

Low Doses of Isosorbide Mononitrate Attenuate the Postprandial Increase in Portal Pressure in Patients With Cirrhosis

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Postprandial hyperemia is associated with a significant increase in portal pressure in cirrhosis, which may contribute to progressive dilation and rupture of gastroesophageal varices. In cirrhosis, an insufficient hepatic production of nitric oxide (NO) may impair the expected hepatic vasodilatory response to increased blood flow, further exaggerating the postprandial increase in portal pressure. This study was aimed at investigating whether low doses of an oral NO donor might counteract the postprandial peak in portal pressure. Twenty-three portal hypertensive cirrhotics, 8 of them under propranolol therapy, were randomized to receive orally 5-isosorbide mononitrate (ISMN; 10 mg; $n = 11$) or placebo ($n = 12$) and a standard liquid meal 15 minutes later. Hepatic venous pressure gradient (HVPG), mean arterial pressure (MAP), and hepatic blood flow (HBF) were measured at baseline and 15, 30, and 45 minutes after a meal. ISMN significantly attenuated the postprandial increase in portal pressure as compared with placebo (peak HVPG increase: 2.4 ± 1.4 mm Hg vs. 5.2 ± 2.1 mm Hg, $P = .002$). Percentual increases in HBF were similar in both groups. MAP decreased slightly in ISMN group ($-7.5\% \pm .5\%$; $P < .01$ vs. baseline). These effects were also observed in patients on chronic propranolol therapy. In conclusion, hepatic NO supplementation by low doses of ISMN effectively reduces the postprandial increase of portal pressure in cirrhosis, with only a mild effect on arterial pressure. The same was observed in patients receiving propranolol. Our results suggest that therapeutic strategies based on selective hepatic NO delivery may improve the treatment of portal hypertension. (HEPATOLOGY 2003;37:378-384.)

Several studies have shown that, in normal subjects, food intake induces marked changes in splanchnic hemodynamics.¹⁻⁵ The main finding is a postprandial increase in splanchnic blood flow, caused by splanchnic arteriolar vasodilatation occurring in the submucosal and mucosal layers of the small intestine. This postpran-

dial splanchnic vasodilatation and hyperemia occur owing to the interaction of intrinsic mechanisms (such as changes in arteriolar transmural pressure and/or increase in vasodilator tissue metabolites) and extrinsic mechanisms (action of autonomic nervous system) and to the effect of gastrointestinal hormones.^{1-4,6,7}

On the other hand, in cirrhotic patients, the postprandial hyperemia determines a significant increase of portal and collateral blood flow, which results in an increased hepatic venous pressure gradient (HVPG).^{3,7-15} This is observed rapidly, the maximum changes in splanchnic hemodynamics being observed at 30 minutes after the meal, returning to basal levels at 120 minutes.^{3,8,9,11-14} These data suggest that, in cirrhotic patients, the repeated increase in portal venous pressure because of food intake may contribute to the progressive portal-systemic collateral dilation and to the development and dilation of the varices that eventually lead to variceal bleeding.

Propranolol administration has been reported to reduce the postprandial peak in portal pressure,¹⁰ but sub-

Abbreviations: HVPG, hepatic venous pressure gradient; NO, nitric oxide; ISMN, 5-isosorbide mononitrate; HBF, hepatic blood flow; WHVP, wedge hepatic venous pressure; MAP, mean arterial pressure.

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Received June 13, 2002; accepted November 2, 2002.

Supported in part by grants (FIS 00/0444; FIS 01/9356 to J.G.A.) from the Fondo de Investigación Sanitaria.

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0270-9139/03/3702-0020\$35.00/0

doi:10.1053/jhep.2003.50053

sequent studies demonstrated that postprandial increases in portal pressure¹⁵ and blood flow^{5,16} are not blunted—the only difference being that the baseline value is lower than before taking β -blockers—because the magnitude of the postprandial peak in portal pressure was essentially unaffected.¹⁵

Several recent studies have shown that the cirrhotic liver exhibits endothelial dysfunction that results in a defective or absent vasodilatory response to acetylcholine and in an insufficient nitric oxide (NO) production by endothelial nitric oxide synthase in the intrahepatic vascular bed.¹⁷⁻¹⁹ Such a deficient NO production increases the hepatic vascular tone and may decrease the intrahepatic vasodilatory adaptive response to sudden increases in blood flow. Thus, the physiologic postprandial hyperemia is likely to result in a higher than anticipated and brisk increase in portal pressure. These observations suggest that, if NO can be provided to the hepatic circulation, the postprandial increase of portal pressure could be prevented or significantly attenuated.

