

## Acute and 14-Day Hepatic Venous Pressure Gradient Response to Carvedilol and Nebivolol in Patients With Liver Cirrhosis

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**Key Words:** portal hypertension; carvedilol, nebivolol; hepatic venous pressure gradient.

**Summary.** Background and Objective. Alternative drug therapies are needed for the treatment of portal hypertension. The aim of this randomized study was to evaluate and compare the effects of carvedilol and nebivolol on the hepatic venous pressure gradient (HVPG) response in the patients with liver cirrhosis.

**Material and Methods.** In total, 20 cirrhotic patients were randomized into 2 groups and treated with carvedilol ( $n=10$ ) or nebivolol ( $n=10$ ). HVPG was measured at baseline, 60 minutes after the administration of carvedilol (25 mg) or nebivolol (5 mg), and after 14 days of carvedilol (25 mg) or nebivolol (5 mg) administered daily.

**Results.** Carvedilol significantly reduced HVPG from 22.2 mm Hg (SD, 4.4) to 15.2 mm Hg (SD, 3.7) after 60 minutes and to 16.4 mm Hg (SD, 2.9) after 14 days ( $P<0.01$ ). Nebivolol reduced HVPG from 19.7 mm Hg (SD, 2.5) to 15.7 mm Hg (SD, 2.6) and 16.7 mm Hg (SD, 3.2), respectively ( $P<0.02$ ). Carvedilol effectively decreased HVPG in a greater proportion of the patients after an acute probe (88% vs. 57%) and after 14 days of the treatment (88% vs. 28%,  $P<0.05$ ) in comparison with nebivolol.

**Conclusion.** Carvedilol and nebivolol reduce HVPG in cirrhotic patients; however, the effect of carvedilol on the HVPG reduction might be superior to that of nebivolol, especially after 14 days of treatment.

### Introduction

Portal hypertension is the most important complication of liver cirrhosis, which is linked with the development of hepatic encephalopathy, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, varices, and ascites (1). Increased portal pressure is the major driving force behind bleeding gastroesophageal varices, which is a life-threatening complication associated with high mortality rates (2). The measurement of hepatic venous pressure gradient (HVPG) is already a well-established gold standard for the assessment of portal pressure in patients with liver cirrhosis (3). The reduction of portal pressure by 20% or to the level of  $\leq 12$  mm Hg provides an effective protection from variceal bleeding (4, 5).

Current treatment guidelines support the use of nonselective  $\beta$ -blockers (NSBBs) or endoscopic band ligation (EBL) for the primary prophylaxis of variceal bleeding (6). Propranolol and nadolol are the drugs that have been most widely used in this

setting. These drugs, however, are not tolerated well by all patients and often do not achieve targeted levels of the reduction in HVPG (7–10). The latest edition of Baveno V consensus clearly outlines the need for further research in the field on alternative treatment options (6).

Carvedilol is a promising NSBB with anti- $\alpha_1$ -adrenergic activity. Accumulating evidence supports the use of carvedilol in the management of patients with portal hypertension; however, whether carvedilol is the best  $\beta$ -blocker for the primary prophylaxis of variceal bleeding remains uncertain (6, 11). Some studies have reported that carvedilol has a stronger effect on the reduction of portal pressure than propranolol (12, 13) and is more effective than EBL for the primary prophylaxis of variceal bleeding (14). A recent study by Reiberger et al. (15) has shown that carvedilol leads to a significantly greater reduction in HVPG than propranolol. Furthermore, the same group has shown that carvedilol may achieve an effective HVPG reduction in a substantial proportion of nonresponders to propranolol. The main obstacle in the administration of carvedilol results from its anti- $\alpha_1$ -adrenergic activity and systemic hypotension, which is the main reason for

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the withdrawal of this drug in patients with liver cirrhosis (13, 14).

