ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Université Paris Cité

Physiopathologie de l'hypertension portale

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MVF CENTRE DE RÉFÉRENCE MALADIES VASCULAIRES DU FOIE

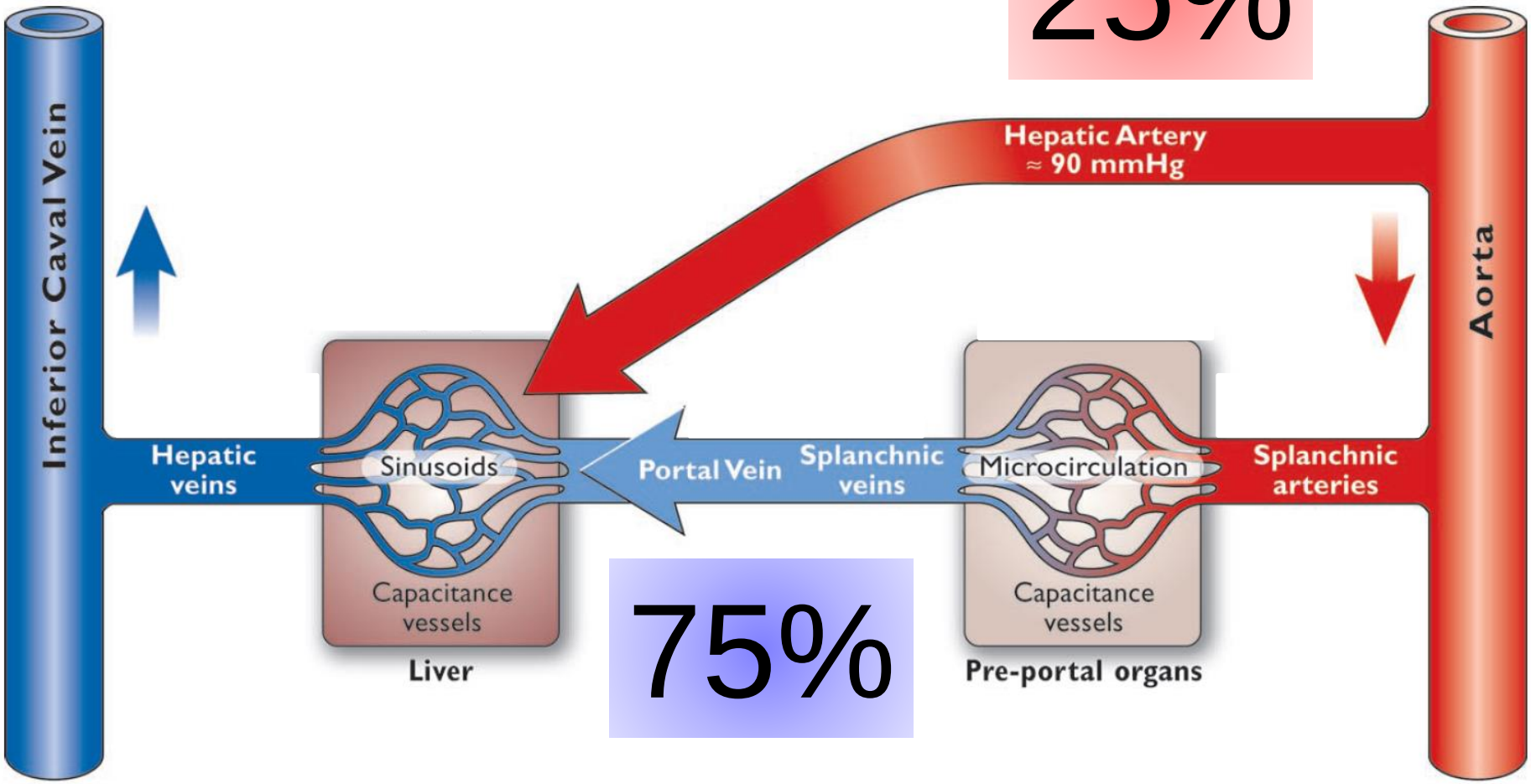
Instituts thématiques Inserm Institut national de la santé et de la recherche médicale

CRI CENTRE de RECHERCHE sur l'INFLAMMATION

I- Physiopathologie de l’hypertension portale

Portal hypertension

- What is portal hypertension?
- Pathophysiology of portal hypertension
- Why to assess portal hypertension?
- How to measure portal hypertension?



Gelman, Anesthesiology. 2004

Portal hypertension

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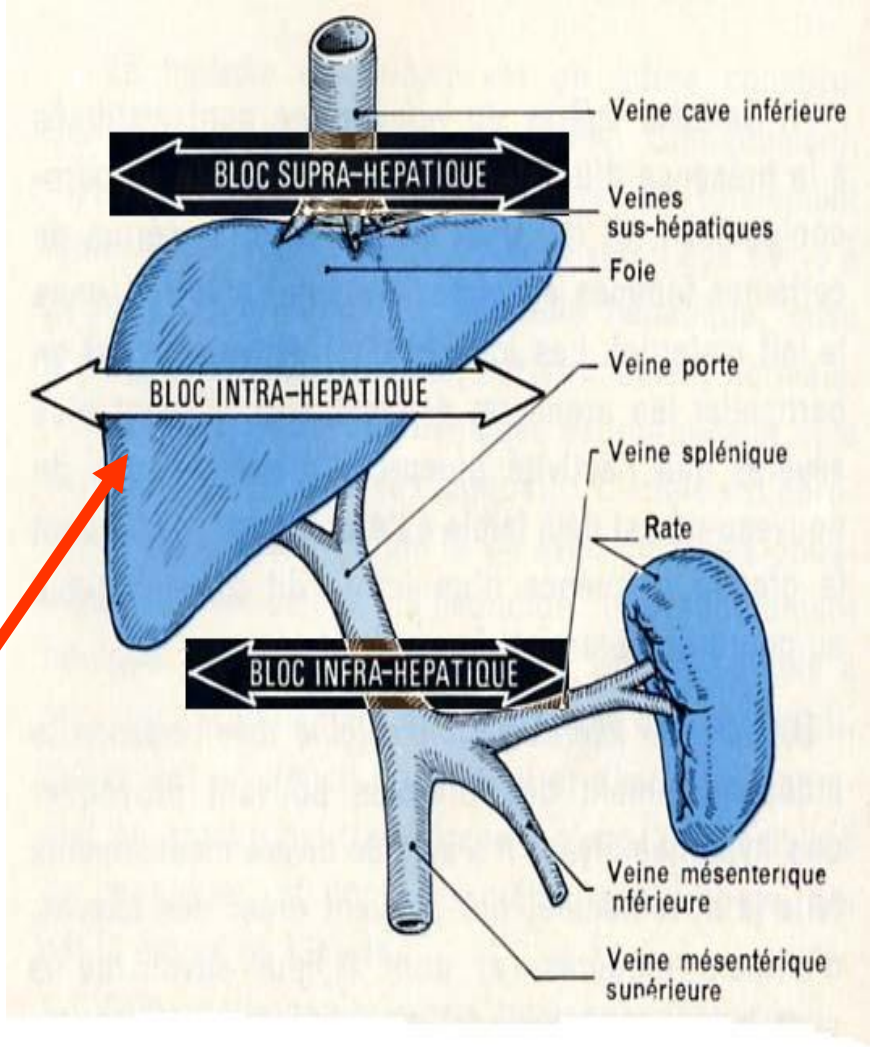
Définition, types d'hypertension portale

- HTP : gradient de pression entre pression veine porte et VCI ≥ 5 mmHg

- Bloc intrahépatique, infra- ou suprahépatique

- HTP sinusoïdale, présinusoïdale et postsinusoïdale



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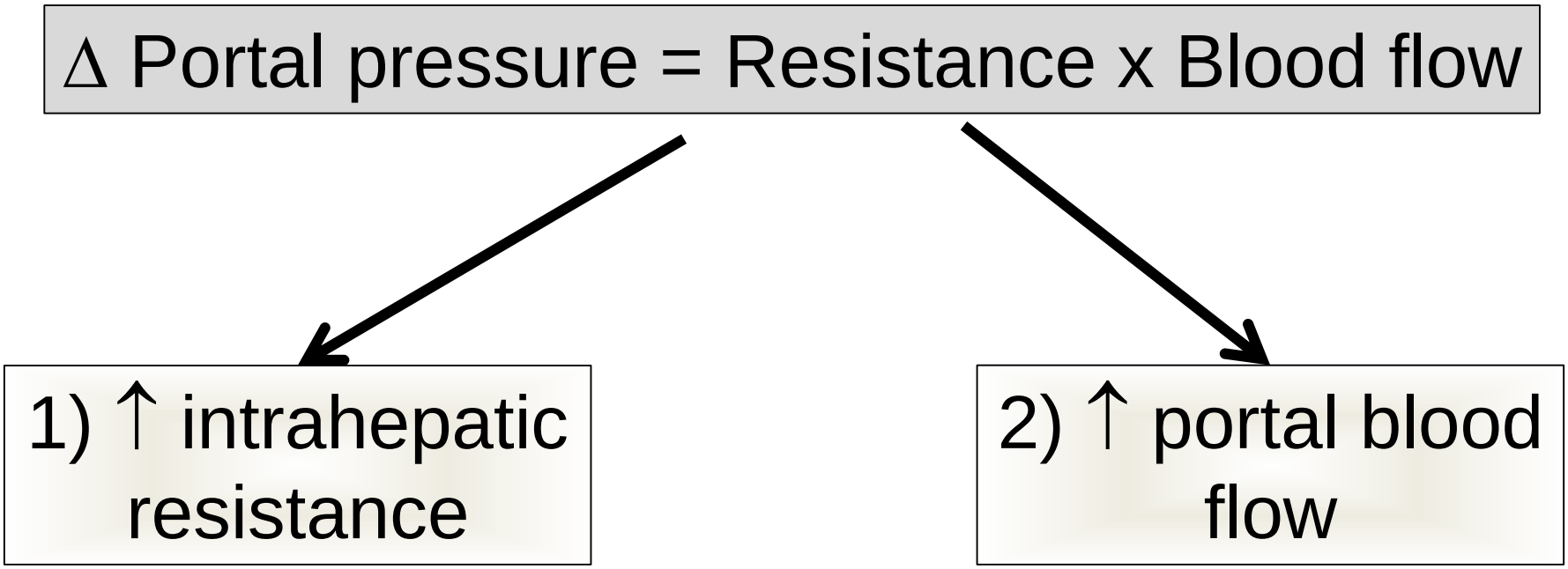
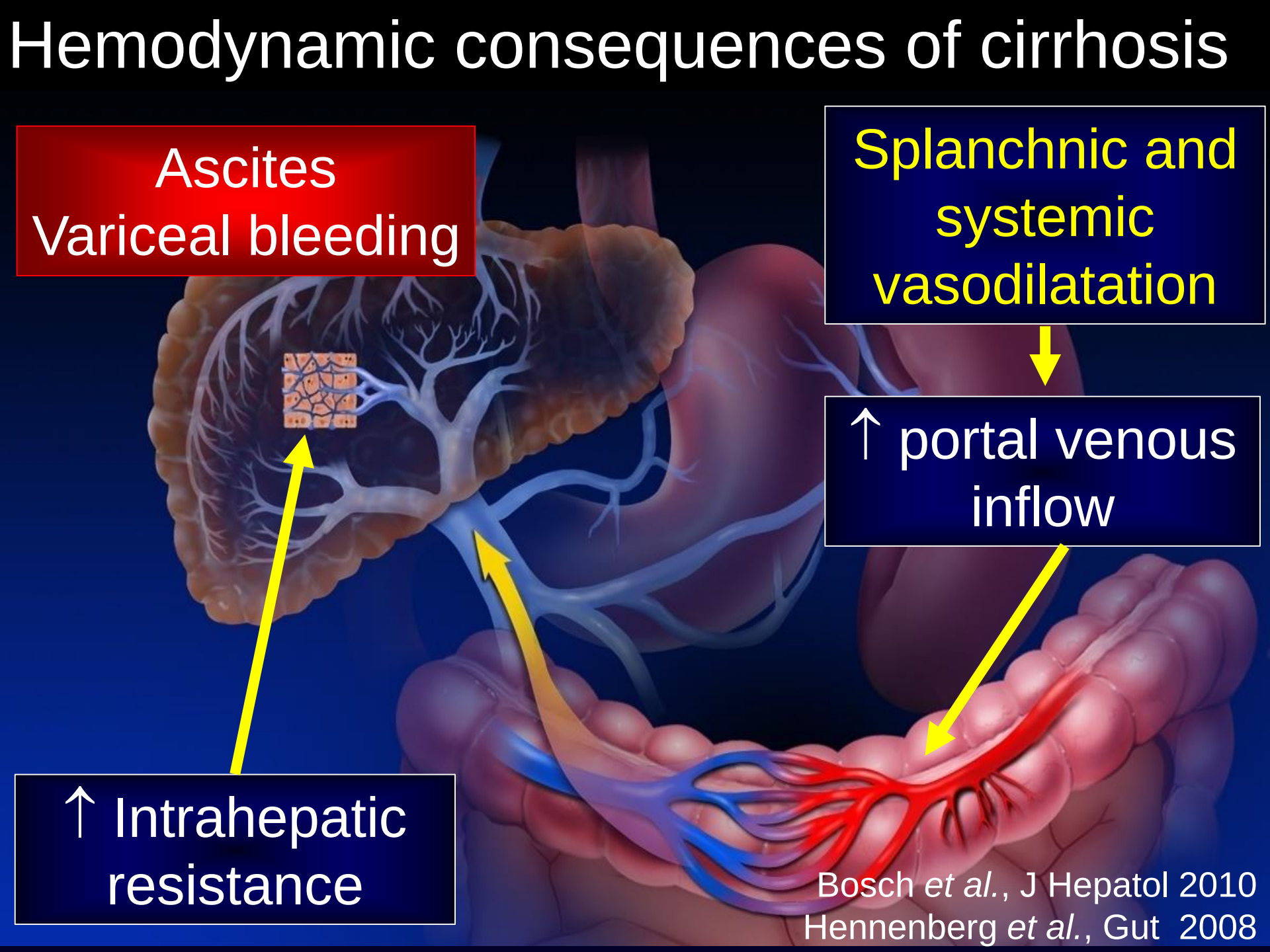
Pathophysiology of portal hypertension



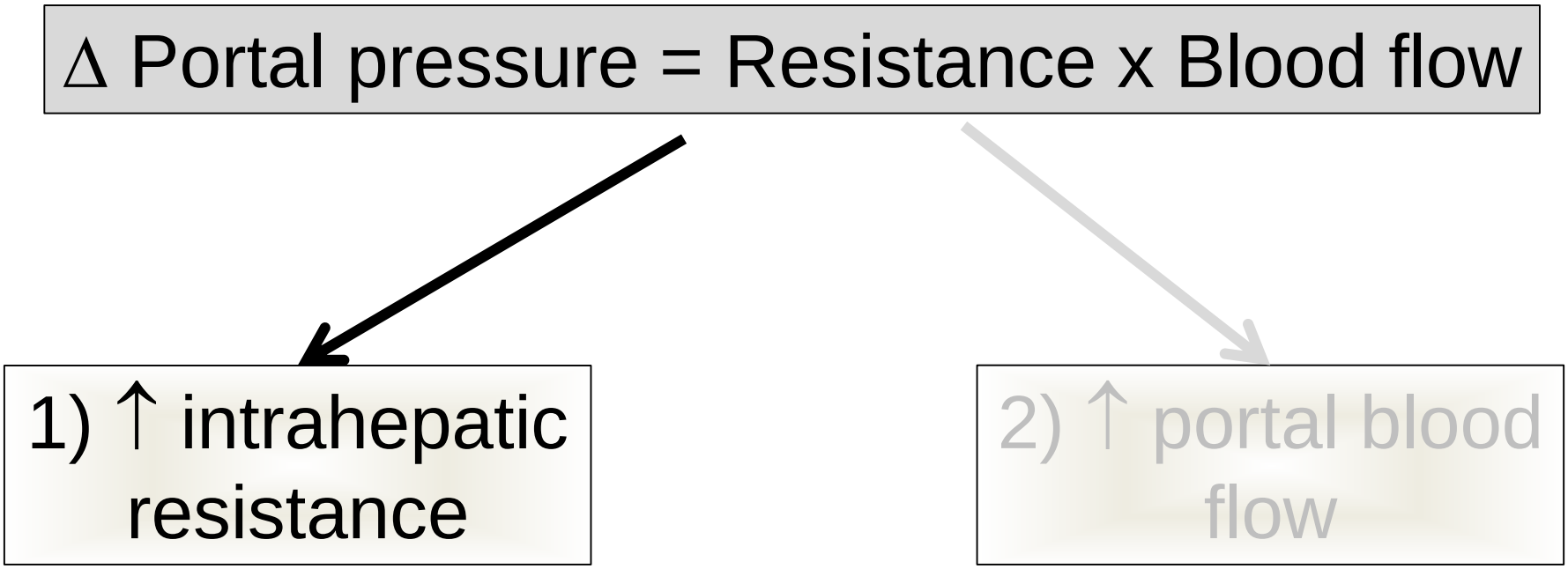
Bosch, J Hepatol 2010

Hemodynamic consequences of cirrhosis



Bosch *et al.*, J Hepatol 2010
Hennenberg *et al.*, Gut 2008

Pathophysiology of portal hypertension



Bosch, J Hepatol 2010

↑ Intrahepatic resistance

Structural factors:

- fibrosis
- regenerative nodule formation
- vascular remodeling
- vascular occlusion

Dynamic component = ↑ hepatic vascular tone:

- ↓ bioavailability of intrahepatic vasodilators (NO)
- ↑ activity of endogenous vasoconstrictors