Isosorbide-5-mononitrate (ISMN) is an NO donor drug completely absorbed after oral administration, which causes dose-related, significant reductions of portal pressure in patients with cirrhosis.²⁰⁻²³ At relatively low doses (20 mg), ISMN has been shown to decrease portal pressure without reducing hepatic blood flow (HBF),²³ suggesting that it decreases hepatic resistance by intrahepatic NO supplementation.

The primary aim of this study was to investigate whether an even lower dose (10 mg) of ISMN, which by itself does not modify baseline HVPG, could prevent the postprandial increase of portal pressure in patients with cirrhosis and portal hypertension. Furthermore, we aimed to study whether ISMN effects on postprandial hemodynamics were also present in patients under continued propranolol therapy.

Patients and Methods

Patients. The study was performed in 23 cirrhotic patients (17 men and 6 women) referred to our unit for hemodynamic evaluation of portal hypertension. The study was performed according to the principles of the Declaration of Helsinki, (revision of Edinburgh 2000) and was approved by the Human Research Committee of the Hospital Clinic in May 2000. The nature of the study was explained to the patients, and written informed consent was obtained in each case.

All patients had cirrhosis diagnosed by clinical, biochemical, ultrasonographic, and/or histologic criteria. Mean age of the patients was 54 ± 11 years. Mean weight was 78.7 ± 11.8 kg. Eleven patients belonged to Child-

Pugh class A, 11 to class B, and 1 to class C. The mean Child-Pugh score was 6.9 ± 1.8 points (range 5-11). The etiology of cirrhosis was hepatitis C virus related in 14 patients, alcoholic in 6, alcoholic and hepatitis C virus in 1, autoimmune cirrhosis in 1, and unknown in 1. Twenty patients had esophageal varices, 12 (that were large in all cases) had previously bled. Four were under propranolol treatment and 8 treated with endoscopic therapy. Among those with no previous bleeding, 4 had large varices and were treated with propranolol. Seven patients had ascites, 4 of them were treated with spironolactone and 3 with the combination of furosemide and spironolactone.

Patients were considered eligible for the study if they were found to have an HVPG ≥ 12 mm Hg during the hemodynamic study. Exclusion criteria were the following: arterial hypotension (defined by a systolic blood pressure of <90 mm Hg), hypersensitivity to isosorbide-5-mononitrate, pregnancy, hepatic failure as defined as prothrombin rate $<40\%$ and bilirubin >5 mg/dL, portal vein thrombosis, diffuse or multinodular hepatocellular carcinoma, and previous surgical or transjugular intrahepatic portosystemic shunt.

Sample Size Calculation. We calculated that, to detect a 50% difference in the postprandial increase in HVPG between placebo and ISMN groups with a 2-tailed test, α risk of 5%, and β risk of 20%, at least 11 patients should be included in each treatment arm. We assumed a standard deviation of 12 from previous unpublished data from our laboratory.

Methods. After an overnight fast, the patients were transferred to the Hepatic Hemodynamic Laboratory. Under local anesthesia, an 8F venous catheter introducer (Axxess; Maxxim Medical, Athens, TX) was placed in the right femoral vein or in the right jugular vein under ultrasonographic guidance using the Seldinger technique. Under fluoroscopic control, a 7F balloon-tipped catheter (Medi-Tech; Boston Scientific Cork Ltd., Cork, Ireland) was advanced into the main right hepatic vein to measure wedged hepatic venous pressure (WHVP) and free hepatic venous pressure. All measurements were performed in triplicate, and permanent tracings were recorded.

Preceded by a priming dose (5 mg), a solution of indocyanine green (ICG; Pulsion Medical Systems, Munich, Germany) 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 HBF as previously described.²³ Mean arterial pressure was measured noninvasively every 5 minutes by an automatic electronic sphygmomanometer (Marquette Electronics, NY). Heart rate was derived from continuous electrocardiogram monitoring.

