Randomized Comparison of Long-Term Carvedilol and Propranolol Administration in the Treatment of Portal Hypertension in Cirrhosis

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Short-term carvedilol administration is more powerful than propranolol in decreasing hepatic venous pressure gradient (HVPG) in cirrhotic patients, but induces arterial hypotension that may prevent its long-term use in portal hypertensive patients. This study compared the HVPG reduction and safety of long-term carvedilol and propranolol. Fifty-one cirrhotic patients were randomly assigned to receive carvedilol (n = 26) and propranolol (n = 25). Hemodynamic measurements and renal function were assessed at baseline and after 11.1 ± 4.1 weeks. Carvedilol caused a greater decrease in HVPG than popranolol (−19 ± 2% vs. −12 ± 2%; $P < .001$). The proportion of patients achieving an HVPG reduction ≥20% or ≤12 mm Hg was greater after carvedilol (54% vs. 23%; $P < .05$). Carvedilol, but not propranolol caused a significant decrease in mean arterial pressure (MAP) (−11 ± 1% vs. −5 ± 3%; $P = .05$) and a significant increase in plasma volume (PV) and body weight (11 ± 5% and 2 ± 1%, respectively; $P < .05$). Glomerular filtration rate (GFR) was unchanged with either drug, but the dose of diuretics was increased more frequently after carvedilol (27% vs. 8%; $P = .07$). Adverse events requiring discontinuation of treatment occurred in 2 patients receiving carvedilol and in 3 receiving propranolol. In conclusion, carvedilol has a greater portal hypotensive effect than propranolol in patients with cirrhosis. However, its clinical applicability may be limited by its systemic hypotensive effects. Further trials are needed to confirm the therapeutic potential of carvedilol. (HEPATOLOGY 2002;36:1367-1373.)

Several studies have shown that to achieve an effective protection from the risk of variceal bleeding by means of continued pharmacologic therapy, the portal pressure gradient (usually measured as the hepatic venous pressure gradient [HVPG]) has to decrease below 12 mm Hg or at least by 20% of baseline values.[1-6] Nonselective β-blockers such as propranolol and nadolol, which are the mainstay of pharmacologic therapy[1,7-9] achieve this goal in 20% to 30% of the patients. Recent studies have shown that the association to propranolol or nadolol of isosorbide-5-mononitrate (5-ISMN) or the α_1-receptor blocker prazosin enhances the decrease in HVPG achieved by β-blockade,[10-13] which may translate into greater clinical benefit.[14,15] Carvedilol is a nonselective β-blocker with intrinsic anti-α_1-adrenergic activity. As such, its effects mimic those of the combination therapy using propranolol and prazosin.[16,17] Carvedilol has been extensively used in congestive heart failure, without adverse effects on renal function.[18] On the contrary, carvedilol improves survival in this condition.[19] Furthermore, we recently showed that acute administration of carvedilol in patients with cirrhosis induces a more pronounced decrease on portal pressure than that obtained with propranolol, and a significantly higher number of patients achieve the target reduction in HVPG.[17] However, carvedilol did decrease arterial blood pressure and systemic vascular resistance in this acute study,[17] raising

Abbreviations: HVPG, hepatic venous pressure gradient; HR, heart rate; WHVP, wedge hepatic venous pressure; FHVP, free hepatic venous pressure; CO, cardiac output; AzBF, azygos blood flow; ICG, indocyanine green; HBF, hepatic blood flow; MAP, mean arterial pressure; SVR, systemic vascular resistance; RAP, right atrial pressure; GFR, glomerular filtration rate; PV, plasma volume; PARA, plasma renin activity; NS, not significant.

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the question of whether, similar to other vasodilators,[13,20-22] it can have an adverse effect on renal function on prolonged administration in patients with cirrhosis.

The present randomized controlled trial was designed to answer this question by comparing the effects of long-term carvedilol therapy versus propranolol on systemic and splanchnic hemodynamics and on renal function in a large series of patients with cirrhosis.