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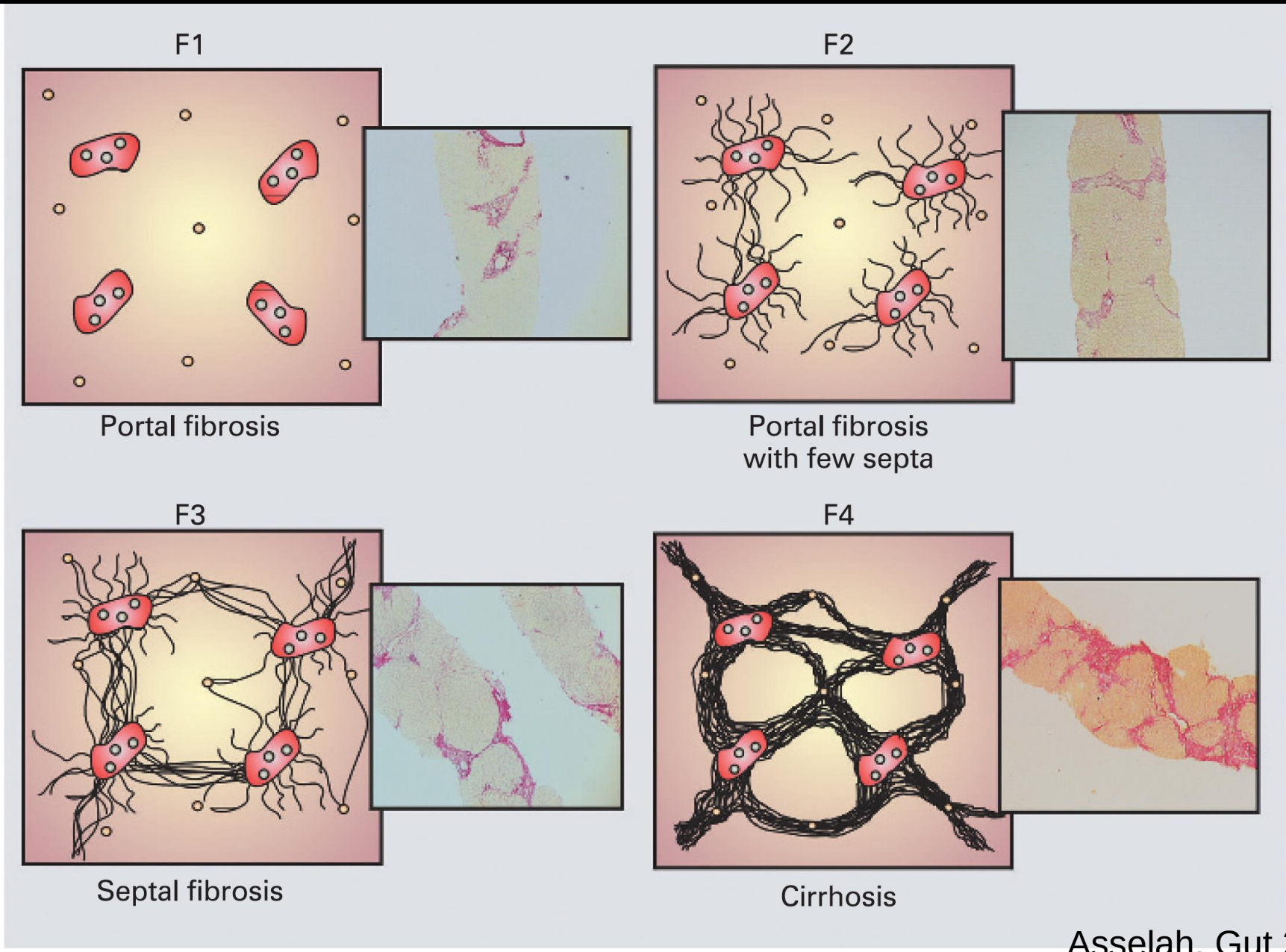
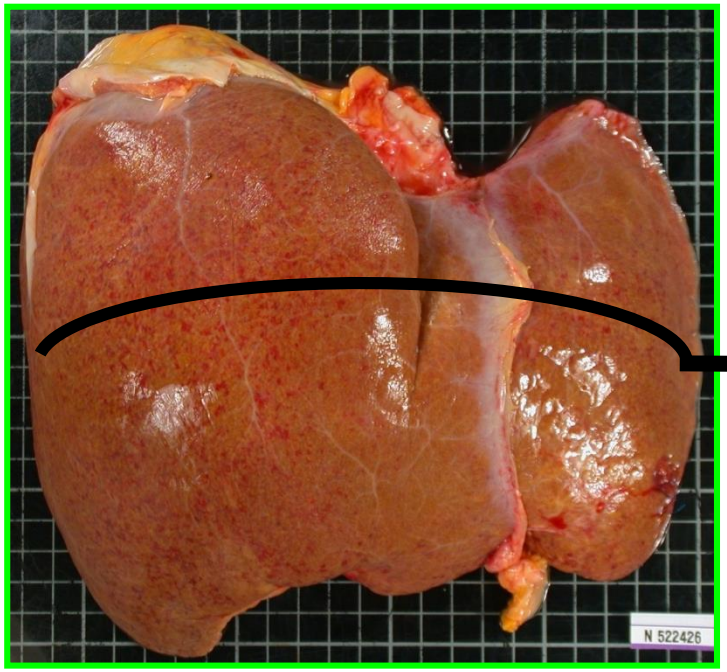
Structural factors: fibrosis and nodules



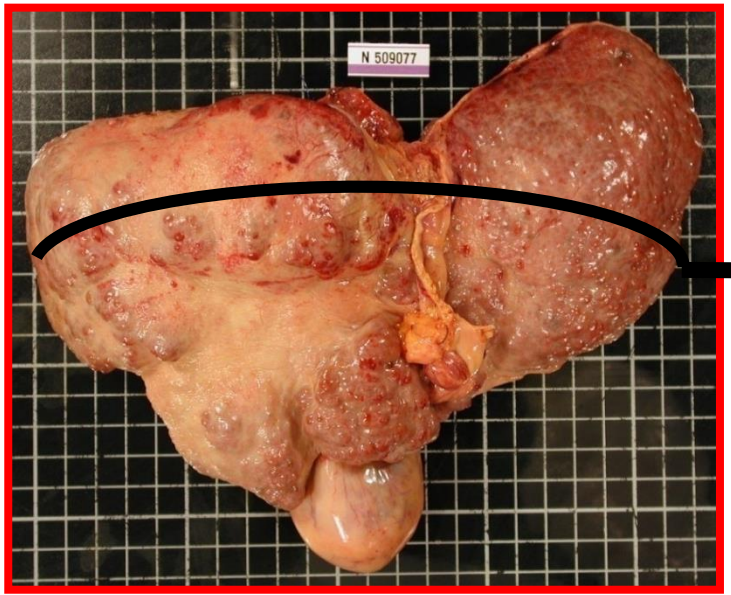
Asselah, Gut 2009

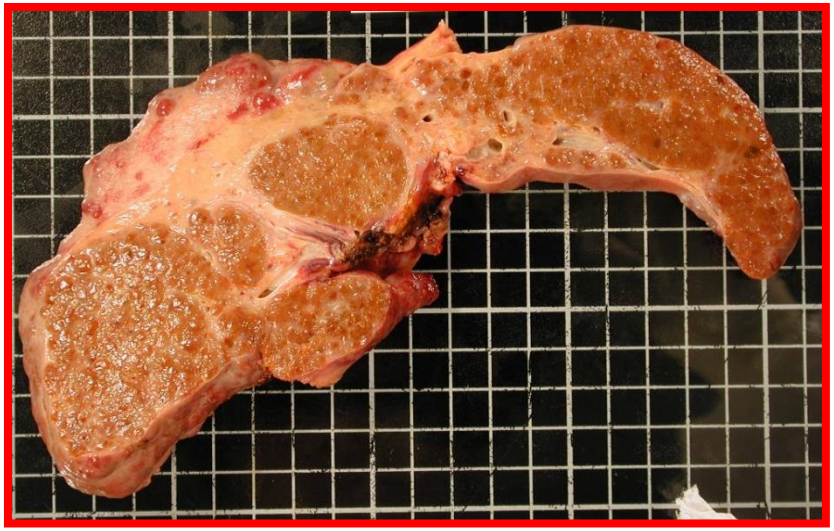
Structural factors: fibrosis and nodules

Normal liver



Cirrhotic liver





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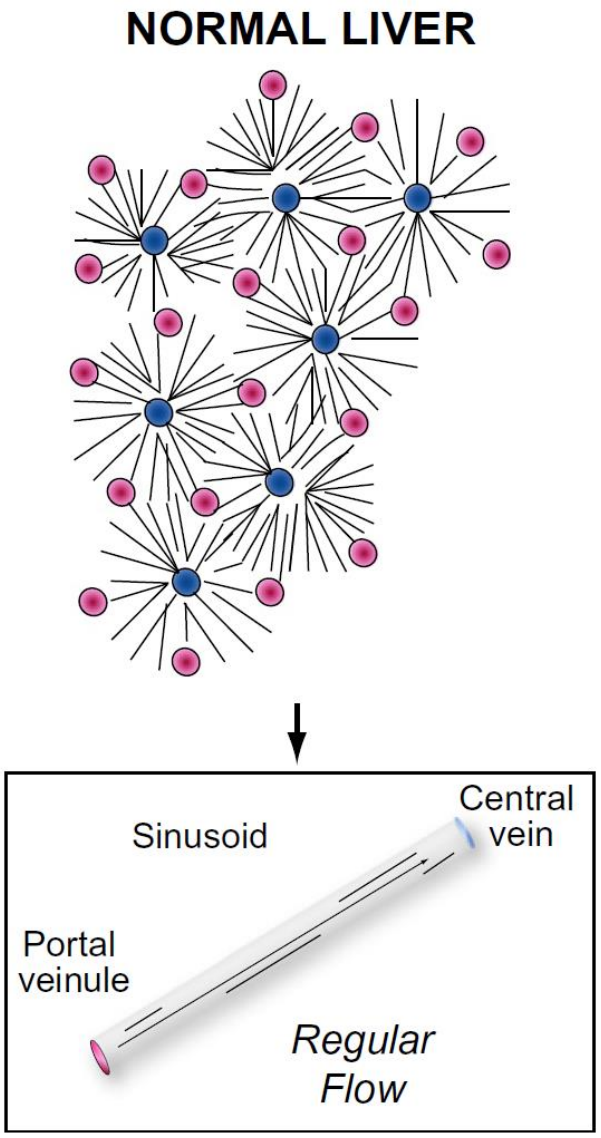
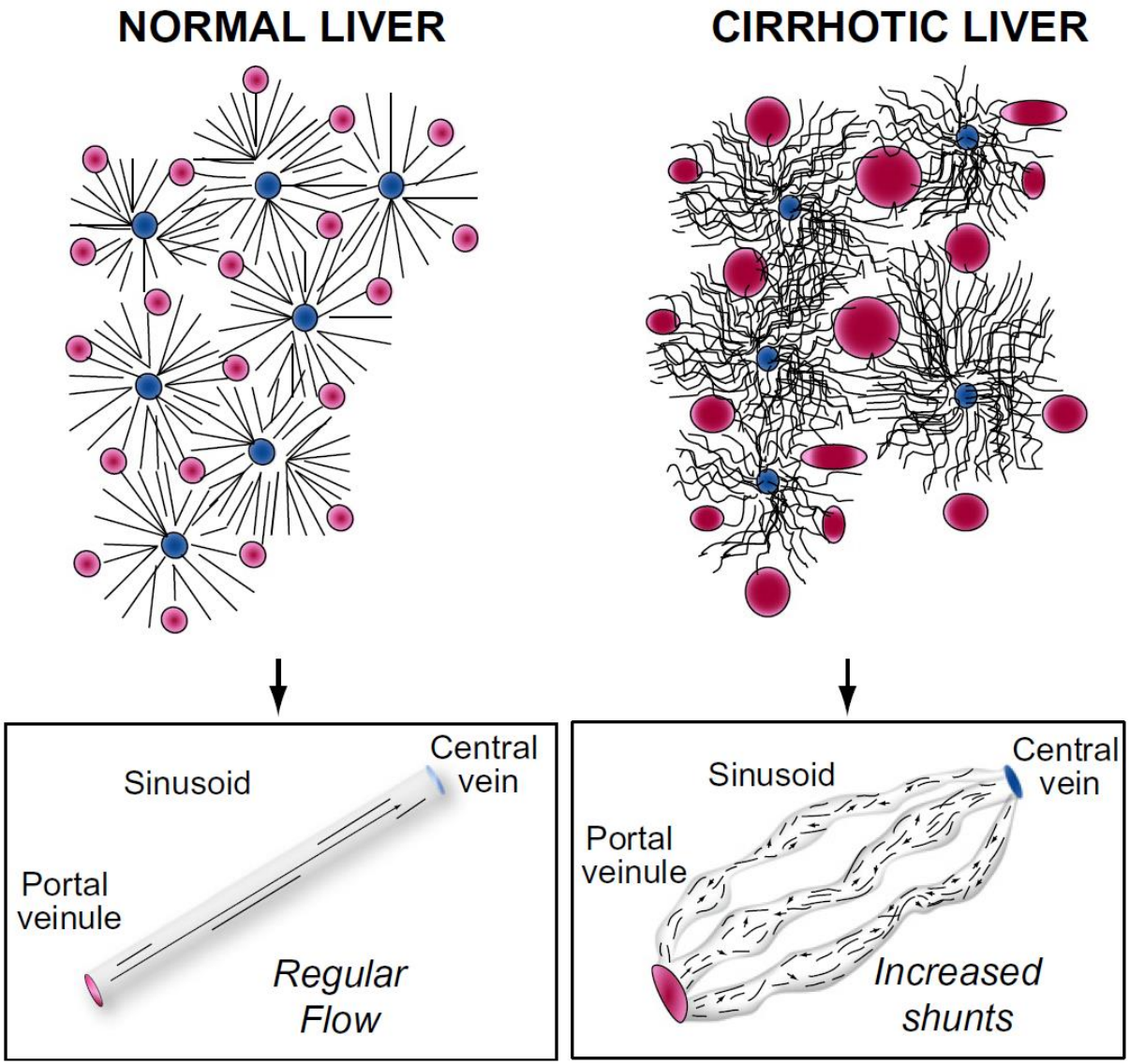
Structural factors: vascular remodeling



Thabut, J Hepatol 2010

Structural factors: vascular remodeling



Thabut, J Hepatol 2010

Structural factors: vascular remodeling

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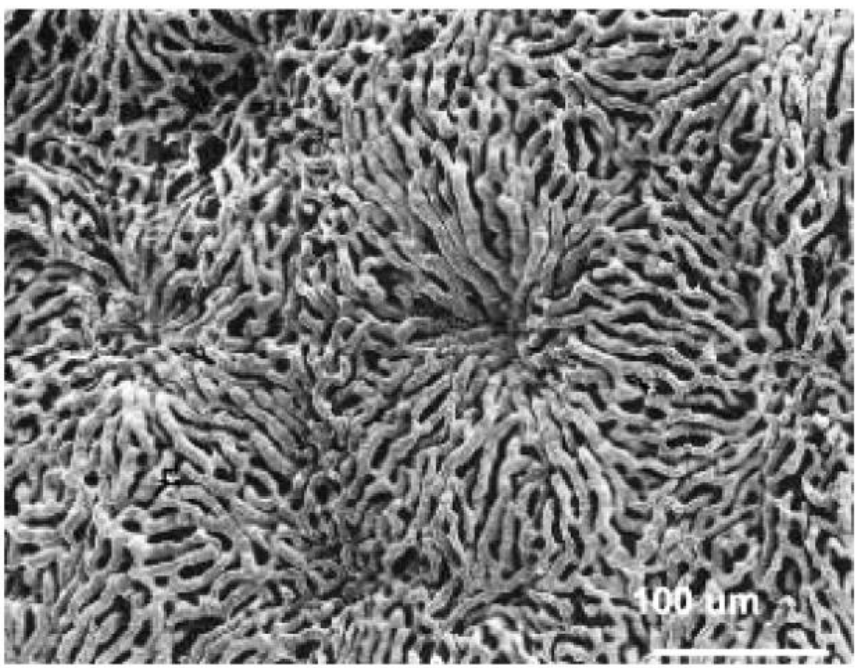

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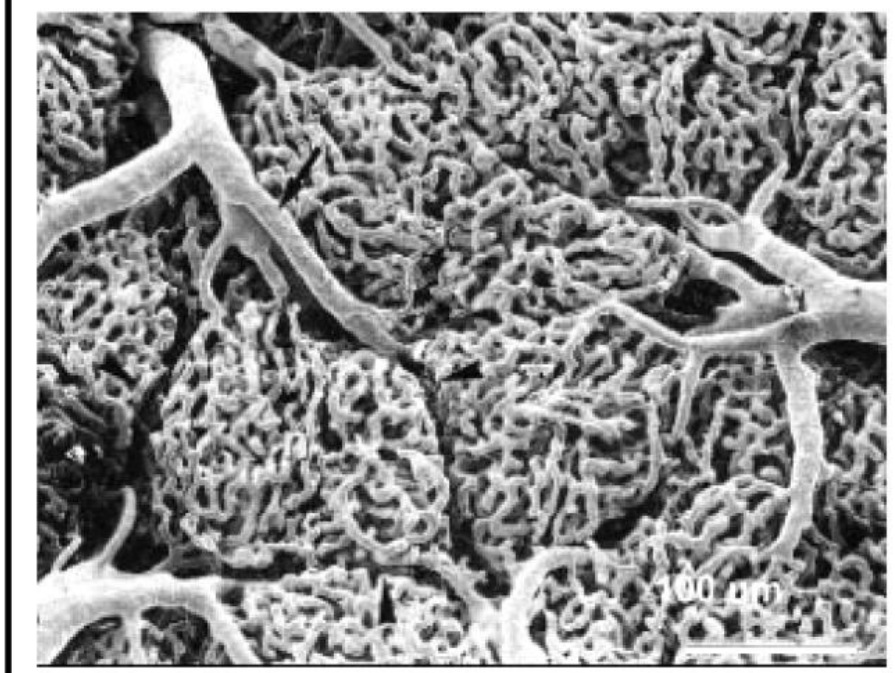

Lee, Hepatology 2007

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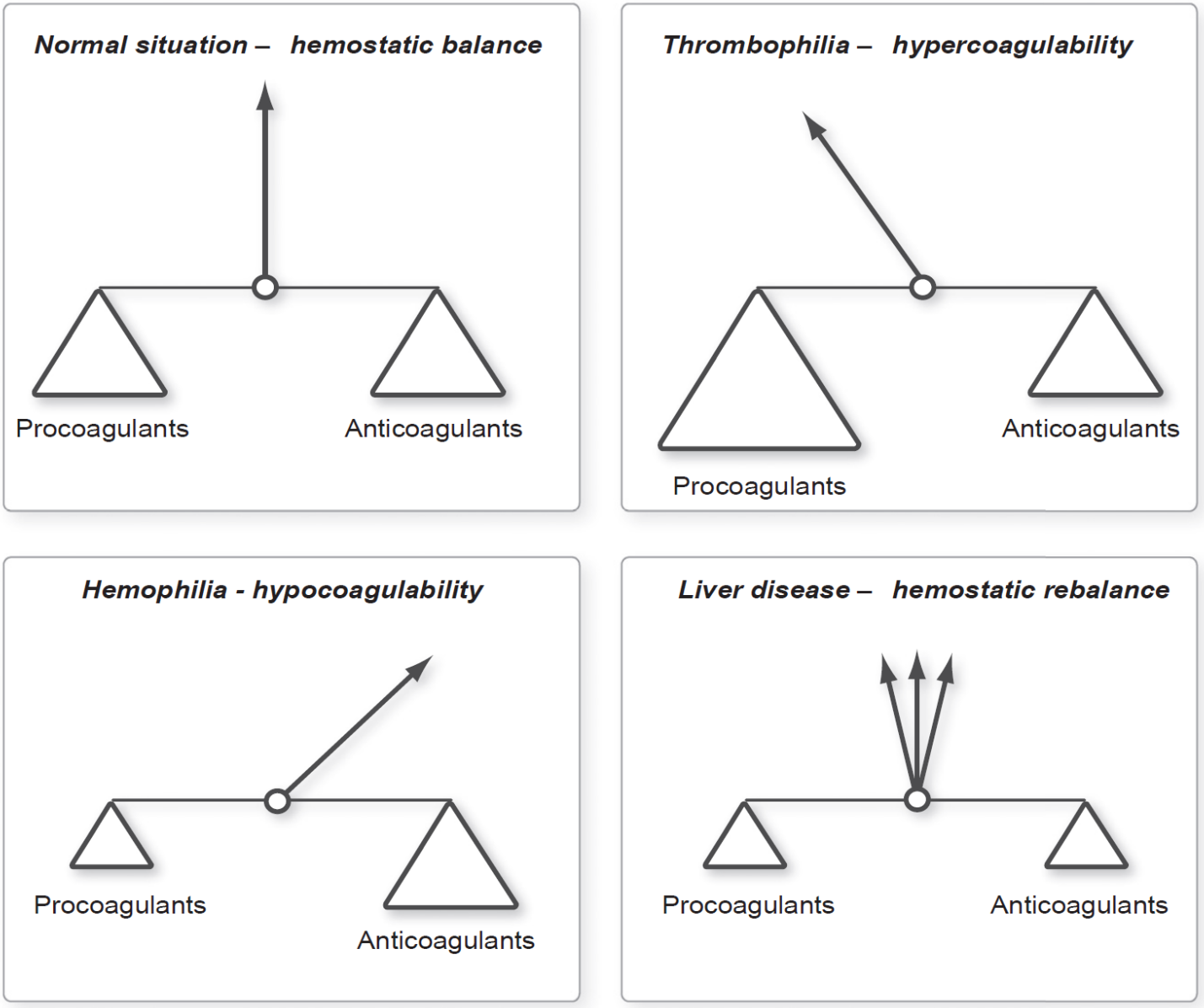
Procoagulant imbalance in cirrhosis