Table 1. Clinical and Hemodynamic Data of the Patients Studied at Baseline

	Placebo (n = 12)	ISMN (n = 11)
Sex (M/F)	10/2	7/4
Age (yr)	58 ± 11	50 ± 11
Child-Pugh (score)	6.7 ± 2.2	7.3 ± 1.3
Varices (%)	92	82
Ascites (%)	17	46
Propranolol Rx (n)	4	4
HVPG (mm Hg)	16.0 ± 2.8	16.9 ± 5.2
MAP (mm Hg)	86 ± 16	82 ± 10
HBF (mL/min)	792 ± 172	977 ± 492
HR (bpm)	72 ± 14	76 ± 14

After completing baseline hemodynamic measurements, patients were randomized to receive in double-blind conditions either ISMN (10 mg, n = 11) or placebo (10 mg lactose, n = 12) orally. This ISMN dose was chosen to minimize the possibility of splanchnic vasoconstriction, following the results obtained in a preliminary dose-finding study in which this dose of ISMN (10 mg) caused a mild decrease in mean arterial pressure (MAP) ($-5\% \pm 6\%$), without significant changes in HVPG ($-2\% \pm 5\%$) (n = 4). Fifteen minutes after drug ingestion, a liquid meal (400 mL) containing 25 g of proteins, 80.8 g of carbohydrates, and 19.68 g of lipids for a total of 600 kcal (Ensure Plus; Abbott Laboratories B.V., Zwolle, The Netherlands) was given to each patient and was ingested within approximately 5 minutes. The onset of meal ingestion was considered as time zero. Postprandial hemodynamic measurements were repeated at minute 15, 30, and 45. At 15 minutes and 30 minutes, 3 separate sets of simultaneous samples of peripheral and hepatic venous blood were taken for HBF measurement.

Statistics. Statistics were performed using SPSS 10.0 statistical package (SPSS Inc., Chicago, IL). All results are expressed as mean \pm SD values. Comparisons within each group were performed with Student's *t* test for paired data and comparisons between groups with Student's *t* test for unpaired data. ANOVA test for repeated measurements

was used when appropriate. Preplanned contrast analysis was performed to compare each time point against baseline. A *P* value of $< .05$ was considered significant.

Results

Baseline clinical and hemodynamic data are shown in Table 1. All studied patients had clinically significant portal hypertension (median HVPG 15 mm Hg, range 12–27.5 mm Hg). There were no significant differences between patients randomized to ISMN or placebo in any parameter at baseline.

The placebo group (n = 12) showed a marked and statistically significant postprandial increase of HVPG (ANOVA, $P < .0001$); in agreement with previous observations, it was mostly due to the increase in WHVP, without significant changes in free hepatic venous pressure (Table 2). The increase in HVPG was already present 15 minutes after the meal ($26\% \pm 17.8\%$; $P < .0001$ vs. baseline); it was maximum at 30 minutes ($29.1\% \pm 14.9\%$; $P < .0001$ vs. baseline) and persisted at 45 minutes ($21.8\% \pm 20.8\%$; $P < .001$ vs. baseline). The peak change of HVPG was of 5.2 ± 2.1 mm Hg. In this group, the HVPG increase was associated with an increase in HBF that averaged $23.1\% \pm 28.4\%$ at 15 minutes ($P = .03$ vs. baseline) and $18.2\% \pm 24.8\%$ at 30 minutes ($P = .04$ vs. baseline). Ingestion of the test meal was not followed by significant changes in MAP and heart rate in patients receiving placebo (Table 2).

In patients receiving ISMN (n = 11), HVPG also increased significantly after the meal (ANOVA, $P < .01$). However, when compared with patients receiving placebo, the postprandial rise in portal pressure was markedly and significantly reduced at every time point: $12.7\% \pm 7.7\%$ vs. $26.0\% \pm 17.8\%$ at 15 minutes ($P < .04$), $10.4\% \pm 9\%$ vs. $29.1\% \pm 14.9\%$ at 30 minutes ($P < .01$), and $5.2\% \pm 8.3\%$ vs. $21.8\% \pm 20.8\%$ at 45 minutes ($P < .03$) (Fig. 1A).

