HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

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

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Nonselective β-blockers are useful to prevent bleeding in patients with cirrhosis and large varices but not to prevent the development of varices in those with compensated cirrhosis and portal hypertension (PHT). This suggests that the evolutionary stage of PHT may influence the response to β-blockers. To characterize the hemodynamic profile of each stage of PHT in compensated cirrhosis and the response to β-blockers according to stage, we performed a prospective, multicenter (tertiary care setting), cross-sectional study. Hepatic venous pressure gradient (HVPG) and systemic hemodynamic were measured in 273 patients with compensated cirrhosis before and after intravenous propranolol (0.15 mg/kg): 194 patients had an HVPG ≥10 mm Hg (clinically significant PHT [CSPH]), with either no varices (n = 80) or small varices (n = 114), and 79 had an HVPG >5 and <10 mm Hg (subclinical PHT). Patients with CSPH had higher liver stiffness ($P < 0.001$), worse Model for End-Stage Liver Disease score ($P < 0.001$), more portosystemic collaterals ($P = 0.01$) and splenomegaly ($P = 0.01$) on ultrasound, and lower platelet count ($P < 0.001$) than those with subclinical PHT. Patients with CSPH had lower systemic vascular resistance (1336 ± 423 versus 1469 ± 335 dyne · s · cm^{-5}, $P < 0.05$) and higher cardiac index (3.3 ± 0.9 versus 2.8 ± 0.4 L/min/m^2, $P < 0.01$). After propranolol, the HVPG decreased significantly in both groups, although the reduction was greater in those with CSPH (-16 ± 12% versus -8 ± 9%, $P < 0.01$). The HVPG decreased ≥10% from baseline in 69% of patients with CSPH versus 35% with subclinical PHT ($P < 0.001$) and decreased ≥20% in 40% versus 13%, respectively ($P = 0.001$). *Conclusion*: Patients with subclinical PHT have less hyperdynamic circulation and significantly lower portal pressure reduction after acute β-blockade than those with CSPH, suggesting that β-blockers are more suitable to prevent decompensation of cirrhosis in patients with CSPH than in earlier stages. (HEPATOLOGY 2016;63:197-206)

Portal hypertension (PHT) is the most common complication of cirrhosis and the main determinant for developing varices or clinical decompensation (appearance of ascites, variceal bleeding, or hepatic encephalopathy). Decompensation, in turn, is the leading cause of mortality in cirrhosis.[1,2] The primary factor in the development of PHT in cirrhosis is an increased vascular resistance to portal flow through

Abbreviations: CI, confidence interval; CO, cardiac output; CSPH, clinically significant portal hypertension; HR, heart rate; HVPG, hepatic venous pressure gradient; MELD, Model for End-Stage Liver Disease; PHT, portal hypertension; RCT, randomized controlled trial; SVR, systemic vascular resistance.

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Received March 6, 2015; accepted September 28, 2015.

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.28264/suppinfo.

ClinicalTrials.gov identifier: NCT01059396.

Supported in part by grants from the Instituto de Salud Carlos III (EC08/00087, PI10/01552, PI13/02535, PS09/00485, PI14/00876, PI13/0341) and by a Juan Rodés career development grant from the Instituto de Salut Carlos III (to S.A.). CIBERehd is funded by the Instituto de Salud Carlos III.

the liver. Later on, PHT is aggravated by splanchnic vasodilatation, increased portal-collateral blood flow, and hyperdynamic circulation.[3,4] This hyperkinetic syndrome can be corrected in part by splanchnic vasoconstrictors such as nonselective β-blockers, which still represent the mainstay for long-term pharmacological treatment of PHT.[5]

A hepatic venous pressure gradient (HVPG) $\geq$10 mm Hg defines clinically significant PHT (CSPH) as both varices and decompensation of cirrhosis may appear once this threshold is reached.[6,7] In patients with CSPH and large varices, β-blockers effectively prevent bleeding and reduce bleeding-related mortality.[8,9] However, β-blockers are ineffective at preventing the development of varices in patients with compensated cirrhosis and elevated portal pressure (with HVPG $\geq$6 mm Hg).[10] The portal pressure lowering effect of β-blockers is based on their ability to ameliorate the hyperdynamic circulation, reducing the portal venous inflow.[2,8] Thus, the low efficacy of β-blockers in early compensated cirrhosis, still without varices, could be due to the underdevelopment of hyperdynamic circulation at this stage. However, whether hyperdynamic circulation is less developed in patients without CSPH than in those who already have CSPH has not been so far prospectively evaluated.

This study was aimed at characterizing the splanchnic and systemic hemodynamic profile of the different evolutionary stages of PHT in compensated cirrhosis, with and without CSPH, and the hemodynamic response to β-blockers in each of these stages.

Patients and Methods

This is a nested cohort study within a multicenter, double-blind, randomized controlled trial (RCT; NCT01059396). Patients with cirrhosis without any previous decompensation were screened for the RCT. After initial HVPG measurements, patients with an HVPG >10 mm Hg were included in the RCT and those with HVPG <10 mm Hg were excluded from the RCT but were invited to participate in this study. The study protocol fulfilled the ethical guidelines of good clinical practice in clinical trials and was approved by the institutional review board at each site and by the Ministry of Health. All patients gave written informed consent before any procedure involved in the study.

