DIU Paris 4 avril 2013

Physiopathologie du Syndrome Hépatorénal

Dr B. Ponte
Cheffe de clinique
Service de Néphrologie

HUG
Hôpitaux Universitaires de Genève

Plan

Introduction

Physiopathologie du SHR

- ✓ Modifications hémodynamiques
  - ✓ Vasodilatation splanchnique
  - ✓ Rôle du NO
- ✓ Dysfonction cardiaque
- ✓ Rôle de l'albumine
- ✓ Eléments déclenchants

Conclusions

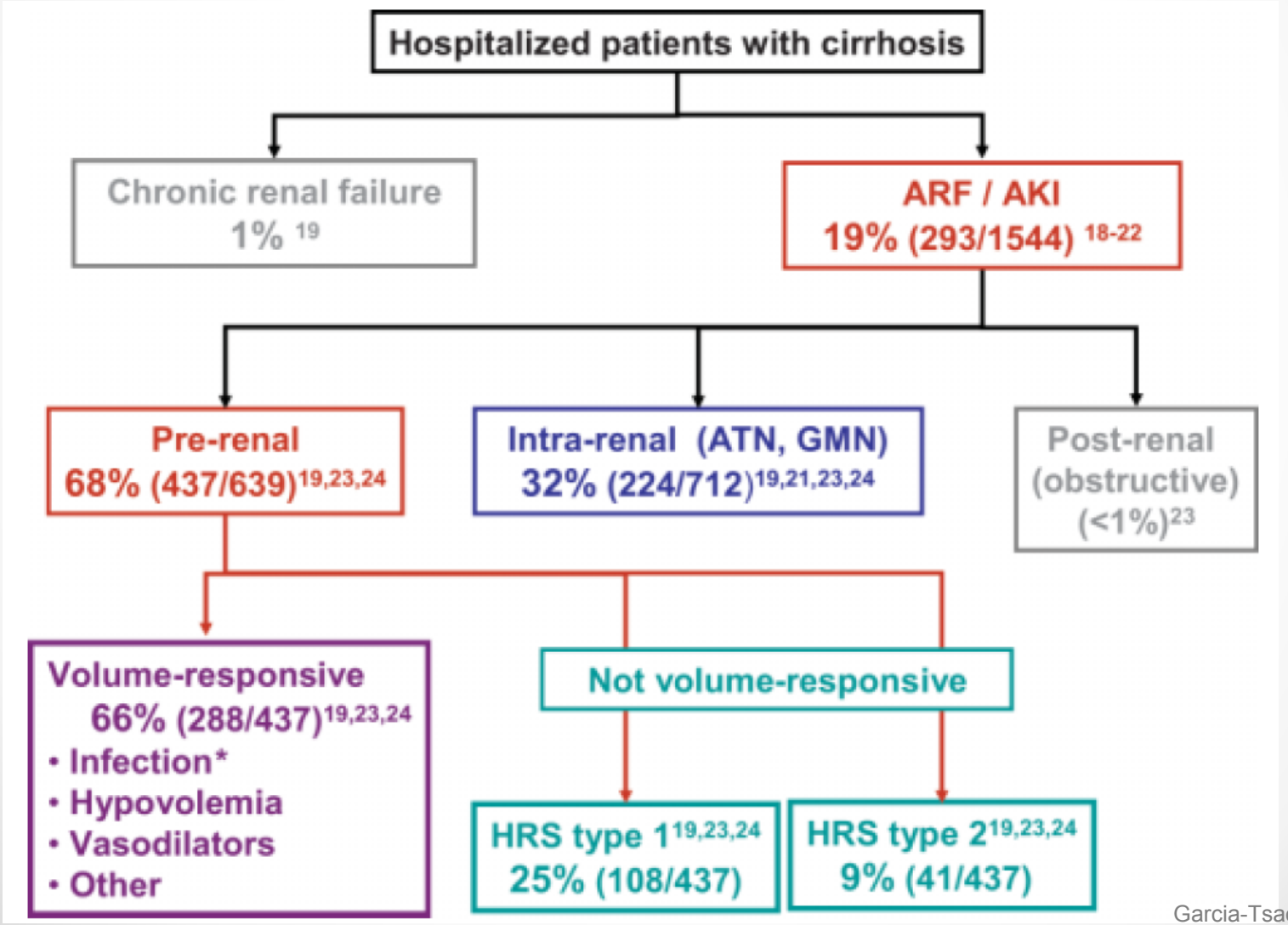
Insuffisance rénale et cirrhose

- ✓ La dysfonction rénale est un facteur pronostic majeur dans la cirrhose (MELD score)
- ✓ Insuffisance rénale survient chez 75% des cirrhotiques durant l'évolution de la maladie hépatique
- ✓ Certaines atteintes rénales sont liées spécifiquement à la maladie hépatique:

  glomérulonéphrite sur HBV, HCV, cryoglobuline, IgA, SHR type 2

Gines P. NEJM 2009
Hampel H. Am J Gasto 2001
Eckardt K. Int Care Med 1999

Insuffisance rénale aigue



Garcia-Tsao: Hepatology 2008

Définition SHR

New diagnostic hepatorenal syndrome criteria in cirrhosis

- Cirrhosis with ascites.
- Serum creatinine >133 μmol/l (1.5 mg/dl).
- No improvement of serum creatinine (decrease to a level of ⩽133 μmol/l) after at least 2 days with diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day.
- Absence of shock.
- No current or recent treatment with nephrotoxic drugs.
- Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhaematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasonography.

Pathophysiologie du SHR

The New England
Journal of Medicine

Copyright, 1969, by the Massachusetts Medical Society

Volume 280 JUNE 19, 1969 Number 25

TRANSPLANTATION OF CADAVERIC KIDNEYS FROM PATIENTS WITH HEPATORENAL SYNDROME*

Evidence for the Functional Nature of Renal Failure in Advanced Liver Disease

MARCELO H. KOPPEL, M.D., JACK W. COBURN, M.D., MATLOCK M. MIMS, M.D.,
HOWARD GOLDSTEIN, M.D., JAMES D. BOYLE, M.D., AND MILTON E. RUBINI, M.D.

Abstract A kidney from each of five patients and both kidneys from a sixth patient dying with the hepatorenal syndrome (severe hepatic failure, oliguria, azotemia, hyponatremia and a urinary sodium of less than 5 mEq per day) were transplanted into seven patients with end-stage kidney disease whose liver function was normal. Diuresis and improvement of renal function occurred in all but one recipient. Because of postoperative complications, two kidneys were removed after diuresis had occurred. Four transplanted kidneys achieved stable function for six months or longer, with creatinine clearances of 25, 42, 50 and 52 ml per minute. The hepatorenal syndrome is functional and potentially reversible.

The New England
Journal of Medicine

©Copyright, 1973, by the Massachusetts Medical Society

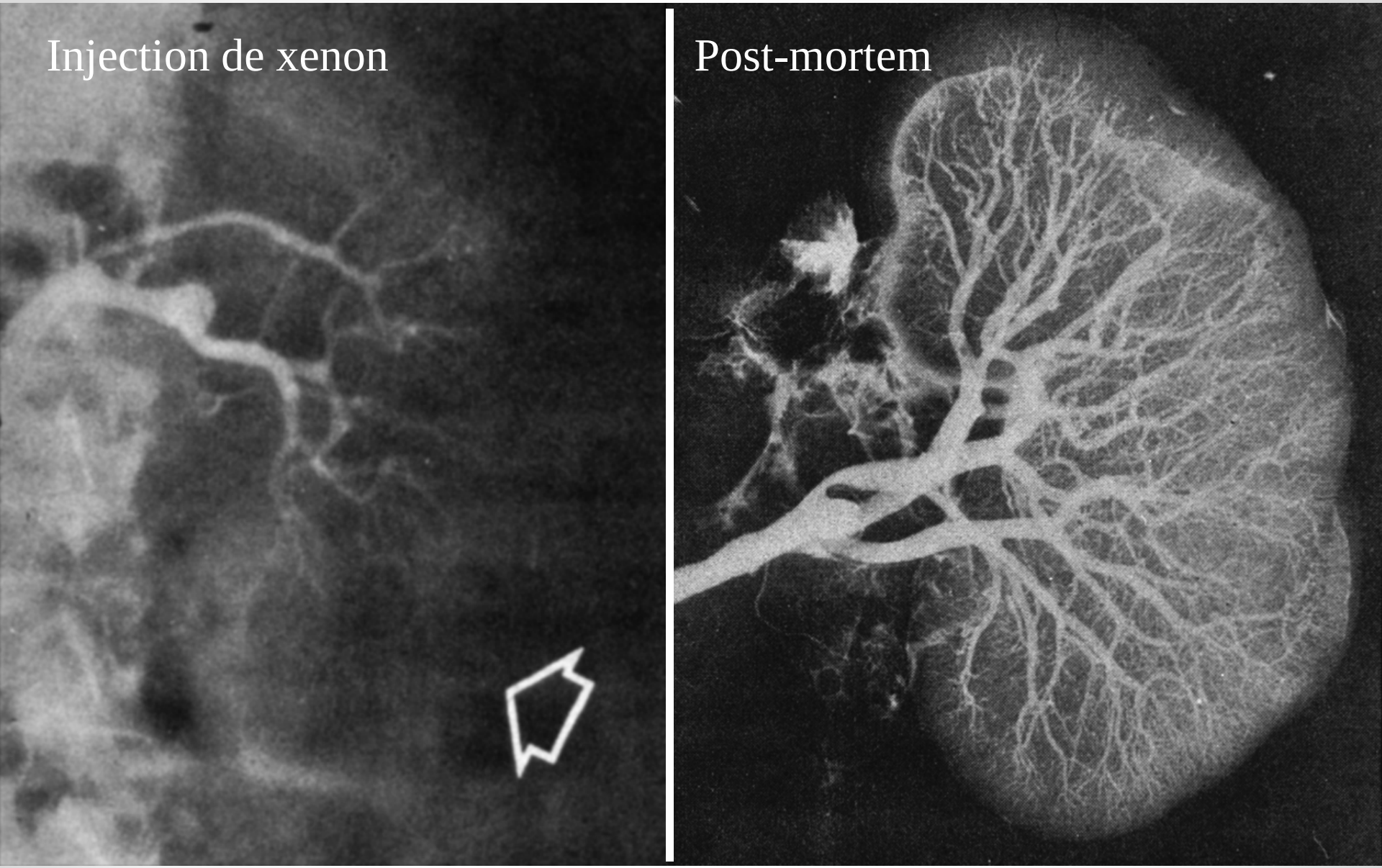
Volume 289 NOVEMBER 29, 1973 Number 22

RECOVERY FROM "HEPATORENAL SYNDROME" AFTER ORTHOTOPIC LIVER TRANSPLANTATION

SHUNZABURO IWATSUKI, M.D., MORDECAI M. POPOVTZER, M.D., JACQUES L. CORMAN, M.D., MAKOTO ISHIKAWA, M.D., CHARLES W. PUTNAM, M.D., FRED H. KATZ, M.D., AND THOMAS E. STARZL, M.D., PH.D.

Abstract Three patients with progressive renal failure and advanced hepatic insufficiency due to cirrhosis of the liver underwent orthotopic liver transplantation. All three patients had immediate improvement in hepatic function and within two weeks after liver replacement regained nearly normal kidney function. However, the renal recovery was delayed in each case, and its course was not uniform. Plasma renin activity was high, and renin substrate was low before transplantation in one case in which these measurements were obtained; both returned to normal soon after liver replacement. (N Engl J Med 289:1155-1159, 1973)