Splanchnic arterial vasodilation results from an excessive release of different endogenous vasodilators. Nitric oxide (NO) is a major player of vasodilation in portal circulation. In patients with liver cirrhosis, changes in endothelial cells result in the decreased function of NO synthetase, while NO deficiency in the liver leads to an increased intrahepatic resistance via a hemodynamic component (16). Portal pressure may be reduced by increasing NO levels in liver circulation (17). Nebivolol is a new third-generation selective  $\beta_1$ -receptor blocker that causes vasodilation by evoking endothelial NO production (18). We hypothesized that nebivolol might improve NO bioavailability in hepatic circulation and, thus, reduce portal pressure. To date, there are no randomized studies that would evaluate the effect of nebivolol in the treatment of portal hypertension by means of HVPg measurement.

The aim of our study was to compare the effect of carvedilol and nebivolol on the reduction of HVPg in the patients with liver cirrhosis. We also aimed to compare the systemic hemodynamic effects of carvedilol and nebivolol. Furthermore, we wanted to assess whether the effects of carvedilol and nebivolol on HVPg after 14 days of the treatment could be predicted by the measurement of HVPg after an acute probe of drug administration. This is the first study, which compares the treatment of portal hypertension with carvedilol vs. nebivolol.

## Material and Methods

**Study Design.** An open, randomized, parallel-group study was performed comparing the efficacy of carvedilol and nebivolol in the treatment of portal hypertension. The study was approved by Kaunas Regional Biomedical Research Ethics Committee. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

**Patients.** The patients for the study were recruited at the Clinic of Gastroenterology, Hospital of Lithuanian University of Health Sciences (Kaunas, Lithuania), between 2008 and 2009. Thirty-two consecutive patients included in the study had biopsy-proven liver cirrhosis, presence of esophageal varices in endoscopy, and no history of previous variceal bleeding. The classification of esophageal varices during endoscopy were done according to the criteria suggested by the guidelines: small straight varices (F1), enlarged tortuous varices that occupy less than one-third of the lumen (F2), and large coil-shaped varices that occupy more than one-third of the lumen (F3) (6).

The patients were excluded from the study if they had at least one of the following: clinical signs or previous history of hepatic encephalopathy, SBP,

renal insufficiency (serum creatinine  $>1.5$  mg/dL), previous EBL, Child-Pugh class C, underlying severe cardiac, respiratory, or psychiatric illness, contraindications to NSBB, and a diagnosis of hepatocellular carcinoma or any other malignancy. The patients with noncirrhotic portal hypertension and the patients receiving pharmacotherapy for the prevention of variceal bleeding ( $\beta$ -blockers, nitrates, or any other drugs) were also excluded from the study. All the patients signed an informed consent form to participate in the study. The patients eligible for the study were randomized into 2 arms: carvedilol and nebivolol groups. Randomization was performed using serially numbered sealed envelopes.

**Dosages of Carvedilol and Nebivolol and Study Protocol.** The selected doses were 25 mg of carvedilol (Roche, Basel, Switzerland) and 5 mg of nebivolol (Menarini, Florence, Italy) administered daily. HVPg was measured at 3 points throughout the study in all the patients: 1) before the administration of carvedilol or nebivolol at the baseline; 2) 60 minutes after the oral administration of 25 mg of carvedilol or 5 mg of nebivolol; 3) 14 days after 25 mg of carvedilol daily or 5 mg of nebivolol daily. The responder status was assigned when HVPg was reduced by  $\geq 20\%$  or to  $\leq 12$  mm Hg (19). Compliance with the therapy was monitored by measuring the heart rate (HR) and the blood pressure during clinical visits.

**Hepatic Venous Pressure Gradient Measurement.** HVPg was measured by the methodology described by Groszmann and Wongcharatrawee (20) and Bosch et al. (5). The standard criteria were applied to confirm an adequate wedging of the portal vein (5, 20). The occluded position of the catheter was checked by the absence of reflux after the injection of 2 mL of a contrast medium and appearance of a sinusoidogram (Infinity R50, Drager, Germany). The mean of at least 3 readings was taken for further analysis. If the difference between the readings was greater than 1 mm Hg, all the previous recordings were cancelled, and new readings were taken. Responders were defined as the patients whose HVPg was reduced by  $\geq 20\%$  or to  $\leq 12$  mm Hg (19).

**Statistical Analysis.** Quantitative data were expressed as the mean (SD) and were compared using the Mann-Whitney test. Correlation, regression, the  $\chi^2$  square or Fisher exact tests were employed in the statistical analysis. The level of significance was set at  $P < 0.05$ . The statistical analysis was performed using the SPSS 20.0 (Illinois, Chicago) software package.

