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

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Only some patients show a substantial hepatic venous pressure gradient (HVPG) reduction after propranolol, which makes it desirable to investigate drugs with greater portal hypotensive effect. The aim of this study was to investigate whether carvedilol, a nonselective beta-blocker with anti-alpha$_1$–adrenergic activity, may cause a greater HVPG reduction than propranolol. Thirty-five cirrhotic patients had hemodynamic measurements before and after the random administration of carvedilol (n = 14), propranolol (n = 14), or placebo (n = 7). Carvedilol markedly reduced HVPG, from 19.5 ± 1.3 to 15.4 ± 1 mm Hg ($P <$ .0001). This HVPG reduction was greater than after propranolol (−20.4 ± 2 vs. −12.7 ± 2%, $P <$ .05). Moreover, carvedilol decreased HVPG greater than 20% of baseline values or to ≤12 mm Hg in a greater proportion of patients (64% vs. 14%, $P <$ .05). Both drugs caused similar reductions in hepatic and azygos blood flows, suggesting that the greater HVPG decrease by carvedilol was because of reduced hepatic and portocollateral resistance. Propranolol caused greater reductions in heart rate and cardiac output than carvedilol, whereas carvedilol caused a greater decrease in mean arterial pressure (−23.1 vs. −11%, $P <$ .05). Thus, carvedilol has a greater portal hypotensive effect than propranolol in patients with cirrhosis, suggesting a greater therapeutic potential. However, it causes arterial hypotension, which calls for careful evaluation before its long-term use. (HEPATOLOGY 1999;30:79-83.)

Propranolol, a nonselective beta-blocker, is widely used in the pharmacological treatment of portal hypertension. Its efficacy has been clearly proven for the prevention of first variceal bleeding[1,2] and rebleeding.[3,4]

Several studies have shown that to achieve effective protection from the risk of variceal bleeding, the portal pressure gradient (usually measured as the hepatic venous pressure gradient [HVPG]) has to decrease to ≤12 mm Hg[5,6] or at least by 20% of baseline values.[6] However, the HVPG response to propranolol administration is heterogeneous, with less than one third of patients achieving such a decrease in portal pressure.[5-8] Combination therapy, associating beta-blockers with nitro-vasodilators, has been introduced to overcome this limitation.[9] Vasodilators such as isosorbide-5-mononitrate enhance the portal pressure reducing effect of beta-blockers by decreasing the portohepatic vascular resistance.[10-13]

Alpha-adrenergic blockers have been used for portal hypertension because the rich adrenergic innervation of the hepatic circulation and the enhanced sympathetic nervous activity of patients with cirrhosis[14,15] may contribute to elevating the vascular resistance of the cirrhotic liver. In addition, the sensitivity of the hepatic vasculature to alpha-adrenergic tone is increased in cirrhosis.[15,16] In accordance with these facts, prazosin, an antagonist of alpha$_1$ adrenoceptors, significantly decreases portal pressure while increasing liver perfusion, suggesting a reduction in hepatic vascular resistance.[17,18] Prazosin has also been shown to enhance the HVPG reduction caused by propranolol during its combined, chronic administration.[19]

Carvedilol is a new nonselective beta-blocker with intrinsic anti-alpha$_1$–adrenergic activity recently introduced in the treatment of arterial hypertension, ischemic heart disease, and heart failure.[20] It has been also suggested that carvedilol may have a potential cardiovascular organ protection effect mediated by its antioxidant activity and by its ability to inhibit vascular smooth muscle cell proliferation.[21] Carvedilol is rapidly absorbed achieving peak plasma concentrations between 1 to 2 hours after oral administration.[22,23]

Thus, carvedilol by combining beta-blocker and anti-alpha$_1$–adrenergic activities has the potential of achieving greater reductions of portal pressure than propranolol. The present study was aimed at testing this hypothesis, by comparing the effects of carvedilol, propranolol, and placebo on hepatic and systemic hemodynamics in patients with cirrhosis.