Atteinte rénale fonctionnelle et réversible

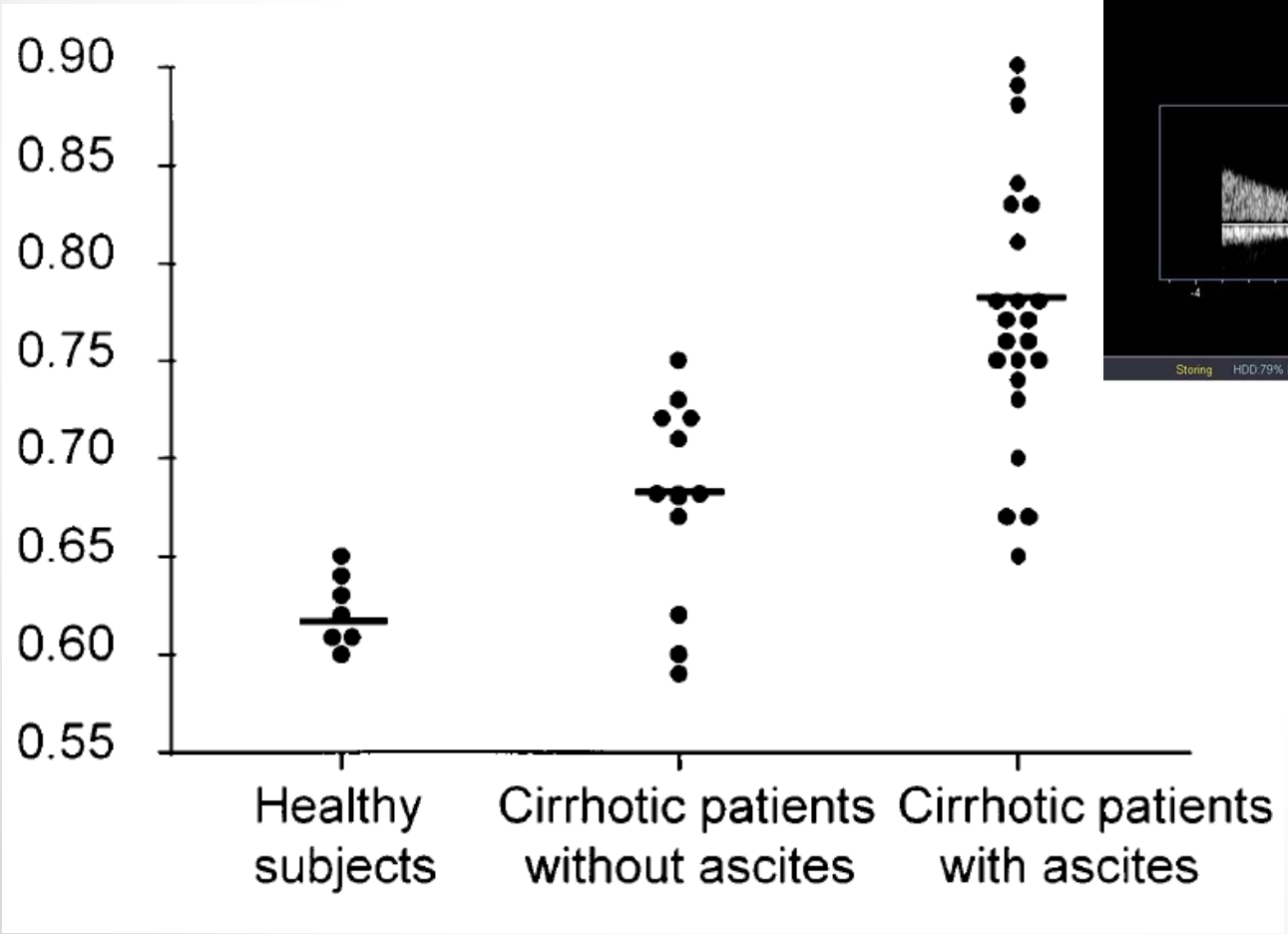


Vasoconstriction rénale

Epstein M et al Am J Med 1970;49:175-85

Vasoconstriction rénale

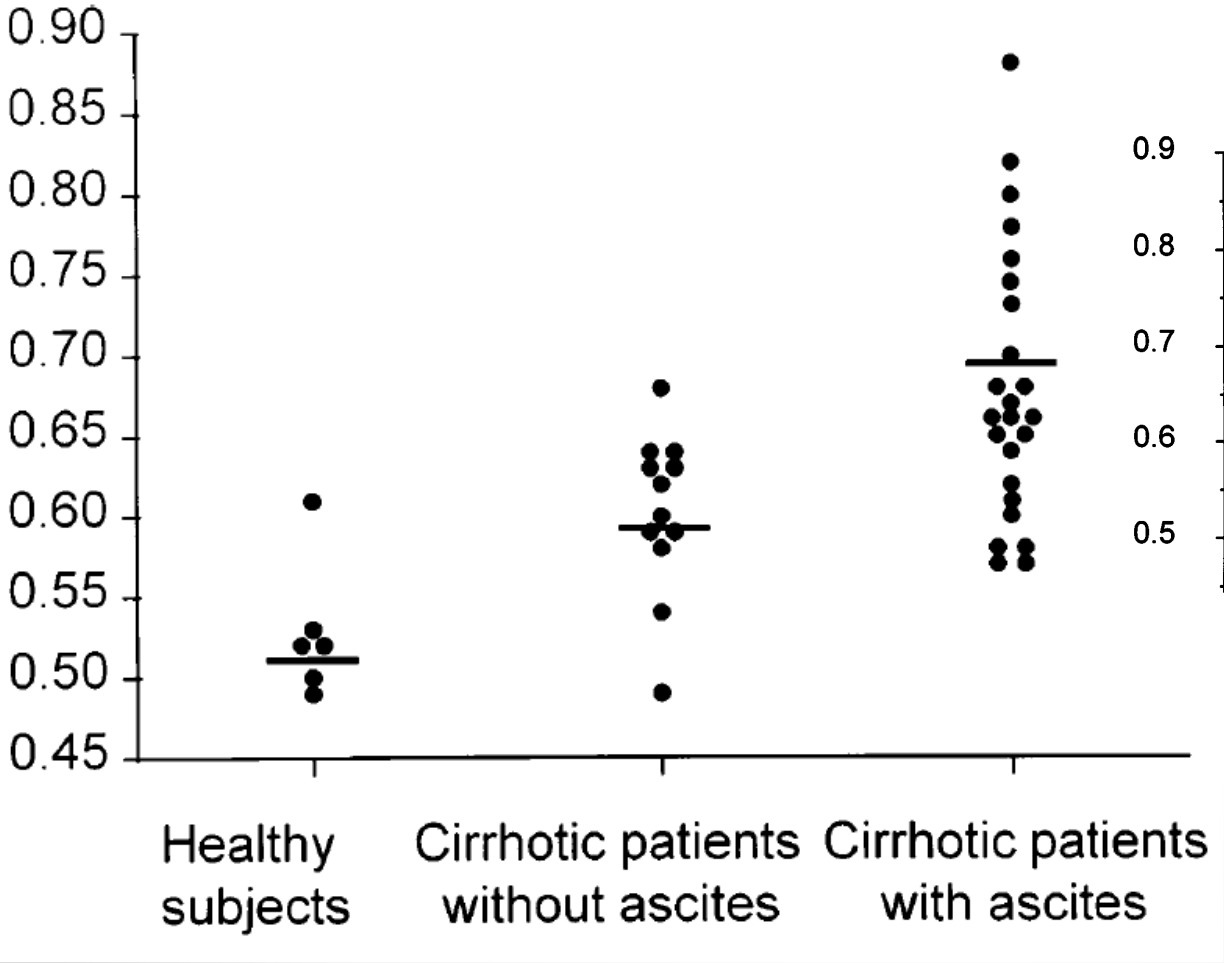
IR rénaux ↑ selon stade de la cirrhose



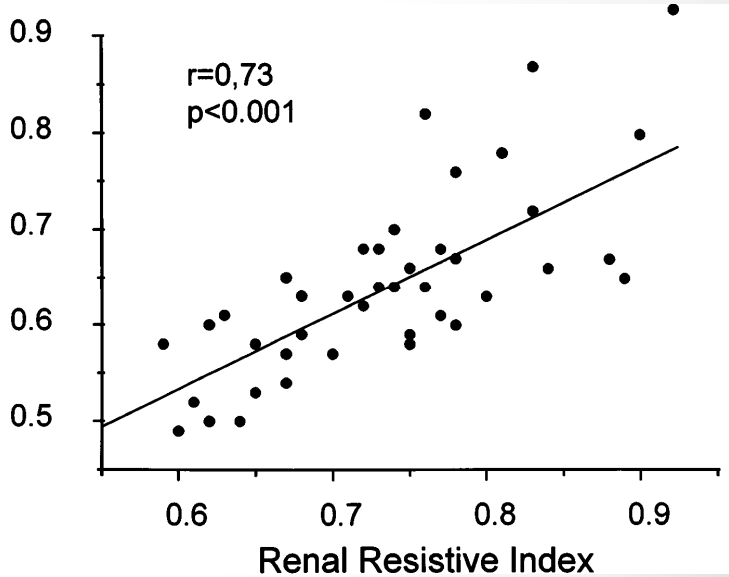
Guevara M et al Hepatology 1998;28:39-44

Vasoconstriction cérébrale

Index de résistance a. cérébrale moy ↑ selon stade de la cirrhose



Corrélé à IR rénal



Guevara M et al Hepatology 1998;28:39-44

SHR: atteinte multi-organique

Avec le SHR on note une défaillance multi-organique:

- ✓ le foie → insuffisance hépatique sévère
- ✓ le rein → insuffisance rénale aigüe sévère
- ✓ le cerveau → encéphalopathie
- ✓ le système vasculaire → hypotension artérielle
- ✓ le cœur → cardiomyopathie
- ✓ les surrénales → insuffisance surrénalienne?

Explication hémodynamique à tout cela?

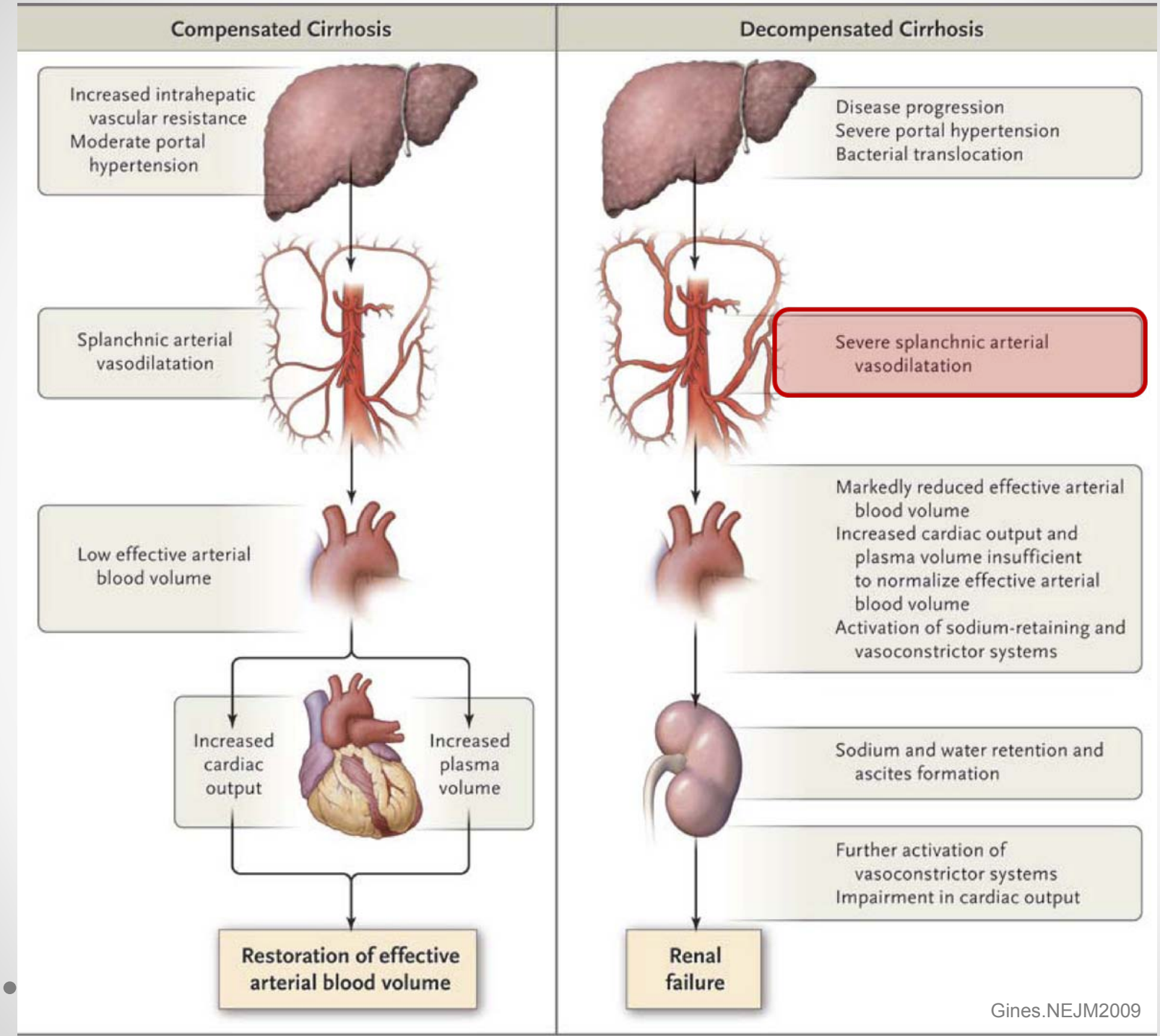
✓Modifications hémodynamiques

- ↑ résistance au flux veineux porte et hypertension portale

- Etat hyperdynamique:
  - Augmentation débit cardiaque
  - Baisse de la pression artérielle moyenne
  - Baisse de la résistance périphérique totale

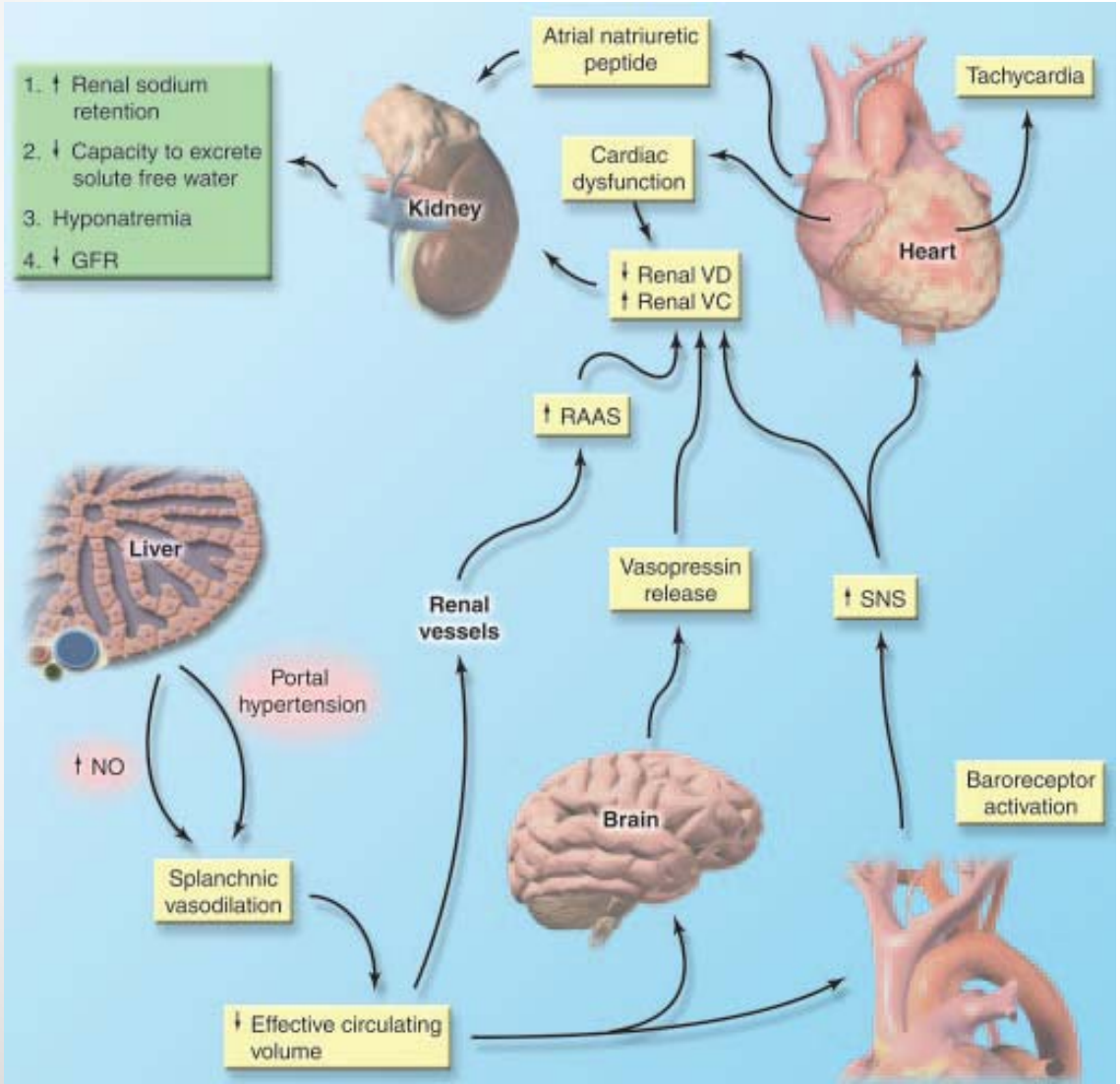
- Vasoconstriction dans les territoires cutanées, cérébraux, musculaires, foie, rein.

