LIVER, PANCREAS, AND BILIARY TRACT

The Portal Pressure Response to β-Blockade Is Greater in Cirrhotic Patients Without Varices Than in Those With Varices

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Background & Aims: **Nonselective β-blockers are effective in reducing portal pressure in cirrhotic patients. However, this beneficial effect is highly variable and may depend on the extent of portal system collateralization. The aim of this study was to compare portal pressure response with timolol, a nonselective β-blocker, in cirrhotic patients with and without varices.** ***Methods:*** **Portal and systemic hemodynamics were measured before and after a single oral dose of 10 mg of timolol in 50 patients with cirrhosis and portal hypertension, 15 with and 35 without esophageal varices.** ***Results:*** **Timolol significantly decreased portal pressure in all patients (mean reduction, 20% ± 13%; $P < 0.0001$). The reduction in hepatic venous pressure gradient was greater in patients without varices (−24% ± 14%) than in those with varices (−12% ± 8%) ($P < 0.01$). A decrease in the hepatic venous pressure gradient of <12 mm Hg was achieved in 7 of 12 (58%) patients without varices and a baseline pressure gradient of ≥12 mm Hg, but only in 3 of 15 patients with varices (20%) ($P < 0.01$).** ***Conclusions:*** **Timolol is effective in reducing portal pressure in cirrhotic patients, more so in patients without varices, suggesting that nonselective β-blockers will be more effective in the treatment of portal hypertension when administered at early stages, before the development of varices.**

Variceal hemorrhage is a frequent and severe complication of cirrhosis. For varices to develop, the hepatic venous pressure gradient (HVPG) has to increase above a threshold value of 12 mm Hg.[1] Prospective hemodynamic studies have shown that cirrhotic patients with varices in whom the HVPG decreases (either pharmacologically or spontaneously) to levels of <12 mm Hg do not develop variceal bleeding and survive longer than patients in whom this decrease does not occur.[2] Moreover, in cirrhotic patients who have had an episode of variceal bleeding, rebleeding does not occur when HVPG is reduced pharmacologically to levels of <12 mm Hg, and rebleeding rates at 1 and 2 years are significantly reduced when HVPG is reduced by more than 20% from baseline.[3] The nonselective β-adrenergic blockers propranolol and nadolol are effective in reducing portal pressure and collateral blood flow in patients with cirrhosis and gastroesophageal varices.[4–6] However, the HVPG response to β-blockers is variable and more than one third of the patients do not show a significant decrease of portal pressure, despite adequate β-adrenergic blockade.[2,3,5] Significant decreases in HVPG were defined as those associated with a low incidence of variceal bleeding, i.e., a final HVPG of <12 mm Hg or a decrease of ≥20% from baseline values.[2,3]

Experimental models of portal hypertension have shown that early treatment with propranolol (before collaterals are formed) ameliorates the development of collaterals, suggesting a possible clinical use of β-blockers in the prevention of the development of varices.[7–9] However, the effect of β-blockers on portal pressure in patients without varices, the target population for such clinical use, has not been evaluated.

Therefore, the aim of this study was to evaluate the effect of β-blockade on the portal pressure of compensated cirrhotic patients without varices and to compare this response with that of patients with varices. The nonselective β-blocker selected for this study was timolol because, like nadolol, timolol has low-lipid solubility and, therefore, lower potential for central side effects.[10] Also, because it has a greater affinity for β-2 than for β-1 adrenoreceptors,[11] an effect that would potentially result in a greater reduction in portal pressure.[12]

Patients and Methods

Fifty-nine patients with compensated cirrhosis were initially included in the study. Diagnosis of cirrhosis was made by liver biopsy in 52 patients and based on clinical, biochemi-

Abbreviations used in this paper: HR, heart rate; HVPG, hepatic venous pressure gradient; MAP, mean arterial pressure.

0016-5085/97/$3.00

Table 1. Characteristics of Patients at Inclusion of Study

	With varices	Without varices	
	HVPG ≥12 mm Hg	HVPG ≥12 mm Hg	HVPG <12 mm Hg
Patients (*n*)	15	12	23
Age (*yr*)	58 ± 9	55 ± 12	58 ± 11
Sex (M/F)	10/5	3/9	14/9
Etiology of cirrhosis			
Alcoholic	5	1	4
Nonalcoholic	10	11	19
Child–Pugh score	5.9 ± 1.2	5.3 ± 0.5	5.3 ± 0.6
Baseline MAP (*mm Hg*)	97 ± 10	105 ± 12	103 ± 12
Baseline HR (*bpm*)	77 ± 9	76 ± 13	78 ± 12
Baseline HVPG (*mm Hg*)	16.5 ± 3.1	14.8 ± 2.3	8.7 ± 1.7[a]

NOTE. Groups were define according to the presence or absence of varices and baseline HVPG. Results are expressed as the mean ± SD.
[a] $P < 0.001$ vs. the other two groups.

cal, and ultrasonographic findings in 7 patients (all of whom had gastroesophageal varices). All patients gave written informed consent to participate in the study, which was approved by the Institutional Review Committee of the Hospital Clínic (Barcelona, Spain); Yale–New Haven and West Haven Veterans Administration Hospital, New Haven and Faulkner Hospital (Boston, MA).

