Hemodynamic Evaluation of the Addition of Isosorbide-5-Mononitrate to Nadolol in Cirrhotic Patients With Insufficient Response to the β-Blocker Alone

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The association β-blockers plus isosorbide-5-mononitrate (I5M) has been proposed for the treatment of portal hypertension in patients with insufficient response to β-blockers alone, according to hemodynamic criteria. The mechanism of action in these patients is not clearly defined. Fifteen patients with cirrhosis and esophageal varices were evaluated by hepatic venous pressure gradient (HVPG) measurement and duplex-Doppler ultrasonography before and after 1 month of treatment with nadolol. Nine patients who did not exhibit a decrease in HVPG to 12 mm Hg or a percent decrease greater than 20% were classified as poor responders, and were studied again with the same methodology after 3 months of chronic administration of nadolol + I5M 20 mg twice per day. In poor responders, mean HVPG decrease after nadolol was 8.9% ± 2.8%, and after the combination, it was 25.7% ± 1.7% (P = .004). All patients except one became good responders to the association. Portal blood flow (PBF) decreased significantly after nadolol (P = .004), and remained unchanged after the addition of nitrates. Resistance to portal blood flow (RPBF) increased after nadolol (P = .02) and returned to baseline values during combined treatment (P = .03). In good responders, an adequate decrease in HVPG was associated with a decrease in PBF (P = .06) but no change in RPBF. A wide spectrum of combined changes in PBF and in RPBF after nadolol was observed in poor responders, ranging from no change in either parameter to a marked decrease in PBF counterbalanced by a marked increase in RPBF. The addition of I5M was followed in most cases by larger effects on resistance than on flow. Doppler parameters were not significantly correlated with the HVPG response to nadolol alone or associated with I5M. It is concluded that good hemodynamic responders to nadolol differ from poor responders in the lack of increase in RPBF after the drug. The addition of nitrates to nadolol is effective in decreasing portal pressure in most poor responders to nadolol alone. A decrease in outflow resistance is the main mechanism involved. (HEPATOLOGY 1997;26:34-39.)

On the basis of several prospective evaluations,[1-3] a decrease in hepatic venous pressure gradient (HVPG) to 12 mm Hg or less, or by at least 12% to 20%, is considered the best predictor of effectiveness of treatment with β-blockers in patients with cirrhosis and portal hypertension.[4] Therefore, alternative treatments are requested for patients who do not meet these criteria. With this aim, the association with long-acting nitrates has been proposed.[5] The association with long-acting nitrates was shown to decrease HVPG to a larger degree than β-blockers alone,[6,7] and to decrease approximately by half the probability of being a poor responder according to hemodynamic criteria.[6,7]

A few questions are still unanswered in the use of long-acting nitrates in association with β-blockers. From a clinical point of view, it is uncertain how effective the association is in the subgroup of patients with insufficient response to β-blockers. From a pathophysiological point of view, the mechanisms of action of the association are not clearly defined, because nitrates may act by enhancing an insufficient decrease in portal blood inflow obtained with β-blockers alone,[8] or by contrasting a possible increase in outflow resistance induced by β-blockers.[9]

In the present study, we assessed the portal hypotensive effect of the addition of isosorbide-5-mononitrate (I5M) to nadolol and the changes in portal hemodynamic variables determining portal pressure (i.e., portal blood flow [PBF] and resistance to portal blood flow [RPBF]) in a group of poor responders to nadolol, and compared them with a group of good responders. Because changes in hepatic artery blood flow may influence portal hypertension, changes in hepatic artery pulsatility index (HAPI) were also assessed.

PATIENTS AND METHODS

Fifteen patients with cirrhosis and portal hypertension who were referred to our liver hemodynamic laboratory for evaluation of portal hypertension took part in this study. Eight patients had alcoholic cirrhosis, and 7 had hepatitis C virus–related cirrhosis. In all cases, diagnosis was based on liver histology; all histological examinations showed micronodular cirrhosis. There were 8 men and 7 women; the mean age was 51 years. No patient had previous variceal bleeding or previous treatments for portal hypertension, including sclerotherapy or drugs. Two patients with ascites were treated with potassium kanrenoate for the whole study period. Five patients were on lactulose for previous episodes of hepatic encephalopathy. The main

Abbreviations: HVPG, hepatic venous pressure gradient; I5M, isosorbide-5-mononitrate; PBF, portal blood flow; RPBF, resistance to portal blood flow; HAPI, hepatic artery pulsatility index; HR, heart rate; MAP, mean arterial pressure.

