenafil
Tx Change	Start Sildenafil		Start ARCET	After 3rd ARCET

Drépanocytose:mécanismes de l'HTP pré-capillaire

- Augmentation du débit cardiaque en rapport avec l'anémie chronique
- Thrombose au niveau des artères pulmonaires (asplénisme, thrombocytose, état d'hypercoagulabilité)
- Modification de la rhéologie sanguine (hyperviscosité) entrainant une élévation des RVP
- **Dysfonction endothéliale entrainant un remodelage des AP de petit calibre (< 500 µ) comme dans l'HTAP**.

Hôpitaux universitaires Paris-Sud

Group 1 Pulmonary Arterial Hypertension (PAH)

- **Idiopathic**
- **Heritable**
- **Drugs and toxins**
- **Associated with other diseases**
  - **Connective tissue diseases**
  - **HIV infection**
  - **Portal hypertension**
  - **Systemic-to-pulmonary shunts**
  - **Schistosomiasis**
  - **Chronic hemolytic anemia**

To belong to Group 1 different subgroups have to share with IPAH

-Major proliferation of the wall of small PA

-Severe PH at diagnosis

-Similar response to PAH specific therapies

Hôpitaux universitaires Paris-Sud

Sickle Cell Disease Pathology

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

Sickle Cell Disease Pathology

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

Sickle Cell Disease Pathology

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)	Po-PAH1 (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.**

Table 2: Hemodynamic Profiles of Patients with Sickle Cell Disease with or without Pulmonary Hypertension: Three Cohorts*

	PH	No PH	*P* Value
NIH cohort	*n* = 56	*n* = 30	
CVP, mm Hg	10 ± 5	6 ± 3	<0.001
mPAP, mm Hg	36 ± 9	19 ± 4	<0.001
PAWP, mm Hg	16 ± 5	12 ± 3	<0.001
CO, L/min	8 ± 3	9 ± 2	0.14
CI, L/min/m^2	5 ± 1	5 ± 1	0.063
PVR, dyn · s · cm^{-5}	229 ± 149	74 ± 38	<0.001
French cohort	n = 24	n = 72	
CVP, mm Hg	10 ± 6	7 ± 2	<0.001
mPAP, mm Hg	30 ± 6	19 ± 3	<0.001
PAWP, mm Hg	16 ± 7	11 ± 3	<0.001
CO, L/min	8.7 ± 1.9	8.4 ± 2.1	0.60
PVR, dyn · s · cm^{-5}	138 ± 58	72 ± 26	<0.001
Brazilian cohort†	n = 8	n = 18	
mPAP, mm Hg	33.1 ± 8.9	18.7 ± 2.8	<0.001
PAWP, mm Hg	16.0 ± 5.7	13.3 ± 2	0.07
CI, L/min/m^2	5 ± 1.36	4.9 ± 1.7	0.85
PVR, dyn · s · cm^{-5}	179 ± 120	64 ± 48	0.002

NIH: Mehari et al. AJRCCM 2013
French: Parent et al. NEJM 2011
Brazil: Fonseca et al. ERJ 2011

HTP et drépanocytose : IPDE-51 (Walk-PHaSST)

- **Etude multicentriques contrôlée : sildénafil 80 mg x 3/j *vs* placebo**
- **Critère d'inclusion : VRT ≥ 2,7 m/s**
- **Critère de jugement principal: TM6' à S16**

Tolérance			
	Placebo	Sildénafil	p
EIG	8(22%)	17(46%)	0,02
CVO	5(14%)	13(35%)	0,03

Effet à S16			
	Placebo	Sildénafil	p
TM6', m	410 ± 105	364 ± 101	NS
VRT, m/s	2,9 ± 0,5	2,9 ± 0,3	NS
NT-BNP, pg/L	2,3 ± 0,6	2,5 ± 0,7	NS

- Etude interrompue par la NIH après 33 inclusions dans chaque groupe car augmentation significative de l'incidence des CVO dans le groupe traité.

- Pas d'efficacité démontrée du sildenafil

Machado RF *et al*. Blood 2011.

Published in final edited form as:
Br J Haematol. 2010 May ; 149(3): 426–435. doi:10.1111/j.1365-2141.2010.08097.x.

