Hypertension pulmonaire: nouveautés et place des vasodilatateurs

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Hypertension pulmonaire

- *PAP_m > 25 mmHg au repos*
- *PAP_m > 30 mmHg à l'effort*
- *Tournant évolutif*

  (cardiopathies, affections respiratoires).

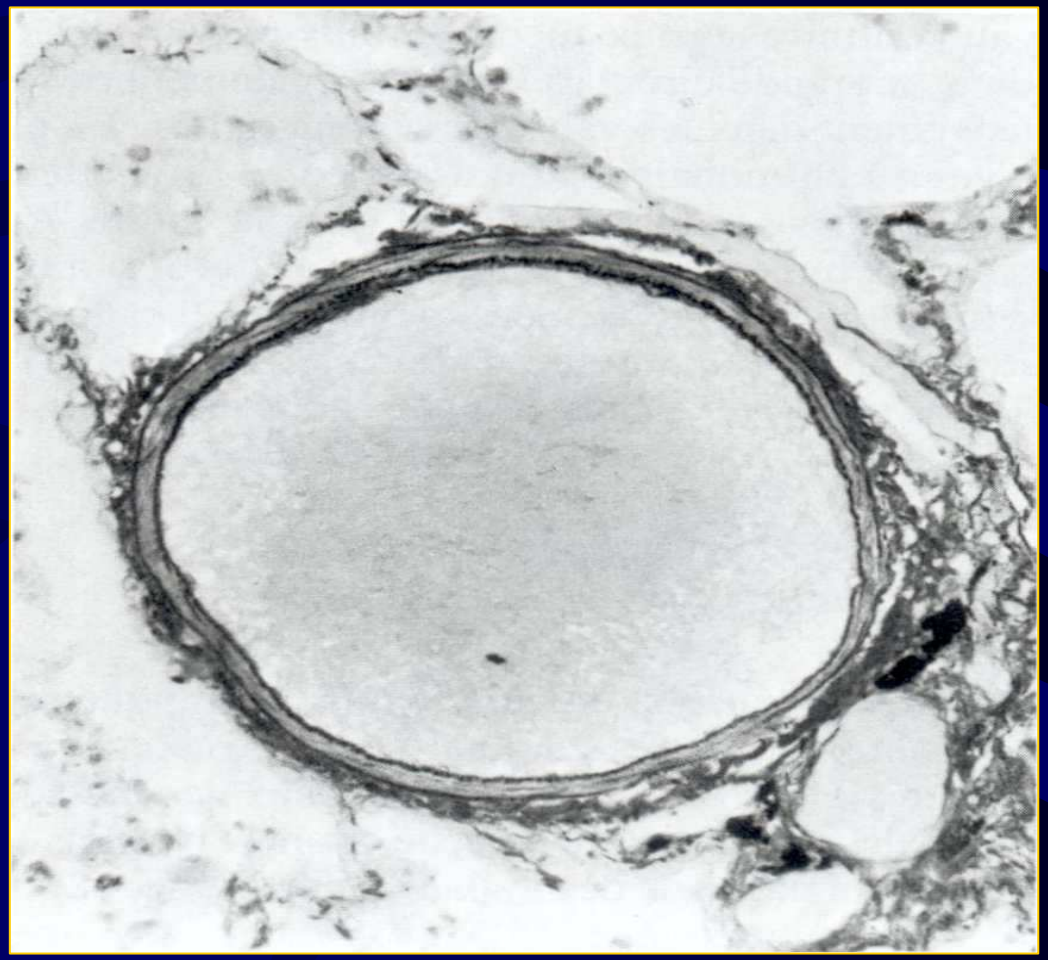
Barst RJ, *JACC* 2004; 43 suppl 40S-47S

Prévalence

- 3e pathologie (HTA, coronaropathies).
- 16 à 38 % des admissions hospitalières pour défaillance cardiaque congestive. (*Rubin LJ - Pulmonary hypertension 1984).*
- 40 % des patients cathéterisés (coronaropathie, cardiopathie valvulaire).
- 25 % des cas de SDRA. *(Jardin F – Curr Opin Crit Care 2005).*

Définition morphologique

- Artère pulmonaire normale

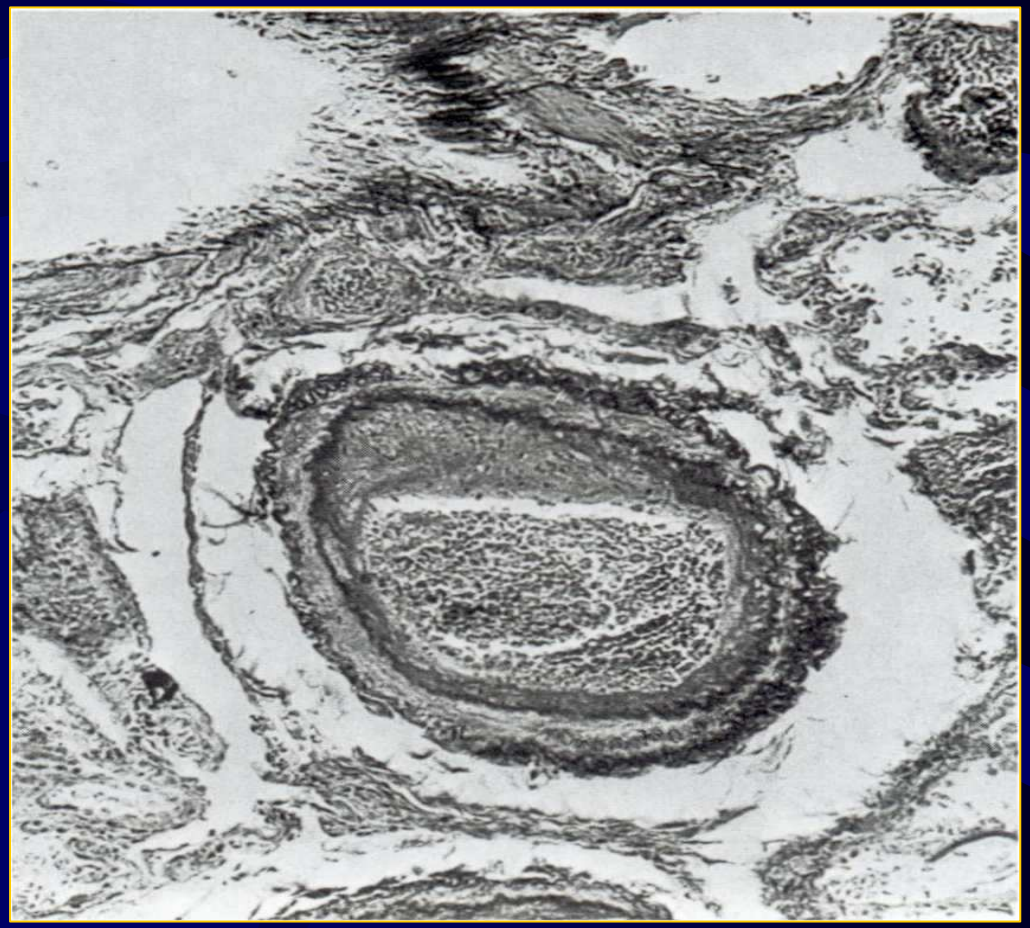


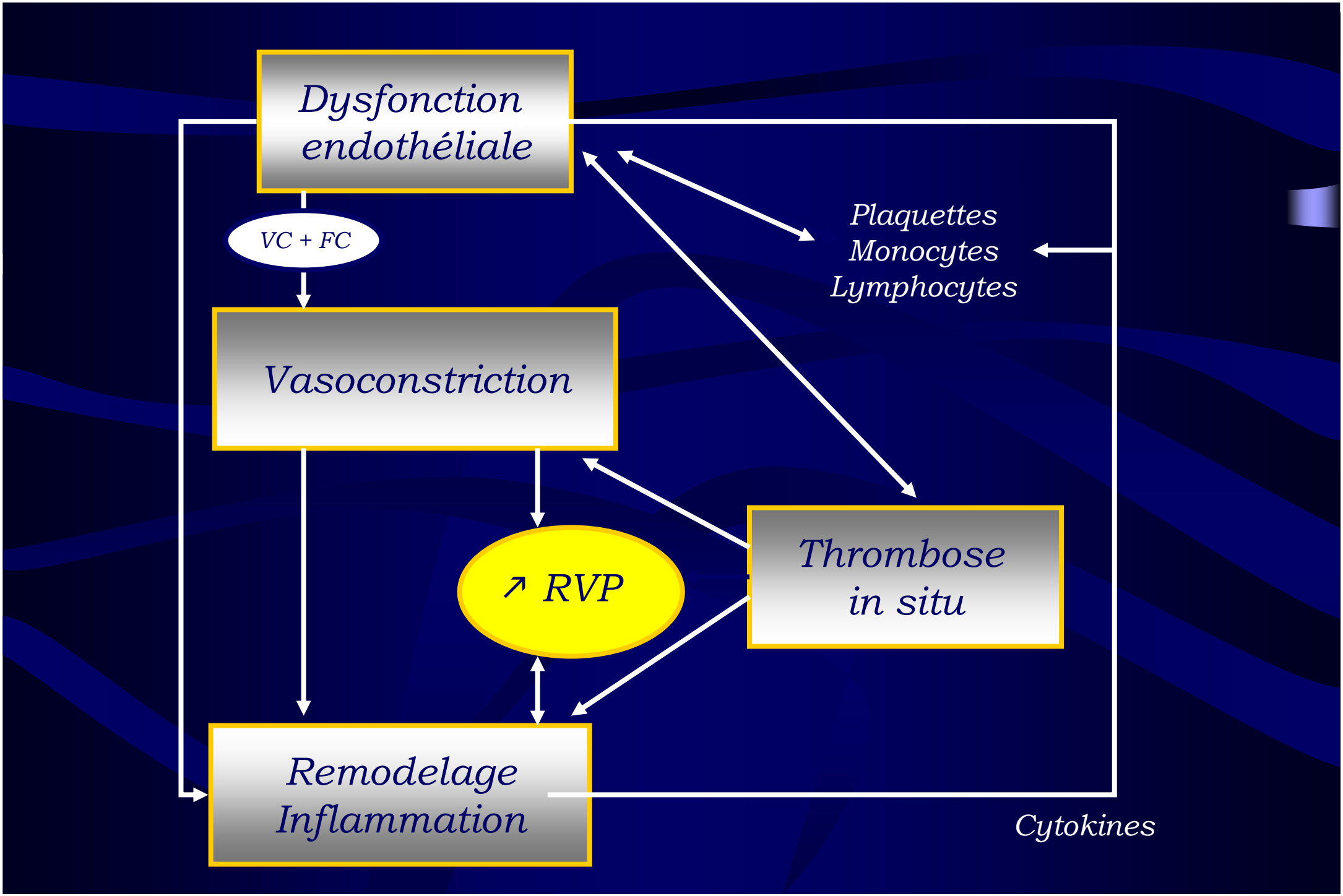
Définition morphologique

- Artériopathie plexogénique

Définition morphologique

- Artériopathie thrombotique




Dysfonction endothéliale
VC + FC
Plaquettes
Monocytes
Lymphocytes
Vasoconstriction
↗ RVP
Thrombose in situ
Remodelage Inflammation
Cytokines

Physiopathologie

VASOCONSTRICTION

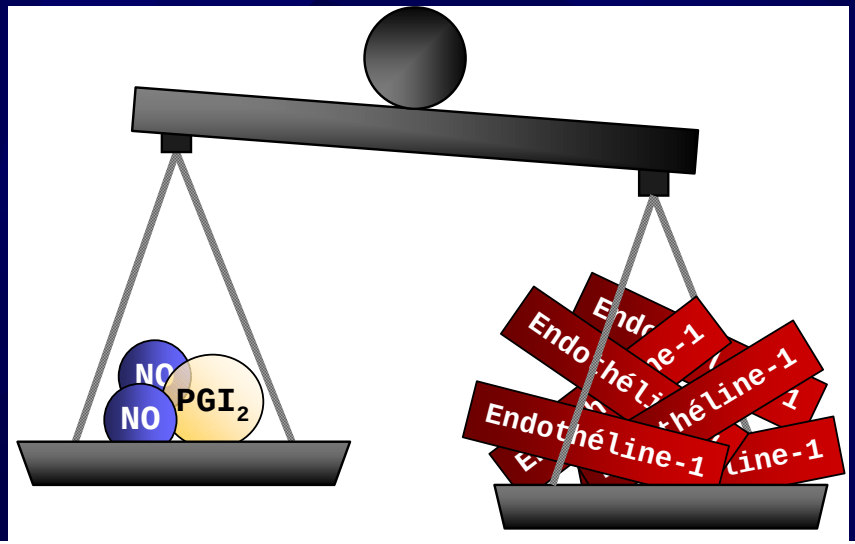
VASOPROLIFERATION

VASOCONSTRICTEURS

- Thromboxane A2
- Endotheline 1
- Angiotensine II
- Prostaglandine D_2

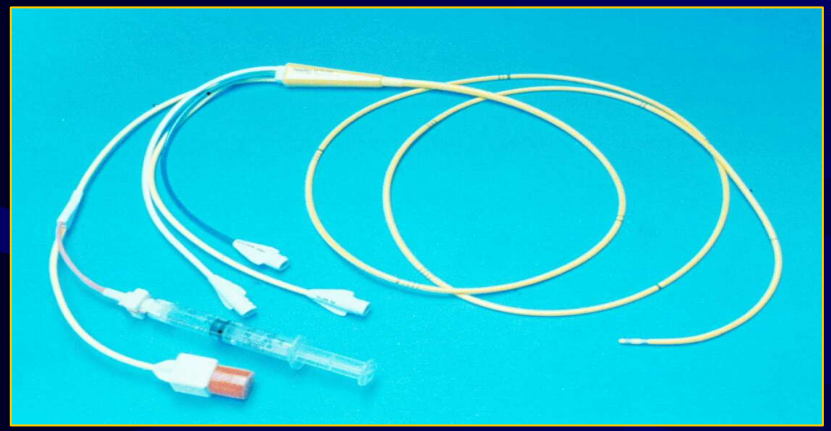
VASODILATATEURS

- Monoxyde d'azote (NO)
- Prostacycline (PGI_2)



Diagnostic paraclinique

Swan-Ganz

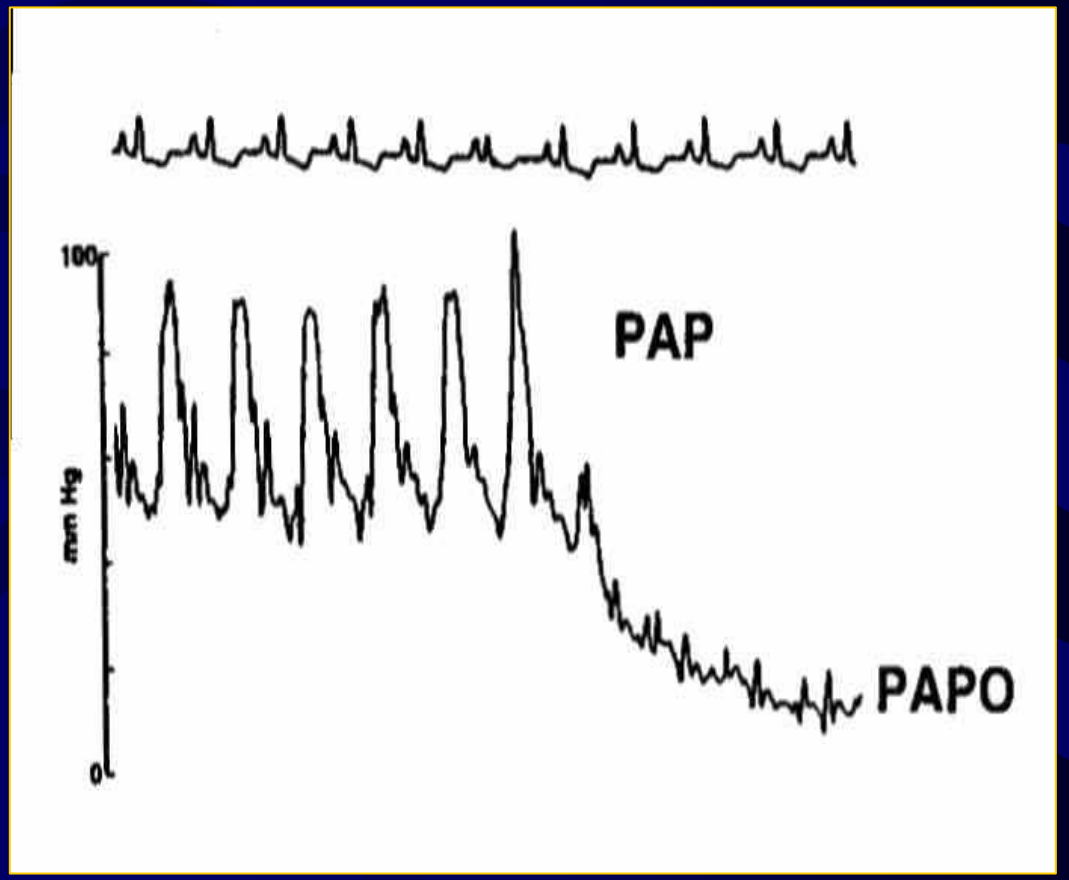


NYHA I: PAP 21-40 mmHg

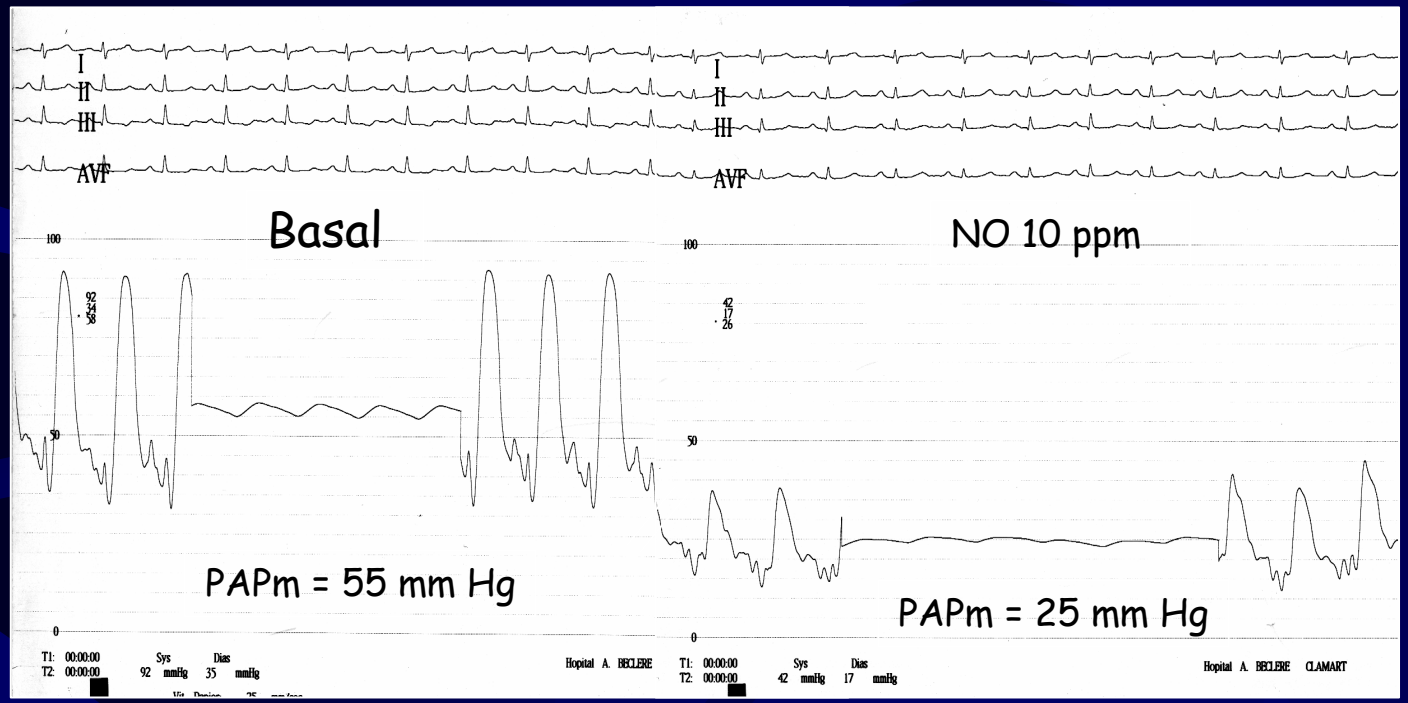
NYHA II: PAP>40 mmHg

NYHA III : PAP>40 mmHg, SvO2<60%

NYHA IV: SvO2<50%



Cathétérisme cardiaque droit



- Réversibilité au test de vasodilatation
- Positif
- Guide le traitement médical

7. In patients with suspected PH, right-heart catheterization is required to confirm the presence of PH, establish the specific diagnosis, and determine the severity of PH. Quality of evidence: good; benefit: substantial; strength of recommendation: A.