Patients and Methods

Patients. The study was performed in 51 cirrhotic patients referred to the Hepatic Hemodynamic Laboratory of the two participating hospitals for evaluation of portal hypertension. Inclusion criteria were the presence of endoscopically proven esophageal varices without previous hemorrhage and a basal HVPG value greater than 12 mm Hg. The diagnosis of cirrhosis was based on liver biopsy specimens or on clinical, biochemical, or ultrasonographic findings. The exclusion criteria were age less than 18 or greater than 75 years; severe liver failure evaluated by the presence of a serum bilirubin level greater than 5 mg/dL, and/or an international normalized ratio greater than 2.5 or uncontrolled hepatic encephalopathy; contraindications to β-blockers (asthma, chronic obstructive lung diseases, atrioventricular block, heart rate [HR] less than 50 bpm, peripheral arterial disease, insulin-dependent diabetes mellitus); active alcoholism; serum creatinine greater than 2 mg/dL; hepatocellular carcinoma; and refusal to participate in the study. The study was conducted following the principles of the Declaration of Helsinki and was approved by the Ethics Committee of each participating hospital. All patients gave written informed consent after a complete explanation of the purpose of the study. Thirty-four patients were men, and the mean age was 58 ± 10 years; 16 patients had ascites on baseline evaluation. Additional clinical information is given in Table 1.

Study Design. The study was a single-blind randomized controlled trial aimed to compare the effects of carvedilol and propranolol on splanchnic and systemic hemodynamics and on renal function and endogenous vasoactive systems.

The sample size calculation was based on previous studies,[1,2] showing a proportion of HVPG responders to long-term propranolol monotherapy of 24%. Our previous study using carvedilol[17] suggested that the rate of responders might be increased to up to 64% of the patients. The sample size needed to detect a 30% increase in HVPG responders was calculated as 50 patients, using a 2-sided test with 80% power at a significance level of 5%.

Table 1. Baseline Clinical and Hemodynamic Characteristics of Patients

	Carvedilol (n = 26)	Propranolol (n = 25)	P
Age (yr)	57.9 ± 1.5	58.4 ± 2.2	NS
Sex			
Male, n (%)	19 (73)	15 (60)	NS
Etiology, n (%)			NS
Alcohol	6 (23)	9 (36)	
HBV	4 (15)	2 (8)	
HCV	14 (54)	14 (56)	
Others	2 (8)	0	
Child-Pugh class			
A/B/C	13/10/3	15/6/4	NS
Variceal size			
Large/small	10/16	14/11	NS
Ascites, n (%)	10 (39)	6 (24)	NS
HVPG (mm Hg)	19.0 ± 1.0	20.3 ± 0.9	NS
Cardiac output (L/min)	7.5 ± 0.4	7.8 ± 0.3	NS

Abbreviations: HBV, hepatitis B virus; HCV, hepatisis C virus.

After baseline clinical and hemodynamic evaluation, patients were randomly allocated to receive carvedilol (n = 26) or propranolol (n = 25) by means of a blocked randomization code generated by computer. The treatment code was kept in sealed opaque envelopes.

Drug titration was performed by trained research nurses. Propranolol was started at a dosage of 10 mg twice daily and carvedilol at a dosage of 6.25 mg daily. The dosage of both drugs was stepwise increased every 4 days until the HR was reduced by 25% or to less than 55 beats/min while systolic pressure was greater than 85 mm Hg. The mean dosages of propranolol and carvedilol were 73 ± 10 mg/d (range, 10-160) and 31 ± 4 mg/d (range, 12.5-50), respectively. The time elapsed until reaching the optimal dosage was similar in both groups (21.6 ± 4.6 vs. 17.3 ± 3.1 days; $P = .45$).

When the dosage of both drugs was stabilized the patients were seen every 2 weeks in the outpatient clinic by physicians inadvertent of treatment allocation. At every follow-up visit the presence of hypotension, orthostatism, and dyspnea and development of ascites or edema was carefully assessed.

All measurements detailed below were performed at baseline and after a mean of 11.1 ± 4.1 weeks of continued therapy at the established dosage. Five patients (2 in the carvedilol group and 3 in propranolol group) were withdrawn before the second hemodynamic evaluation due to side effects and therefore are not included in the analysis of the hemodynamic effects.