PATIENTS AND METHODS

Patients. The study was performed in 35 patients with cirrhosis and endoscopically proven esophageal varices, referred for a hemodynamic evaluation of portal hypertension. The diagnosis of cirrhosis was based on liver biopsy specimens or on clinical, biochemical,

Abbreviations: HVPG, hepatic venous pressure gradient; WHVP, wedged hepatic venous pressure; FHVP, free hepatic venous pressure; AzBF, azygos blood flow; HBF, hepatic blood flow; SVR, systemic vascular resistance; MAP, mean arterial pressure; CO, cardiac output; HR, heart rate; NS, not significant.

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and ultrasonographic findings. At the time of the study all patients were clinically stable. The study protocol was approved by the Ethical Committee of each participating hospital. All patients gave written consent to participate after a complete explanation of the purpose of the study. Twenty-three patients were men, and the mean age was 55 ± 9 years. Twenty-two patients had a history of variceal bleeding and 20 had ascites. Additional clinical information on the patients studied is given in Table 1.

In addition, another group of 14 patients with cirrhosis and esophageal varices were included in a preliminary dose-finding study.

Hemodynamic Studies. After an overnight fast, the patients were transferred to the Hepatic Hemodynamics Laboratory. Under local anesthesia, 2 venous introducers were placed in the right femoral vein using the Seldinger technique. 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). The second introducer was used to advance first, a Swan-Ganz catheter (Abbott Laboratories, Chicago, IL) into the pulmonary artery for measurements of cardiopulmonary pressures and cardiac output, and then a continuous thermal dilution catheter (Webster Laboratories, Inc., Baldwin Park, CA) 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). A solution of indocyanine green (ICG; Pulsion Medical Systems, München, Germany) containing 2% serum albumin, was infused intravenously at a constant rate of 0.2 mg/min. 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.[11]

Portal pressure was estimated from the HVPG as the difference between WHVP and FHVP. Mean arterial pressure was measured noninvasively with an automatic sphygmomanometer (Hewlett-Packard M1008B; Hewlett-Packard, Palo Alto, CA). Heart rate 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) is the cardiac output.

Study Protocol. After completing baseline hemodynamic measurements, the patients randomly received carvedilol (Boehringer Mannheim, Mannheim, Germany) (25 mg orally, n = 14), propranolol (0.15 mg/kg intravenously, followed by a continuous infusion of 0.2 mg/kg, n = 14), or placebo (n = 7), and the hemodynamic measurements were repeated after 1 hour. In addition, 6 patients receiving carvedilol had a second set of measurements at 2 hours.

All tracings were evaluated blindly after completing the study.

The dose of 25 mg of carvedilol was chosen according to the results of a preliminary dose-finding study performed in 14 patients. These patients had measurements of HVPG, MAP, and heart rate (HR) before and 1 hour after administration of 2 different dosages of carvedilol: 12.5 mg (n = 7) or 25 mg (n = 7). The findings of this preliminary study (Table 2) showed that the lower dose of carvedilol (12.5 mg) significantly decreased the arterial blood pressure (although less than the 25 mg dose), but had only a mild, nonsignificant effect on HVPG. Therefore, the low dose of carvedilol appeared to have no potential for the treatment of portal hypertension.

TABLE 1. Clinical Characteristics of the Patients Studied

	Carvedilol (n = 14)	Propranolol (n = 14)	Placebo (n = 7)	*P*
Age (yr)*	54.6 ± 8.8	51.4 ± 8.5	57 ± 10.8	NS
Alcoholics (n)	8	8	4	NS
Previous ascites (n)	7	7	6	NS
Esophageal varices (n)	14	14	7	NS
Previous variceal bleeding (n)	9	9	4	NS
Previous encephalopathy (n)	2	2	1	NS
Child-Pugh class (A/B/C)	8/4/2	5/6/3	0/5/2	NS

*Mean ± SD.