A similar blunting of the postprandial increase in HVPG was observed when expressing the results as abso-

Table 2. Postprandial Change in Hepatic Venous Pressures After Placebo Versus ISMN

	Placebo (n = 12)				ISMN (n = 11)			
	Baseline	15 Min	30 Min	45 Min	Baseline	15 Min	30 Min	45 Min
WHVP (mm Hg)	23.2 ± 3.3	28.6 ± 4.5*	28.8 ± 4.7*	27.7 ± 5.3*	26.5 ± 4.8	29.4 ± 5.7*	28.9 ± 6.1*	27.1 ± 5.0*
FHVP (mm Hg)	7.2 ± 2.0	8.4 ± 2.8	8.2 ± 2.6	7.9 ± 2.8	9.6 ± 2.8	10.4 ± 2.8	10.3 ± 3.0	10.4 ± 3.2
HVPG (mm Hg)	16.0 ± 2.8	20.2 ± 4.4*	20.6 ± 3.8*	19.8 ± 4.6*	16.9 ± 5.2	19.0 ± 6.0*	18.6 ± 6.0*	16.7 ± 4.2
HBF (mL/min)	792 ± 172	993 ± 370*	963 ± 376*	—	977 ± 492	1,199 ± 481*	1,018 ± 263	—
MAP (mm Hg)	86 ± 16	89 ± 17	88 ± 16	88 ± 16	82 ± 10	76 ± 9*	75 ± 8*	76 ± 9*
HR (bpm)	72 ± 14	74 ± 15	75 ± 14	76 ± 16	76 ± 14	79 ± 14	78 ± 16	79 ± 16

**P* < .05 vs. baseline.

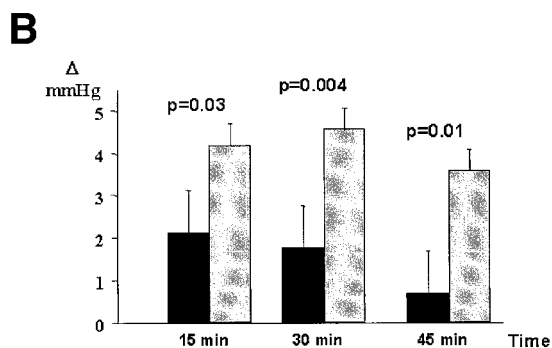
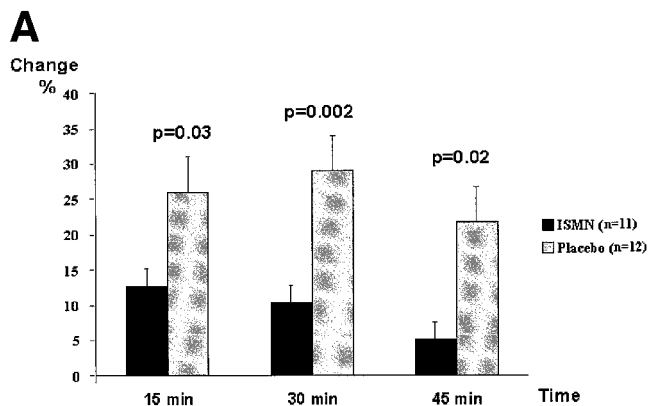


Fig. 1. Postprandial changes of HVPG in patients receiving ISMN or placebo. Data are shown as percentage change from baseline (mean \pm SEM) (A) and as absolute changes (B).

lute changes (Fig. 1B). Also, the peak increase in HVPG was significantly lower in these patients (2.4 ± 1.4 mm Hg) than in those receiving placebo (5.2 ± 2.1 mm Hg; $P = .002$).

The percentage increase in HBF after food intake in patients receiving ISMN was similar to that observed in the placebo group. However, in ISMN group, HBF at 30 minutes returned to values that were not different from baseline and, in the placebo group, remained increased at all time points (Fig. 2, Table 2).

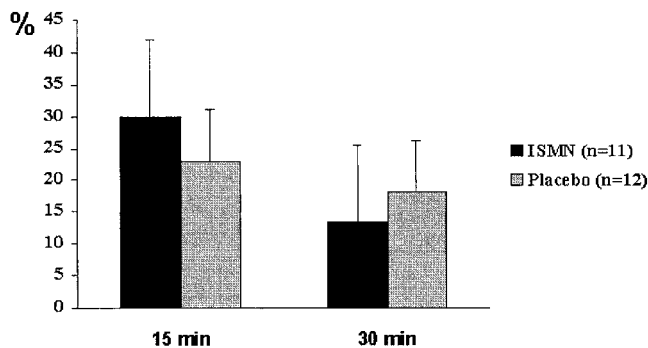


Fig. 2. Postprandial changes of HBF in patients receiving ISMN or placebo. Data are shown as percentage change from baseline (mean \pm SEM).