Hemodynamic Studies. Under fluoroscopic control a 7F balloon-tipped catheter (MediTech Cooper Scientific Corp., Watertown, MA) was advanced into the main right hepatic vein to measure wedged and free hepatic

venous pressures (WHVP and FHVP, respectively). A Swan-Ganz catheter (Abbott Labs, Abbott Park, IL) was advanced into the pulmonary artery for measurements of cardiopulmonary pressures and cardiac output (CO). A continuous thermal dilution catheter (Webster Laboratories, Inc., Baldwin Park, CA) was placed into the azygos vein for measurement of azygos blood flow (AzBF), according to previously described methods.[24] All measurements were performed in triplicate, and permanent tracings were recorded on a multichannel recorder (Letica Polygraph 4006, Barcelona, Spain). All tracings were evaluated blindly by the same observer (J.B.). A solution of indocyanine green (ICG; Pulsion Medical Systems, München, DFR) containing 2% serum albumin, was infused intravenously at a constant rate of 0.2 mg · min^{-1}. After an equilibration period of at least 40 minutes, 4 separate sets of simultaneous samples of peripheral and hepatic venous blood were obtained for the measurement of hepatic blood flow (HBF) as previously described.[23] The intrinsic hepatic clearance of ICG was calculated according to the sinusoidal model as $-HBF \times \ln (1 - E)$ in which E represents the extraction ratio of ICG calculated at steady state as: Cp − Ch/Cp, in which Cp and Ch represent the ICG concentrations in peripheral venous blood and in the hepatic venous blood, respectively.[23] Portal pressure was estimated from the HVPG, the difference between WHVP and FHVP. Mean arterial pressure (MAP) was measured noninvasively with an automatic sphygmomanometer (Hewlett-Packard M1008B, McMinnville, OR). HR was derived from continuous electrocardiogram monitoring. Systemic vascular resistance (SVR) (dyn · s · cm^{-5}) was calculated as (MAP − RAP)/CO × 80, in which MAP (mm Hg) is the mean arterial pressure, RAP (mm Hg) is the right atrial pressure and CO (L · min^{-1}) is the cardiac output. Patients showing a reduction in HVPG ≥20% of the baseline values or to values ≤12 mm Hg were considered responders.

Renal Function and Endogenous Vasoactive Systems. Glomerular filtration rate (GFR) and plasma volume (PV) were measured as previously described by the clearance and the volume of distribution of ^{51}Cr-ethylendiaminetetraacetic acid and ^{125}I-labeled human seroalbumin, respectively.[13] Plasma renin activity (PARA) and plasma aldosterone were measured by radioimmunoassay following previously described methods.[13]

Statistical Analysis. Data are shown as mean ± SE. The Kolmogoroff-Smirnoff test was used for assessing the normal distribution of variables. Paired Student's *t* test was used to assess the significance of comparisons with baseline within each group and nonpaired Student's *t* test for comparisons between groups. Proportional data were analyzed by χ^2 test and Fisher's exact test when appropriate. Significance was established at $P < .05$. All statistics were computed using the SPSS statistical package (SPSS 9.0, Chicago, IL).

Results

Baseline Data. All patients had severe portal hypertension as shown by the presence of esophageal varices and an HVPG above 12 mm Hg. Both groups of patients were similar regarding baseline clinical and systemic and splanchnic hemodynamic values (Table 1).

Effects of Propranolol and Carvedilol on Hepatic Hemodynamics. Propranolol significantly decreased HVPG (−12 ± 2%; $P < .01$) and portocollateral (azygos) blood flow (−24 ± 7%; $P < .01$) (Table 2). This is in accordance with previous reports from our laboratory. Five patients (23%) decreased the HVPG ≤ 12 mm Hg or by ≥20% of baseline.

Table 2. Splanchnic and Systemic Hemodynamics at Baseline and After the Administration of Carvedilol and Propranolol