## Results

**Study Population.** During 2008 through 2009, 32 cirrhotic patients without a history of variceal bleeding were referred for the inclusion into the

study. However, 5 patients dropped out of the study due to the absence of esophageal varices or baseline HVPG lower than 12 mm Hg, while 7 patients matched other exclusion criteria. In total, 20 cirrhotic patients with esophageal varices and baseline HVPG greater than 12 mm Hg met the inclusion criteria and were enrolled into the study. The patients were randomized into 2 study arms with 10 patients in the carvedilol group and 10 patients in the nebivolol group. The characteristics of the patients for both study arms are presented in Table 1. In all the patients, cirrhosis was related to alcohol or hepatitis C virus infection. There were more men (70%) in both the study arms, and the mean age was 56.7 (SD, 1.6) and 58.2 (SD, 2.2) years for the carvedilol and nebivolol groups, respectively. There were no significant differences between the carvedilol and nebivolol groups with respect to age, gender, etiology of liver cirrhosis, Child-Pugh score of liver insufficiency, size of varices, and HVPG measured at the baseline (Table 1). Due to a relatively short period of drug administration and time between HVPG measurement procedures, all the participants were inpatients, and compliance with the therapy was monitored by a ward nurse. Based on the medical records, the compliance rate was 100%

Table 1. Characteristics of Cirrhotic Patients in Carvedilol and Nebivolol Groups

Characteristic	Carvedilol (n=10)	Nebivolol (n=10)	P
Age, years	56.7 (1.6)	58.2 (2.2)	NS
Men, n (%)	7 (70)	7 (70)	NS
Etiology, n (%)			
Alcohol	4 (40)	5 (50)	NS
HCV	6 (60)	5 (50)	
Child-Pugh class, n A/B	4/6	4/6	NS
Varices, n F1/F2/F3	0/4/6	0/5/5	NS
HVPG at baseline, mm Hg	21.2 (4.4)	19.4 (2.4)	NS
MAP at baseline, mm Hg	98.3 (7.7)	92.3 (3.6)	NS
HR at baseline, bpm	75.0 (5.0)	74.2 (6.3)	NS

Values are mean (standard deviation), unless otherwise stated. HVPG, hepatic venous pressure gradient; NS, not significant; HCV, hepatitis C virus; MAP, mean arterial pressure; HR, heart rate; bpm, beats per minute.

in both the patients' groups.

*Effect of Carvedilol and Nebivolol on Hemodynamic Parameters After Acute Probe Administration.* The mean arterial pressure (MAP) at baseline was 98.3 mm Hg (SD, 7.7) in the carvedilol group and 92.3 mm Hg (SD, 3.6) in the nebivolol group ( $P>0.05$ ). The MAP was significantly reduced in both the carvedilol and the nebivolol group after the administration of the acute probe by 10.5 mm Hg (SD, 3.9) and 14.5 mm Hg (SD, 4.3), respectively (Table 2). The HR was also significantly reduced in both patients taking carvedilol (9.8 bpm [SD, 2.9]) and those taking nebivolol (10.6 bpm [SD, 4.0]). There were no significant differences between the changes in the MAP and the HR in the patients receiving carvedilol and those receiving nebivolol (Table 2). One patient in the carvedilol group and 2 patients in the nebivolol group dropped out of the study after the administration of the acute probe of the drug due to adverse effects of the drugs, i.e., hypotension or bradycardia. Thus, of the 10 patients in the carvedilol group and of the 10 patients in the nebivolol group, 9 and 8, respectively, were eligible for per-protocol (PP) analysis.