→ vasoconstriction systémique



Gines.NEJM2009

Vasodilatation splanchnique

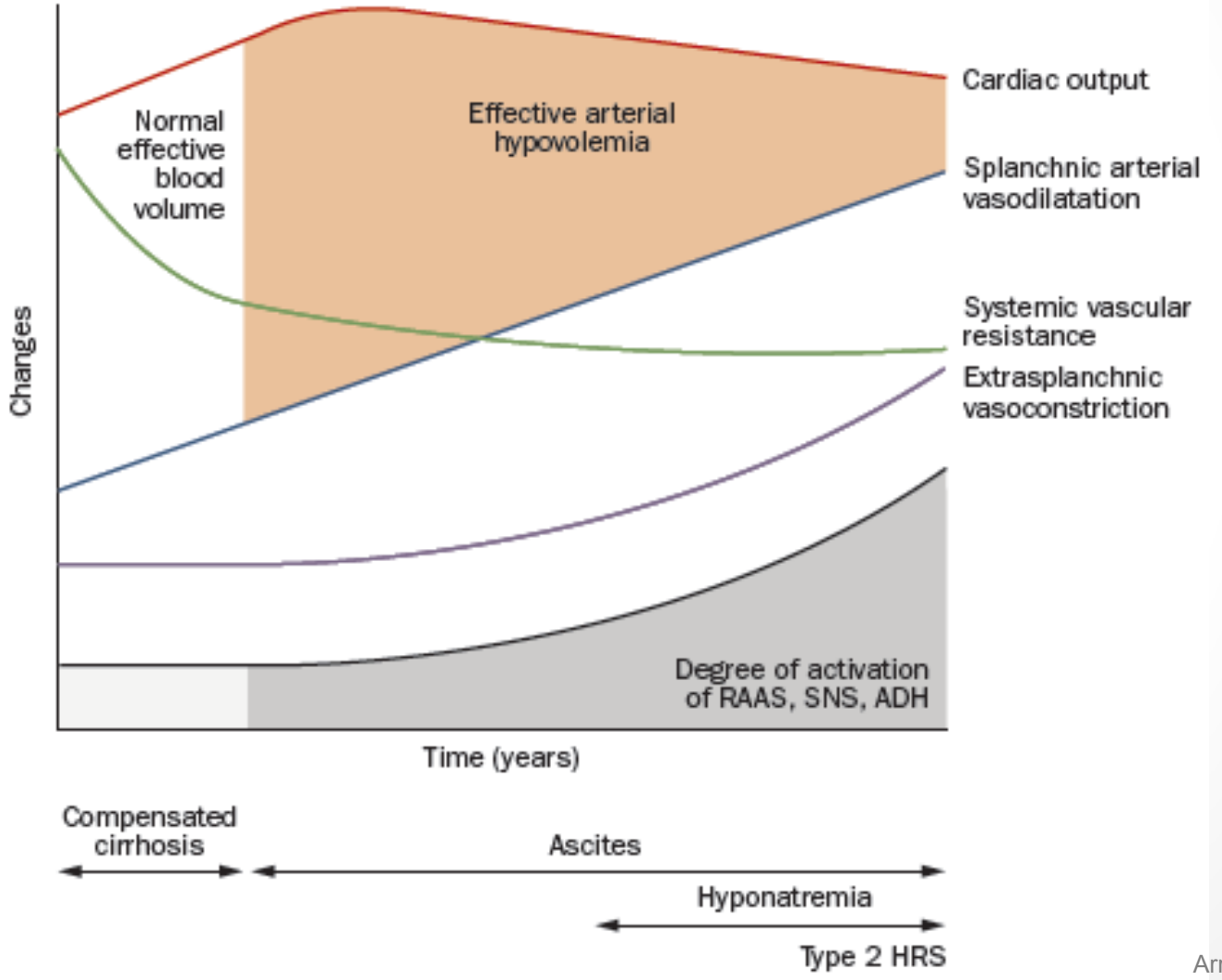


↓ volume circulant

Activation systèmes
- ✓RAA
- ✓ADH
- ✓SNS
- ✓ANP

Effets rénaux

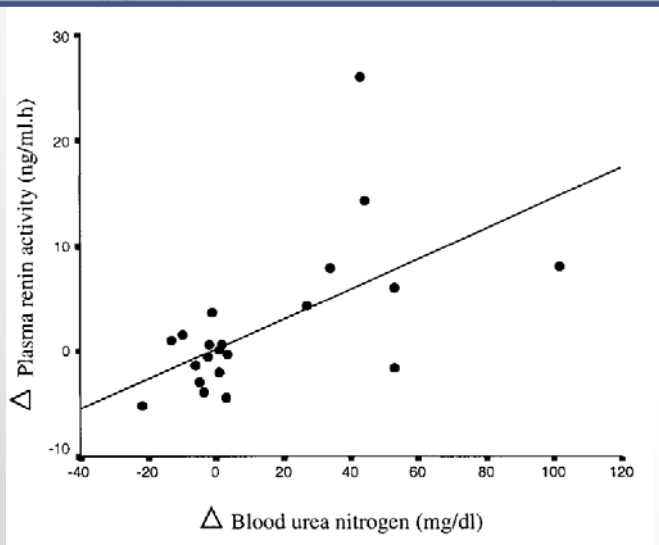
Vasodilatation splanchnique

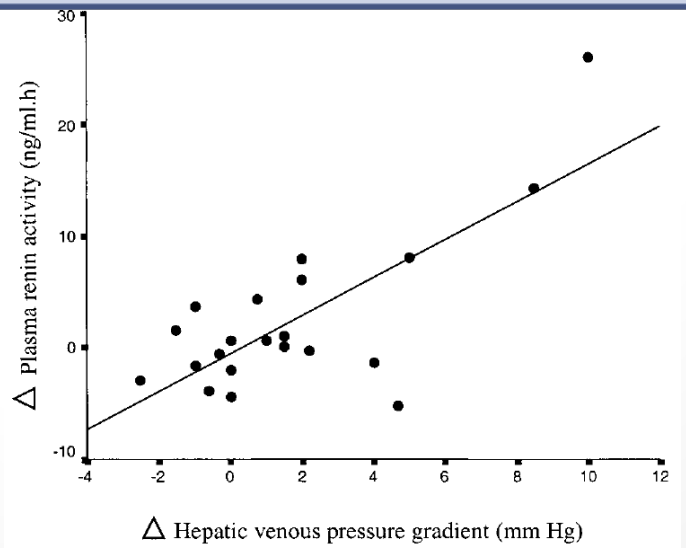


Arroyo. Nat rev nephrol2011

Activation rénine dans cirrhose avec IRA

	Renal Failure Group (n = 8)			Group Without Renal Failure (n = 15)		
	At Diagnosis of Infection	Following Resolution of Infection	P	At Diagnosis of Infection	Following Resolution of Infection	P
Hematocrit (%)	32.2 ± 2.7	31.1 ± 1.9	NS	30.0 ± 6.8	30.2 ± 3.7	NS
Serum bilirubin (mg/dL)	5.0 ± 5.0	6.6 ± 7.8	NS	3.6 ± 3.0	3.1 ± 3.2	NS
Serum albumin (g/L)	25.0 ± 2.0	22.4 ± 2.4	NS	27.3 ± 7.0	28.4 ± 6.5	NS
Prothrombin time (%)	57 ± 20	43 ± 14*	<.02	57 ± 16	67 ± 19	NS
Child-Pugh score (points)	10.2 ± 1.2	11.7 ± 1.6*	<.01	9.5 ± 1.5	9.0 ± 1.5	NS
BUN (mg/dL)	37.4 ± 9.5†	81.2 ± 25.2*	<.02	19.0 ± 9.0	15.6 ± 5.5	NS
Serum creatinine (mg/dL)	1.3 ± 0.6	2.5 ± 0.4*	<.02	1.0 ± 0.3	0.9 ± 0.2	NS
Serum sodium (mmol/L)	132 ± 3.2	127 ± 2.2*	NS	135 ± 4.0	136 ± 3.9	NS
PRA (ng/mL · h)	18.4 ± 11.2†	28.3 ± 12.4*	<.02	3.9 ± 3.6	2.8 ± 3.6	NS
Plasma ALDO (ng/dL)	149.5 ± 106.8†	251.7 ± 156.7*	<.02	27.6 ± 10.9	20.0 ± 19.5	NS
Plasma NE (pg/mL)	797.3 ± 226.6†	1290.5 ± 415.3*	<.02	315.7 ± 172.8	317.0 ± 195.3	NS





Ruiz del Arbol. Hepatology 2005

SHR: déséquilibre vasodilatation-vasoconstriction ?

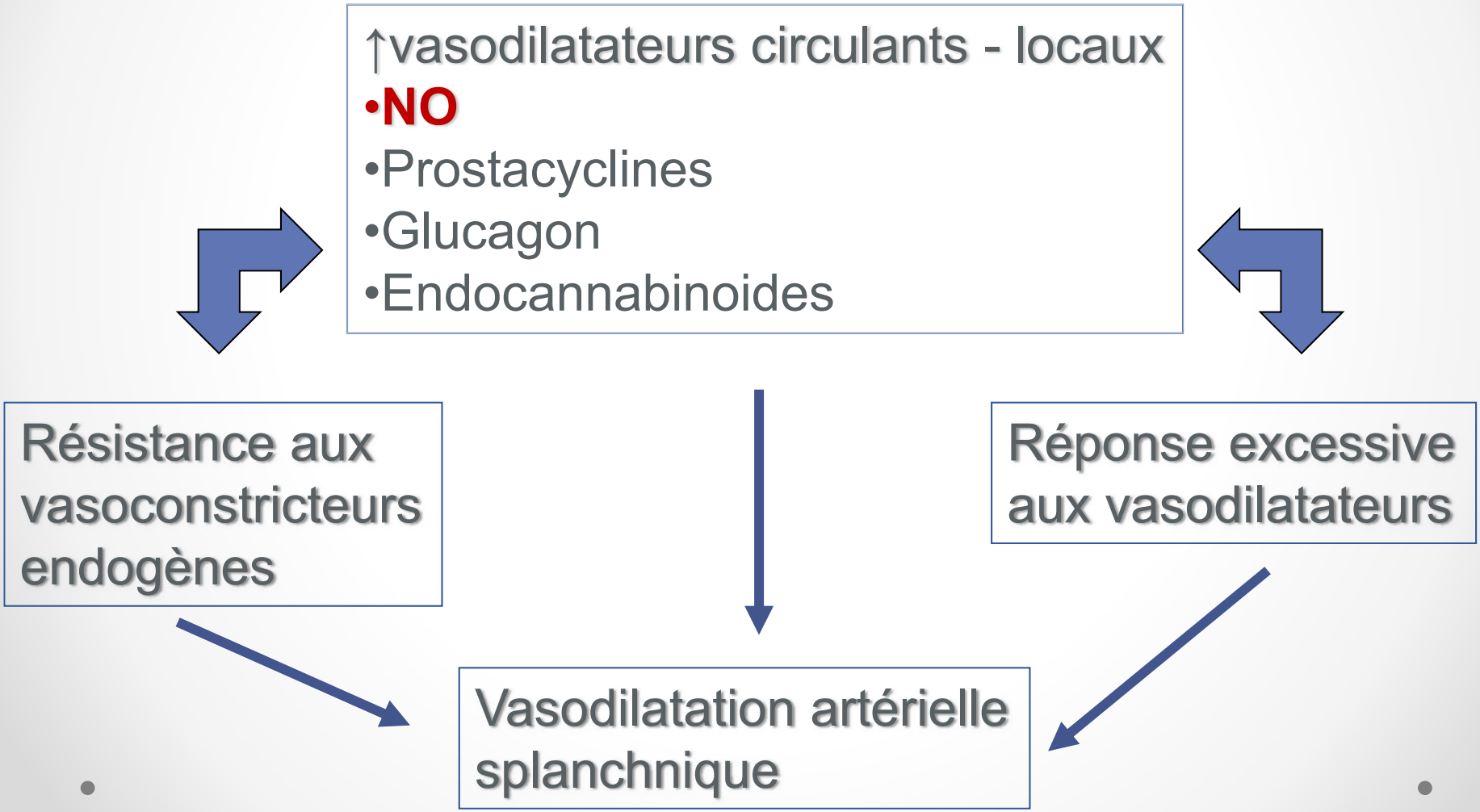
Vasoconstricteurs

- ✓ RAA
- ✓ SNS
- ✓ AVP
- ✓ Endothélines
- ✓ Adénosine

Vasodilatateurs

- ✓ Prostaglandines
- ✓ Facteurs natriurétiques
- ✓ NO
- ✓ Glucagon
- ✓ CO
- ✓ Système kinine-kallikréine
- ✓ Endocannabinoïdes

Vasodilatation splanchnique: facteurs impliqués



Rôle du nitride oxyde (NO):

Evidences expérimentales

Reversal of impaired pressor response to vasoconstrictors in isolated aortic rings or splanchnic vascular preparations by inhibition of nitric oxide synthase[33-36]

Enhanced vasodilator response to nitric oxide–dependent vasodilators[37]

Increased pressor effect of systemic inhibition of nitric oxide synthase[38-41]

Increased nitric oxide synthesis in vascular tissue[42-46]

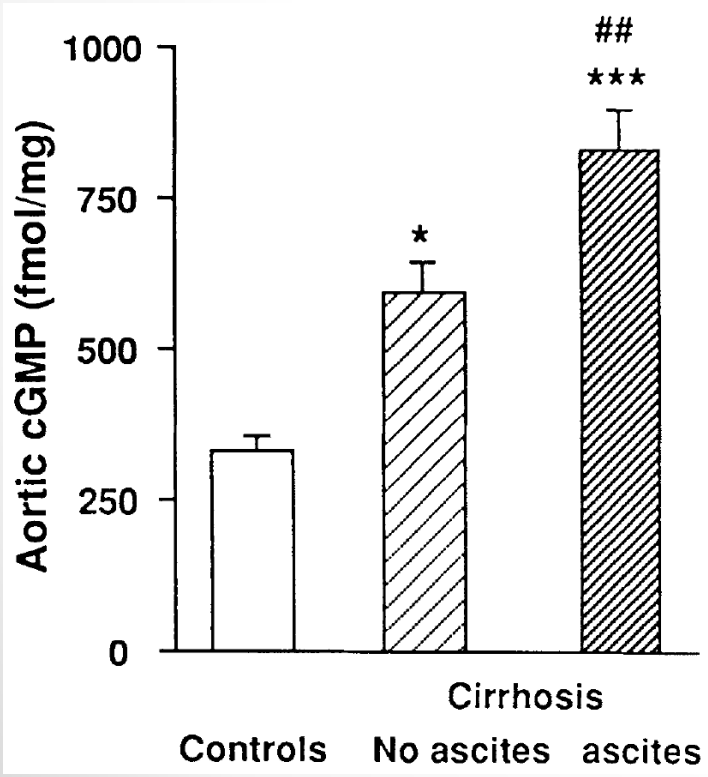
Normalization of hyperdynamic circulation by long-term inhibition of nitric oxide synthase[47]

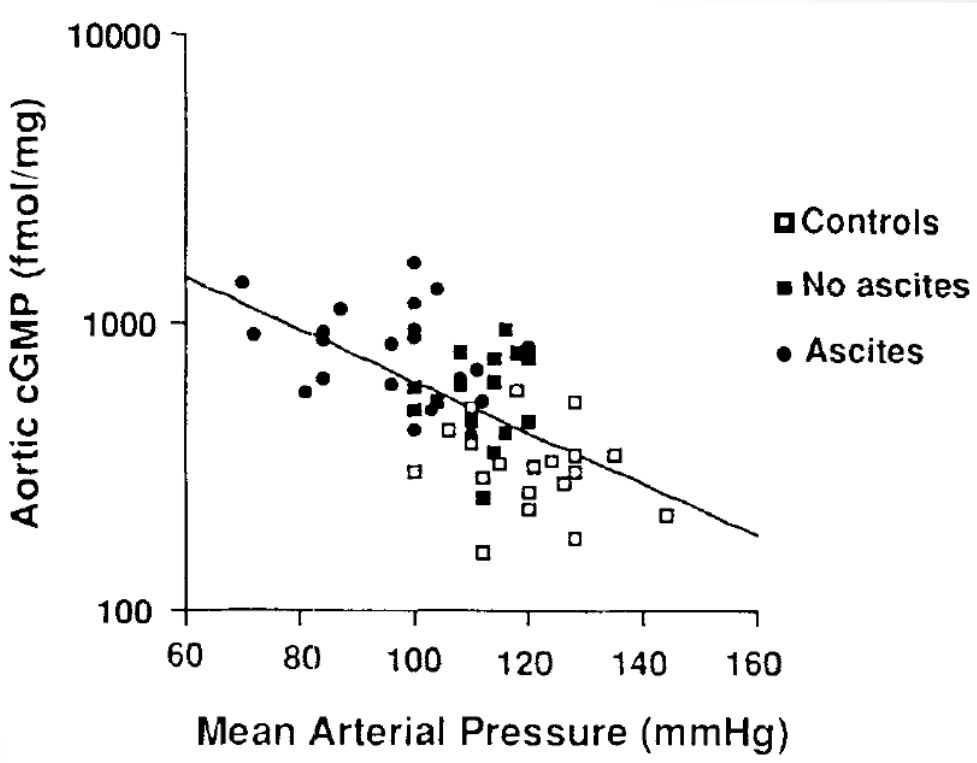
Increased expression of nitric oxide synthase in vascular tissue[45,46,48,49]