Statistics. Results are reported as mean ± SD. Statistical analysis of the results was performed using the paired Student's *t* test, to assess the significance of comparisons with baseline within each group, and the analysis of variance for comparisons between groups, using the Bonferroni correction for multiple comparisons. Significance was established at $P < .05$. All statistics were computed using the SPSS statistical package (SPSS, Chicago, IL).

RESULTS

Baseline Data. All patients had severe portal hypertension, as shown by a HVPG above 12 mm Hg and by the presence of esophageal varices and other complications of portal hypertension (Table 1). The 3 groups of patients studied were similar with regards to HVPG, AzBF, CO, cardiopulmonary pressures, and clinical characteristics (Tables 1 and 3).

Effects of Placebo Administration. Placebo administration had no significant effects on systemic and splanchnic hemodynamics (Table 3).

Effects of Carvedilol. One hour after the administration of 25 mg of carvedilol there was a reduction in HVPG (from 19.5 ± 1.3 to 15.4 ± 1 mm Hg; $P < .001$), because of a significant reduction in WHVP (from 29.5 ± 1.5 to 25.4 ± 1.4 mm Hg; $P < .001$), with no changes in FHVP. In the 6 patients that had serial measurements, the decrease in HVPG was maintained after 2 hours of administration (baseline, 17.8 ± 2.1 mm Hg; 1hour, 13.6 ± 2 mm Hg [$P < .01$ vs. baseline]; 2 hours, 13.7 ± 2 mm Hg [not significant (NS) vs. 1 hour; $P < .01$ vs. baseline]). The decrease in HVPG induced by carvedilol was similar in Child's class A and in Child's class B/C patients (−19.4 ± 6.8% vs. −21.8 ± 10.6%; NS). The administration of carvedilol also caused a significant decrease in AzBF (−20 ± 6%; $P = .017$). HBF was also reduced (−9.6 ± 3.8%; $P = .05$).

On systemic hemodynamics, carvedilol caused a significant decrease in HR (−10.5 ± 2.3%; $P = .001$), CO (−9.5 ± 2.7%; $P < .01$), and MAP (−17.2 ± 2.4%; $P < .001$). The reduction in MAP was associated with a significant decrease in SVR (−9.9 ± 3.1%; $P < .01$). There were no significant changes in mean pulmonary artery pressure, pulmonary capillary pressure, and right atrial pressure (Table 2). None of our 7 patients with ascites had any deterioration of renal function on the following days, as assessed by measurements of blood urea nitrogen and plasma creatinine concentration. The decrease in HVPG showed no correlation with changes in other hemodynamic parameters.

Effects of Propranolol. Propranolol significantly reduced HVPG, WHVP, AzBF, HBF, HR, and CO whereas there were no significant changes in MAP. As for carvedilol, the decrease in HVPG caused by propranolol was similar in Child's class A patients (−11.9 ± 8.7%) compared with patients in Child's class B and C (−13.08 ± 7%; NS). Propranolol significantly increased FHVP, cardiopulmonary pressures, and SVR (Table 3).

Comparison of the Effects of Carvedilol and Propranolol. Carvedilol caused a significantly greater reduction in HVPG than propranolol (Fig. 1). Moreover, the number of patients in whom HVPG decreased ≥20% of the baseline values or to values ≤12 mm Hg was greater after carvedilol than after propranolol (64% vs. 14%; $P < .05$). The reduction in AzBF

TABLE 2. Results of the Preliminary Dose-Finding Study Comparing the Effects of Two Different Doses of Carvedilol on Splanchnic and Systemic Hemodynamics in Patients With Cirrhosis and Portal Hypertension

	Carvedilol 12.5 mg (n = 7)			Carvedilol 25 mg (n = 7)		
	Baseline	1 Hour	% Change	Baseline	1 Hour	% Change
HVPG mm Hg	22.2 ± 1.2	20 ± 1	−7.8 ± 4.4	19.4 ± 1.6	15.2 ± 1.2*	−20.8 ± 3.8
MAP mm Hg	82.1 ± 3.3	75 ± 3.4†	−8.2 ± 3.8	89 ± 4.2	71.8 ± 5.6*	−19.8 ± 3.4
HR (beats per min)	83.4 ± 3.8	77.4 ± 4.1	−6.7 ± 4.4	74.6 ± 2.8	67.1 ± 2.6*	−9.9 ± 4.5

*$P < .05$ vs. baseline.
†$P = .07$ vs. baseline.

and in HBF caused by propranolol was slightly greater than that caused by carvedilol, but the difference was not significant (AzBF, −27.1 ± 9.6% vs. −19.7 ± 5.9%, NS; HBF, −14.1 ± 5.4% vs. −10.4 ± 4.5%, NS).