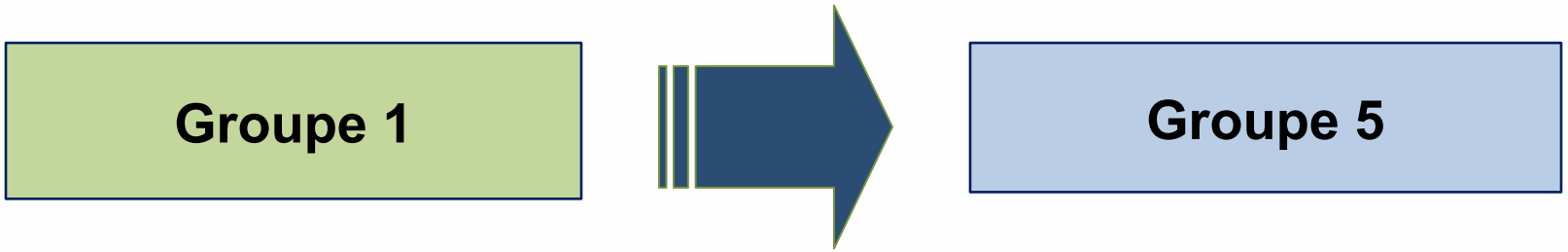
Exercise Capacity and Hemodynamics in Patients with Sickle Cell Disease with Pulmonary Hypertension Treated with Bosentan: Results of the ASSET studies

RJ Barst[1], KK Mubarak[2], RF Machado[3], KI Ataga[4], RL Benza[5], O Castro[6], R Naeije[7], N Sood[8], PS Swerdlow[9], M Hildesheim[10], MT Gladwin[11], and on behalf of the ASSET study group*

Number of AEs, SAEs, and VOC AES by treatment group, ASSET-1 and ASSET-2 – All subjects.

	Treatment Group				
Number of Events	Bosentan N subjects=11		Placebo N subjects=15		Wilcoxon's Exact p
	Mean (std)	Median (min - max)	Mean (std)	Median (min - max)	
AEs	5.1 (2.5)	6 (1 - 8)	5.2 (3.9)	5 (1 – 13)	0.9
VOC AEs	0.8 (1.3)	0 (0 – 3)	0.7 (1.4)	0 (0 – 4)	0.8
SAEs	1.5 (1.9)	1 (0 – 5)	1.1 (1.9)	0 (0 – 6)	0.5
Severe SAEs	0.7 (1.3)	0 (0 – 4)	1.0 (1.9)	0 (0 – 4)	1.0

HTP et drépanocytose



- Présentation clinique et hémodynamique différente
- Hypertension pulmonaire multifactorielle
- Physiopathologie méconnue
- Lésions plexiformes inhabituelles
- Pas d'efficacité démontrée des traitements spécifiques HTAP

Group 1 Pulmonary Arterial Hypertension (PAH)

- **Idiopathic**
- **Heritable**
- **Drugs and toxins**
- **Associated with other diseases**
  - **Connective tissue diseases**
  - **HIV infection**
  - **Portal hypertension**
  - **Systemic-to-pulmonary shunts**
  - **Schistosomiasis**
  - **Chronic [redacted]ytic anemia**