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TABLE 1. Main Clinical, Biochemical, and Endoscopic Data of the 15 Patients With Cirrhosis

	Good Responders (n = 6)	Poor Responders (n = 9)
Age (yr)	55 ± 8	53 ± 12
Sex (M/F)	3/3	5/4
Etiology (alcoholic/HCV$^+$)	4/2	4/5
Ascites	1	1
Encephalopathy	1	0
Serum bilirubin (μmol/L)	23 ± 9	27 ± 11
Serum albumin (g/L)	34 ± 3	35 ± 3
Prothrombin index (%)	70 ± 11	65 ± 13
Child-Pugh score	7 ± 1	6 ± 1
Child-Pugh class (A/B/C)	1/4/1	4/4/0
Variceal size (F1/F2/F3)	0/4/2	1/5/2
Red weal marks (−/+/++/+++)	3/2/1/0	5/1/1/1
Portal hypertensive gastropathy (absent/mild/severe)	1/4/1	2/3/3

Abbreviation: HCV, hepatitis C virus.

clinical and laboratory data at inclusion in the study are given in Table 1. The study protocol conformed to the Declaration of Helsinki and was approved by the competent Ethics Authorities. Consent to the study was obtained by all participating subjects.

Procedure. After an overnight fast, the patients were brought to the hemodynamic laboratory, and duplex Doppler examination of the portal vein was first performed according to a previously described methodology[10] using a Toshiba Sonolayer SSA-270 apparatus (Toshiba, Tokyo, Japan) with color Doppler sonography and a 3.75-MHz sector electronic probe. PBF was calculated according to the following formula[11]:

PBF = portal cross-sectional area

× portal blood maximum velocity × 0.57

In our laboratory, the coefficient of variation of PBF for replications after 1 month was 11.9% ± 9.2%, as determined in nine control subjects.[12]

Then the left and right hepatic artery branches were visualized by color Doppler, the sample volume of the Doppler system was placed inside the vessels, and the blood flow velocity waveforms were recorded. Hepatic artery pulsatility index (HAPI), expression of resistance to blood flow in the hepatic artery, was calculated as the mean of the indices calculated in the two branches according to the formula:

HAPI = (peak systolic velocity − minimum velocity)/mean velocity.

The coefficient of variation of HAPI for replications after 1 month was 9.8% ± 5.6%.[12] Further details on the hepatic artery Doppler measurements are given elsewhere.[13]

Immediately afterward, hepatic vein catheterization was performed using a balloon catheter, according to a previously described procedure.[14] In brief, a sheath introducer was placed in the right femoral vein under local anesthesia, and a balloon catheter (Meditech F7, Watertown, MA) was advanced under fluoroscopic control to a main hepatic vein (usually the right hepatic vein). HVPG, an index of the portal pressure in conditions of sinusoidal or postsinusoidal portal hypertension,[15,16] was calculated as occluded − free hepatic venous pressure. In all cases, three measurements were performed, electronic means were recorded, and results were expressed as the mean of the three values. Permanent tracings of the pressure measurements were always obtained. RPBF was calculated as HVPG/PBF and expressed as millimeters of mercury × minutes per liter.

Patients then received a chronic nadolol treatment at a dose that reduced resting heart rate by approximately 25%, and were followed in the outpatient clinic. After 1 month of effective β-blockade, they were admitted again and studied by hepatic vein catheterization and duplex-Doppler ultrasonography. The mean dose administered was 80 mg/d. Procedures were performed in the morning approximately at the same hour with the same methodology, in fasting patients who were given the usual morning dose of nadolol. Nine patients who did not show a decrease in HVPG to 12 mm Hg or a decrease larger than 20% were considered poor responders, while the remainders were good responders.

Then, poor responders received a chronic treatment with nadolol at the usual dose plus I5M at the dose of 20 mg twice per day. They were followed in the outpatient clinic and were admitted to the hospital for a further hemodynamic study with the same procedure after 3 to 4 months.

During the whole evaluation period, patients were seen every 2 weeks as outpatients. Compliance was assessed according to anamnesis and heart rate (HR) measurements. Blood levels of nadolol or I5M were not measured. No patient reported side-effects suggesting the withdrawal of any drug.

Statistics. Results are given as means ± SEM. Comparisons were made by Wilcoxon's test or Mann-Whitney's test, when applicable. The null hypothesis was rejected at the 0.05 probability level.