Lisman, J Hepatol 2010

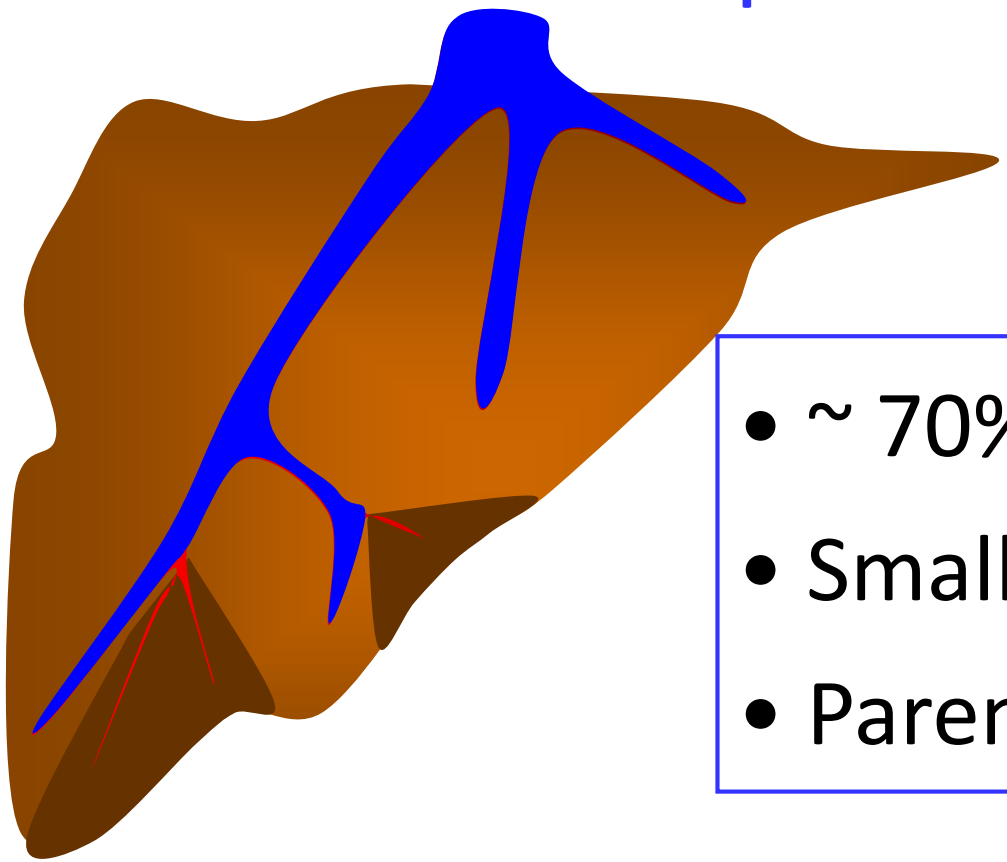
Procoagulant imbalance in cirrhosis

- Portal vein thrombosis: 8-25% in candidates for LT
- Relative risk of DVT/PE: 1.5

Valla, Hepatology 2008
Tripodi, J Thromb Haemost 2011

Vascular occlusions

Hepatic vein thromboses

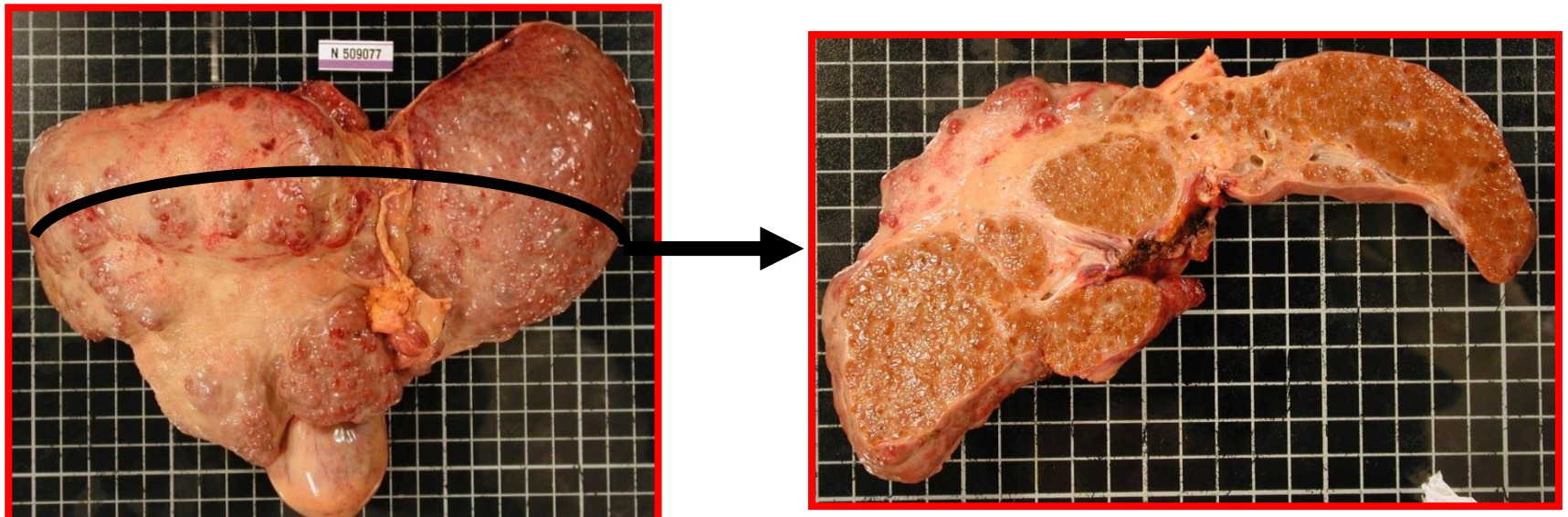


- ~ 70% of veins involved
- Smallest first
- Parenchymal extinction

Wanless, Hepatology 1995. Shimamatsu, Hepatology 1997

Vascular occlusions

Cirrhotic liver



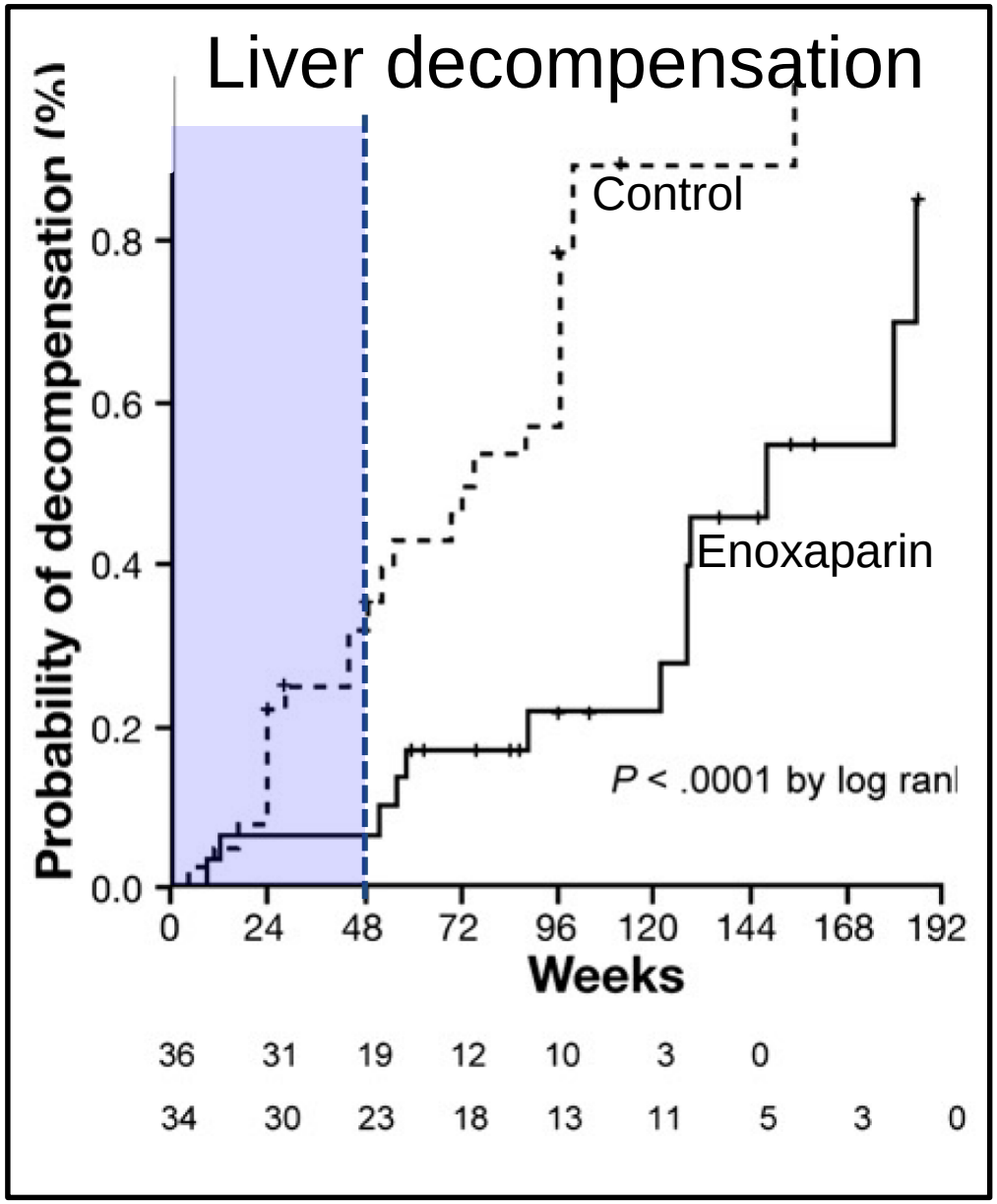
Intrahepatic vascular occlusions in cirrhosis

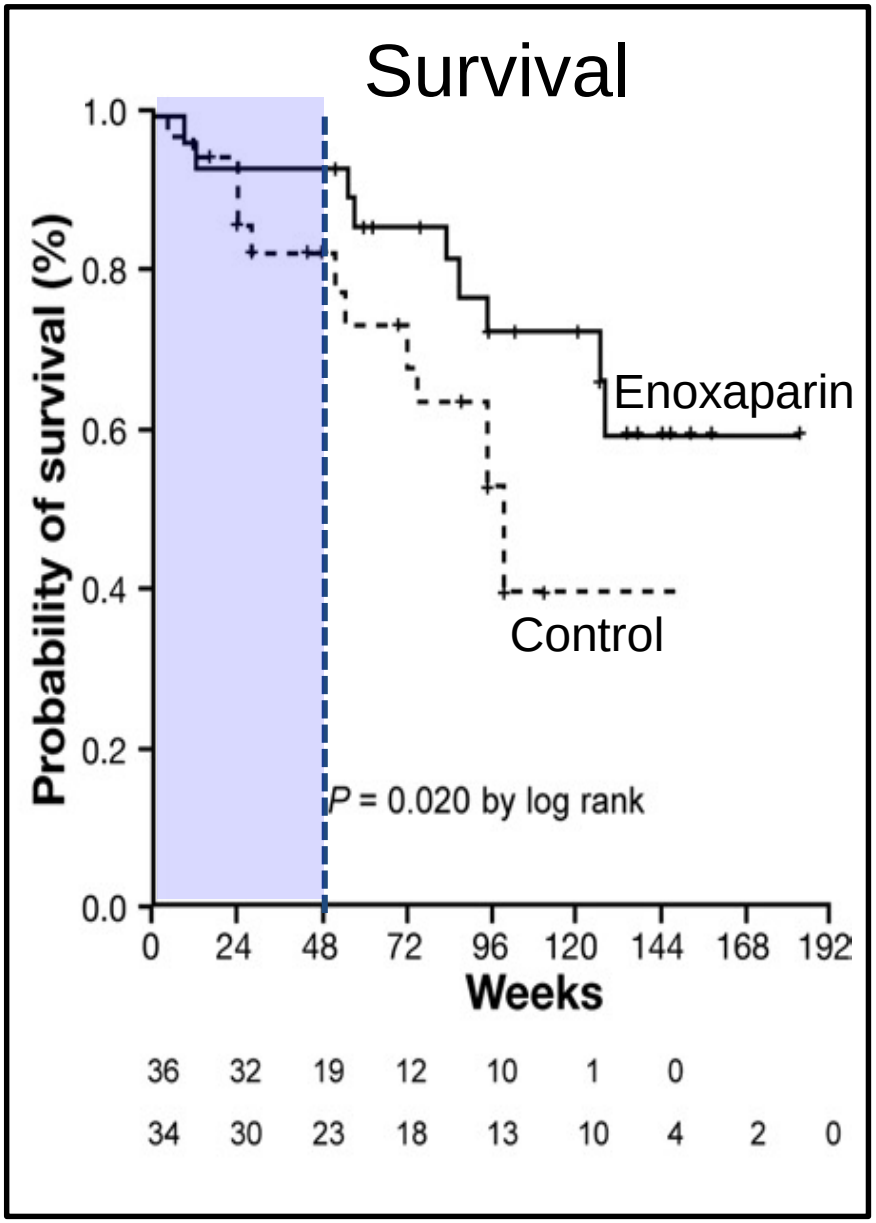
PVT Prophylaxis – Cirrhosis (CTP B7-C10)

	Control	Enoxaparin
N. of patients	36	34
Partial PVT	3	0
Complete PVT	3	0

Villa. Gastroenterology 2012. Enoxaparin 4.000 UI/d, for 12 mo.

Intrahepatic vascular occlusions in cirrhosis





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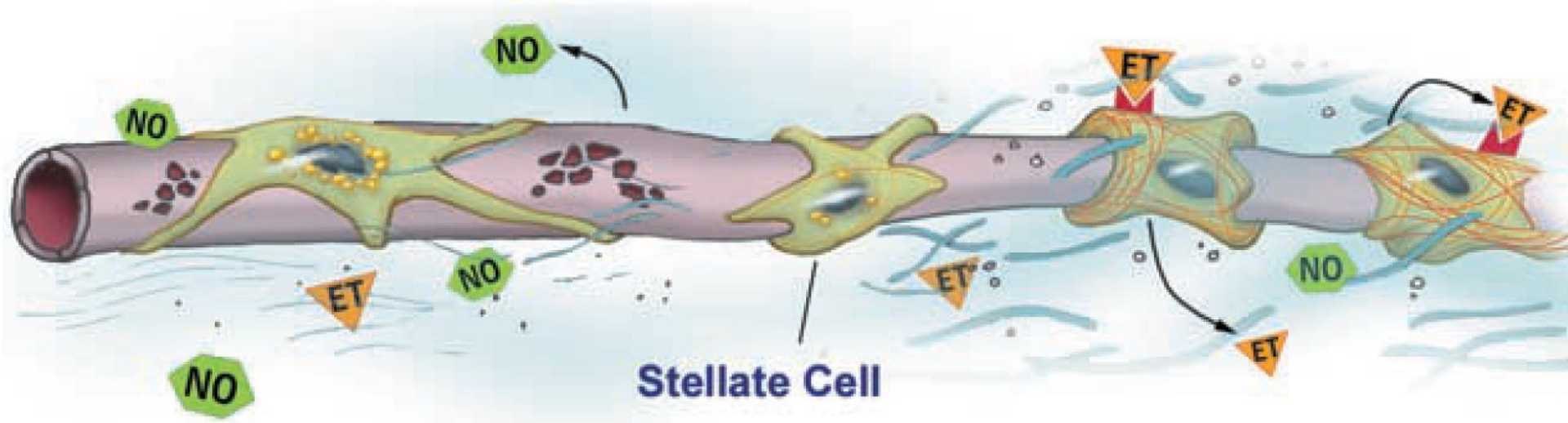