18. In patients with suspected PH, right-heart catheterization is required to guide therapy. Quality of evidence: low; benefit: substantial; strength of recommendation: B.

Mc Goon, ACCP; Chest July 2004

Échocardiographie

1. Diagnostic
   - HTP
   - Etiologie

2. Retentissement VD

Recommendations

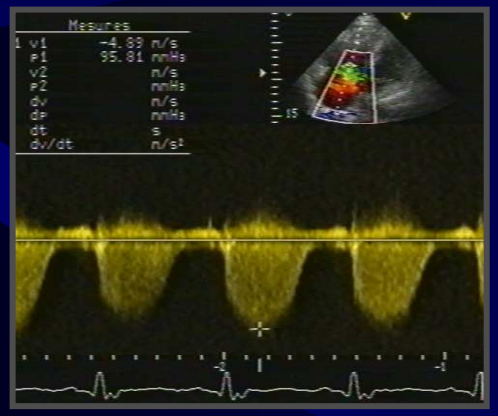
5. **In patients with a clinical suspicion of PAH, Doppler echocardiography should be performed as a noninvasive screening test that can detect PH, though it may be imprecise in determining actual pressures compared to invasive evaluation in a portion of patients.** Quality of evidence: fair; benefit: substantial; strength of recommendation: A.

Mc Goon, ACCP; Chest July 2004

Diagnostic échographique

Élévation « physiologique » des PAPs:

- Age, *(Mc Quillan BM. Circulation 2001 ; 104 : 2797-2802)*
- BMI, *(Mc Quillan BM. Circulation 2001 ; 104 : 2797-2802)*
- HTA *(Abergel. J Hypertens 2001; 19: 2055)*



	SPAP mm Hg (95% CI)	
Age, y	Femmes (n = 2065)	Hommes (1147)
< 20	18.6-34.2	18.2-36.2
20 to 29	19.2-34.4	19.9-36.3
30 to 39	19.3-35.7	18.7-37.5
40 to 49	19.9-37.5	19.1-38.3
50 to 59	20.2-39.4	21.0-40.6
≥ 60	20.5-42.1	21.2-43.6

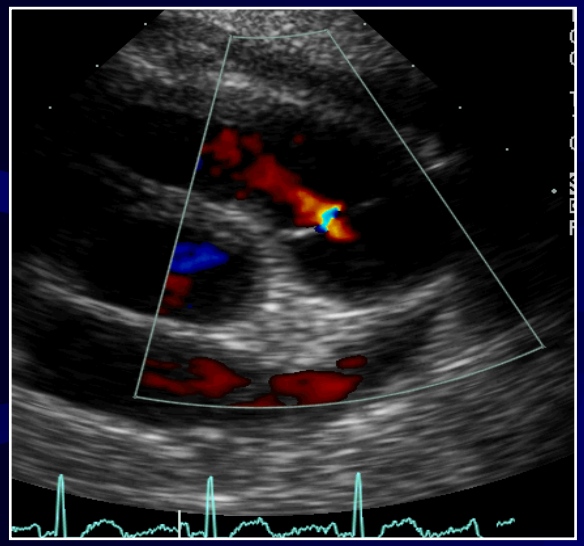
Diagnostic échographique

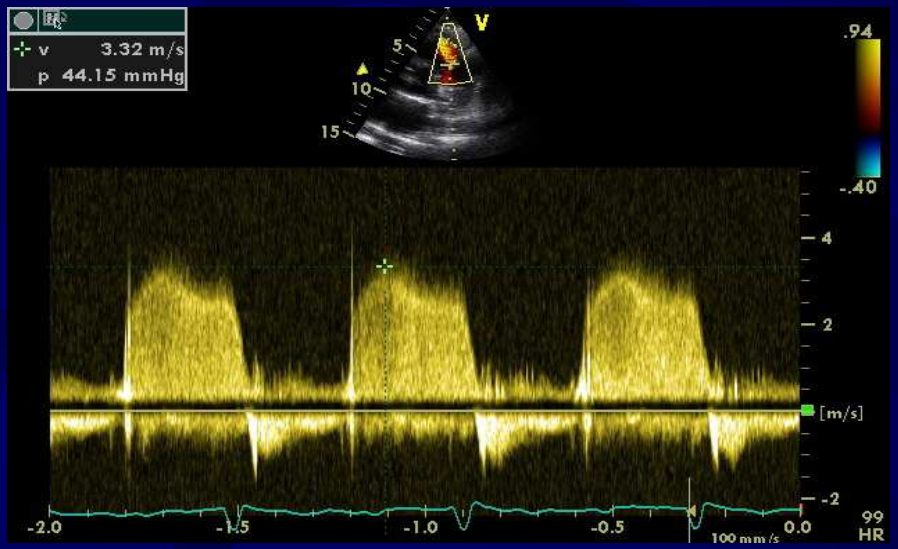
HTP = PAP systolique > 35 mmHg au repos

PAPS = 4VITmax² + POD

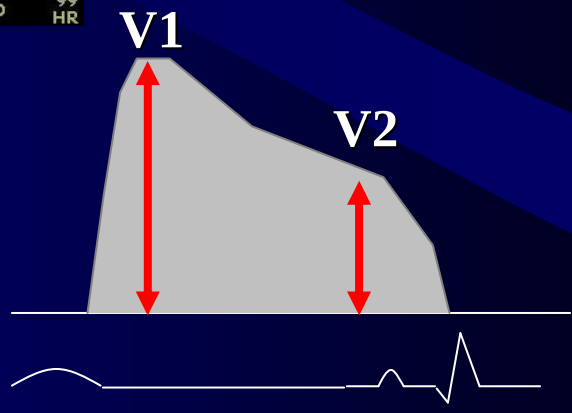
Évaluation des PAPs: Insuffisance Pulmonaire

PAP moyenne > 25 mmHg au repos





- PAP moyenne = 4 V_{IPPD}^{2} + PTDVD (=POD)
  - PAP diastolique = 4 V_{IPTD}^{2} + POD
  - PAP systolique = 3 PAPm – 2 PAPd

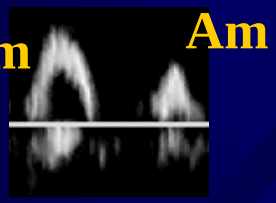


Diagnostic étiologique

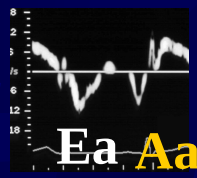
Fonction systolique VG

Valvulopathie (mitrale++)

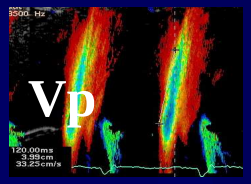
Pressions de remplissage VG
(+ PAP systolique > 35 mmHg au repos)



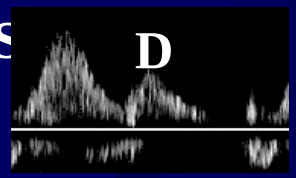
Em/Am
DTE
dAm



Em/Ea



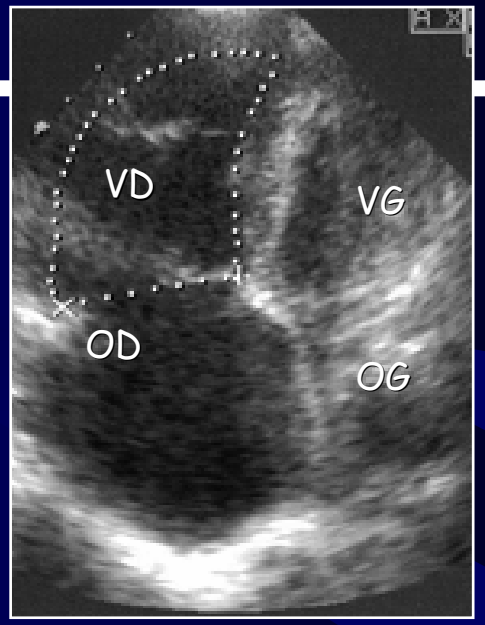
Em/Vp

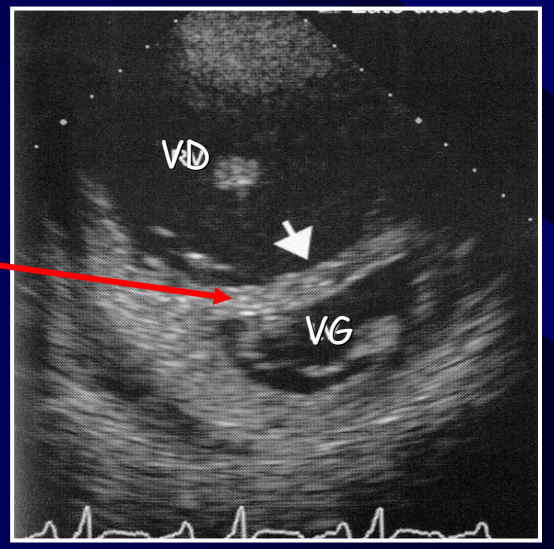


$dA_p - dA_m$

Retentissement d'aval

- Dilatation VD
  (STDVD/STDVG > 0,6)
- Dilatation OD.
- Fonction systolique VD.
- Compression VG.
- Septum paradoxal.
- Remplissage VG

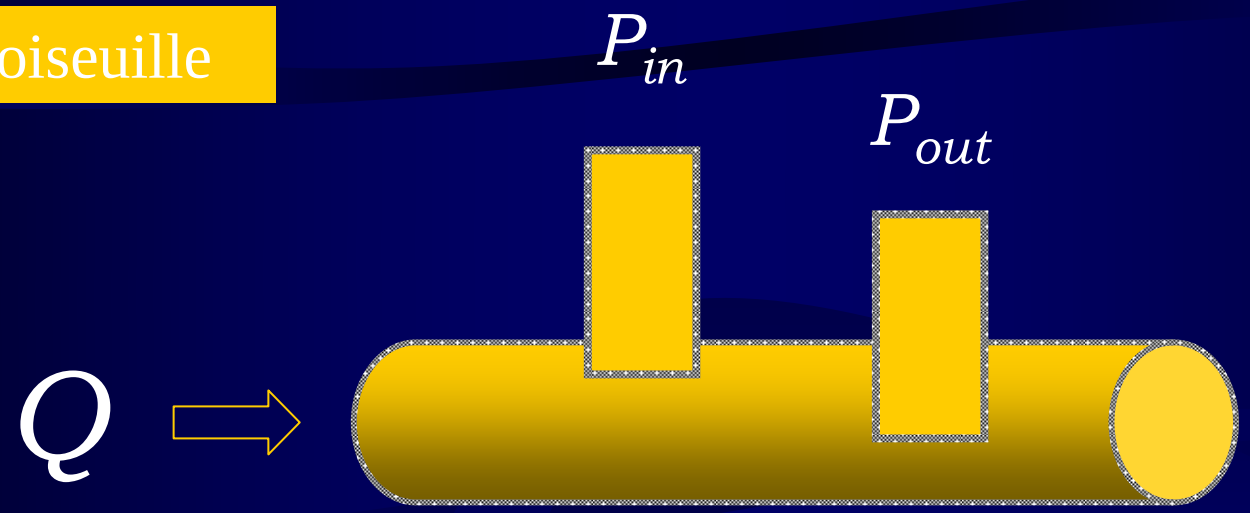




(Vieillard-Baron et al-Am J Respir Crit Care Med 2002)

Etiologies

Loi de Poiseuille



$$RVP = (PAP - POG) / Q$$

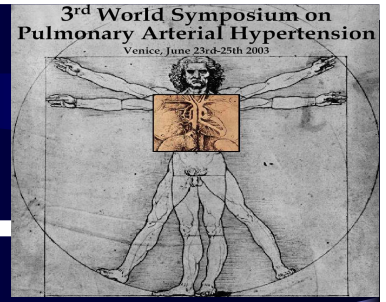
$$PAP_m = Q \times RVP + P_{OG}$$

↗ P_{OG} : *cardiopathies gauches décompensées* *(HTP post-capillaire).*

↗ *RVP : affections respiratoires chroniques* *(HTP pré-capillaire).*

↗ *Q : cardiopathies congénitales.*

HTAP: Classification (Venise 2003)
« Hypertension Pulmonaire »



1. Hypertension Artérielle Pulmonaire

- HTAP idiopathique
- HTAP familiale
- HTAP associée à:
  - Connectivite
  - Infection VIH
  - Hypertension portale
  - Anorexigènes
  - Cardiopathies Congenitales
- HTAP persistante du nouveau-né
- HTAP avec atteinte capillaire ou veinulaire

2. H. Pulmonaire et cardiopathie gauche

- Dysfonction ventriculaire
- Valvulopathies

3. H. Pulmonaire et pathologies respiratoires

- BPCO
- Pathologies interstitielles
- Syndrome d'apnée du sommeil

4. Hypertension pulmonaire due à une maladie thrombo-embolique

- Obstruction proximale
- Obstruction distale
- Embolies pulmonaires non thromb.

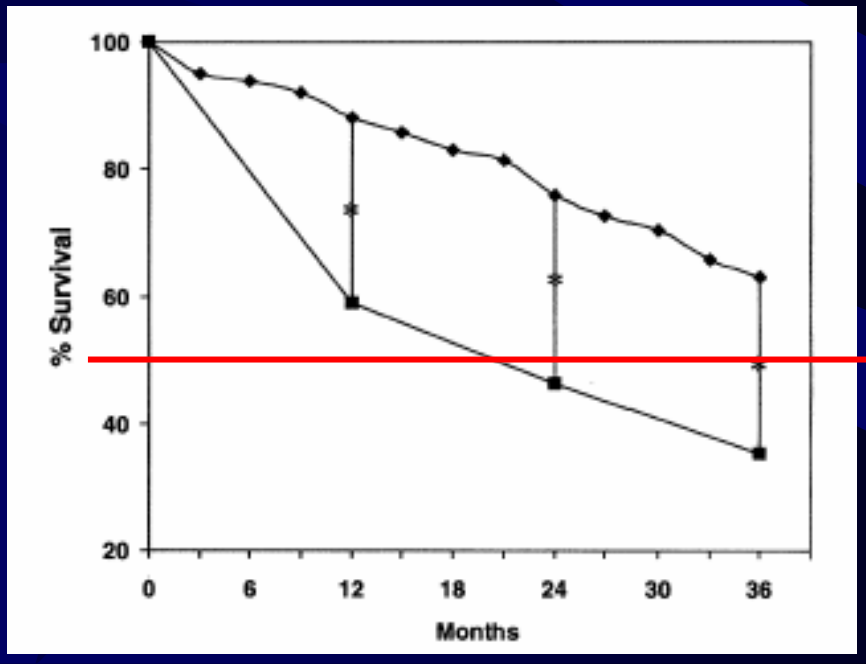
5. Divers (Sarcoidose....)