Patients. Patients were enrolled between September 2009 and June 2013. Patients were eligible when they had cirrhosis without any previous decompensation (ascites, bleeding, encephalopathy, or jaundice), without esophageal varices or with small varices without red signs, and were aged between 18 and 80 years. Patients with one or more of the following criteria were excluded: previous decompensation of cirrhosis, splenic or portal vein thrombosis, hepatocellular carcinoma, bilirubin >3 mg/day or platelets $<30 \times 10/^9$ or international normalized ratio >2.7, renal failure with creatinine >2 mg, any comorbidity expected to decrease life expectancy to <12 months, absolute contraindication or hypersensitivity to treatment with β-blockers, pregnancy or lactation, treatment with anticoagulants, use of any drug potentially affecting splanchnic hemodynamics or portal pressure within the previous 2 weeks, and active antiviral therapy.

Cirrhosis was diagnosed by previous liver biopsy or by clinical, biochemical, and ultrasonographic findings, in addition to transient elastography higher than 14 kPa. The absence of medium or large varices was determined by endoscopy and the absence of ascites by ultrasonography, both performed within the previous 3 months. Presence of free intraperitoneal fluid on ultrasonography, not detectable on physical examination, was considered equivalent to clinical ascites and a cause of patient exclusion. Variceal size was defined according to the Baveno II to V criteria.

Study Design. A hemodynamic study was performed in all eligible patients. According to the baseline HVPG, patients were classified into two groups, one including those with CSPH (defined by an HVPG $\geq$10 mm Hg) and the other including those with subclinical PHT (defined by an HVPG >5 mm Hg and <10 mm Hg).

Baseline systemic and hepatic hemodynamic measurements were performed in both groups to assess differences in hyperdynamic circulation. Measurements were repeated after intravenous β-blocker administration to assess response. Blood test and abdominal ultrasound

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View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.28264

Potential conflict of interest: Dr. Morillas advises and is on the speakers' bureau for AbbVie, Bristol-Myers Squibb, and Gilead. She is on the speakers' bureau for MSD and Janssen. Dr. Bosch consults for Gilead, Conatus, and Intercept.

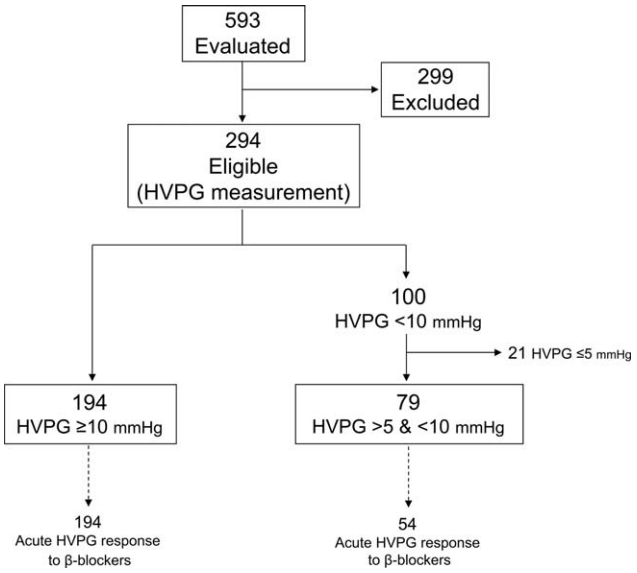

Fig. 1. Patients assessed and enrolled in the study. During the study period 593 patients with compensated cirrhosis were evaluated, of whom 299 had one or more exclusion criteria. Refused consent (n = 94) and presence of large esophageal varices (n = 33) were the main reasons for exclusion. Of the 294 patients eligible, 194 had CSPH and 100 had an HVPG <10 mm Hg, of whom 79 had subclinical PHT. The acute β-blockers test was performed in all patients with CSPH and in 54 of the 79 with subclinical PHT. It was not performed in 25 patients for scheduling reasons.

were also performed at baseline to analyze differences between both groups in liver function and in PHT-related features. Nodularity of liver surface, spleen size, and portal-systemic collaterals were assessed on ultrasound examinations. Liver stiffness, evaluated by transient elastography, was also measured in both groups.