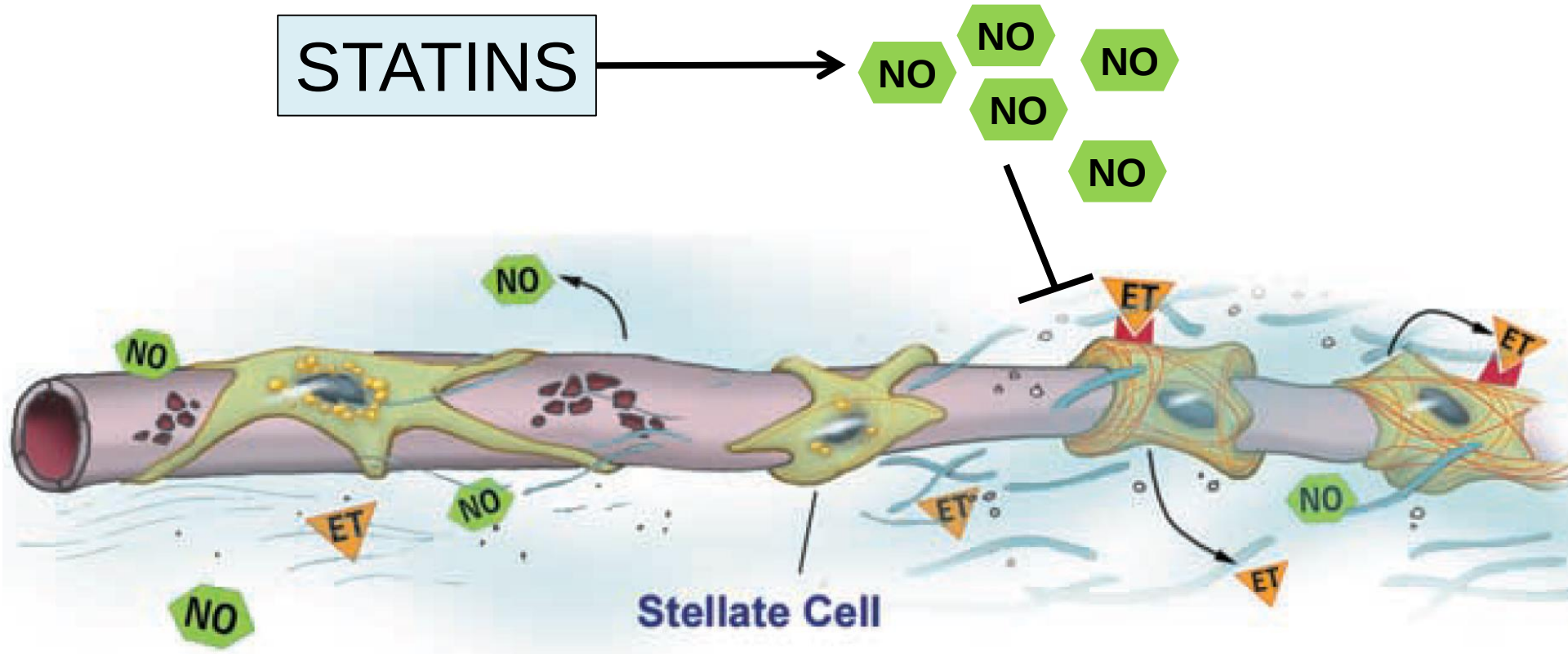
NORMAL LIVER

CIRRHOSIS

ET: endothelin
NO: nitric oxide

Rockey, Hepatology 2008
Garcia-Pagan, J Hepatol 2012

↑ hepatic vascular tone in cirrhosis



NORMAL LIVER

CIRRHOSIS

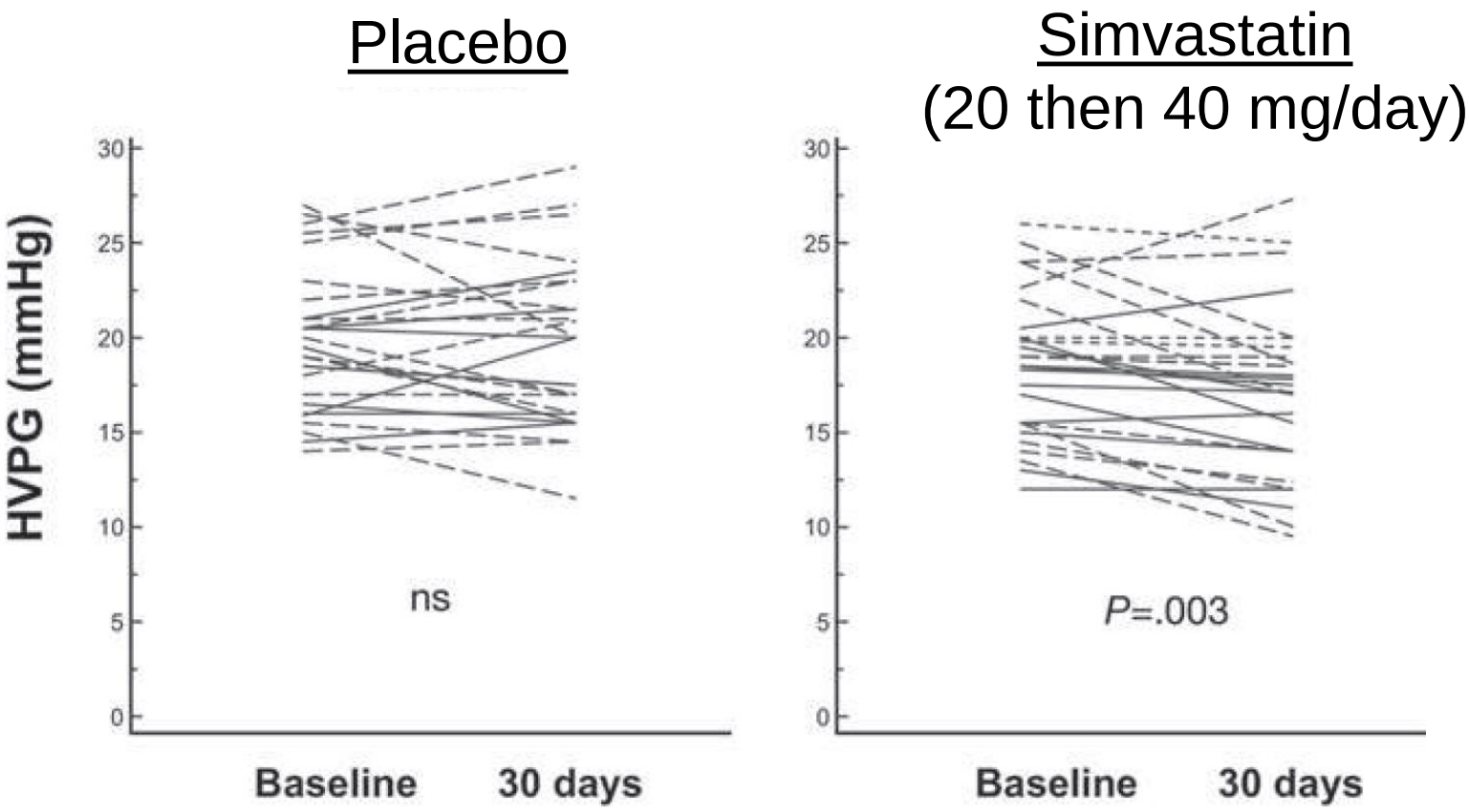
ET: endothelin
NO: nitric oxide

Trebicka, Hepatology 2007
Marrone, J Hepatol 2013

Rockey, Hepatology 2008
Garcia-Pagan, J Hepatol 2012

Simvastatin to target hepatic vascular resistance

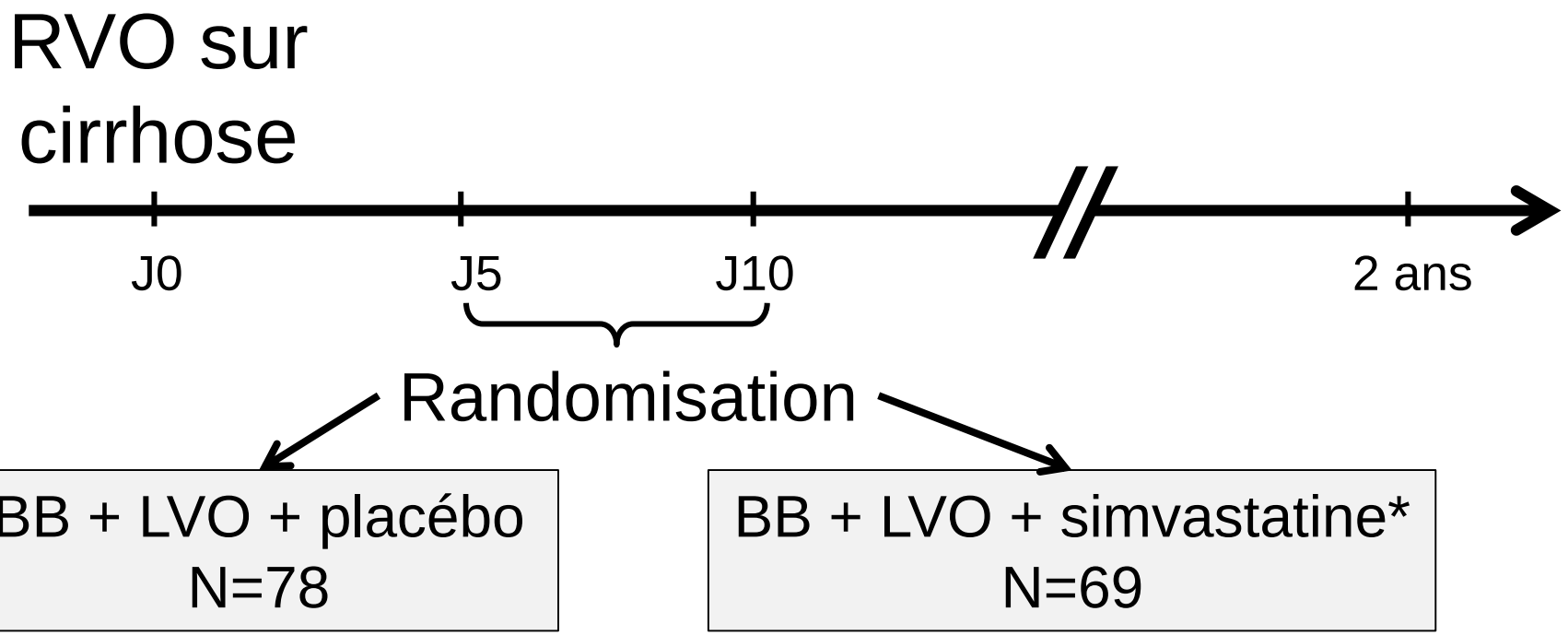
Double-blind randomized trial, 59 patients



Abraldes, Gastroenterology. 2009

Simvastatin to target hepatic vascular resistance

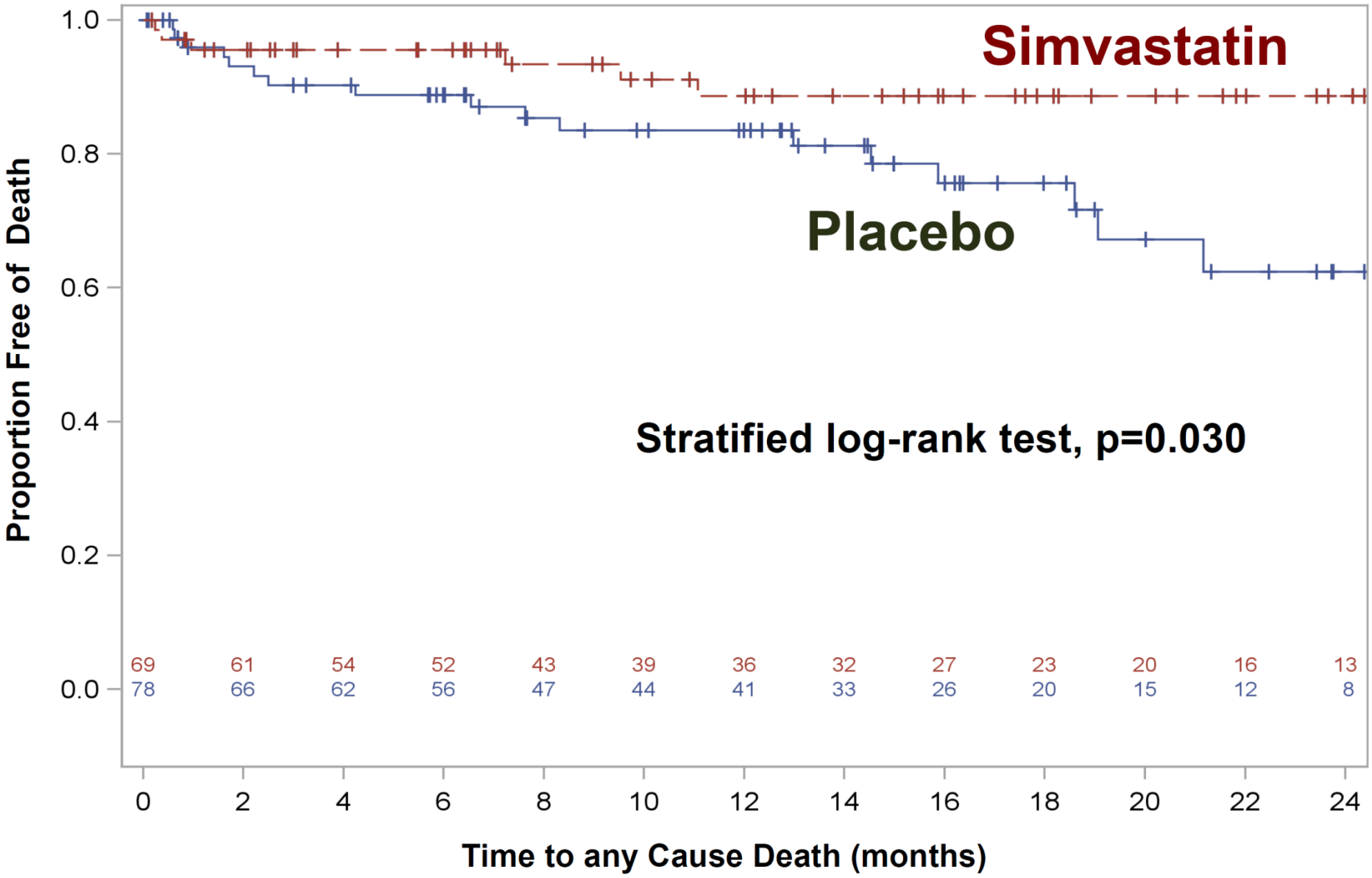
14 centres espagnols
Oct 2010 à Oct 2013



Abraldes, Gastroenterology 2016

* 20 mg/j pdt 2 sem puis 40 mg/j si bonne tolérance

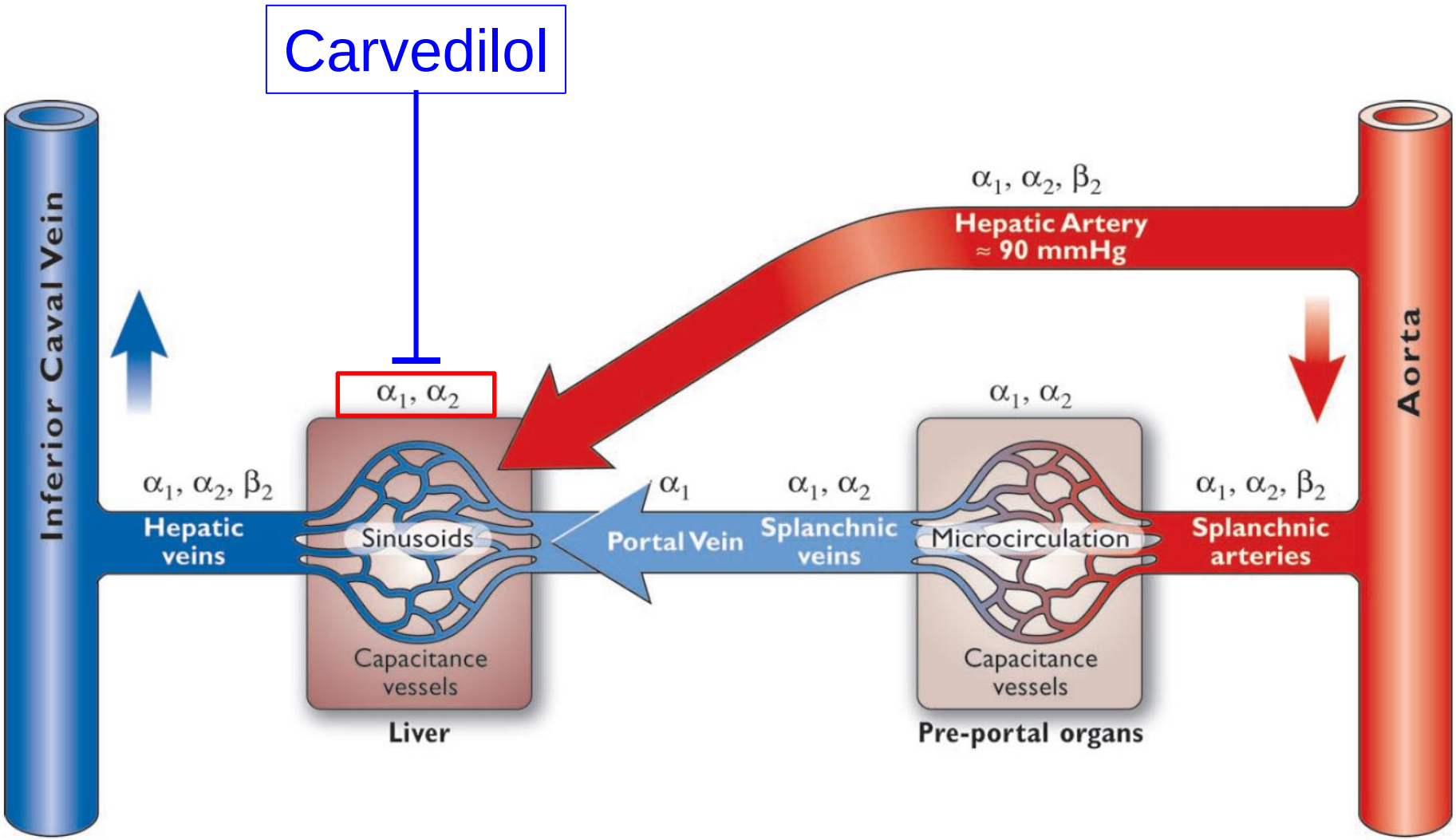
Simvastatin to target hepatic vascular resistance



Abraldes, Gastroenterology 2016

Cause of death	Placebo (n = 78)	Simvastatin (n = 69)
Overall	17 (21.5)	6 (8.6)
Bleeding	5 (6.4)	1 (1.4)
Spontaneous bacterial peritonitis	3 (3.8)	0 (0)
Other infections	0 (0)	1 (1.4)
Alcoholic hepatitis	0 (0)	1 (1.4)
Progression of liver disease	3 (3.8)[a]	3 (4.3)
Hemoperitoneum	1 (1.3)	0 (0)
Cholangiocarcinoma	1 (1.3)	0 (0)
Lymphoproliferative disease	1 (1.3)	0 (0)
Small-cell lung cancer	1 (1.3)	0 (0)
Cerebral edema post correction of severe hyperglycemia	1 (1.3)	0 (0)
Incarcerated umbilical hernia secondary to tense ascites	1 (1.3)	0 (0)

