Pathophysiology of portal hypertension in PVT without cirrhosis: similarities and differences with cirrhosis

Juan Carlos Garcia-Pagán
Barcelona Hepatic Hemodynamic Lab. Liver Unit.
Hospital Clinic

Paris Portal Vein thrombosis meeting

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Increased resistance: Main pathophysiological mechanism leading to PH

Cirrhosis

Increased Vascular Tone

Structural Alterations

Increased Intrahepatic Resistance

Portal Hypertension

Porto-systemic Collaterals

Splanchnic and Systemic vasodilatation

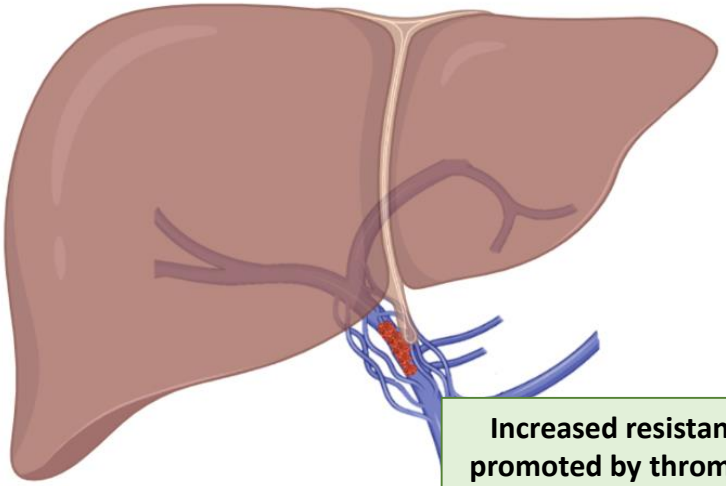
Increased Portal Blood Flow

Arterial Hypotension Effective Hypovolemia

Vasoactive system Activation(NE, A-II, etc.)

Hypervolemia NA and wáter retention

PVT



Increased resistance promoted by thrombus

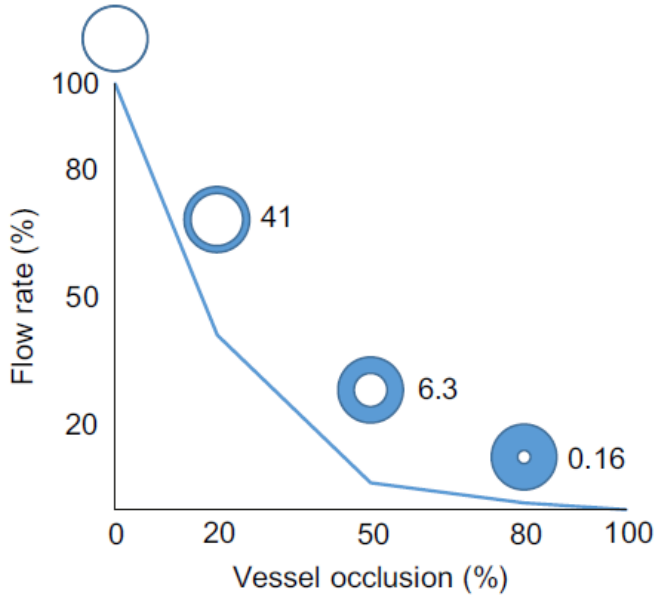
Portal Hypertension

Thrombosis does not require to be occlusive to markedly increase portal pressure.