Martin PY. NEJM 1998

NO et vasodilatation systémique

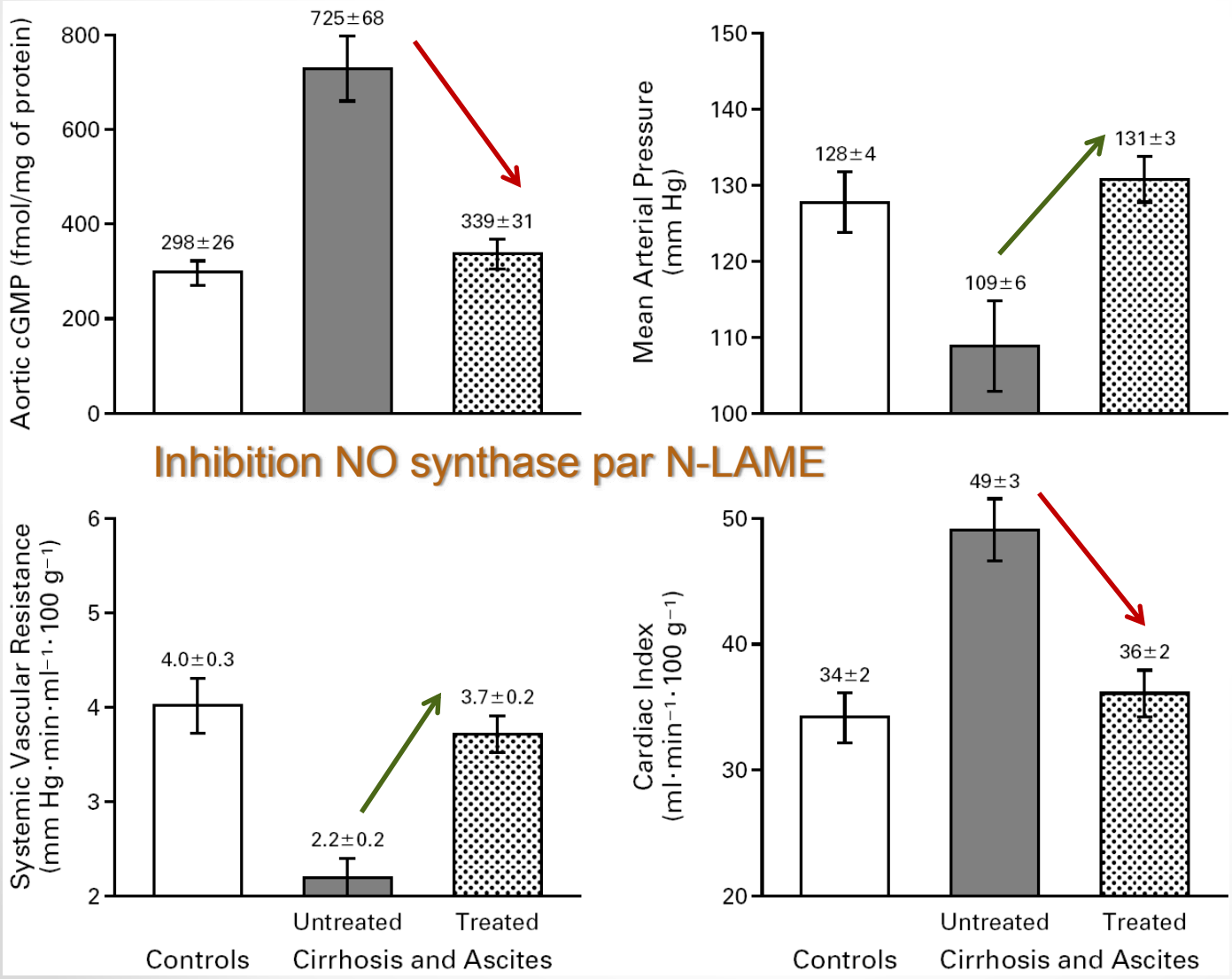
Chez le rat: ↑ cGMP (2ème messager NO) dans cirrhose
corrélation à PAM et vasodilatation systémique





Niederberger. Hepatology 1995

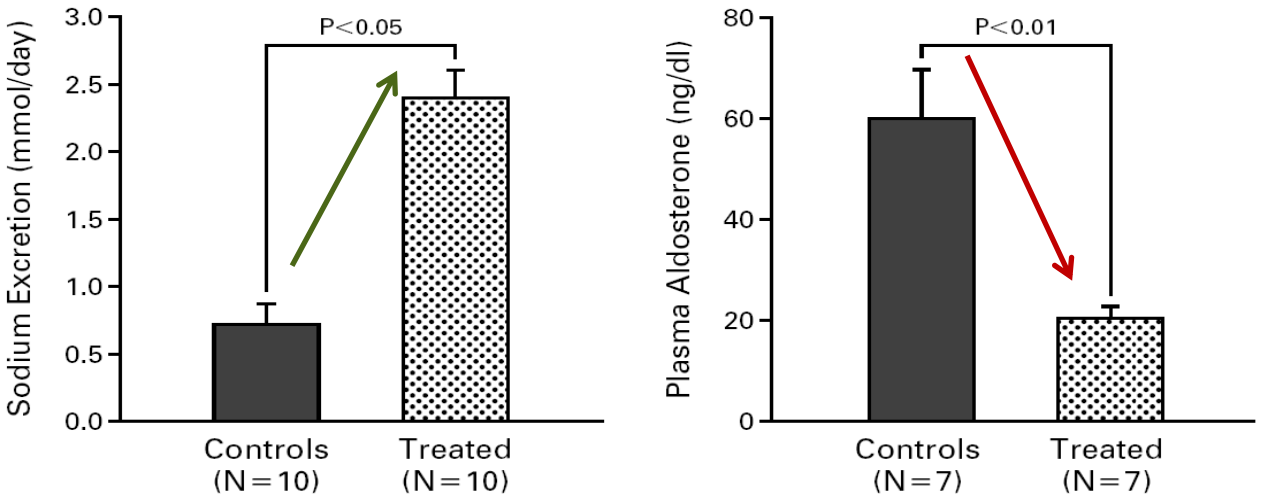
Inhibition NO réverse vasodilatation



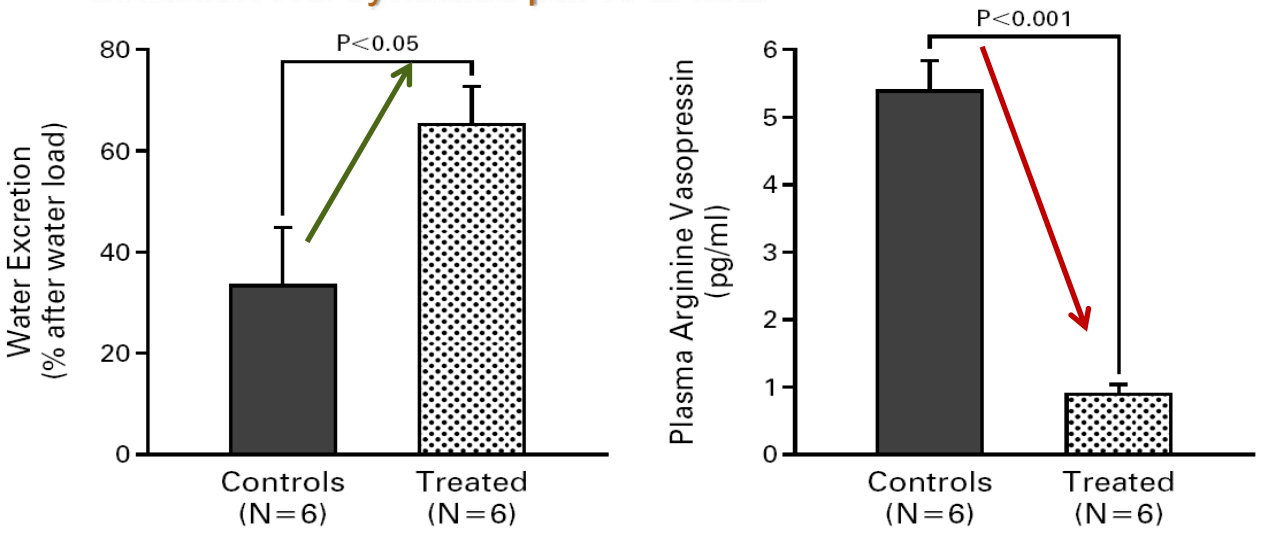
↑PAM
↑R vasculaires syst
↓cGMP
↓ Index cardiaque

Niederberger. Gastroenterology

Inhibition NO: effet sur le sel et l'eau



Inhibition NO synthase par N-LAME



↑ Excrétion Na_u
↑ Excrétion H_2O
↓ Aldostérone
↓ ADH

Martin PY. J Clin Invest1998

Evidence chez l'Homme

Correction of arterial hyporesponsiveness to vasoconstrictors by inhibition of nitric oxide synthase[65]

Enhanced vasodilative response to a nitric oxide–dependent vasodilator[66]*

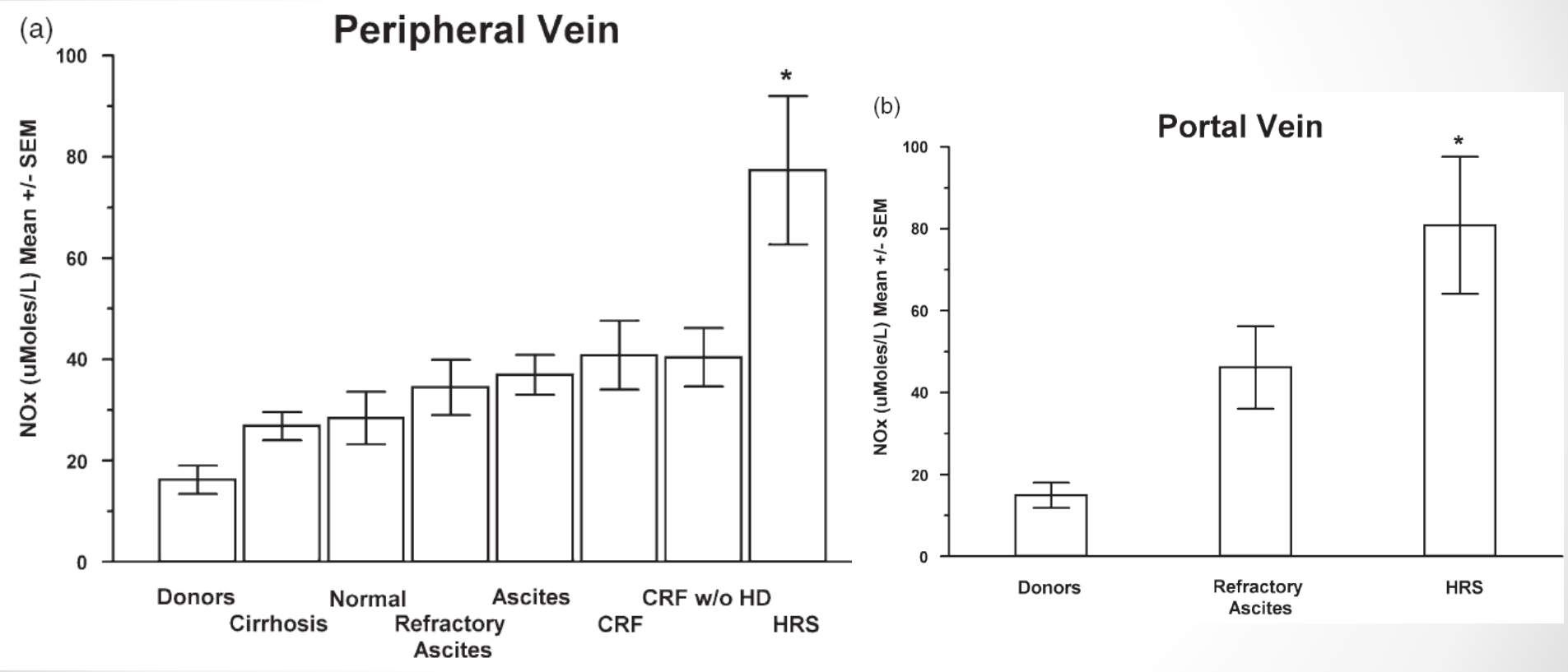
Increased plasma concentrations of nitric oxide and its metabolites[66-68]*

Increased nitric oxide in exhaled air[69,70]*

Increased nitric oxide synthase activity in polymorphonuclear cells and monocytes[71,72]