Abraldes, Gastroenterology 2016



Reiberger, J Hepatol 2017

Gelman, Anesthesiology. 2004

Vascular tone in cirrhosis

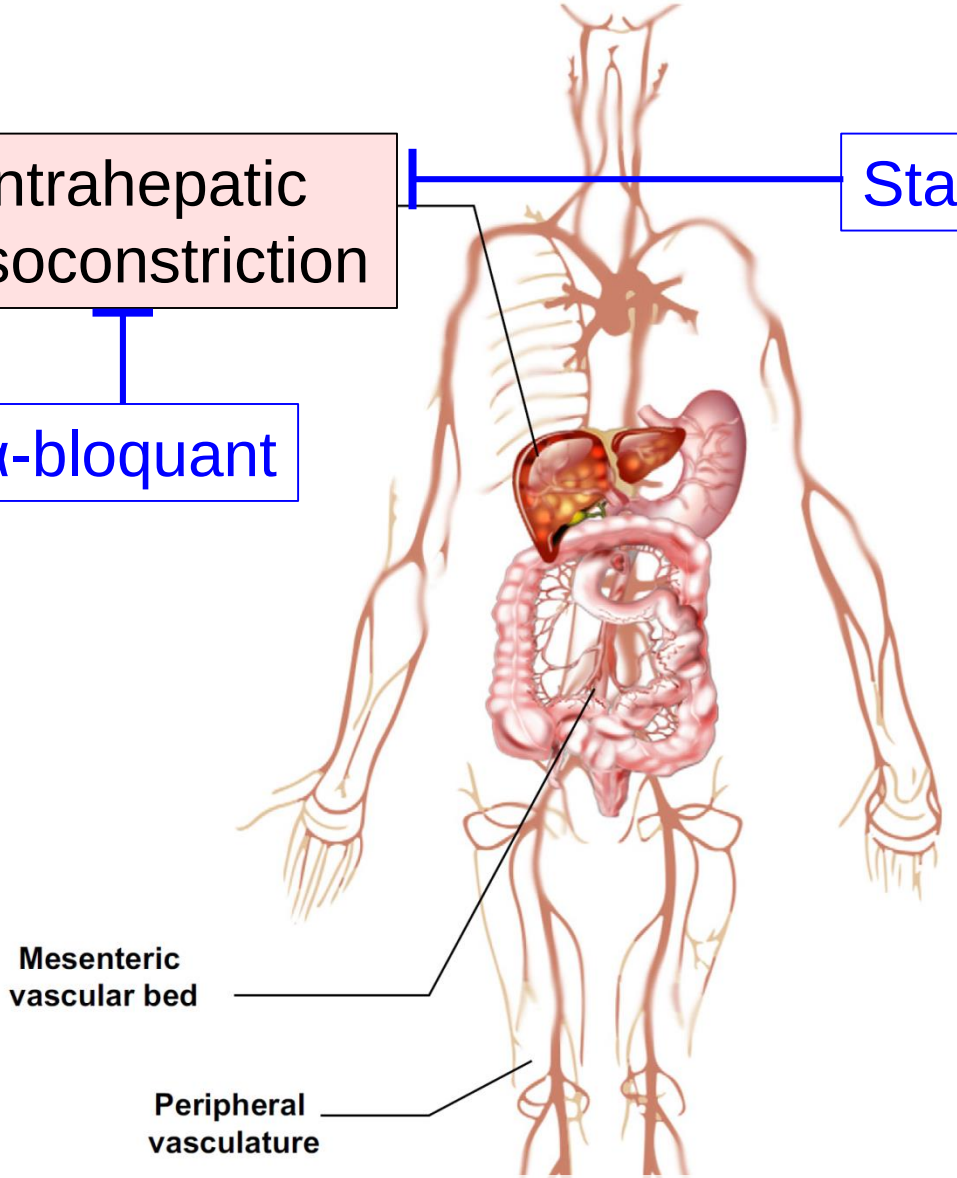
↑ Intrahepatic resistance

Intrahepatic vasoconstriction

Statins

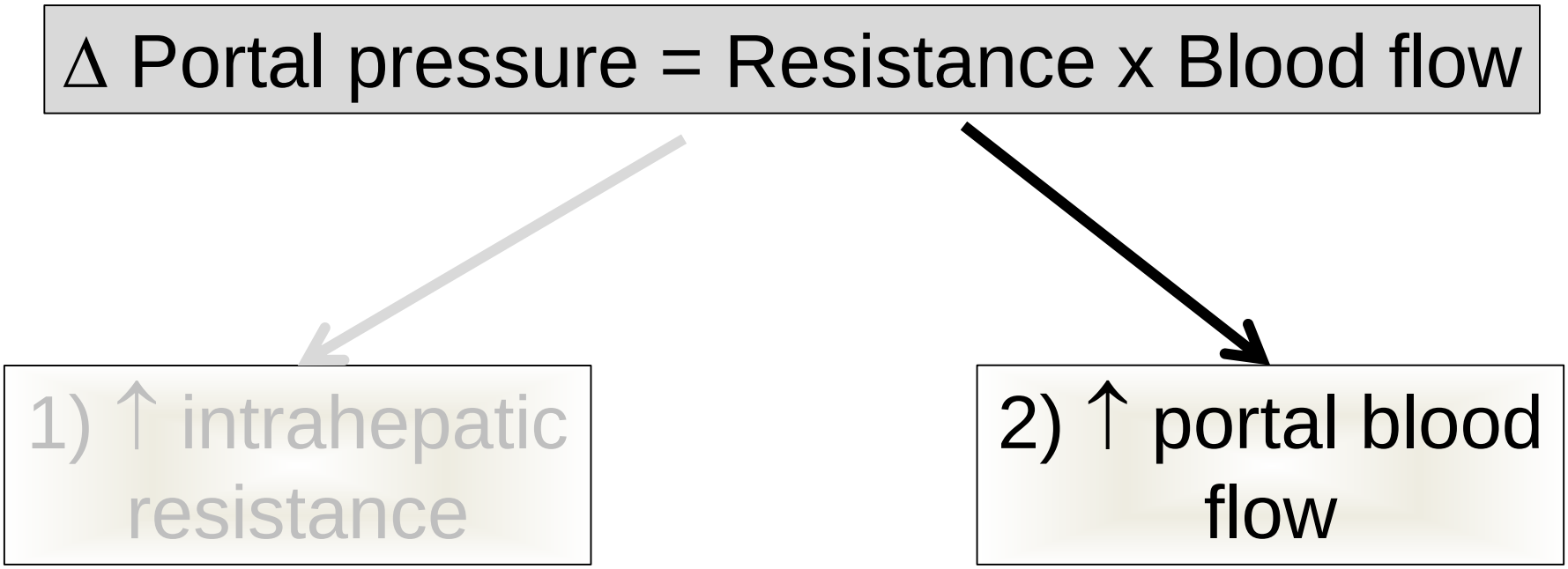
α-bloquant

PORTAL HYPERTENSION



Iwakiri, J Hepatol 2014
Garcia-Pagan, J Hepatol 2012

Pathophysiology of portal hypertension



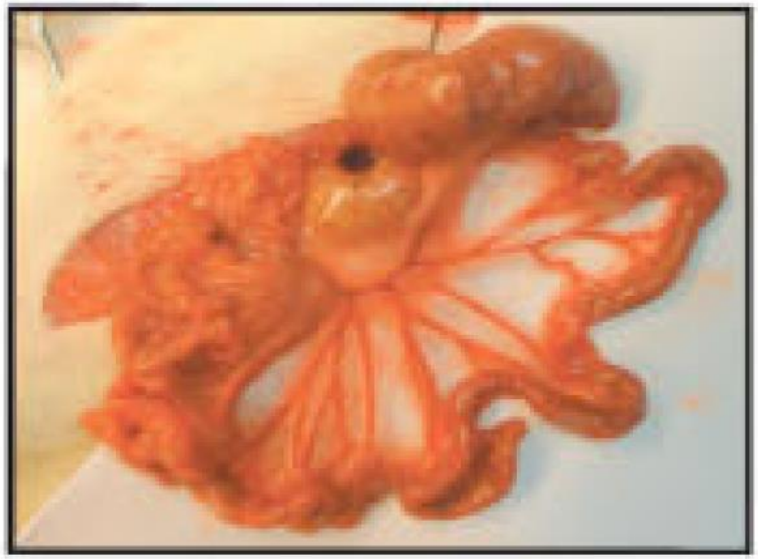
Bosch, J Hepatol 2010

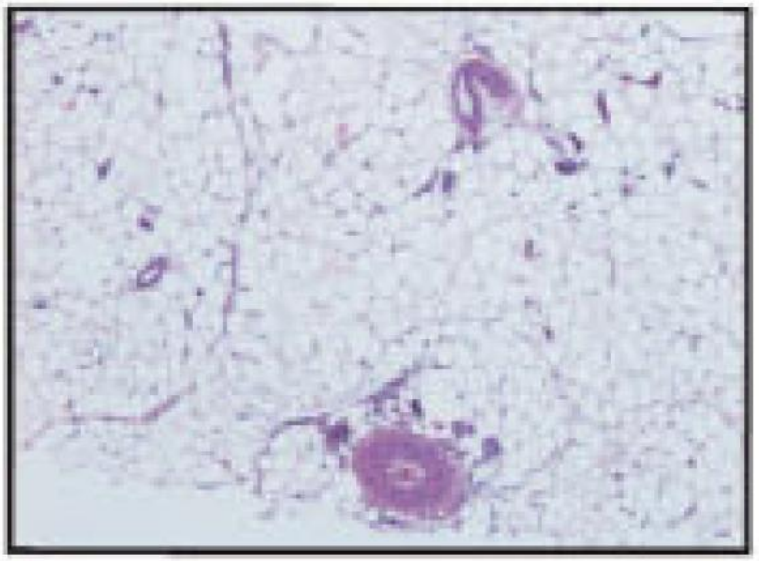
Splanchnic and systemic consequences of portal hypertension

- Dilation of splanchnic arteries
- Increased cardiac output and portal blood flow
- Increased plasma volume
- Portosystemic venous collaterals

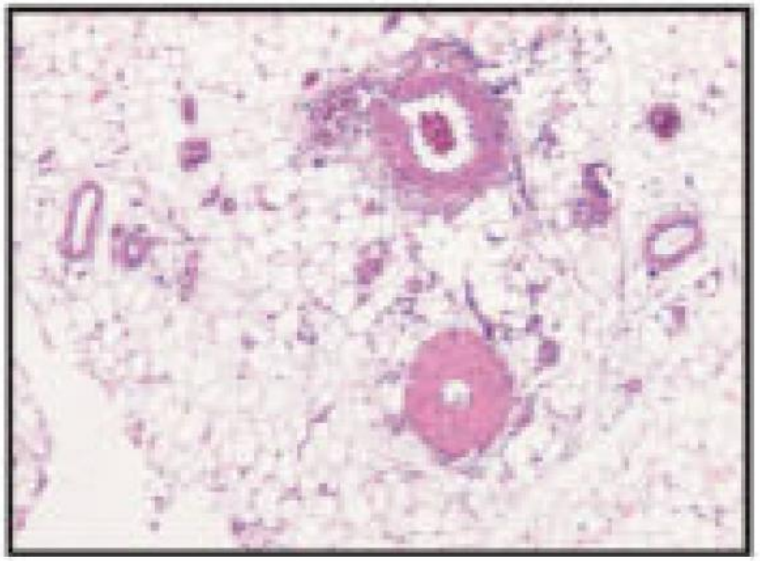
Arterial dilation and angiogenesis

Control rat

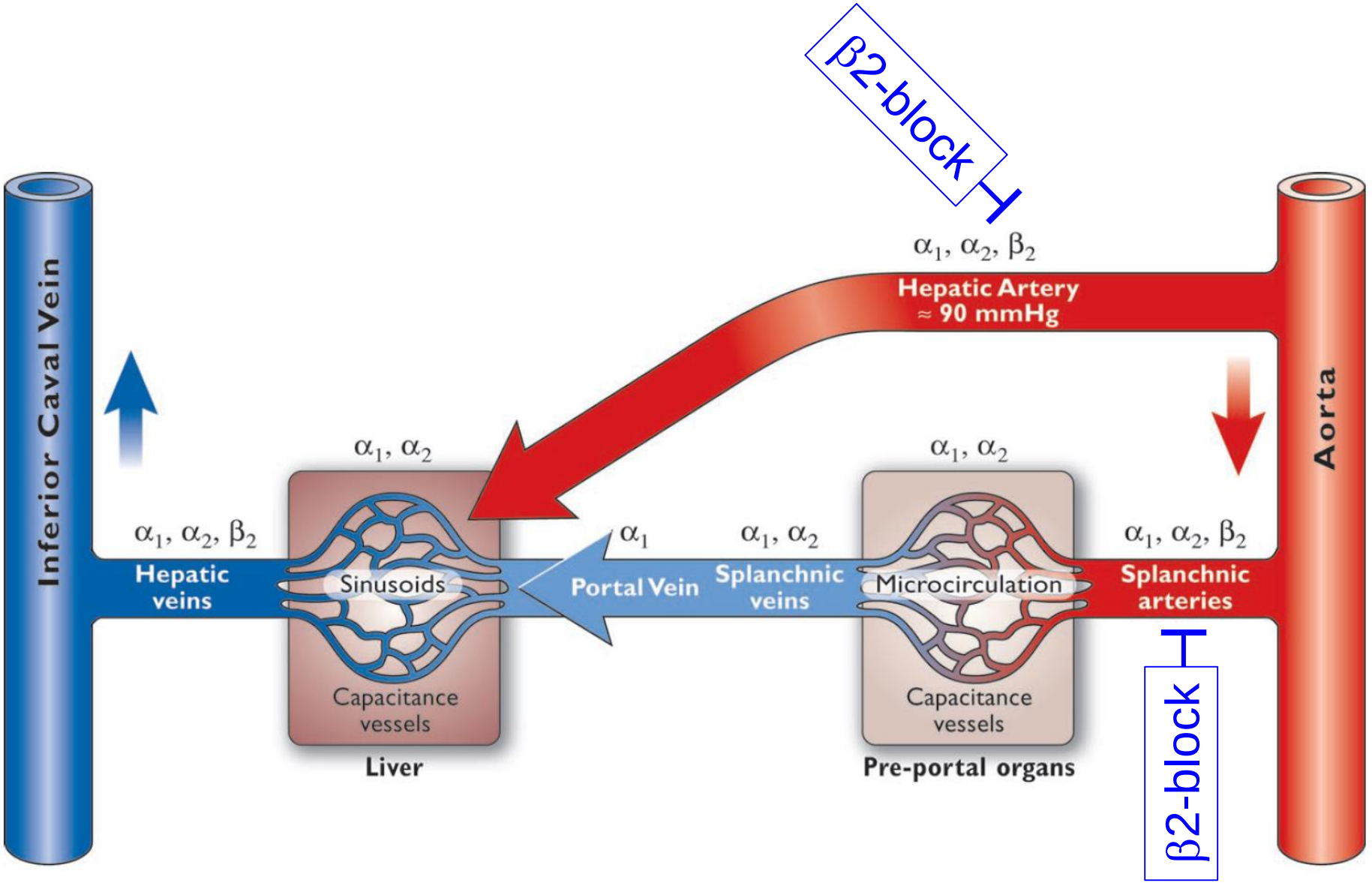




Portal vein stenosis rat



Fernandez *et al.* Hepatology 2007



Gelman, Anesthesiology. 2004

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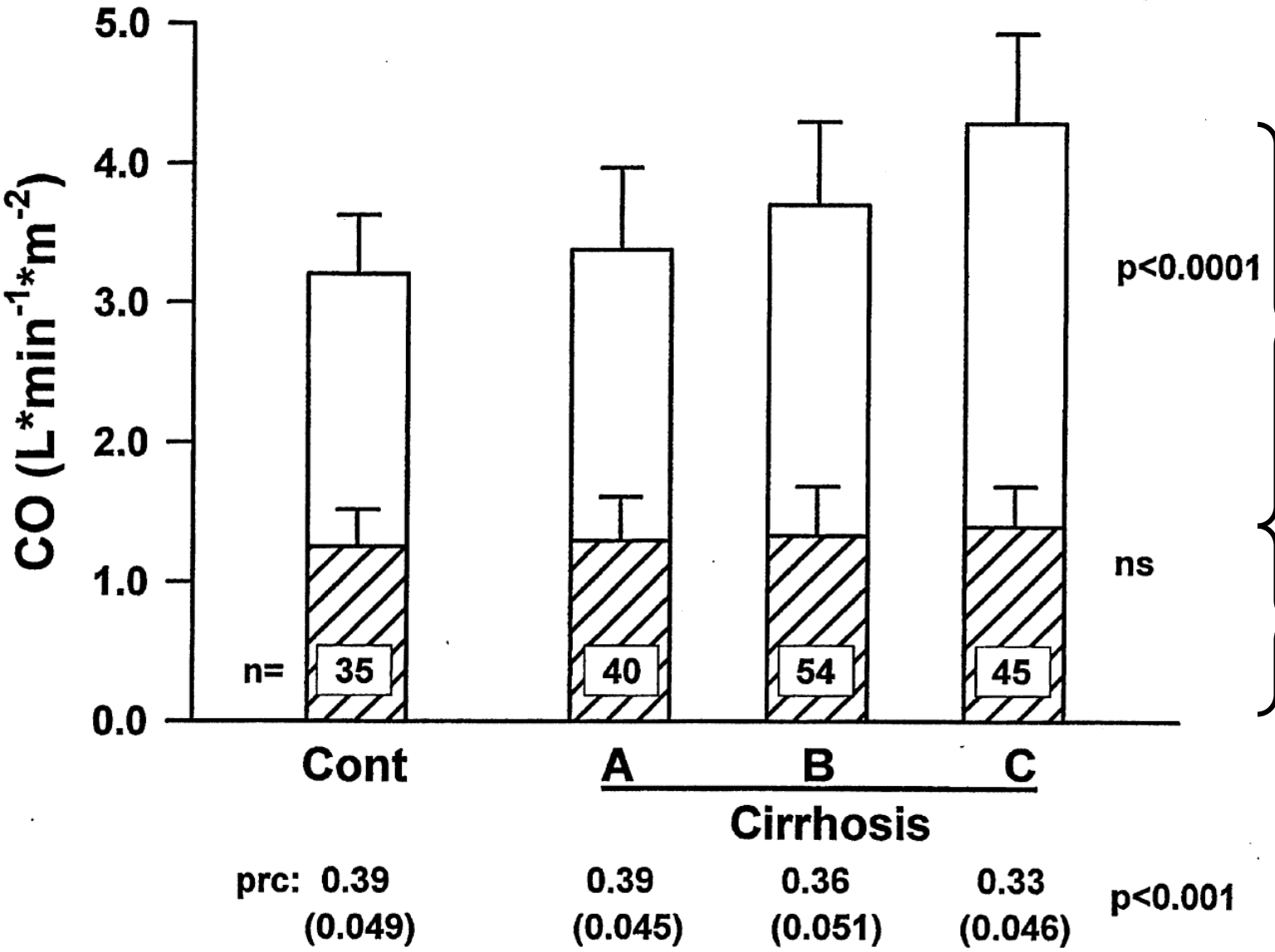
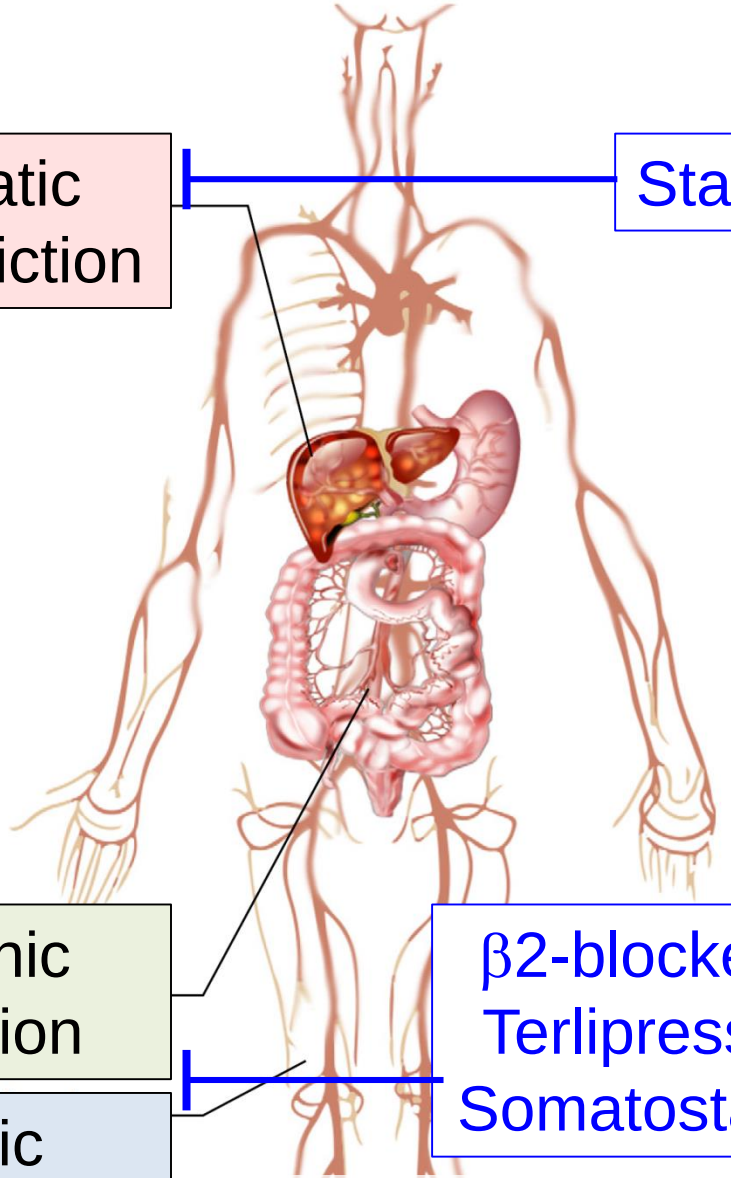
Increased cardiac output and plasma volume



