Interactions foie-poumon

Laurent SAVALE

Centre de Référence de l'Hypertension Pulmonaire Sévère
Hôpital Universitaire de Bicêtre – INSERM U999
Université Paris-Sud – Le Kremlin-Bicêtre – France

UNIVERSITÉ PARIS SUD
Comprendre le monde, construire l'avenir
université PARIS-SACLAY

centre de référence maladies rares

Instituts thématiques
Inserm
Institut national de la santé et de la recherche médicale

LabEx LERMIT
Laboratoire d'Excellence en Recherche sur le Médicament et l'Innovation Thérapeutique

TORINO
DHU Thorax Innovation

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Introduction

DYSPNEE

Symptôme fréquent chez le patient cirrhotique mais
dont la prévalence est mal évaluée
≅70% des patients en bilan prétransplantation hépatique

PATHOLOGIES VARIEES

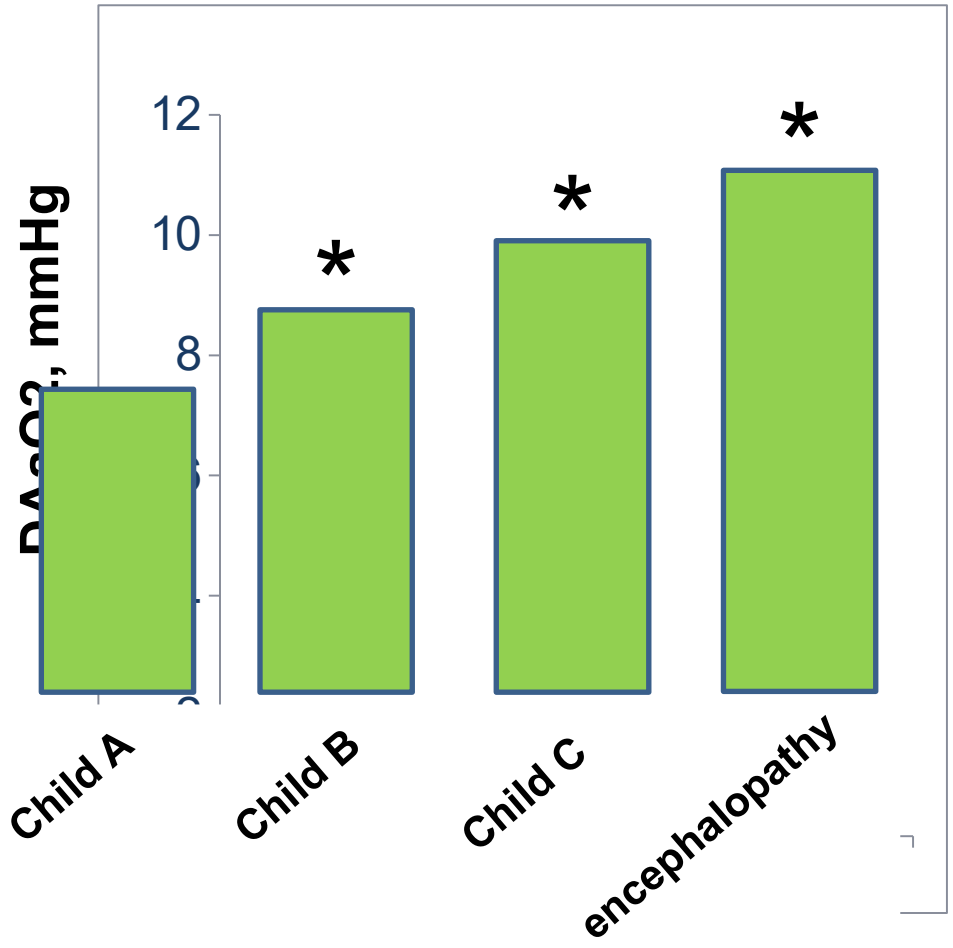
dont certaines ont un réel impact sur la survie des patients cirrhotiques

Prise en charge spécifique

Indication à une TH

Contre-indication à une TH

Prévalence de l'hypoxémie au cours de la cirrhose



- ⇒ Prévalence élevée d'hypoxémie chez les patients cirrhotiques
- ⇒ Plus fréquent et plus sévère chez les patients avec cirrhose décompensée
- ⇒ Mécanismes variés

Prévalence de l'hypoxémie 22%

Moller et al, Gut 1998

Interactions foie-poumon

Maladie causale

Maladie hépatique

+

Maladie pulmonaire

Hypertension portale (avec ou sans cirrhose)

Maladies vasculaires pulmonaires
SHP et HTPoP

Hydrothorax hépatique

Pathologies cardiopulmonaires non spécifiques
BPCO…
Cardiomyopathie dilatée….

Interactions foie-poumon

Maladie causale

Maladie hépatique

+

Maladie pulmonaire

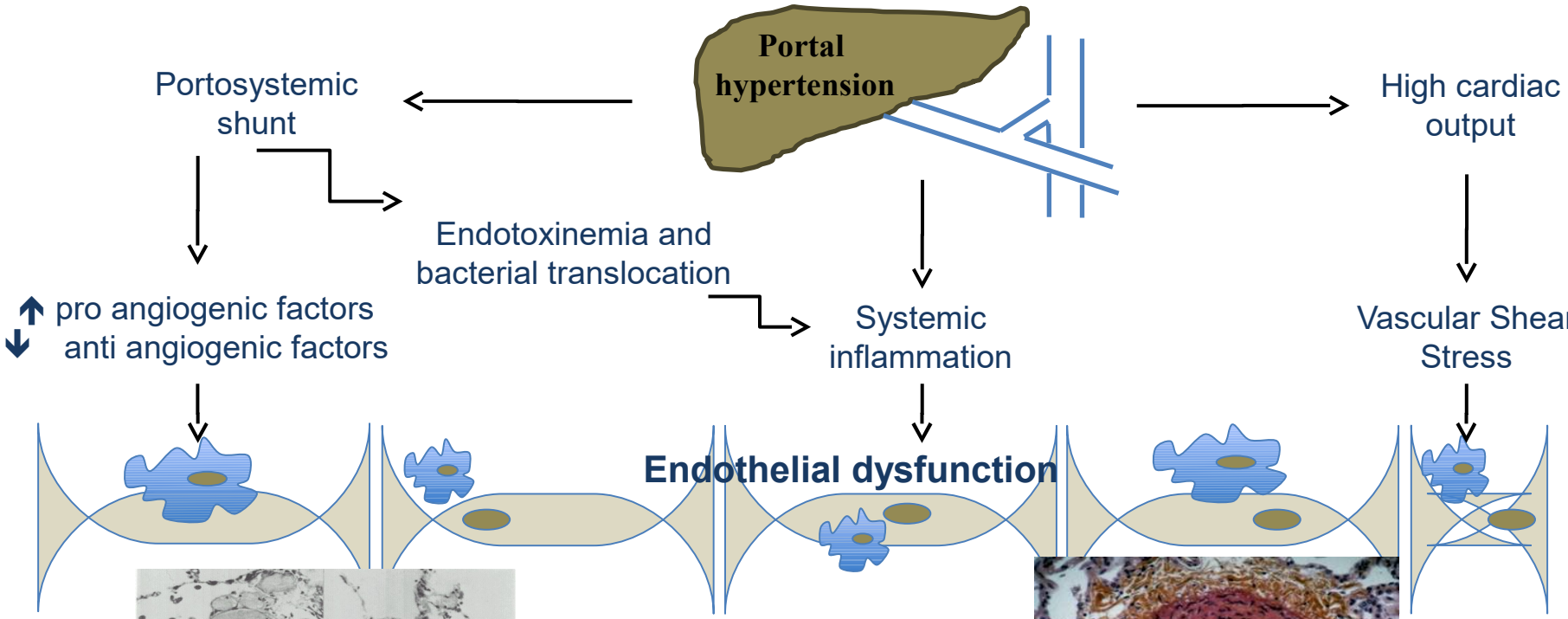
Hypertension portale (avec ou sans cirrhose)

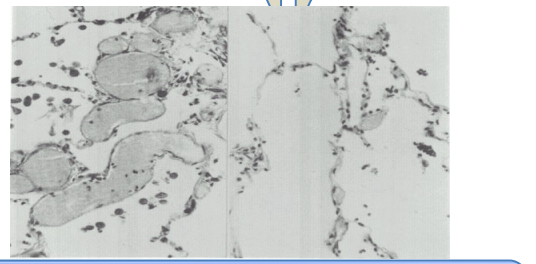
Maladies vasculaires pulmonaires
SHP et HTPoP

Hydrothorax hépatique

Pathologies cardiopulmonaires non spécifiques
BPCO…
Cardiomyopathie dilatée….

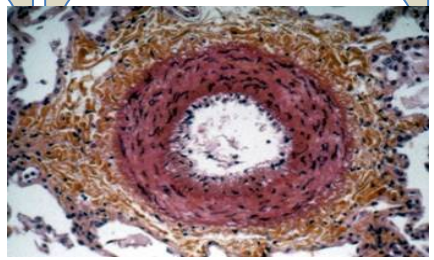
Interactions foie-poumon: physiopathologie





Angiogenesis
Capillary dilatation

HEPATOPULMONARY SYNDROME



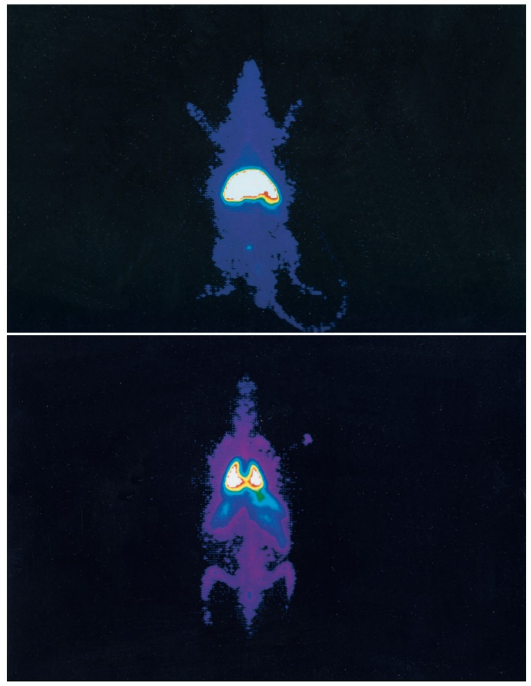
Pulmonary vascular remodeling

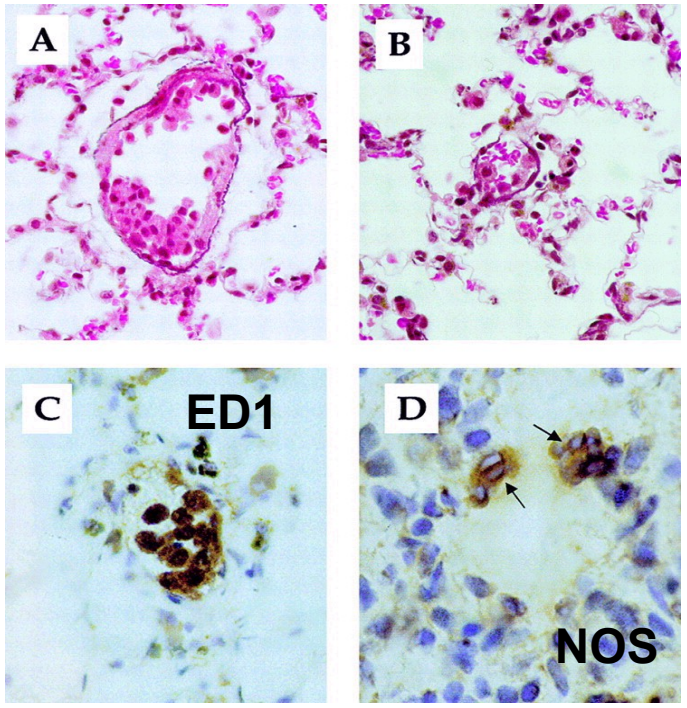
PORTOPULMONARY HYPERTENSION

Savale et al, int j clinical practice 2011

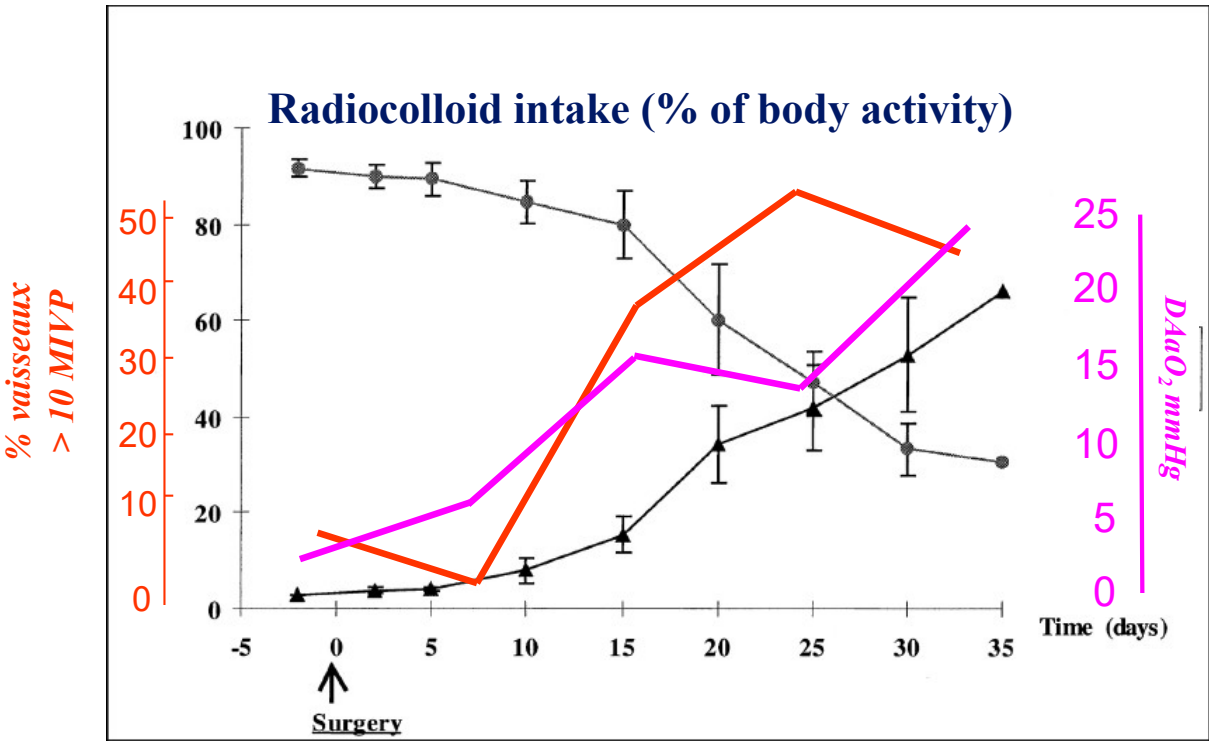
Interactions foie-poumon : physiopathologie

Cirrhose induite par ligature des voies biliaires chez le rat



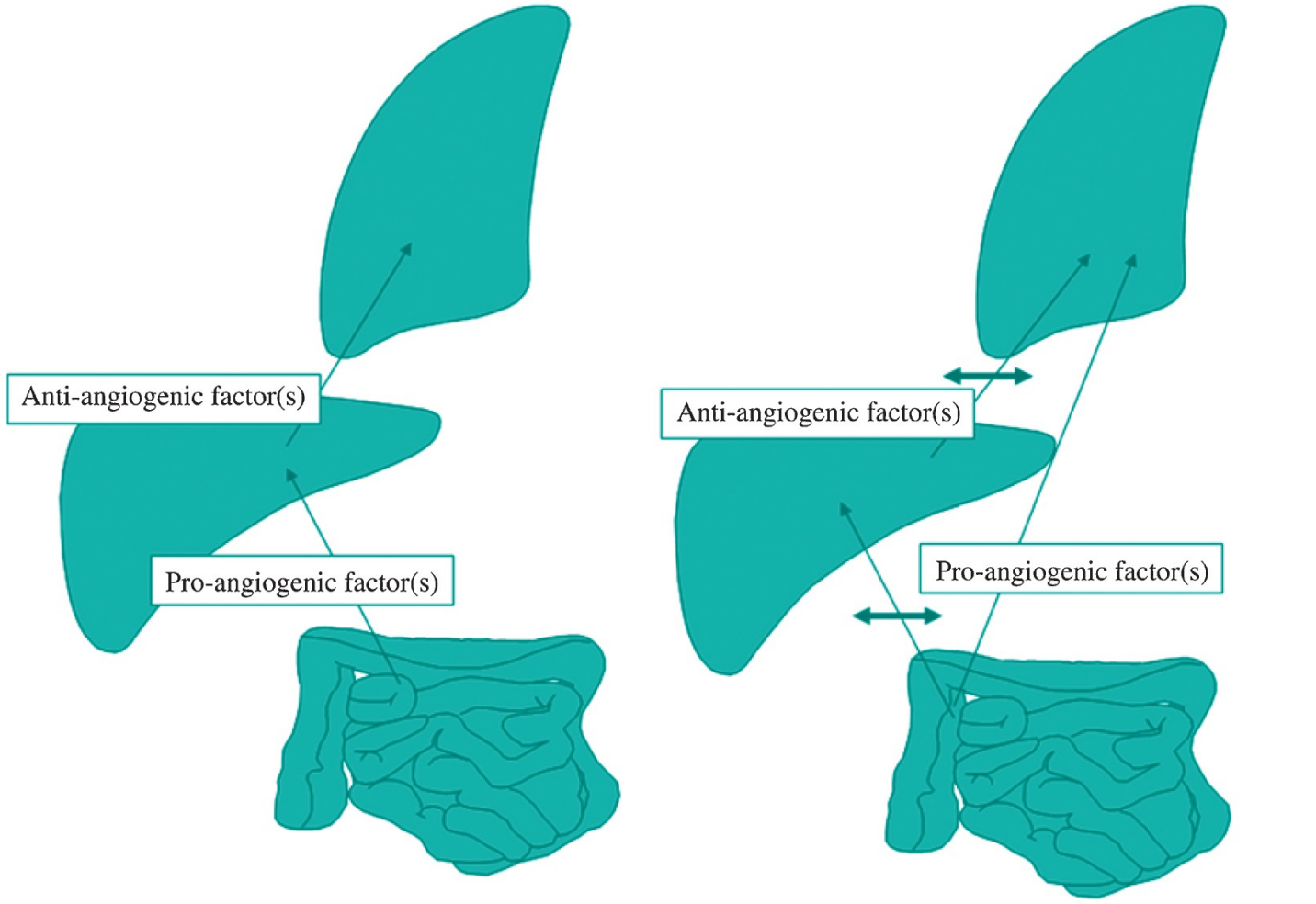


Le Pape *Chest 2001*



- Regression de la capacité phagocytaire du foie et recrutement de macrophages intravasculaires pulmonaires
- Agmentation de l'acivité de la NO synthase (endotheliale and inductible)
- Diltation intravasculaire pulmonaire
- Altération progressive des échanges gazeux