Thirty-one patients were men and 28 were women. The mean age was 57 ± 10 years (mean ± SD), and the age range was 34–73 years. All patients in this study underwent an upper endoscopy, which showed presence of esophageal varices in 15 patients and absence of varices in the remaining 44. No patient had gastric varices or portal-hypertensive gastropathy.

Hemodynamic studies were performed according to previously described methods.[13] After an overnight fast and under local anesthesia, a 7F balloon-tipped catheter (Medi Tech; Cooper Scientific Corp., Watertown, MA) was advanced under fluoroscopic guidance to the main right hepatic vein, where it remained during the whole study. This catheter allowed repeated measurements of the HVPG, the difference between wedged and free hepatic venous pressure.

Nine patients without varices had no evidence of portal hypertension (HVPG of <6 mm Hg) and were excluded from the study. Therefore, 50 patients met entry criteria and were included in the study.

After obtaining baseline hemodynamic measurements, 10 mg of timolol was administered orally and HVPG, heart rate (HR), and mean arterial pressure (MAP) were measured again at 30 and 60 minutes after drug administration.

All measurements were performed in triplicate during each study period, and permanent tracings were obtained on a multichannel recorder (7754B; Hewlett Packard, Waltham, MA). An automatic sphygmomanometer (Dinamap; Critikon Inc., Tampa, FL) was used to monitor noninvasively MAP and HR.

All values are reported as mean ± SD. Analysis of variance for repeated measurements was used to evaluate the effect of timolol within the same group. Comparisons between groups were performed by analysis of variance using the Bonferroni correction for multiple comparisons. A P value of <0.05 was considered significant. After the identification of variables that distinguished patients with and without a significant HVPG response to timolol, stepwise logistic regression[14] was performed to identify variables with an independent predictive value for a significant HVPG response.

Results

As shown in Table 1, patients included in the study were divided in two groups according to the presence or absence of varices. All patients with esophageal varices (n = 15) had a baseline HVPG of ≥12 mm Hg; among patients without varices (n = 35), 12 had a baseline HVPG of ≥12 mm Hg (high HVPG) and 23 had an HVPG of <12 mm Hg (low HVPG). The three groups of patients were comparable in baseline demographic, clinical, and hemodynamic parameters, except for baseline HVPG, which was significantly lower in patients without varices and with a low HVPG (8.7 ± 1.7 mm Hg; $P < 0.001$). However, patients with varices and patients without varices and a high HVPG had similar baseline HVPGs (16.5 ± 3.1 vs. 14.8 ± 2.3 mm Hg; NS). All patients had compensated cirrhosis, and according to the Child–Pugh classification, 46 (92%) patients were classified as Child A and 4 patients were classified as Child B (mean Child–Pugh score, 5.5 ± 0.8). The esophageal varices, when present, were small in size (<5 mm in diameter).

Effects of timolol on splanchnic hemodynamics. The oral administration of 10 mg of timolol significantly decreased the HVPG in all groups; the mean re-

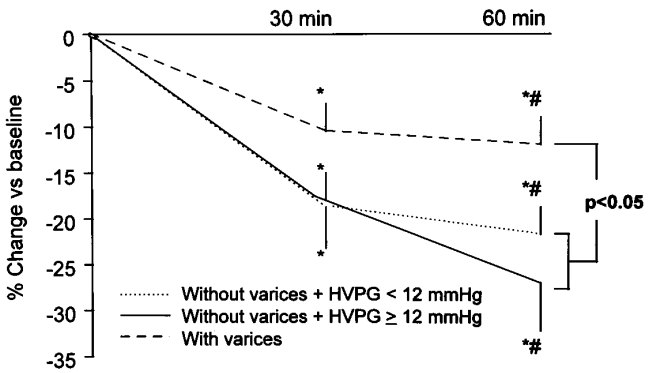

Figure 1. Effects of timolol administration on HVPG, expressed as percentage of change from baseline value. HVPG decreased in the three groups of patients studied. However, this reduction was significantly greater in patients without varices compared with those with varices, regardless of their baseline HVPG. *$P < 0.001$ vs. baseline; #$P < 0.05$ vs. 30 minutes.