*Effect of Carvedilol and Nebivolol on Reduction of Hepatic Venous Pressure Gradient After 1 Hour and After 14 Days of Treatment.* The mean values of HVPG at baseline after 1 hour and after 14 days of the treatment in the carvedilol and nebivolol groups are presented in Fig. 1. Carvedilol significantly reduced HVPG from 22.2 mm Hg (SD, 4.4) to 15.2 mm Hg (SD, 3.7) after 60 minutes ( $P<0.01$ ) and to 16.4 mm Hg (SD, 2.9) after 14 days ( $P<0.01$ ) by PP analysis. Nebivolol also markedly reduced HVPG when compared with the baseline: from 19.7 mm Hg (SD, 2.5) to 15.7 mm Hg (SD, 2.6) after 1 hour ( $P<0.01$ ) and to 16.7 mm Hg (SD, 3.2) after 14 days of the treatment ( $P<0.05$ ) by PP analysis. HVPG was reduced by 29.6% (SD, 11.7) ( $P<0.01$ ) after 1 hour and by 26.2% (SD, 4.2) ( $P<0.01$ ) after 14 days of the treatment in the carvedilol group, while in the nebivolol group, HVPG was reduced by 20.1% (SD, 10.0) ( $P<0.01$ ) after 1 hour and by 15.3% (SD, 12.6) ( $P<0.05$ ) after 14 days (Fig. 2). Carvedilol reduced HVPG by  $\geq 20\%$  compared with the baseline values or to  $\leq 12$  mm Hg in a greater proportion of the patients after the acute probe than nebivolol (88% vs. 57%,  $P=0.14$ ) by PP analysis

Table 2. Effect of Carvedilol and Nebivolol on Hemodynamic Parameters 1 Hour After Drug Administration

Parameter	Carvedilol (n=10)				Nebivolol (n=10)			
	Baseline	After 1 h	Change	P	Baseline	After 1 h	Change	P
MAP, mm Hg	98.3 (7.7)	87.8 (8.5)	10.5 (3.9)	0.014	92.3 (3.6)	77.8 (6.2)	14.5 (4.3)	<0.001
HR, bpm	75.0 (5.0)	65.2 (4.4)	9.8 (2.9)	<0.001	74.2 (6.3)	63.6 (4.6)	10.6 (4.0)	0.002

Values are mean (standard deviation). MAP, mean arterial pressure; HR, heart rate; bpm, beats per minute.

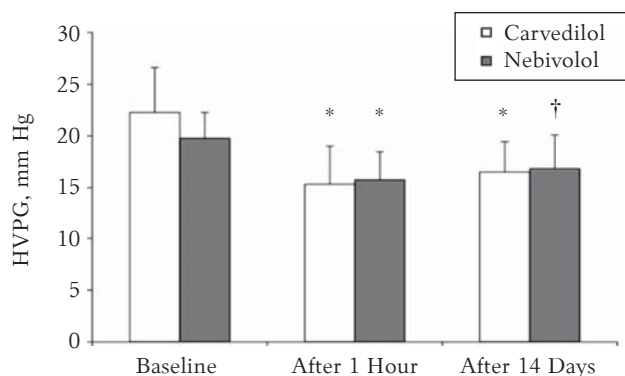


Fig. 1. Comparison of the mean values of hepatic venous pressure gradient (HVPG) in the carvedilol and nebivolol groups after 1 hour and 14 days among the patients by per-protocol analysis

\* $P < 0.01$  and † $P < 0.05$  when compared with baseline values.

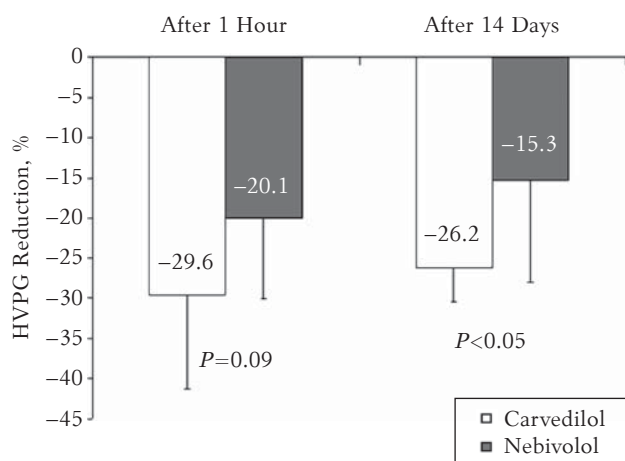


Fig. 2. Comparison of the reduction in hepatic venous pressure gradient (HVPG) in the carvedilol and nebivolol groups after 1 hour and 14 days of the treatment by per-protocol analysis