Henriksen, J Hepatol 2001

Vascular tone in cirrhosis



↑ Intrahepatic resistance

Intrahepatic vasoconstriction

Statins

PORTAL HYPERTENSION

↑ Portal blood flow

β1-block

Splanchnic vasodilation

β2-blockers
Terlipressin
Somatostatin

↑ Cardiac output

Systemic vasodilation

Iwakiri, J Hepatol 2014
Garcia-Pagan, J Hepatol 2012

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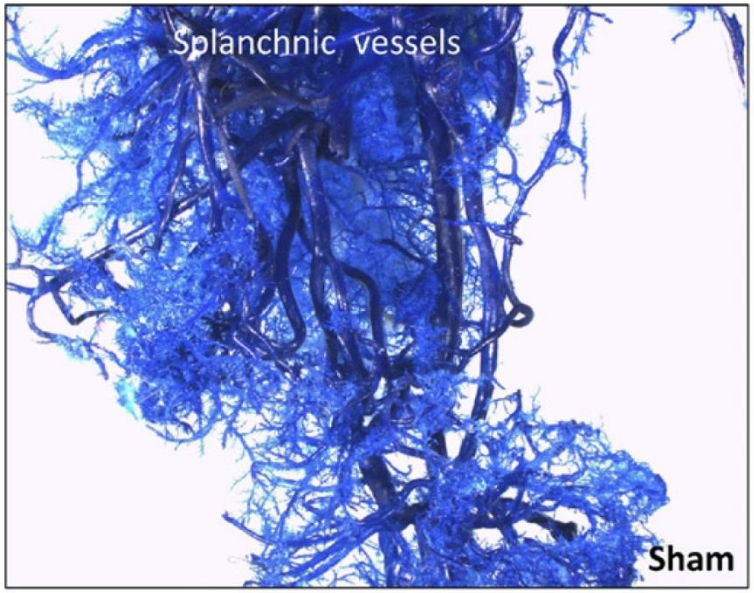
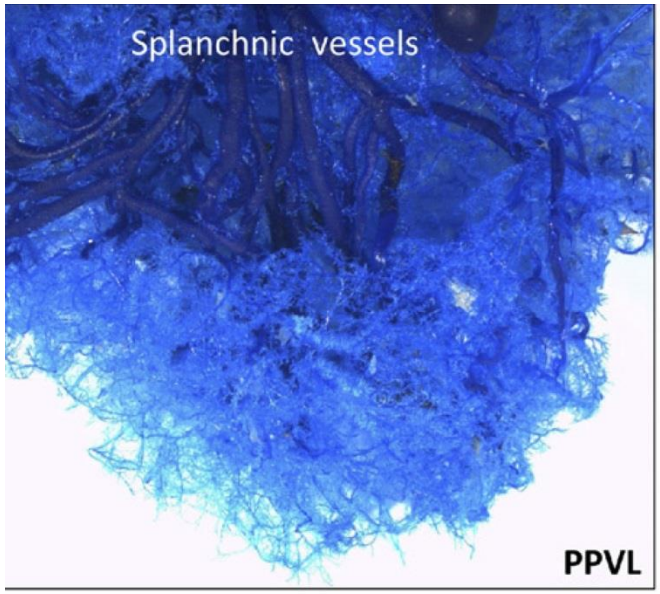
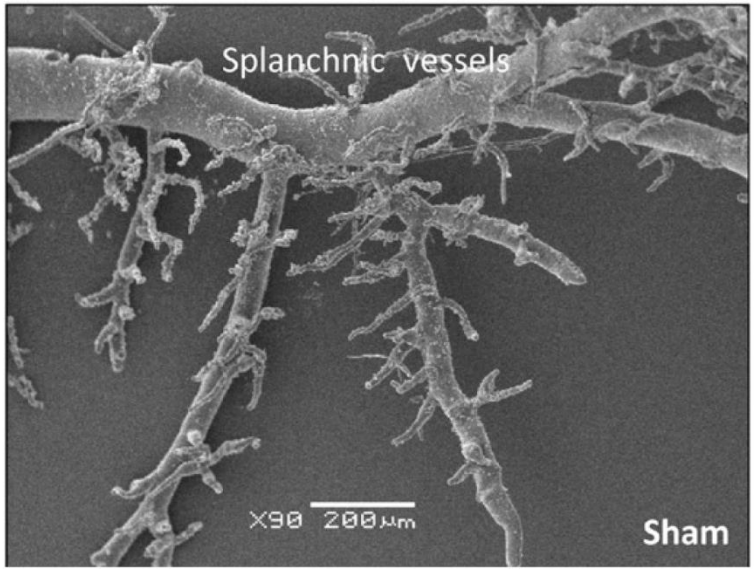
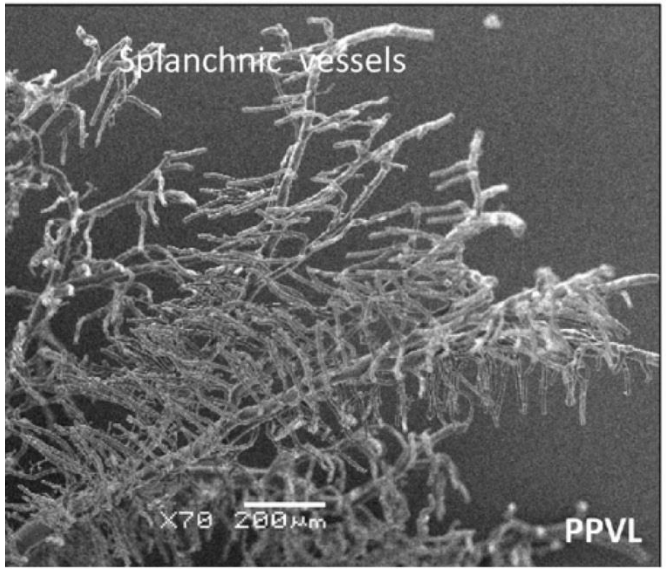
Portosystemic collaterals









Van Steenkiste Gastroenterology 2009

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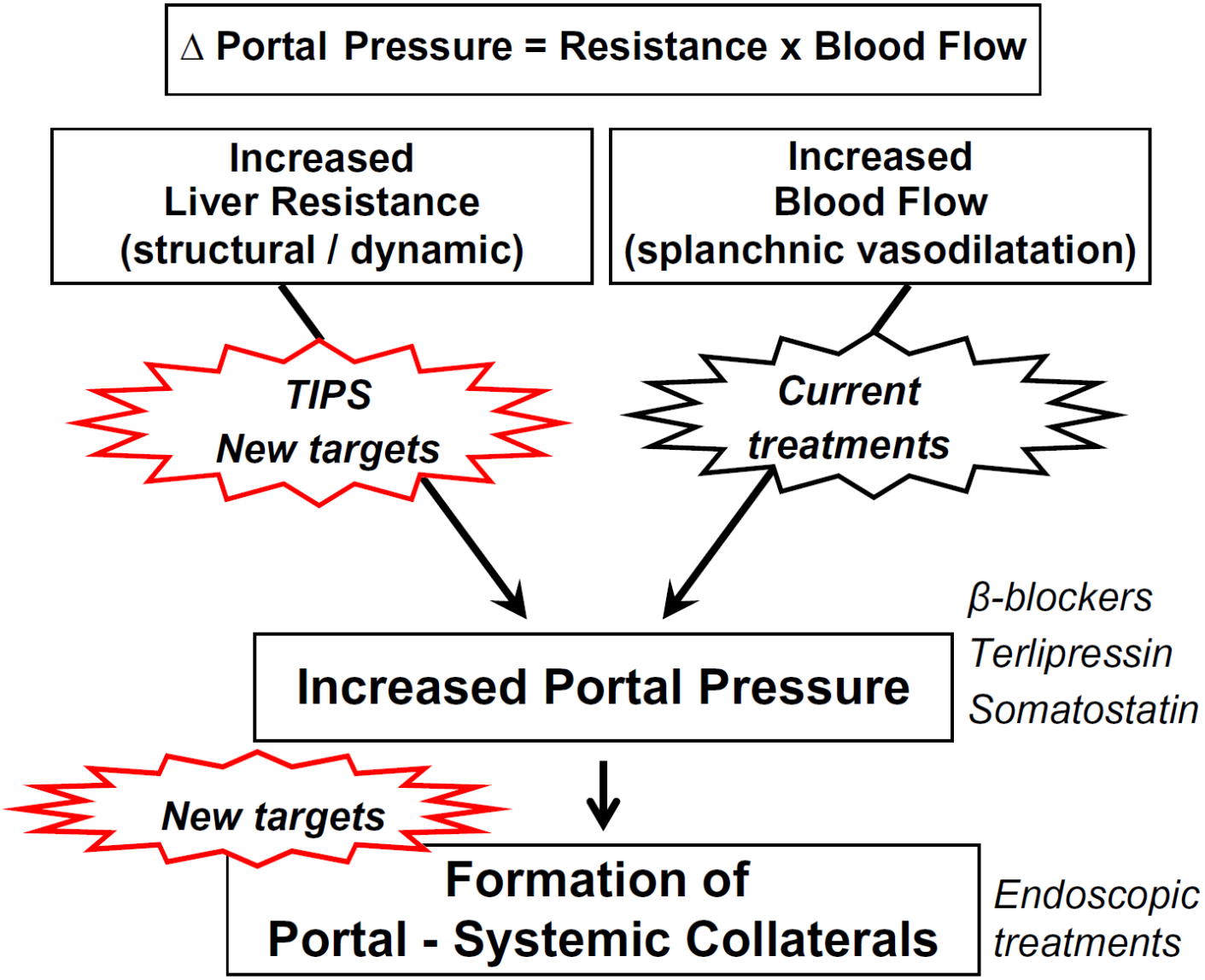

Bosch, J Hepatol 2010

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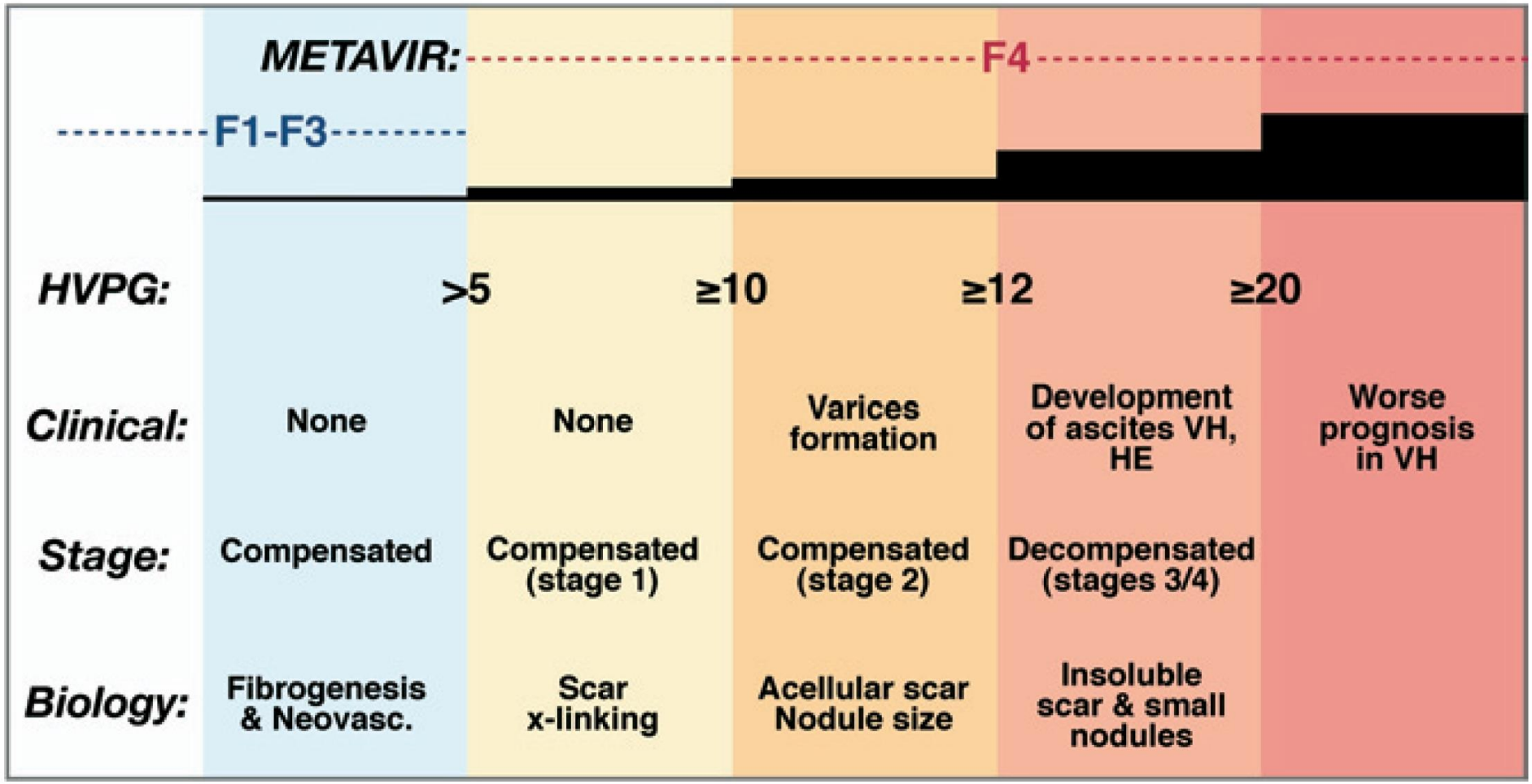
Portal pressure and liver disease progression



HVPG: hepatic venous pressure gradient

Friedman, Gastroenterology 2008

Many applications of HVPG measurement

- Diagnosis and classification of portal hypertension (*e.g.* ascites of unkown origin)
- Preoperative evaluation (hepatic resection)
- Prognosis of portal hypertension and cirrhosis
- Assessment of new agents for portal hypertension
- Surrogate marker in clinical trials (viral and metabolic liver disease)

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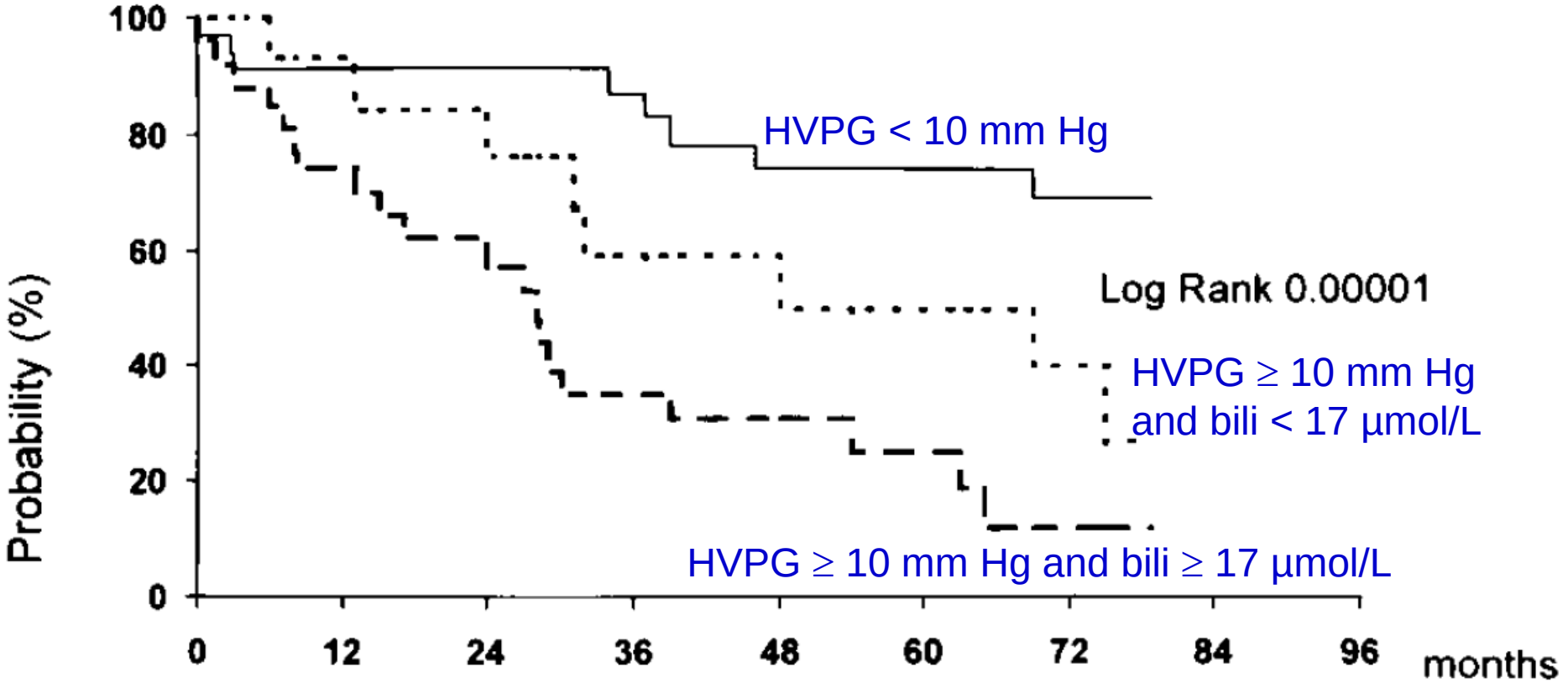
HVPG for preoperative evaluation



Berzigotti Hepatology 2014
Boleslawski *et al.*, Br J Surg 2012
Llovet *et al.*, Hepatology 1999

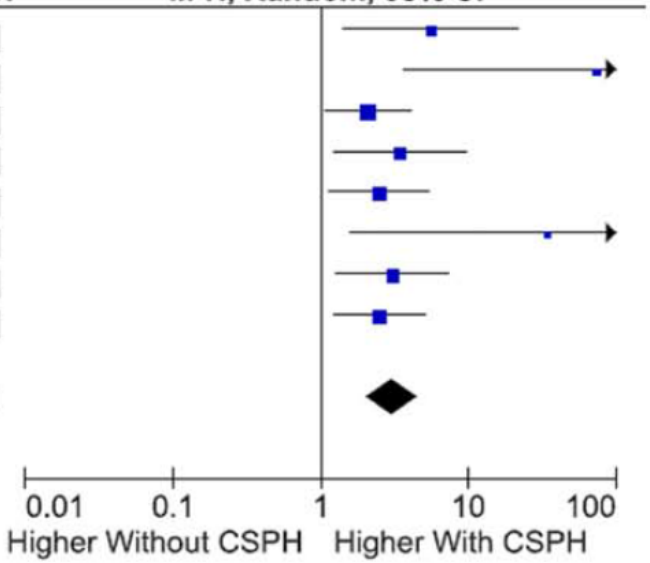
HVPG before liver resection

Décompensation hépatique post-résection hépatique

Study or Subgroup	With PH Events	With PH Total	Without PH Events	Without PH Total	Weight	Odds Ratio M-H, Random, 95% CI
Boleslawski 2012	13	18	7	22	7.7%	5.57 [1.42, 21.86]
Bruix 1996	11	15	0	14	1.8%	74.11 [3.61, 1522.44]
Capussotti 2006	27	99	18	118	22.1%	2.08 [1.07, 4.07]
Cucchetti 2009	11	89	6	152	12.2%	3.43 [1.22, 9.63]
Hidaka2012	15	48	20	129	18.4%	2.48 [1.14, 5.37]
Llop 2012	3	10	0	36	1.7%	34.07 [1.59, 730.64]
Ruzzenente2011	14	44	12	91	15.5%	3.07 [1.28, 7.39]
Santambrogio 2013	18	63	22	160	20.6%	2.51 [1.24, 5.09]
Total (95% CI)		**386**		**722**	**100.0%**	**3.04 [2.02, 4.59]**
Total events	112		85			