RESULTS

HR and Mean Arterial Pressure. In baseline conditions, good and poor responders did not differ in HR (83 ± 3 beats/min vs. 87 ± 2 beats/min, respectively; $P = .14$), or in mean arterial pressure (MAP) (96 ± 5 mm Hg vs. 105 ± 2 mm Hg, respectively; $P = .08$). In both groups, HR decreased significantly after nadolol (in good responders: HR = 56 ± 2 beats/min; $P = .03$; mean decrease = 32%; in poor responders: HR = 59 ± 2 beats/min; $P = .004$; mean decrease = 32%). In poor responders, the addition of I5M did not provoke additional changes in HR (59 ± 2 beats/min; $P = .61$). In both groups, MAP did not change significantly after nadolol (in good responders: MAP = 93 ± 5 mm Hg; $P = .25$; in poor responders: MAP = 100 ± 3 mm Hg; $P = .13$). In poor responders, MAP also remained unchanged after the addition of I5M (MAP = 102 ± 3 mm Hg; $P = .41$).

HVPG. In baseline conditions, the six good responders and the nine poor responders did not differ significantly for any portal hemodynamic parameter. In the nine patients with poor response to nadolol alone, baseline HVPG was 18.1 ± 0.6 mm Hg, which decreased significantly to 16.6 ± 1.8 mm Hg after nadolol ($P = .03$), the mean decrease being 8.9% ± 2.8% (range, 0%-19.5%). No patient had HVPG after nadolol ≤ 12 mm Hg. After chronic administration of nadolol + I5M, HVPG was 13.4 ± 0.5 mm Hg (vs. baseline: $P = .004$; vs. nadolol: $P = .004$). After nadolol + I5M, one patient had HVPG below the threshold value of 12 mm Hg. The mean percent decrease after nadolol + I5M was 25.7 ± 1.7% (range, 18%-33%), significantly larger than after nadolol ($P = .004$). Only one patient had a percent decrease smaller than 20% after nadolol + I5M, which qualified him as a poor responder.

In the six good responders, baseline HVPG was 22.8 ± 2.0 mm Hg, which decreased significantly to 15.1 ± 0.8 mm Hg ($P = .03$), the mean decrease being 29.8% ± 4.3% (range, 21%-50%). One patient had HVPG after nadolol equal to the threshold value of 12 mm Hg. Percent HVPG changes after nadolol in good responders were significantly greater than in poor responders ($P = .001$), but it was not significantly different from those in poor responders after combined treatment ($P = .64$). Individual changes in good and poor responders are given in Fig. 1A.