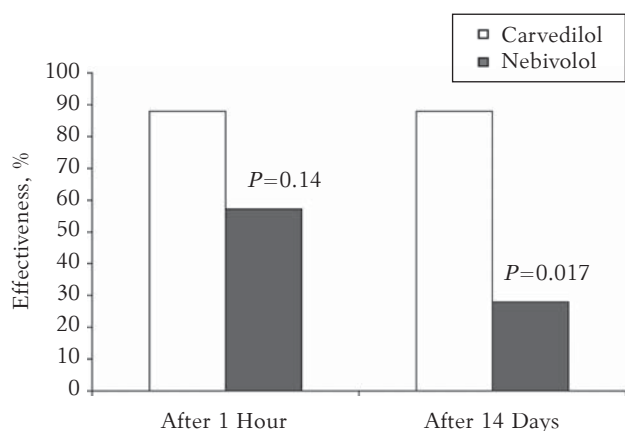


Fig. 3. Comparison of the response rates (decrease in hepatic venous pressure gradient by  $\geq 20\%$  or to  $< 12$  mm Hg) in the carvedilol and nebivolol groups after 1 hour and 14 days (per-protocol analysis)

(Fig. 3). The effect of carvedilol was also significantly superior to that of nebivolol after the 14-day treatment (88% vs. 28%,  $P < 0.05$ ) by PP analysis (Fig. 3).

*Changes in Effectiveness of Treatment in Carvedilol and Nebivolol Groups After Acute Probe and 14 Days of Treatment.* A reduction in HVPG after 1 hour strongly correlated with that after 14 days of the treatment in the carvedilol group ( $r = 0.541$ ,  $P = 0.024$ ) (Fig. 4). However, in the nebivolol group, the correlation did not achieve the statistically significant level ( $r = 0.453$ ,  $P = 0.067$ ) (Fig. 5). All the responders and nonresponders observed by the HVPG measurement after the acute probe in the carvedilol group retained the identical status after 14 days of the treatment. There were 8 responders in the carvedilol group after the acute drug administration and all of them remained in the responder group after 14 days of the treatment. After the acute probe, 1 nonresponder in the carvedilol group did not achieve the targeted reduction in HVPG even after 14 days of the continuous treatment with 25 mg of carvedilol. In the nebivolol group, 4 patients were identified as responders after the administration of the acute probe, but after 14 days of the treatment, 2 of them became nonresponders. The remaining 4 patients who did not achieve the targeted reduction in HVPG after the acute probe of nebivolol (5 mg) retained the nonresponders' status after 14 days of the treatment.

## Discussion

Despite certain advances in pharmaceutical and endoscopic treatment options, the management of portal hypertension still remains a significant challenge in daily clinical practice (6). The aim of this study was to compare the effects of carvedilol and nebivolol on the reduction of HVPG in the patients with liver cirrhosis and esophageal varices with no history of variceal bleeding. This is the first study that compared the treatment of portal hypertension with carvedilol vs. nebivolol. The results showed that carvedilol had a superior effect on the reduction of HVPG than nebivolol in the treatment of portal hypertension. In the carvedilol group, a significantly higher reduction of HVPG was observed than in the nebivolol group both after 1 hour (29.6% vs. 20.1%) and after 14 days (26.2% vs. 15.3%). In summary, 88% of the patients in the carvedilol group achieved an effective reduction in HVPG after 1 hour and after 14 days of the treatment when compared with 57% (after 1 hour) and 28% (after 14 days) of the responders in the nebivolol group. These data suggest that the NSBB activity of carvedilol is superior to the NO-donating effect of nebivolol.