Hemodynamic Studies. Hemodynamic measurements were performed after an overnight fast according to reported standards.[11] Under local anesthesia a catheter introducer was placed in the right internal jugular vein using the Seldinger technique and used to advance, under fluoroscopy guidance, a 7F balloon-tipped catheter into the right main hepatic vein and a Swan-Ganz catheter into the pulmonary artery. Portal pressure was measured as the HVPG that is the difference between wedged and free hepatic venous pressure. Free pressure was measured close to the inferior cava vein (1-3 cm). All intravascular pressure measurements were performed in triplicate using a previously calibrated highly sensitive transducer, with external zero at the midaxillary line and a permanent recording of tracings was obtained. The occluded position was checked by the absence of reflux after injection of contrast medium. Cardiopulmonary pressures were also obtained as well as cardiac output that was measured by thermodilution. Cardiac output (CO) was divided by the body surface area and also expressed as cardiac index (in liters per minute per square meters). Electrocardiography, arterial pressure, and oxygen saturation were monitored noninvasively throughout the study with automatic vital signs monitors. Heart rate (HR) was derived from continuous electrocardiogram monitoring and systemic vascular resistance (SVR; dynes per second per centimeter to the fifth) was calculated as follows: (mean arterial pressure - right atrial pressure [in millimeters of mercury])/(CO [in liters per minute] $\times$ 80).

After completing baseline hemodynamic measurements, a single intravenous bolus of propranolol (0.15 mg/kg) was slowly injected, and 15-20 minutes later the hemodynamic measurements were repeated.

Statistical Analysis. Categorical variables, reported as frequencies, were compared with Fisher's exact test. Continuous variables, reported as mean $\pm$ standard deviation, were compared using the Student t test for paired data within each group. Comparisons between groups were performed by the unpaired Student t test or the nonparametric Mann-Whitney rank-sum test. Analysis of variance for repeated measurements was used when appropriate. The Bonferroni correction was applied for comparisons between each level of the variables and baseline values. A multivariable backward stepwise logistic regression analysis was used to compare the two groups with respect to HVPG response to β-blockers (defined as a decrease $\geq$10% from baseline) with adjustment for risk factors. Significance was established at $P < 0.05$. All P values were two-tailed. Calculations were performed with the SPSS 19.0 statistical package (SPSS, Chicago, IL).

Results

During the study period 593 patients with compensated cirrhosis were evaluated, and 299 had one or more exclusion criteria (Fig. 1). In the 294 who were eligible a hemodynamic study was performed. Of them, 194 (66%) had CSPH, 80 (41%) without esophageal varices and 114 (59%) with small varices without red signs. One hundred patients (34%) had an HVPG <10 mm Hg, of whom 79 (27%) had subclinical PHT, with HVPG >5 mm Hg and <10 mm Hg, and the remaining 21 had a normal HVPG (with a median of 4 mm Hg and range of 3 to 4.5 mm Hg).

Baseline Clinical Characteristics. Patients with CSPH and those with subclinical PHT had similar demographic data, comorbidities (except arterial hypertension, which was more frequent in patients with CSPH), and cause of cirrhosis (Table 1; Supporting Table S1). Both groups had good liver function with a

Table 1. Characteristics of Patients With HVPG ≥10 mm Hg and Patients With HVPG <10 mm Hg at Admission*

	HVPG ≥10 mm Hg (n = 194)	HVPG <10 mm Hg (n = 79)	*P*
Sex, M/F (%)	116 (60)/78 (40)	53 (67)/26 (33)	0.27
Age (years)	62 ± 10	59 ± 10	0.07
Cause of cirrhosis (%)			0.46
Alcohol	39 (20)	14 (18)	
HCV	120 (62)	45 (57)	
Alcohol + HCV	16 (8)	11 (14)	
NASH	8 (4)	7 (9)	
Diabetes (%)	41 (21)	16 (20)	0.99
Arterial hypertension (%)	75 (39)	19 (24)	0.02
Dyslipidemia (%)	23 (12)	12 (15)	0.43
Albumin, g/L	37.7 ± 4.9	40.2 ± 4.4	<0.001
Bilirubin, mg/L	1.32 ± 0.73	0.81 ± 0.38	<0.001
Prothrombin time, INR	1.16 ± 0.16	1.05 ± 0.12	<0.001
Creatinine, mg/dL	0.76 ± 0.19	0.86 ± 0.17	0.002
Blood urea nitrogen, mg/dL	34 ± 9	37 ± 10	0.02
Hemoglobin, g/L	138 ± 18	147 ± 15	<0.001
Platelet count, $\times 10^{-3}$	104 ± 47	145 ± 49	<0.001
Leukocyte count, $\times 10^{-3}$	5.1 ± 1.9	5.9 ± 1.5	<0.001
Child-Pugh class, A/B/C (%)	152 (78)/42 (22)/0	79 (100)/0/0	<0.001
Child-Pugh score	5.7 ± 0.8	5.1 ± 0.3	<0.001
MELD score	6.5 ± 2.6	5.6 ± 2.1	0.02
Esophageal varices, no/small (%)†	80 (41)/114 (59)	69 (87)/10 (13)	<0.001
Portal hypertensive gastropathy	73 (38)	12 (15)	<0.001
Gastric varices (%)‡	3 (1)	1 (1)	1.0
Nodular LLS (%)§	147 (76)	39 (49)	<0.001
Portal-systemic collaterals by US (%)¶	30 (15)	3 (4)	0.007
Portal velocity, m/s‖	18.2 ± 5.6	16.3 ± 8.1	0.21
Splenomegaly (%)**	122 (63)	31 (39)	<0.001
Liver stiffness, kPa††	30.2 ± 14.2	18.6 ± 6.9	<0.001
Body mass index, kg/m^2	27.1 ± 4.5	26.1 ± 3.7	0.11