Simonneau G, *JACC* 2004; 43 suppl 5S-12S

HTAP idiopathique

- Symptomatologie a-spécifique
- Rare (incidence: 15 cas /10^6 / an)
- Absence de toute cause respiratoire ou cardiaque
- Idiopathique (39 %), familiale (4 %) ou formes associées (Connectivites, cardiopathies congénitales, anorexigènes, HTP, VIH)
- Diagnostic difficile, retardé
- Médiane de survie: 2,8 ans

Humbert M, *Am J Resp Crit Care Med* 2004; 169: A56



Mc Laughlin et al. *Circulation* 2002; 106: 1477-82

HTAP pré-capillaire

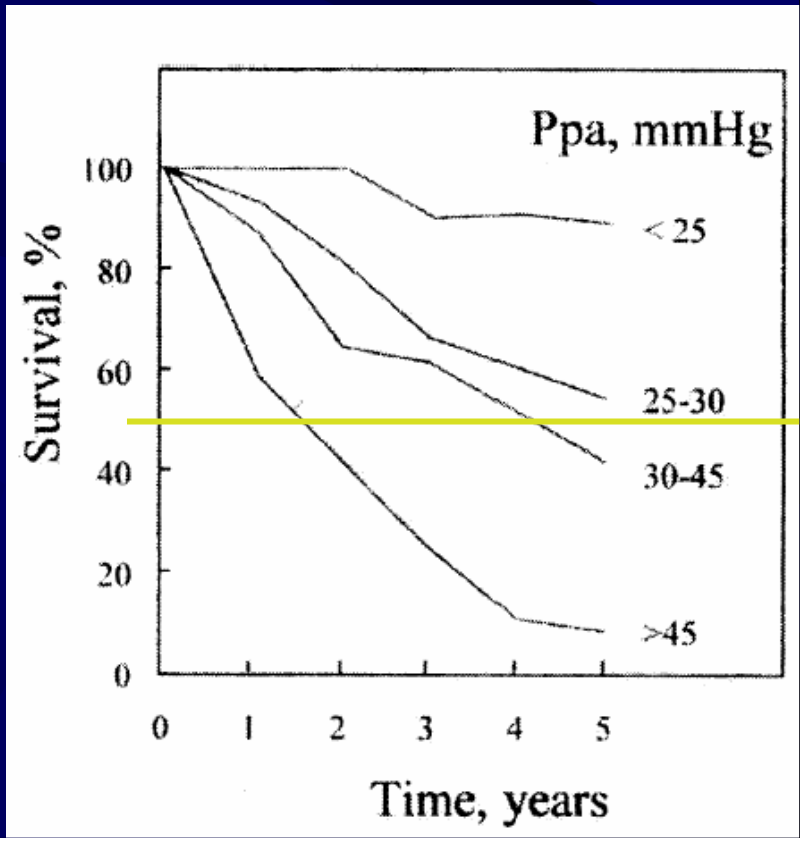
- BPCO sévère / Embolie pulmonaire
- Emphysème
- Fibrose pulmonaire idiopathique / scolioses
- Hypoventilation d'origine centrale (SAS)

50% de décès avec IVD

50% d' HTAP après 50 ans

Chaouat et al. *Proc Am J Respir Crit Care Med* 2005; 172: 189-94

Naeije et al. *Proc Am Thorac Soc* 2005; 2: 20-22



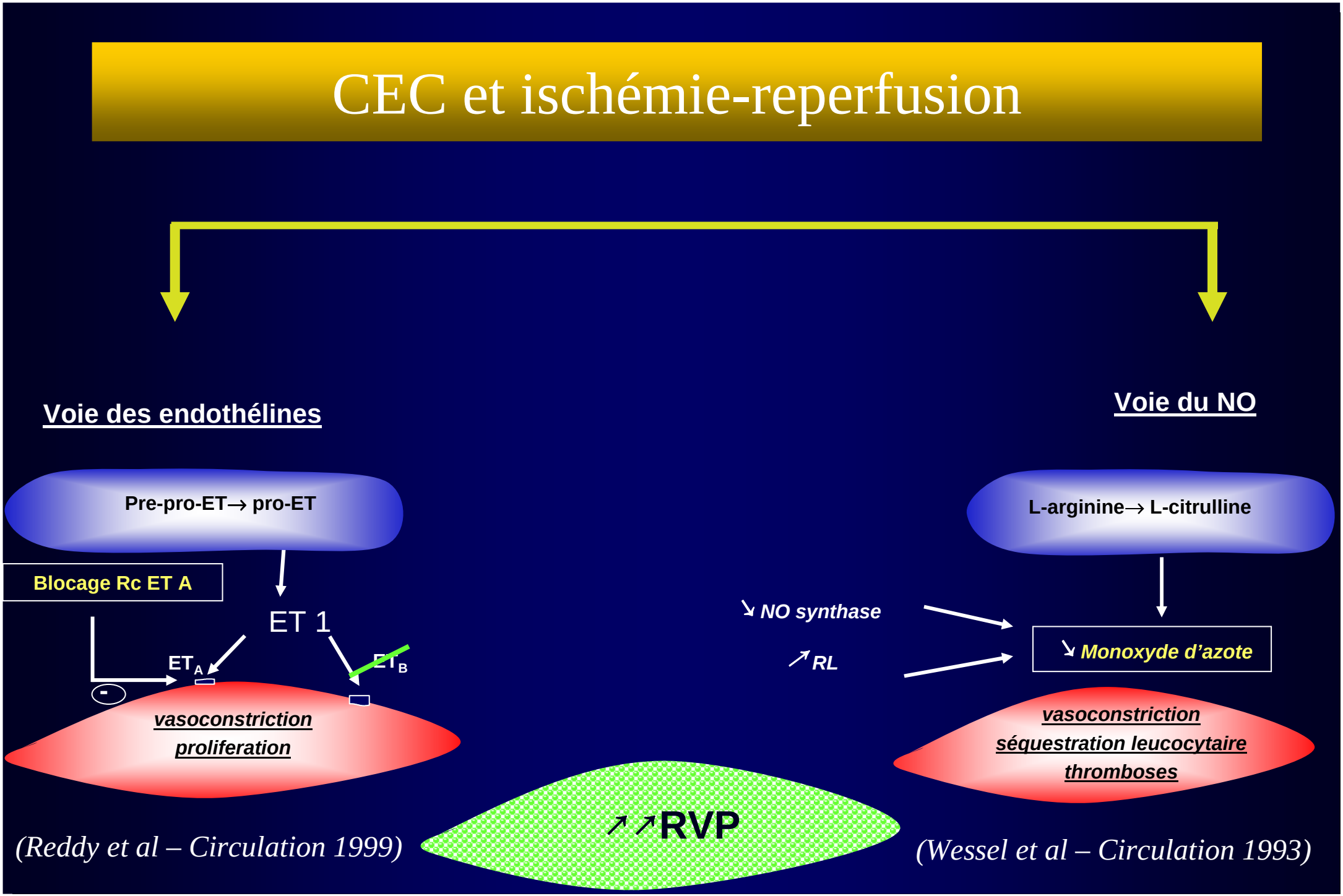
HTAP post-capillaire

- Cardiopathies acquises
  - Ischémiques
  - Valvulopathies mitrale et aortique, hypertensive

⇒ HTAP longtemps réversible

Artériolite oblitérante (HTAP « fixée »)

CEC et ischémie-reperfusion



Place des nouveaux vasodilatateurs

TRAITEMENT HTAP

- Transplantation coeur-poumon (phase terminale)
  - Sélection sévère
  - Peu de donneurs

80’

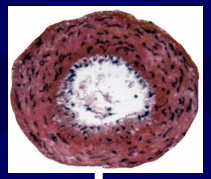
- Prostacycline IV = Alternative à la transplantation

90’

- Approche physiopathologique
- Nouvelles molécules !

2000

HTAP: Principes des traitements spécifiques



Voie de l'Endothéline

ENDOTHÉLIUM

Antagonistes des récepteurs de l'endothéline

Endothéline-1

ET_A ET_B

vasoconstriction
prolifération

Voie du Monoxyde d'Azote

ENDOTHÉLIUM

Monoxyde d'Azote

GMPc vasodilatation
anti-prolifération

PDE5

Inhibiteurs des PDE5

Voie de la Prostacycline

ENDOTHÉLIUM

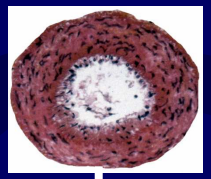
Prostacycline

Dérivés de la prostacycline

AMPc vasodilatation
anti-prolifération

Humbert M, *JACC* 2004; 43 suppl 13S-24S

HTAP: Principes des traitements spécifiques



Voie de l'Endothéline

ENDOTHÉLIUM

BOSENTAN

Endothéline-1

ET_A ET_B

vasoconstriction
prolifération

Voie du Monoxyde d'Azote

ENDOTHÉLIUM

Monoxyde d'Azote

GMPc vasodilatation
anti-prolifération

PDE5

SILDENAFIL

Voie de la Prostacycline

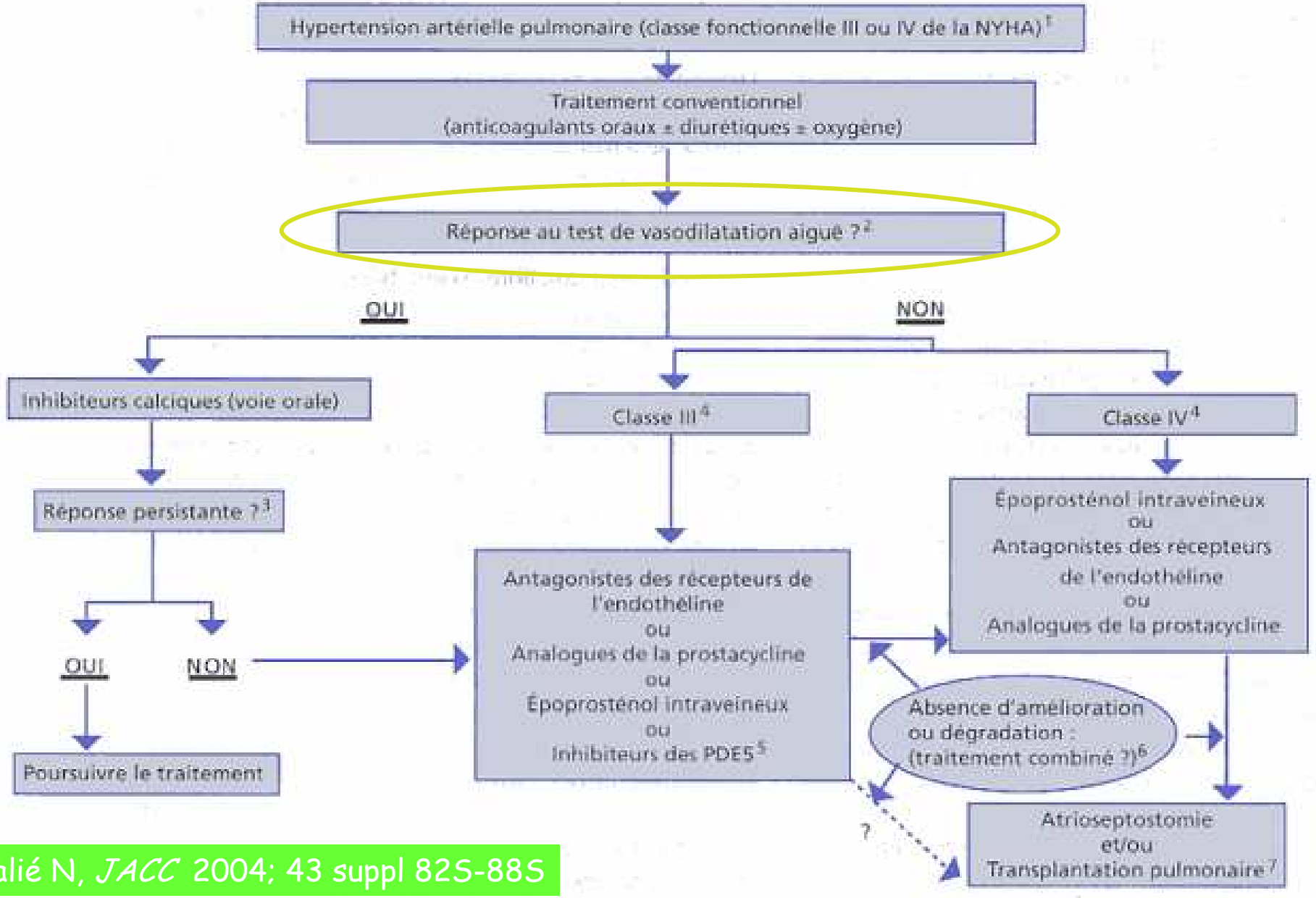
ENDOTHÉLIUM

Prostacycline

EPOPROSTENOL
ILOPROST
BERAPROST
TREPROSTINIL

AMPc vasodilatation
anti-prolifération

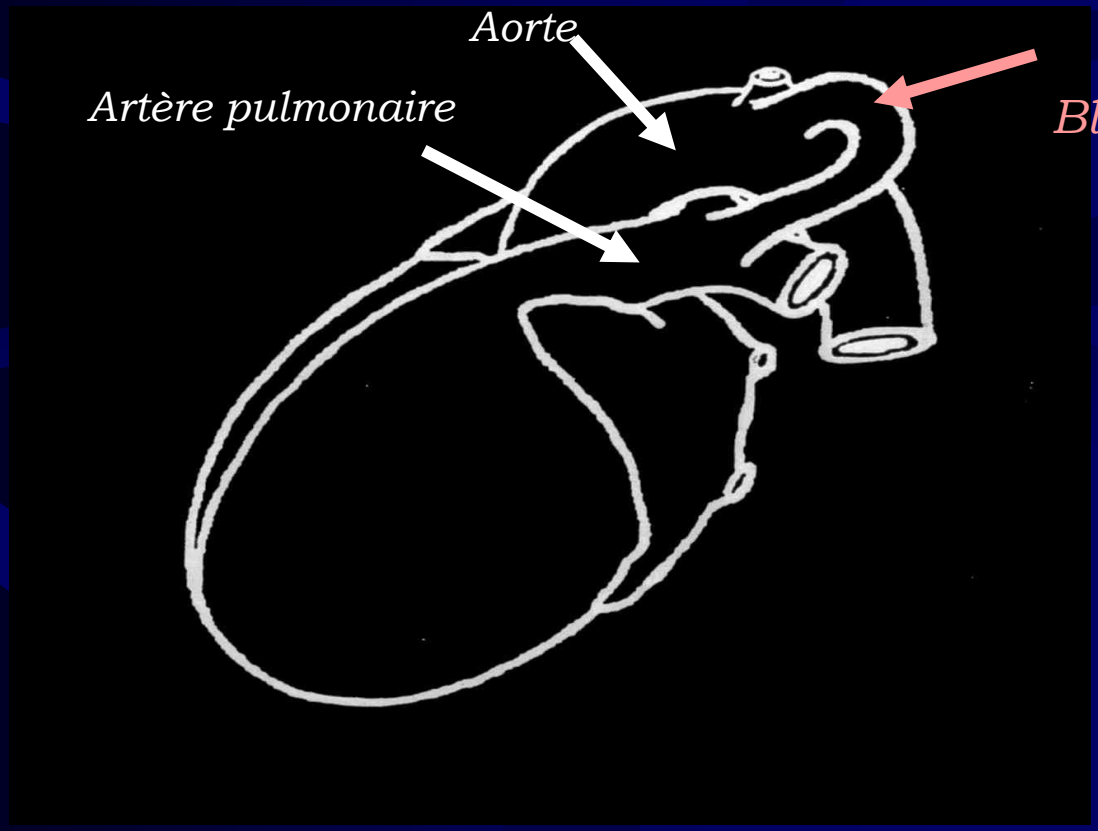
Humbert M, *JACC* 2004; 43 suppl 13S-24S



Galié N, *JACC* 2004; 43 suppl 82S-88S

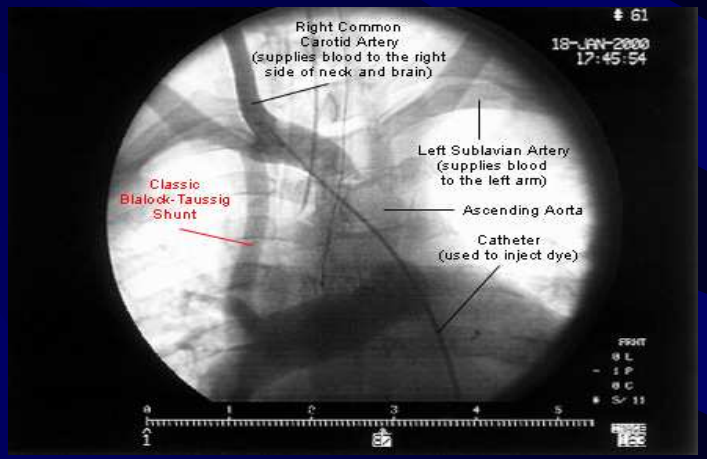
Apport des modèles expérimentaux

Modèle expérimental



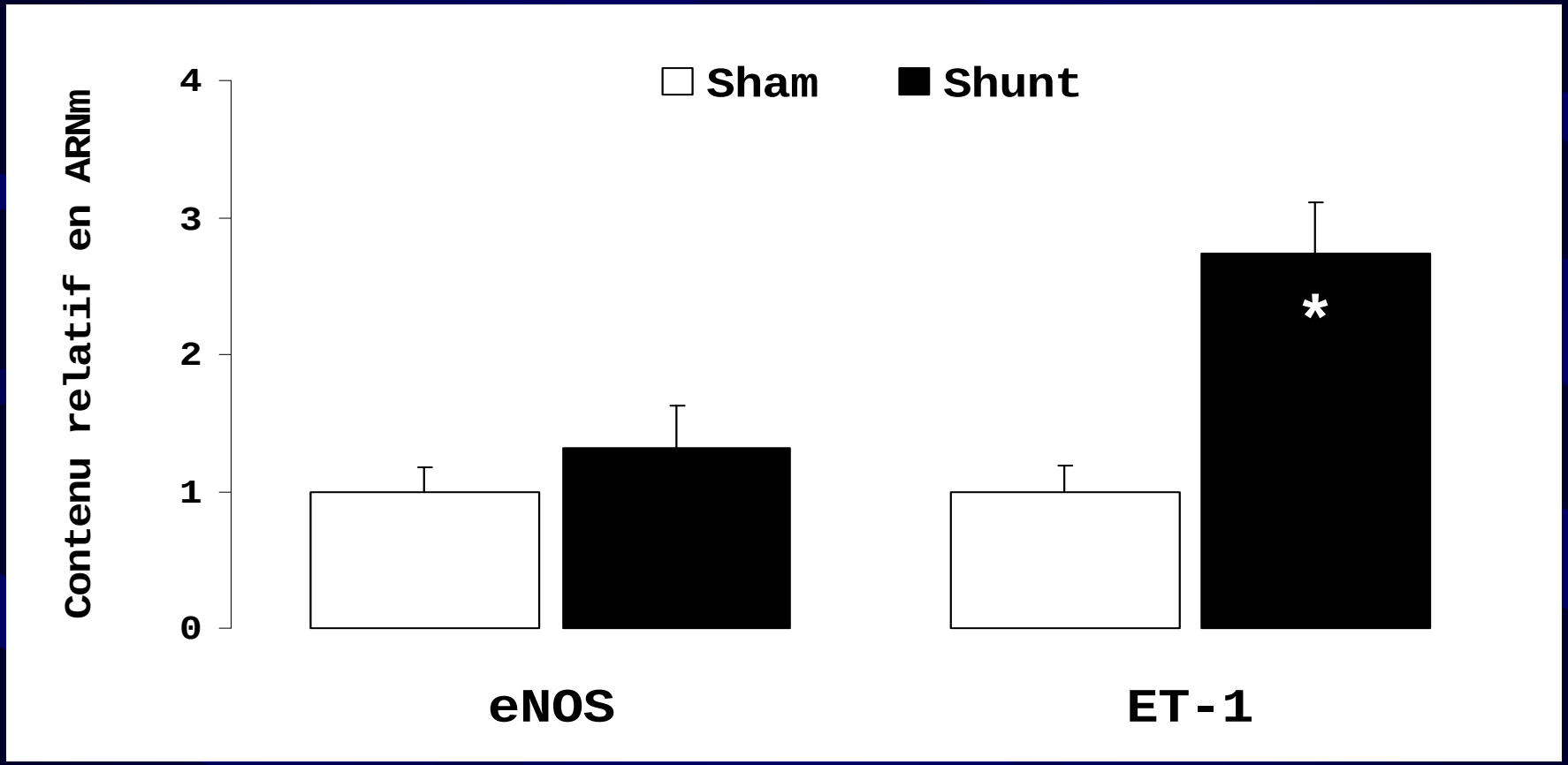
Shunt

Blalock-Taussig



Rondelet B, Kerbaul F. *Circulation* 2003; 107:1329-35, *Circulation* 2004; 110:2220-5.