Martin PY. NEJM 1998

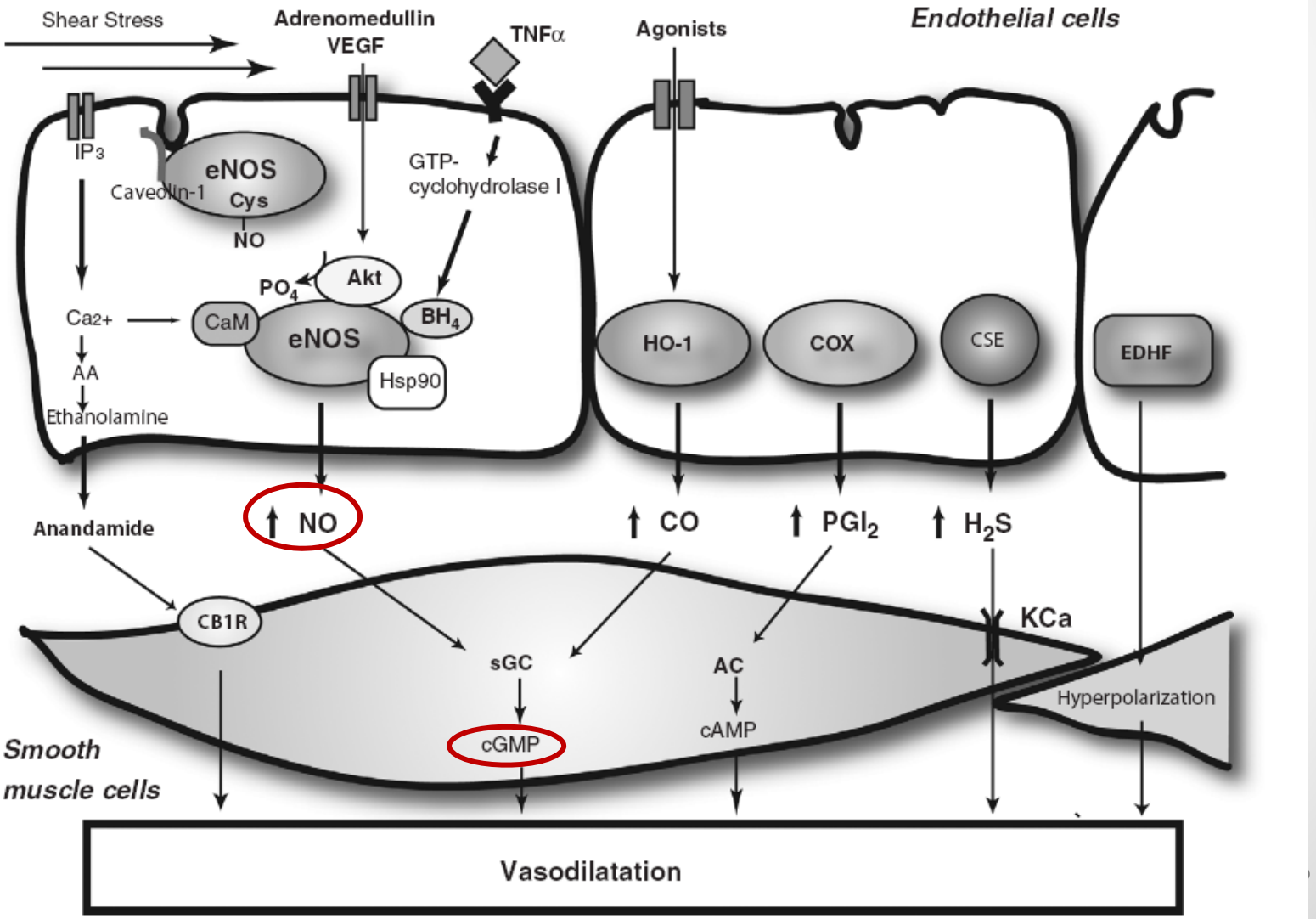
↑ NO plasmatique chez l'homme

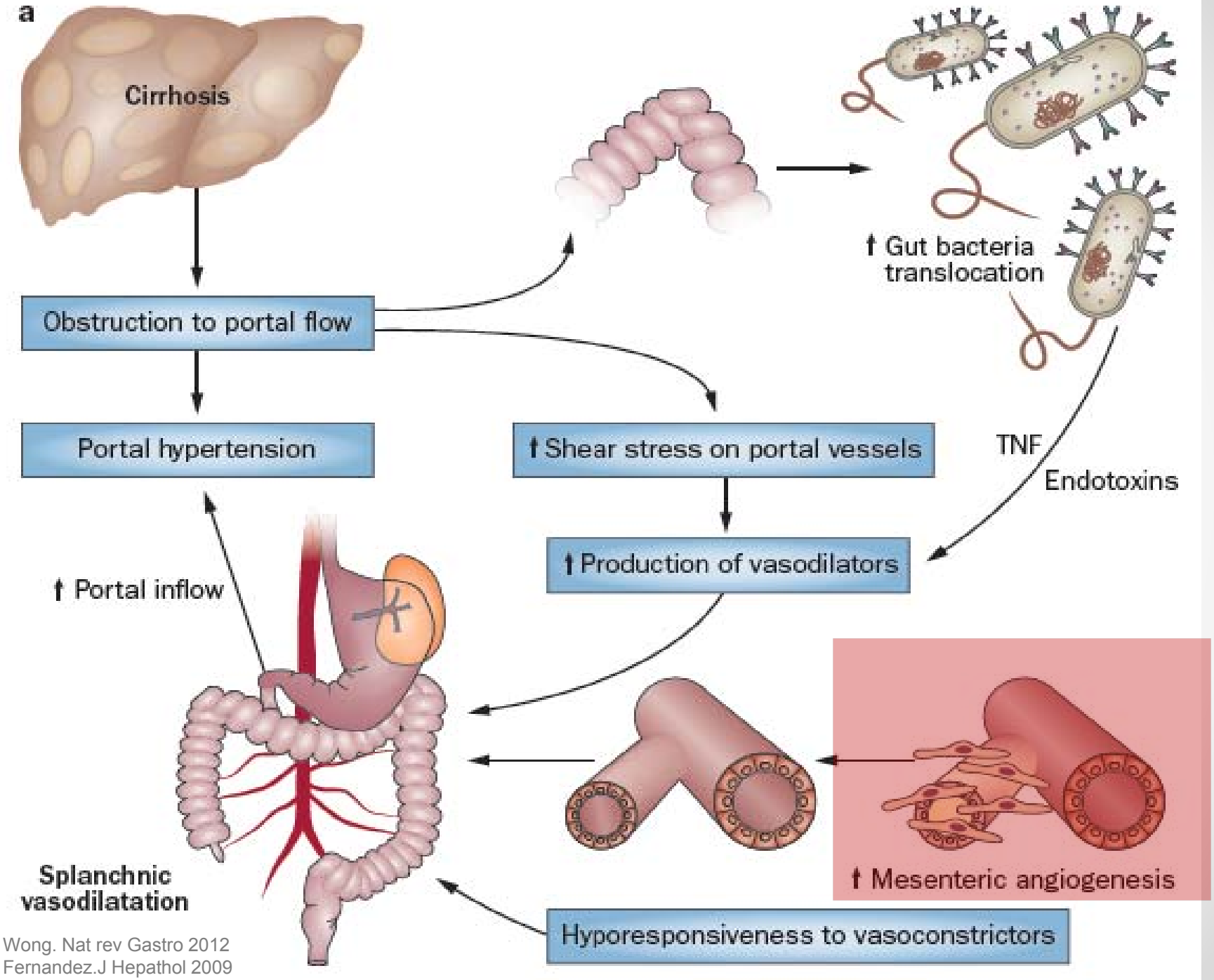


Increased plasma nitric oxide, L-arginine, and arginase-1 in cirrhotic patients with progressive renal dysfunction

Battista. J Hepatol 1997
Kayali. J Gastroenterol Hepatol 2007

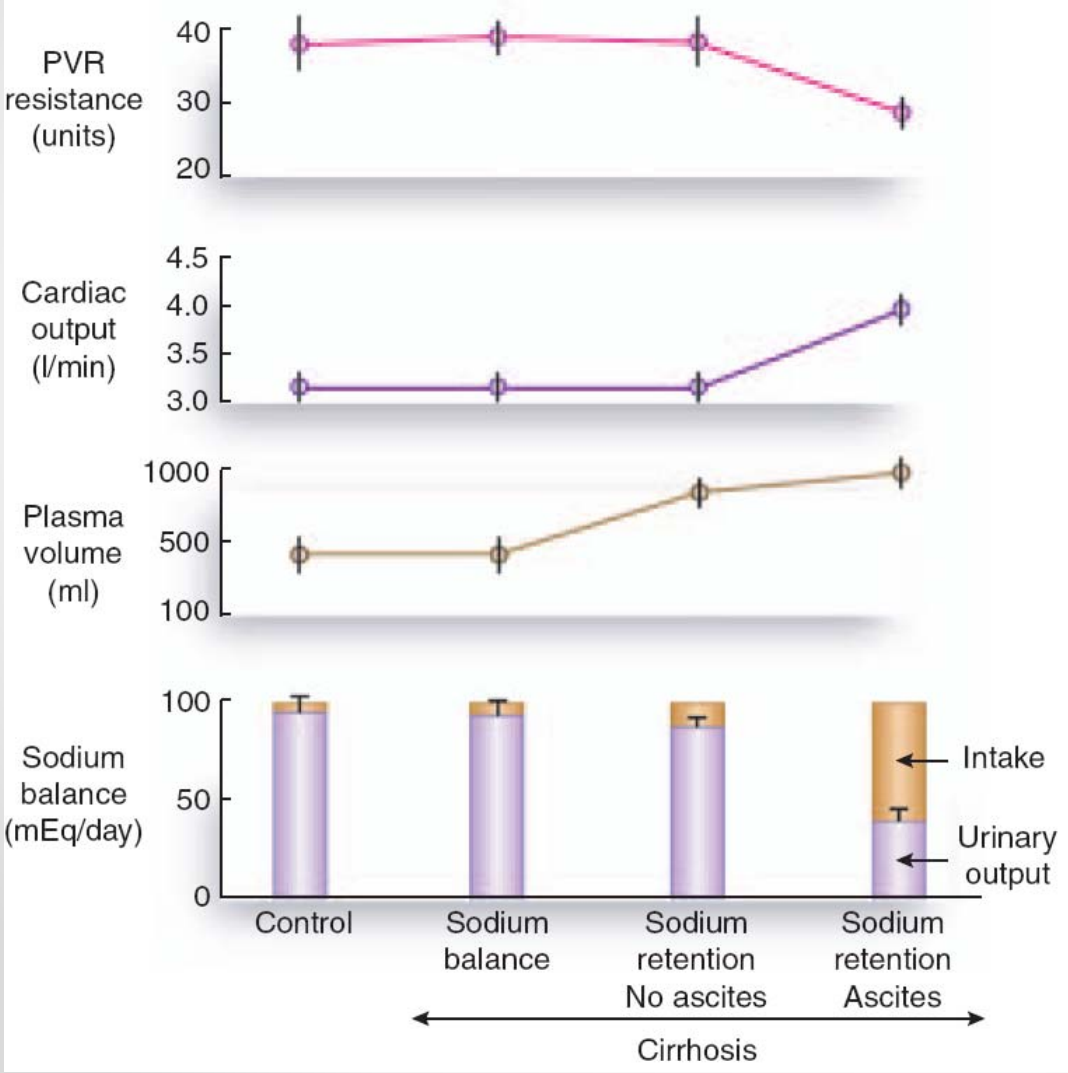
Mécanismes vasodilatation





Wong. Nat rev Gastro 2012
Fernandez.J Hepathol 2009

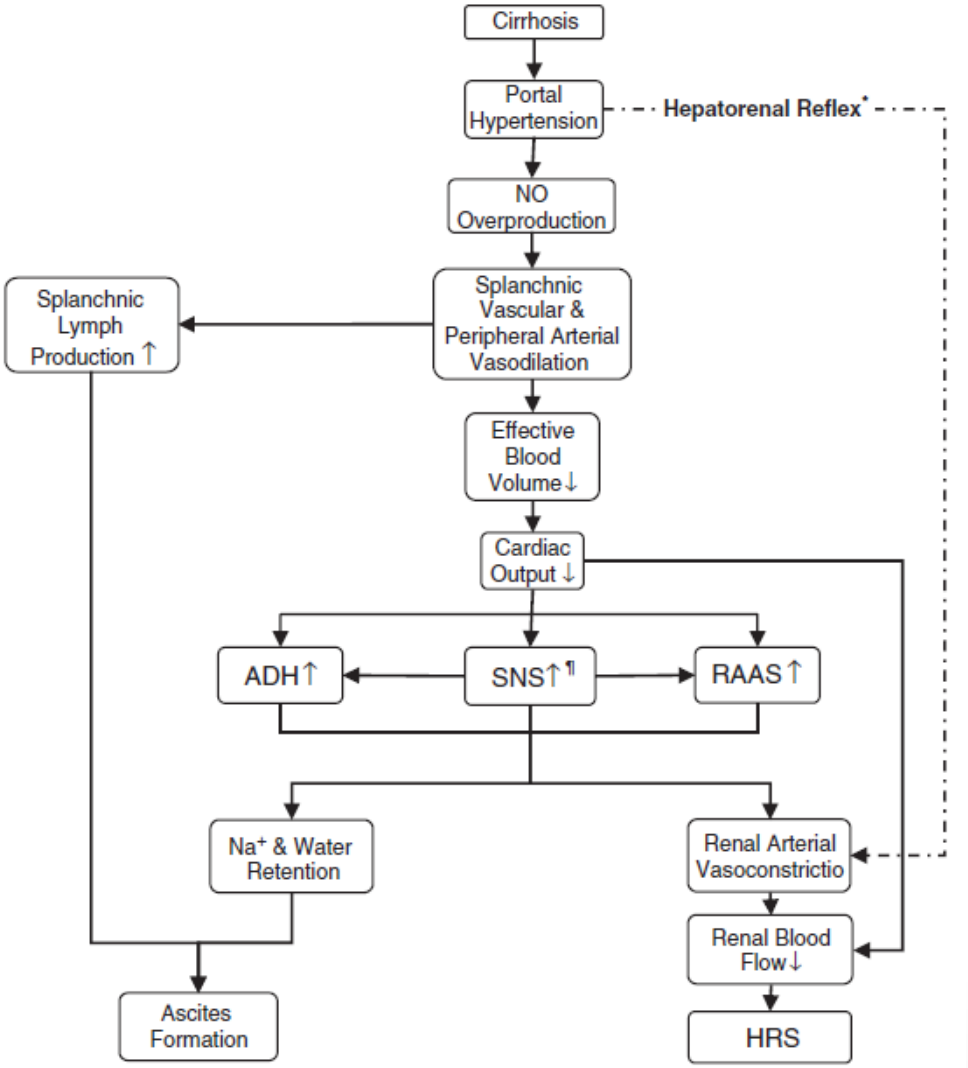
Vasodilatation et rétention hydrosodée: cause ou conséquence?



- Pas de démonstration définitive que la vasodilation précède clairement la rétention sodée
- Méthodologie très imprécise car basée sur l'évaluation des réponses efférentes.
- Pas de bonnes caractérisations afférences (type, molécule, etc.)
- L'administration de volume entraine une vasodilatation.
- Les états de rétention hydrosodée sont en moyenne des états avec une vasodilatation systémique.

Levy M J Lab Clin Med 1978
Oliver JA Kidney Int 2010

Réflexe hépato-rénal?

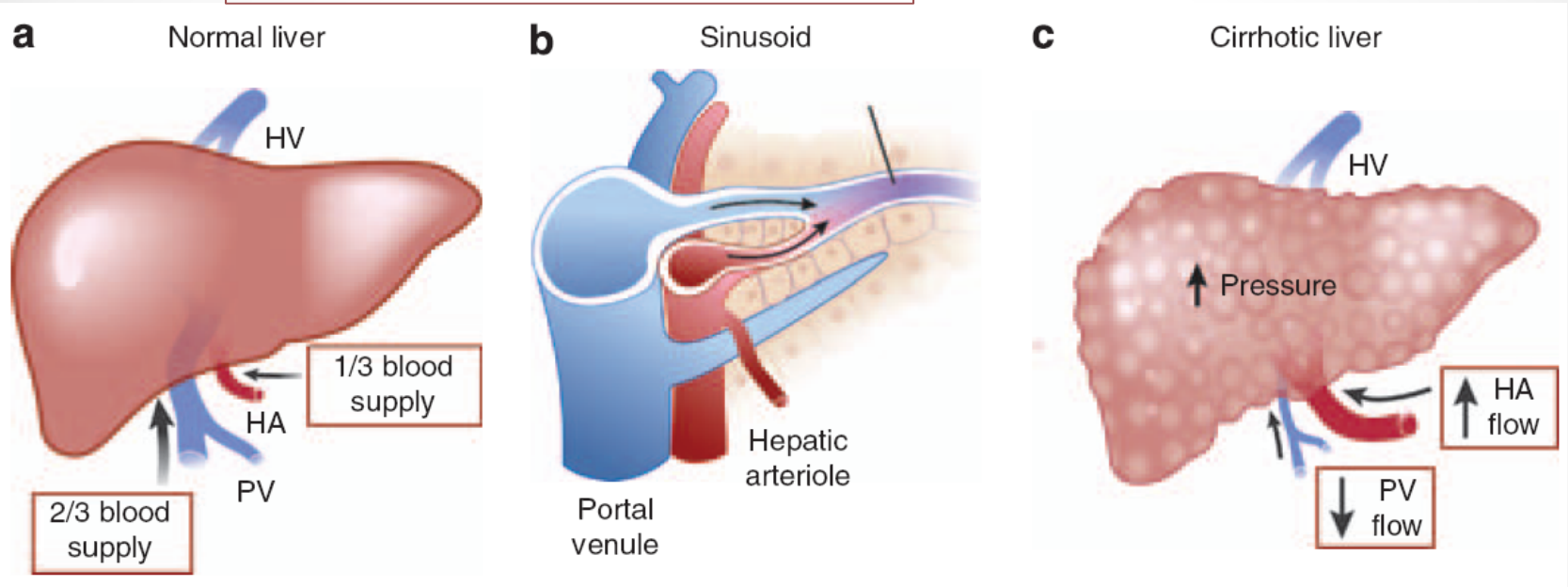


- Barorécepteurs hépatiques régulent activité SNS rénal.
- Œdème hépatique ↓ flux rénal *mais* inhibé si dénervation foie/rein.
- Charge sodée ↑ENa et ↓ activité SNS rénal *mais* inhibé si dénervation foie.
- ↑ P hépatique avec ou sans cirrhose→rétention hydrosodée.
- Animaux cirrhotiques dénervés développement oedèmes plus lentement
- Transplantés hépatiques sans anomalies rénales développent moins d'oedèmes

Oliver JA Kidney Int 2010

Nature et localisation réflexe hépato-rénal?