*Plus or minus values are means ± standard deviation.
†"No" varices denotes absence of esophageal varices on endoscopy, and "small" varices denotes varices that were flattened by insufflation,
‡Patients with esophageal and fundal varices (gastroesophageal varices type 2 according to Sarin's classification).
§Nodular left hepatic lobe on ultrasound examination. Missing data occurred in 2% of cases.
¶Presence of portal-systemic collaterals on ultrasound examination. Missing data occurred in 3% of cases.
‖Missing data occurred in 32% of cases.
**Spleen diameter >12 cm on ultrasound.
††Liver stiffness by transient elastography. Missing data occurred in 9% of cases.
Abbreviations: HCV, hepatitis C virus; INR, international normalized ratio; LLS, left lobe liver surface; NASH, nonalcoholic steatohepatitis; US, ultrasound.

median Child-Pugh score of 5 (range 5-8) and a median Model for End-Stage Liver Disease (MELD) of 5.5 (range 4-15). However, liver function was significantly worse in patients with CSPH than in those with subclinical PHT as indicated by worse MELD and Child-Pugh scores as well as each of their components (Table 1). As expected, parameters related with PHT, such as platelet count or the presence of portal-systemic collaterals or splenomegaly at ultrasound, were significantly worse in patients with CSPH than in those with subclinical PHT. Liver stiffness as well as the proportion of patients with nodular liver surface at ultrasound were significantly higher in patients with CSPH.

Hepatic and Systemic Hemodynamics and Hyperdynamic Circulation. In addition to a higher HVPG, patients with CSPH featured a more developed hyperdynamic circulatory state than those with subclinical PHT, which was evidenced by a significantly greater CO and cardiac index and a significantly lower SVR (Table 2; Supporting Table S2). Both groups had similar mean arterial pressure and HR. Cardiopulmonary pressures were also similar.

In a subgroup analysis, we compared patients with subclinical PHT to those with CSPH subdivided according to the presence or not of small esophageal varices. The HVPG progressively increased from subclinical PHT to CSPH without varices and from this to CSPH plus varices (Table 3). Parameters related to the hyperdynamic circulation progressively worsen from patients with subclinical PHT to those with CSPH without varices and from these to those with CSPH plus varices (Table 3): CO and cardiac index progressively increased and SVR progressively decreased. Mean arterial pressure and HR were

Table 2. Baseline Hemodynamic Characteristics of Patients With HVPG ≥10 mm Hg and Patients With HVPG <10 mm Hg*

	HVPG ≥10 mm Hg (n = 194)	HVPG <10 mm Hg (n = 79)	P
Wedged hepatic venous pressure (mm Hg)	23.6 ± 5.4	17.4 ± 3.9	<0.001
Free hepatic venous pressure (mm Hg)	9.0 ± 3.5	9.3 ± 3.6	0.51
HVPG (mm Hg)	14.7 ± 4.0	7.3 ± 1.2	<0.001
CO (liters/min)†	5.9 ± 1.7	5.1 ± 1.1	0.001
Cardiac index (L/min/m^2)†	3.3 ± 0.9	2.8 ± 0.4	<0.001
Mean arterial pressure (mm Hg)‡	96 ± 12	93 ± 12	0.09
HR (beats/min)‡	72 ± 10	70 ± 10	0.13
SVR (dyne · s · cm^{-5})†	1336 ± 423	1469 ± 335	0.02
Pulmonary artery pressure (mm Hg)†	16.5 ± 4.5	16.7 ± 5.5	0.84
Pulmonary wedge pressure (mm Hg)†	9.3 ± 4.3	9.4 ± 4.8	0.89
Right atrial pressure (mm Hg)‡	5.1 ± 2.8	5.8 ± 3.1	0.09

*Plus or minus values are means ± standard deviation.
†Missing data in 10%-25% of cases.
‡Missing data in <10% of cases.

similar in the three subgroups, as well as cardiopulmonary pressures.

Response to β-Blockers. Response to β-blockers was assessed in all patients with CSPH and in 54 of the 79 with subclinical PHT (Fig. 1). The degree of β-blockade achieved with acute propranolol administration was similar in patients with CSPH and in those with subclinical PHT, as indicated by a similar percent decrease in HR and in CO (Table 4). After the acute β-blocker administration, both groups had a similar slight increase in mean arterial pressure and a similar increase in SVR. Cardiopulmonary pressures also increased similarly in the two groups. Among patients with CSPH, hemodynamic changes with β-blocker administration were similar in those without varices and in those with small varices (Supporting Table S3).