Interactions foie-poumon. Interactions foie-poumon

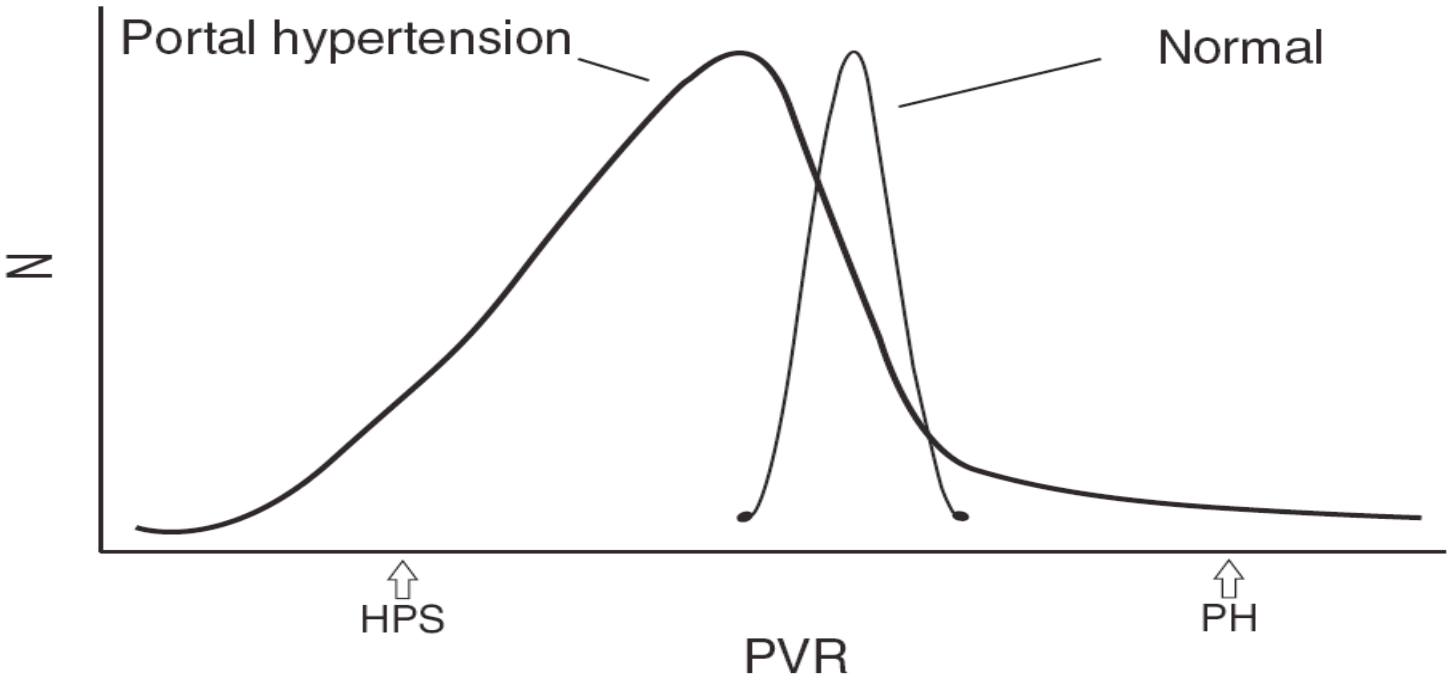


Normal Hepato-Portal Physiology

Hepatic Disease and/or Portal Hypertension

Herve & Al, Eur Respir J 1998

Introduction



Syndrome hépatopulmonaire

Prolifération et dilatation capillaire pulmonaire

Anomalies des échanges gazeux

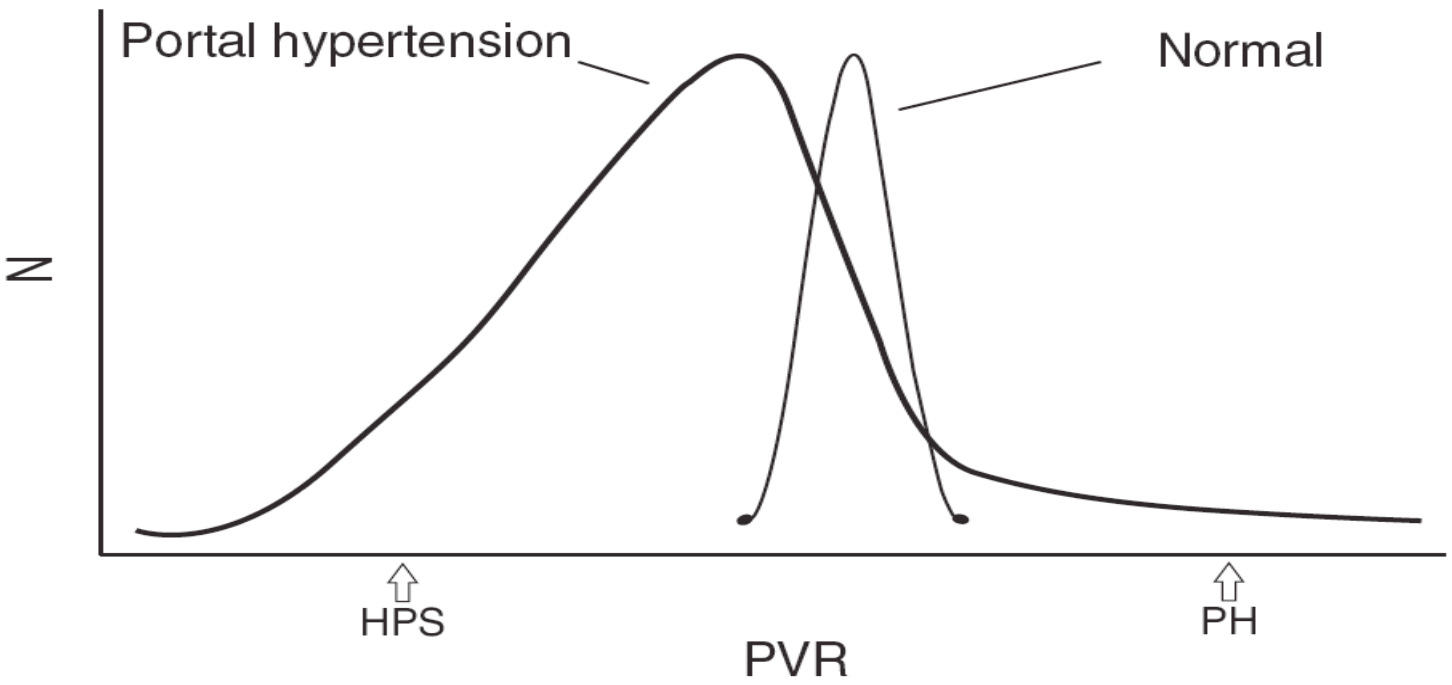
Hypertension portopulmonaire

HTP précapillaire

Remodelage vasculaire pulmonaire

Herve & Al, Eur Respir J 1998

Syndrome hépatopulmonaire



Syndrome hépatopulmonaire

Prolifération et dilatation capillaire pulmonaire

Anomalies des échanges gazeux

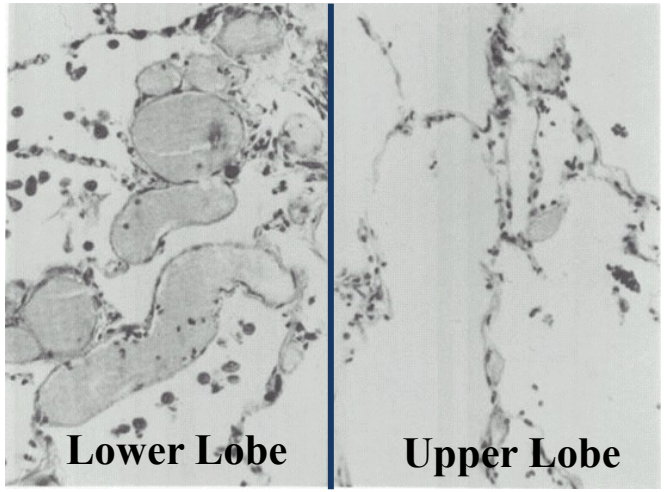
Hypertension portopulmonaire

HTP précapillaire

Remodelage vasculaire pulmonaire

Herve & Al, Eur Respir J 1998

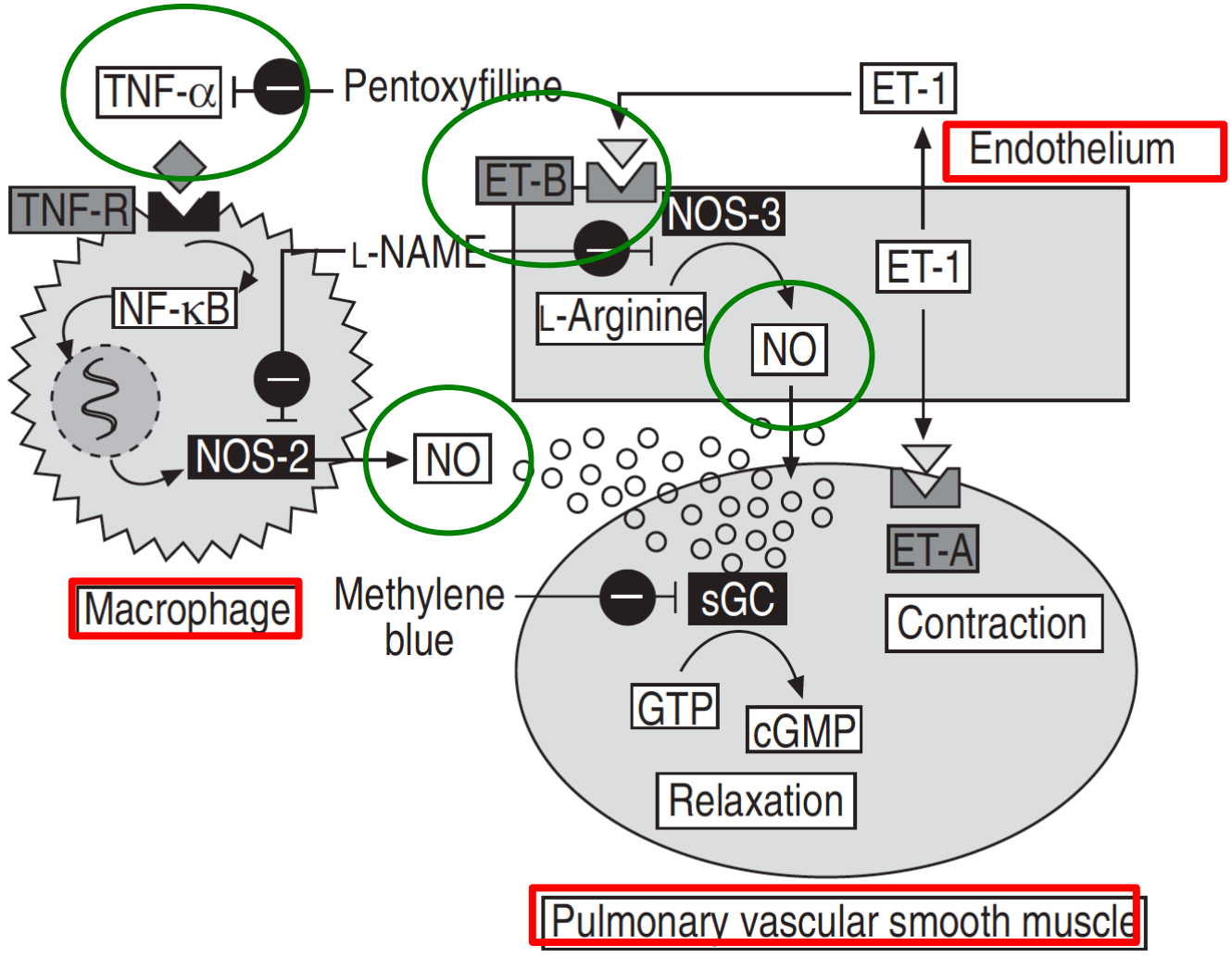
Syndrome hépatopulmonaire



Dilatation capillaire

Néoangiogénèse

Physiopathologie



Dinh-Xuan AT & Naeije R. Eur Respir J 2004.

- **Inflammation systémique et vasculaire pulmonaire**
  - Translocation bactérienne/Endotoxinemie
  - Macrophages intravasculaires pulmonaires
  - Cytokines pro inflammatoires(IL1-IL6-TNF)

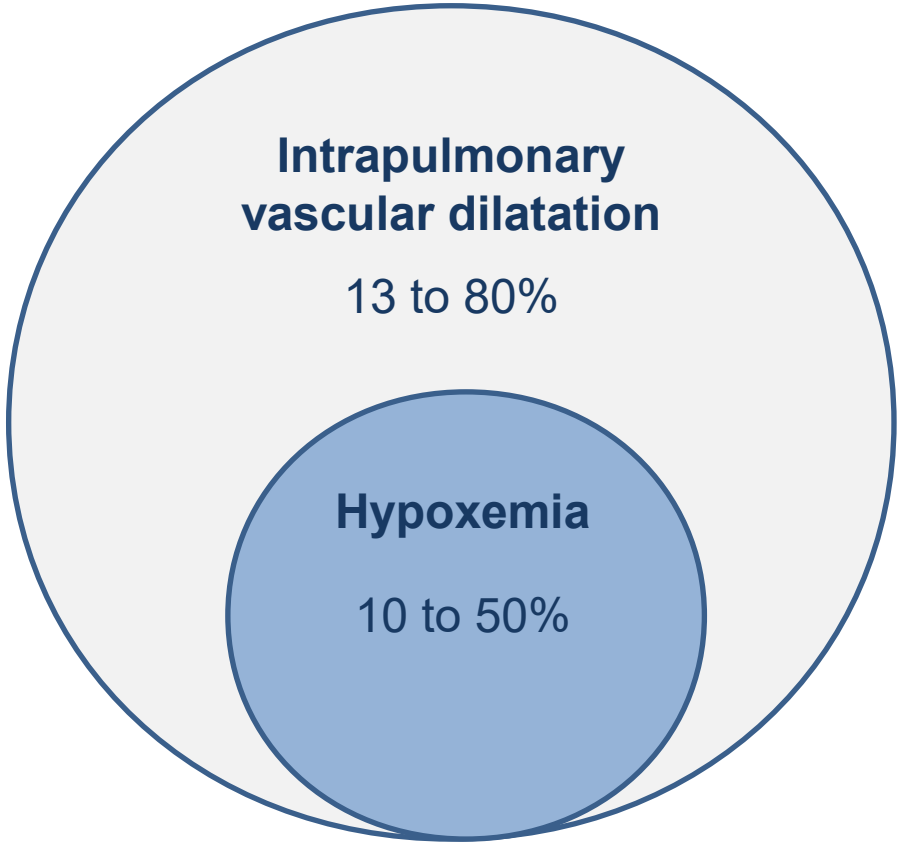
- **Vasodilatation**
  - ↑ production de NO
  - ↑ production des recepteurs B de l'ET
  - Défaut de la vaso-réactivité

- **Néoangiogénèse**
  - Inflammation
  - Autres facteurs pro-angiogéniques? (VEGF, PDGF)

Prévalence du SHP

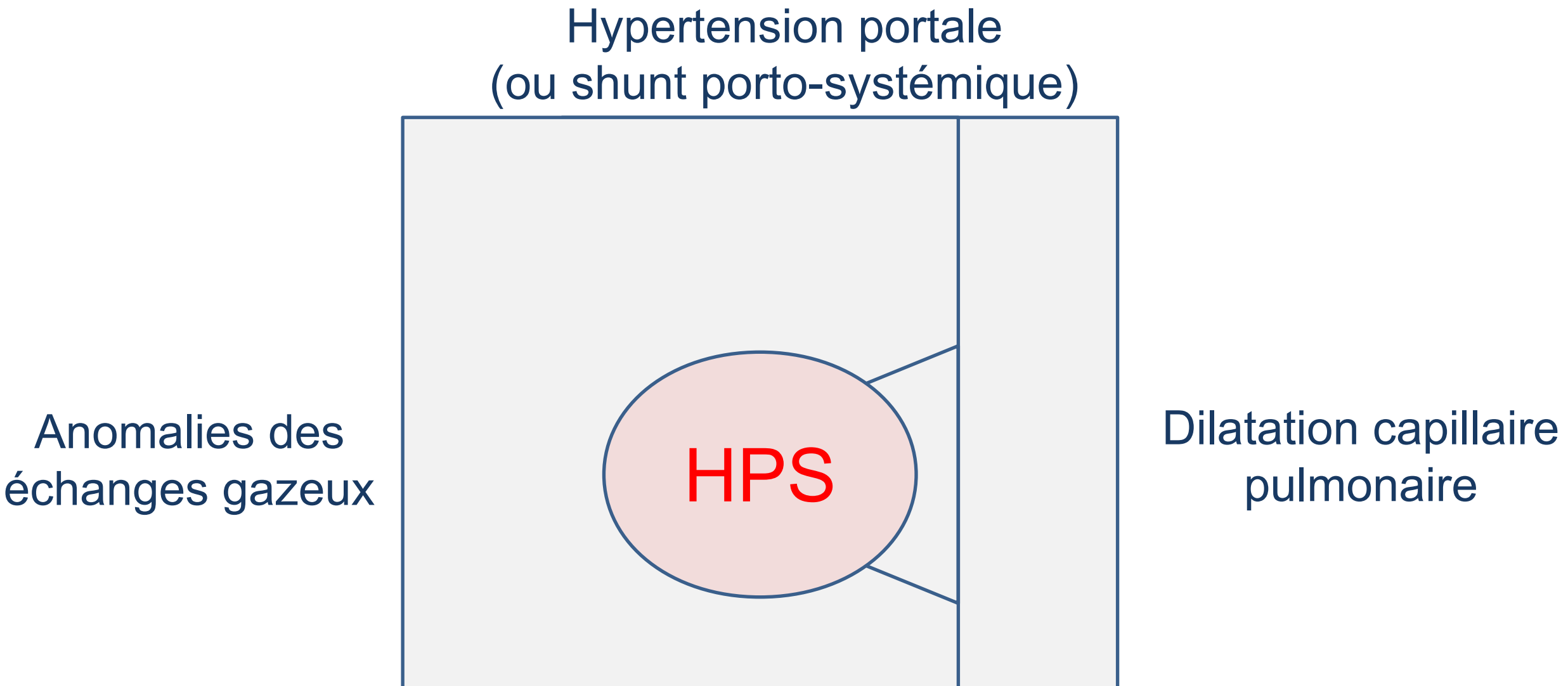
Grande variation de la prevalence : 4 to 47%

- Hétérogénéité des critères diagnostiques et de la population étudiée (candidats à une TH)
- Peut se developer à tous les stades de sévérité de la cirrhose ou en cas d'HTPo sans cirrhose
- Plus frequent chez les patients avec cirrhose sévère

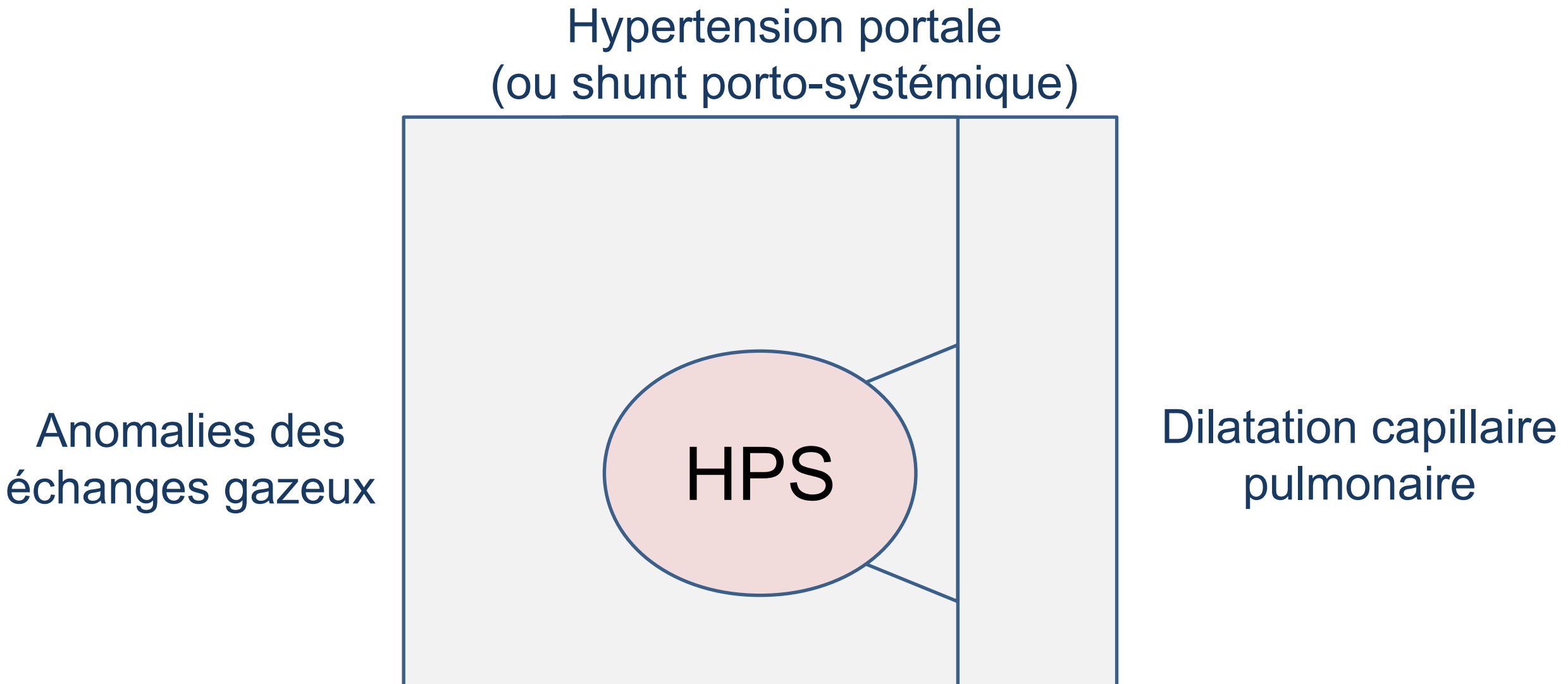


(1): Park SC, Am J Cardiol 1985
(2): Kayamakoglu S, Dig Dis Sci 2003
(3): De BK, Gastroenterology 2002
(4): Regev A, J Viral Hepat 2001
(5): Barbe T, J Pediatr 1995

Diagnostic du SHP



Diagnostic du SHP



Mécanismes physiopathologiques de l'hypoxémie dans le SHP

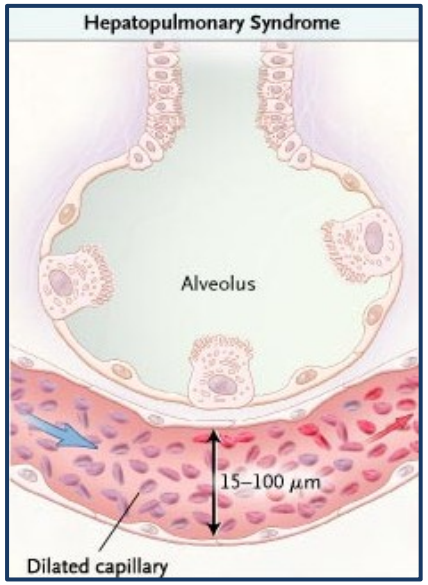
V/Q ratio mismatch

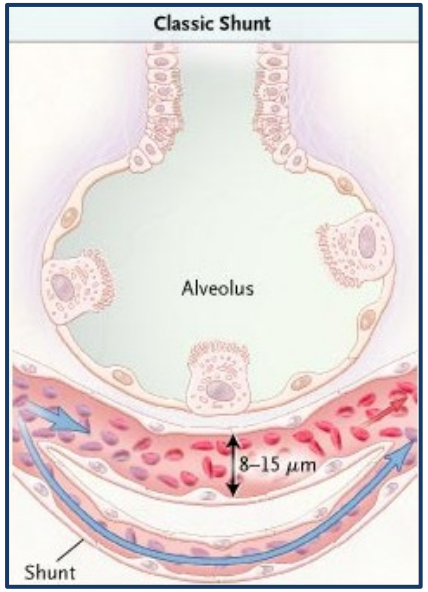
- ✓ *Decreased vascular tone*
- ✓ *Decreased hypoxic pulmonary vasoconstriction*
- ✓ *High cardiac output*

Diffusion impairment

- ✓ *O2 diffusion impairment due to capillary diameter enlargement*
- ✓ *Decreased blood transit time due to high cardiac output*

Anatomic intrapulmonary shunt (only in severe HPS)