In the systemic circulation propranolol caused greater reductions in HR and CO than carvedilol (−16.7 ± 1.7% vs. −10.5 ± 2.3%, $P < .05$; and −22.4 ± 2.3% vs. −9.5 ± 2.7%, $P < .05$, respectively), whereas carvedilol caused a more pronounced decrease in MAP than propranolol (−17.2 ± 2.4% vs. −3.4 ± 2.3%; $P < .01$) (Fig. 2). Peripheral resistance increased after propranolol but decreased after carvedilol (23.1 ± 6.9% vs. −10.7 ± 13.1%; $P < .05$).

DISCUSSION

The results of the present study show that the acute administration of carvedilol induces a marked decrease in the HVPG of patients with cirrhosis and esophageal varices. It is important to remark that the magnitude of the reduction in portal pressure caused by carvedilol was more pronounced than that achieved after the administration of propranolol. Indeed, a decrease in HVPG greater than 20% of baseline values or below 12 mm Hg, which represents a clinically significant decrease in portal pressure,[5,19] was obtained in a much higher (4-fold) proportion of patients after carvedilol administration than after propranolol. This suggests that carvedilol has a greater therapeutic potential than propranolol in the prevention of variceal hemorrhage in patients with cirrhosis. However, the greater portal hypotensive effect of carvedilol was accompanied by a more pronounced effect lowering the MAP than that caused by propranolol, which is a matter of concern in patients with cirrhosis.[25]

The dose of 25 mg of carvedilol was chosen after a preliminary dose-finding study showed that a lower dose of carvedilol (12.5 mg) still significantly decreased the arterial pressure (although less than the 25-mg dose) but had only a mild, nonsignificant effect on HVPG. Therefore, halving the dose of carvedilol neither maintained its beneficial effect reducing the HVPG nor prevented the adverse effect on arterial pressure. Based on these findings, we chose the 25-mg dose for the study.

These hemodynamic effects of carvedilol in patients with cirrhosis are not unexpected, because they reflect its pharmacological properties of being a nonselective beta-blocker with intrinsic anti-alpha$_1$–adrenergic activity. The beta-blocking effects of carvedilol on systemic and splanchnic hemodynamics are responsible for the significant decrease in HR and CO, as well as for the reduction of portocollateral blood flow (AzBF) and HBF. However, the effects of carvedilol on the HR and CO were significantly less pronounced than those caused by propranolol, indicating that carvedilol induced less pronounced beta$_1$-blockade. The effects of carvedilol and propranolol on AzBF exceeded those on CO and HR, suggesting that splanchnic vasoconstriction, due in part to beta$_2$-adrenergic blockade, contributed to the similar reduction in AzBF caused by these agents.[7,26] Thus, despite a clearly lower beta$_1$-blocking activity, carvedilol appears to exert a similar beta$_2$-blockade to propranolol. This is also suggested by the similar effect of both drugs on HBF.