In the two groups of patients, acute propranolol administration induced a significant decrease in HVPG: from 14.7 ± 4.0 to 12.2 ± 3.6 mm Hg ($P < 0.0001$) in patients with CSPH and from 7.3 ± 1.3 to 6.6 ± 1.1 mm Hg in patients with subclinical PHT ($P < 0.0001$) (Table 4). The decrease in HVPG was significantly greater in patients with CSPH than in those with subclinical PHT, when considering the percentage decrease (16 ± 12% versus 8 ± 9%, $P < 0.0001$) and when absolute changes were analyzed (Fig. 2). Patients with CSPH had a decrease in HVPG of 2.5 ± 2.6 mm Hg (95% confidence interval [CI] 2.13-2.87), and patients with subclinical PHT had a decrease of 0.6 ± 0.7 mm Hg (95% CI 0.41-0.79) ($P < 0.0001$). In the two groups of patients, the decrease in HVPG was a consequence of both a significant increase in free hepatic venous pressure and a decrease in wedged hepatic venous pressure, although the effect on free pressure was more marked (Table 4). Among patients with CSPH, the decrease in HVPG was slightly greater in those without varices than in those with small varices (Table 3), although the difference was not significant (18 ± 13% versus 15 ± 12%, $P = 0.08$).

Patients with CSPH also had better response to β-blockers than those with subclinical PHT when considering rates of change in HVPG with prognostic significance in clinical practice. A decrease in HVPG >10% from baseline was observed in 19 patients (35%) with subclinical PHT compared to 133 (69%) with CSPH ($P < 0.001$), and a decrease in HVPG >20% was observed in 13% (n = 7) versus 40% (n = 78), respectively ($P = 0.001$). A decrease in HVPG >30% was observed in 14% (n = 27) of patients with CSPH but in none with subclinical PHT ($P = 0.001$). In patients with CSPH a decrease in HVPG to <10 mm Hg was observed in 54 cases (28%). A decrease in HVPG to <6 mm Hg was observed in 11 patients (20%), all with subclinical PHT, while a decrease to <5 mm Hg was not observed in any case of either group.

On multivariate analysis, CSPH was an independent predictor of HVPG response to β-blockers (odds ratio = 5.1, 95% CI 2.3-10.1) in a model adjusted for MELD score, presence of varices, baseline HVPG, HR decrease, and etiology of cirrhosis.

Discussion

The present study shows that patients with early compensated cirrhosis have different systemic hemodynamic patterns according to the presence or absence of CSPH. Patients with CSPH have more advanced features of a hyperdynamic circulatory state, with significantly higher CO and cardiac index and lower SVR, than those with subclinical PHT. The study also shows that this translates into a substantially different hemodynamic response to β-blockers, which induce a markedly greater

Table 3. Characteristics of Patients in Each Evolutionary Stage: HVPG <10 mm Hg, HVPG ≥10 mm Hg Without Varices, and HVPG ≥10 mm Hg With Varices

	HVPG <10 mm Hg (n = 79)	HVPG ≥10 mm Hg Without Varices (n = 80)	HVPG ≥10 mm Hg With Varices (n = 114)
Child-Pugh class, A/B (%)	79 (100)/0	60 (75)/20 (25)**	92 (81)/22 (19)**
Child-Pugh score	5.1 ± 0.3	5.7 ± 0.9**	5.7 ± 0.8**
MELD score	5.6 ± 2.1	5.9 ± 2.5	6.9 ± 2.7‖,††
Hemoglobin, g/L	147 ± 15	139 ± 15**	137 ± 19**
Platelet count, $\times 10^{-3}$	145 ± 49	109 ± 44**	100 ± 49**
Nodular LLS (%)*	39 (49)	57 (71)**	90 (79)**
Portosystemic collaterals by US (%)†	3 (4)	11 (14)‖	19 (17)**
Splenomegaly (%)‡	31 (39)	42 (52)	80 (70)**,††
Liver stiffness, kPa (transient elastography)§	18.6 ± 6.9	28.9 ± 13.7**	30.8 ± 14.6**
Portal hypertensive gastropathy	12 (15)	23 (29)‖	50 (44)**,††
CO (L/min)¶¶	5.1 ± 1.1	5.4 ± 1.6	6.3 ± 1.7**,‡‡
Cardiac index (L/min/m^2)¶¶	2.8 ± 0.4	3.1 ± 0.8**	3.4 ± 0.9**,††
Mean arterial pressure (mm Hg)§§	93 ± 12	97 ± 12	96 ± 12
HR (beats/min)§§	70 ± 10	72 ± 10	72 ± 11
SVR (dyne · s · cm^{-5})¶¶	1469 ± 335	1408 ± 451	1235 ± 378**,‡‡
Pulmonary artery pressure (mm Hg)¶¶	16.7 ± 5.5	16.1 ± 5.0	16.8 ± 4.2
Right atrial pressure (mm Hg)§§	5.8 ± 3.1	4.8 ± 2.5‖	5.3 ± 3.1
HVPG (mm Hg)¶			
Baseline	7.3 ± 1.3	13.8 ± 4.1**	15.4 ± 3.9**,‡‡
After propranolol			
Value	6.6 ± 1.1	11.1 ± 3.3**	13.0 ± 3.4**,‡‡
Decrease from baseline, mm Hg	−0.6 ± 0.7	−2.7 ± 3.2**	−2.3 ± 2.1**
Decrease from baseline, %	−8 ± 9%	−18 ± 13%**	−15 ± 12%**

Results expressed as mean ± standard deviation.