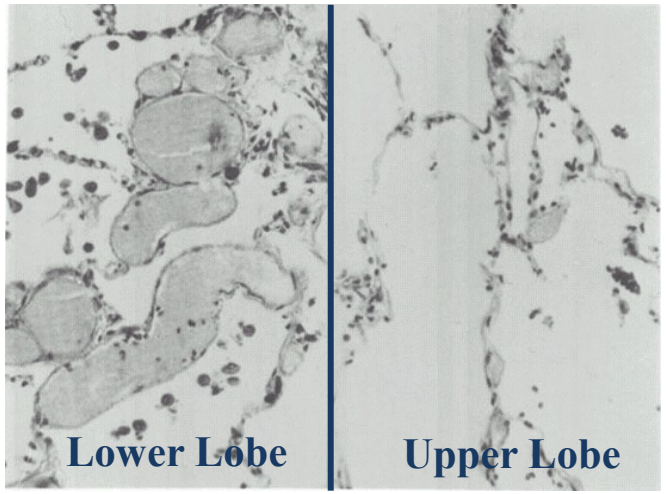




EFR et SHP

Anomalies des échanges gazeux

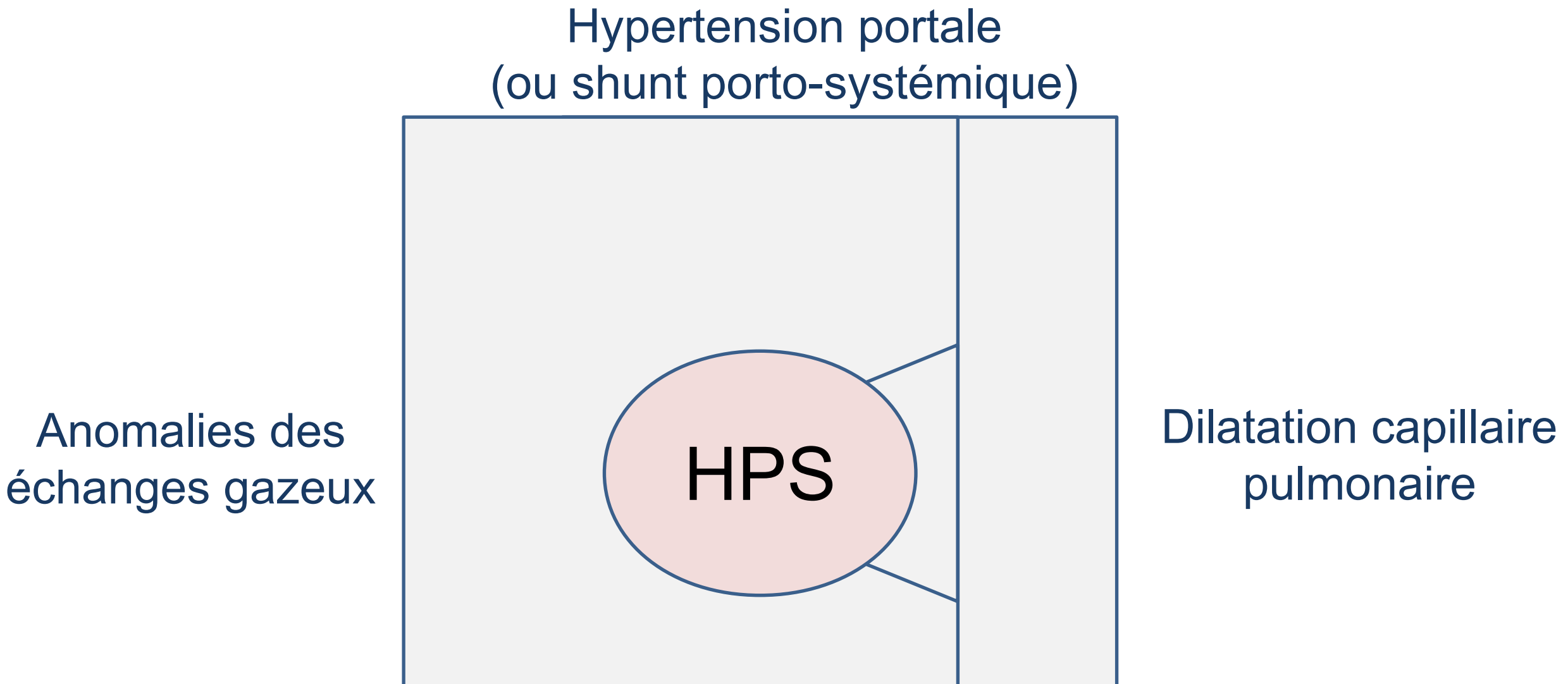
- DAaO2 ≥15 mmHg (ou ≥20 mmHg si age>65 ans)
- Sévérité du SHP
  - Pa02≥80 mmHg SHP léger
  - Pa02 60-80 mmHgSHP modéré
  - Pa02 50-60 mmHgSHP sévère
  - Pa02<50 mmHg SHP très sévère
- Test d'hyperoxie (FIO2 100%) peut être normal
- Orthodéoxie / platypnée



Volumes et débits pulmonaires normaux

DLCO basse => non spécifique (fréquent chez le patient cirrhotique)

Diagnostic du SHP



Echographie avec épreuve de contraste

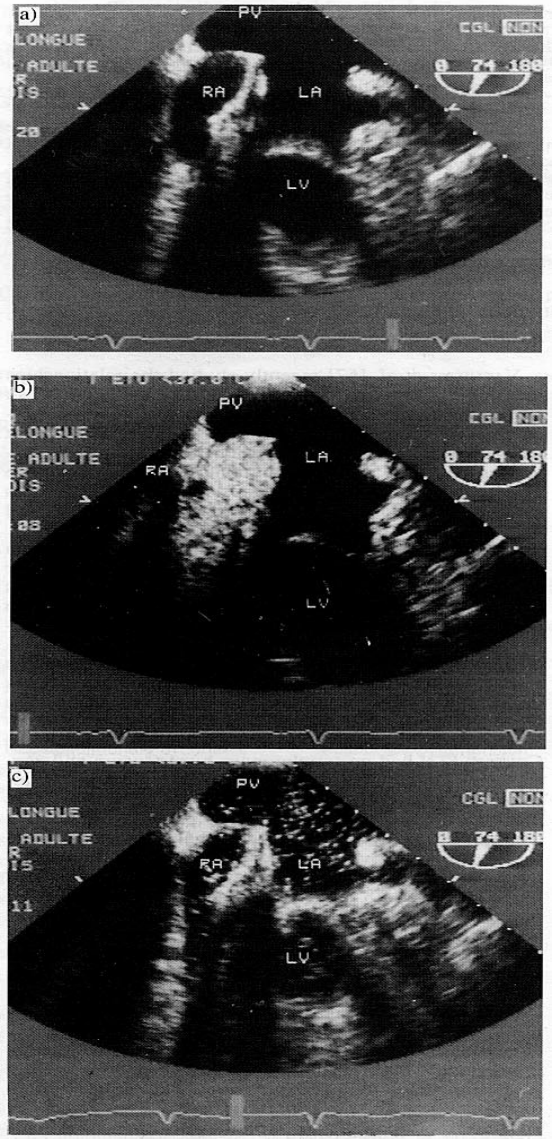
Injection de micro bulles (<90 μm) par veine étage supérieur

Détection des bulles dans cavités gauches

- Apparition après 3 cycles cardiaques = shunt intra pulmonaire
- Apparition avant 3 cycles = shunt intra cardiaque

11 à 47 % de positivité en présence de maladies hépatiques 1
32 à 59 % hypoxémies 1

Meilleures sensibilité et spécificité (CIA) de l'ETO, mais à risque dans cette population (varices oesophagiennes) 2



(1): Krowka MJ, Chest 1990
(2): Aller R, Dig Dis Sci 1999

Scintigraphie corps entier (99m-Technetium-labelled macroaggregated albumin scan)

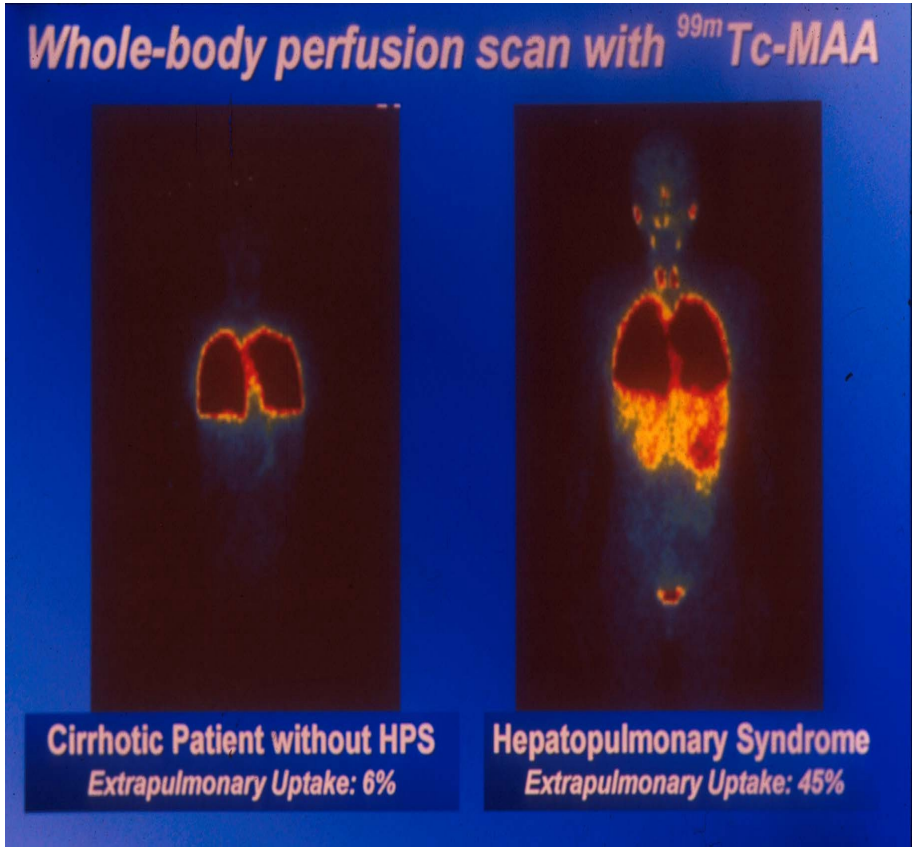
Utilisation de macro agrégats albumine TC – 99 (> 20 μm)

Fixation extra pulmonaire (reins, cerveau, rate, foie) atteste l'existence d'un shunt anatomique

Pas de distinction de la nature anatomique du shunt

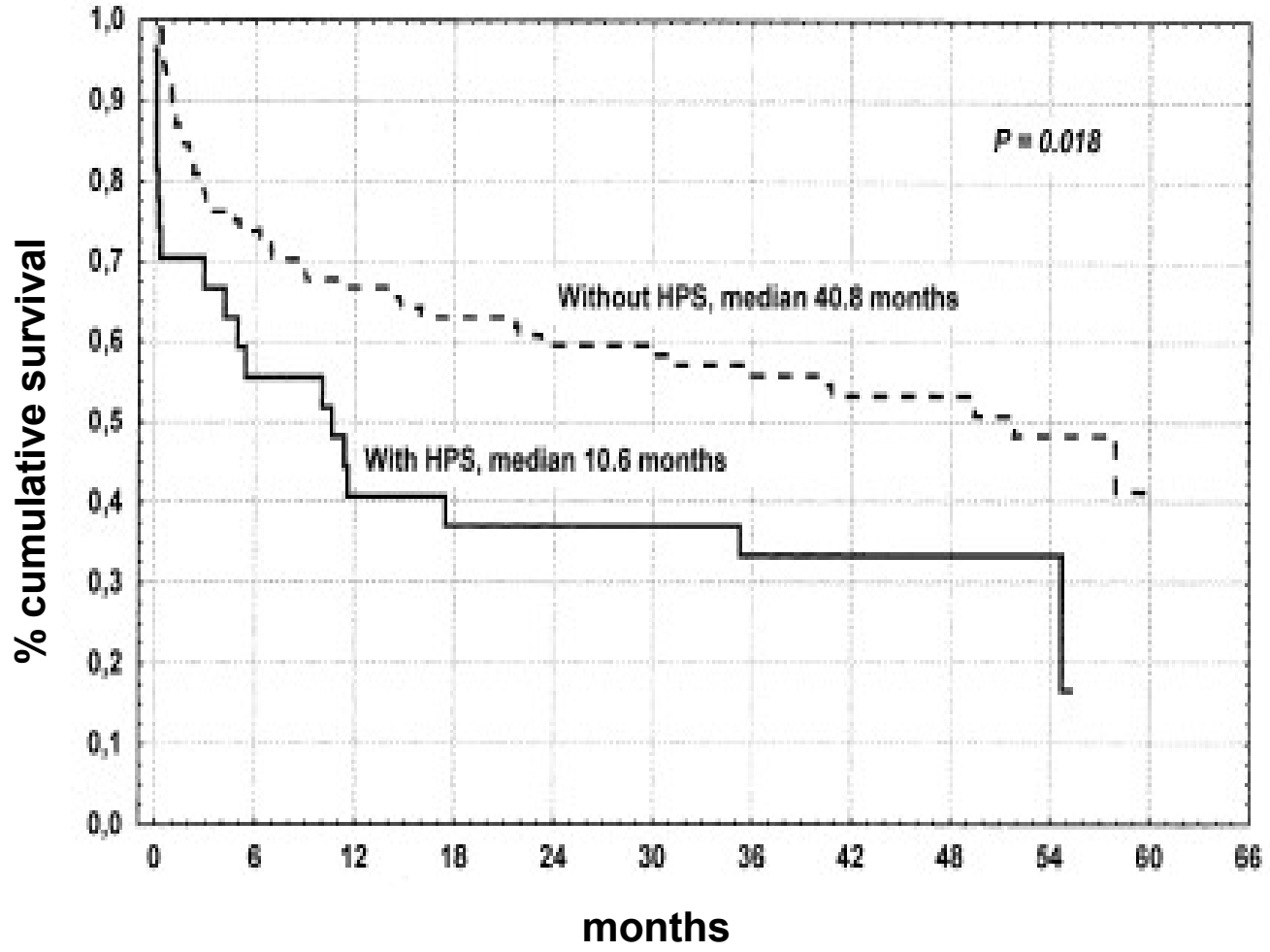
Sensibilité inférieure à l'échographie 1

Technique possible de quantification du shunt



(1): Abrams GA, Gastroenterology 1995
(2): Krowka MJ, Chest 2000

Impact du SHP sur le pronostic



Schenk P, gastroenterology 2003

Traitement medical?

Inflammation

- Pentoxyfilline
- Anti-TNF
- Prednisolone
- Plasmatic exchanges
- Aspirine
- Norfloxacine

NO overproduction

- Methylen blue (GC inhibitor)
- Garlic powder
- L-NAME

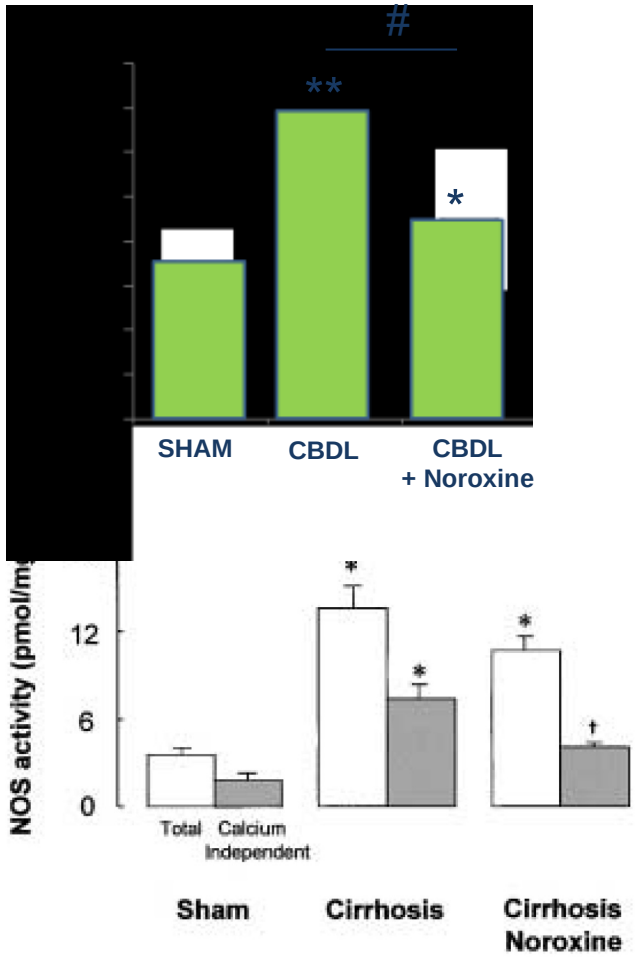
Angiogenesis

- Mycophenolate
- Anti-VEGF

Aucun traitement medical n’a démontré un effet sur le long terme

Effet des quinolones

Animal model

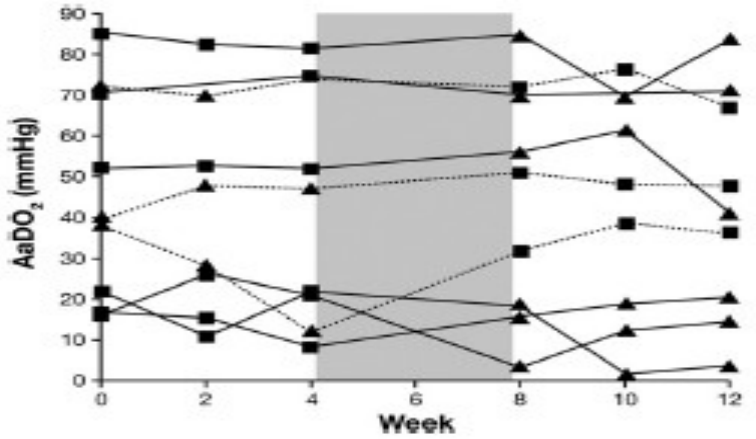


Rabiller et al, Am J Respir Crit Care Med 2002

Norfloxacin Therapy for Hepatopulmonary Syndrome: A Pilot Randomized Controlled Trial

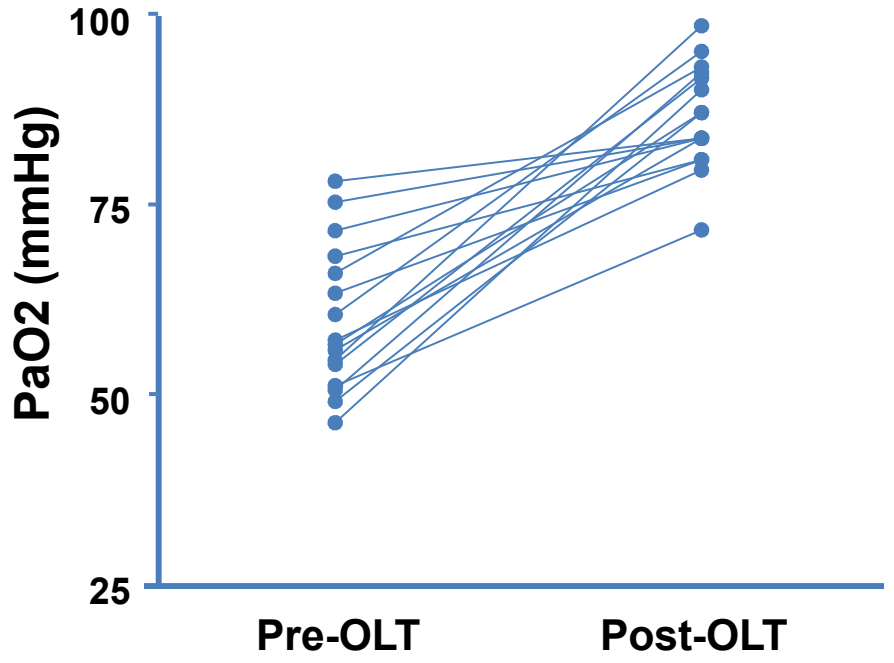
SAMIR GUPTA,[*,‡,§] MARIE E. FAUGHNAN,[*,‡,§] LES LILLY,[‖] STUART HUTCHISON,[¶] ROBERT FOWLER,[*,#,**] and AHMED M. BAYOUMI,[*,‡‡,§§,‖‖]

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2010;8:1095–1098



respectively ($P = .59$). **CONCLUSIONS: Recruitment difficulties and variability of the primary outcome measure suggest the need for a multicenter clinical research network for future therapeutic trials in this disease. There was no major effect of norfloxacin on gas exchange in patients with hepatopulmonary syndrome.**

Le SHP est reversible après transplantation hépatique



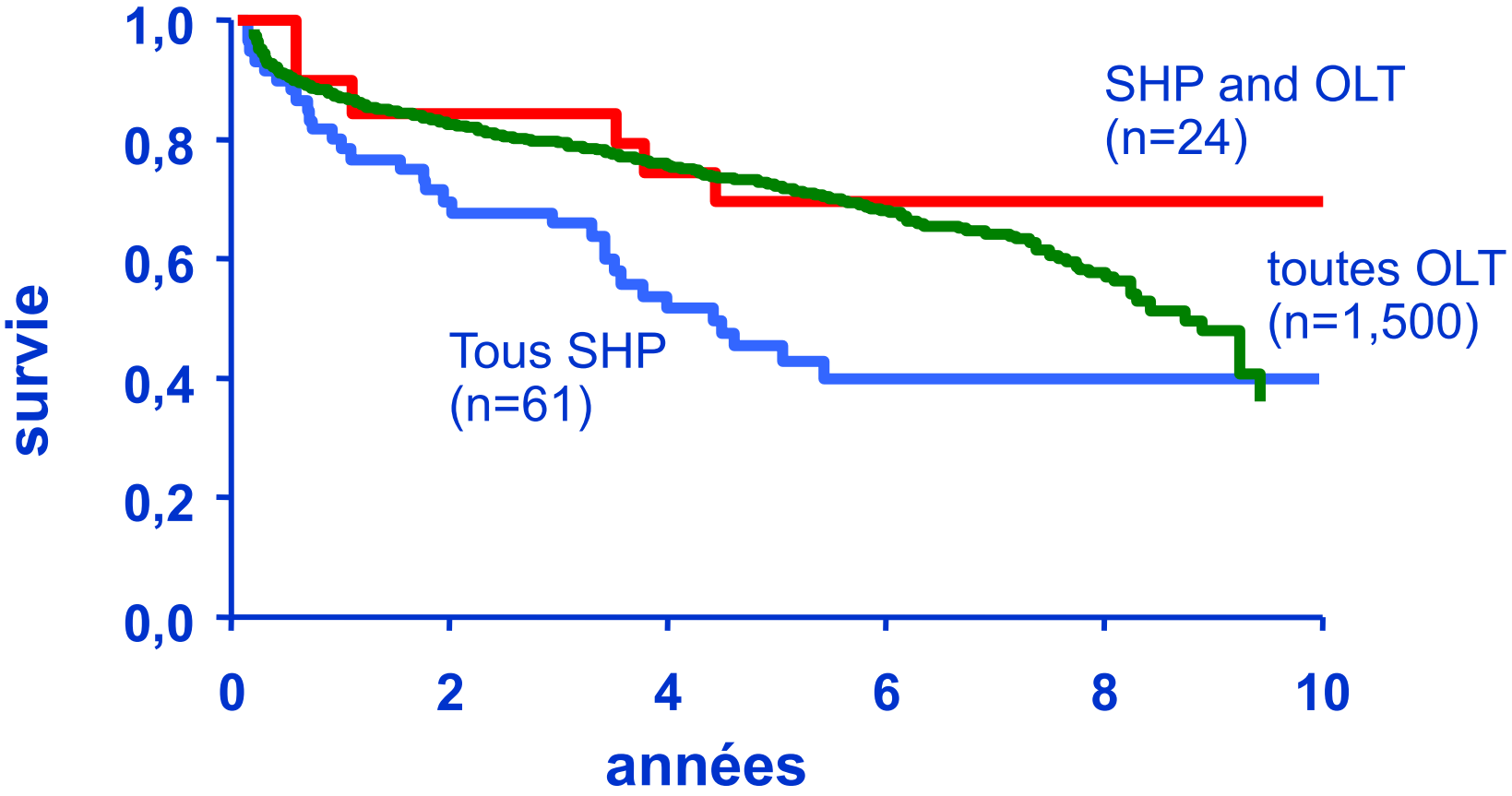
⇒ Réversibilité complète du SHP après TH (après 6 à 12 mois) dans environ 80%

⇒ La TH améliore lr pronostic des patients avec SHP

⇒ Surmortalité post-TH si Pa02<50 mmHg

- En cas de SHP sévère: indication à une TH quelque soit la gravité de la cirrhose sous-jacente
- Les patients avec un SHP sévère (PaO2< 60 mmHg) peuvent bénéficier d'une exception MELD pour accéder à la greffe dans un délai de 3 à 6 mois.