	Carvedilol (n = 24)		Propranolol (n = 22)	
	Baseline	End of Treatment	Baseline	End of Treatment
WHVP (mm Hg)	26.4 ± 1	23.5 ± 0.9*	28.8 ± 1	25.9 ± 0.7*
FHVP (mm Hg)	7.3 ± 0.5	8.2 ± 0.5*	8.5 ± 0.7	8.3 ± 0.6
HVPG (mm Hg)	19.0 ± 1.1	15.2 ± 0.8*	20.3 ± 0.9	17.6 ± 0.7*
HBF (L/m)	1.39 ± 0.1	1.28 ± 0.1	1.25 ± 0.1	1.01 ± 0.1*
AzBF (mL/m)	442 ± 38	375 ± 41*	472 ± 38	362 ± 44*
MPAP (mm Hg)	13.8 ± 0.7	15.1 ± 0.9*	16.7 ± 0.9	18.2 ± 1.6
WPAP (mm Hg)	7.7 ± 0.7	9.6 ± 0.8*	10.4 ± 0.9	11.8 ± 1.3
RAP (mm Hg)	4.6 ± 0.6	5.5 ± 0.5†	5.8 ± 0.5	6.4 ± 0.7
MAP (mm Hg)	91.4 ± 2.5	81.2 ± 2.9*	88.6 ± 4.5	83.8 ± 3.1
CO (L/m)	7.5 ± 0.3	6.4 ± 0.3*	7.6 ± 0.3	5.8 ± 0.2*
HR (beats/min)	79.9 ± 3.7	65.6 ± 2*	77.3 ± 2.6	58.2 ± 1*
SVR (dyn · s · cm^{-5})	953 ± 44	993 ± 51	926 ± 58	1,099 ± 69*

NOTE. Data (mean ± SEM) are shown for the patients reaching the second hemodynamic study.
*$P < .05$.
†$P = .078$.

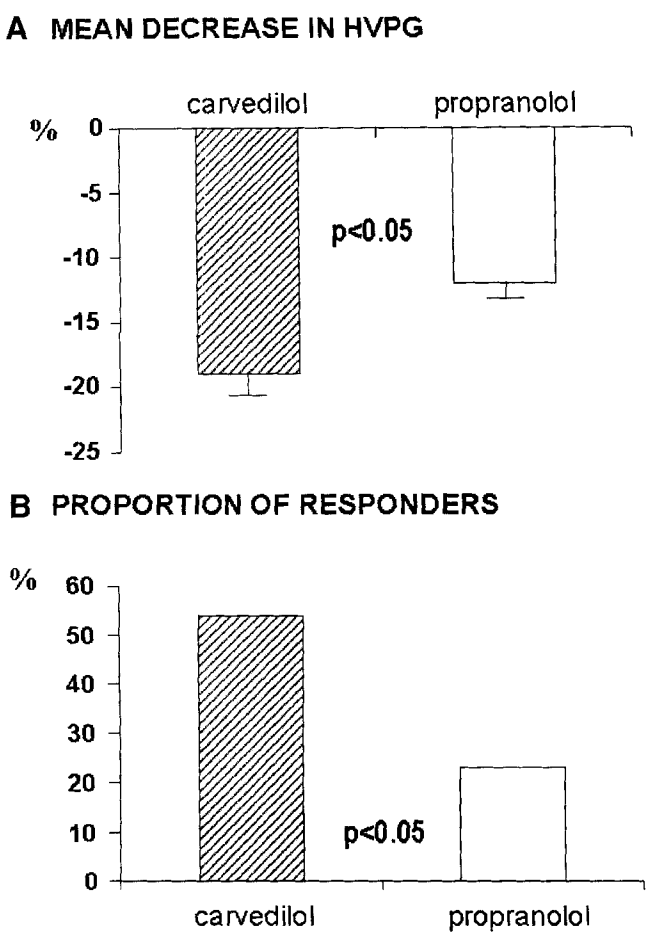

Fig. 1. Comparison of the effects of carvedilol and propranolol on HVPG. As shown, carvedilol caused a more pronounced decrease in HVPG than propranolol (A), which resulted in a significantly greater proportion of patients exhibiting a good hemodynamic response (B).

Long-term carvedilol caused a pronounced decrease in HVPG (−19 ± 2%; $P < .001$). This decrease in HVPG significantly exceeded that achieved by propranolol ($P < .05$) (Fig. 1). Moreover carvedilol decreased the HVPG ≤12 mm Hg or by ≥20% of baseline in 13 patients (58%), which is also significantly greater than what was observed in the propranolol group ($P < .05$) (Fig. 1).

Carvedilol significantly decreased AzBF (−14 ± 6%; $P = .017$). This effect was slightly less pronounced than after propranolol, but the difference was not statistically significant. Carvedilol did not significantly change HBF (−6 ± 7%; $P = .243$) and hepatic intrinsic clearance (1 ± 5%; $P = .44$), which were significantly decreased by propranolol (−18.1 ± 4.7%; $P < .01$ and −5 ± 7%; $P = .02$, respectively).