*Nodular left hepatic lobe on ultrasound examination. Missing data occurred in 2% of cases.

†Presence of portal-systemic collaterals on ultrasound examination. Missing data occurred in 3% of cases.

‡Spleen diameter >12 cm on ultrasound.

§Liver stiffness by transient elastography. Missing data occurred in 9% of cases.

¶In patients with HVPG <10 mm Hg the acute response to β-blocker was assessed in 54 cases, and in those with HVPG ≥10 mm Hg the acute response to β-blocker was assessed in all cases.

‖$P \leq 0.05$ for comparison with the group with HVPG <10 mm Hg.

**$P \leq 0.01$ for comparison with the group with HVPG <10 mm Hg.

††$P \leq 0.05$ for comparison with the group with HVPG ≥10 mm Hg and without varices.

‡‡$P \leq 0.01$ for comparison with the group with HVPG ≥10 mm Hg and without varices.

§§Missing data in <10% of cases.

¶¶Missing data in 10% to 25% of cases.

Abbreviations: LLS, left lobe liver stiffness; US, ultrasound.

effect on HVPG in patients with CSPH than in those with subclinical PHT, achieving a reduction twice greater.

This study shows that hyperdynamic circulation is more developed in patients with CSPH than in those with subclinical PHT and that, among patients with CSPH, hyperdynamic circulation is less developed in those without varices than in those who already have varices. This is in keeping with experimental studies which have suggested that the development of hyperdynamic circulation is progressive over the course of the different stages of the portal hypertensive syndrome.[12-14] In early stages of cirrhosis, PHT is mainly due to an increased resistance to blood flow.[3,14] Later on, a marked increase of portal venous inflow as a consequence of the development of hyperdynamic circulation maintains and aggravates PHT.[12-14] Studies performed in patients with cirrhosis have also suggested a strong relationship between the development of hyperdynamic circulation and worsening of PHT.[15] The results of the current study indicate that, in patients with early compensated cirrhosis, the institution of hyperdynamic circulation is progressive and much more developed when the HVPG reaches the level of 10 mm Hg. Once this threshold has been reached the hyperkinetic syndrome develops further, especially after the formation of varices, markedly worsening PHT. It is important to note that this effect was distinctly evident in our study, despite the fact that patients with large varices were not included. Our results are in keeping with previous studies assessing transient elastography, a technique which measures liver stiffness and estimates fibrosis, to evaluate

Table 4. Changes in Hemodynamic Variables With Acute β-Blocker Test in the Two Groups of Patients

	HVPG ≥10 mm Hg		HVPG <10 mm Hg	
	Baseline	β-Blocker*	Baseline	β-Blocker†
Wedged hepatic venous pressure (mm Hg)	23.6 ± 5.4	22.3 ± 5.3§	16.8 ± 3.6	16.5 ± 3.5‖
Change from baseline, %		−5 ± 9%		−1 ± 7%‖
Free hepatic venous pressure (mm Hg)	9.0 ± 3.5	10.3 ± 3.9§	9.4 ± 3.6	10.0 ± 3.5§
Change from baseline, %		18 ± 27%		8 ± 13%‖
HVPG (mm Hg)	14.7 ± 4.0	12.2 ± 3.6§	7.3 ± 1.3	6.6 ± 1.1§,‖
Change from baseline, %		−16 ± 12%		−8 ± 9%‖
CO (L/min)	5.9 ± 1.7	5.0 ± 1.3§	5.2 ± 1.1	4.3 ± 0.9§,¶
Change from baseline, %**		−20 ± 12%		−17 ± 9%
Cardiac index (L/min/m^2)	3.3 ± 0.9	2.7 ± 0.5§	2.8 ± 0.4	2.4 ± 0.5§,¶
Change from baseline, %**		−21 ± 12%		−15 ± 10%
Mean arterial pressure (mm Hg)	96 ± 12	98 ± 13‡	94 ± 11	96 ± 13‡
Change from baseline, %††		2 ± 8%		3 ± 10%
HR (beats/min)	72 ± 10	59 ± 8§	70 ± 11	59 ± 7§
Change from baseline, %††		−17 ± 8%		−14 ± 10%
SVR (dyne · s · cm^{-5})	1336 ± 423	1538 ± 502§	1445 ± 342	1698 ± 468§
Change from baseline, %**		26 ± 24%		26 ± 22%
Pulmonary artery pressure (mm Hg)	16.5 ± 4.5	20.2 ± 5.3§	17.1 ± 6.6	20.0 ± 6.6§
Change from baseline, %‡‡		24 ± 23%		19 ± 16%
Pulmonary wedge pressure (mm Hg)	9.3 ± 4.3	13.3 ± 4.4§	9.9 ± 5.2	13.2 ± 5.1§
Change from baseline, %‡‡		47 ± 39%		34 ± 28%
Right atrial pressure (mm Hg)	5.1 ± 2.8	7.7 ± 3.9§	6.1 ± 3.4	9.0 ± 4.3§
Change from baseline, %††		57 ± 58%		47 ± 46%

Results expressed as mean ± standard deviation.