Biologie Endothélium



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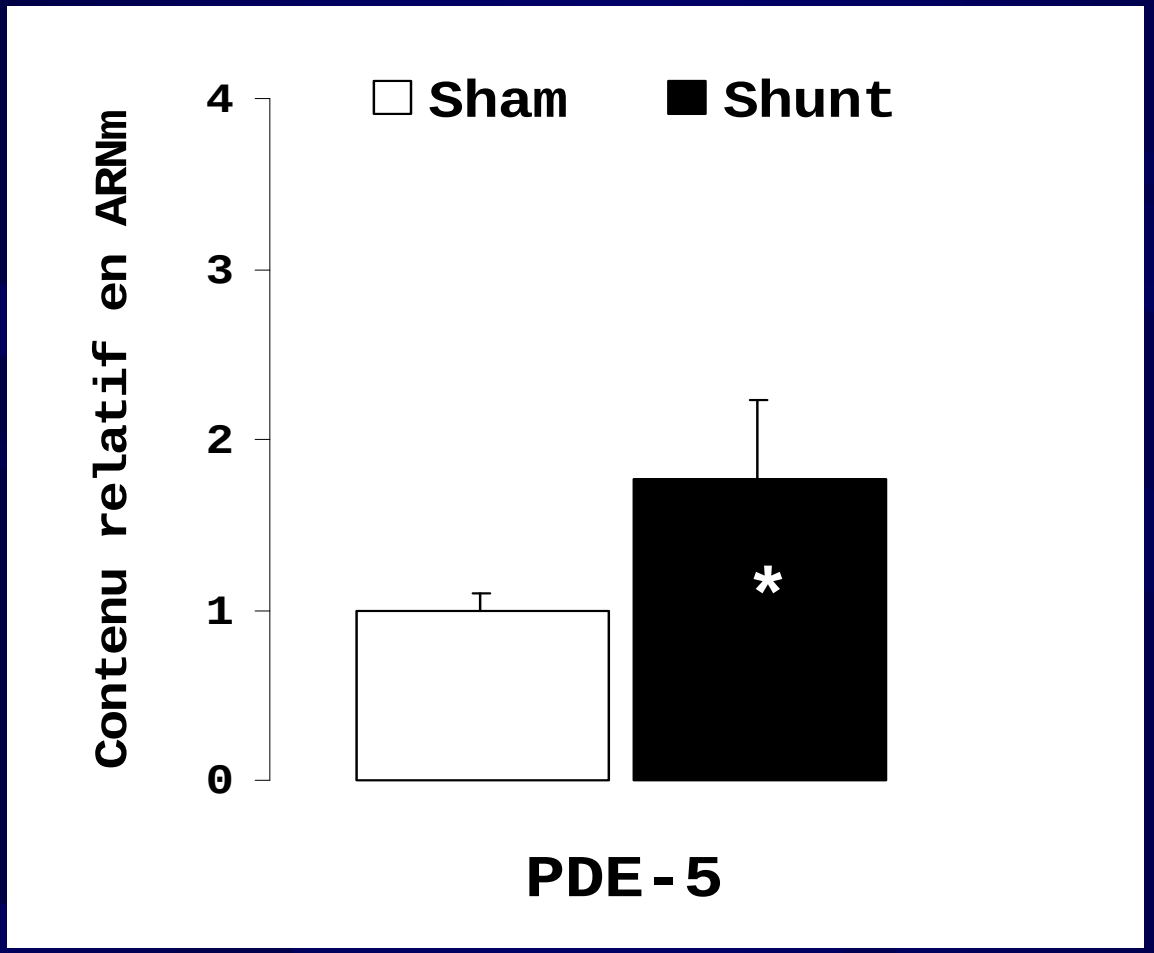
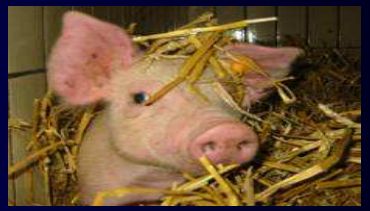
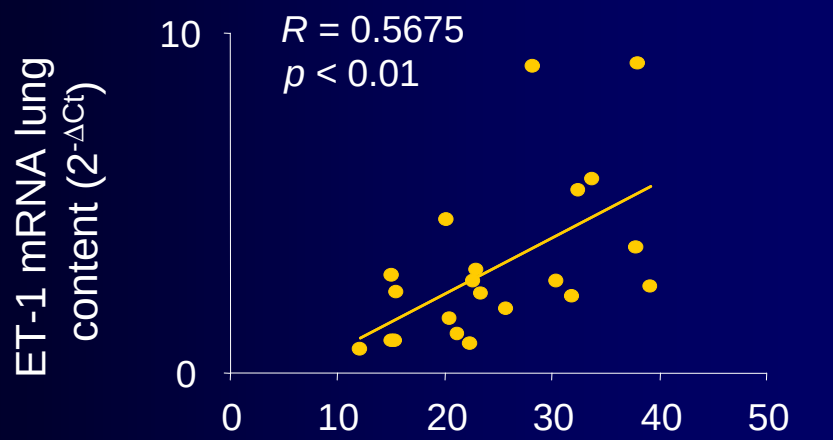
Biologie Endothélium

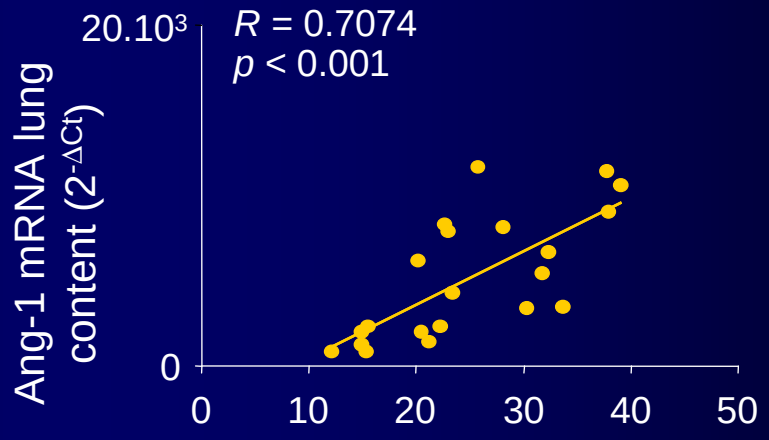


Rondelet B, Kerbaul F. *Circulation* 2003; 107:1329-35, *Circulation* 2004; 110:2220-5.

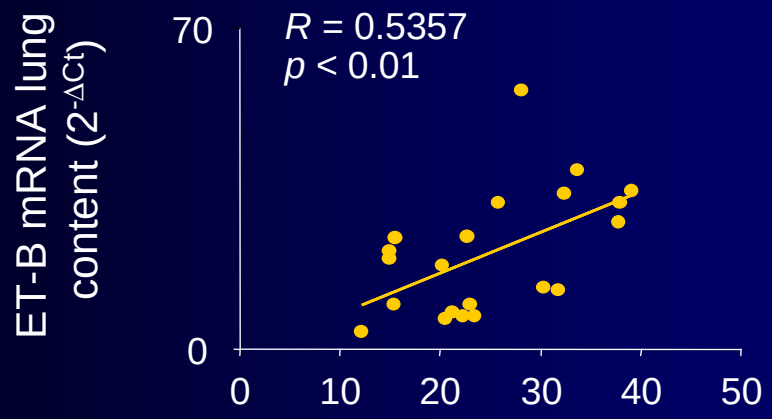
Expression de ET-1, ET_B, angiopoiétine-1 dans un modèle expérimental d'HTAP

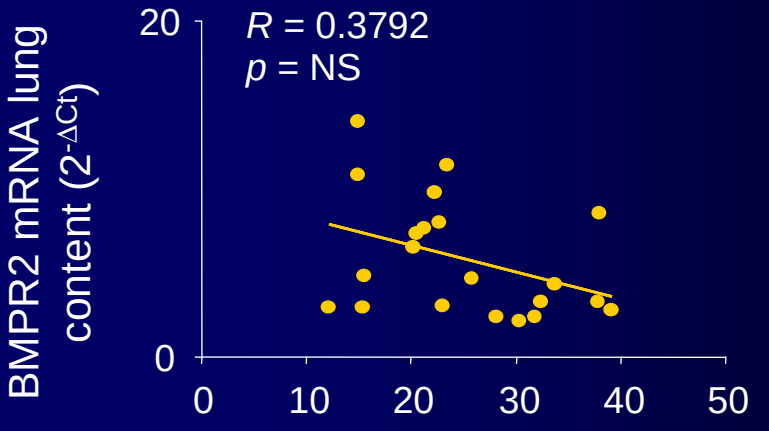






Ppa_m (mmHg)

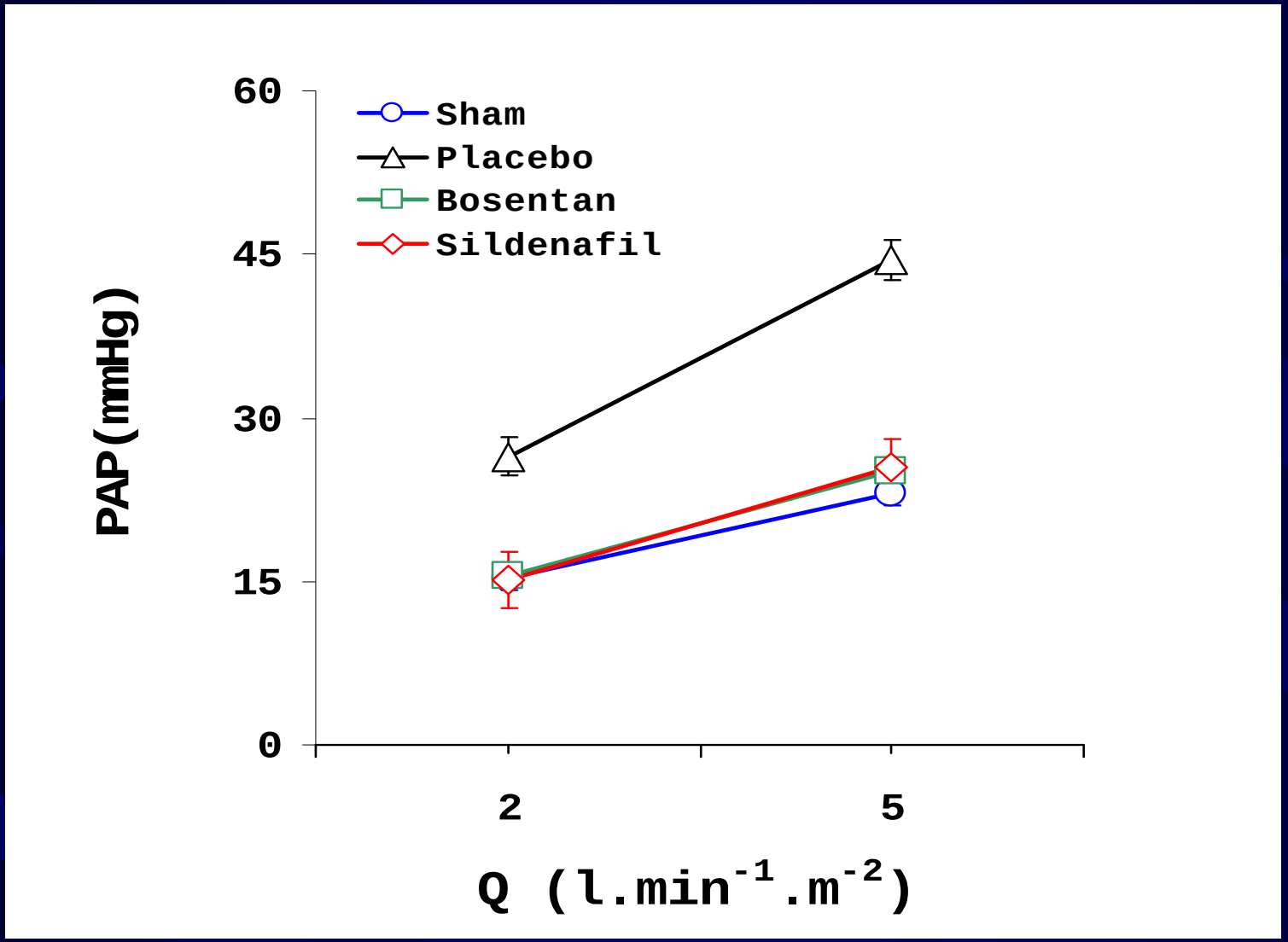




Ppa_m (mmHg)

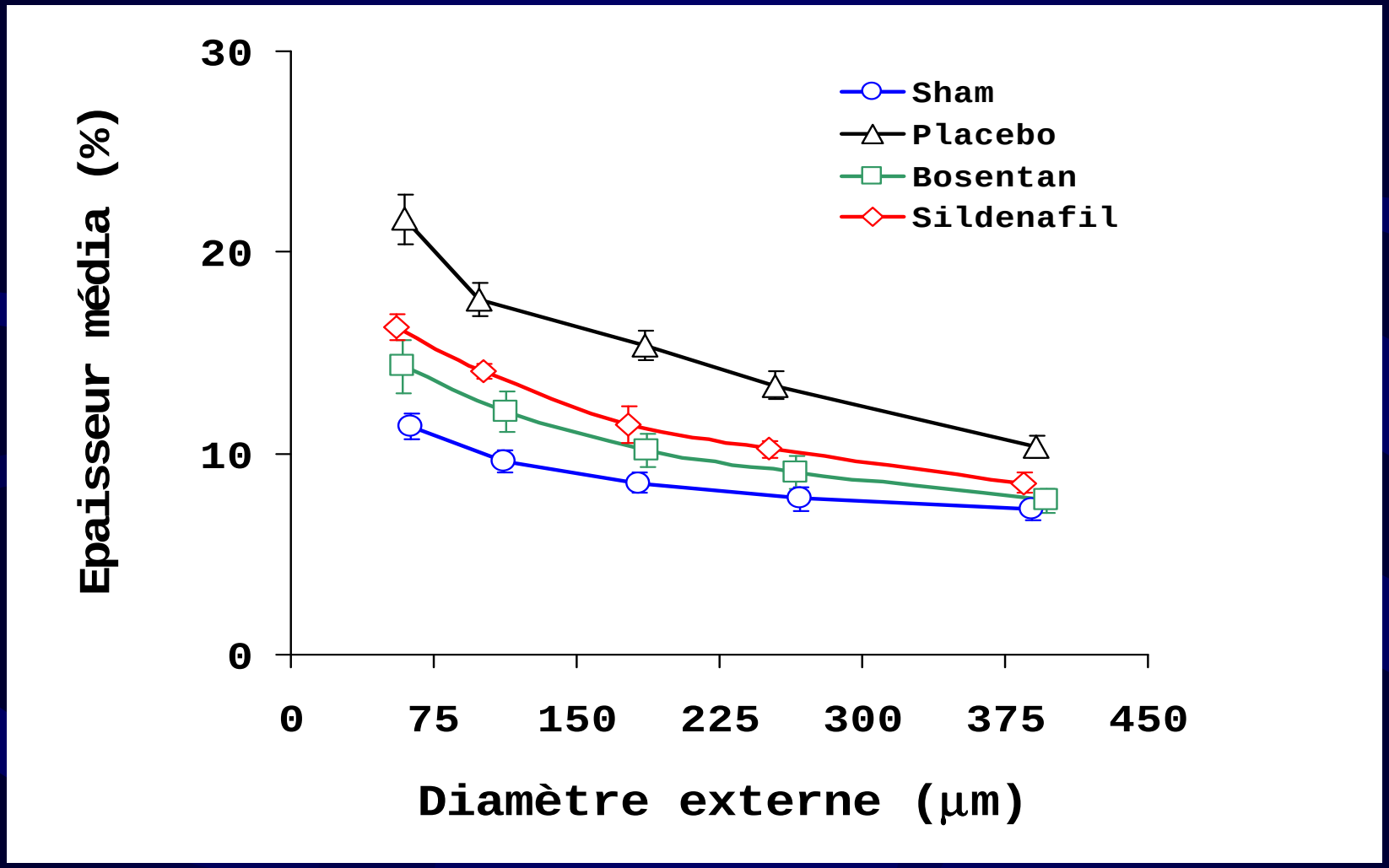
Rondelet B, Kerbaul F *et al. Circulation* 2003; 107:1329-35, *Circulation* 2004; 110:2220-5.

Hémodynamique



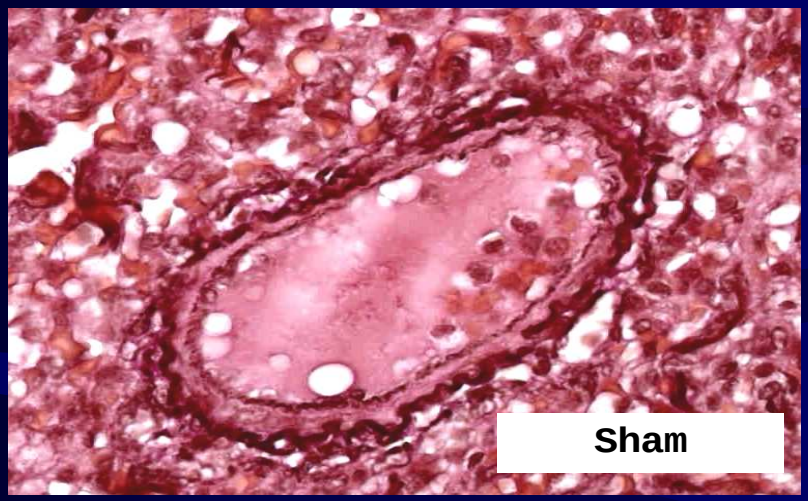
Rondelet B, Kerbaul F. *Circulation* 2003; 107:1329-35, *Circulation* 2004; 110:2220-5.