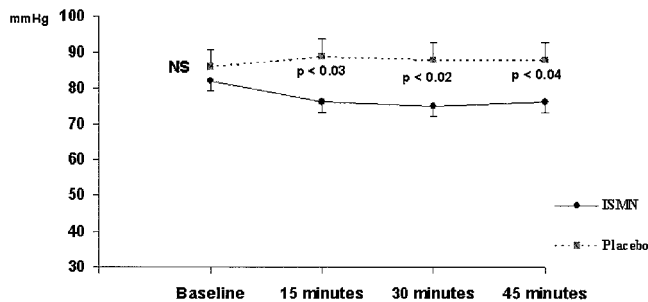


Fig. 3. Postprandial changes of MAP in ISMN vs. placebo (mean \pm SEM).

MAP decreased significantly by a value of $6.5\% \pm 8.2\%$ at minute 15, $7.5\% \pm 6.5\%$ at minute 30, and $6.2\% \pm 8.7\%$ at minute 45 in the ISMN group (maximum observed decrease: 6 ± 5 mm Hg or $7.5\% \pm 6.5\%$) (Fig. 3, Table 2). Heart rate remained unchanged.

Patients who were under chronic propranolol therapy had similar baseline HVPG as patients who were not (16.6 ± 2.7 mm Hg vs. 16.3 ± 4.8 mm Hg, respectively; NS). These patients also exhibited a significant and marked rise in HVPG in the placebo group ($n = 4$; peak increase 5.1 ± 1.3 mm Hg) that was significantly blunted in ISMN-treated patients ($n = 4$; peak increase 2.6 ± 1.0 mm Hg; $P = .02$ vs. placebo) (Fig. 4). At each measurement point, there were no differences in HBF in ISMN-treated patients as compared with placebo. However, although MAP did not change after placebo, it decreased significantly in the ISMN group (-8 ± 5 mm Hg at 30 minutes). There were no adverse reactions during or as a consequence of the study.

Discussion

Portal hypertension in cirrhosis results from the interaction of an increased resistance to portal blood flow through the cirrhotic liver and an increased portal venous inflow. Most attempts to correct the portal hypertensive syndrome have been based on the pharmacologic reduc-

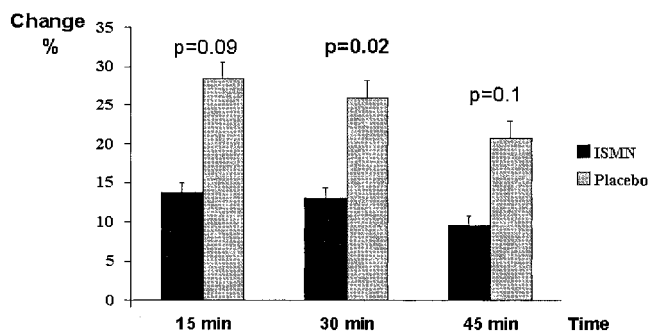


Fig. 4. Postprandial changes of HVPG in ISMN vs. placebo, in patients on long-term propranolol (mean \pm SEM).