According to Poiseuille's law

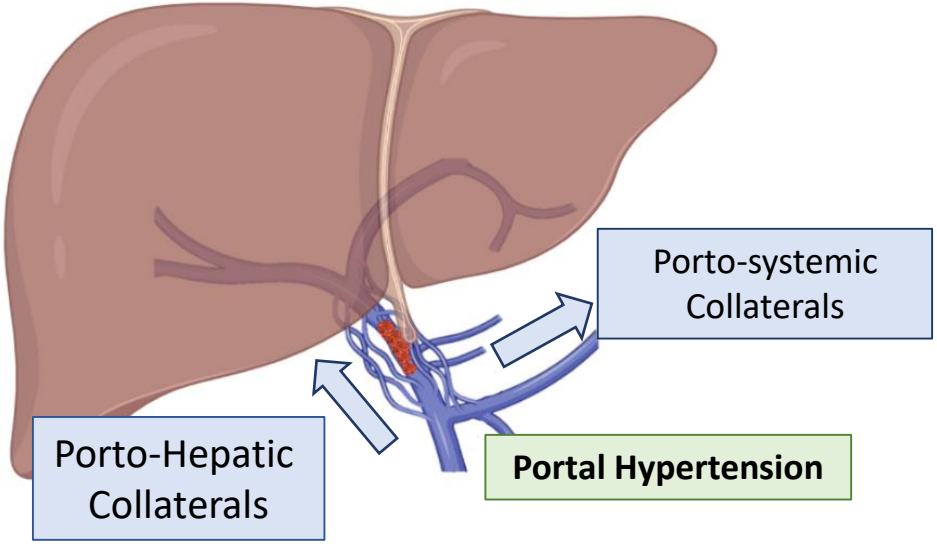
- Δp is the pressure difference,
- L is the length of pipe,
- μ refers to viscosity,
- Q is the flow,
- R is the radius,

$$\Delta p = \frac{8\mu LQ}{\pi R^4}$$



Occlusion of 50% of the vessel, already marked increases in resistance and then in Pressures!

PVT



- Patients with PVT, also develop **porto-hepatic collaterals** that try to decompress the system but **perfusing the liver**
- Porto-splenic-mesenteric/hepatic collaterals (US-Doppler) very rare in diseases with PH and with increased resistance at intrahepatic level (Cirrhosis; PSVD with PH)

Do patients with PVT develop systemic/splanhnic vasodilatation?

Hemodynamic Changes in Patients with Portal Venous Obstruction

DIDIER LEBREC, CHRISTIAN BATAILLE, ERIC BERCOFF, AND DOMINIQUE VALLA

Hepatology 1983

	PVO (n=5)	Cirrhosis (n=10)	Healthy (n=10)
Cardiac Index (l.min.m-2)	3.78 ± 0.63*	3.54 ± 0.59*	2.90 ± 0.38
SVR (dynes.sec.cm-5)	1.24 ± 269*	1.39 ± 373*	1.61 ± 283

- Conclusion of the study: PVO Hyperdynamic circulation/systemic vasodilatation similar to that observed in cirrhosis.
- Few patients
- No data on patients characteristics. No adequate matching.

Hyperkinetic circulatory syndrome in patients with presinusoidal portal hypertension

Effect of propranolol

Alain Braillon, Richard Moreau, Antoine Hadengue, Dominique Roulot, Raymond Sayegh and Didier Lebrec

Journal of Hepatology, 1989;9:312–318

	PVO (n=11)	Normal Values		Baseline (n=12; 10 PVO)	15 min afer Propranolol
Heart Rate (bpm)	81.3 ± 11.9	60-95	Heart Rate (bpm)	85.1 ± 9.7	70 ± 8.6*
MAP (mmHg)	86.3 ± 17.2	80-95	MAP (mmHg)	86.4 ± 16.2	88.8 ± 14
Cardiac Index (l.min-1.m-2)	4.63 ± 1.26	2.5-4.0	Cardiac Index (l.min-1.m-2)	4.6 ± 1.74	3.3 ± 0.6*
iSystemic VR (dyn.s.cm-5.m-2)	1578 ± 598	1600-2580	iSystemic VR (dyn.s.cm-5.m-2)	1597 ± 609	2104 ± 625*
Azygos blood flow (l.min-1)	0.45 ± 0.18		Azygos blood flow (l.min-1)	0.45 ± 0.19	0.28 ± 0.2*

- PVO Hyperdynamic circulation/Systemic vasodilatation . No data on patients characteristics.
- **Increased Porto-collateral blood flow**

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Systemic Hemodynamics in patients with Cirrhosis and in patients with NCPVT and **good liver function**

Variables	NCPVT $n = 39$	Cirrhosis $n = 39$
Age[a] (years)	48 ± 14	60 ± 11
Gender[b] (male)	26 (66%)	27 (70%)
Signs of portal hypertension at study[l]		
Varices	39 (100%)	36 (92%)
Variceal bleeding	9 (23%)	2 (5%)
Ascites	5 (13%)	6 (15%)
Patients receiving NSBB	14/39 (36%)	10/39 (26%)
Child-Pugh score[a]	5.5 ± 0.9	5.8 ± 1.1
Child-Pugh class[b]	A 33 (85%)	A 29 (74%)
	B 6 (15%)	B 10 (26%)