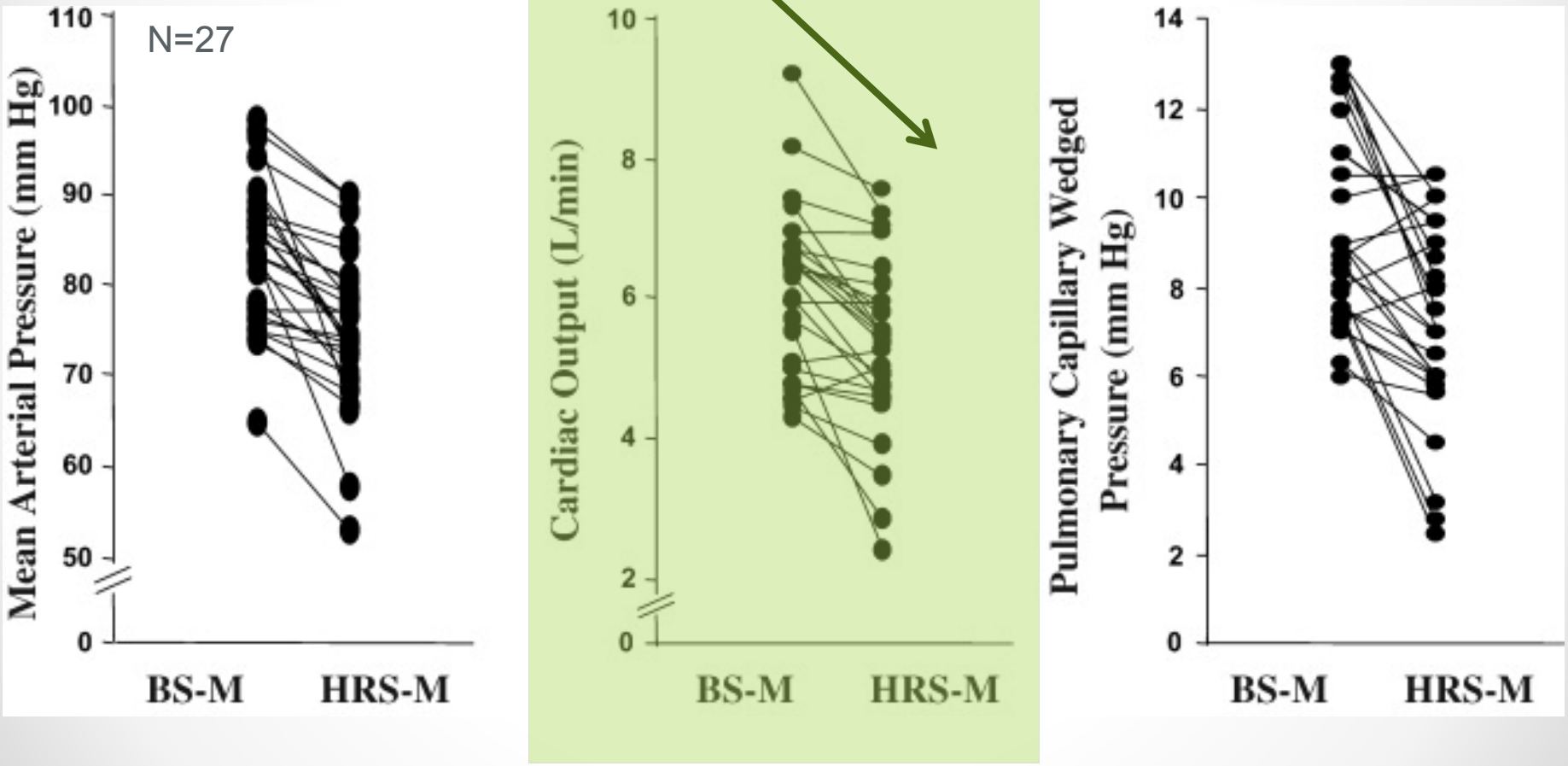
2 circulations (porte PV et artérielle HA) avec P différentes



- Nature moléculaire inconnue
- Senseurs afférents probablement au niveau de circulation sinusoidale ou postsinusoidale. La rétention hydrosodée corrèle avec ↑ de ces pressions dans la cirrhose.
- A. hépatique est capable d'auto-régulation dans sa réponse volume/pression: vasodilatation lors de chute de P pour maintenir flux.
- Vasodilatation a. hépatique si chute de flux portal→ senseur a. hépatique?

Oliver JA Kidney Int 2010

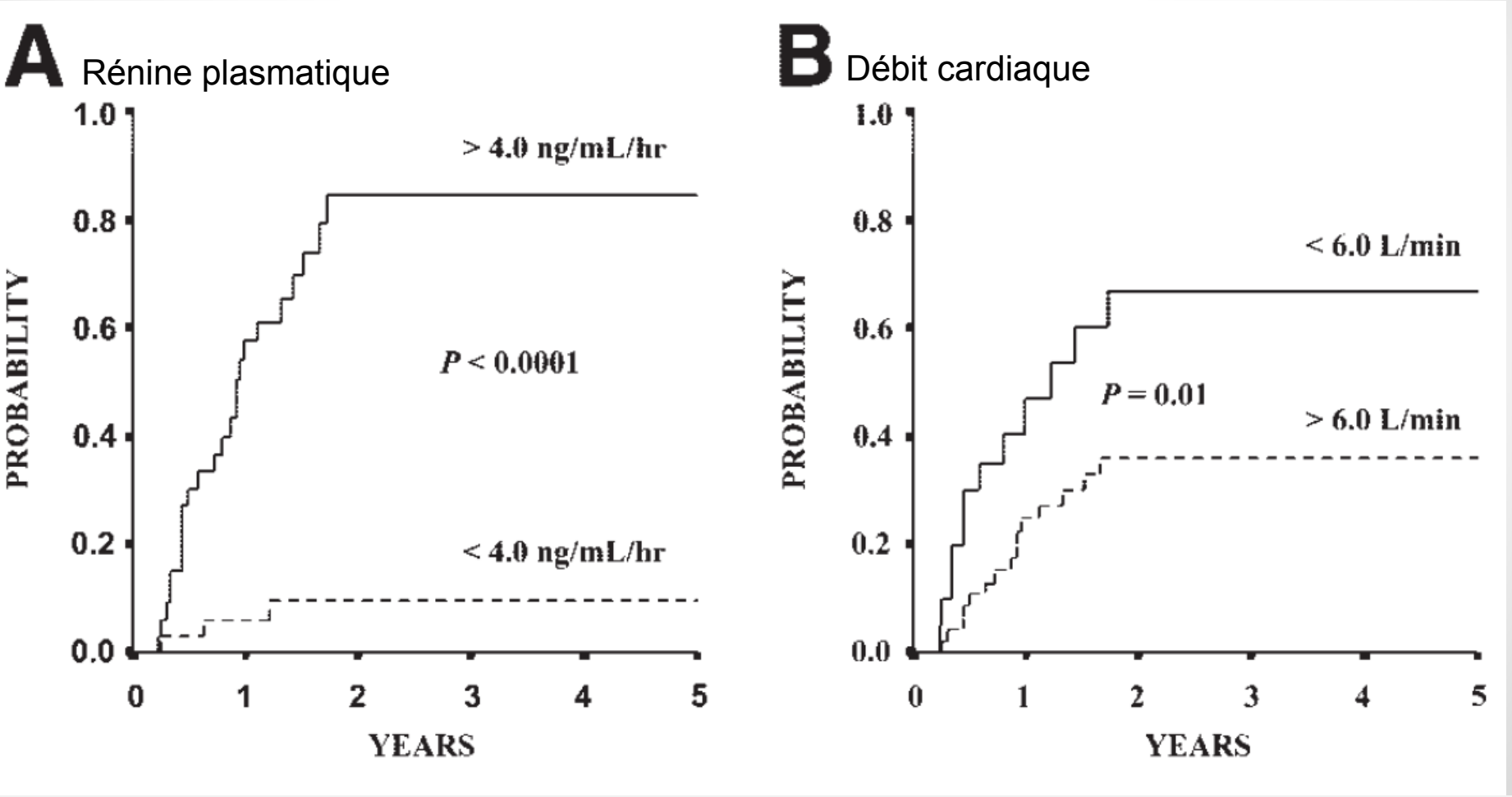
Dysfonction cardiaque dans cirrhose



Chute du Débit cardiaque lors de développement SHR

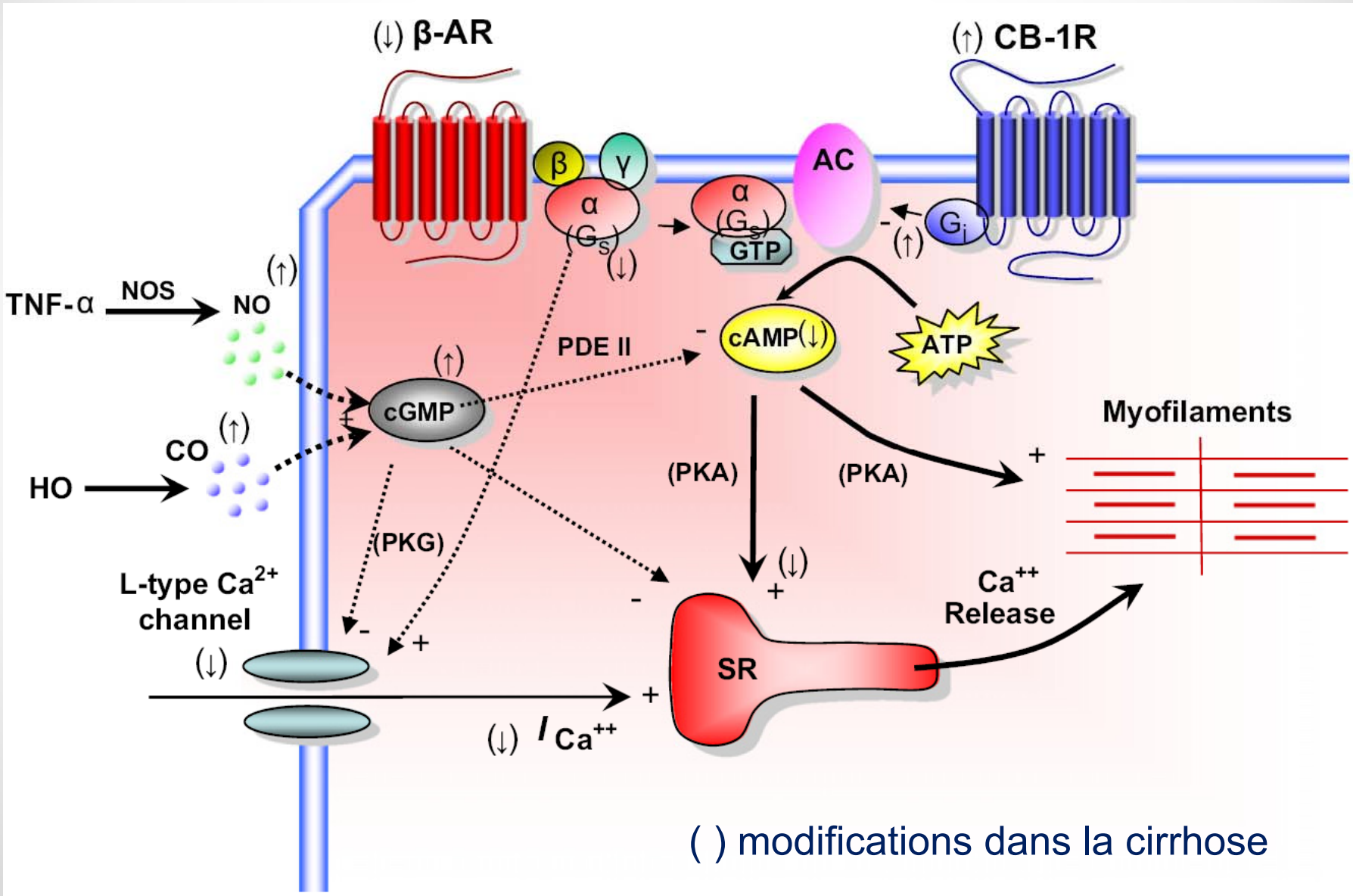
Ruiz del Arbol. Hepathology 2005

Développement SHR selon taux de rénine et débit cardiaque



Taux rénine + élevé mais débit cardiaque + bas chez patient développant SHR

Régulation contractilité cardiomyocyte



( ) modifications dans la cirrhose

Lee RF. Best Pract Gastroent hepatol 2007

Mécanismes potentiels dysfonction cardiaque

Changes in receptor affinity
- Down regulation and desensitisation of myocardial β-adrenergic receptors
- Upregulation of cannabinoid 1-receptor stimulation [32]

Changes in intracellular signalling
- Changed expression of regulators of G-protein signalling [24,30]
- Changed adenylcyclase inhibition or stimulation [29]
- Over-expression of regulators of G-protein signalling [36]

Changes in ion fluxes
- Altered function and reduced conductance of potassium channels [66]
- Inhibition of L-type calcium channels [26]

Contractility defects
- Overexpression of the β-myosin heavy chain [29]
- Altered ratio of collagens and titans [24]

Biochemical changes
- Increased inhibitory effects of haemeoxygenase and carbon monoxide [5]
- Nitration of proteins [28]
- Increased nitric oxide synthase-induced nitric oxide release [33]
- Increased tumour necrosis factor-α release [5]
- Increased fluidity of the plasma membrane [27]
- Increased cholesterol/phospholipid ratio [5,29]

Moller. Int J Cardiology 2012

Critères diagnostics cardiomyopathie-cirrhotique

A cardiac dysfunction in patients with cirrhosis characterised by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease

Diagnostic criteria

Systolic dysfunction

- Blunted increase in CO with exercise, volume challenge or pharmacological stimuli
- Resting EF <55%

Diastolic dysfunction

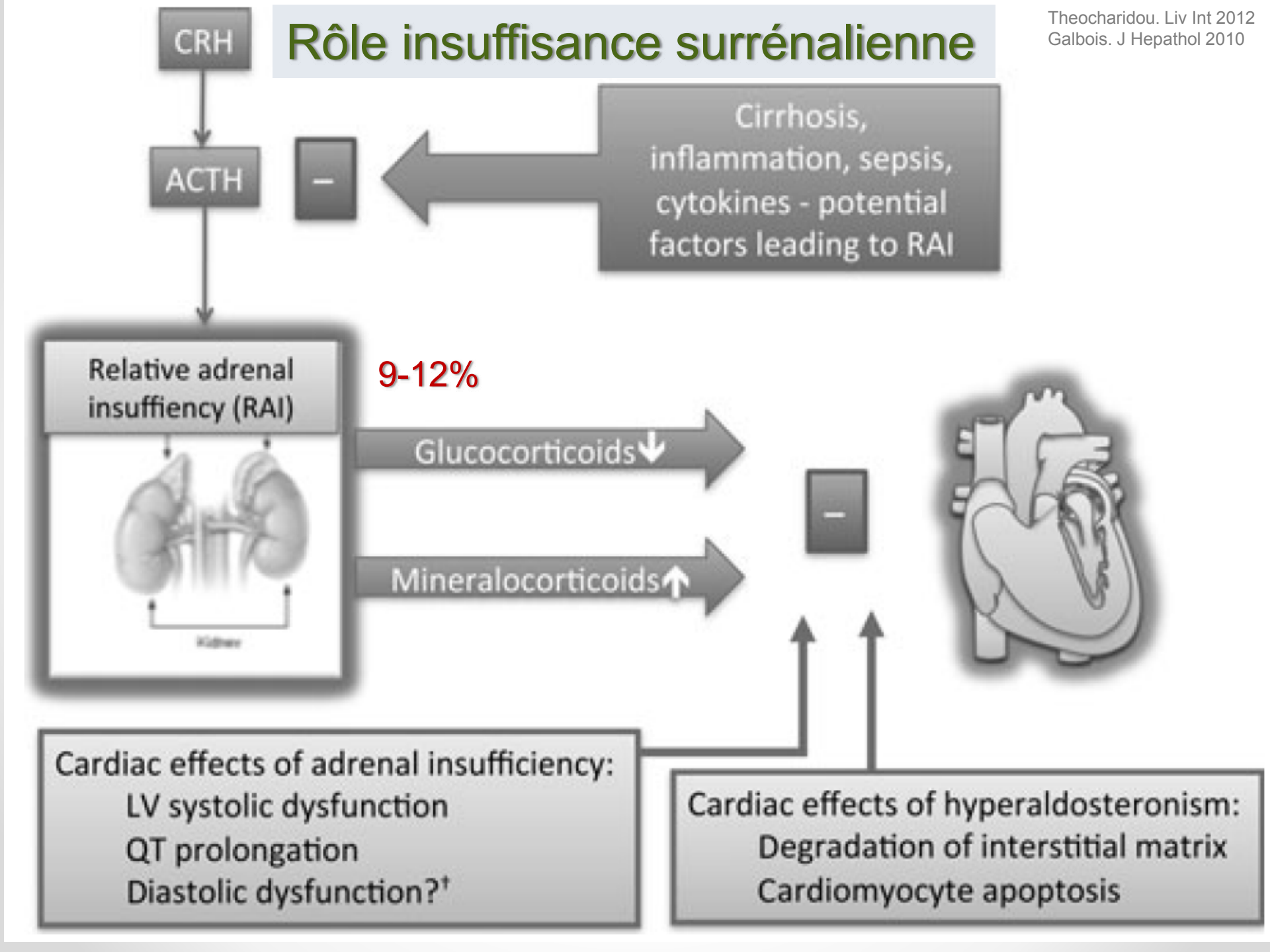
- E/A ratio <1.0 (age-corrected)
- Prolonged deceleration time (>200 ms)
- Prolonged isovolumetric relaxation time (>80 ms)