tion of the increased portal inflow by means of nonselective β -blockers or other splanchnic vasoconstrictors such as terlipressin, somatostatin, or somatostatin derivatives.²⁴ However, recent investigations have shown that, in cirrhosis, the increased hepatic resistance is not only a mechanical consequence of the distortion of the intrahepatic vascular architecture because of fibrosis, scarring, and nodule formation but that there is also a dynamic component because of the active contraction of different cells with contractile activity, such as vascular smooth muscle cells, activated hepatic stellate cells around the sinusoids, and myofibroblasts in the fibrous septa.²⁵⁻²⁷ In experimental models, this dynamic component is exaggerated by a deficit in the production of the endogenous vasodilator NO in the intrahepatic circulation, which appears to be due to a decreased activity of endothelial nitric oxide synthase.^{17,19,28,29} Such an insufficient hepatic production of NO provides a rationale for the use of nitrovasodilators in the treatment of portal hypertension because it is conceivable that supplementation of NO in the intrahepatic circulation will reduce the hepatic resistance and, hence, portal pressure. Indeed, previous studies from our laboratory have shown that the administration of ISMN causes dose-related reductions of portal pressure in cirrhosis.^{20,23} At relatively low doses (20 mg) or during continued administration, the fall in portal pressure was almost entirely due to a decrease in hepatic resistance because there was no decrease in HBF. However, ISMN does not allow a selective delivery of NO at the intrahepatic circulation, which means that this agent causes systemic hypotension, undesirable in patients with cirrhosis. However, this and previous studies from our laboratory have shown that this effect is also dose related and mild at relatively low doses.²³ Although it has been proposed that other agents such as NCX-1000, a NO-releasing derivative of ursodeoxycholic acid, would allow such a targeted hepatic delivery of NO,³⁰ this has not been studied in portal hypertensive subjects. Another possibility is to overexpress the nitric oxide synthase gene in the liver by the use of gene therapy,^{31,32} but this is far from being clinically applicable.

In the present study, we hypothesized that, given the fact that ISMN is totally absorbed after its oral administration, the administration of a very low dose of ISMN will allow it to reach a high enough hepatic concentration as to dilate effectively the intrahepatic circulation while limiting its unwanted systemic vasodilatory effect. We further proposed that this hepatic NO supplementation could abrogate the postprandial increase in portal pressure. Finally, we also aimed at examining whether this effect may also be observed in patients under continued propranolol therapy.

The results of our study confirm that the intake of a test meal causes a rapid and pronounced increase in portal pressure both in patients under no treatment or in those taking propranolol, thus confirming previous studies.¹⁵ More importantly, the study demonstrates that the administration of a low dose of ISMN (10 mg), but not of placebo, largely prevented the postprandial increase in portal pressure. Again, this effect was also observed in patients under continued propranolol therapy. It is of note that ISMN not only ameliorated both postprandial HVPG peak and hyperemia but also shortened them, whereas, in the placebo group, HBF values at 30 minutes and HVPG at 45 minutes were still higher than baseline values; in the ISMN group, they were not any more. This also raises the possibility of some degree of splanchnic vasoconstriction because of the persistent, although mild, significant decrease in mean arterial pressure, as has been shown in experimental models.³³ These findings may have relevant implications both in the understanding of the pathophysiology of the increased intrahepatic resistance in cirrhosis and in the treatment of portal hypertension.

From a conceptual point of view, our findings strongly support the view that, as shown in experimental models,^{17,19,28,29} patients with cirrhosis may have an insufficient production of NO in the hepatic circulation (which has been called intrahepatic "endothelial dysfunction").¹⁷ Such decreased availability of NO in the hepatic circulation may play a key role in increasing hepatic resistance and aggravating the postprandial increase in portal pressure. The repeated postprandial increase in portal pressure may be an important determinant of the progressive dilation of the varices.

From a practical standpoint, our findings provide further support for the use of low doses of ISMN in conjunction with propranolol therapy. We have previously demonstrated that the combined administration of ISMN and propranolol has a synergistic effect decreasing portal pressure without causing adverse renal effects.³⁴ Although there is no direct evidence to conclude that this combination fares better than propranolol alone in preventing variceal rebleeding,³⁵ 2 large randomized controlled trials have supported the view that it may be superior to endoscopic injection sclerotherapy or to band ligation.^{36,37} An issue that remains unanswered in this study is whether tolerance develops for this particular effect of ISMN, but previous hemodynamic studies showed that systemic hypotension and the portal pressure-lowering effect of ISMN are maintained after long-term, continuous administration in patients with cirrhosis.^{20,38,39}

The above considerations should not be taken as an argument against the search for other agents for the treat-

ment of portal hypertension. On the contrary, the need of further investigation is emphasized by our findings because the response to therapy may be improved significantly by associating agents acting through different mechanisms, and that may correct in part, in that way, the multiple abnormalities leading to portal hypertension. In summary, our results suggest that therapeutic strategies based on selective hepatic NO delivery may improve the treatment of portal hypertension.

Acknowledgment: The authors thank Angels Baringo, Laura Rocabert, and Rosa Sáez for their expert assistance and Encarna Gutierrez for secretarial support.

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