*In patients with HVPG ≥10 mm Hg (n = 194), the acute response to β-blocker was assessed in all cases. Patients received 11.5 ± 2 mg of intravenous propranolol.

†In patients with HVPG <10 mm Hg, the acute response to β-blocker was assessed in 54 cases of the 79 included in the group. Patients received 11.2 ± 2 mg of intravenous propranolol ($P = 0.44$ compared with HVPG ≥10 mm Hg group). Baseline values in the table correspond to the subgroup of 54 patients who had acute β-blocker test.

‡$P < 0.05$ for comparison with the baseline value.

§$P < 0.01$ for comparison with the baseline value.

¶$P \leq 0.05$ for comparison between both groups.

‖$P \leq 0.01$ for comparison between both groups.

**Missing data in 26%-33% of cases.

††Missing data in <10% of cases.

‡‡Missing data in 10%-25% of cases.

noninvasively PHT.[16,17] These studies have shown a good correlation with portal pressure for HVPG values below 10 mm Hg (i.e., up to the presence of CSPH) but not above this threshold. This suggests that below a certain degree of PHT, close to the level indicating CSPH, the accumulation of fibrillar extracellular matrix, which is responsible for the increase in liver stiffness, is the main determinant of PHT. However, above this level the development of hyperdynamic circulation and the vascular resistance along portal-systemic collaterals markedly contribute to the rise of portal pressure.[16,17] Furthermore, our results also indicate that the development of CSPH is accompanied by a significant worsening of different clinical parameters related to portal hypertensive syndrome, such as decreased platelet count or the presence of portal-systemic collaterals or splenomegaly on ultrasound, and by a significant worsening of liver function (reflected by MELD and Child-Pugh scores).

A relevant finding of the current study is that nonselective β-blockers have less of an HVPG-lowering effect in patients with subclinical PHT than in those with CSPH, in whom β-blockers achieved a double mean reduction in HVPG, reaching a decrease of 16% which is similar to that reported in patients treated for primary or secondary prophylaxis of variceal bleeding.[18-20] The rates of patients decreasing HVPG ≥10% and ≥20% from baseline were significantly higher in those with CSPH than in those with subclinical PHT. These results may explain why previous RCTs have demonstrated the efficacy of nonselective β-blockers to prevent variceal bleeding in patients with high-risk esophageal varices and to prevent rebleeding,[2,8] while in the prophylactic timolol study such drugs were ineffective at preventing the development of varices or variceal bleeding in patients with early cirrhosis without varices.[10] In this regard, the timolol study showed that varices are prevented when the HVPG is decreased by more than 10%, which in the current study was rarely obtained with propranolol in patients without CSPH.[10] The present study further suggests that the modest effect of β-

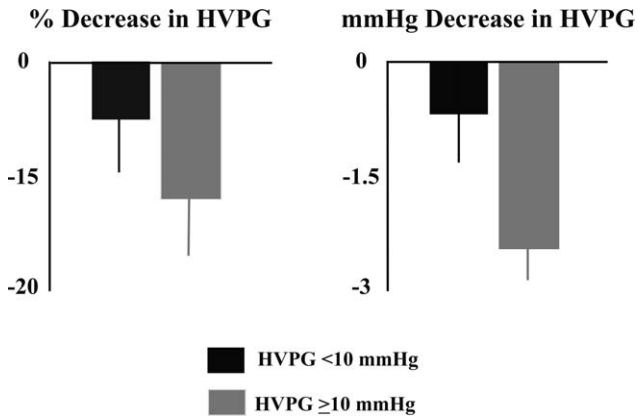

Fig. 2. Decreases of the HVPG achieved with propranolol in patients with CSPH and in patients with subclinical PHT. Panel on the left shows the percentage decrease in HVPG after administration of propranolol in both groups of patients. Patients with CSPH had a decrease in HVPG of 16 ± 12%, and patients with subclinical PHT had a decrease of 8 ± 9% ($P < 0.0001$). Panel on the right shows the absolute decrease in HVPG in both groups of patients. Patients with CSPH had a decrease in HVPG of 2.5 ± 2.6 mm Hg, and patients with subclinical PHT had a decrease of 0.6 ± 0.7 mm Hg (difference = 1.90, 95% CI 1.20-2.60, $P < 0.0001$).

blockers in patients with subclinical PHT may be attributed to the fact that the systemic and splanchnic hyperdynamic circulatory state is still underdeveloped in this early phase of compensated cirrhosis. In this early stage, increased intrahepatic resistance to portal blood flow is the main factor leading to PHT and is related with sinusoidal remodeling, endothelial dysfunction, accumulation of fibrillar extracellular matrix, vascular occlusion, and nodule formation[3,4]; and none of these abnormalities is corrected by β-blockers. Therefore, in this very early stage of cirrhosis, it appears logical to advocate using other agents that reduce portal pressure by decreasing intrahepatic resistance. Several recent studies suggest that administration of antifibrotic agents, antioxidants, biopterins, antiangiogenic treatments, simvastatin, or atorvastatin may achieve this goal.[21-24] At this point it would be of interest to study if carvedilol, a nonselective β-blocker that is emerging as the β-blocker of choice in cirrhosis due to its greater efficacy at lowering HVPG,[25] may also be effective in subclinical PHT because its intrinsic vasodilator activity (due to its anti-α-adrenergic effect and to enhanced release of nitric oxide) may contribute to a decrease the hepatic vascular tone and hence achieve an additional decrease in portal pressure over the mild reduction that could be expected from its nonselective β-blocker activity.