Effects of Propranolol and Carvedilol on Systemic Hemodynamics and Renal Function. Long-term administration of carvedilol and propranolol showed effective β-blockade as reflected by a significant decrease in HR and CO (Table 2). However, propranolol caused greater reductions in HR and CO than carvedilol (−23.7 ± 2% vs. −16.4 ± 2.6%, $P = .034$; and −21.5 ± 2.3% vs. −15 ± 2.7%, $P = .08$, respectively). In contrast, carvedilol but not propranolol, significantly decreased MAP (−11 ± 1% vs. −5 ± 3%; $P = .05$).

RAP, pulmonary artery pressure, and pulmonary capillary pressure were significantly increased by carvedilol but not by propranolol (Table 2).

Chronic carvedilol administration was associated with a significant increase in PV (from 3.1 ± 0.2 to 3.4 ± 0.1 L; or +11.4 ± 5%; $P < .05$) and body weight (from 75.6 ± 2.7 to 76.6 ± 2.7 kg; or +1.6 ± 0.7%; $P < .05$). There were no changes in GFR (from 90 ± 4 to 84 ± 5 mL/min; −6.6 ± 4.5%; not significant [NS]) or urinary sodium excretion (from 159 ± 96 to 157 ± 84 mmol/d; NS) following chronic carvedilol. Chronic carvedilol significantly reduced PARA (from 1.99 ± 0.8 to 1.3 ± 0.8 ng/mL/h; $P < .05$).

Propranolol did not cause any change in urinary sodium excretion, PV, GFR, and PARA (Table 3).

Hemodynamic Effects of Carvedilol According to Child-Pugh Class. Carvedilol caused a greater decrease in HVPG in patients with advanced liver failure (Child class B and C) than in those with good liver function (Child class A) (−25 ± 2% vs. −14 ± 3%, respectively;

Table 3. Renal Function and Plasma Volume at Baseline and After Long-Term Propranolol or Carvedilol Administration

	Carvedilol (n = 24)		Propranolol (n = 22)	
	Baseline	End of Treatment	Baseline	End of Treatment
GFR (mL/min)	90 ± 4	84 ± 5	102 ± 6	97 ± 7
Serum creatinine (mg/dL)	0.95 ± 0.05	0.98 ± 0.04	0.90 ± 0.03	0.96 ± 0.04
Serum sodium (mEq/L)	138.2 ± 0.7	137.0 ± 0.8	137.8 ± 0.7	137.1 ± 0.7
Serum potasium (mEq/L)	3.9 ± 0.1	4.1 ± 0.1	3.9 ± 0.1	4.2 ± 0.1
Urinary sodium excretion (mEq/d)	160 ± 23	157 ± 20	109 ± 15	121 ± 15
Plasma renin activity ($\mu g \cdot mLz^{-1} \cdot h^{-1}$)	1.99 ± 0.86	1.30 ± 0.76*	2.01 ± 0.90	1.73 ± 0.78
Plasma volume (L)	3.1 ± 0.2	3.4 ± 0.1*	3.0 ± 0.1	3.0 ± 0.1
Body weight (kg)	75.6 ± 2.7	76.6 ± 2.7*	72.3 ± 2.3	72.3 ± 2.2

NOTE. Data are expressed as mean ± SEM.
*$P < .05$.

$P = .01$). Propranolol caused a similar decrease in both groups ($-15 \pm 2\%$ vs. $-11 \pm 3\%$; NS). The greater effect of carvedilol in Child class B or C patients was associated with a greater decrease in HR ($-22 \pm 11\%$ vs. $-12 \pm 13\%$ in Child class A patients; $P = .07$) despite this group receiving lower doses of the drug (25 ± 13 vs. 35 ± 27 in Child class A patients; $P = .27$). The decrease in MAP was similar in both groups ($-11 \pm 7\%$ vs. $-11 \pm 7\%$, not sigficant). There were no differences in the effects of carvedilol on PV, body weight, and GFR in Child class A vs. Child class B or C patients (data not shown).