Variables	NCPVT $n = 34$	Cirrhosis $n = 39$	Normal values
MAP (mmHg)[a]	88 ± 13	89 ± 11	80–95
HR (bpm)[a]	72 ± 14	73 ± 13	60–95
CO ($L\,min^{-1}$)	6.95 ± 2.1	6.8 ± 1.7	4.4–8.3
CI ($L\,min^{-1}\,m^{-2}$)	3.9 ± 1.2	3.8 ± 0.7	2.5–4.0
RAP (mmHg)	5.4 ± 2.5	5.3 ± 2.3	2–10
PAP (mmHg)	15.3 ± 5.6	14.9 ± 4.2	7–19
PCP (mmHg)	9.4 ± 4.4	8.5 ± 3.5	8–12
SVR ($dyne\,s\,cm^{-5}$)	1017 ± 296	1034 ± 246	900–1440
PVR ($dyne\,s\,cm^{-5}$)	73 ± 37	79 ± 25	11–99
SVRI ($dyne\,s\,cm^{-5}\,m^{-2}$)	1802 ± 495	1831 ± 360	1.600–2580
HVPG (mmHg)	3.5 ± 2.0	17.0 ± 3.0	

Some PVT patients had Hyperdynamic circulation but this is not universal……as in cirrhosis

S. Seijo et al. / Digestive and Liver Disease 44 (2012) 855–860

The relationship of hyperdynamic circulation and cardiodynamic states in cirrhosis

Alvarado et al. Journal of Hepatology **2018** vol. 69 | 746–758

	HVPG<10mmHg	CSPH No Varices	CSPH and Varices	Compensated + large varices	Decompensated cirrhosis
CI (L.min.m-2)	2.8 ± 0.4	3.1 ± 0.8	3.4 ± 0.9	4.1 ± 1.3	4.5 ± 1.3
MAP (mmHg)	93 ± 12	97 ± 12	96 ± 12	92 ± 13	86 ± 12
SVR (dyn.s.cm-5)	1.469 ± 335	1.408 ± 451	1.235 ± 378	1.042 ± 307	858 ± 282
HVPG (mmHg)	7.3 ± 1.3	13.8 ± 4.1	15.4 ± 3.9	17.5 ± 4	19.3 ± 4

In patients with cirrhosis, the hyperdynamic circulation appears and progressively aggravates in the more severe forms of cirrhosis

Development of Hyperdynamic Circulation and Response to β-Blockers in Compensated Cirrhosis With Portal Hypertension

Càndid Villanueva,[1,2] Agustín Albillos,[2,3] Joan Genescà,[2,4] Juan G. Abraldes,[2,5] Jose L. Calleja,[6] Carles Aracil,[7] Rafael Bañares,[2,8] Rosa Morillas,[2,9] María Poca,[1,2] Beatriz Peñas,[2,3] Salvador Augustin,[2,4] Joan Carles Garcia-Pagan,[2,5] Oana Pavel,[1,2] and Jaume Bosch[2,5]

HEPATOLOGY, January 2016

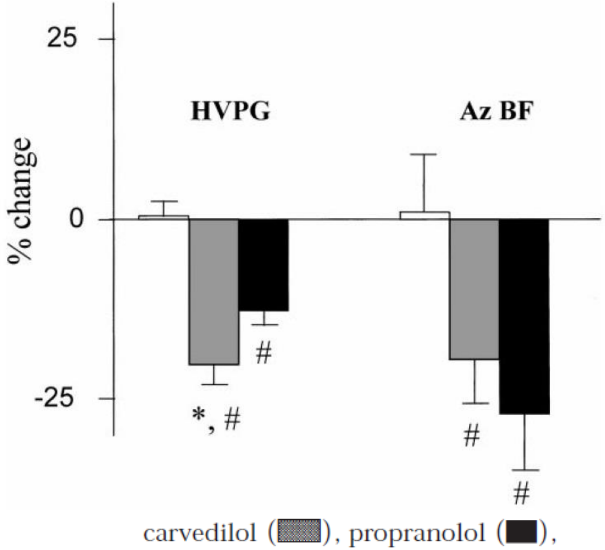
- In patients with cirrhosis, **those with less hyperdynamic circulation** have a significantly **lower reduction in portal pressure after acute non-selective beta-blockade**