To belong to Group 1 different subgroups have to share with IPAH

-Major proliferation of the wall of small PA

-Severe PH at diagnosis

-Similar response to PAH specific therapies

Hôpitaux universitaires Paris-Sud

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

PH in SCD : Take home messages

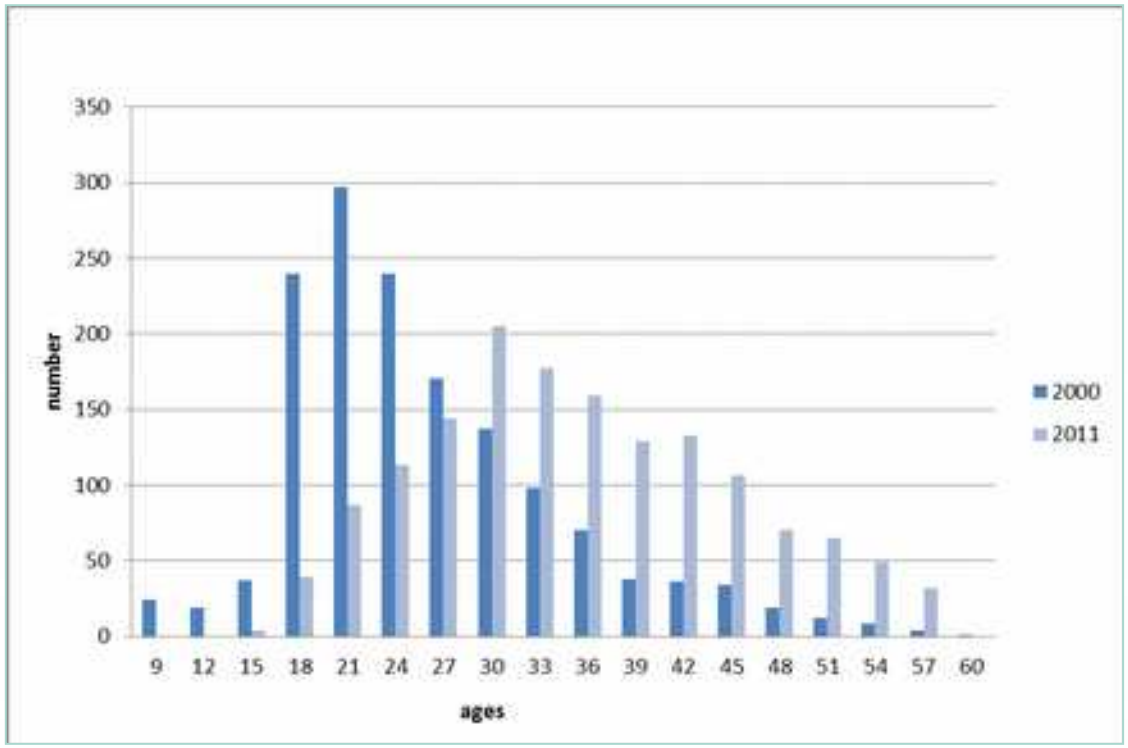
- Pulmonary Hypertension, confirmed by RHC in adults with SCD, is less frequent than expected on the basis of echocardiograhic estimation
- Post- capillary pulmonary hypertension represents the most frequent cause
- Pre-capillary pulmonary hypertension is less frequent and multifactorial associating : high cardiac output ,thrombosis, hyperviscosity and may be endothelial dysfunction
- PH represents an important risk of death
- The optimal management of this severe complication remains to be properly evaluated

Parent F. *New Engl J Med* 2011
**** Fonseca GH. Eur respir j2012**
*****Gladwin M, *et al. New Engl J Med* 2004**

Hôpitaux universitaires Paris-Sud

Syndromes drépanocytaires majeurs

- SS, SC, Sbthal, SD Punjad, SO Arab
- Prévalence: 1 - 5 /10 000
  - 250 nouveaux cas / an en France métropolitaine
  - 250 000 nouveaux cas / an dans le monde
- Cohorte Hôpital Mondor: âge des patients suivis



Hôpitaux universitaires Paris-Sud

RESULTS: Characteristics of patients

Characteristics	N=385
Age *(yr)*	34 ~ 10
Female sex *(%)*	60%
TRJ velocity (m/sec)	2.3 ~ 0.4
History of ACS *(%)*	34%
History of stroke *(%)*	5%
Hemogobin SS **Hemogobin SC** **Hemogobin S-thalassemia**	98.5% 0% 1.5%
Systolic blood pressure *(mmHg)*	118 ~ 16
Blood transfusion	36%
Hydroxyurea therapy *(%)*	23%

Characteristics	N=385
Hemoglobin *(g/dl)*	9.0 ~ 4.6
Creatinine *(mmol/l)*	65 ~ 23
Bilirubin : direct *(mmol/l)* **total** *(mmol/l)*	11 ~ 8 59 ~ 54
Aspartate aminotransferase *(U/L)*	40 ~ 20
Alanine aminotransferase *(U/L)*	25 ~ 18
Lactate dehydrogenase *(U/L)*	496 ~ 284
SaO2 *(%)*	95 ~ 3