Adverse Effects. Both treatments were well tolerated. Mild side effects occurred slightly more frequently in the carvedilol group (Table 4). Seven patients in the carvedilol group and 2 in the propranolol group required an increase in the dosage of diuretics (27% vs. 8%; $P = .07$) for the treatment of new onset or worsening of previous ascites (3 carvedilol, 1 propranolol) or for the treatment of ankle edema (4 carvedilol, 1 propranolol). All patients were successfully treated by increasing the dosage of the combination of furosemide and spironolactone (maximal dosages required were 80 mg/d and 200 mg/d, respectively). Two patients in the carvedilol group and 3 in propranolol group required discontinuation of the treatment because of severe adverse events (NS). All patients who required discontinuation of the treatment had advanced cirrhosis (Child-Pugh class B or C).

Discussion

The target in the pharmacologic treatment of portal hypertension should be to reduce the HVPG by at least 20% of baseline values and, preferably, below 12 mm Hg. This has prompted investigations looking for more powerful portal hypotensive agents than propranolol or nadolol, either administered alone or associated with nitrovasodilators or α-adrenergic blockers.

In a previous study we have shown that the acute administration of carvedilol, a nonselective β-blocker with intrinsic anti-α_1-adrenergic activity, has a greater effect on decreasing portal pressure than propranolol, although caused systemic hypotension,[17] which is a matter of concern due to its potential adverse effects on renal function and sodium retention in patients with cirrhosis.[24]

Table 4. Adverse Events

	Carvedilol n = 26 n (%)	Propranolol n = 25 n (%)	P
Orthostatic hypotension	9 (35)	5 (20)	NS
Encephalopathy	3 (12)	4 (16)	NS
Shortness of breath	6 (23)	4 (16)	NS
Need for increasing diuretics	7 (27)	2 (8)	.07
Adverse events requiring discontinuation of treatment	2 (8)*	3 (12)†	NS

*One patient developed pericardial effusion and another heart failure. An ultrasonographic examination disclosed that the patient had an underlying mitral and aortic valve disease.

†Encephalopathy in one case and severe fatigue in two patients.

The present randomized controlled trial was conducted to verify if the greater portal hypotensive effect of carvedilol, as compared with propranolol, is maintained on continued administration, and to assess the relative impact of both treatments on endogenous vasoactive systems and renal function.

The results of the study indeed show that long-term administration of carvedilol markedly reduces portal pressure in cirrhotic patients with severe portal hypertension and esophageal varices. More important, the magnitude of the decrease in portal pressure caused by long-term carvedilol significantly exceeds that obtained after long-term propranolol. Actually the magnitude of the decrease in HVPG was 50% greater than that afforded by propranolol. Furthermore, the percentage of patients that achieved the target reduction in HVPG (a decrease of $\geq 20\%$ of baseline values or to ≤ 12 mm Hg), was significantly greater after carvedilol (58%) than after propranolol (23%, $P < .05$). These results confirm that carvedilol has a good potential for the treatment of portal hypertension, at least in patients with insufficient response to propranolol.

It should be noted that the decrease in HVPG induced by carvedilol was not accompanied by a concomitant decrease in HBF, suggesting that a reduction of hepatic vascular resistance contributed to the portal pressure lowering effect of carvedilol. This finding contrasts with the significant reduction in liver perfusion following propranolol, but it is not surprising given the fact that carvedilol is both a nonselective β-blocker and has intrinsic anti-α_1-adrenergic activity. In that regard, the effects of carvedilol mimic those obtained by the combined administration of propranolol and the α_1-adrenergic antagonist prazosin, which also decreases portal pressure while maintaining liver perfusion.[12] The magnitude of the decrease of HVPG in patients treated with carvedilol was greater in patients with more advanced liver disease. This fact was associated with a higher degree of β-blockade, as indicated by a greater decrease in HR. This may be related to the unpredictable bioavailability of the drug in cirrhotic patients, leading to different plasmatic levels of the R (+) and S (−) enantiomer than in healthy subjects.[16,25] Carvedilol is a racemic compound of R (+) and S (−) enantiomers. The S (−) enantiomer is responsible for the nonselective β-adrenoceptor antagonism and the S (−) and R (+) have a similar α_1-adrenoceptor antagonism.[26] In healthy patients stereoselective first pass leads to a dif-

ferent bioavalability of both enantiomers with a higher concentration of the S (−) enantiomer. Previous studies[25] have shown that in patients with severe liver disease the stereoselectivity of carvedilol metabolism is different than that of healthy subjects and the bioavalability of both enantiomers differs. It is also possible that in patients with more advanced liver disease the differences in plasma levels were further exaggerated as compared with patients with less severe liver failure.[16]