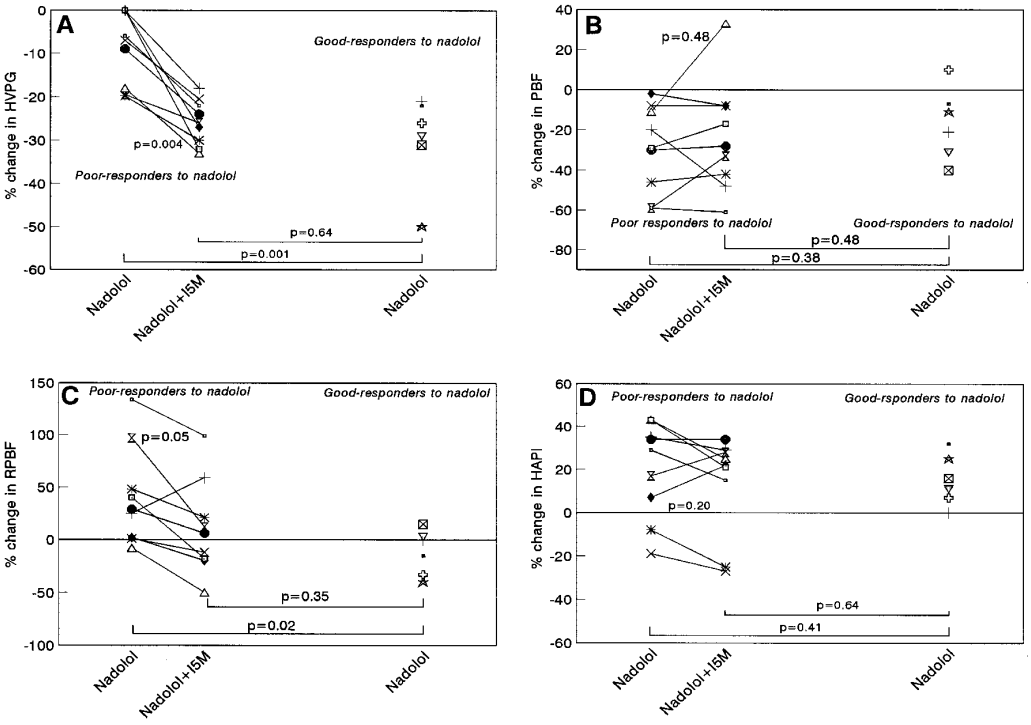

FIG. 1. (A) Changes in HVPG during chronic therapy with nadolol and with nadolol plus I5M in 9 cirrhotic patients with poor response to nadolol alone, and changes during chronic therapy with nadolol in 6 good responders. (B) Changes in PBF during chronic therapy with nadolol and with nadolol plus I5M in 9 cirrhotic patients with poor response to nadolol alone, and changes during chronic therapy with nadolol in 6 good responders. (C) Changes in RPBF during chronic therapy with nadolol and with nadolol plus I5M in 9 cirrhotic patients with poor response to nadolol alone, and changes during chronic therapy with nadolol in 6 good responders. (D) Changes in HAPI during chronic therapy with nadolol and with nadolol plus I5M in 9 cirrhotic patients with poor response to nadolol alone, and changes during chronic therapy with nadolol in 6 good responders.

PBF. In the nine poor responders, baseline PBF was 1,021 ± 183 mL/min, which decreased to 648 ± 68 mL/min after nadolol (P = .004), the mean decrease being 29.3 ± 7.1% (range, 2%-59%). After chronic administration of nadolol + I5M, PBF was 711 ± 107 mL/min (vs. baseline: P = .03; vs. nadolol: P = .59). The mean percent decrease after nadolol + I5M from baseline was 23.5% ± 9.2% (ranging from an increase by 33% to a decrease by 61%), which was not significantly different from changes after nadolol alone (P = .48).

In the six good responders, baseline PBF was 1,024 ± 172 mL/min, which decreased to 816 ± 109 mL/min after nadolol (P = .06), the mean decrease being 16.7% ± 7.3% (ranging from an increase by 10% to a decrease by 40%). Percent changes were not significantly different from those in poor responders during treatment with nadolol (P = .38), or with nadolol + I5M (P = .48). Individual changes in good and poor responders are given in Fig. 1B.

RPBF. In the nine poor responders, baseline RPBF was 21.9 ± 3.2 mm Hg × min/L, which increased significantly to 28.3 ± 3.8 mm Hg × min/L after nadolol (P = .02). The mean percent increase was 40.7% ± 15.5%. In one patient, there was a small decrease in RPBF (−8%), while, in the others, RPBF increased up to 132%. After chronic administration of nadolol + I5M, RPBF was 21.9 ± 3.1 mm Hg × min/L, which was significantly lower than after nadolol (P = .03) and very close to baseline (P = .86). The mean percent change after nadolol + I5M was 10.7% ± 15.0%, which was significantly lower than after nadolol alone (P = .05). The percent change after nadolol + I5M from baseline ranged from a decrease by 50% to an increase by 99%.

In the six good responders, baseline RPBF was 24.5 ± 4.1 mm Hg × min/L, and did not change significantly after nadolol (20.4 ± 3.3 mm Hg × min/L; P = .56). The mean percent variation was −12.3% ± 9.2%. The percent change was significantly smaller than that in poor responders after nadolol alone (P = .02), but was not different from that after nadolol + I5M (P = .35). Individual changes are given in Fig. 1C.

HAPI. In the nine poor responders, baseline HAPI was 1.11 ± 0.08 and showed a trend to increase after nadolol to 1.31 ± 0.09 (P = .06); the mean increase was 20.0% ± 7.5%. After chronic administration of nadolol + I5M, it was 1.24 ± 0.08, which was not significantly different either from baseline (P = .37) or from after nadolol (P = .11). The mean percent increase after nadolol + I5M was not significantly different from after nadolol alone (13.7% ± 7.7%; P = .20).

In the six good responders, baseline HAPI was 1.20 ± 0.06, which increased significantly to 1.37 ± 0.06 after nadolol (P = .03). The mean percent increase was 15.4% ± 4.8%, which was not significantly different from that in poor responders after nadolol alone (P = .41) or after nadolol + I5M (P = .64). Individual changes are reported in Fig. 1D.