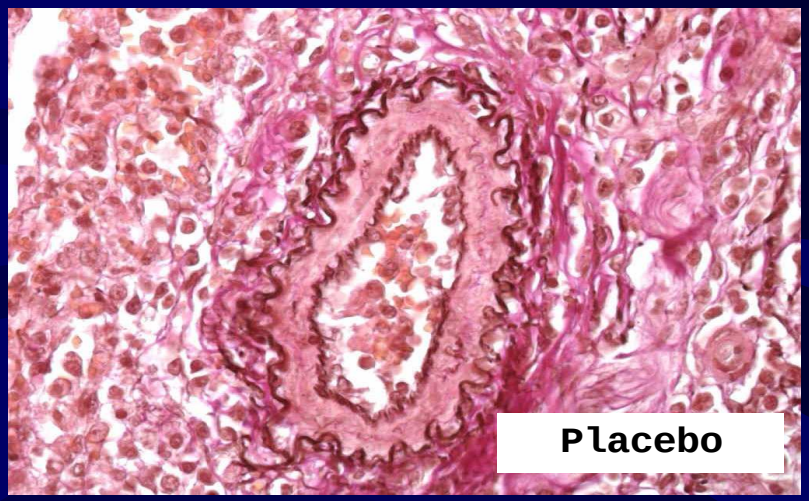
Morphométrie

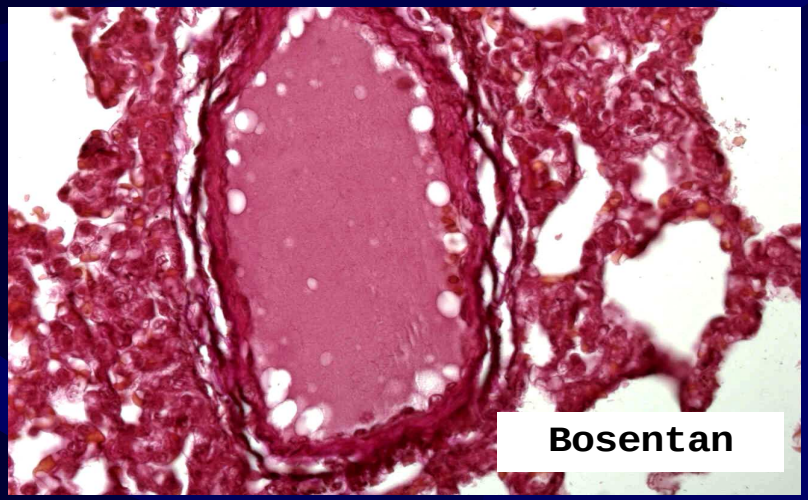


Rondelet B, Kerbaul F. *Circulation* 2003; 107:1329-35, *Circulation* 2004; 110:2220-5.

Morphométrie







Rondelet B, Kerbaul F. *Circulation* 2003; 107:1329-35, *Circulation* 2004; 110:2220-5.

Quels traitements ??

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Pharmacology & Therapeutics 102 (2004) 139–153
Pharmacology & Therapeutics
www.elsevier.com/locate/pharmthera
Associate editor: R.M. Wadsworth

Prostacyclin and its analogues in the treatment of pulmonary hypertension

Horst Olschewski*, Frank Rose, Ralph Schermuly, H. Ardeschir Ghofrani, Beate Enke, Andrea Olschewski, Werner Seeger

Medical Clinic II, Klinikstrasse 36, D-35392 Giessen, Germany

Prostacyclines

Dérivés des prostaglandines (I2)

Vasodilatation pulmonaire prédominante (forme inhalée)

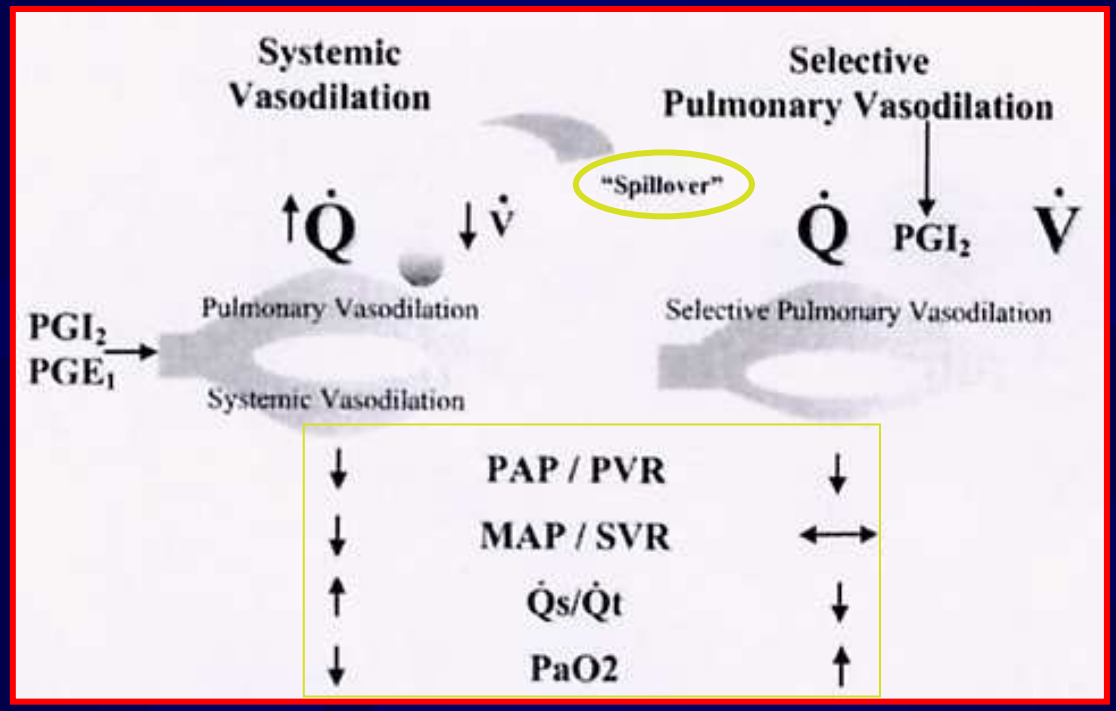
Vasodilatation systémique (IV)

Majoration du débit cardiaque (inotropisme non renforcé ??)

TTT référence HTAP stade III NYHA

Maintien VA/Q – Stabilité PaO2 *(Siobal et al – Respir Care 2004)*

Effet anti-inflammatoire, anti-agrégant


Systemic Vasodilation
Selective Pulmonary Vasodilation
"Spillover"
↑Q̇ ↓V̇
Q̇ PGI2 V̇
PGI2
PGE1
Pulmonary Vasodilation
Selective Pulmonary Vasodilation
Systemic Vasodilation
↓ PAP / PVR ↓
↓ MAP / SVR ↔
↑ Q̇s/Q̇t ↓
↓ PaO2 ↑

Prostacyclines

Epoprosténol IV, inhalé (FLOLAN ®)

Demi-vie courte: < 6 min

Stabilité du produit: 24 h

A l'abri de la lumière

Doses: 2-100 ng/kg/min

Effets secondaires (hypotension artérielle) +++

Tréprostinil (SC), Béraprost (oral)

Iloprost inhalé (VENTAVIS ®)

Demi-vie: 25 min

Efficacité thérapeutique: 90 min

Stable à T ambiante

Doses: 10-30 µg (6-9 nébulisations /j – durée: 15 min)

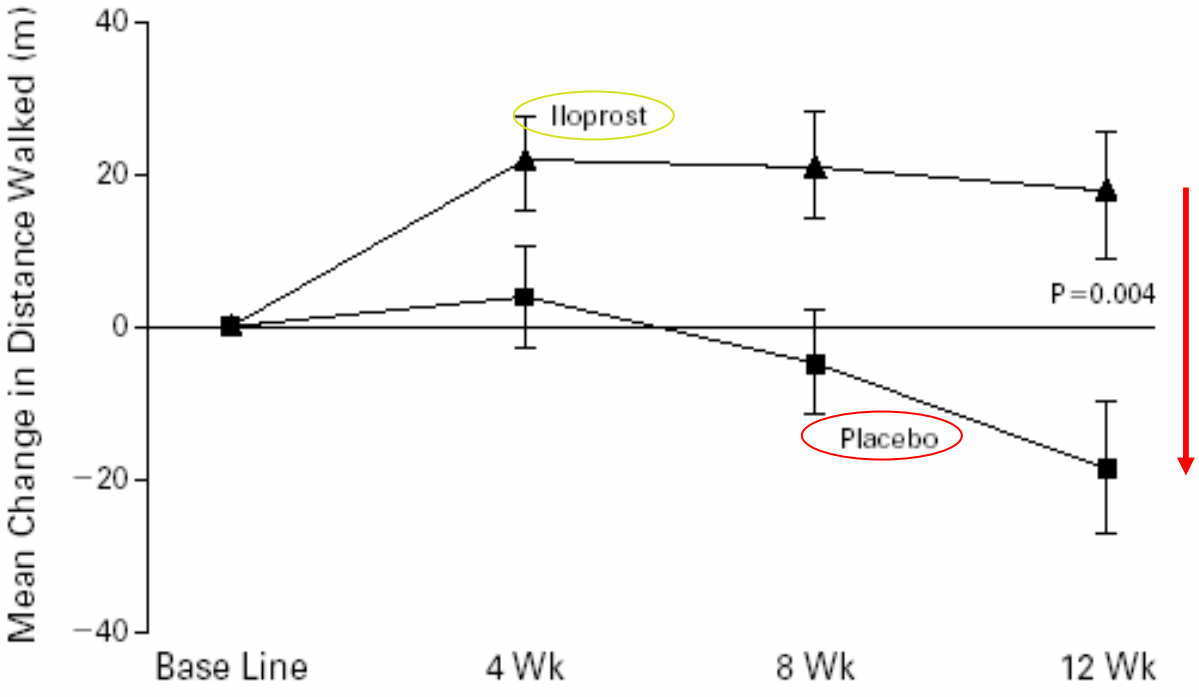
Effets secondaires « spillover » ++

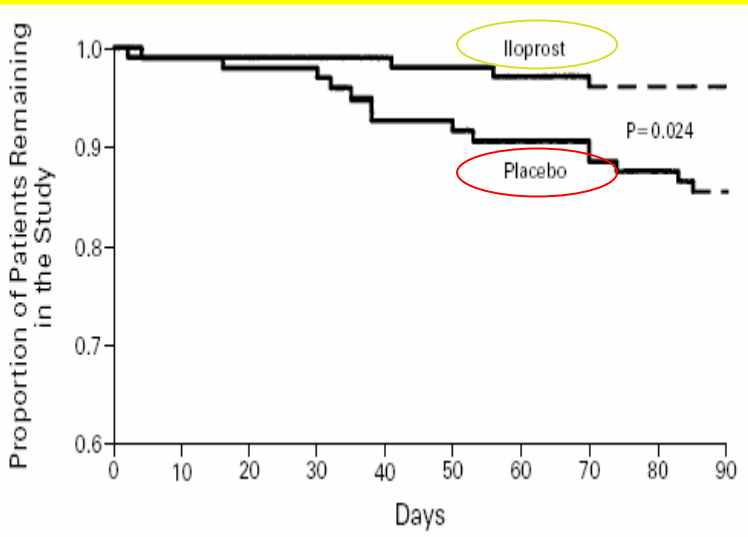
(Siobal et al – Respir Care 2004)

The New England Journal of Medicine

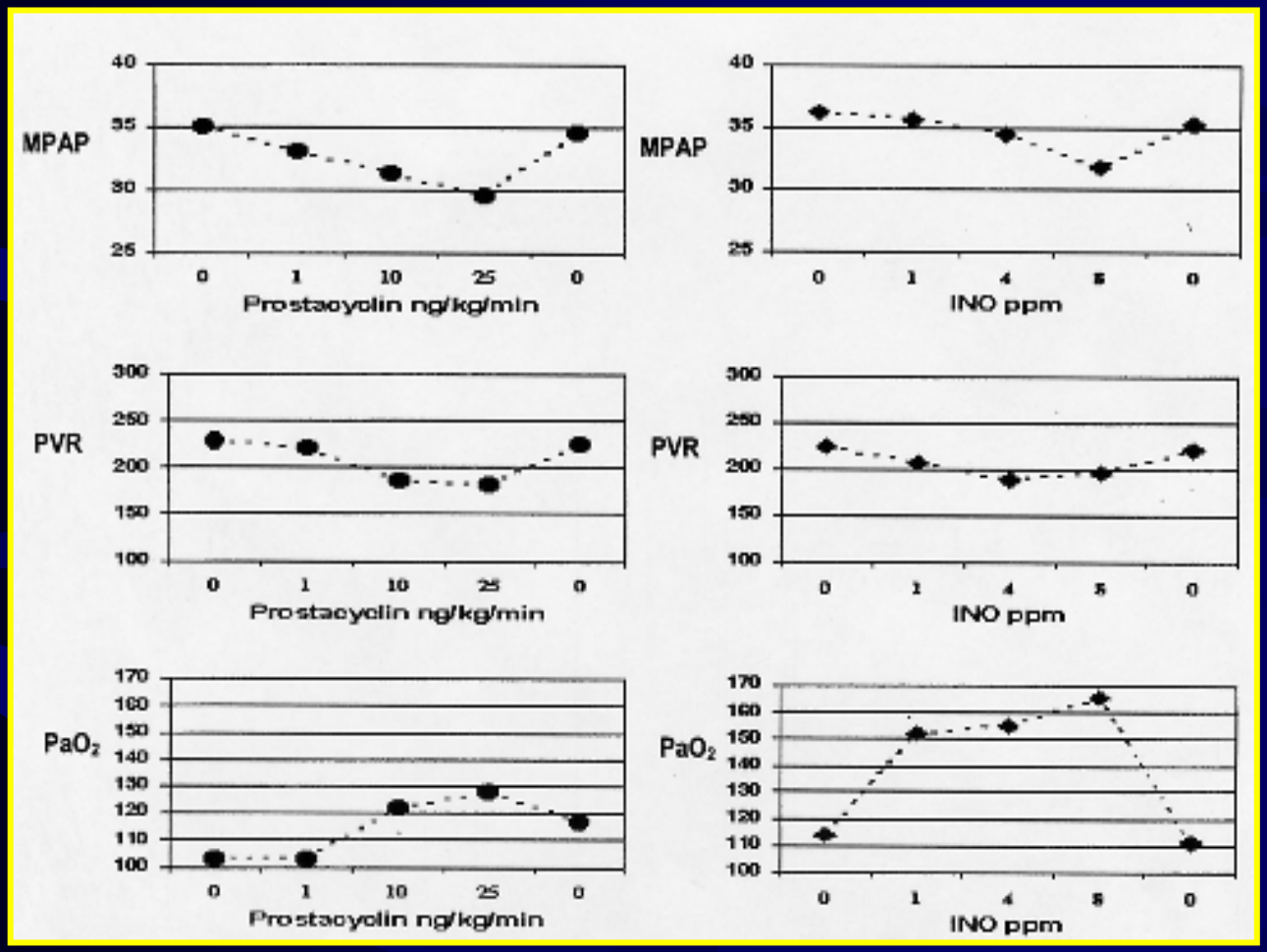
INHALED ILOPROST FOR SEVERE PULMONARY HYPERTENSION

HORST OLSCHEWSKI, M.D., GERALD SIMONNEAU, M.D., NAZZARENO GALIÈ, M.D., TIMOTHY HIGENBOTTAM, M.D., ROBERT NAEIJE, M.D., LEWIS J. RUBIN, M.D., SYLVIA NIKKHO, M.D., RUDOLF SPEICH, M.D., MARIUS M. HOEPER, M.D., JÜRGEN BEHR, M.D., JÖRG WINKLER, M.D., OLIVIER SITBON, M.D., WLADIMIR POPOV, M.D., H. ARDESCHIR GHOFRANI, M.D., ALESSANDRA MANES, M.D., DAVID G. KIELY, M.D., RALPH EWERT, M.D., ANDREAS MEYER, M.D., PAUL A. CORRIS, F.R.C.P., MARION DELCROIX, M.D., MIGUEL GOMEZ-SANCHEZ, M.D., HARALD SIEDENTOP, DIPL.STAT., AND WERNER SEEGER, M.D., FOR THE AEROSOLIZED ILOPROST RANDOMIZED STUDY GROUP*

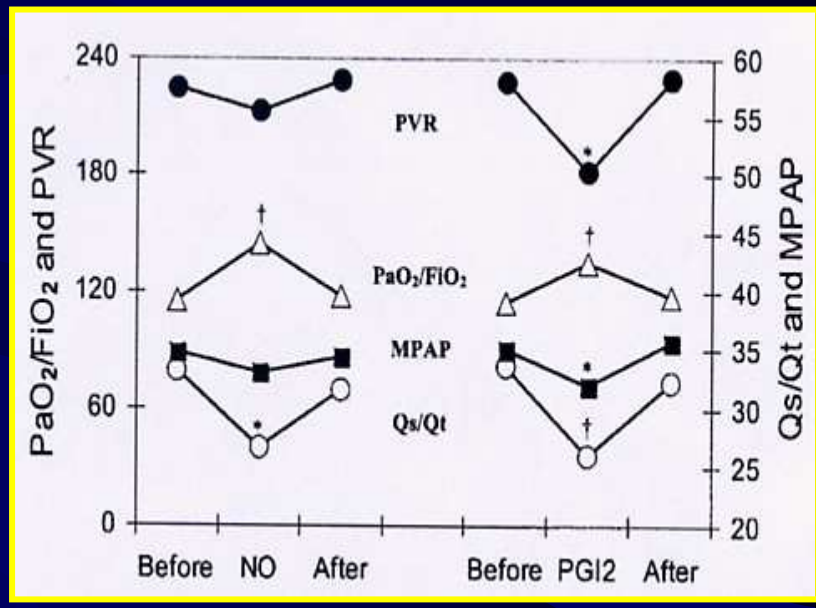




Prostacyclines – HTP pré capillaire



Zwissler at al. Am J Resp Crit Care Med 1996



Walmrath at al. Am J Resp Crit Care Med 1996

Prostacyclines – HTP pré capillaire

ELSEVIER

European Journal of Cardio-thoracic Surgery 28 (2005) 882–888

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

www.elsevier.com/locate/ejcts

Inhaled iloprost to control residual pulmonary hypertension following pulmonary endarterectomy

Thorsten Kramm[a,*], Balthasar Eberle[b], Stefan Guth[a], Eckhard Mayer[a]

[a] *Department of Cardiothoracic and Vascular Surgery, Johannes Gutenberg University Medical School, Langenbeckstr. 1, D-55131 Mainz, Germany*
[b] *Department of Anesthesiology, Johannes Gutenberg University Medical School, D-55131 Mainz, Germany*

Prostacyclines – HTP post capillaire

Inhaled iloprost controls pulmonary hypertension after cardiopulmonary bypass

[L'inhalation d'iloprost permet de contrôler l'hypertension pulmonaire après la circulation extracorporelle]

Kassiani Theodoraki MD DEAA,* Panagiota Rellia MD,* Apostolos Thanopoulos MD,* Loukas Tsourelis MD,† Dimitrios Zarkalis MD,† Petros Sfyrakis MD,† Theophani Antoniou MD*