Characteristic	TRV < 2.5 m.s-1 *N=289*	*P value*	TRV ≅ 2.5 m.s-1 without PH *N=72*
Age *(yr)*	33 ± 9	*0.03*	36 ± 11
Female sex *(%)*	32%	*0.11*	51%
NYHA I/II *(%)* NYHA III *(%)*	94.5 5.5	*0.4*	93.1 6.9
Systolic blood pressure *(mm Hg)*	116 ± 16	*0.03*	121 ± 14
6MWD *(m)*	520 ± 88	*0.49*	527 ± 62
PaO2 *(mmHg)*	87 ± 11	*0.38*	86 ± 11
Urea *(mmol/l)*	3.3 ± 1.4	*0.26*	3.7 ± 2.2
LDH *(U/L)*	466 ± 224	*0.32*	501 ± 274
Bilirubin: total *(mmol/l)* direct *(mmol/l)*	58 ± 44 11 ± 8	*0.6* *0.9*	62 ± 86 11 ± 6
NT–proBNP *(pg/ml)*	121 ± 185	*0.44*	107 ± 101

Characteristic	TRV < 2.5 m.s-1 *N=289*	*P value*	TRV ≅ 2.5 m.s-1 without PH *N=72*	*P value*	TRV ≅ 2.5 m.s-1 with PH *N=24*
Age *(yr)*	33 ± 9	*0.03*	36 ± 11	*<0.001*	45 ± 10
Female sex *(%)*	32%	*0.11*	51%	*0.10*	71%
NYHA I/II *(%)* NYHA III *(%)*	94.5 5.5	*0.4*	93.1 6.9	*0.0001*	62.5 37.5
Systolic blood pressure *(mm Hg)*	116 ± 16	*0.03*	121 ± 14	*0.31*	124 ± 15
6MWD *(m)*	520 ± 88	*0.49*	527 ± 62	*<0.0001*	404 ± 94
PaO2 *(mmHg)*	87 ± 11	*0.38*	86 ± 11	*0.04*	80 ± 12
Urea *(mmol/l)*	3.3 ± 1.4	*0.26*	3.7 ± 2.2	*0.17*	5.0 ± 4.2
LDH *(U/L)*	466 ± 224	*0.32*	501 ± 274	*0.009*	901 ± 606
Bilirubin: total *(mmol/l)* direct *(mmol/l)*	58 ± 44 11 ± 8	*0.6* *0.9*	62 ± 86 11 ± 6	*0.9* *0.02*	60 ± 35 16 ± 15
NT–proBNP *(pg/ml)*	121 ± 185	*0.44*	107 ± 101	*<0.0001*	1020 ± 2153

HTP et Drépanocytose: Caractéristiques

- Marqueurs d'hémolyse sont associés à la présence d'HTP, de façon variable, dans les 3 études
- Dans les 3 études, patients sont plus âgés (45±10 / 39±12 / 38±11) , et ont une créatinine plus élevée

HTP et Drépanocytose: Mécanismes

- Données autopsiques montrent des lésions d'HTAP chez ¾ patients (Haques Hum Pathol 2002;33).
- Hémolyse intravasculaire chronique
  - Déplétion de NO par captation par Hb plasmatique libre
  - Augmentation de l'endotheline-1
  - Activation plaquettaire
  - Libération accrue de l'arginase érythrocytaire qui diminue la biodisponibilité du NO
- Thrombose: Etat d'hypercoagulabilité; présence de thrombi des AP en cas de STA, asplénie
- Hypoxie chronique
- Hyperviscosité sanguine