Heterogeneity: Tau² = 0.08; Chi² = 9.29, df = 7 (P = 0.23); I² = 25%

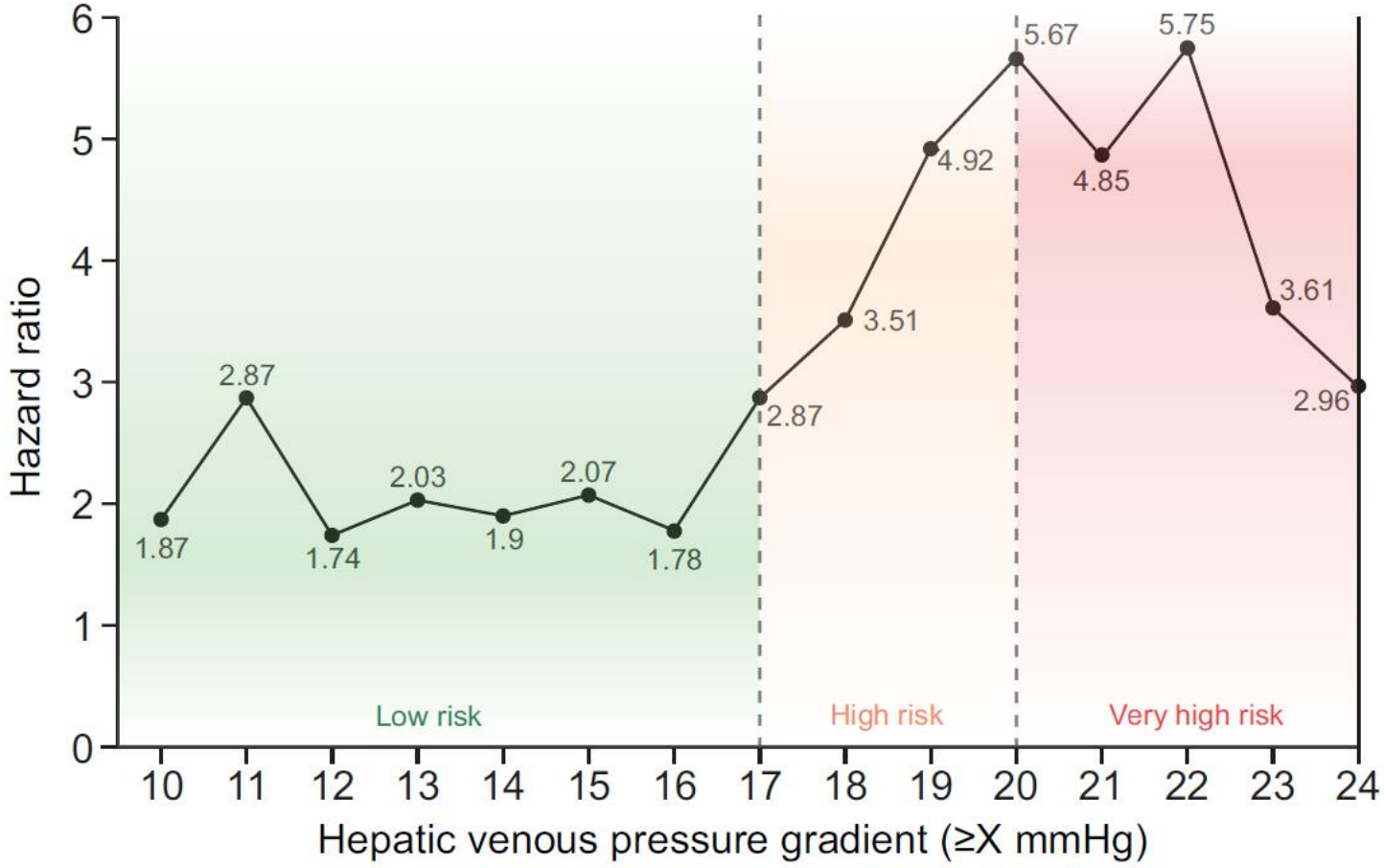
Test for overall effect: Z = 5.31 (P < 0.00001)



Résultats similaires pour mortalité à 1 et 5 ans

Berzigotti, Hepatology 2015

HVPG before extrahepatic surgery



Events	22	22	20	20	19	18	16	16	15	14	14	11	6	4	3
Patients	116	104	98	92	88	75	65	56	46	36	32	20	10	8	7

- 140 patients with cirrhosis: Child-Pugh A/B/C: 59/37/4%
- elective extrahepatic surgery: 121 abdo; 9 cardiovascular/thoracic; 10 ortho

Reverter E, J Hepatol 2019

Many applications of HVPG measurement

- Diagnosis and classification of portal hypertension (*e.g.* ascites of unkown origin)
- Preoperative evaluation (hepatic resection)
- Prognosis of portal hypertension and cirrhosis
- Assessment of new agents for portal hypertension
- Surrogate marker in clinical trials (viral and metabolic liver disease)

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Portal hypertension

- What is portal hypertension?
- Pathophysiology of portal hypertension
- Why to assess portal hypertension?
- How to measure portal hypertension?

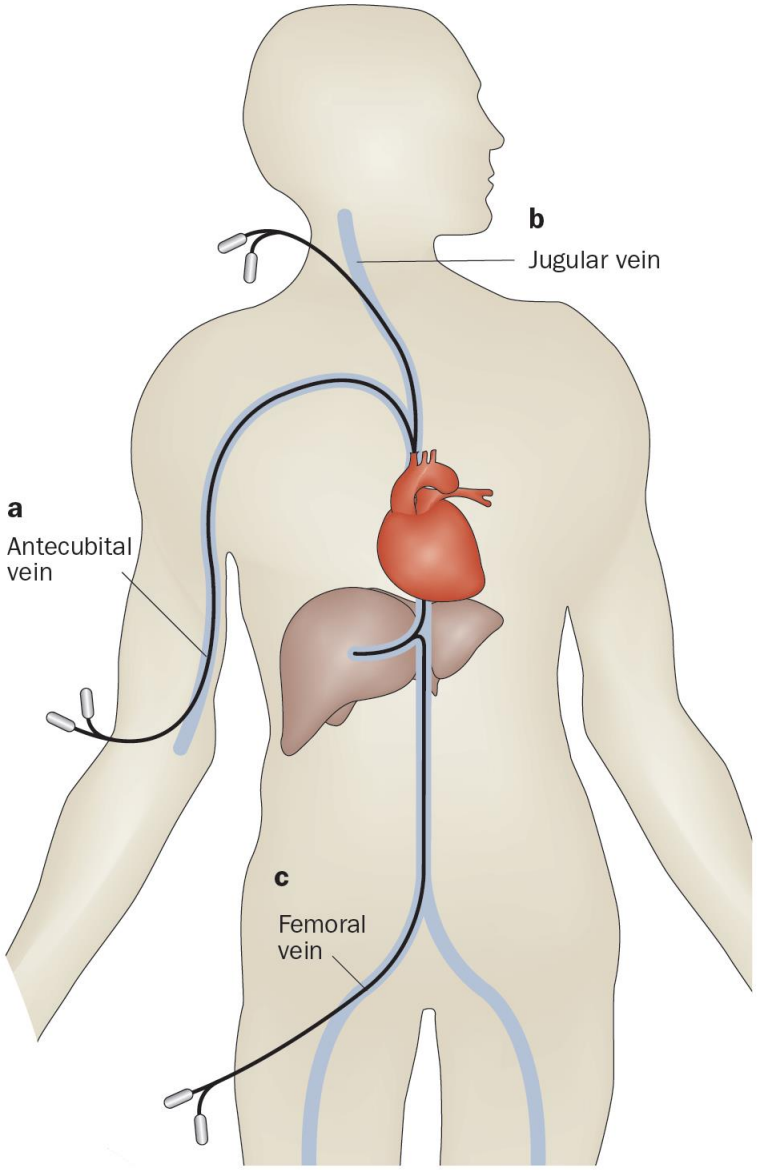
How to measure portal hypertension?

- DIRECT measurement into the portal vein
  - Invasive
  - Tricky

How to measure portal hypertension?

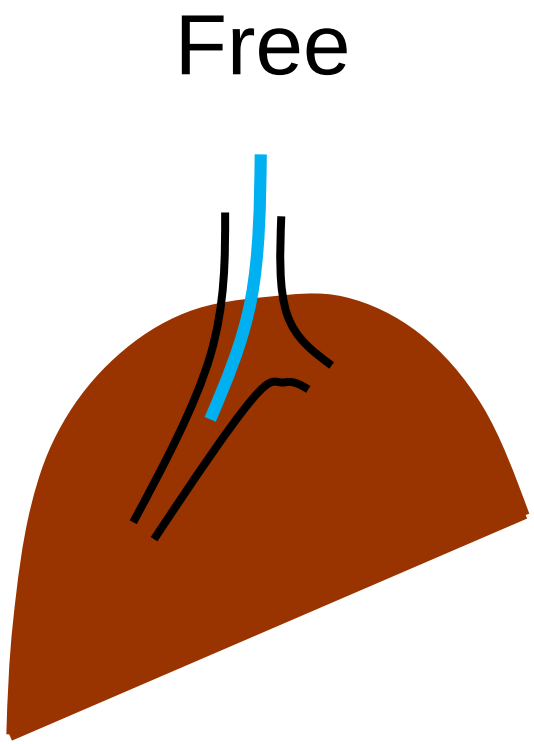
- <u>Indirect:</u> Hepatic venous pressure gradient (HVPG)