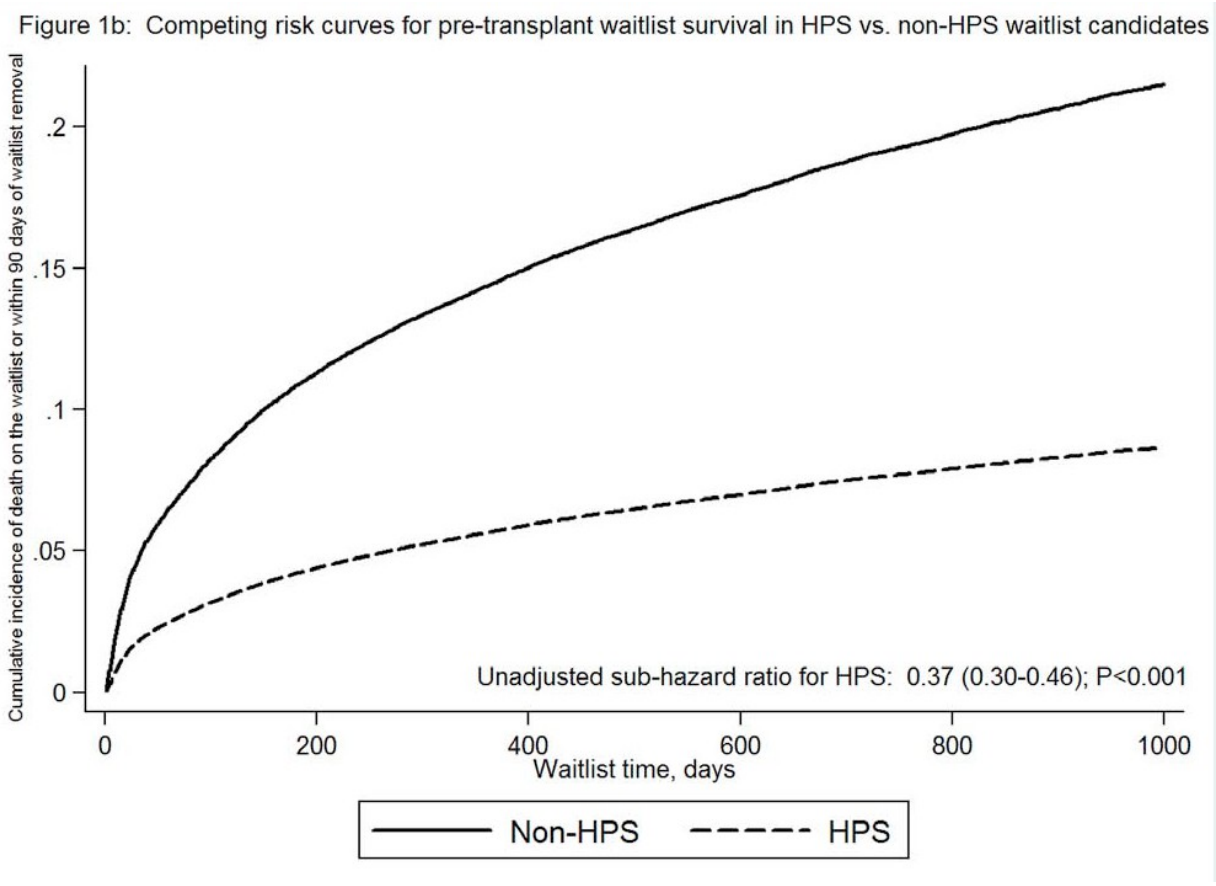
Impact de la TH sur la survie des patients (Mayo-Clinic)



LT improves the prognosis of patients with HPS

Postoperative mortality

With the MELD exception system, better prognosis of patients with HPS in comparison with non-HPS



Goldberg, Gastroenterology 2014

Evolution postopératoire immédiate

TABLE 4. Early postoperative evolution of HPS

Patient number	Preop PaO_2[c] (mm Hg)	Periop PaO_2[a] (mm Hg)	Duration of MV (days)	ICU stay duration (days)
1	44	35	1	30
2	32	33	2	8
3	55	40	1	6
4	43	38	1	8
5	67	68	2	27
6	32	PaO_2/ FIO_2=30	52	52
7	48	52	2	14
8	49	35	30	52
9	46	40	7	20
10	45	75	15	23
11	58	58	10	20
12	52	PaO_2/ FIO_2=40	16	16
13	52	45	2	6
14	45	43	3	11
15	51	60	120	120
16	59	60	1	8
17	64	70	1	11
18	62	60	49	67
19	34	30	1	13
20	53	49	1	3
21	64	66	1	11
22	60	64	2	19
23	54	51	2	12

Taillé C, Transpl 2003

Risk of Gaz exchanges worsening after liver transplantation

Management:

- Trendelenburg 2
- Inhaled NO 1, 3
- V-V ECMO 4

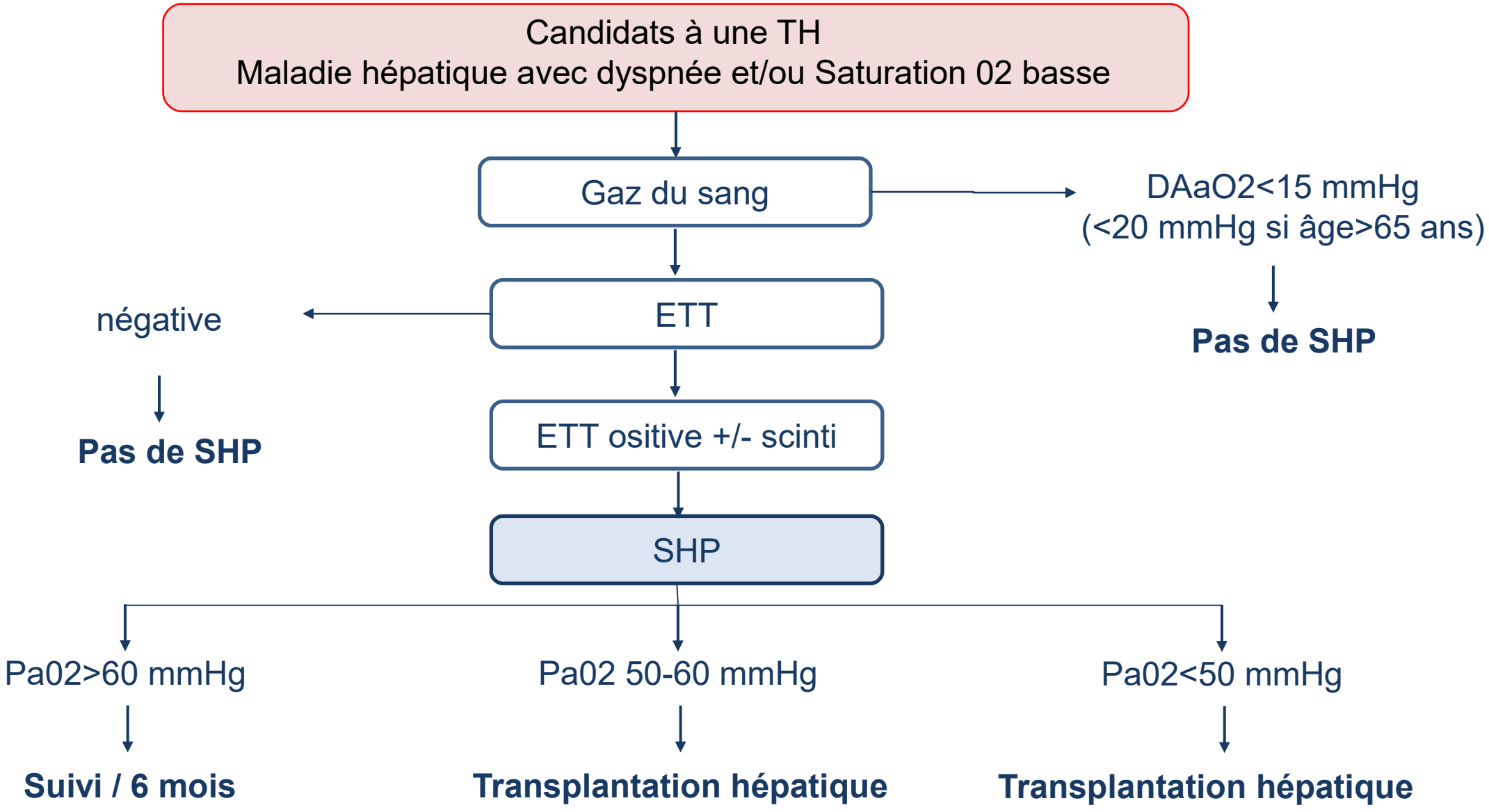
(1): Taillé C, Transpl 2003

(2): Meyers C Liver Transpl Surg 1996

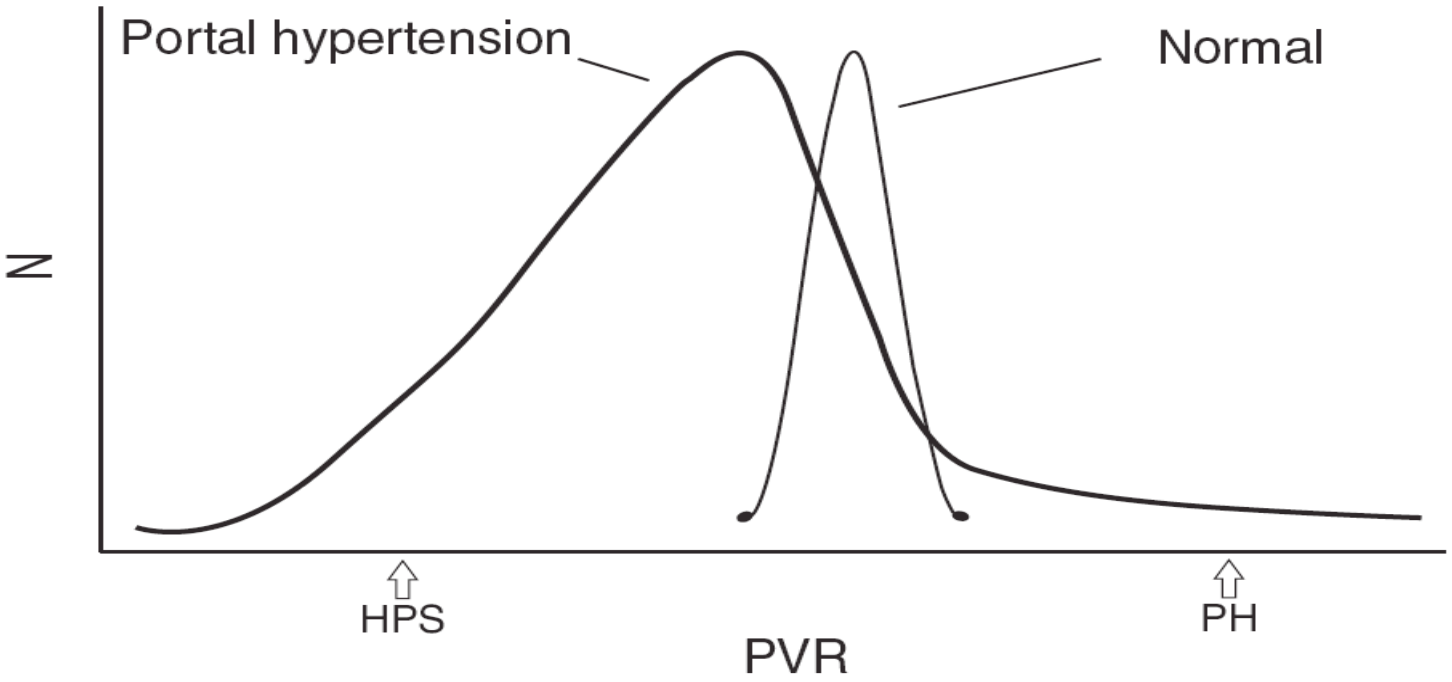
(3): Durand P, Transpl 1998

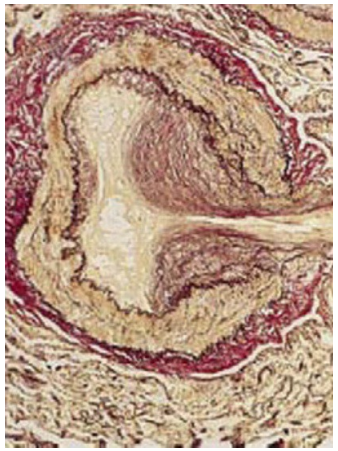
(4) Kumar, BMJ case report 2017

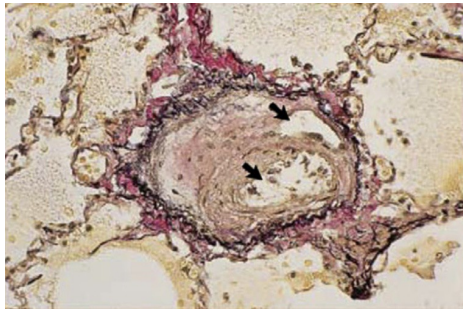
Algorithme

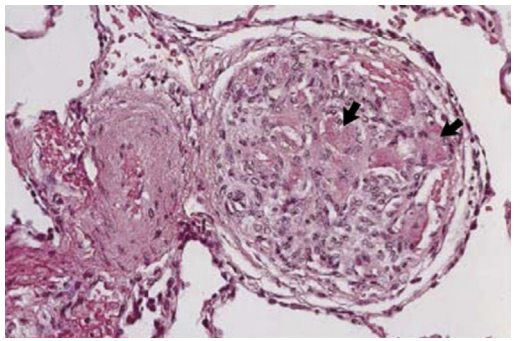

Candidats à une TH
Maladie hépatique avec dyspnée et/ou Saturation 02 basse
Gaz du sang
DAaO2<15 mmHg
(<20 mmHg si âge>65 ans)
Pas de SHP
ETT
négative
Pas de SHP
ETT ositive +/- scinti
SHP
Pa02>60 mmHg
Suivi / 6 mois
Pa02 50-60 mmHg
Transplantation hépatique
Pa02<50 mmHg
Transplantation hépatique

Hypertension portopulmonaire









Syndrome hépatopulmonaire

Prolifération et dilatation capillaire pulmonaire

Anomalies des échanges gazeux

Hypertension portopulmonaire

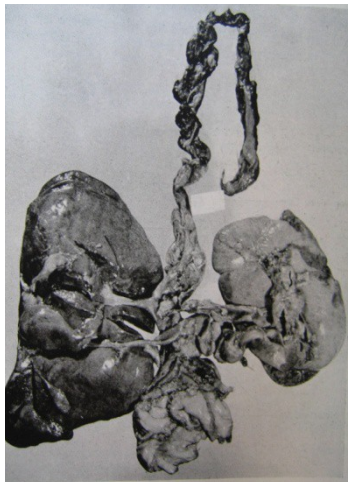
HTP précapillaire

Remodelage vasculaire pulmonaire

Herve & Al, Eur Respir J 1998

Mécanismes d'élévation des pressions pulmonaires au cours de l'hypertension portale

	PAP	PAWP	CO	PVR
Hyperdynamic	↗	N or ↗	↗↗	↘
Volume overload	↗	N or ↗	N or ↗	↘
PoPH	↗↗	N	N, ↘ or ↗	↗



PoPH décrit la première fois par Mantz and Craige en 1951

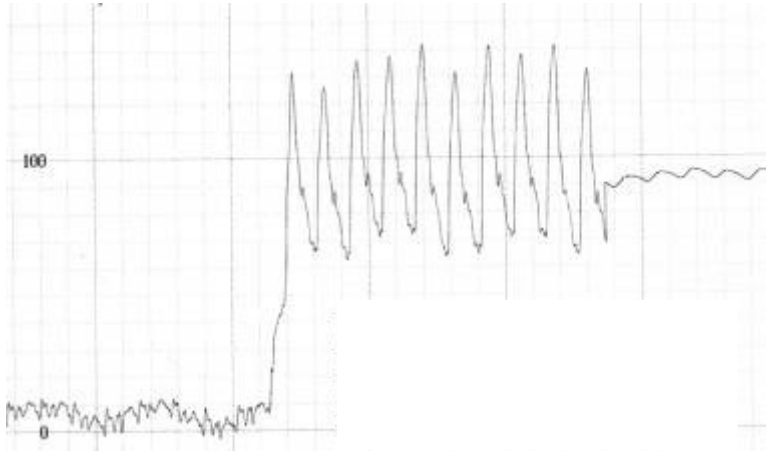
"*Portal thrombosis with portocaval shunt an resultant cor pulmonale*"

Herve & Al, Eur Respir J 1998

Review

International Liver Transplant Society Practice Guidelines: Diagnosis and Management of Hepatopulmonary Syndrome and Portopulmonary Hypertension

Michael J. Krowka, MD,[1] Michael B. Fallon, MD,[2] Steven M. Kawut, MD, MS,[3] Valentin Fuhrmann, MD,[4] Julie K. Heimbach, MD,[5] Michael A. E. Ramsay, MD,[6] Olivier Sitbon, MD,[7] and Ronald J. Sokol, MD[8]



- Hypertension portale (avec ou sans cirrhose), présente au diagnostic d'HT pulmonaire
- PAPm de repos > 25 mm Hg
- PAPO < 15 mm Hg
- RVP [=(PAPm - PAPO) / Qc] > 3.0 Wood units (240 dynes/s per cm-5)

→ **KT droit indispensable pour établir le diagnostic d'HTPoP**

Krowka MJ, *et al. Transplantation* 2016;100: 1440–52.