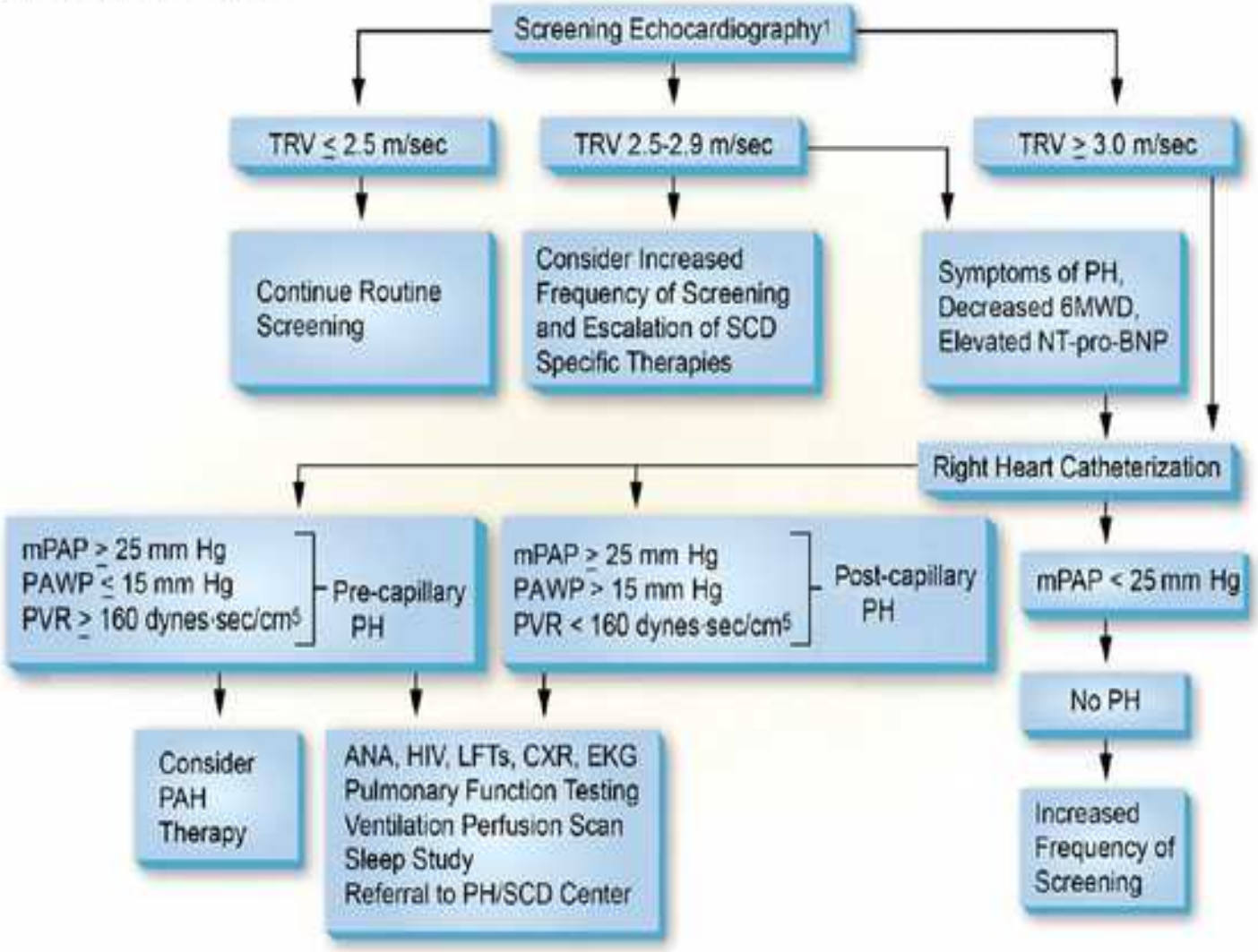
AMERICAN THORACIC SOCIETY DOCUMENTS

An Official American Thoracic Society Clinical Practice Guideline: Diagnosis, Risk Stratification, and Management of Pulmonary Hypertension of Sickle Cell Disease

Elizabeth S. Klings[1], Roberto F. Machado[2], Robyn J. Barst[3], Claudia R. Morris, Kamal K. Mubarak, Victor R. Gordeuk, Gregory J. Kato, Kenneth I. Ataga, J. Simon Gibbs, Oswaldo Castro, Erika B. Rosenzweig, Namita Sood, Lewis Hsu, Kevin C. Wilson, Marilyn J. Telen, Laura M. DeCastro, Lakshmanan Krishnamurti, Martin H. Steinberg, David B. Badesch, and Mark T. Gladwin; on behalf of the ATS Ad Hoc Committee on Pulmonary Hypertension of Sickle Cell Disease

THE OFFICIAL CLINICAL PRACTICE GUIDELINE OF THE AMERICAN THORACIC SOCIETY WAS APPROVED BY THE ATS BOARD OF DIRECTORS, NOVEMBER 2013. THIS GUIDELINE WAS ALSO APPROVED BY THE AMERICAN COLLEGE OF CHEST PHYSICIANS, OCTOBER 2013, AND BY THE PULMONARY HYPERTENSION ASSOCIATION, NOVEMBER 2013.

AJRCCM: 189; 6, 727–740



Risk stratification by measurement of N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels in adults with sickle cell disease.