We did not observe significant differences in MAP and HR changes after drug administration between

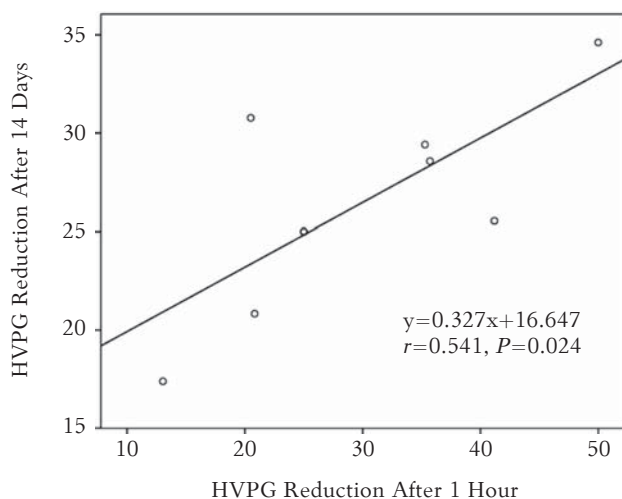


Fig. 4. Correlation between acute and 14-day hepatic venous pressure gradient (HVPG) reduction (%) by carvedilol (n=9)

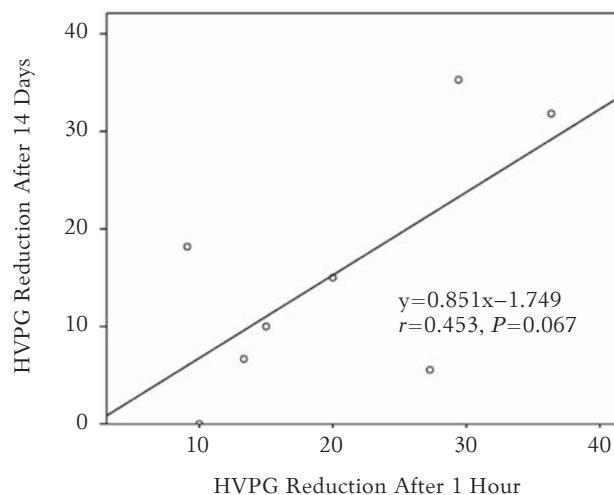


Fig. 5. Correlation between acute and 14-day hepatic venous pressure gradient (HVPG) reduction (%) by nebivolol (n=8)

the carvedilol and nebivolol groups. The mean values of the MAP and the HR after the acute probe in both groups indicate adequate dosing of the drugs. One patient (10%) in the carvedilol group and 2 patients (20%) in the nebivolol group dropped out of the study after the administration of the drug due to the side effects related to bradycardia or hypotension. The side effect profile for carvedilol in our study group resembles the data reported in other studies, where carvedilol had to be discontinued in 9% to 13% of the patients (12, 14, 21). Since there are no studies that would evaluate the side effects of nebivolol in the treatment of portal hypertension, no comparison related to the intolerance of the drug could be made.

Current guidelines state that carvedilol is a promising alternative in the treatment of portal hypertension; however, further studies are needed to establish the ultimate role of this NSBB in the management of patients with portal hypertension (6, 22). In the present study, carvedilol was found to be effective in reducing the portal pressure both after 1 hour of the administration of carvedilol (25 mg) and after 14 days of the continuous treatment with this drug in 88% of the patients. The high response rate to the dose of carvedilol (25 mg) might be also related to the inclusion of only Child-Pugh A–B class patients into our study because higher doses of the medication might be tolerated worse in a more advanced liver disease (23). In the carvedilol group, HVPG was reduced by 29.6% after 1 hour and by 26.2% after 14 days of the treatment. The extent of the portal hypertension reduction in the carvedilol group is comparable to other hemodynamic studies that report the HVPG reduction of 18%–23% (12–15, 21, 24). The optimal dosage of carvedilol in the treatment of portal hypertension, however, remains to be determined (11).