PoPH : groupe 1 (HTAP)

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

2. Pulmonary Hypertension Due to Left Heart Disease

2.1 Left Ventricular Systolic Dysfunction
2.2 Left Ventricular Diastolic Dysfunction
2.3 Valvular disease
2.4 Congenital / acquired left heart inflow / outflow tract obstruction and, congenital cardiomyopathies

3. Pulmonary Hypertension Due to Lung Diseases and/or Hypoxia

3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases

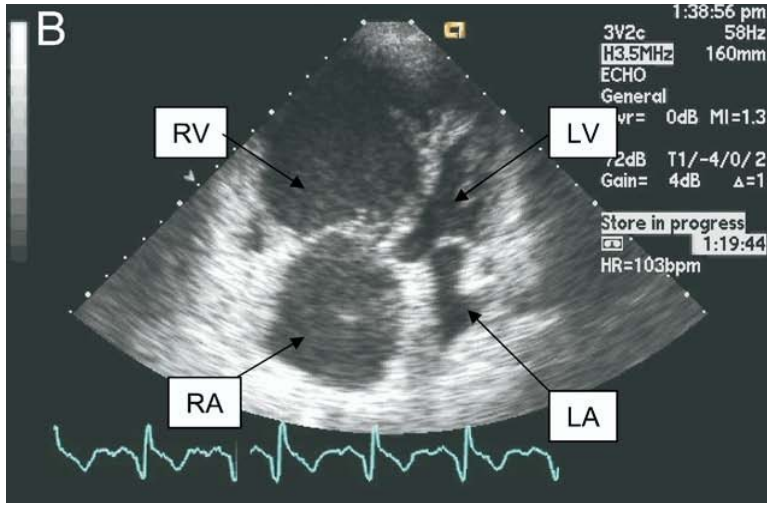
4. Chronic Thromboembolic Pulmonary Hypertension

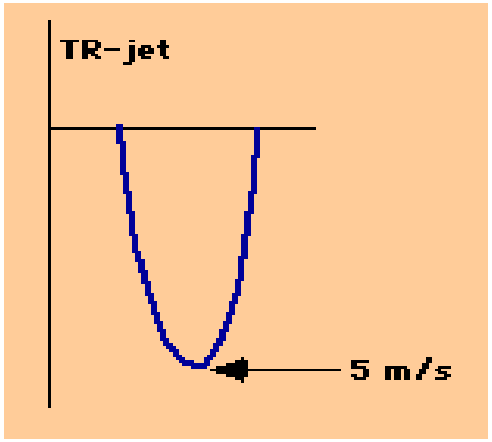
5. Pulmonary Hypertension with Unclear Multifactorial Mechanisms

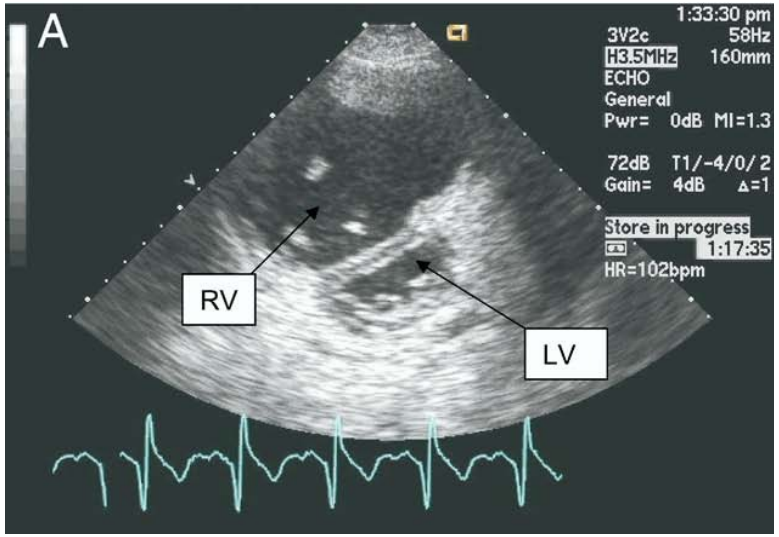
5.1 Hematologic disorders: chronic hemolytic anemias, myeloproliferative disorders splenectomy,
5.2 Systemic disorders, sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleio-myomatosis, neurofibromatosis, vasculitis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Simonneau et al. J Am Coll Cardiol 2013; 62:D34-41.

Dépistage par ETT







Estimated sPAP
= (4 x TRVmax2)
+ RAP (estimated)

Dépistage de l'hypertension (porto)pulmonaire: échographie cardiaque

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo "PH signs"[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

A: The ventricles[a]	B: Pulmonary artery[a]	C: Inferior vena cava and right atrium[a]
Right ventricle/left ventricle basal diameter ratio >1.0	Right ventricular outflow Doppler acceleration time <105 m/sec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole).	Early diastolic pulmonary regurgitation velocity >2.2 m/sec	Right atrial area (end-systole) >18 cm^2
	PA diameter >25 mm	

Galie et al. Eur Respir J 2015 & Eur Heart J 2016

Chez qui dépister l'Hypertension Portopulmonaire ?

1. **Dépistage systématique uniquement si:**
   - bilan prétransplantation hépatique
   - mise en place d'un TIPS

2. **Dépistage non systématique chez les patients cirrhotiques**
   - ETT si dyspnée inexpliquée et/ou signes d'IVD

Recommendations	Class[a]	Level[b]
Echocardiographic assessment for signs of PH is recommended in symptomatic patients with liver disease or portal hypertension and in all candidates for liver transplantation	I	B

Galie N, et al. *Eur Respir J* 2015 & *Eur Heart J* 2016.

Chez qui dépister l'Hypertension Portopulmonaire ?

1. **Dépistage systématique uniquement si:**
   - bilan prétransplantation hépatique
   - mise en place d'un TIPS

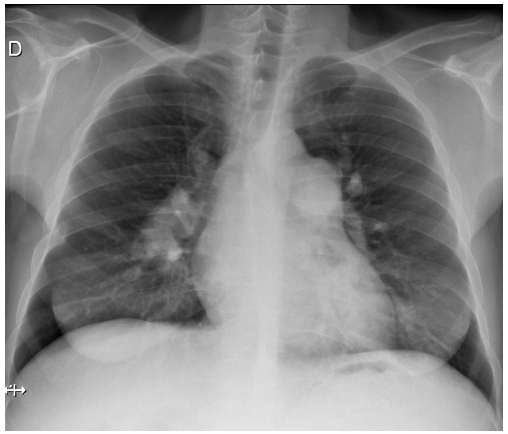
2. **Dépistage non systématique chez les patients cirrhotiques**
   - ETT si dyspnée inexpliquée et/ou signes d'IVD

Si suspicion d'HTAP ➔ KT droit dans un centre de compétence

A l'inverse, recherche systématique d'une hypertension portale ou d'un shunt porto-systémiques en cas de premier bilan d'HTAP:

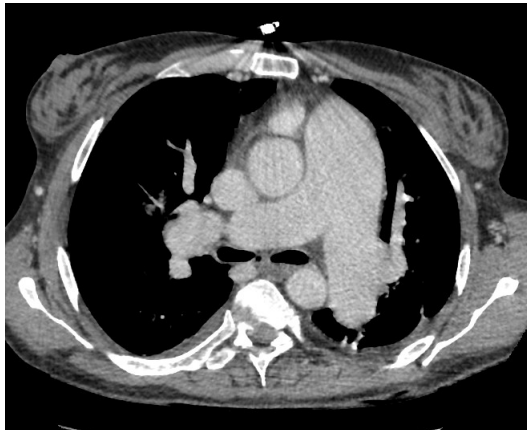
- Sérologies VHB, VHC, VIH:
- Echographie doppler hépatique +/- FOGD
- Mesure du GPTH lors du KT droit (>5 mmHg)

Exemple 1: dépistage PoPH avant TIPS



Echographie cardiaque :
- FEVG 63%
- Vmax IT 2,7 m/s
- Cavités cardiaques droites non dilatées,
- TAPSE 17mm, Onde S 10 cm/s

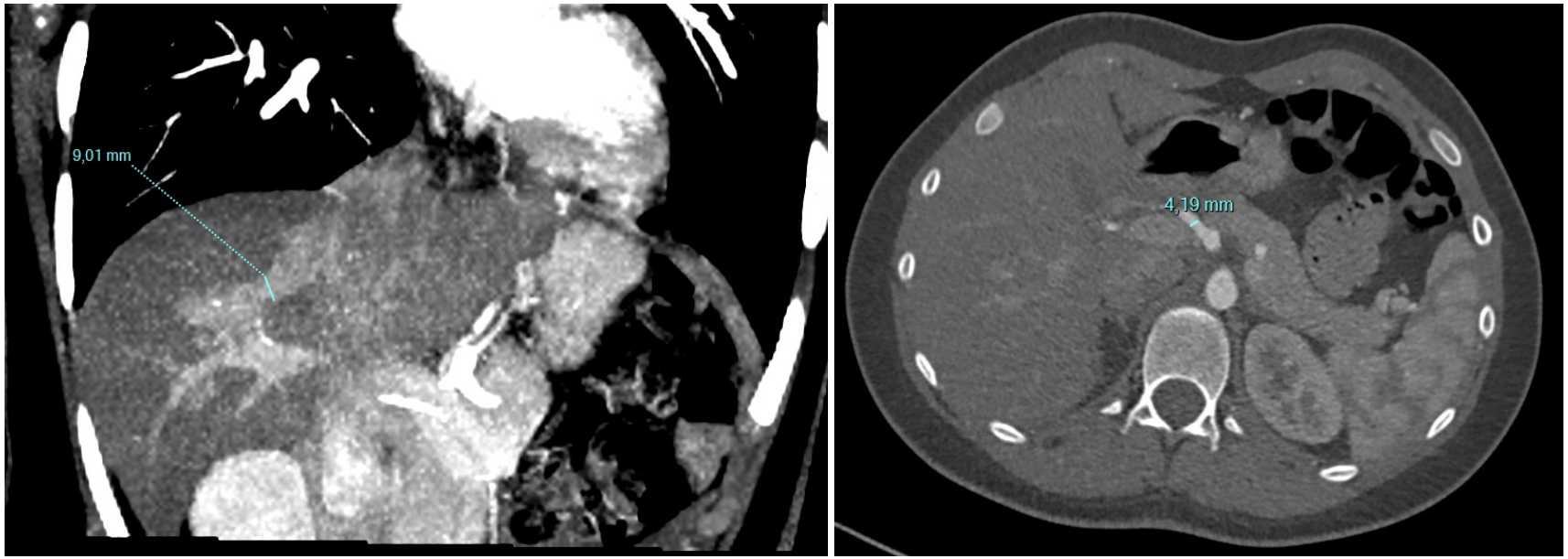
Poussée d'insuffisance ventriculaire droite sévère après TIPS



Cathétérisme cardiaque droit:
- POD 8 mmHg
- PAPm 36 mmHg
- PAPO 8 mmHg
- Qc 5 l/min/m2

Exemple 2: dépistage hypertension portale au cours d'un bilan d'HTAP "idiopathique"

- Jeune fille de 16 ans, DE-CF III de la NYHA depuis un à deux ans
- Adressée pour premier bilan d'HTAP d'allure "idiopathique"



Prevalence of portopulmonary hypertension

	n	Patients	Diagnostic method	Prevalence
Hadengue, *Gastroenterology 1991*	507	Cirrhosis (all stages)	- RHC in all patients - mPAP > 25 mmHg	**2%**
Castro, *Mayo Clin Proc* 1996	362	LT candidates	- RHC in operating room (LT) - mPAP > 25 mmHg and PVR > 120 dyn.s.cm-5	**4%**
Colle, *Hepatology* 2003	165	LT candidates	- RHC if hepatic biopsy (trans-jugular) - mPAP > 25 mmHg and PVR >120 dyn.s.cm-5	**6%**

France : 1530 patients on LT waiting list in 2011 (Agence de Biomédecine)

→ **potentially 30 to 90 patients/year with PoPH awaiting for LT**

Registre français de l'TP

	IPAH	PoPH
Age, *yrs*	56 ± 19	54 ± 11
Ratio F:M	1.21	0.86
RAP, *mmHg*	9 ± 5	9 ± 6
mPAP, *mmHg*	51 ± 14	48 ± 12
PAWP, *mmHg*	9 ± 4	10 ± 4
CI, *L/min/m2*	2.4 ± 0.8	2.9 ± 0.9
PVR, *WU.*	10.8 ± 6.0	8.1 ± 5.0

PoPH in US: ≈ 5% of Group 1

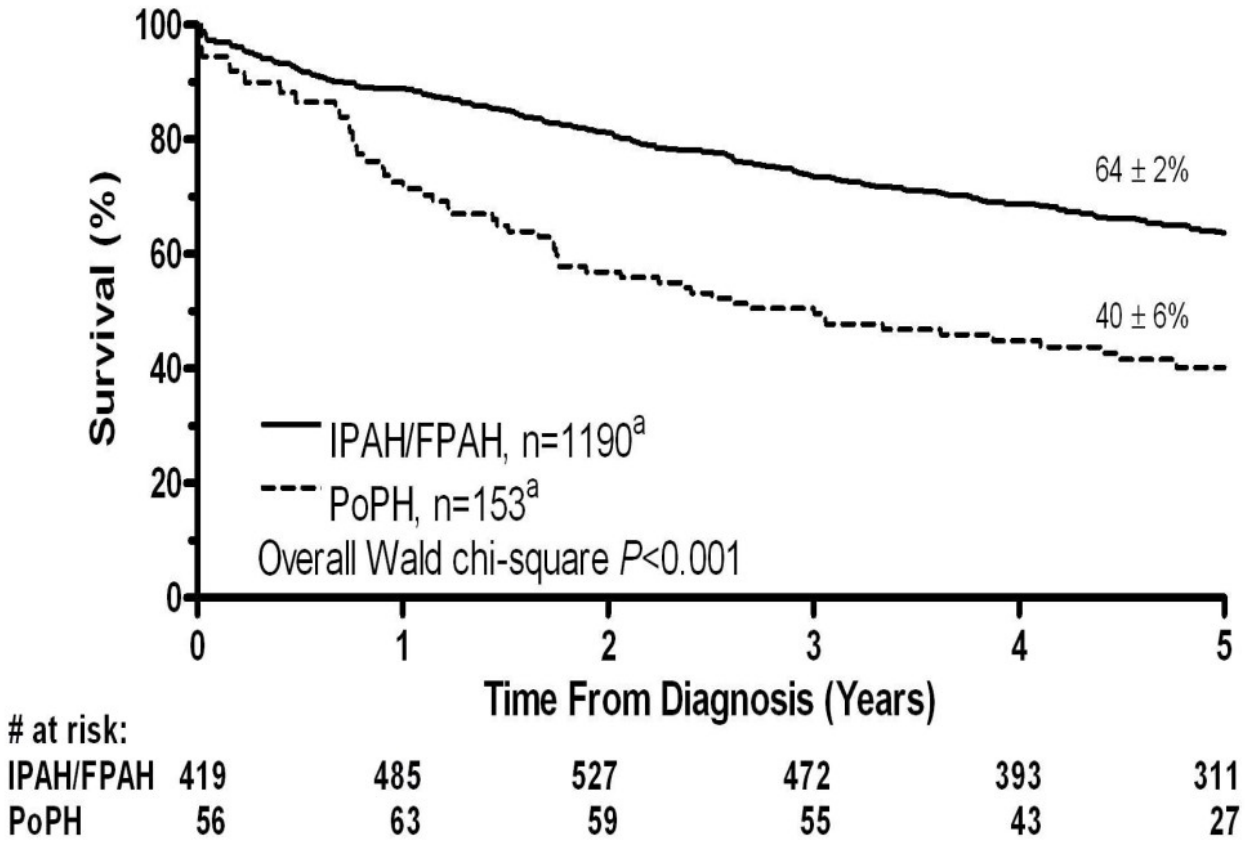
Badesch DB, *et al. CHEST* 2010; 137(2):376–87.

Etiologies de l'HTPo

Cirrhosis n=136 Child Pugh A, *n = 61* Child Pugh B, *n = 45* Child Pugh C, *n = 13*	*Alcohol*	n=76
	Viral hepatitis	n=30
	Cryptogenic	n=11
	Auto-immune	n=8
	Biliary cirrhosis	n=5
	Hemochromatosis	n=3
	Toxic	n=3
PoH without cirrhosis n=18	*Portal thrombosis*	n=13
	Budd Chiari	n=3
	Schistosomiasis	n=2

Le Pavec J, *et al. Am J Respir Crit Care Med* 2008; 178: 637–43.

Survie *(US cohort)*

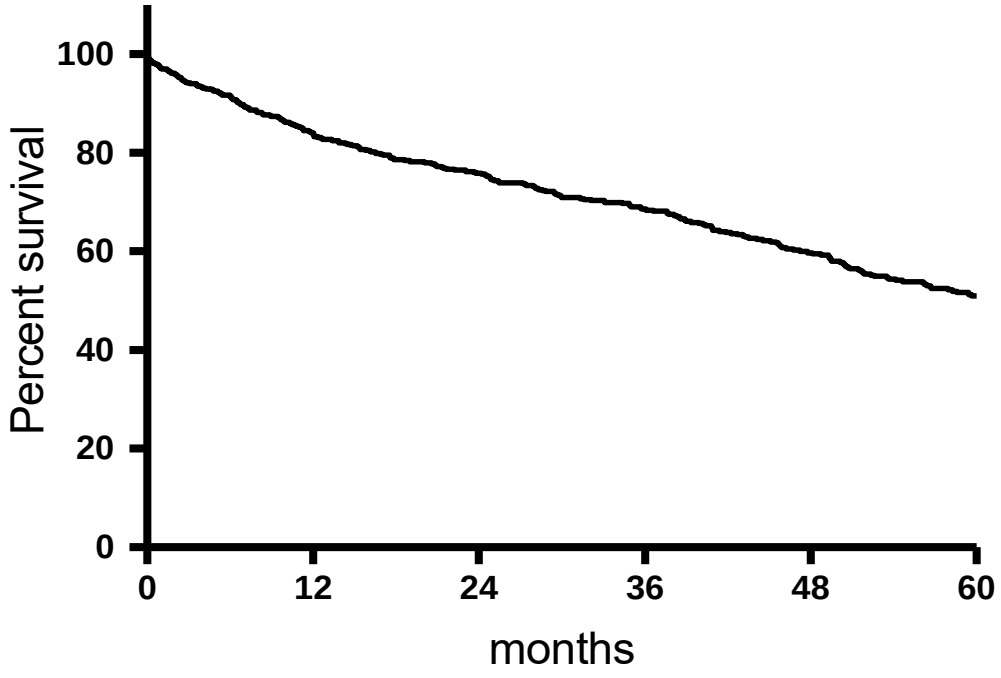


PoPH
50% survival @ 3 yrs

Krowka M, *et al. Chest* 2012; 141: 906–15.

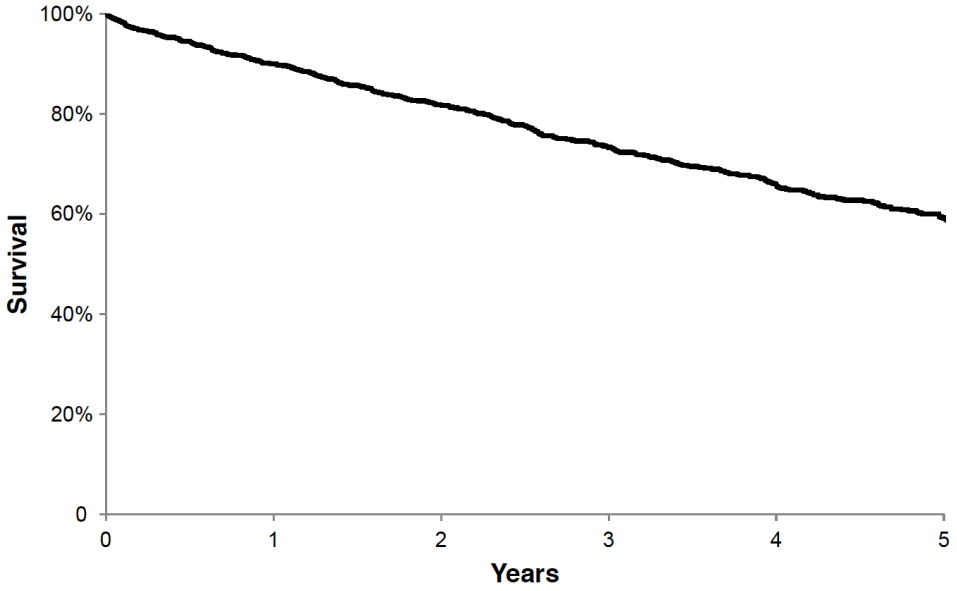
Survie (*French cohort 2006-2016)*

PoPH (n = 637)1



Survival @ 1 yr	84%
Survival @ 3 yrs	68%
Survival @ 5 yrs	51%

IHA PAH (n = 1591)2



Patients at risk, n	1591	1063	823	605	417	285
Overall survival		90%	82%	73%	66%	59%

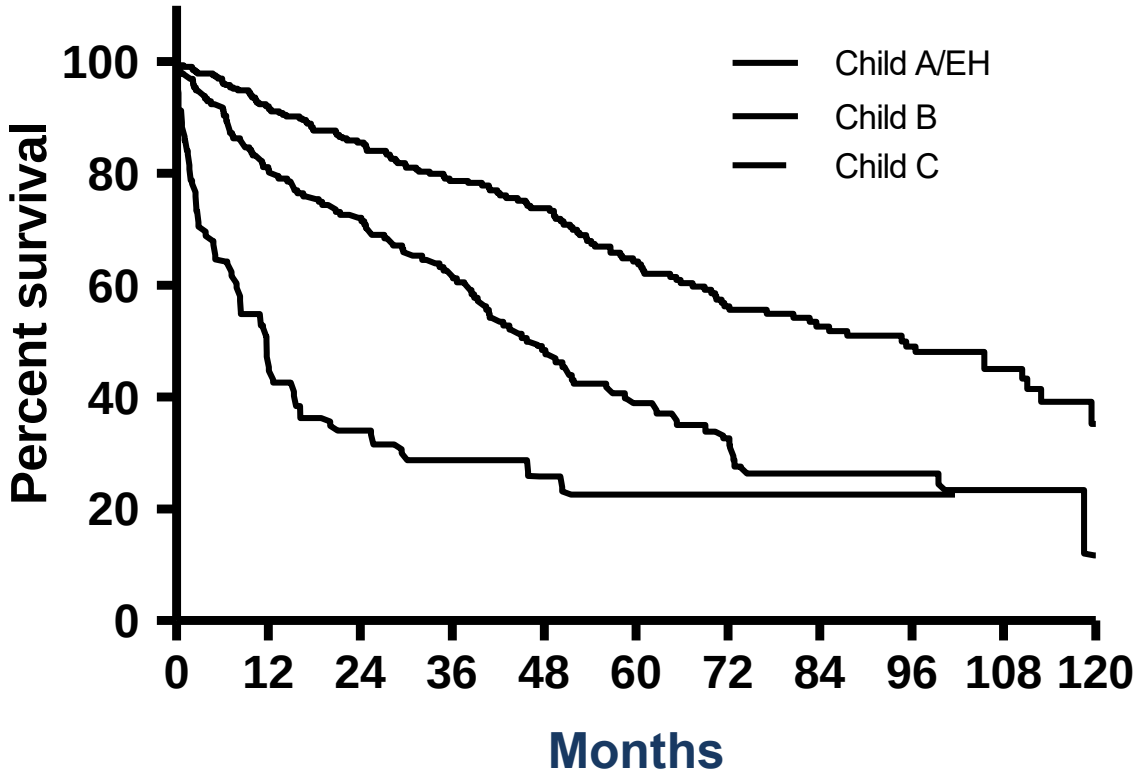
1. Savale L. Data on file.
2. Boucly A, et al. Eur Respir J 2017 50: 1700889.