CAN J ANESTH 2002 / 49: 9 / pp 963–967

Iloprost improves hemodynamics in patients with severe chronic cardiac failure and secondary pulmonary hypertension

[L'iloprost améliore l'hémodynamique chez des malades souffrant d'insuffisance cardiaque chronique et d'hypertension artérielle pulmonaire]

Armin Sablotzki MD PhD,* Elke Czeslick MD,* Susann Schubert MD,* Ivar Friedrich MD,† Jörg Mühling MD,‡ Marius G. Dehne MD,‡ Stefan Grond MD PhD,* Thomas Hentschel MD*

CAN J ANESTH 2002 / 49: 10 / pp 1076–1080

Prostacyclines – Intérêt clinique

HTAP stade III et IV *(Badesch et al – J Am Coll Cardiol 2004)* AMM

HTP II aire pré capillaire (SDRA)

(Walmrath et al – Am J Resp Dis Crit Care Med 1996)

(Zwissler et al – Am J Resp Dis Crit Care Med 1996)

(Domenighetti et al – Crit Care Med 2001)

(Van Heerden et al – Chest 2000)

HTP II aire post capillaire *(Haraldsson et al – Chest 1998)*

Post-CEC *(Fortier et al – J Thorac Cardiovasc Surg 2004)*

(Fattouch et al- J Card Surg 2005)

Sildénafil

Inhibiteur sélectif PDE V

Vasodilatation pulmonaire prédominante mais aussi systémique

Inhibition remodelage vasculaire pulmonaire

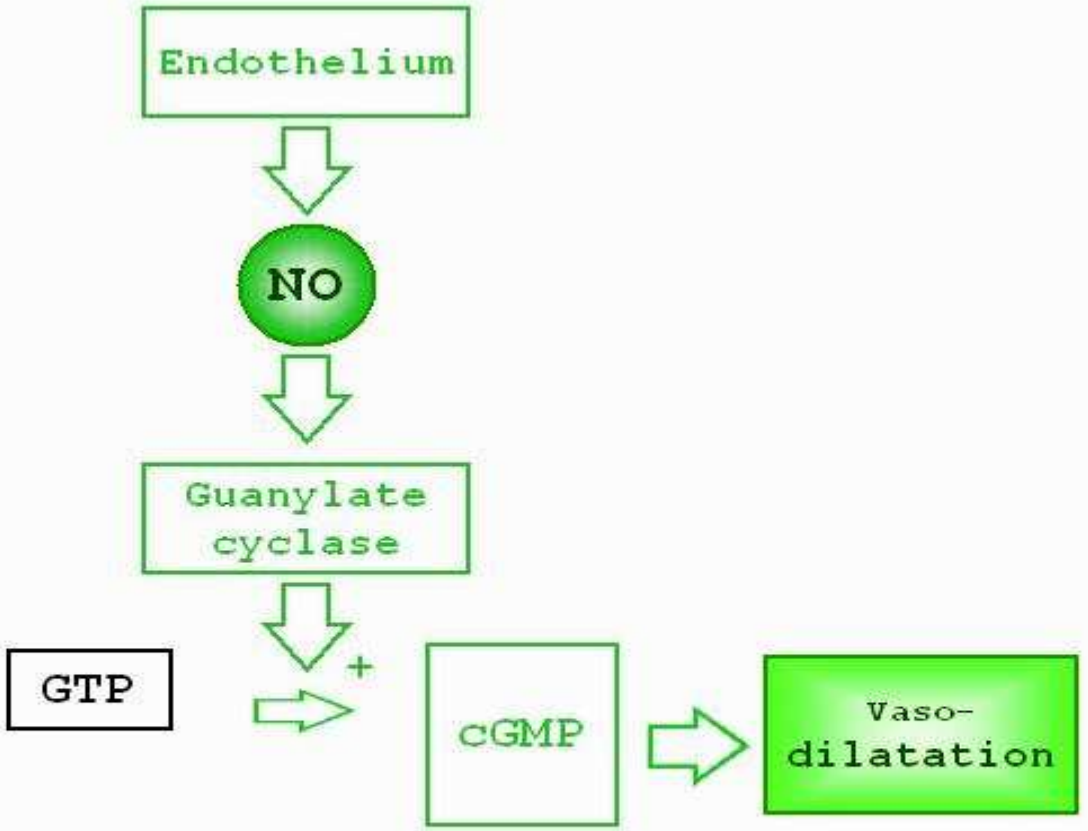
(Sebkhi et al – Circulation 2003)

Maintien VA/Q – Stabilité PaO_2 *(Trachte et al – Ann Thorac Surg 2005)*

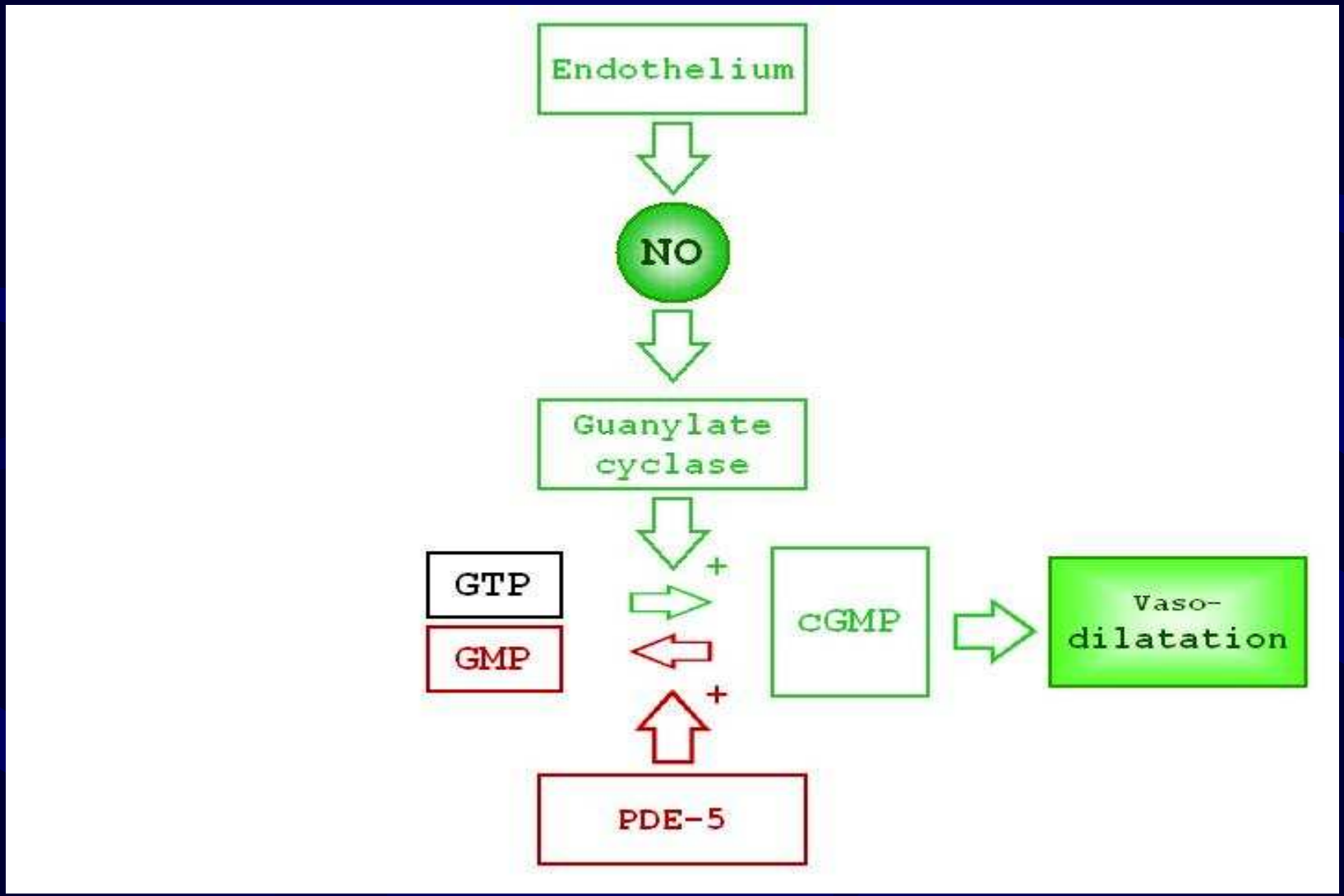
(Stocker et al – Intensive Care Med 2003)

Prolongation effets NO – Relais thérapeutique

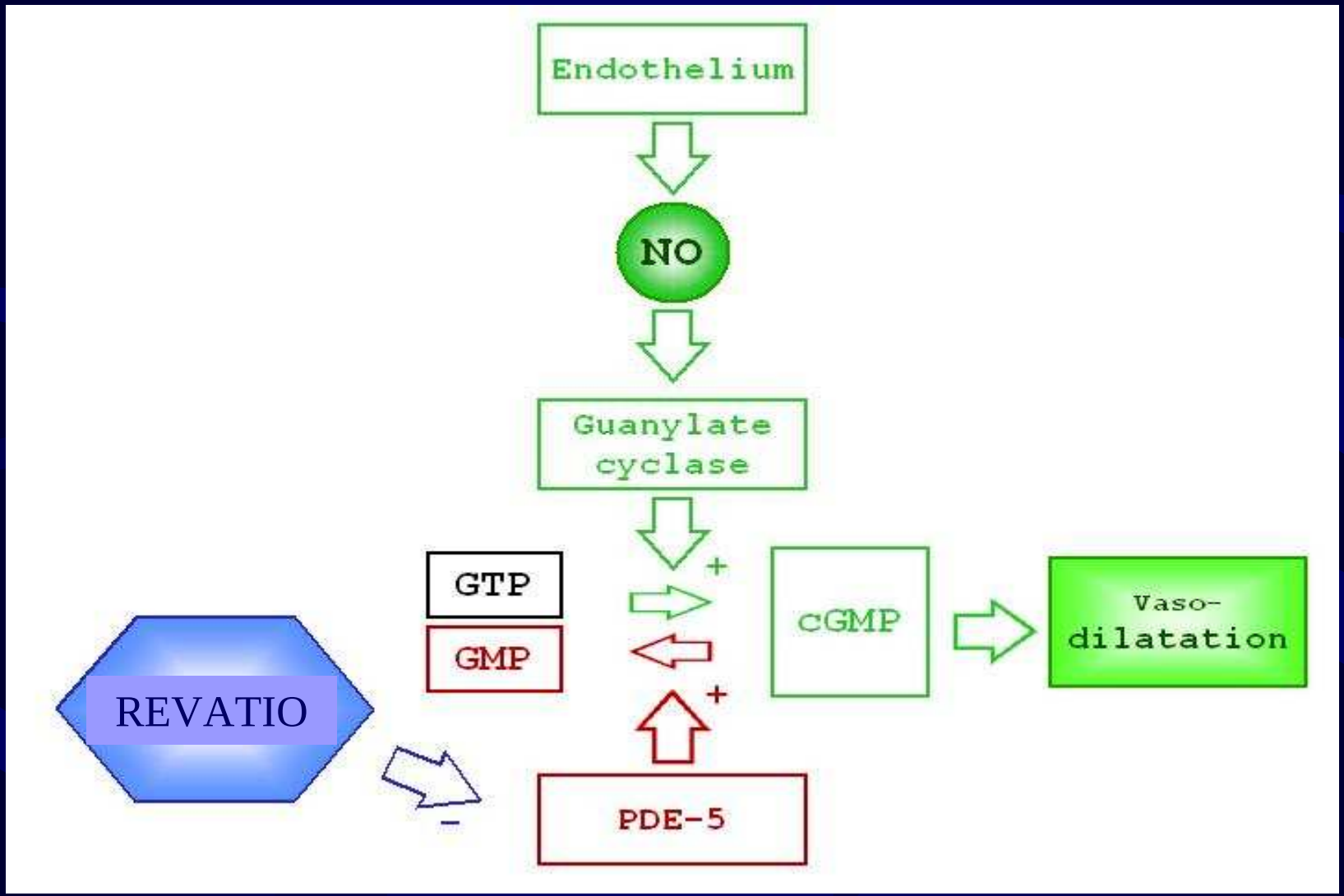
Sildénafil


Endothelium
NO
Guanylate cyclase
GTP
+
cGMP
Vaso-dilatation

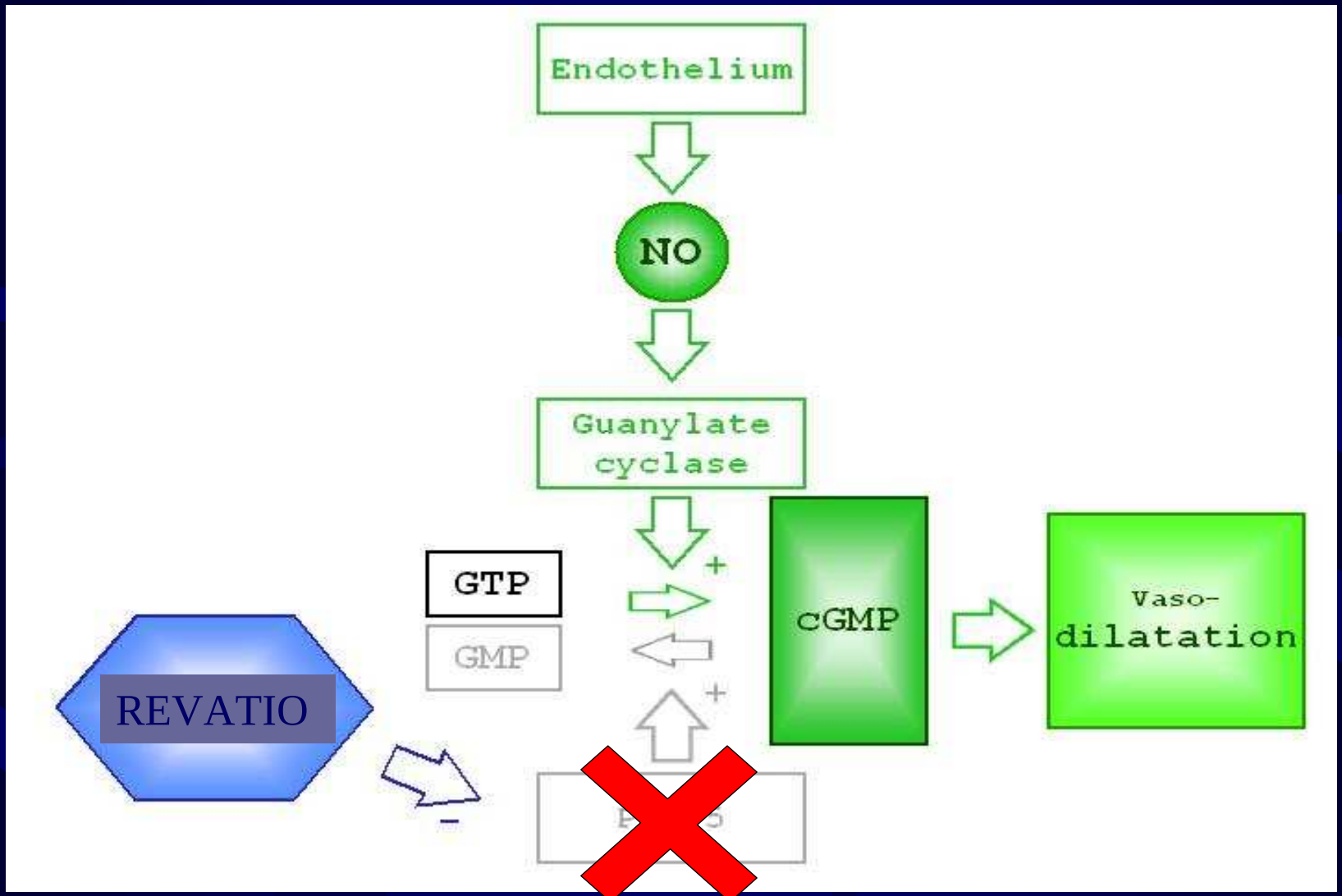
Sildénafil


Endothelium
NO
Guanylate cyclase
GTP
GMP
+
+
cGMP
Vaso-dilatation
PDE-5

Sildénafil


Endothelium
NO
Guanylate cyclase
GTP
GMP
+
cGMP
Vaso-dilatation
REVATIO
+
PDE-5
–

Sildénafil


Endothelium
NO
Guanylate cyclase
GTP
GMP
+
+
cGMP
Vaso-dilatation
REVATIO
-

Sildénafil- Cinétique

Début d'action court (15 min)

Bonne résorption digestive

Equilibre plasmatique: 60-90 min

T½ β = 4 heures

Formes galéniques: orale (REVATIO® 20 mg)

IV (40 mg ≒ 100 mg per os)

Dose: 20 -100 mg/jour *(Lowson et al – Crit Care Med 2005)*

Pas d'effet adverse connu

Sildénafil – Intérêt clinique

HTAP stade III *(Wilkins et al – Am J Resp Dis Crit Care Med 2005)* AMM

HTP II aire pré capillaire *(Ng et al – Br J Anaesth 2005)*

(Ghofrani et al – Lancet 2002)