Ref	Type of study	Type of patients (n)	Numerator	Denominator	Mortality risk
a	Observational study evaluating the risk of death	Two cohorts, consecutive patients with SCD (230 & 121).	Mortality among patients with an NT-pro-BNP ≥160 pg/mL	Mortality among patients with an NT-pro-BNP <160 pg/mL	RR 5.1 (95% CI 2.1-12.5) in cohort #1 RR 2.9 (95% CI 1.2-6.6) in cohort #2 Absolute values not provided
b	Observational study evaluating the risk of death	Consecutive patients with SCD (758).	Mortality among patients with an NT-pro-BNP ≥160 ng/L	Mortality among patients with an NT-pro-BNP <160 ng/L	Adjusted RR 6.87 (95% CI 3.0-16.0) Absolute values not provided

NT-pro-BNP: N-terminal pro-brain natriuretic peptide. SCD: Sickle cell disease.

Machado et al. JAMA 2006; 296(3):310-318.
Machado et al. Br J Haematol 2011;

Hypertension Artérielle Pulmonaire

- *Maladie rare: 10/million en France*
- *Augmentation progressive de la pression artérielle pulmonaire*
- *Installation d'une insuffisance cardiaque droite*

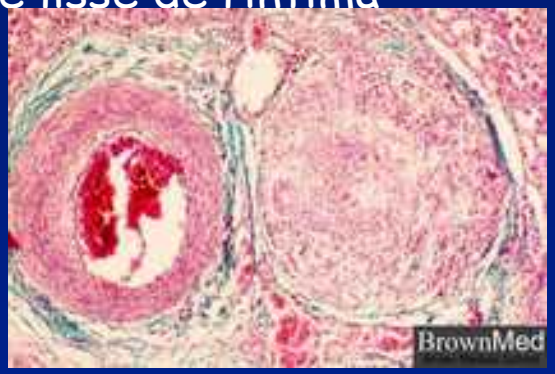
Lésions anatomiques – HTP de la drépanocytose

- Première étude anatomopathologique:

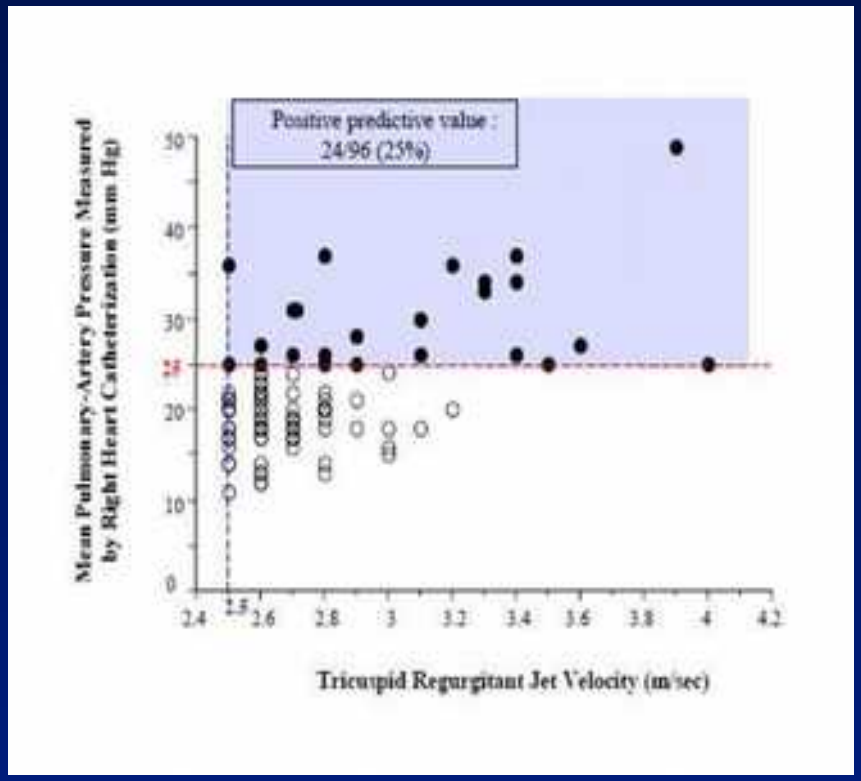
HAQUE, AK., pulmonary hypertension in sickle cell hemoglobinopathy: a clinicopathomologic study of 20 cases Hum Pathol 2002