Facteurs pronostiques

PoPH (before 2004)1

Variables	Hazard Ratio	95% CI	P-value
No cirrhosis	0.20	0.07 – 0.59	0.003
Child Pugh B cirrhosis.	2.05	1.22 – 3.43	0.007
Child Pugh C cirrhosis	2.42	1.26 – 4.65	0.008
Cardiac index	0.56	0.38 - 0.83	0.004

PoPH (2006-2016)2



1. Le Pavec J, *et al. Am J Respir Crit Care Med* 2008; 178: 637–43.
2. Savale L. Data on file.

Prise en charge

1. **Non specific therapies**
   - Similar to iPAH (diuretics, oxygen, exercise limitation)
   - Avoid beta-blockers. May be deleterious in PoPH1
   - Oral anticoagulation: not indicated
   - Treatment of HCV hepatitis
     - IFN: possible risk factor for PAH2,3
     - New medications (proteases inhibitors) under surveillance
2. **Targeted-PAH therapies**
   - Retrospective experience on small series
   - A single recent RCT with macitentan (PORTICO)
3. **Impact of liver transplantation on PoPH**

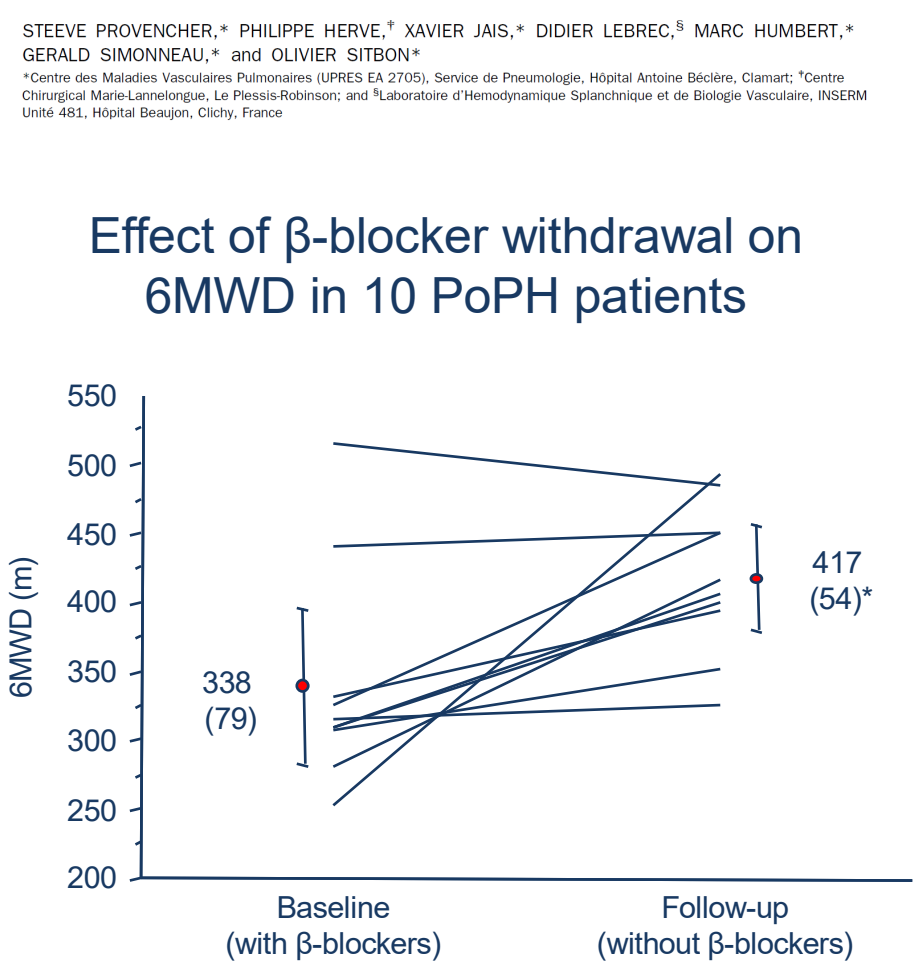
1. Provencher S, *et al*. *Gastroenterology* 2006
2. Savale L, *et al. Eur Respir J* 2014.
3. Simonneau G, *et al. J Am Coll Cardiol* 2013.

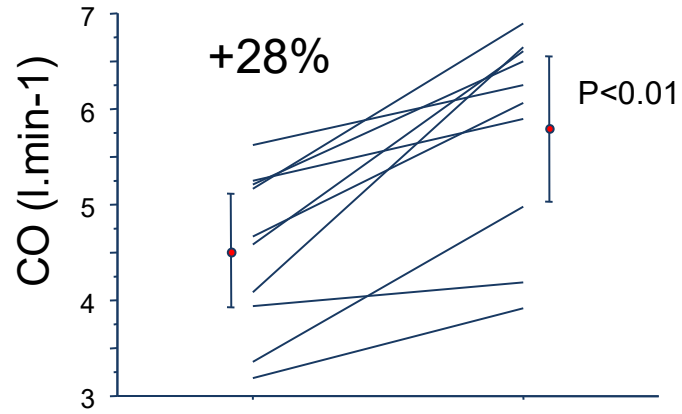
Effet de l’arrêt des bétabloquants

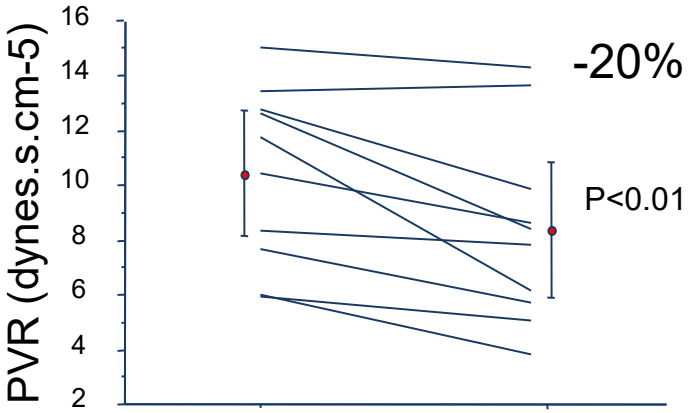
Deleterious Effects of β-Blockers on Exercise Capacity and Hemodynamics in Patients With Portopulmonary Hypertension

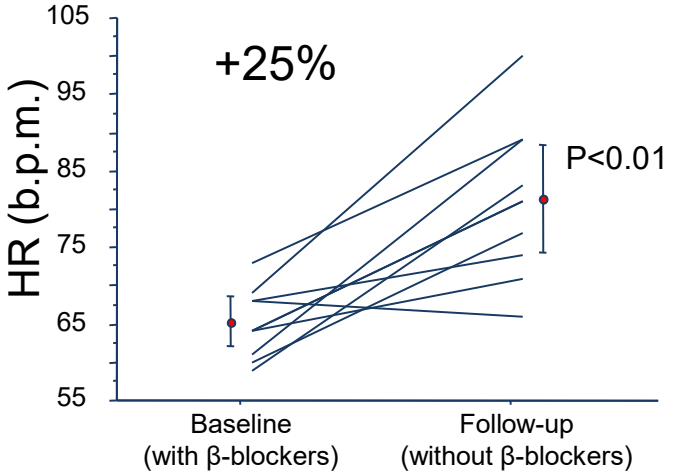
STEEVE PROVENCHER,* PHILIPPE HERVE,† XAVIER JAIS,* DIDIER LEBREC,§ MARC HUMBERT,* GERALD SIMONNEAU,* and OLIVIER SITBON*

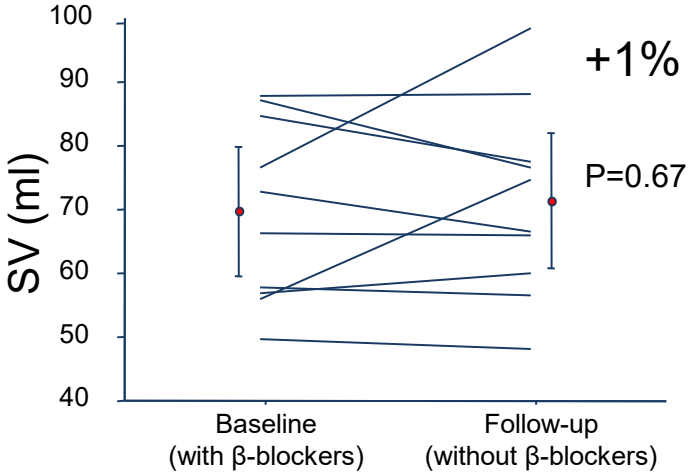
*Centre des Maladies Vasculaires Pulmonaires (UPRES EA 2705), Service de Pneumologie, Hôpital Antoine Béclère, Clamart; †Centre Chirurgical Marie-Lannelongue, Le Plessis-Robinson; and §Laboratoire d'Hemodynamique Splanchnique et de Biologie Vasculaire, INSERM Unité 481, Hôpital Beaujon, Clichy, France





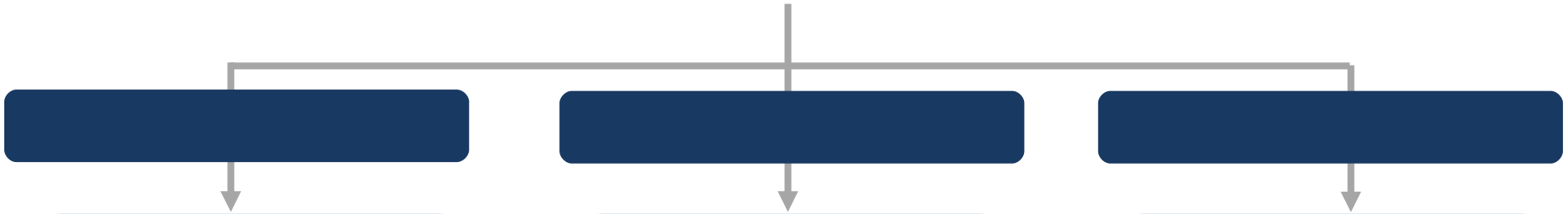






Provencher S et al. Gastroenterology 2006.

Traitements spécifiques de l'HTAP



Endothelin receptor antagonists (ERAs)

- Ambrisentan
- Bosentan

PDE5 inhibitors

- Sildenafil
- Tadalafil

Prostanoids

- Beraprost
- Epoprostenol iv
- Iloprost iv, inhaled
- Treprostinil iv, sc, inhaled, oral

Endothelin receptor antagonists (ERAs)

- Macitentan

sGC stimulators

- Riociguat

Non prostanoids IP receptor agonist

- Selexipag (oral)

Adapted from Galiè N et al. J Am Coll Cardiol 2013;62:D60–72.

Traitements spécifiques dans l'HTPoP

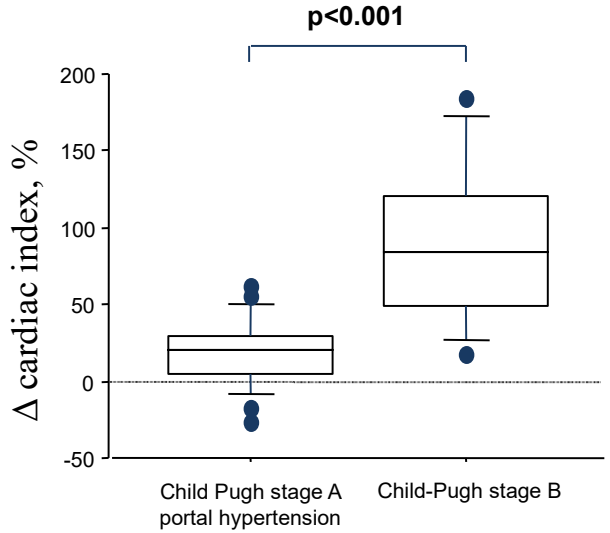
- Pas d'indication aux Ica (pas de répondeurs au NO parmi les HTPoP)
- L'Epoprostenol, le bosentan, l'ambrisentan, le sidenafil améliorent l'hemodynamique et/ou les capacités à l'exercice dans des études rétrospectives de faible effectif
- Impact des traitements spécifiques sur la survie

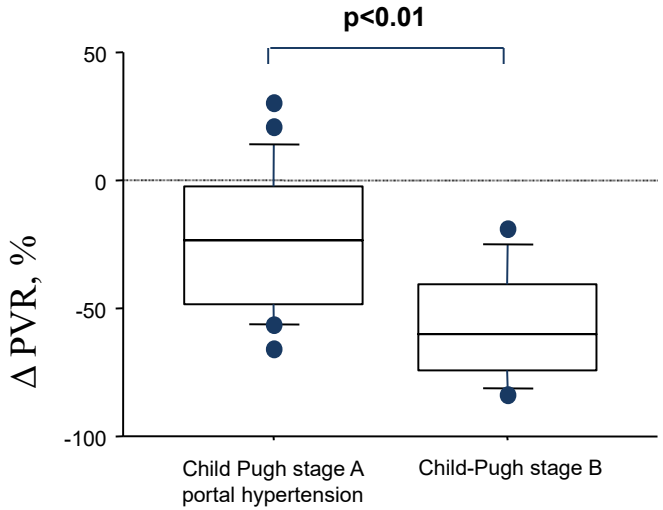
Choix du traitement en fonction:

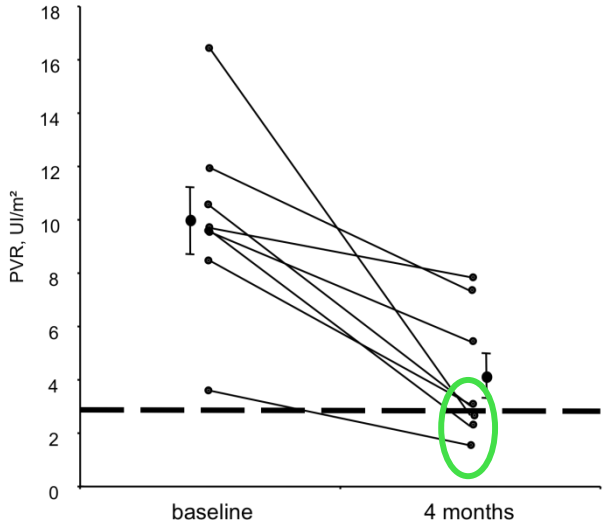
1. de la sévérité de l'HTAP
2. de la sévérité de l'atteinte hépatique sous jacente
   - Cytolyse hépatique (ERA)
   - risque aggravation rétention hydrosodée.
   - risque aggravation de l'HTPortale?
3. d'un projet de transplantation hépatique

1. Krowka M, *et al. Hepatology* 1999.
2. Hoeper MM, *et al. Eur Respir J* 2005.
3. Savale L, *et al. Eur Respir J* 2012.
4. Cartin-Ceba R, *et al. CHEST* 2010.
5. Makisalo, *et al. Liver Transpl* 2004.

Bosentan dans l'HTPoP





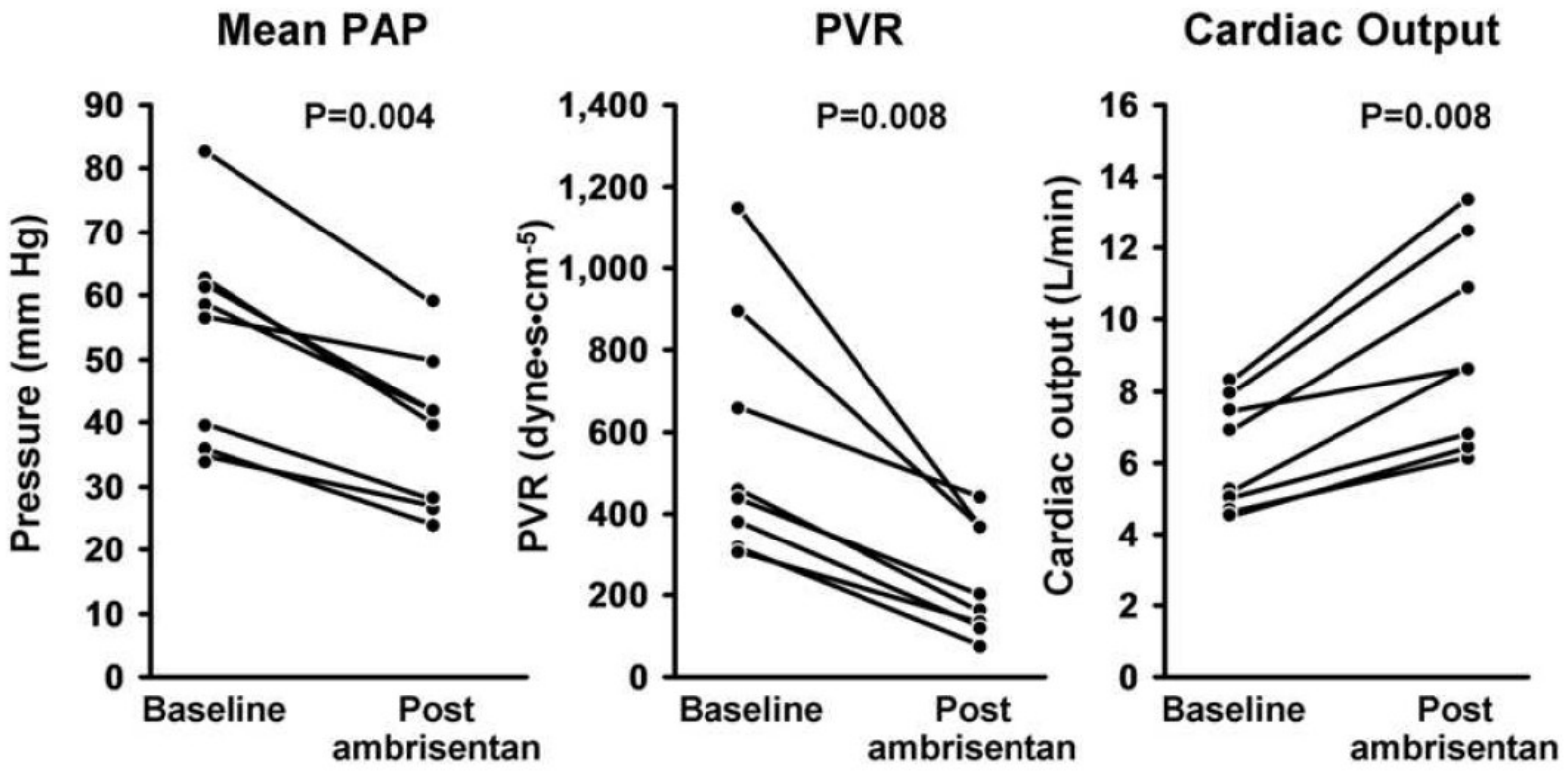


- Short-term hemodynamic response was significantly better in patients with CP stage B cirrhosis vs. those with CP stage A cirrhosis or with non cirrhotic portal HT
- A subset of patients with cirrhosis child Pugh stage B had a near-normalization in PVR after 4 months of bosentan treatment

Savale L, *et al, Eur Respir J* 2013; 41: 96–103.