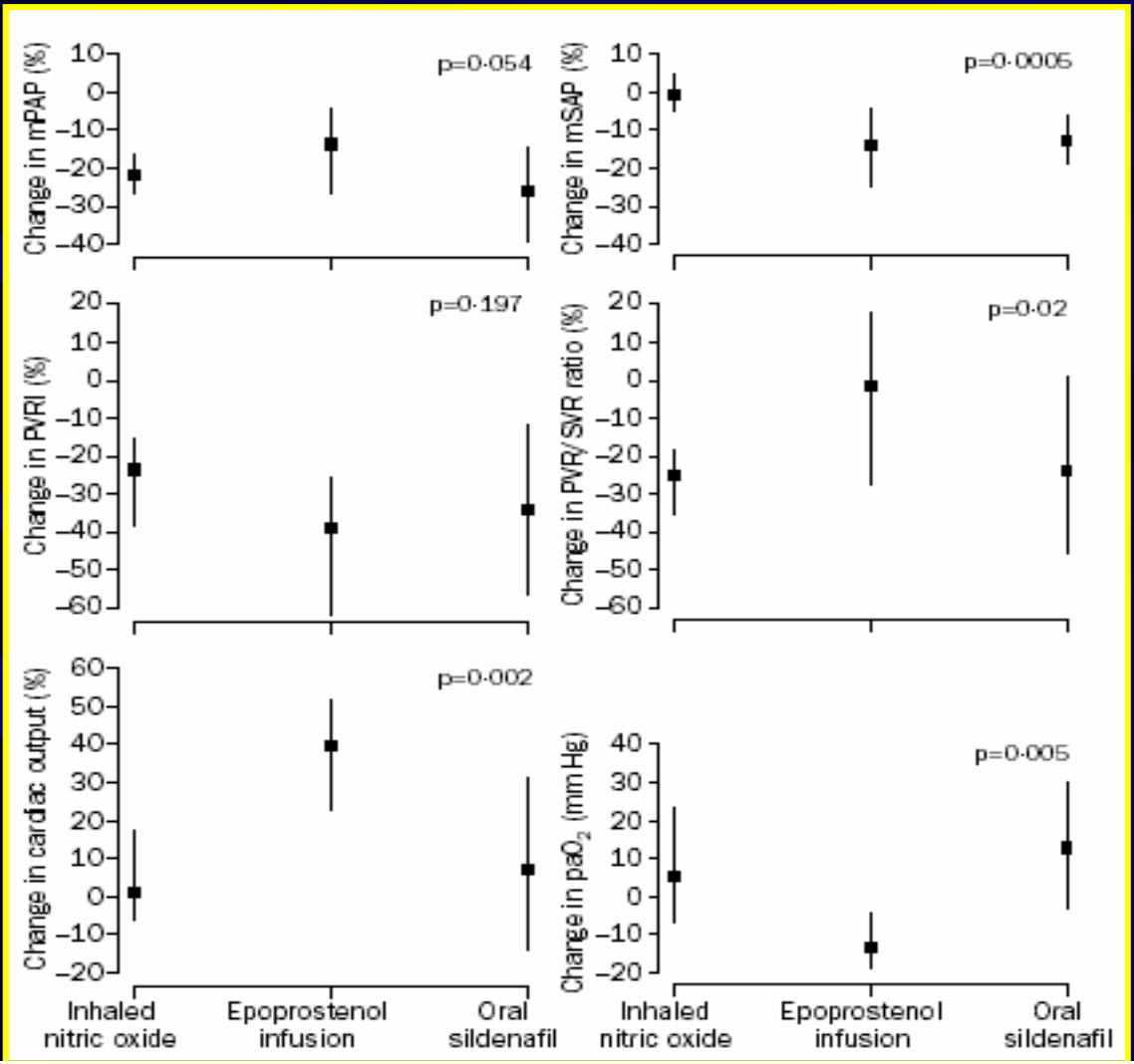
HTP II aire post capillaire *(Lepore et al – Chest 2005)*

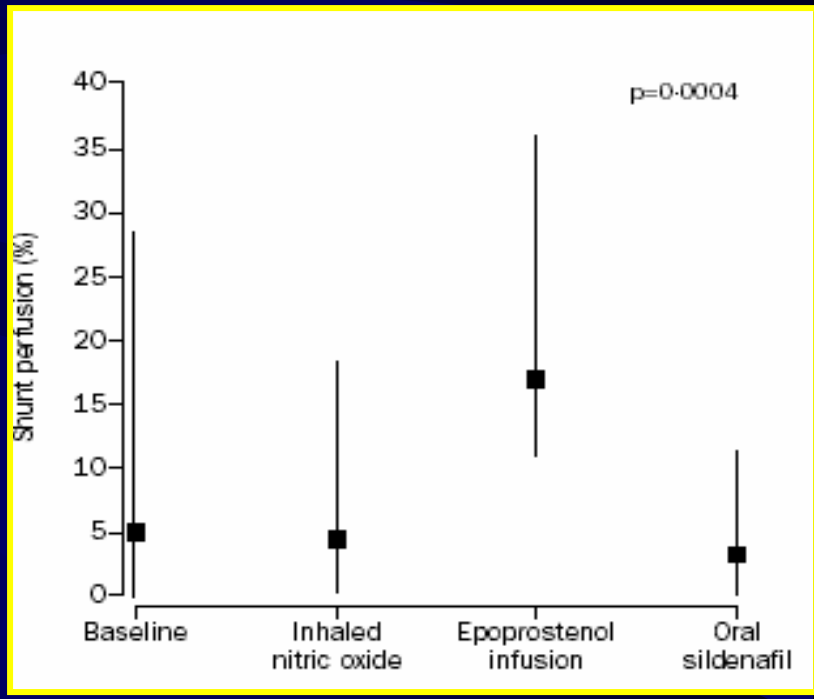
Post-CEC *(Stocker et al – Intensive Care Med 2003)*
(Trachte et al – Ann Thorac Surg 2005)

Sildénafil – HTP pré capillaire

Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial

Hossein Ardeschir Ghofrani, Ralph Wiedemann, Frank Rose, Ralph T Schermuly, Horst Olschewski, Norbert Weissmann, Andreas Gunther, Dieter Walmrath, Werner Seeger, Friedrich Grimminger





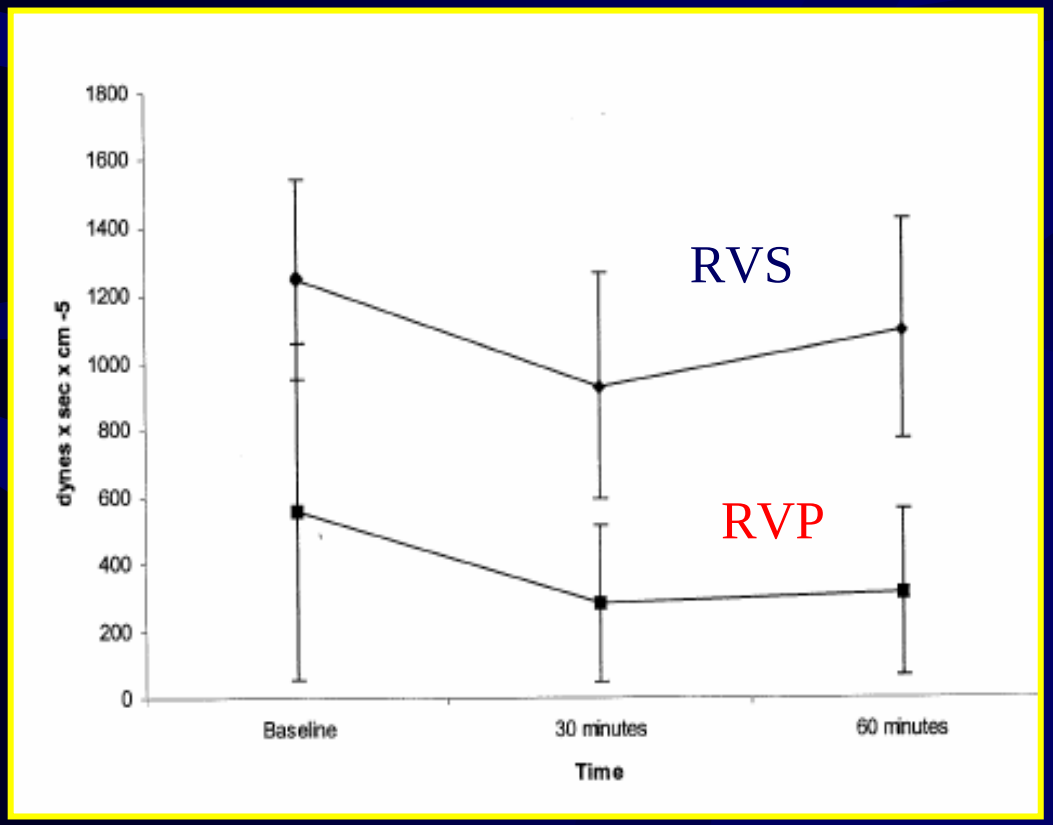
Lancet 2002; **360:** 895–900

Sildénafil – HTP post capillaire

Oral Sildenafil Reduces Pulmonary Hypertension After Cardiac Surgery

Aaron L. Trachte, MD, Emilio B. Lobato, MD, Felipe Urdaneta, MD, Phillip J. Hess, MD, Charles T. Klodell, MD, Tomas D. Martin, MD, Edward D. Staples, MD, and Thomas M. Beaver, MD

(Ann Thorac Surg 2005;79:194–7)

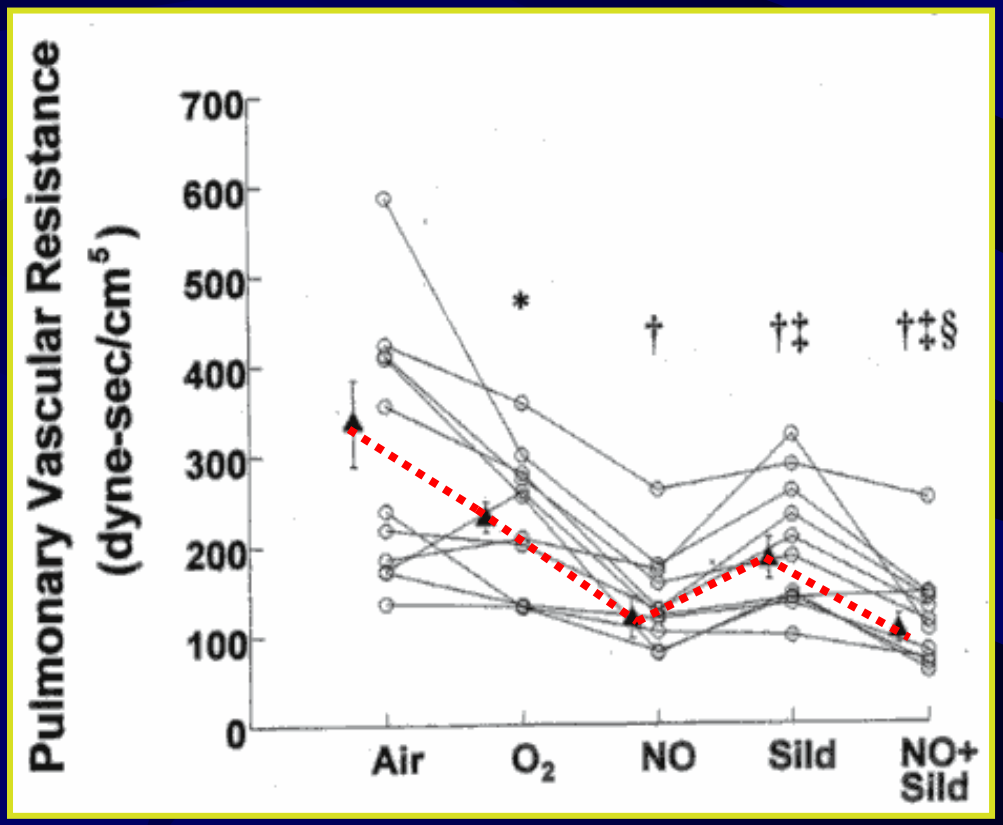


Hemodynamic Effects of Sildenafil in Patients With Congestive Heart Failure and Pulmonary Hypertension*

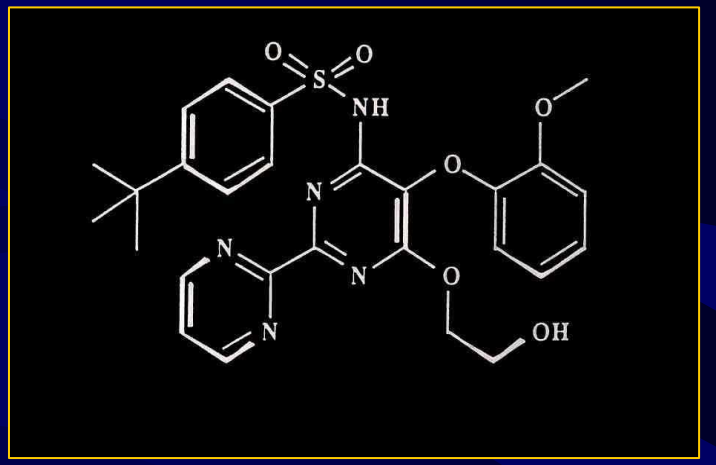
Combined Administration With Inhaled Nitric Oxide

John J. Lepore, MD†; Anjli Maroo, MD; Luca M. Bigatello, MD; G. William Dec, MD; Warren M. Zapol, MD; Kenneth D. Bloch, MD; and Marc J. Semigran, MD

(CHEST 2005; 127:1647–1653)



Bosentan



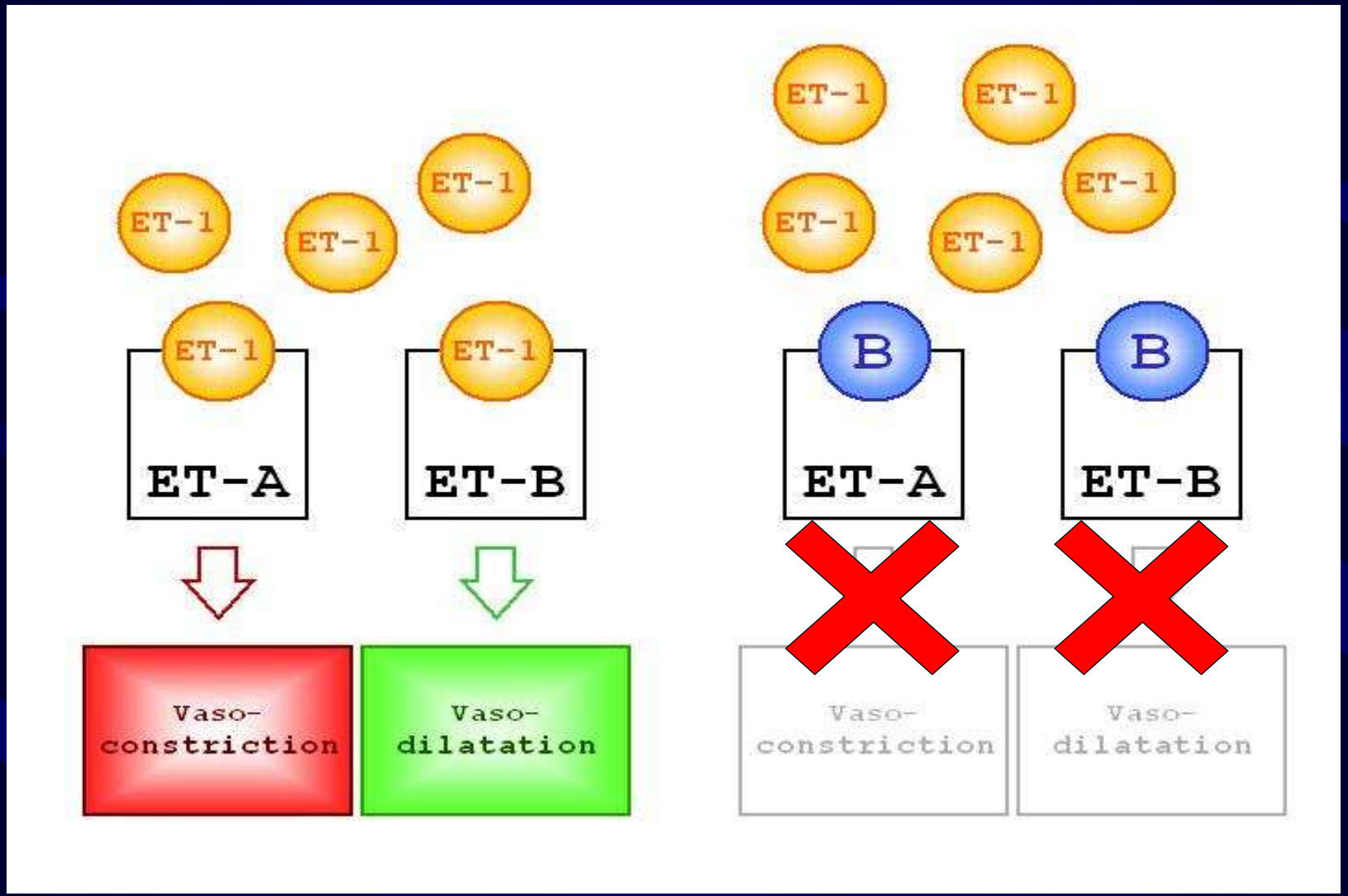
Inhibiteur non-sélectif des Rc ET A et B

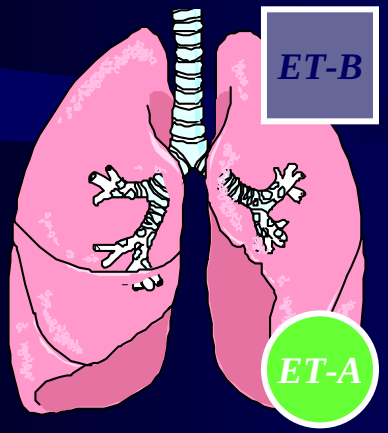
Vasodilatation pulmonaire prédominante

Inhibition remodelage vasculaire pulmonaire

(Rondelet et al – Circulation 2003)

Bosentan

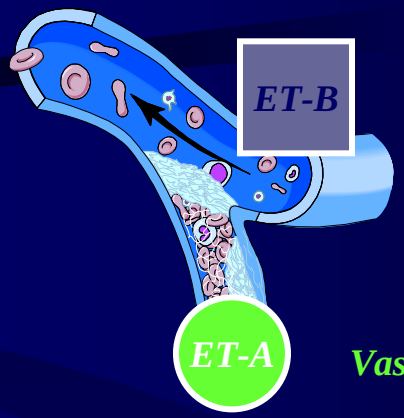

ET-1
ET-1
ET-1
ET-1
ET-1
ET-A
ET-B
Vaso-
constriction
Vaso-
dilatation
ET-1
ET-1
ET-1
ET-1
ET-1
B
B
ET-A
ET-B
Vaso-
constriction
Vaso-
dilatation



Clairance ET-1

Vasodilatation

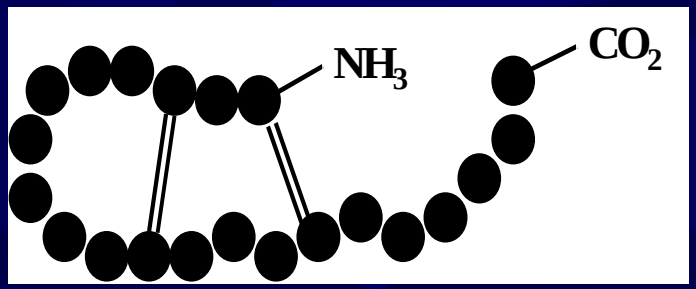
Vasoconstriction



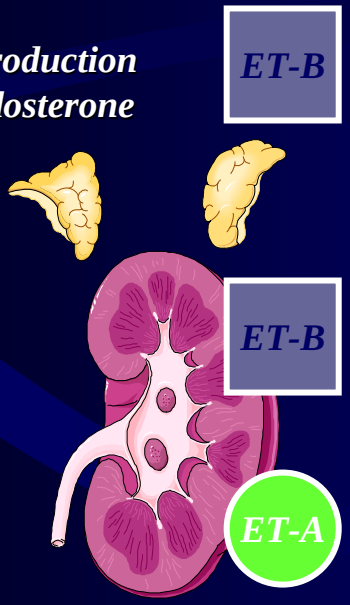
↗ sensibilité catécholamines

Vasodilatation

Vasoconstriction



Production aldosterone

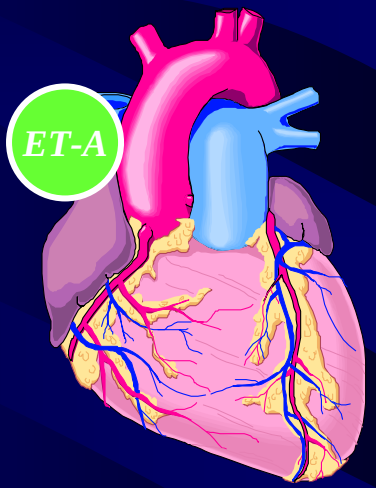


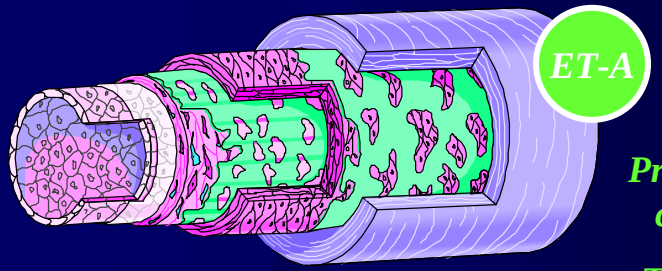
Rétention hydrosodée

Inotropisme

Hypertrophie

↗ANP





Prolifération cellulaire

Thromboses

ELSEVIER

Cardiovascular Research 61 (2004) 227–237

Cardiovascular Research

www.elsevier.com/locate/cardiores

Review

The endothelin system in pulmonary arterial hypertension

Nazzareno Galié*, Alessandra Manes, Angelo Branzi

Institute of Cardiology, University of Bologna, via Massarenti 9, 40138-Bologna, Italy

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

Learn and Live.