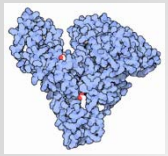
Supportive criteria

- Electrophysiological abnormalities
- Abnormal chronotropic response
- Electromechanical uncoupling/dyssynchrony
- Prolonged Q-Tc interval
- Enlarged left atrium
- Increased myocardial mass
- Increased BNP and pro-BNP
- Increased troponin I

Rôle insuffisance surrénalienne

Theocharidou. Liv Int 2012
Galbois. J Hepathol 2010



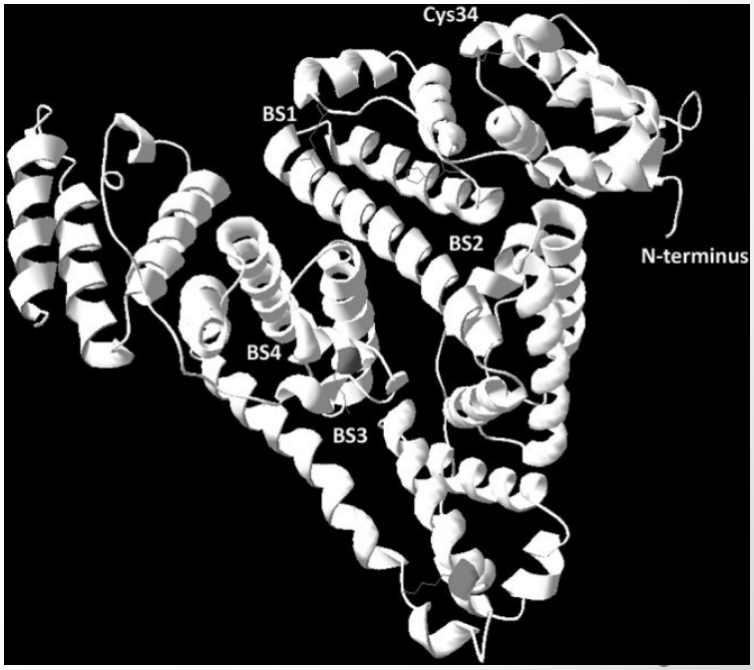


Perte de la capacité fonctionnelle de l'albumine

Albumine→transport molécules hydrophobiques, acides gras, hormones, substances toxiques, médicaments, anti-oxydant…

Dans la cirrhose : ↓ synthèse, ↓ capacité transport et ↓ anti-oxydant

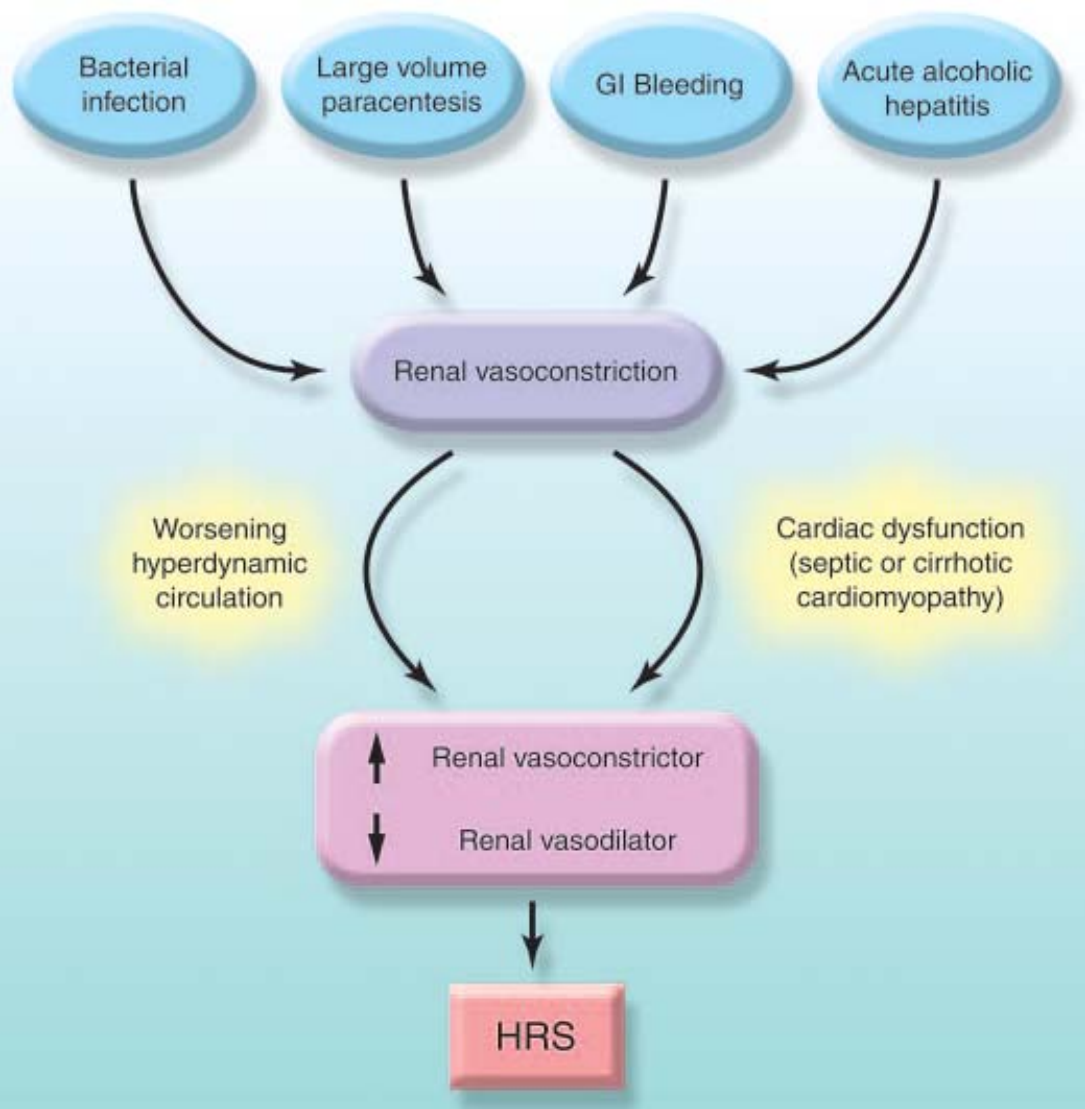
Measure	Healthy	Cirrhosis, No Organ Dysfunction (n = 12)	ACLF (n = 22)
EPR spectroscopy			
Binding coefficient (high-affinity K_{B1})	97.4 (15.6)	27.5 (5.6)*	17.9 (3.5)*
Number of labels (high-affinity site, N1)	3.1 (0.1)	2.4 (0.1)	2.5 (0.9)
Binding coefficient (low-affinity K_{B2})	58.3 (11)	20.1 (3.1)*	14.1 (1.8)*,†
Number of labels (low-affinity site, N2)	2.9 (0.2)	3.1 (0.1)	2.6 (0.1)*,†
Calculated real transport efficiency	75 (6.9)	27.5 (5.1)*	14.3 (1.9)*,†
Calculated detoxification efficiency	120 (33)	28.2 (5.3)*	11.6 (2.6)*,‡
Effective albumin	50.26 (3.02)	25.6 (3.1)*	20.98 (2.2)*
IMA	0.69 (0.034)	0.64 (0.022)	0.64 (0.017)
IMAR	0.010 (0.001)	0.021 (0.001)	0.03 (0.002)*,‡



Jalan. Hepatology 2009

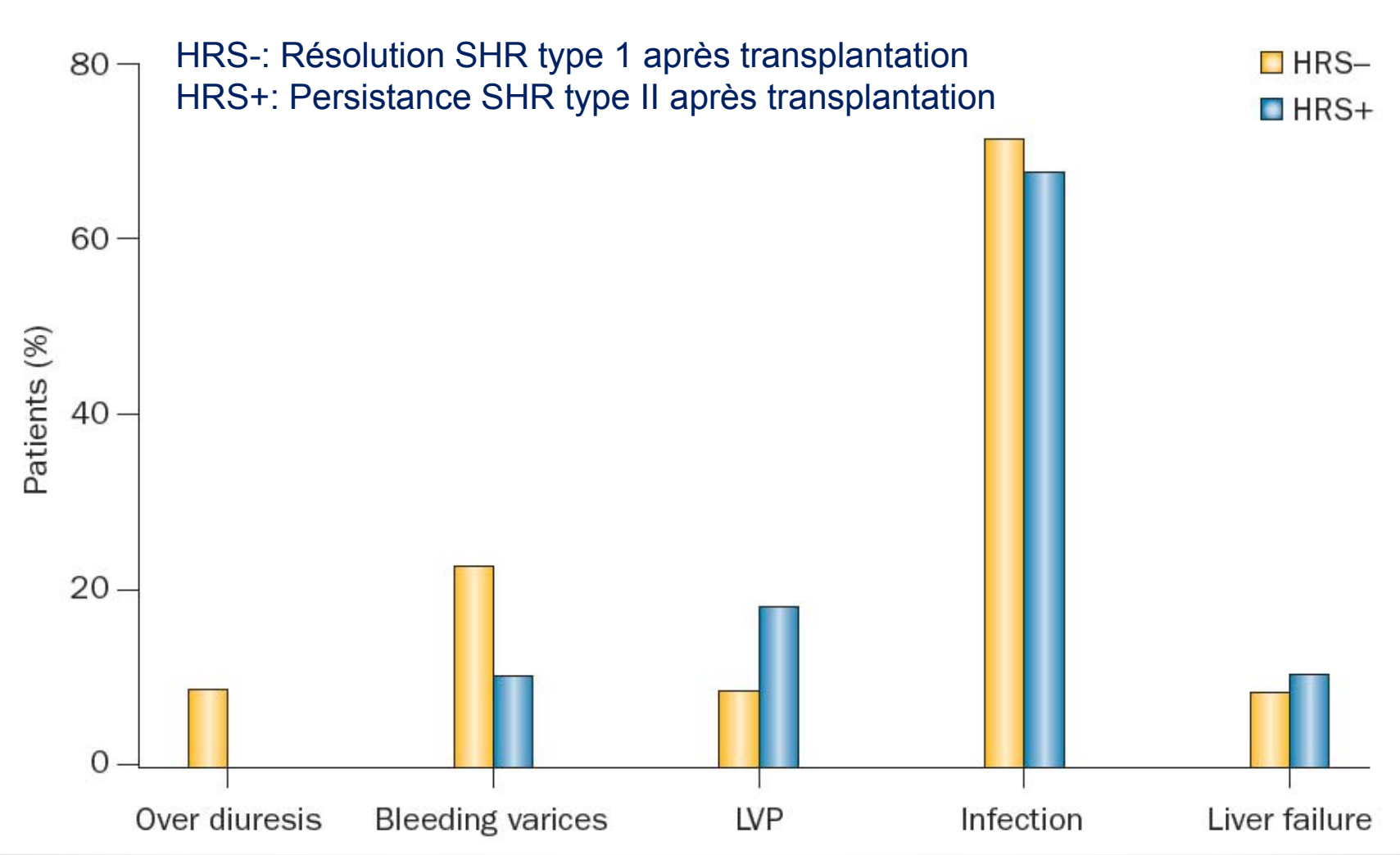
Facteurs déclenchant SHR

AINS !