Ambrisentan dans l'HTPoP

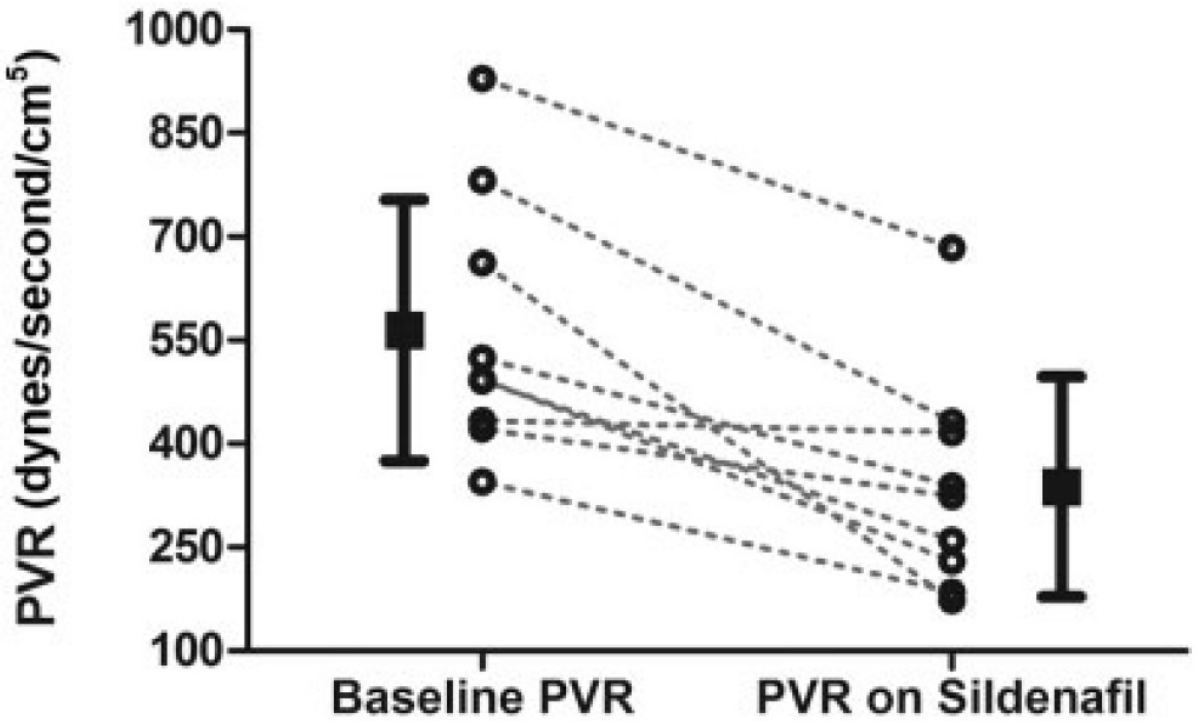
N= 13 (8 Child-Pugh A cirrhosis).
Median ambrisentan time 390 days
RHC data available in exposure 8 patients



Median PVR from 445 (329-834) to 174 dyn.s/cm5 (121-361), p=0.008

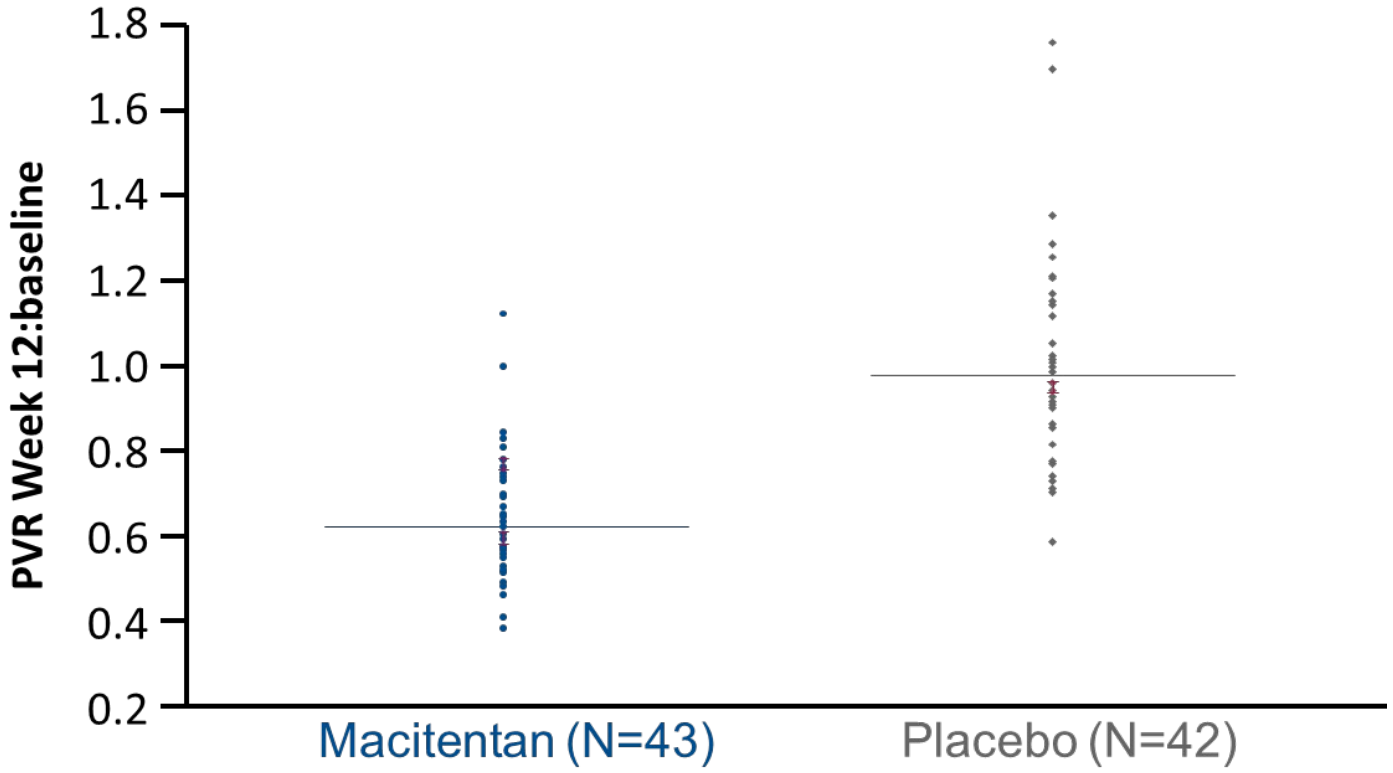
Cartin-Ceba R, et al. CHEST 2010.

Sildenafil et HTPoP



Gough et al, liver transplantation 2013.

PORTICO primary endpoint – PVR at Week 12 expressed as ratio of baseline



Other endpoints

- Improvement in other HD parameters
- No change in 6MWD, FC and NT-proBNP
- No safety issue (clinical, liver enzymes, Hb…)
- No death

Sitbon O, et al. Presented at ERS Congress, September 2018.

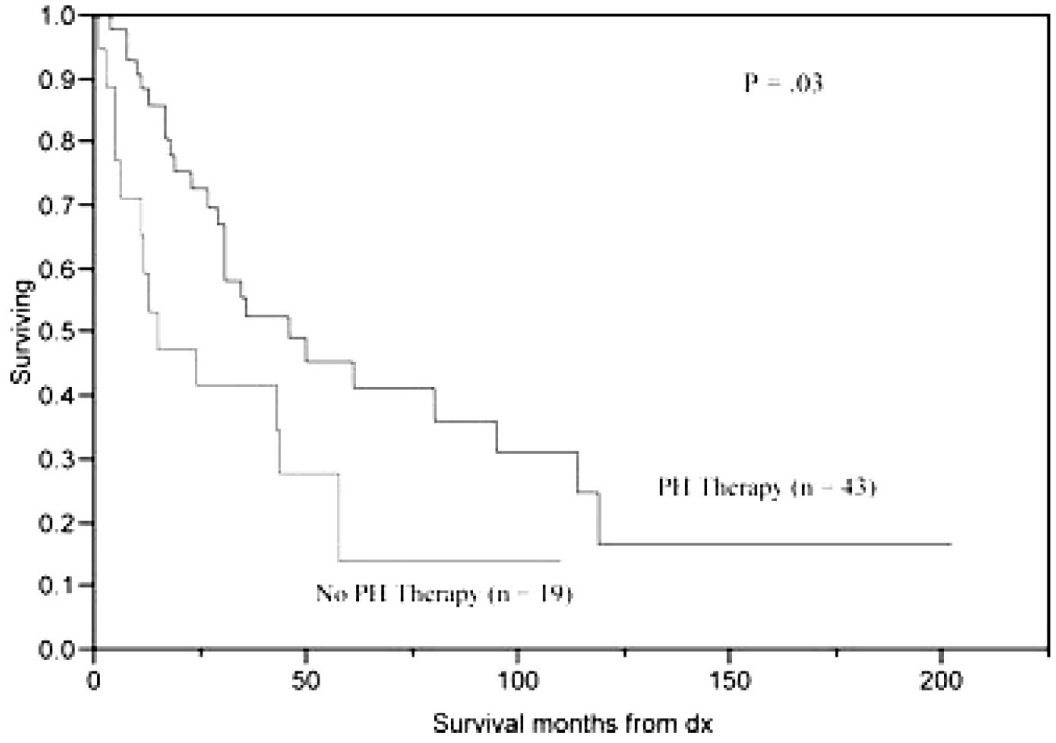
2015 ERS / ESC Guidelines

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended that patients affected by PAH associated with portal hypertension should be referred to centres with expertise in managing both conditions	I	C	[344]
It is recommended that the treatment algorithm for patients with other forms of PAH should be applied to patients with PAH associated with portal hypertension, taking into account the severity of liver disease	I	C	[214, 350–356]

Galie, Eur Respir J 2015 and Eur Heart J 2016.

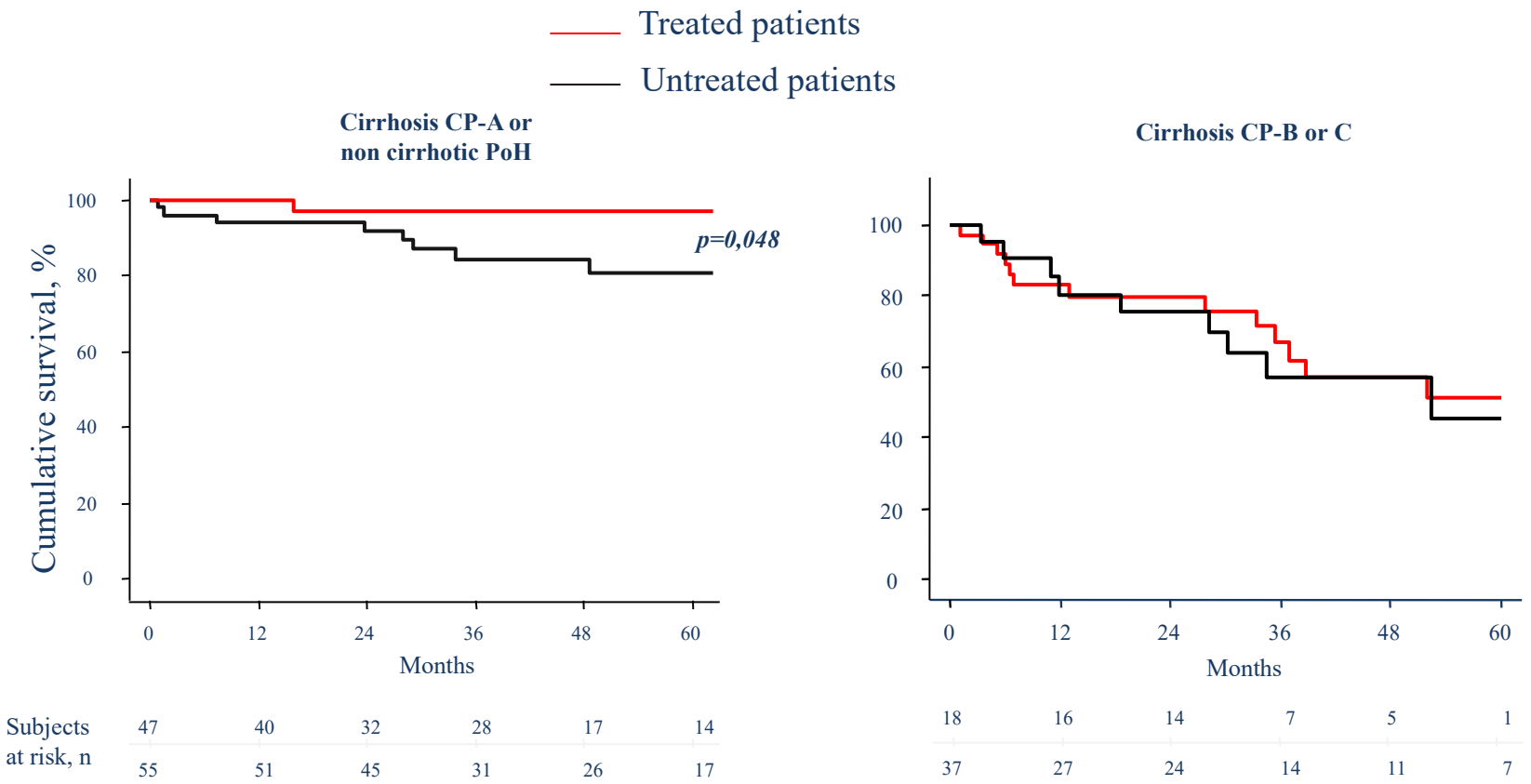
Impact des traitements de l'HTAP sur la survie

- Retrospective study: 62 patients without indication for OLT
  - 43 PAH specific therapies
  - 19 no PAH therapy
- No indication on the severity of liver disease



Swanson KL, *et al*. *Am J Transplant* 2008; 8: 2445-53.

Impact des traitements ciblés de l'HTAP sur la survie?



PAH-specific therapy may impact survival of patients with mild cirrhosis or portal HT without cirrhosis

Savale et al, *ATS 2010*

Prise en charge

1. **Non specific therapies**
   - Similar to iPAH (diuretics, oxygen, exercise limitation)
   - Avoid beta-blockers. May be deleterious in PoPH1
   - Oral anticoagulation: not indicated
   - Treatment of HCV hepatitis
     - IFN: possible risk factor for PAH2,3
     - New medications (proteases inhibitors) under surveillance
2. **Targeted-PAH therapies**
   - Retrospective experience on small series
   - A single recent RCT with macitentan (PORTICO)
3. **Impact of liver transplantation on PoPH**

1. Provencher S, *et al*. *Gastroenterology* 2006
2. Savale L, *et al. Eur Respir J* 2014.
3. Simonneau G, *et al. J Am Coll Cardiol* 2013.

Original Clinical Science—Liver

Predictors of Waitlist Mortality in Portopulmonary Hypertension

Hilary M. DuBrock, MD,[1] David S. Goldberg, MD, MSCE,[2] Norman L. Sussman, MD,[3] Sonja D. Bartolome, MD,[4] Zakiyah Kadry, MD,[5] Reena J. Salgia, MD,[6] David C. Mulligan, MD,[7] Walter K. Kremers, PhD,[8] Steven M. Kawut, MD, MS,[2] Michael J. Krowka, MD,[9] and Richard N. Channick, MD[1]

Multivariate predictors of waitlist mortality or removal for clinical deterioration

DuBrock HM, *et al. Transplantation* 2017;101: 1609–15.

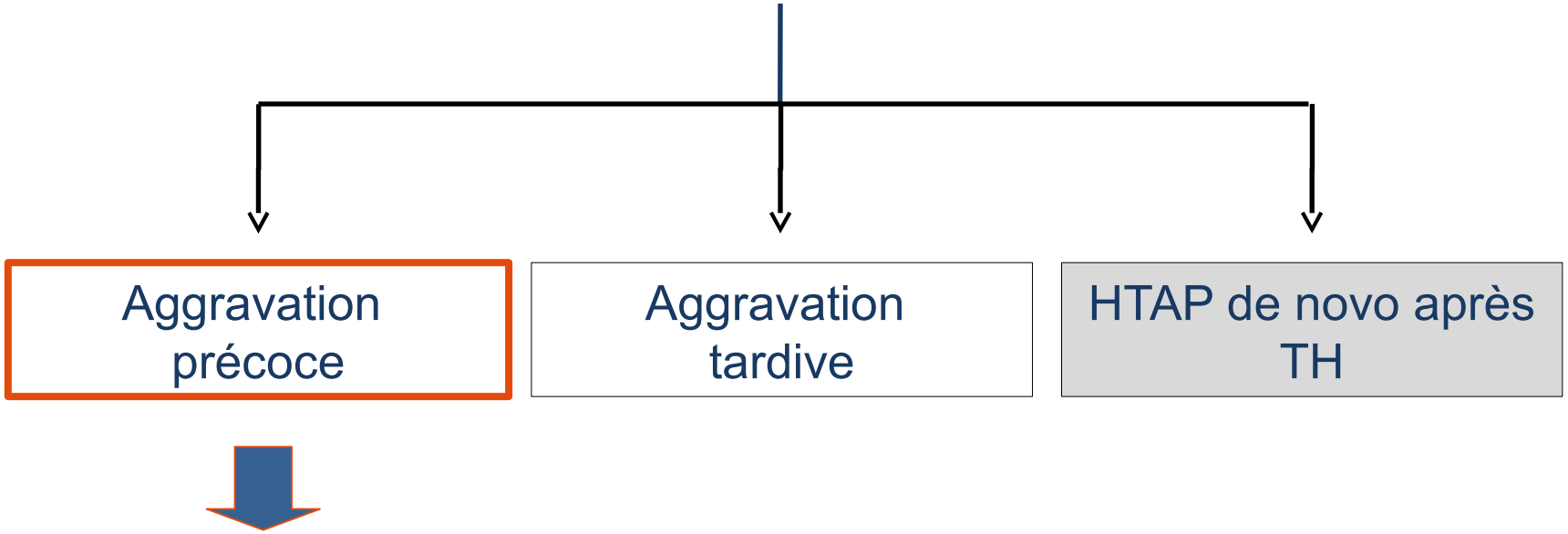
Hemodynamics and cardiopulmonary mortality after LT

Mean PAP	Recommandation for LT	Cardiopulmonary mortaliy
< 35 mmHg	Perform LT	0/14 (0%)
35-50 mmHg	If PVR < 250 dyn.s.cm-5 Perform LT	0/6 (0%)
	If PVR >250 dyn.s.cm-5 Cancel LT	7/14 (50%)
>50 mmHg	Cancel LT	6/6 (100%)

HTPoP : contre indication à la greffe

Krowka M. Liver Transplantation 2000
ERS Task Force. Eur Respir J 2004

Aggravation HTPoP après la TH



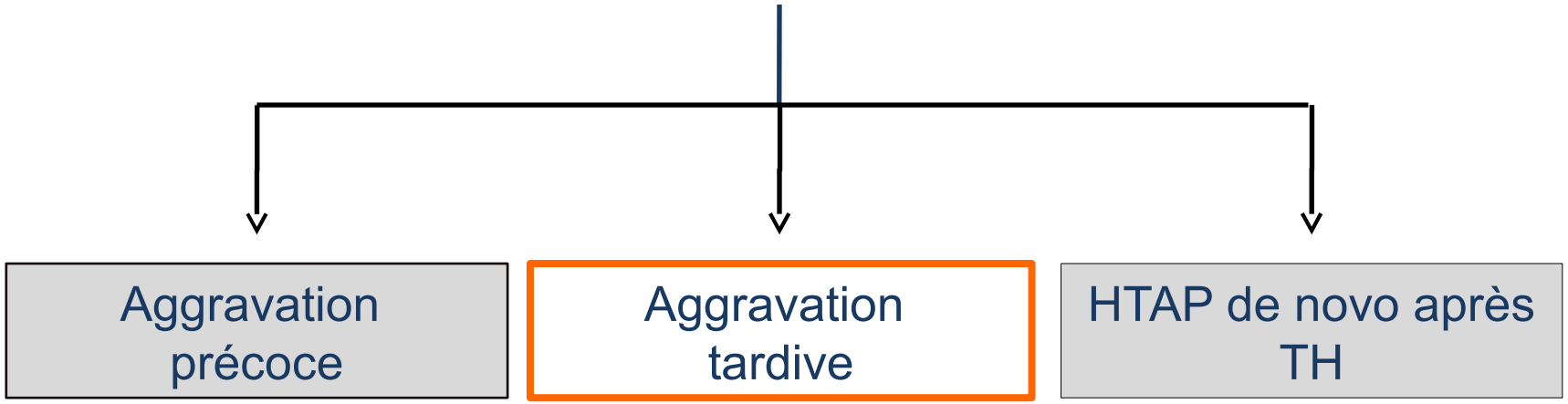
–

–

–

Taura P, Anesth. Analg. 1996; Ramsay, Liver Transplant. 2000; Budhiraja R., Chest 2003; Acosta, Transpl. Proceed. 2005; Ozier Y, Current Opinion in Anesthesiology 2008

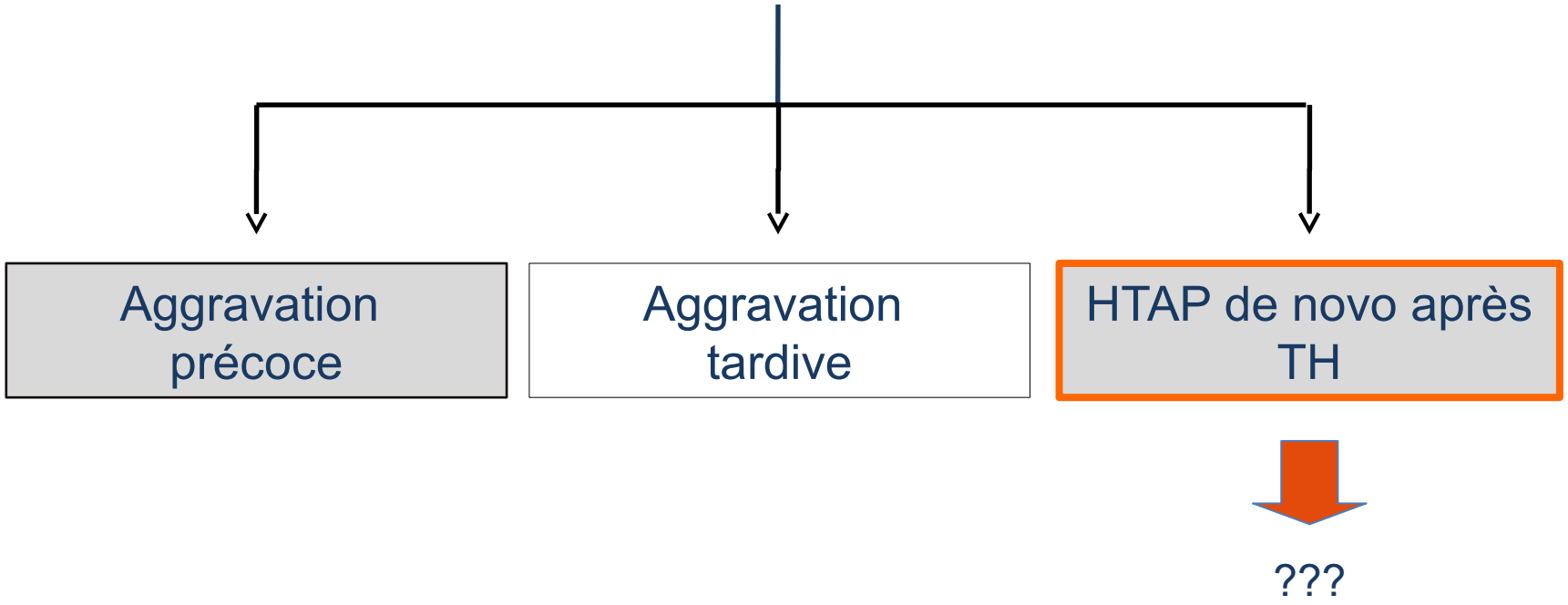
Aggravation HTPoP après la TH



Jusqu'à 3 à 6 mois après la TH
Mécanismes physiopathologiques??