Mechanisms of Insufficient Effect of Nadolol and the Effect of Nadolol + I5M. The combined effect of nadolol on the two major mechanisms determining portal hypertension, namely PBF and RPBF, is shown in Fig. 2A. A wide spectrum of combined changes in PBF and in RPBF was observed in the nine poor responders, ranging from no change in either parameter to a marked decrease in PBF counterbalanced by a marked increase in RPBF. At variance, good responders showed a similar decrease in PBF (P = .38, Mann-Whitney test), but no tendency to increase in RPBF (P = .02, Mann-Whitney test).

The addition of I5M was followed in 8 of 9 patients by a decrease in RPBF, which, in the cases with scarce increase after nadolol, brought RPBF to levels lower than baseline. In one patient who, after nadolol, had a 20% decrease in PBF and a 25% increase in RPBF, the association provoked a marked decrease in PBF (48%) and a concomitant increase in RPBF (59%). This subject was the only one who remained a poor responder after nadolol + I5M. The relationships

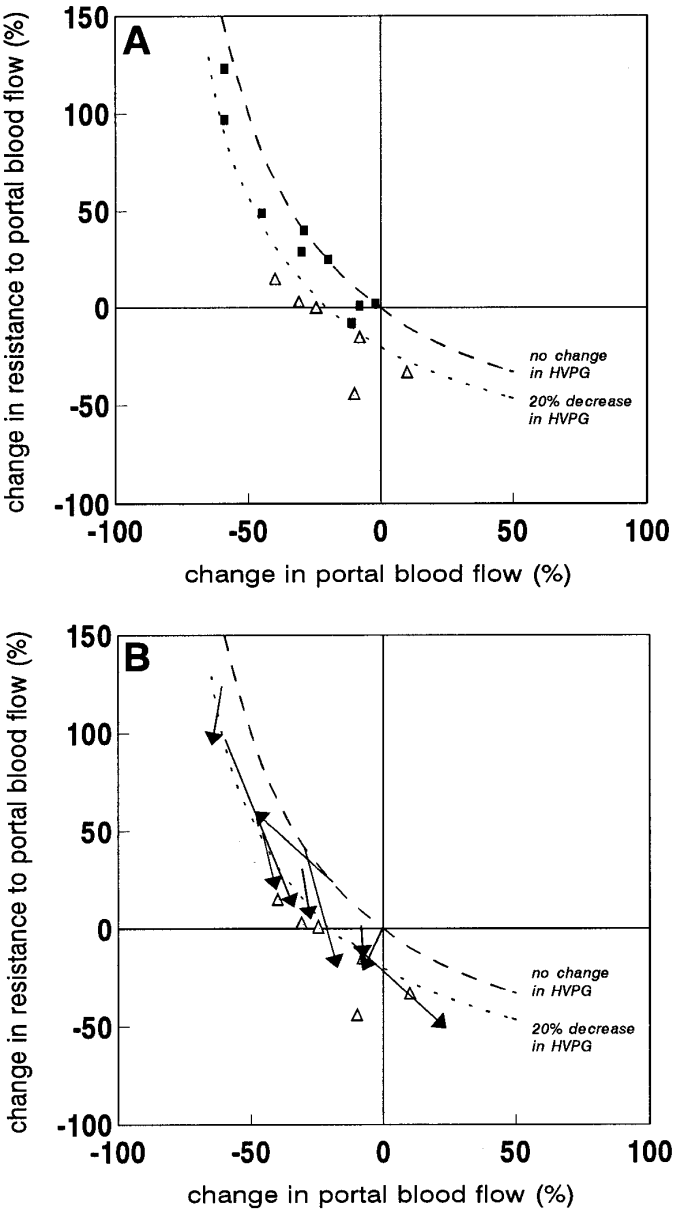

FIG. 2. (A) Changes in PBF and in RPBF after nadolol expressed as percent of baseline values in the 9 poor responders (■) and in the 6 good responders (△). The *dashed line* indicates the combinations of values of changes in PBF and in RPBF leading to a lack of change in HVPG. The *dotted line* indicates the combinations of values of changes in PBF and in RPBF leading to a 20% decrease in HVPG, thus discriminating good from poor responders. (B) Changes in PBF and in RPBF expressed as a percent of baseline values after nadolol and nadolol plus I5M in the 9 cirrhotic patients with poor response to nadolol alone. The *arrows* indicate the direction of changes from nadolol to nadolol plus I5M. △, Hemodynamic changes in good responders to nadolol alone.

between individual variations in PBF and in RPBF are shown in Fig. 2B.

No significant correlation was observed between changes in HVPG and in PBF either in patients receiving nadolol ($r = .08$; $P = .78$) or in those receiving nadolol + I5M ($r = -0.54$; $P = .13$).