As already stated, the more salient finding of our study is the demonstration that the acute administration of carvedilol causes a greater reduction in portal pressure than propranolol. Such a greater portal hypotensive effect of carvedilol with similar or less marked effects on cardiac index and splanchnic blood flows (evaluated by measurements of HBF and AzBF) is

TABLE 3. Splanchnic and Systemic Hemodynamics at Baseline and After the Administration of Placebo, Carvedilol, or Propranolol

	Placebo (n = 7)		Carvedilol (n = 14)		Propranolol (n = 14)	
	Baseline	1 Hour	Baseline	1 Hour	Baseline	1 Hour
WHVP (mm Hg)	29.6 ± 1.8	29.5 ± 1.5	29.5 ± 1.5	25.4 ± 1.4*	29.8 ± 1.3	28.4 ± 1.2*
FHVP (mm Hg)	9.6 ± 0.8	9.6 ± 1	9.9 ± 1.1	9.9 ± 0.9	9.4 ± 0.9	10.7 ± 1*
HVPG (mm Hg)	19.9 ± 1.7	19.9 ± 1.6	19.5 ± 1.3	15.4 ± 1*	20.4 ± 1.1	17.7 ± 0.8*
AzBF (mL/m)	572 ± 77	593 ± 107	736 ± 112	540 ± 65*	557 ± 60	425 ± 62*
HBF (L/m)	1.52 ± 0.21	1.45 ± 0.33	1.35 ± 0.21	1.21 ± 0.19†	1.42 ± 0.12	1.22 ± 0.11*
MAP (mm Hg)	76 ± 3.4	75 ± 3.4	89 ± 4	73 ± 3*	87 ± 3	83 ± 3
HR (beats/min)	69 ± 3	67 ± 3	76 ± 3.4	68 ± 2.3*	80 ± 3	67 ± 3*
CO (L/m)	6.8 ± 0.4	6.9 ± 0.3	7.4 ± 0.4	6.6 ± 0.4*	8.6 ± 0.5	6.6 ± 0.4*
MPAP (mm Hg)	15.7 ± 1.4	17 ± 1.7	13.2 ± 1.2	13.9 ± 1.1	16.4 ± 1.2	18.3 ± 1*
WPAP (mm Hg)	9.2 ± 1.2	9.9 ± 1.5	8.1 ± 1.3	8.8 ± 0.8	10.6 ± 1.1	13.2 ± 1.2*
RAP (mm Hg)	5.7 ± 0.9	6.8 ± 1.1	4.6 ± 1	5.5 ± 1	6.2 ± 1	8.3 ± 1*
SVR (dyn · s · cm^{-5})	855 ± 76	806 ± 51	938 ± 51	845 ± 54*	797 ± 86	962 ± 130*

*$P < .05$ vs. baseline.
†$P = .05$ vs. baseline.

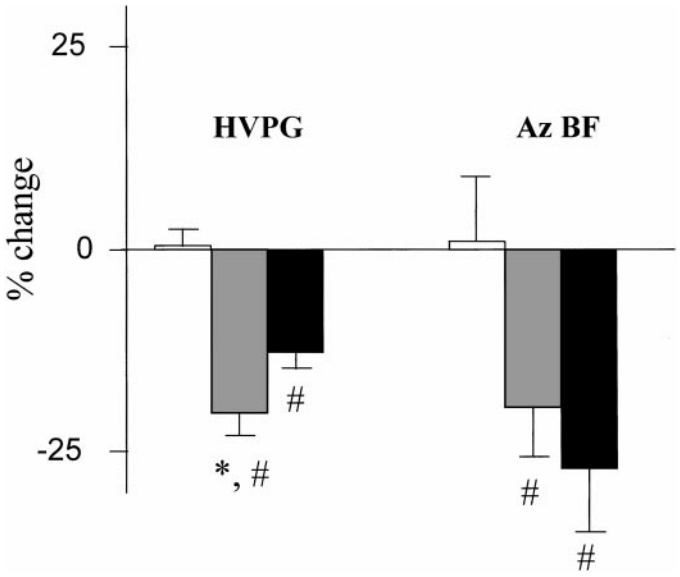

FIG. 1. Comparison of the effects of carvedilol (▨), propranolol (■), and placebo (□) on splanchnic hemodynamics. *Significantly different from propranolol. #Significantly different from placebo.