HVPG = Wedge – Free hepatic venous pressure

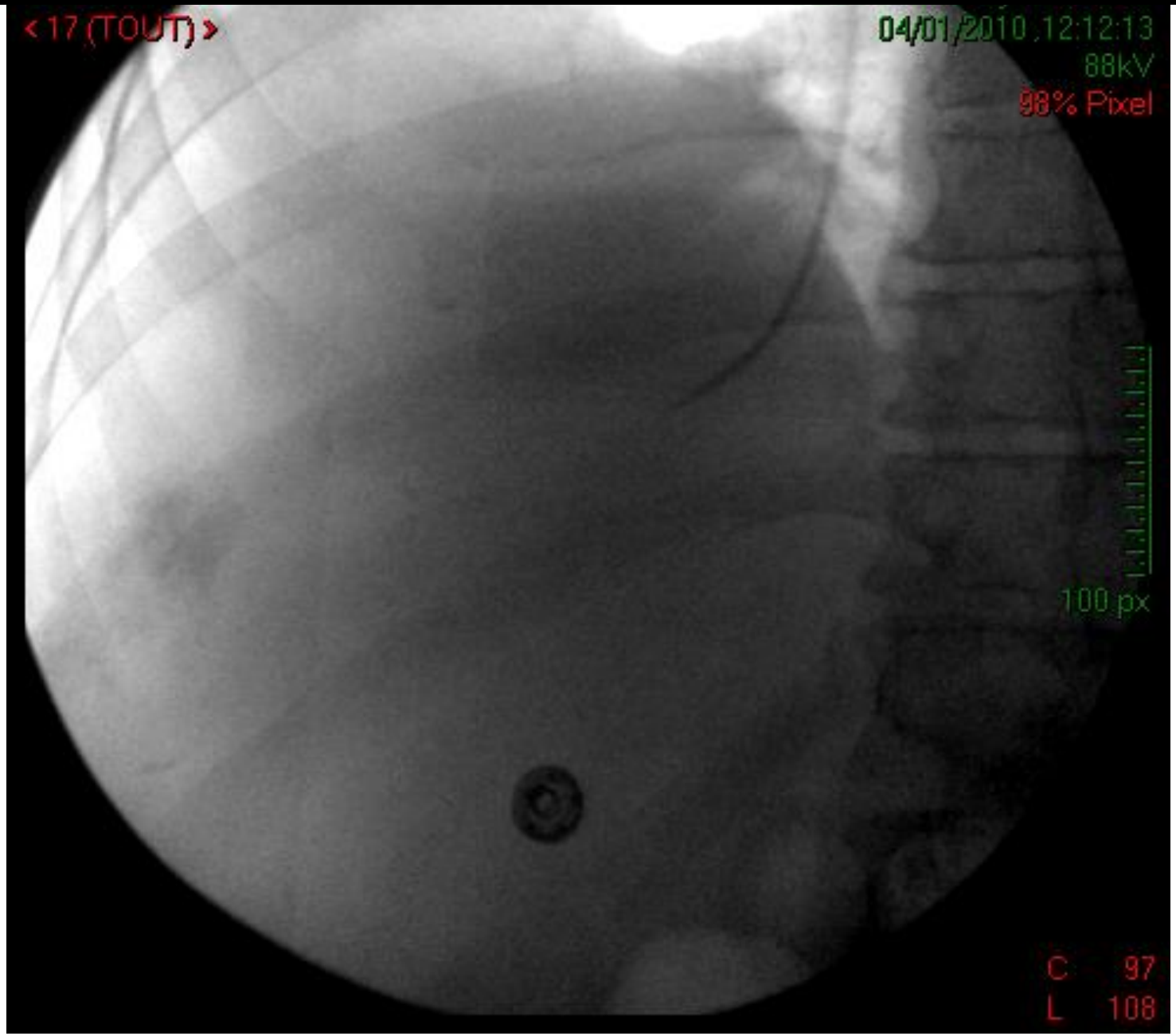


Bosch, Nat Rev Gastroenterol Hepatol 2009

Free hepatic venous pressure

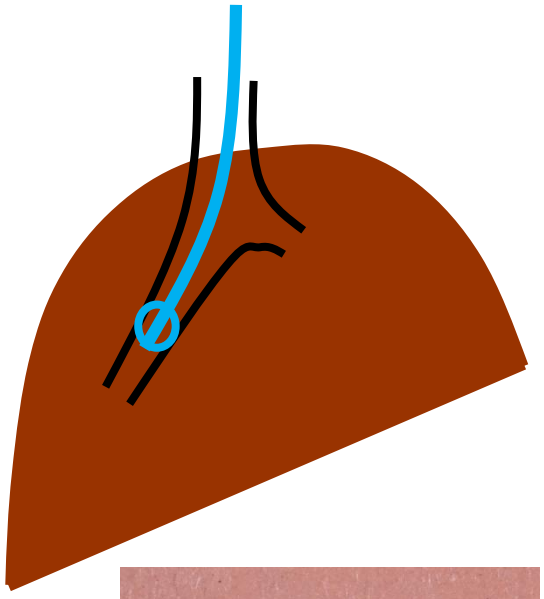


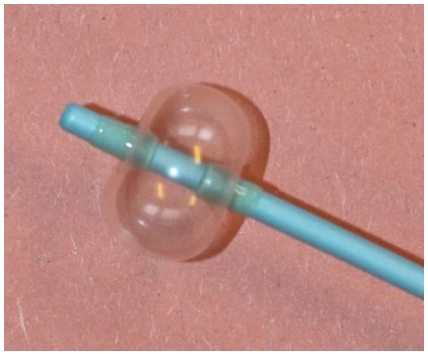
Free hepatic venous pressure



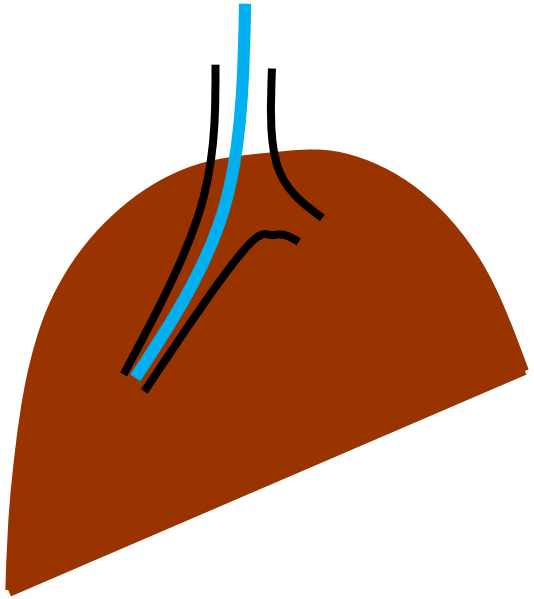
Wedge hepatic venous pressure

Balloon

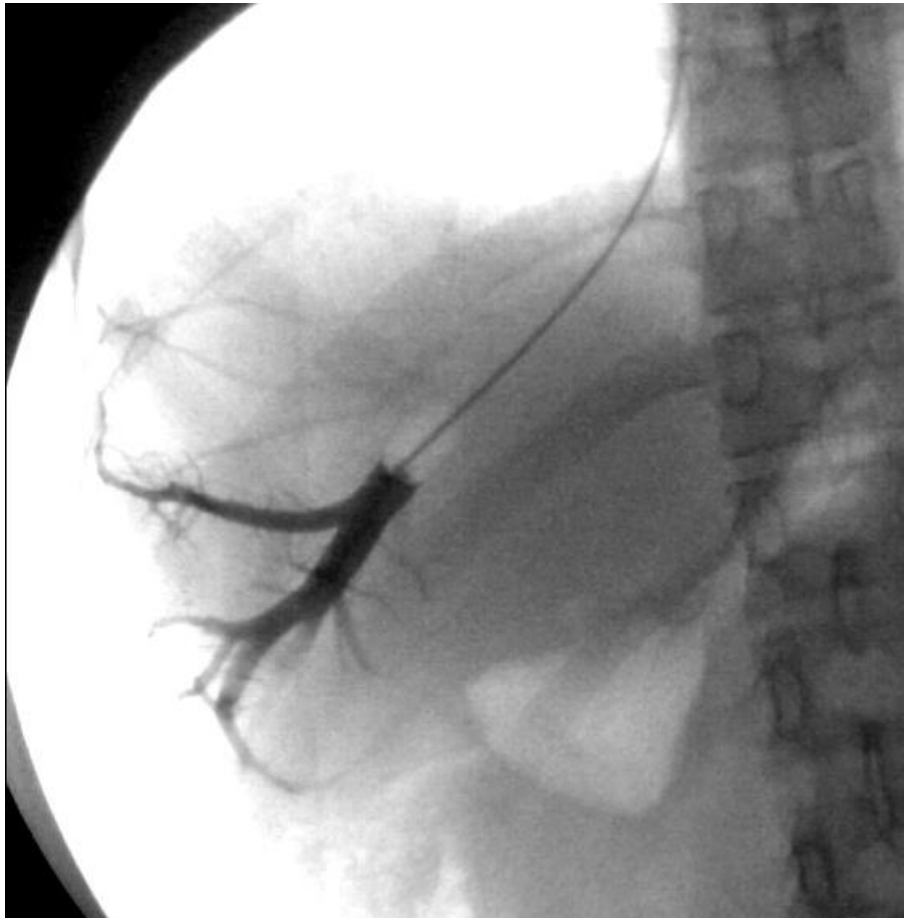


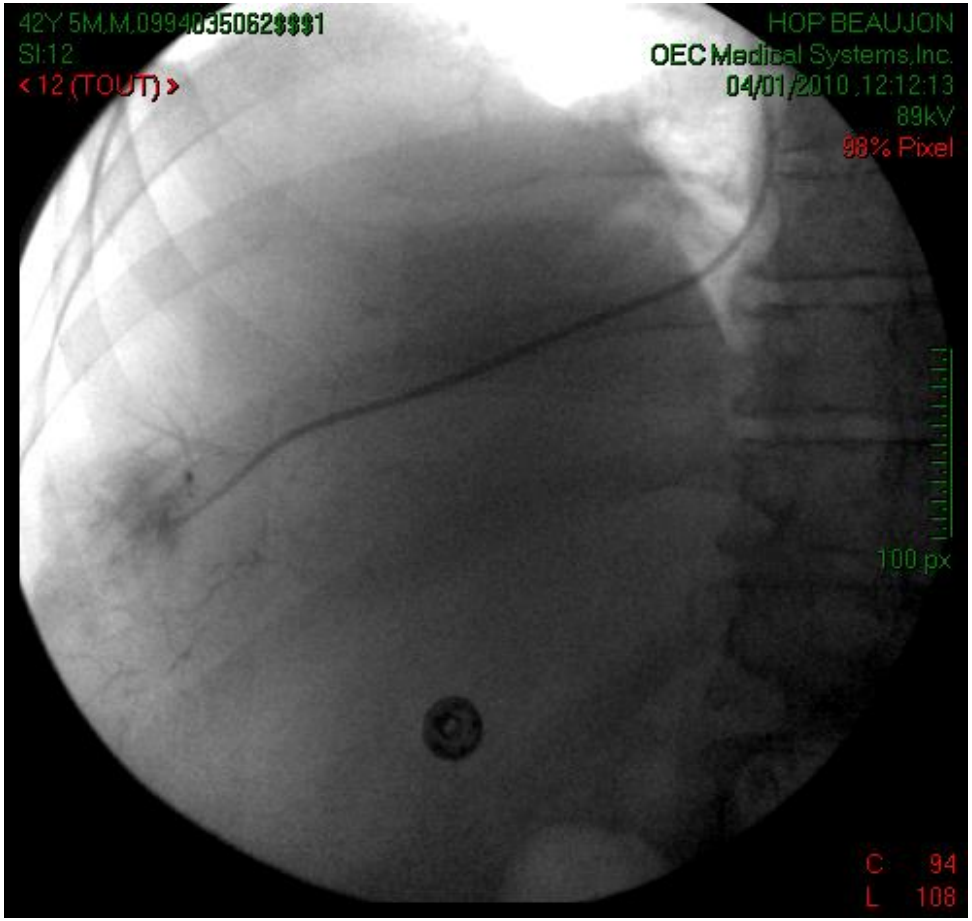


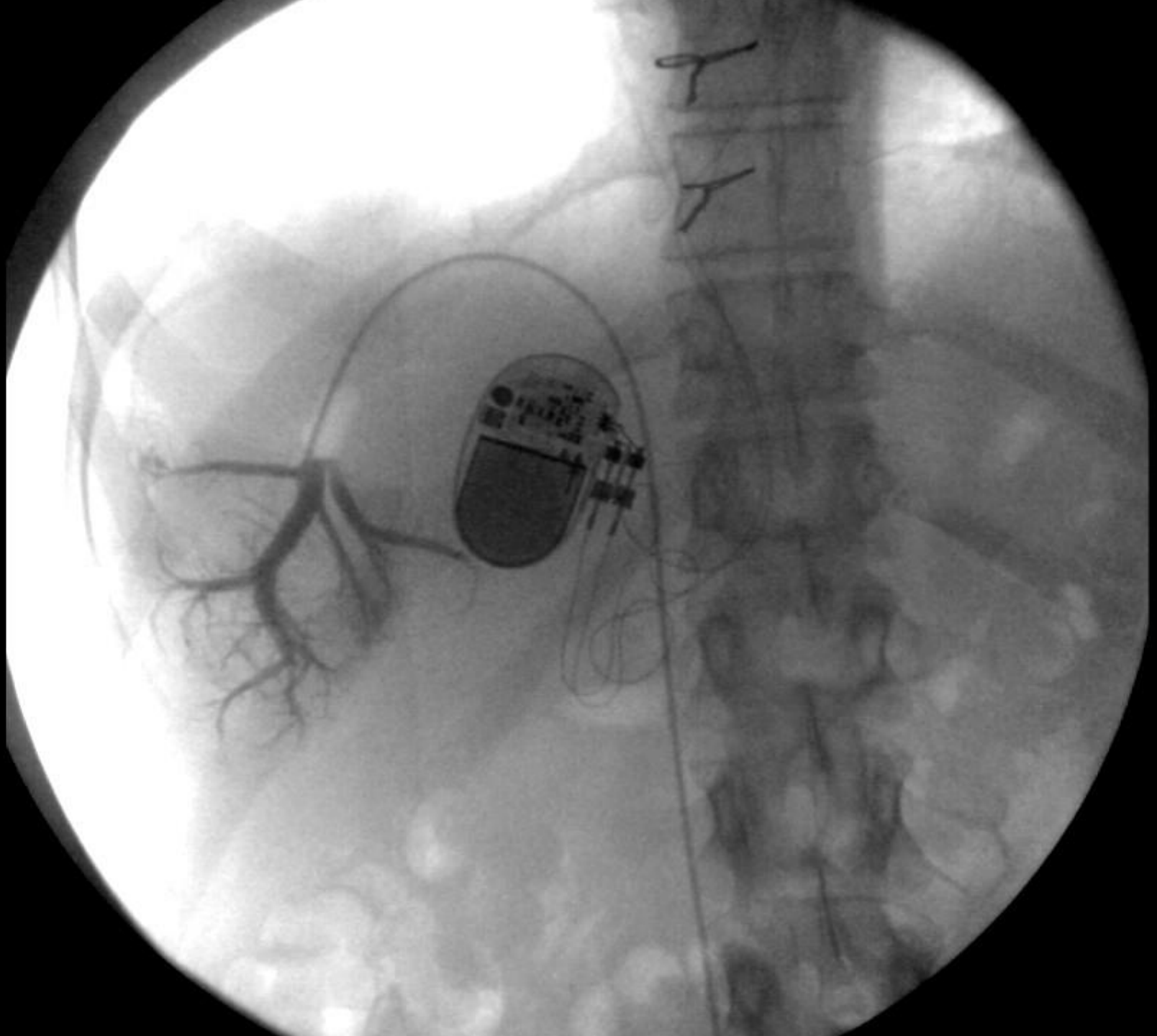
Wedged



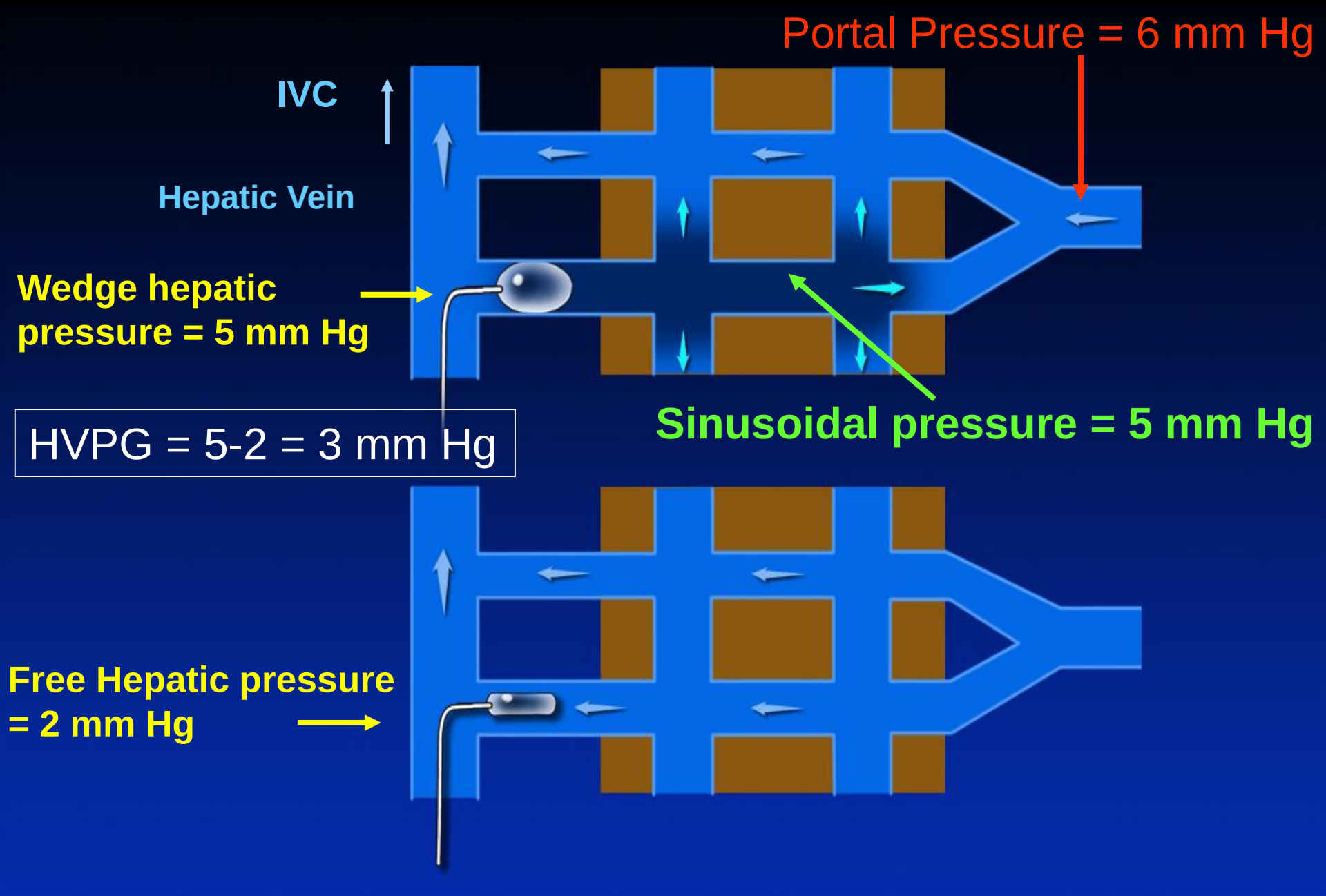
Wedge hepatic venous pressure



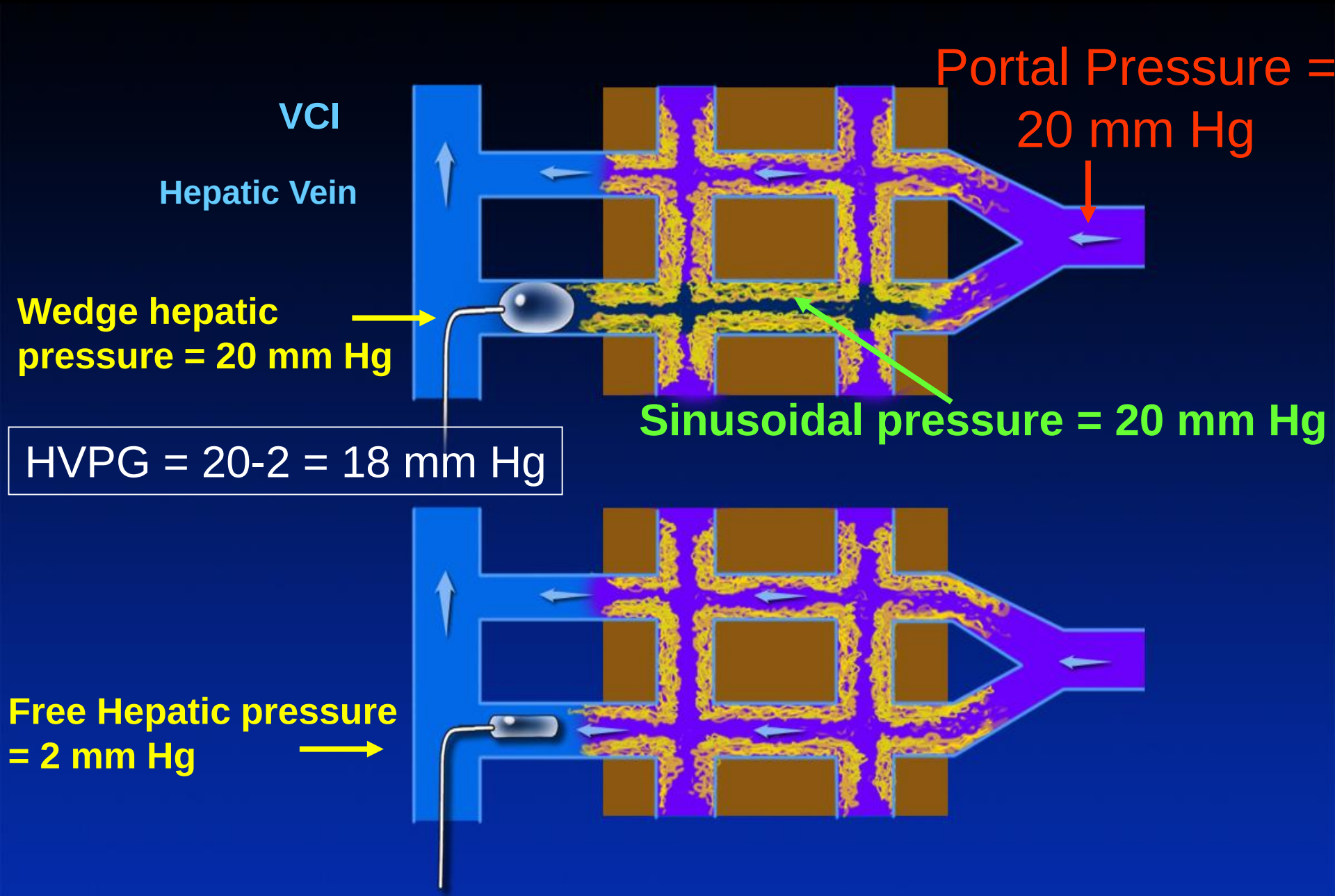




Normal HVPG: 3-5 mmHg



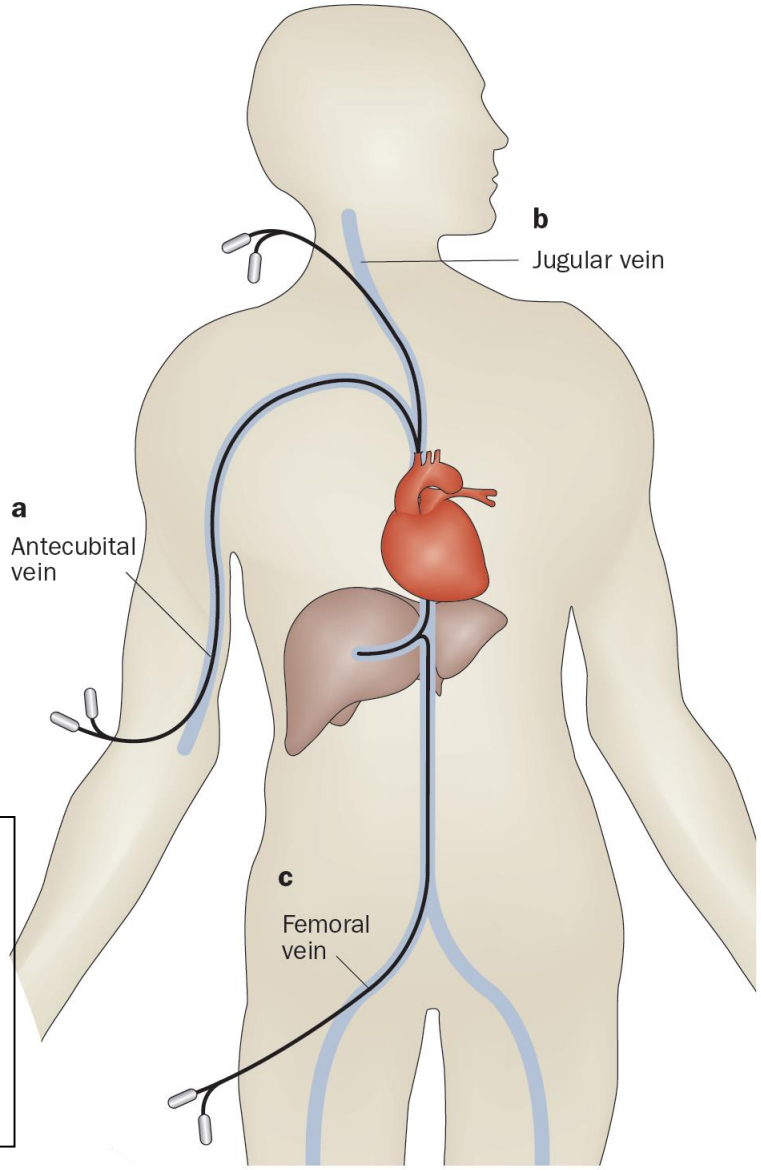
Increased HVPG in Cirrhosis



How to measure portal hypertension?

- <u>Indirect:</u> Hepatic venous pressure gradient (HVPG)

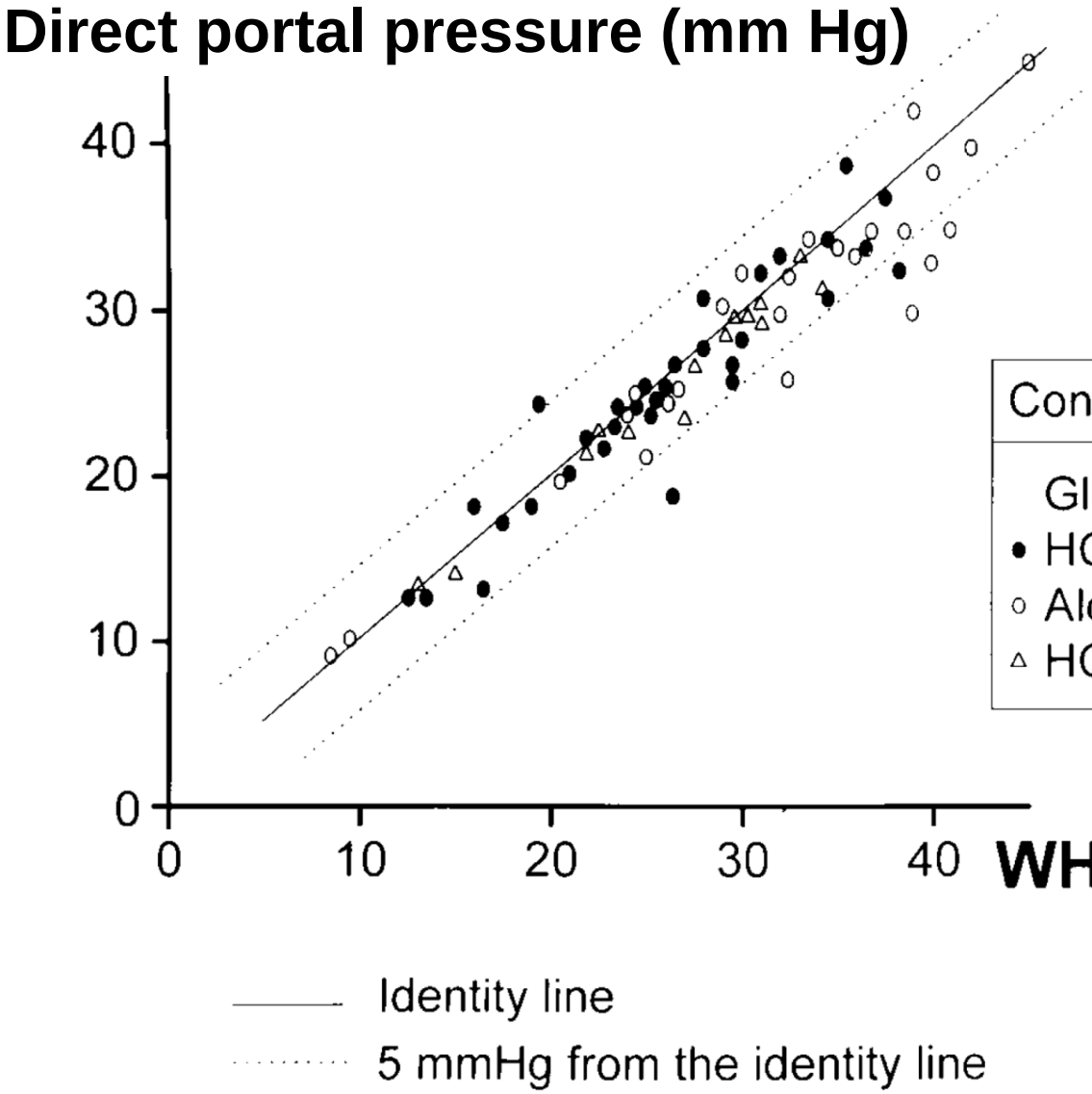
HVPG = Wedge – Free hepatic venous pressure



<u>Not influenced by:</u>
- Changes in intra-abdominal pressure
- Inadequate positioning of the external zero reference point

Bosch, Nat Rev Gastroenterol Hepatol 2009

How to measure portal hypertension?



Concordance	r	Ri
Global series (n=71)	0.95	0.99
• HCV-infection (n=32)	0.95	0.94
○ Alcohol (n=25)	0.91	0.93
△ HCV+ alcohol (n=14)	0.92	0.97

p<0.00001 in all cases

Perello, Hepatology 1999

Conclusions : Portal hypertension

- Portal hypertension is responsible for the main complications of cirrhosis
- Although the increase in intrahepatic resistance accounts for 2/3 of portal hypertension, current therapies act on the systemic component
- HVPG reliably assesses portal pressure
- HVPG is particularly useful when the cause of ascites is unclear and to predict post-operative outcome