Carvedilol, as well as other NSBB, is associated with important side effects related to bradycardia or hypotension and, therefore, has to be withdrawn in a large subgroup of cirrhotic patients, especially with ascites (11). Current guidelines encourage studies on alternative treatment options, other than NSBBs, in the management of portal hypertension (6). When designing this study, we speculated that nebivolol, which is a selective  $\beta_1$ -blocker with the NO-donating effect, might be associated with fewer systemic side effects than carvedilol as it is usually well tolerated in patients with primary arterial hypertension (25). Different studies have shown a reduced intrahepatic production of NO in molecular studies of liver cirrhosis (16, 17). The present study data are in accordance with the results of a small study with nebivolol (2.5 mg/d) (26), where the reduction of the portal pressure by nebivolol was observed in patients with Child-Pugh class A cirrhosis without ascites. Interestingly, a recent animal study has shown that nebivolol increases the portal pressure in a cirrhotic rat model by increasing the splanchnic blood flow via modulation of NO signaling (26). It remains speculative why nebivolol increased the portal pressure in an animal bile duct ligation model (25) but decreased it in the present randomized study in the humans. In the abovementioned study by Reiberger et al. (26), an increase in the portal pressure was observed only in the rats receiving the highest doses (10 mg·kg<sup>-1</sup>·d<sup>-1</sup>) of nebivolol. It could be speculated that an increased generation of splanchnic NO exceeds a modest and beneficial increase in intrahepatic NO in bile duct ligation model rats receiving the highest dose of nebivolol. On the other hand, animal models cannot be completely extrapolated into human studies, especially taking into account the model-dependent

effect of  $\beta$ 1-blockers. Fizanne et al. have shown that propranolol had a significant hemodynamic effect only in the  $\text{CCl}_4$ -induced portal hypertension but not in the bile duct ligation model (27).

Our small pilot study indicates that nebivolol significantly reduces HVPG in cirrhotic patients by  $\geq 20\%$  or to  $\leq 12$  mm Hg after 1 hour; however, a low percentage of the responders after 14 days of the treatment (20%) raise the cautiousness of the potential use of this drug in clinical settings. The role of nebivolol in the treatment of portal hypertension should be evaluated in a larger independent cohort of patients, including alternative dosages. Such studies might be addressed to solve the paradox of liver and splanchnic NO generation in cirrhosis – too much or not enough – ensuring the maintenance of blood flow in the liver, whilst achieving an effective reduction in intrahepatic resistance (28). To our best knowledge, this report is the first randomized study on the reduction of HVPG in cirrhotic patients treated with nebivolol.

In this study, we wanted to assess whether the reduction of HVPG after the acute probe of the drug correlated with the reduction of HVPG after 14 days of the treatment. All the responders and nonresponders observed by the HVPG measurement after the acute probe in the carvedilol group retained the identical response status after 14 days of the treatment. In the nebivolol group, 75% of the responders and the nonresponders after 1 hour retained the identical response status to that of the treatment after 14 days. Our results suggest that the measurement of HVPG after the acute probe of the drugs correlates with the response rates after 14 days of the treatment. This finding is in line with other studies showing that the reduction of HVPG by  $\geq 20\%$  or to  $\leq 12$  mm Hg after the acute administration of carvedilol or propranolol correlate with the response rates to the drug in the long run (29–31).

There are certain limitations related to the de-

sign of this study. First of all, the numbers of the individuals within the study arms of carvedilol and nebivolol are relatively small. The number of the patients did not allow us to test different dosage regimens of carvedilol and nebivolol, and alternative doses of the drugs might be more effective or safe, especially in the long run. Due to the small number of individuals within the study, we chose to present the combined data of effectiveness; however, as discussed above, both the reductions in HVPG by  $\geq 20\%$  or to  $\leq 12$  mm Hg are good indicators of drug effectiveness in cirrhotic patients (19). The design of the study does not allow us to speculate whether the reduction of HVPG observed in the carvedilol and nebivolol groups could lead to clinical or survival benefits. In the present study, we did not include the patients receiving propranolol, a standard drug, since the aim of the study was to evaluate hemodynamic responses to carvedilol and nebivolol in particular, as it has been tested only in one small-scale study with cirrhotic patients. The study did not involve the measurement of the hepatic blood flow before and after the drug administration; however, we believe that the measurement of HVPG is a reliable indicator of drug effectiveness in this group of the patients. The small number of the individuals did not allow us to test the sensitivity and the specificity of the responder status after the acute probe for the prediction of drug effects after 14 days of the treatment.

### Conclusions

Carvedilol and nebivolol reduce hepatic venous pressure gradient in cirrhotic patients after 1 hour and after 14 days of treatment. This small pilot study shows that the effect of carvedilol on the reduction of hepatic venous pressure gradient might be superior to that of nebivolol, especially after 14 days of treatment.

### Statement of Conflict of Interest

The authors state no conflict of interest.

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