Because in patients with subclinical PHT portal pressure is only slightly increased, great reductions can hardly be expected. However, it should be noted that even a modest effect, such as that achieved with β-blockers in this study, may be relevant in patients with early subclinical PHT. Even such a minimal effect could be useful to maintain HVPG below the 10 mm Hg threshold of risk. Furthermore, in up to 20% of patients with subclinical PHT the HVPG was reduced below the threshold of 6 mm Hg that defines the presence of PHT. The relevance of these effects of β-blockers in subclinical PHT should be adequately investigated in future studies.

In concordance with previous studies,[26] we also observed that among patients with CSPH the hemodynamic response to β-blockers was slightly worse in those with varices than in those without varices. This is probably related to the effects of collateralization, because once collaterals have developed the use of β-blockers, in addition to reducing portal venous inflow, they may also induce an increase in portal-collateral resistance which partially offsets the effect on portal pressure.[27] In fact, this is one of the reasons that combination therapy of nonselective β-blockers and vasodilators has been advocated.

Both in patients with CSPH and in those with subclinical PHT, the effect of β-blockers on HVPG was a consequence of a significant decrease in the wedged hepatic venous pressure and a significant increase in the free hepatic venous pressure. In the two groups of patients the effect on free pressure was larger than that observed on wedged pressure. This is also what occurred in previous studies assessing the acute effect of β-blockers in patients with and in those without varices.[18,26] It has been shown that such a marked effect on free hepatic venous pressure is, at least in part, related to a significant decrease of total venous compliance,[28,29] which is markedly increased in cirrhosis.[30] The present study suggests that such an increase in venous compliance occurs early in the course of compensated cirrhosis, even before reaching the level of CSPH.

This study has several limitations. The first is that the results cannot be generalized to all patients with PHT because patients with noncirrhotic PHT and those with presinusoidal PHT (such as those with primary biliary cirrhosis) were not included. Different experimental models have shown that systemic vasodilatation and the progressive development of hyperdynamic circulation are similarly observed in all forms of PHT.[3] However, whether the relationship between the development of a hyperdynamic circulatory state, severity of PHT, and response to β-blockers in patients with noncirrhotic PHT or presinusoidal PHT is similar to that observed in this study should be specifically investigated. Nevertheless, because cirrhosis is by far the most frequent cause of clinical PHT, the relevance of not including other forms of PHT is limited. Besides, in noncirrhotic PHT HVPG is not a reliable measurement of portal pressure,[11]

which requires more invasive methods. Secondly, this study was not blinded, and this may have introduced bias, particularly in assessing the response to β-blockers. This can be particularly relevant in patients with subclinical PHT, due to the small changes of HVPG that are measured in such cases which are close to the coefficient of variation between repeated measurements of HVPG.[11,18] However, to optimize accuracy, in the present study hemodynamic measurements were performed strictly following currently accepted standards,[31] while we included a much larger number of patients than previous studies, which confers statistical robustness to our results. Furthermore, the study was not placebo-controlled, and previous studies on chronic hemodynamic effects of β-blockers have shown changes in HVPG with placebo,[10] which can be due to factors such as abstinence or use of concomitant medications. However, such a placebo effect is very unlikely when acute response to β-blockers is assessed, as in the present study. In fact, previous studies investigating the acute hemodynamic effects of β-blockers have shown no effect with placebo administration.[27,28] Finally, chronic hemodynamic response to β-blockers was not assessed in this study, and it may be argued that the results could have been different using this approach. However, a good correlation has been shown between acute and chronic hemodynamic responses to β-blockers when intravenous propranolol is used for the acute test, as in this study.[32,33]

In summary, this study shows that, in patients with compensated cirrhosis, features of hyperdynamic circulation are more developed in those with CSPH than in those with subclinical PHT. In keeping with this, our study also shows that β-blockers induce a markedly greater portal pressure-lowering effect in patients with CSPH than in those with subclinical PHT. These findings suggest that β-blockers may be suitable to prevent decompensation of cirrhosis with CSPH but that their potential benefit on the progression of PHT may be lower at earlier stages of cirrhosis.

Acknowledgment: We thank the following additional investigators: Alba Ardevol, Edilmar Alvarado, Annalisa Berzigotti, Xavi Diaz, Cristina Martín, Javier Martínez, Laura Millán, Lara Orts, Enric Reverter, Rosa Saez, Susana Seijo, Fanny Turon, and all the investigators involved in each of the participating centers.

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Supporting Information

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