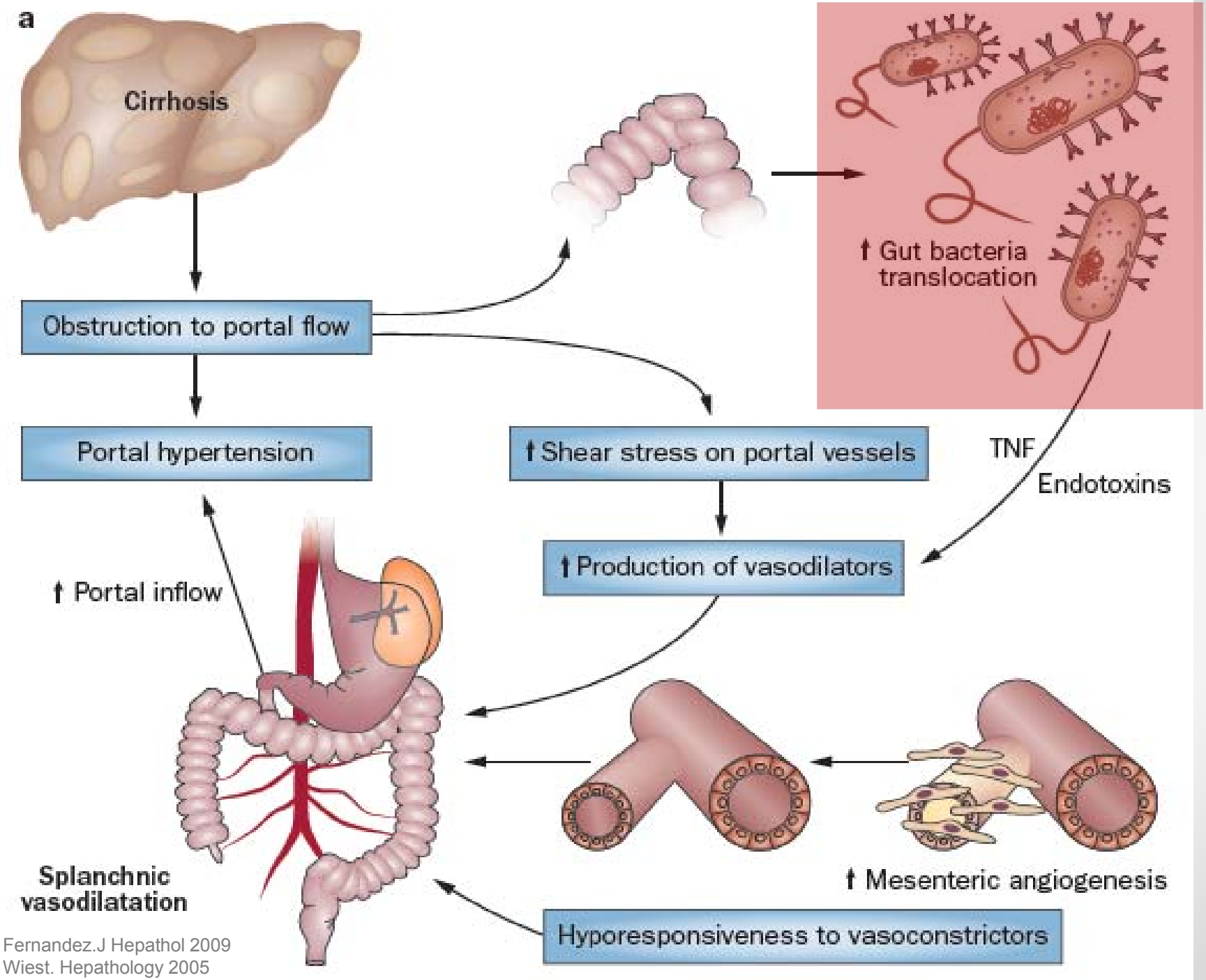


Wadei. CJASN2006

Facteurs déclenchant SHR

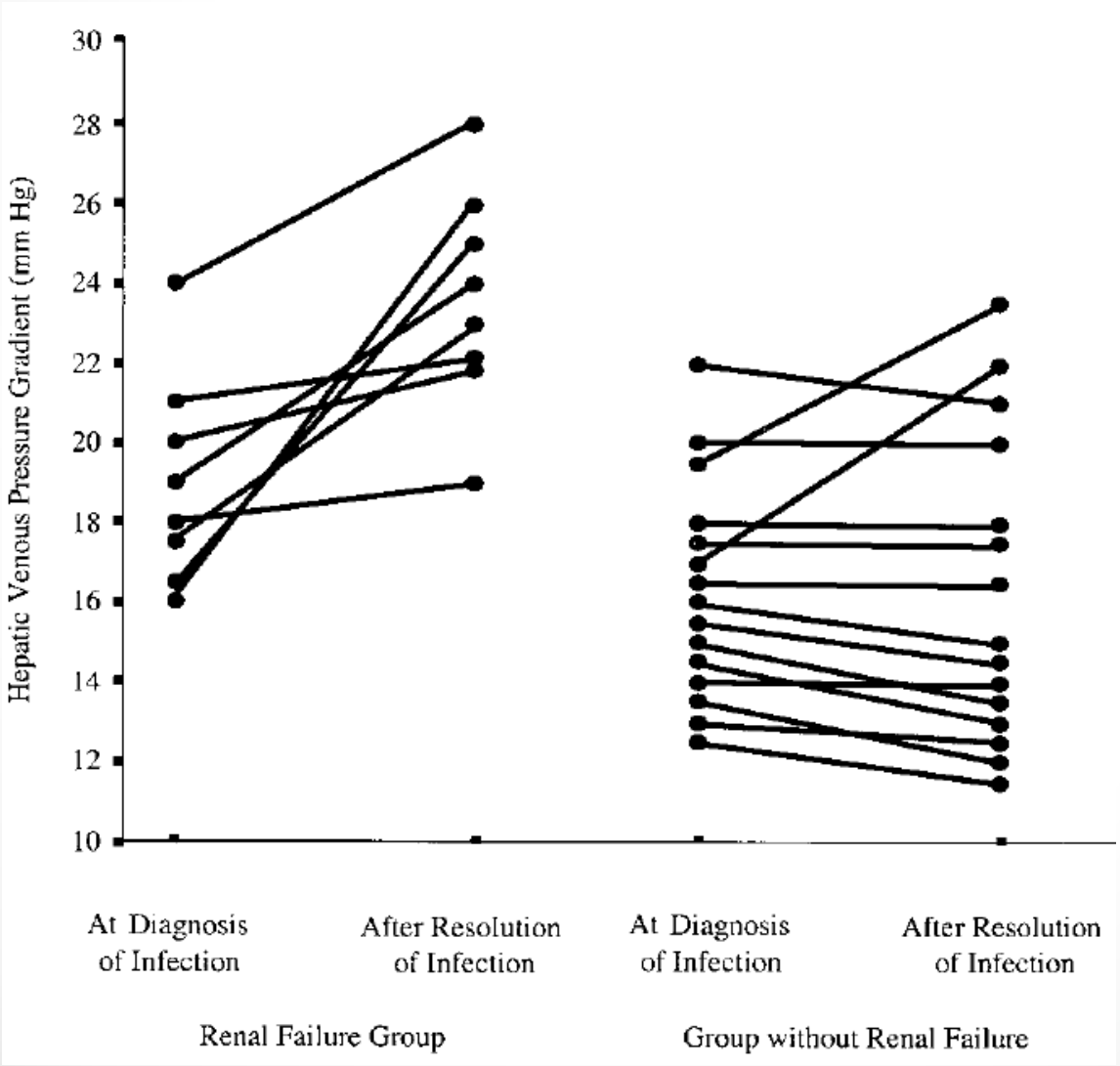


Leung: J Hepatol 2012



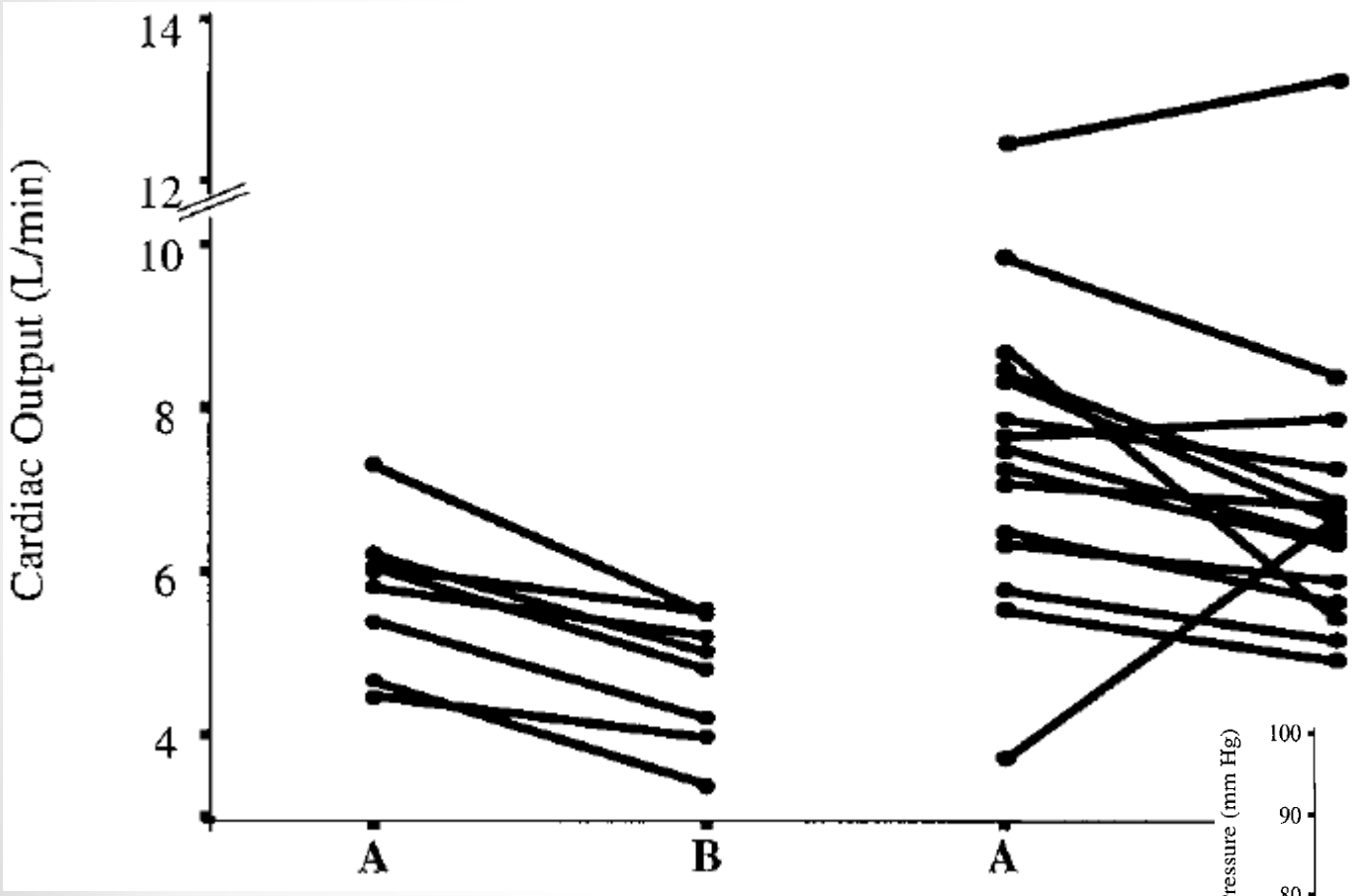
Fernandez.J Hepathol 2009
Wiest. Hepathology 2005

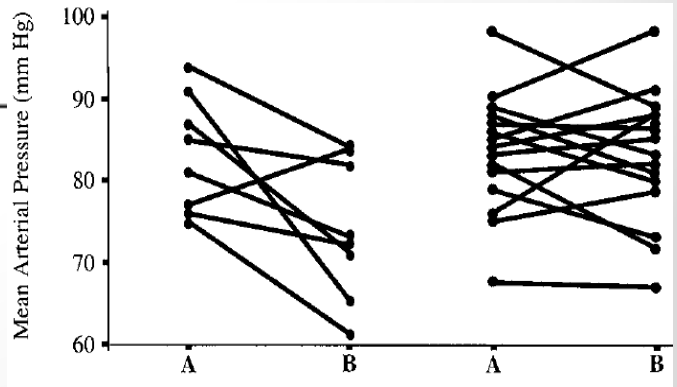
Pression hépatique ↑ avec PBS



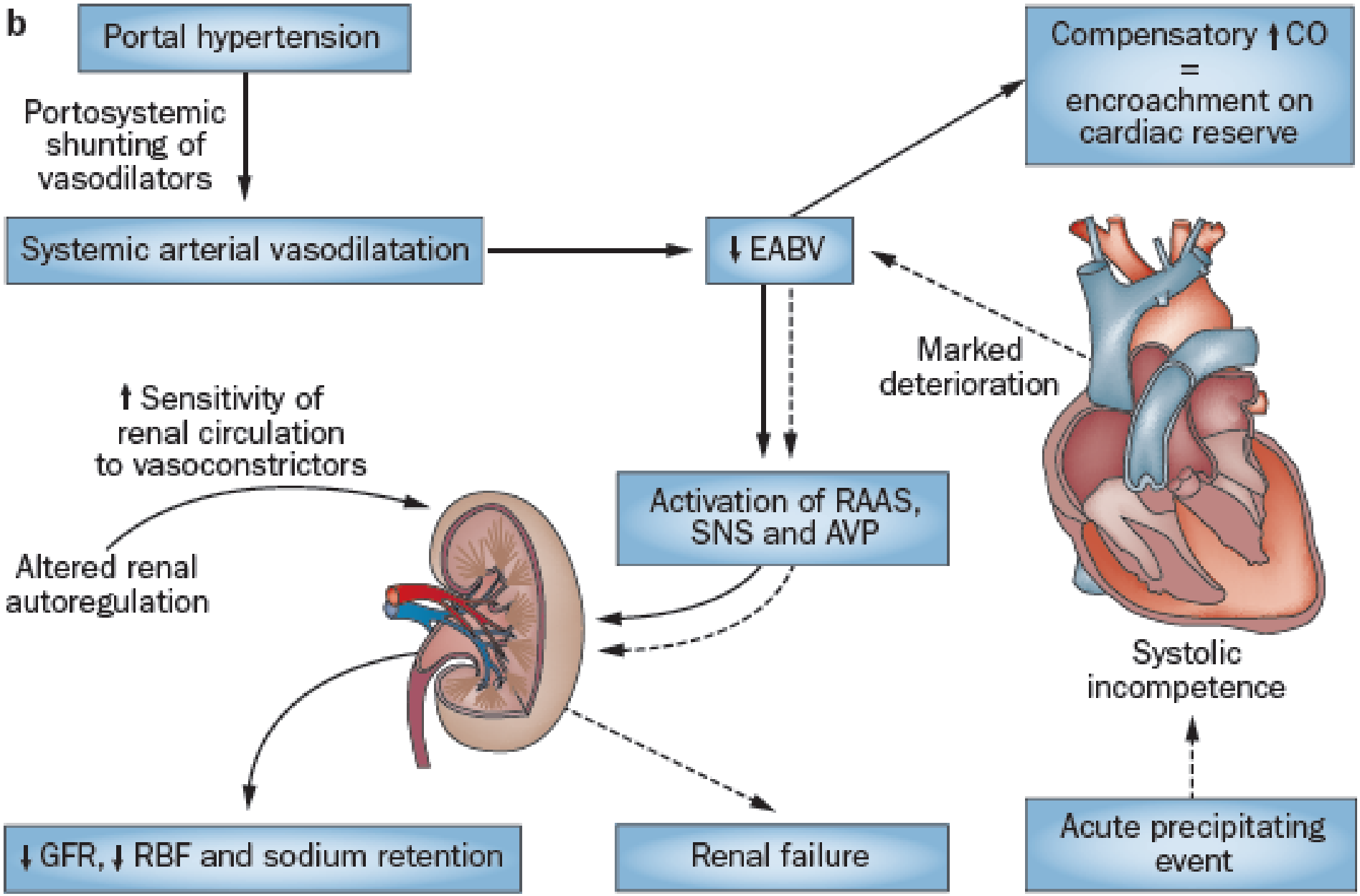
Ruiz del Arbol Hepatology 2003

Modifications hémodynamique PBS





- ↓ débit cardiaque et P artérielle chez patient développant IRA suite à PBS


b
Portal hypertension
Portosystemic shunting of vasodilators
Systemic arterial vasodilatation
↓ EABV
Compensatory ↑ CO = encroachment on cardiac reserve
Marked deterioration
↑ Sensitivity of renal circulation to vasoconstrictors
Altered renal autoregulation
Activation of RAAS, SNS and AVP
Systolic incompetence
↓ GFR, ↓ RBF and sodium retention
Renal failure
Acute precipitating event

Conclusions (I)

- Le SHR se caractérise par une **vasoconstriction rénale intense** en réponse à une baisse des résistances systémiques, principalement dues à une **vasodilatation artérielle splanchnique**
- Parmi les médiateurs impliqués dans la vasodilatation splanchnique, une **production accrue de NO** joue un rôle essentiel.
- Cette production accrue de NO s'accompagne de **défauts des mécanismes de vasoconstriction** qui touchent les voies de signalisation du muscle lisse
- La cause de cette production accrue est inconnue et de nouvelles pistes notamment au niveau de la circulation hépatique devrait être explorées.

Conclusions (II)

- Parmi les éléments associés au développement du SHR on retient une **cardiomyopathie cirrhotique.**
- **Une insuffisance surrrénalienne** contribue à la dysfonction
- Une altération des fonctions détoxifiantes et antioxydantes de l'**albumine** doit également être évoquée.
- **Un épisode infectieux digestif** (translocation bactérienne) est le mécanisme déclencheur le plus fréquent et le plus probable.

Wong F. Nat Rev Gastroenterology 2012(9): 382-391
Oliver J. Kidney International 2010(77): 669-680
Moler S. New insights into cirrhotic cardiomyopathy. International J Cardiology 2012
Gines P. Renal failure in cirrhosis. NEJM 2009; 361(13):1279-1290