compatible with an effect of carvedilol lowering hepatic and portocollateral resistance because of its anti-alpha$_1$–adrenergic activity. This fact is well in accordance with our previous studies suggesting the possibility of decreasing the hepatic vascular resistance in patients with cirrhosis by the administration of alpha adrenergic blocking agents like clonidine[27] or prazosin[17,18] alone or associated with propranolol.[19] In that regard, carvedilol would combine in a single molecule the effects that can be achieved by 2 drug combinations: propranolol plus isosorbide mononitrate[12,13] or, even more closely, those of propranolol plus prazosin.[19]

The major caution when considering the use of carvedilol is its systemic vasodilatory effect, responsible for the significant decreases of MAP and SVR. These effects represent a potential problem for the use of this drug for long-term therapy in patients with cirrhosis. Indeed, several studies have shown that in these patients, especially in those with ascites, the use of vasodilators may enhance the activation of the endogenous vasoactive systems that prompt sodium and water retention, plasma volume expansion, and reduction of glomerular filtration rate.[18,19,25,26,28,29] However, previous studies have shown that the combination of isosorbide-5-mononitrate[30] or prazosin[19] with propranolol is safer than the isolated administration of isosorbide-5-mononitrate[28] or prazosin[18,19] in terms of preventing the activation of the endogenous vasoactive systems and causing side effects on renal function. This decreased renal toxicity of prazosin when combined with propranolol has been related to the suppression of renin release induced by beta-blockade, an effect that has also been shown with carvedilol.[31,32] It is possible that carvedilol administration, which combines alpha- and beta-blocking activities, may have a profile of effects similar to that of the association of propranolol and prazosin and is therefore not likely to cause as many adverse effects as it has been documented with the isolated administration of prazosin.[17,18] Actually, the acute administration of carvedilol did not decrease the renal blood flow in patients with cirrhosis.[33]

On the other hand, carvedilol has been extensively used in other clinical settings associated with sodium retention, as in chronic heart failure, without being associated with renal failure or with a worsening of the sodium retention.[34,35] On the contrary, carvedilol has been found to have a beneficial effect on survival in these patients.[34,35] Nevertheless, the possibility that carvedilol may exert adverse effects on renal function and sodium retention should be considered in the studies assessing its prolonged administration in patients with cirrhosis, which should be done preferably in nonascitic patients. Despite this inconvenience, the pronounced portal hypotensive effect of carvedilol calls for further careful investigations evaluating its long-term efficacy reducing portal pressure and its side effects in patients with cirrhosis and portal hypertension. When considering the long-term administration of carvedilol in patients with cirrhosis, it is strongly advised to progressively adjust the dose over a careful titration period, starting with doses as low as 3.125 mg twice daily, as it has been recently recommended for heart failure patients.[36]

In conclusion, our study shows that carvedilol has a greater portal hypotensive effect than propranolol in patients with cirrhosis, suggesting a therapeutic potential. These findings provide the rationale for designing long-term administration studies to test whether the beneficial effect of a marked reduction in portal pressure is not outweighed by adverse effects on renal function and endogenous vasoactive systems due to arterial hypotension.

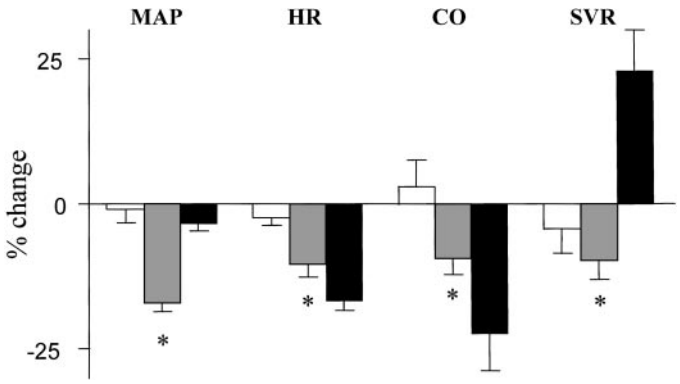

FIG. 2. Comparison of the effects of carvedilol (▨), propranolol (■), and placebo (□) on systemic hemodynamics. *Significantly different from propranolol and placebo.

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