- However, patients with less hyperdynamic circulation also have less portal hypertension even non-clinical significant portal hypertension. This is not the case in PVT

Carvedilol, a New Nonselective Beta-Blocker With Intrinsic Anti-Alpha$_1$–Adrenergic Activity, Has a Greater Portal Hypotensive Effect Than Propranolol in Patients With Cirrhosis

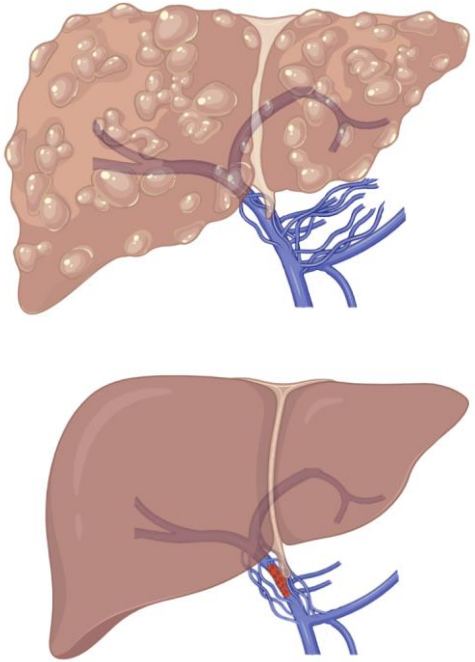
RAFAEL BAÑARES,[1] EDUARDO MOITINHO,[2] BELÉN PIQUERAS,[1] MARTA CASADO,[1] JUAN-CARLOS GARCÍA-PAGÁN,[2] ALEJANDRO DE DIEGO,[1] AND JAUME BOSCH[2]

(HEPATOLOGY 1999;30:79-83.



carvedilol (▒), propranolol (■),

Carvedilol **Higher reduction in HVPG, with similar reduction in porto-collateral blood flow**



Carvedilol in addition to reduce portal blood flow is supposed to reduce the increased intrahepatic resistance (vascular tone)

Is there a rationale in PVT?. Probably not. But….

Do patients with PVT activate vasoactive systems or expand Plasma Volume?

Data from the Partial Portal Vein Ligated Model (PPVL):

- Develop Systemic vasodilatation and by promoting sodium retention expands plama volume

Albillos A et al. *Gastroenterology* 1992

- PPVL rats are not a good model for PVT.
  - Maximum increase in PP 24 h after PPVL.
  - Degree of porto-collateral blood flow approaches 100% in less than 7 days

Systemic Hemodynamics, Vasoactive Systems, and Plasma Volume in Patients With Severe Budd-Chiari Syndrome

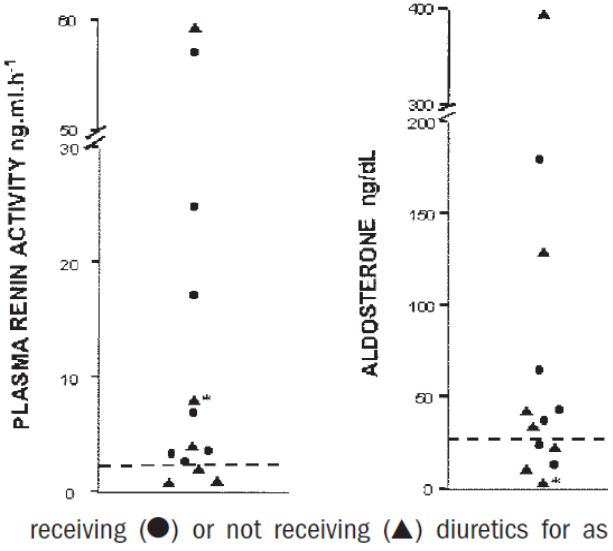
Manuel Hernández-Guerra,[1] Eric López,[1] Pablo Bellot,[1] Carlos Piera,[2] Juan Turnes,[1] Juan G. Abraldes,[1] Jaime Bosch,[1] and Juan C. García-Pagán[1]