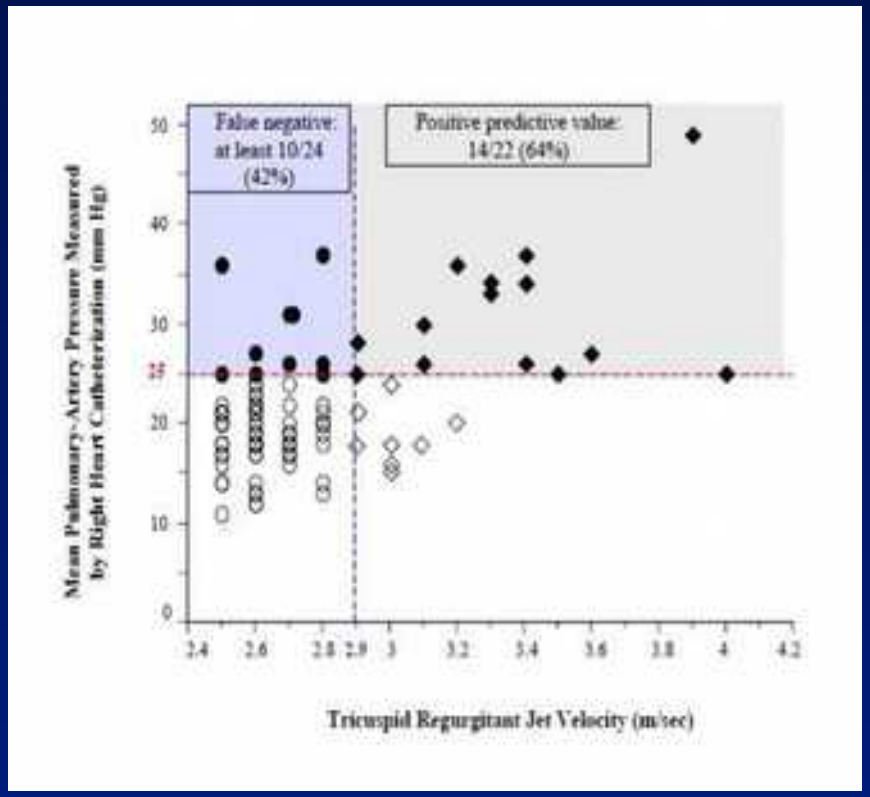
  - 20 autopsies de drépanocytaires SS

- Résultats:
  - Tous présentaient des lésions de remodelage vasculaire pulmonaire caractéristiques de l'HTAP
  - 60% de lésions plexogéniques décrites: (artères de 80 à 150: dilatation par destruction pariétale artérielle et amincissement de la média avec perte du muscle lisse avec rupture ou perte de la limitante élastique externe)
  - hypertrophie de la média et hyperplasie musculaire lisse de l'intima