Endothelin Receptor Blockers in Cardiovascular Disease

Stuart Rich and Vallerie V. McLaughlin

Circulation 2003;108:2184-2190

DOI: 10.1161/01.CIR.0000094397.19932.78

Bosentan - Cinétique

Biodisponibilité absolue 50 %

Equilibre plasmatique: 3-6 heures

T½ β = 5,4 heures

Métabolisme et excrétion hépatiques

Formes galéniques: orale (TRACLEER ®: 62,5 et 125 mg)

IV

Dose: 125 – 250 mg/jour

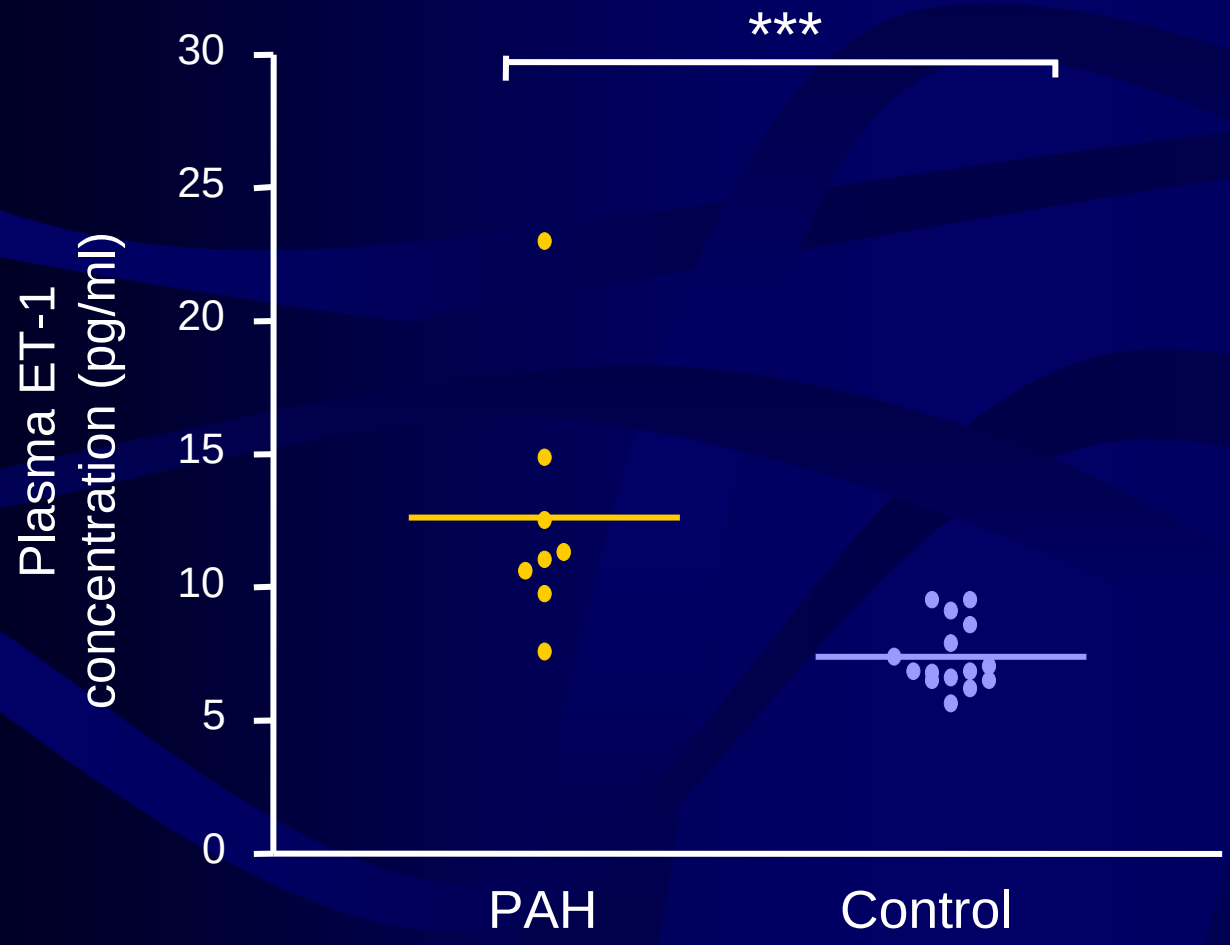
Cytolyse hépatique (TGP) dans 10 % des cas

Bosentan

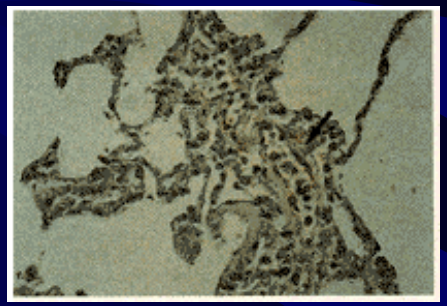
- *Atténue la réponse de vasoconstriction hypoxiques chez le rats et le cochon (bolus iv).*
- *Prévient et reverse l'HTAP hypoxique chez le rat.*
- *Amélioration de l'état clinique, des paramètres hémodynamiques, et de l'espérance de vie chez l'humain atteint d'HTAP.*

Eddahibi S, Am J Physiol, 1995.
Holm P, J Thorac Cardiovasc Surg,1996.
Chen SJ, JAP, 1995.
Channick, Circulation, 2000.

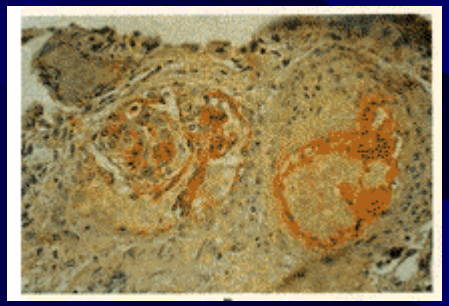
Increased ET plasma levels and ET production in PAH



Normal

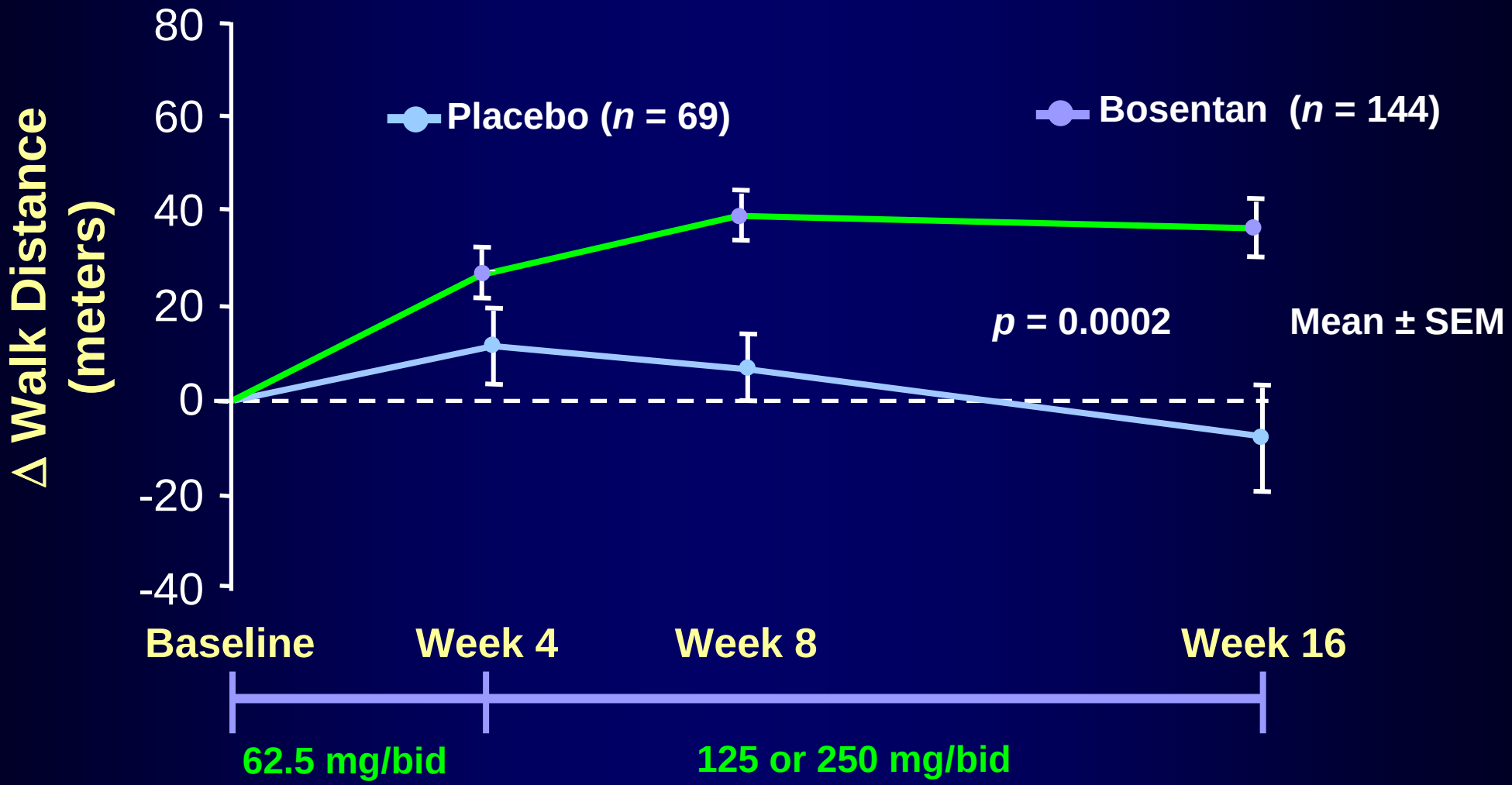


PAH



Giaid A, *et al. N Engl J Med* 1993; 328:1732

Dual endothelin A and B receptor blockade by bosentan improves PAH patients



Rubin LJ et al. N Engl J Med 2002; 346: 896-903.

Blocage Rc ET– Intérêt clinique

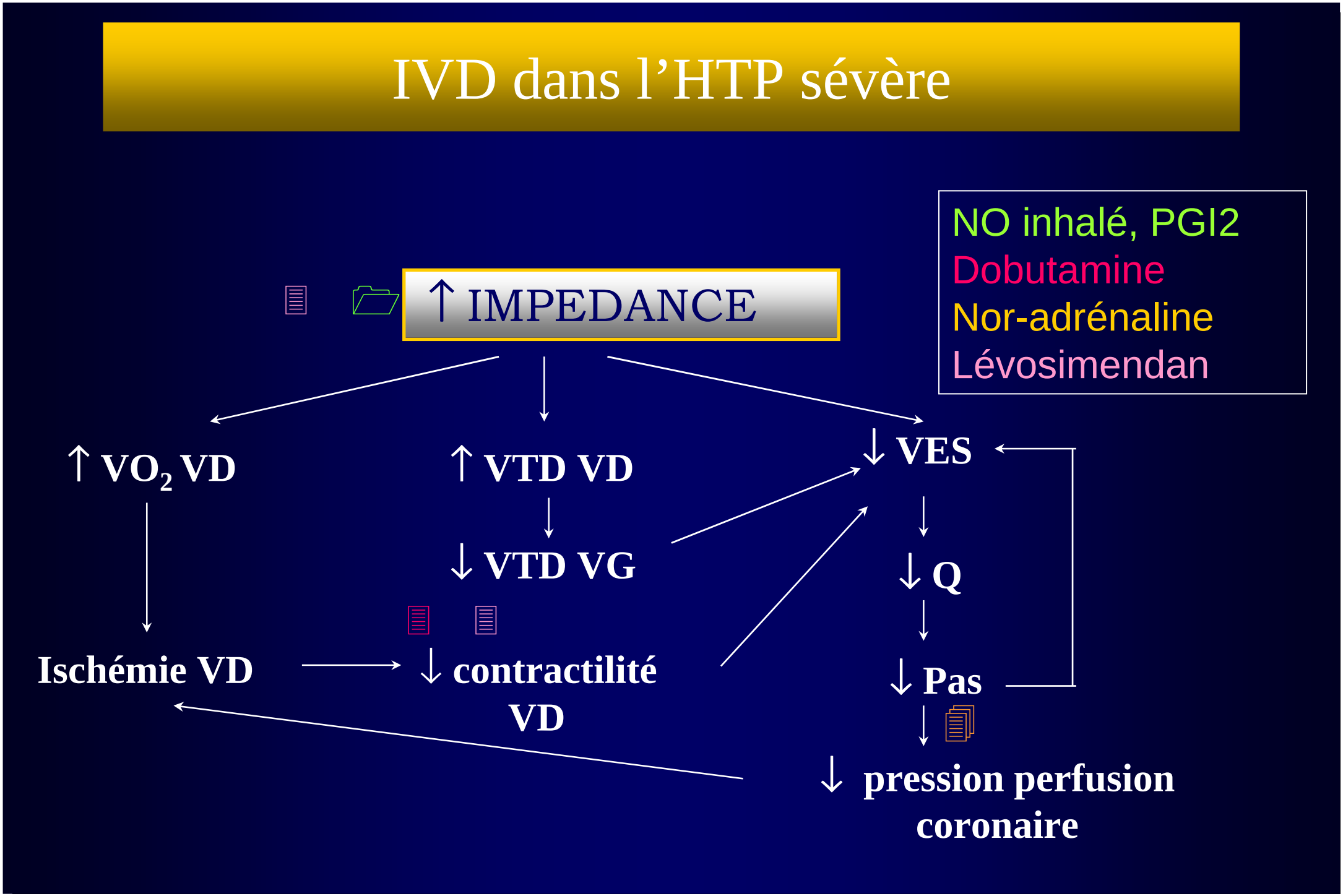
HTAP stade III (idiopathique, sclérodermie) (BREATHE 1, 2, 3) AMM

Insuffisance cardiaque congestive (RITZ) ??

HTA systémique *(Krum et al – N Engl J Med 1998) ??*

Coronaropathies *(Kyriakides et al – Am J Cardiol 2001) ??*

IVD dans l'HTP sévère

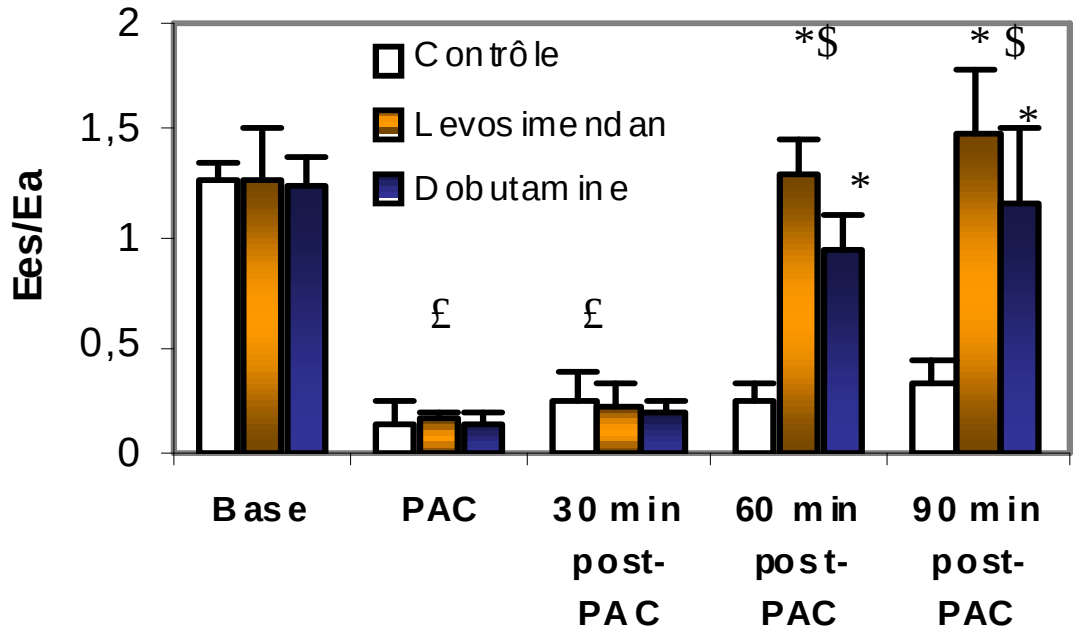


IVD et catécholamines

£: P<0,05 vs. Base

*: P<0,05 vs. Contrôle

$: P<0,05 vs. dobutamine



Kerbaul et al. Crit Care Med 2005 en cours de révision

Avenir

- Associations médicamenteuses
  - potentialisation des effets
  - bénéfice clinique
  - effets adverses
- Autres traitements pharmacologiques
  - Antagonistes Rc TxA2
  - L arginine, VIP, adrénomédulline
- Place des traitements non médicaux
  - Atrio-septostomie
  - Transplantation pulmonaire

Conclusion

- Nouvelle classification +++
- Meilleure compréhension de la physiopathologie et des mécanismes
  - ⇒ hémodynamique invasive et non-invasive
  - ⇒ biologie moléculaire

- Manque actuel de grosses séries randomisées et comparatives

(Wilkins et al. *Am J Resp Crit Care Med* 2005; 171: 1292-7)
(Leuchte et al. *Chest* 2004; 180: 580-6)

- Attention au mésusage (T2A)…..