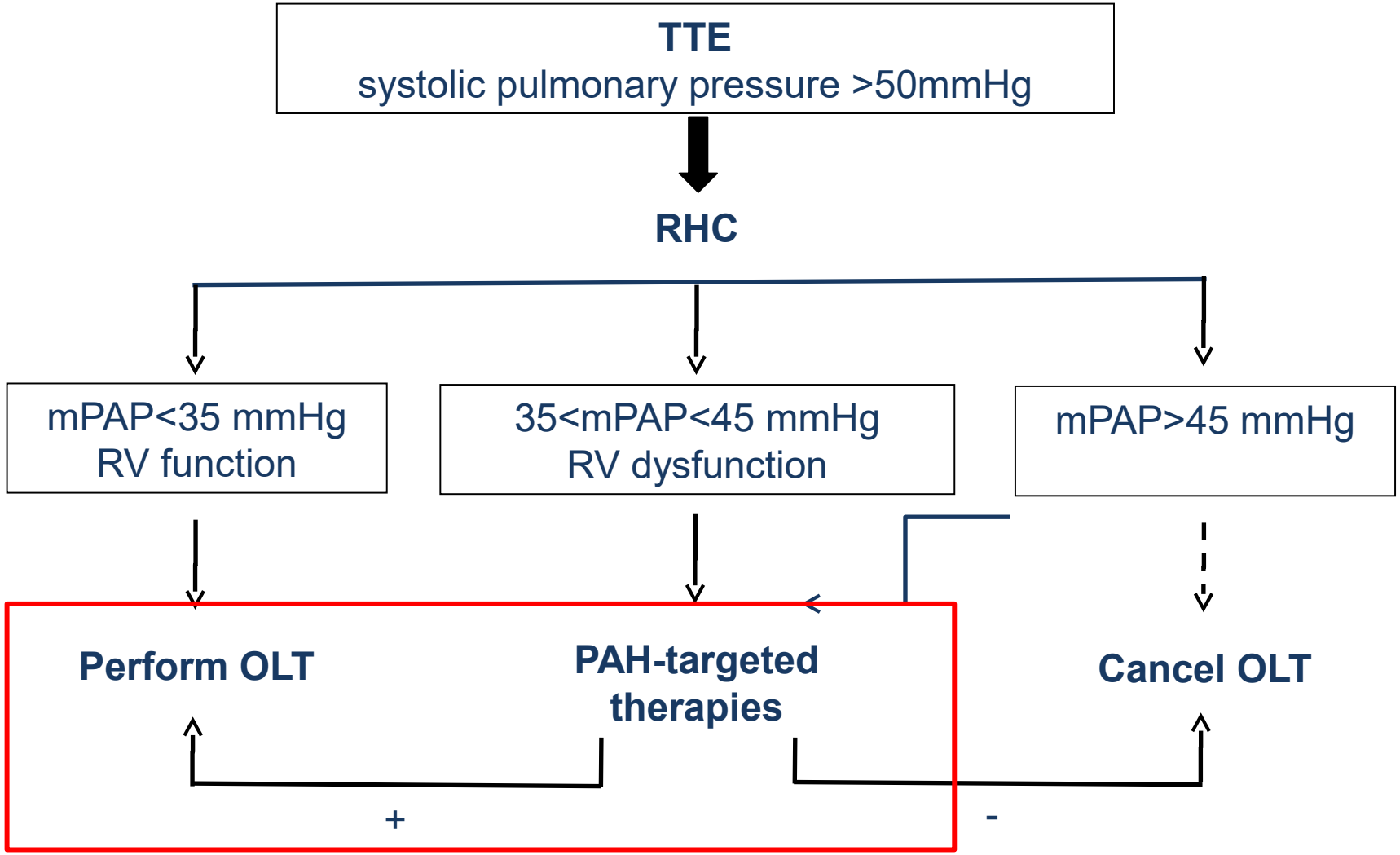
Taura P, Anesth. Analg. 1996; Ramsay, Liver Transplant. 2000; Budhiraja R., Chest 2003; Acosta, Transpl. Proceed. 2005; Ozier Y, Current Opinion in Anesthesiology 2008

Aggravation HTPoP après la TH



Taura P, Anesth. Analg. 1996; Ramsay, Liver Transplant. 2000; Budhiraja R., Chest 2003; Acosta, Transpl. Proceed. 2005; Ozier Y, Current Opinion in Anesthesiology 2008

ERS Task force 2004



Long term outcomes after LT of PoPH remains hazardous

ERS Task Force. Eur Respir J 2004

Review

International Liver Transplant Society Practice Guidelines: Diagnosis and Management of Hepatopulmonary Syndrome and Portopulmonary Hypertension

Michael J. Krowka, MD,[1] Michael B. Fallon, MD,[2] Steven M. Kawut, MD, MS,[3] Valentin Fuhrmann, MD,[4] Julie K. Heimbach, MD,[5] Michael A. E. Ramsay, MD,[6] Olivier Sitbon, MD,[7] and Ronald J. Sokol, MD[8]

Krowka MJ, *et al. Transplantation* 2016;100: 1440–52.

Long-Term Outcome in Liver Transplantation Candidates With Portopulmonary Hypertension

Laurent Savale,[1] Caroline Sattler,[1] Audrey Coilly,[2*] Filoména Conti,[3*] Sébastien Renard,[4] Claire Francoz,[5] Hélène Bouvaist,[6] Cyrille Feray,[7] Patrick Borentain,[8] Xavier Jaïs,[1] David Montani,[1] Florence Parent,[1] Caroline O'Connell,[1] Philippe Hervé,[1] Marc Humbert,[1] Gérald Simonneau,[1] Didier Samuel,[2] Yvon Calmus,[3] Christophe Duvoux,[7] François Durand,[5] Jean Charles Duclos-Vallée,[2] and Olivier Sitbon[1]

49 patients with PoPH candidates for liver transplantation (for liver disease)

Age, *years (mean±SD)*	48±8
Female:Male, *n*	14:35
BMI, *kg/m²*	26.5±4.5
Aetiology of cirrhosis, *n (%)*	
Alcoholic	14 (29)
Chronic HCV and/or HBV infection	15 (31)
Mixed (alcohol + virus)	13 (27)
Other	7 (14)
Child-Pugh score, *n (%)*	
A	6 (12)
B	21 (43)
C	22 (45)
MELD score, *median (IQR 25-75)*	20 (16.5-23)
Indication for liver transplantation	
Decompensated cirrhosis, *n (%)*	35 (71)
Hepatocellular carcinoma, *n (%)*	14 (29)

6-MWD, *m (mean±SD)*	393±89
Haemodynamics	
mPAP, *mmHg*	44±10
Cardiac index, *L/min/m2*	3.5±0.9
RAP, *mmHg*	7±3
PAWP, *mmHg*	10±4
PVR, *Wood Units*	5.6±2.8
mPAP<35 mmHg and 2≤PVR<3 WU, *n (%)*	4 (8)
mPAP<35 mmHg and PVR≥3 WU, *n (%)* — 20%	5 (10)
35≤mPAP<50 mmHg and 2≤PVR<3 WU, *n (%)*	1 (2)
35≤mPAP<50 mmHg and PVR≥3 WU, *n (%)*	27 (55.5)
mPAP≥50 mmHg, *n (%)* — 80%	12 (24.5)

Savale L, *et al*, *Hepatology* 2017;65:1683-92.

Effet des ttt spécifiques HTAP avant TH (n=34)

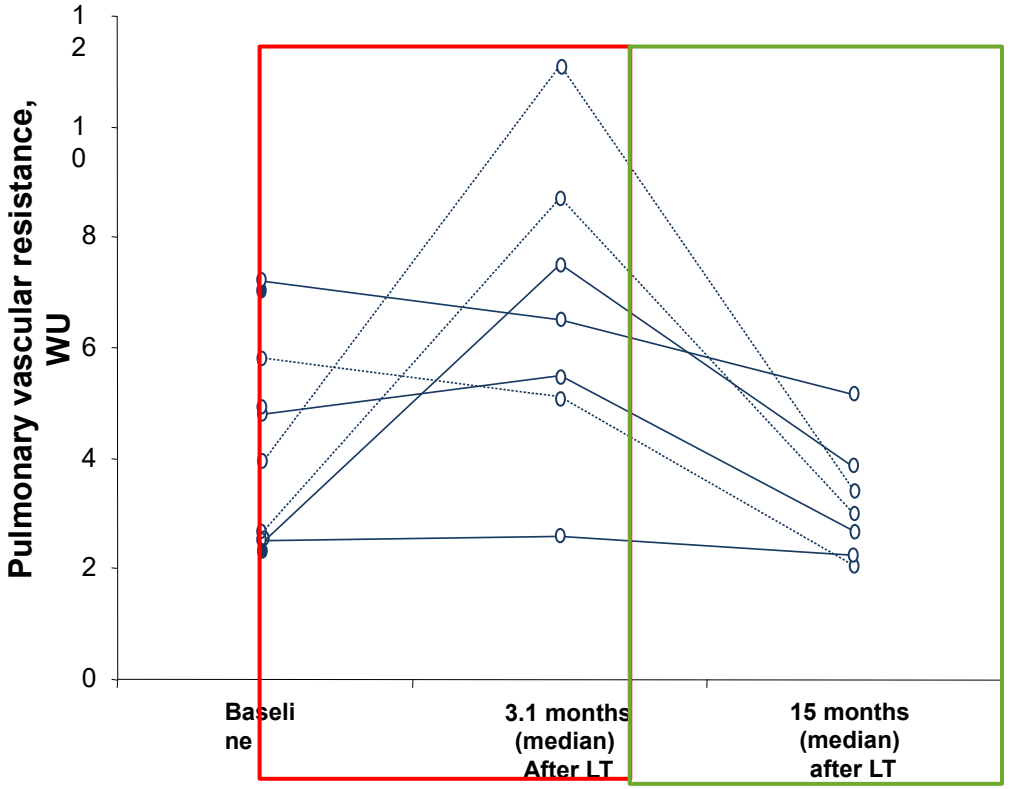
	Baseline	After *5* months (IQR25-75, 2.6 – 15)
6MWD, m	385±95	414±88
RAP, mmHg	7±3	7±4
mPAP, mmHg	47±10	36±7*
PAWP, mmHg	9±3	11±4
Cardiac output, L/min	6.7±1.6	10±2.2**
Cardiac index, L/min/m²	3.5±0.8	4.7±1**
PVR, Wood units	6.1±3.1	3±1.4**
mPAP<35 mmHg, n (%)	2 (6%)	15 (44%)
35≤mPAP<50 and PVR<3 WU, n (%)	0 (0%)	9 (26%)
35≤mPAP<50 and PVR≥3 WU, n (%)	23 (68%)	9 (26%)
mPAP≥50 mmHg, n (%)	9 (26%)	1 (3%)

6%

70%

Savale L, *et al*, *Hepatology* 2017;65:1683-92.

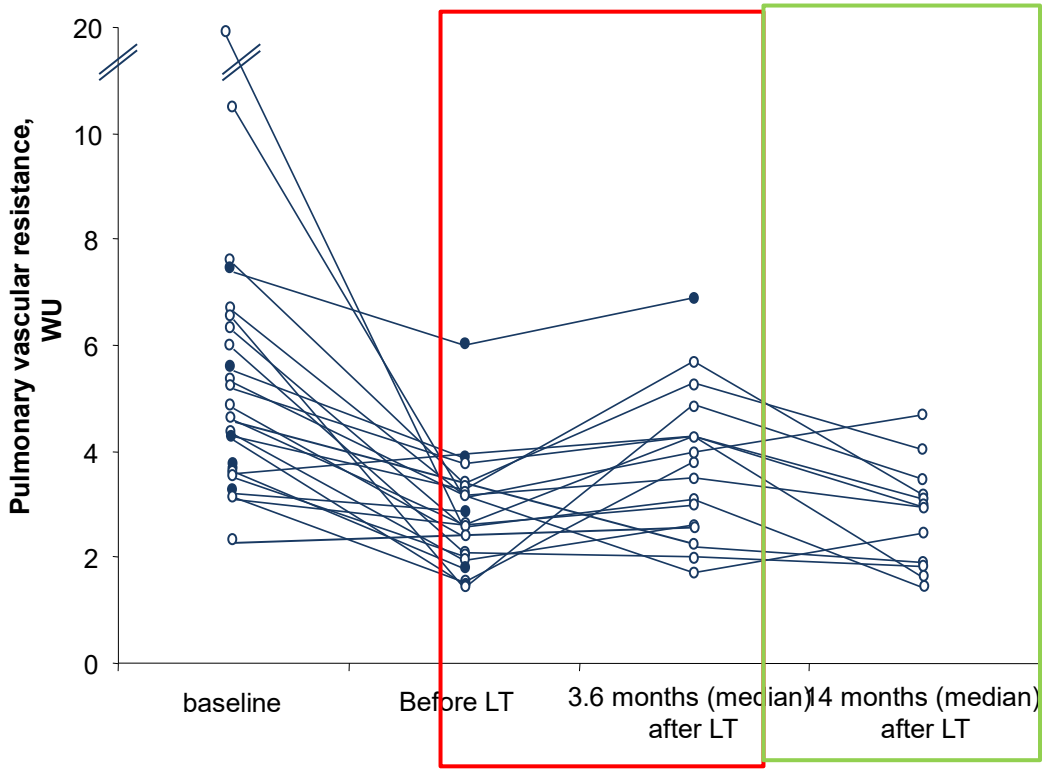
Evolution of PVR after LT in patients not receiving PAH-targeted therapies before LT (n=10)



- Increase in PVR within 6 months after LT
- Two deaths (one due to PoPH) at day 1 and 5
- PAH targeted-therapies initiation after LT in 3 patients

Savale L, *et al*, *Hepatology* 2017;65:1683-92.

Evolution of PVR after LT in patients receiving PAH-targeted therapies before LT (n=25)

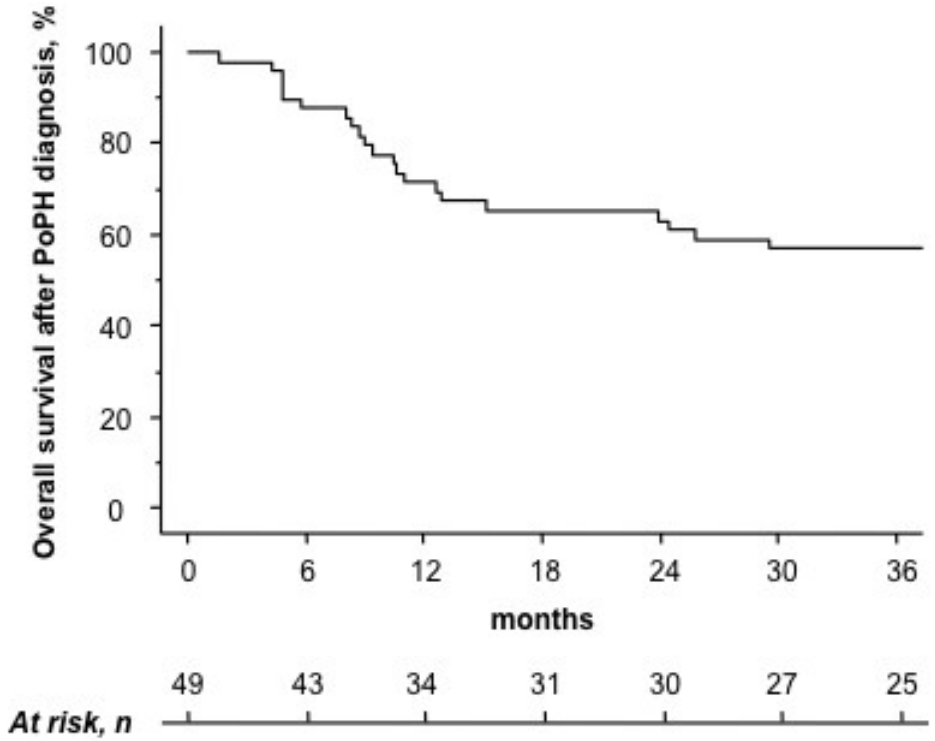


- Increase in PVR within 6 months after LT in some patients
  (only one patient needed reinforcement of PAH-targeted therapy after LT)
- Six deaths (4 due to PoPH at day 7, one, two and six months)

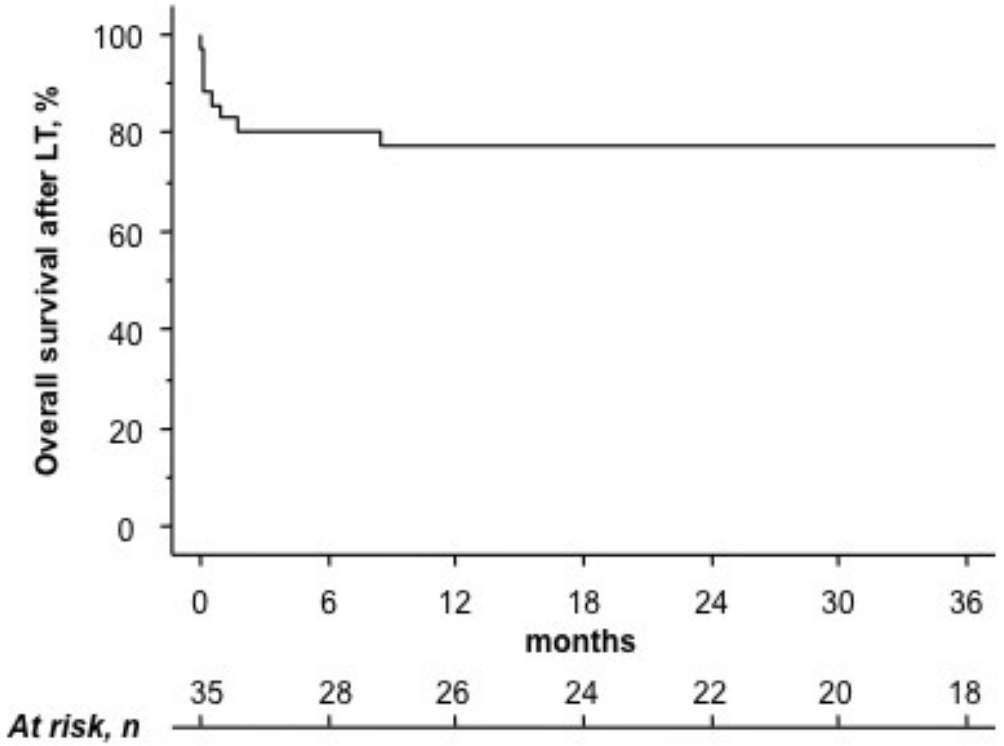
Savale L, *et al*, *Hepatology* 2017;65:1683-92.

Survival of PoPH patients who are candidates for LT

After PoPH diagnosis

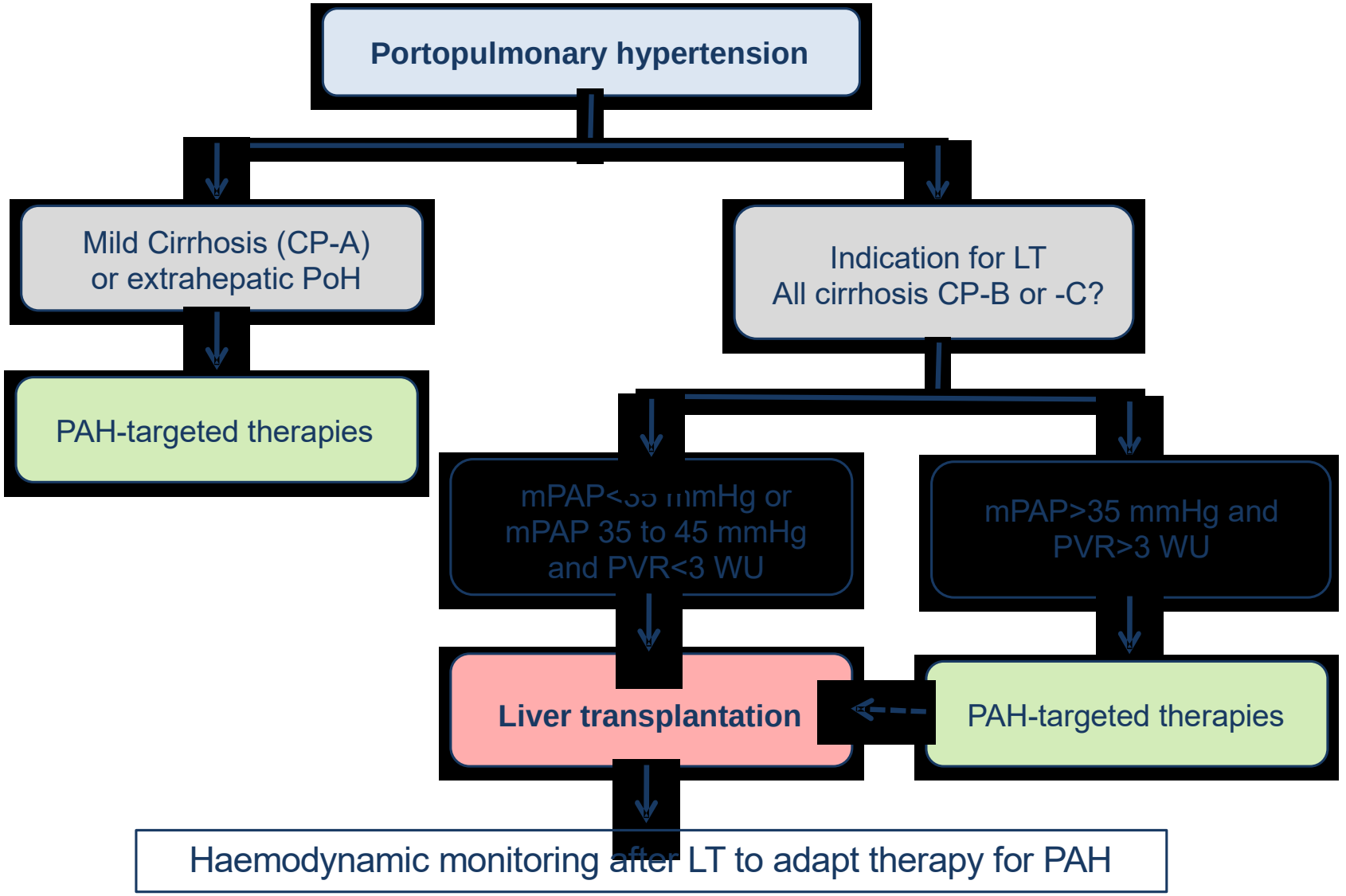


After liver transplantation



Savale L, *et al*, *Hepatology* 2017;65:1683-92.

En pratique…


Portopulmonary hypertension
Mild Cirrhosis (CP-A)
or extrahepatic PoH
PAH-targeted therapies
Indication for LT
All cirrhosis CP-B or -C?
mPAP<35 mmHg or
mPAP 35 to 45 mmHg
and PVR<3 WU
mPAP>35 mmHg and
PVR>3 WU
Liver transplantation
PAH-targeted therapies
Haemodynamic monitoring after LT to adapt therapy for PAH

Démarche diagnostique des complications pulmonaires de l'hypertension portale