The significant reductions on HR and CO as well as the reduction of portocollateral blood flow (AzBF) after carvedilol are expected because of the β-blocking activity of the drug. The magnitude of the reduction on HR and CO caused by carvedilol was less pronounced than that induced by propranolol, indicating less pronounced β_1-blockade. However, both drugs caused a similar reduction of portocollateral blood flow as assessed by measurements of AzBF. This probably reflects a similar degree of β_2-adrenergic blockade in the splanchnic circulation.

Another relevant finding of this study is that the long-term effects of carvedilol on arterial pressure and SVR are less pronounced than those observed after acute administration. While acute carvedilol administration markedly decreased MAP and SVR,[17] long-term administration did not decrease SVR, and there was only a mild decrease in arterial pressure. Such an attenuation of the systemic vasodilatory effect has also been described in cirrhotic patients receiving long-term treatment with the α_1-adrenergic blocker, prazosin.[22] This may be related to development of true tolerance, involving a decreased expression of α_1-adrenoreceptors, but also with pseudotolerance, associated with hemodynamic adjustments in response to arterial hypotension.

Because acute administration of carvedilol was associated with systemic hypotension, which may have deleterious effects on renal function,[24] we have taken special care to evaluate the effects of carvedilol on renal function and sodium retention. Previous studies showed that, in patients with cirrhosis, vasodilators may reduce GFR, increase PV, and activate endogenous vasoactive systems.[24] However, recent studies have shown that combination therapy using propranolol plus 5-ISMN or propranolol plus prazosin does not impair renal function.[10,12,27] This is probably related in part to the suppression of renin activity induced by β-blockers, an effect that has also been documented with carvedilol.[28,29]

Our results confirm these findings, showing that chronic carvedilol administration neither adversely affects renal function, nor increased endogenous vasoactive systems, but reduced PARA. Nevertheless, we cannot exclude a transient effect causing some degree of sodium retention, since carvedilol administration, similarly to the association of propranolol plus prazosin,[12] significantly increased PV and body weight, and was associated with worsening of preexisting ascites in one third of ascitic patients. These symptoms were easily controlled with sodium restriction and diuretics and did not require discontinuation of the drug. However, it is possible that the enhancement of sodium retention has been concealed in part by the increased use of diuretics. This may limit the clinical application of carvedilol, which should probably be restricted to nonascitic patients. Another possible consequence of volume expansion was the increases in right atrial, pulmonary arterial, and capillary pressures in patients receiving carvedilol.

A previous study[30] showed that the 4-week administration of 25 mg of carvedilol was associated with a marked hypotension leading to discontinuation of the treatment in a significant proportion of patients. This fact contrasts with the results of our study in which both treatments were equally well tolerated. Only 10% of patients required discontinuation of the treatment because of adverse events. Mild, self-limited shortness of breath was observed in both groups. The differences on clinical tolerance between both studies is likely to be due to our careful adjustment of the dosage of carvedilol over a titration period, starting with a very low dosage, as recommended for patients with heart failure.[19] A recent report suggest that a low dosage of carvedilol (12.5 mg/d) is well tolerated and maintains its portal hypotensive effect.[31]

In conclusion, the results of the present study show that long-term carvedilol treatment in patients with cirrhosis and esophageal varices decreases portal pressure more than propranolol and induces more frequently a beneficial hemodynamic response, as indicated by a decrease in HVPG of at least 20% of baseline values, and/or reaching values ≤12 mm Hg. However, the decrease of arterial pressure and the trend for sodium retention and PV expansion may limit the clinical applicability of this therapy. However, we believe that the safety profile of carvedilol allows the performance of a larger randomized clinical trial with clinical end points and careful assessment of adverse events. Because of the potential adverse effects on sodium retention, it seems reasonable to propose that the first of these studies should be restricted to nonascitic cirrhotic patients.

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