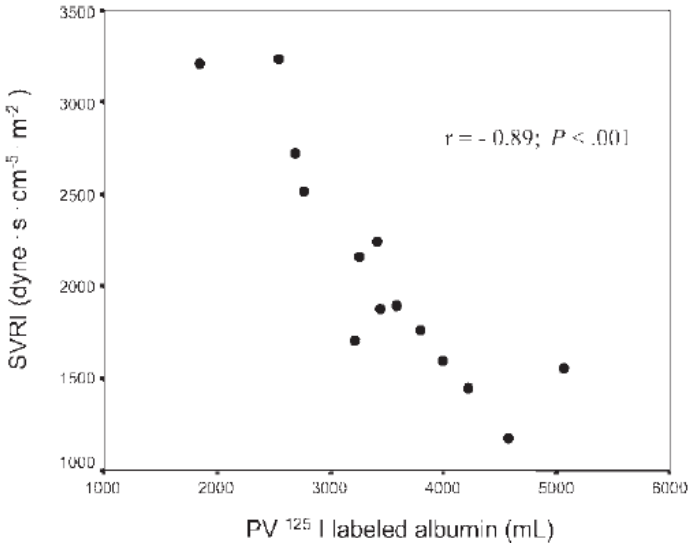
HEPATOLOGY 2006;43:27-33.

	BCS (n=21)	Cirrhosis (n=21)	
MAP (mmHg)	85 ± 12	85.6 ± 11	80-95
CI (L.min-1.m-2)	3.1 ± 0.7	4.9 ± 1.2*	2.5-4.0
iSVR (dyn.s.cm-5.m-2)	2.189 ± 736	1.377 ± 422*	1600-2580

However, 1/3 of BCS had iSVR slightly below normal values (those patients with more advanced disease)

	BCS (n=14)	Healthy (n=9)
Plasma Volume/body weight (ml/Kg)	50.9 ± 18.2*	34.8 ± 5.8





Vasodilated BCS had greater PV, but PV was also increased in BCS without systemic vasodilatation

Summary

- Increase resistance to portal blood flow is the main factor leading to PH either in Cirrhosis or in PVT.
- PVT develop hepato-petal collaterals through which blood flow reaches the liver. These rarely, if ever, appear in patients with cirrhosis.
- Patients with PVT may develop hyperdynamic circulation. However, this is not universal (similar to cirrhosis). Lack of hyperdynamic circulation may impact the capacity of NSBB to reduce portal pressure (not proven in PVT but in cirrhosis).

Summary

- Contrary to what happens in cirrhosis, there is no a clear rationale to think that carvedilol may be more effective than propranolol reducing portal pressure in patients with PVT.
- There are no data evaluating vasoactive systems and plasma volume in PVT. However, it is likely that, as it happens in patients with cirrhosis, they may be activated/increased, at least in the subgroup of PVT patients with hyperdynamic circulation.

Opened Questions

- Does the amount of portal blood flow reaching the liver (hepato-petal collaterals –Cavernoma?) influence the outcome of patients with chronic PVT?
- What factors are involved in the development of systemic vasodilatation in patients with PVT?.
- Has the presence of systemic vasodilatation a prognostic value in patients with PVT? Does systemic vasodilatation promote the activation of vasoactive system? Favor the development of ascites? of other PH complications? or with the efficacy of NSBB?

Hepatic Vascular Diseases Team. Hospital Clínic.

J Bosch
M Hernández-Guerra
S Seijo
A Baringo
L Rocabert
R Saez
C Ballesteros
C Bru
X Muntaña
MI Real
O Ros

Hepatology

V Hernández-Gea
F Turon
A Baiges
E Reverter
M Magaz
P. Olivas
V Perez-Campuzano
O Farcau
S Shalaby
M Thompson
M Sanz
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A Henriquez

R Gonzalez
MJ Serrano
L Orts
J Codina
A Recuerda
P Fuentes
H Garcia
G Camprecios
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A Darnell
M Barrufet
M Burrel
R Gilabert
I Nuñez
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P Bermudez

Surgery

J Fuster
JC Garcia-Valdecasas
Y Fundora
F Ausonia

Hematology/Hemotherapy

F Cervantes
JC Reverter
A Alvarez
D Tassies
M Nomdedeu

Hepatology General Ward; ICU Staff members; Administrative assistants