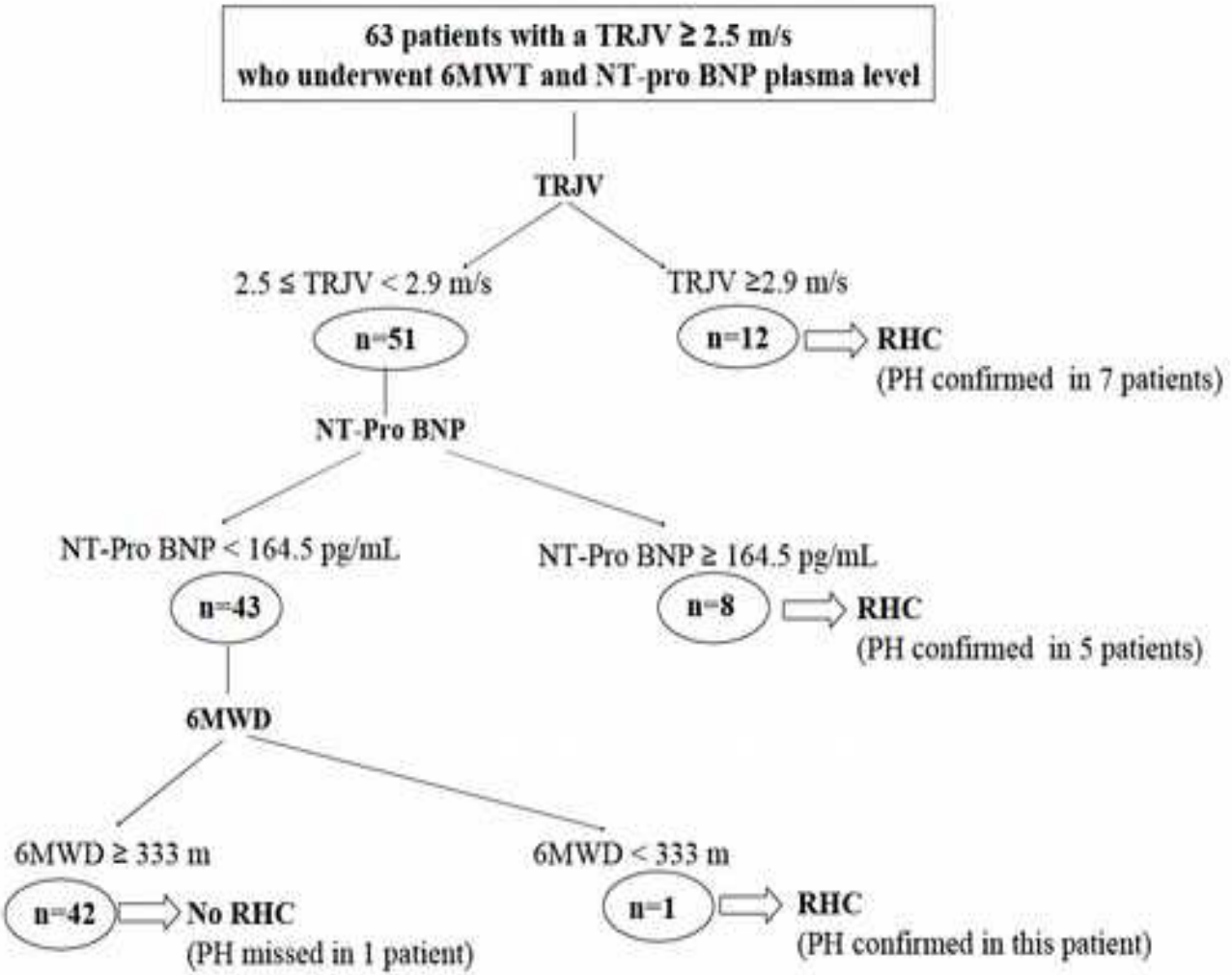


HTP et Drépanocytose: Screening?





Intérêt d'associer plusieurs tests: TM – BNP – Echocardiographie?



- 21 KT au lieu de 63
- VPP : 62%
- FN: 7%

Hôpitaux universitaires

N Engl J Med 2011;365:44-53.

Effects of Sildenafil in PAH associated with SCD

- 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 were likely to have more likely sickle cell pain crisis (35%) compared to placebo-treated patients (14%).

- Furthermore,there was no evidence of treatment-related improvement at time of study

R Machado et al . Blood, 2011

Hôpitaux universitaires Paris-Sud

HTP et drépanocytose : ARE (ASSET 1 et 2)

- **Etude multicentriques contrôlée : bosentan 125 mg x 2/j *vs* placebo**
- **Critère d'inclusion :**
  - **ASSET-1: PAPm≥25, Pcp≤15 et RVP≥160**
  - **ASSET-2: PAPm≥25, Pcp≤15 er RVP 100-160 ou Pcp 16-25 et RVP≥100**
- **Critère de jugement principal: RVP à S16**

Number of AEs, SAEs, and VOC AES by treatment group, ASSET-1 and ASSET-2 – All subjects.

	Treatment Group				
Number of Events	Bosentan N subjects=11		Placebo N subjects=15		Wilcoxon's Exact p
	Mean (std)	Median (min - max)	Mean (std)	Median (min - max)	
AEs	5.1 (2.5)	6 (1 - 8)	5.2 (3.9)	5 (1 – 13)	0.9
VOC AEs	0.8 (1.3)	0 (0 – 3)	0.7 (1.4)	0 (0 – 4)	0.8
SAEs	1.5 (1.9)	1 (0 – 5)	1.1 (1.9)	0 (0 – 6)	0.5
Severe SAEs	0.7 (1.3)	0 (0 – 4)	1.0 (1.9)	0 (0 – 4)	1.0

- Etude interrompue pour défaut d'inclusion (n=26)
- Bonne tolérance sur la population étudiée
- Pas d'efficacité démontrée

Barst RJ *et al*. Br J Haematol. 2010