DISCUSSION

The association β-blockers plus nitrates was found to be superior to β-blockers alone in decreasing portal pressure,[6,7,17] and showed promising results in therapeutic trials.[18-20] Although the association was found to provoke a greater decrease in HVPG than β-blockers alone, and to decrease the probability of being a poor responder, according to hemodynamic criteria,[6,7] the effect of the association in the subgroup of patients who are poor responders to β-blockers alone (i.e., those patients who are likely to benefit to a greater extent by the association) is still undetermined. Indeed, available evidence is limited to comparisons of groups of unselected patients treated with β-blockers or β-blockers plus nitrates,[6,7,17] or to analyses of changes after acute administration of nitrates in patients under chronic therapy with β-blockers.[21] In addition, the mechanism of action of the additive effect of nitrates is not known, because these drugs may act by enhancing an insufficient decrease in portal blood inflow,[8] or contrasting a possible increase in RPBF.[9]

In the present study, a group of patients who did not meet the criteria for good response to nadolol alone (decrease in HVPG during chronic therapy to values $\leq$12 mm Hg or a percent decrease $>$20%)[3] were also investigated after chronic therapy with nadolol + I5M, and were compared with a group of good responders to the β-blocker. In all poor responders, the association was more effective from a hemodynamic point of view, because, in all patients, HVPG during combined therapy was much lower than after nadolol alone, and, in eight of nine cases, patients could be considered good responders according to hemodynamic criteria (Fig. 1). Therefore, the association also appears to be effective from a hemodynamic point of view in those patients who are likely to need it, because, for them, the single treatment is probably of limited value.[3] This cannot be considered as a demonstration that the association is clinically preferable to β-blockers alone, but gives a reasonable explanation for the beneficial effect of the association, which has recently been described in reports of prevention of rebleeding and of prophylaxis of first bleeding.[18-20]

The mechanisms causing the insufficient response to β-blockers include: 1) an insufficient decrease in PBF[8]; and 2) an increase in RPBF, induced by exalted α-adrenergic tone, not counterbalanced by the β-adrenergic tone actually blocked by the drug.[9] The relative role of these two mechanisms, frequently postulated, is not defined, because no study simultaneously examined PBF and RPBF in patients chronically treated with β-blockers. Simultaneous assessment by hepatic vein catheterization and duplex-Doppler ultrasonography is the less-invasive method to evaluate these portal hemodynamic variables. Despite some criticisms on the reliability of duplex-Doppler measurements,[22] there is agreement that these measurements are adequately reproducible in assessing chronic changes, provided a strict protocol of data recording is followed, such as the one we helped to develop.[10] A possible role of changes in hepatic artery blood flow may also be postulated, considering that hepatic artery blood flow feeds the sinusoids directly.[23] However, in the present series, such a role can be excluded, because changes in HAPI were nearly identical in good and poor responders.

The mechanisms underlying the variability in the degree of increase in portal resistance after nadolol observed in our patients are largely speculative. They include the different extent of activation of the adrenergic system,[9] the various degrees of collateralization of the portal system, and the response of collateral bed to vasoactive stimuli.[8,24] In particular, in a patient with extensive collateral circulation, an increase

in portocollateral resistance after a decrease in collateral blood flow induced by β-blockers may be explained by the decrease in the radius of collapsible vessels.[9] However, very similar values of azygos blood flow, an index of collateralization of PBF, were observed in good and poor responders by Feu et al.[25]

In the present series, the main difference among good and poor responders is in the effect of nadolol on RPBF. Indeed, the group of good responders showed no significant change in RPBF, while the group of poor responders had a significant increase in RPBF, averaging 40%; percent changes in the latter patients were significantly larger than in the former ones. On the contrary, the course of PBF in the two groups was nearly identical. When observed changes were considered individually (Fig. 2A), the pattern of possible variations in the two mechanisms conditioning poor or good response was more complex. Indeed, a wide spectrum of combined changes in PBF and in RPBF was observed, which ranged from minor changes in PBF and RPBF in three subjects to an evident increase in outflow resistance, counterbalancing an adequate decrease in PBF, observed in four patients. Among these extreme patterns, there were two patients exhibiting a balance between a decrease in PBF and an increase in RPBF.

The effect of nitrates in patients with insufficient response to nadolol might be the consequence of enhancement of a decrease in PBF caused by baroreflex-mediated splanchnic vasoconstriction, or to a decrease in cardiac output.[26,27] It may also be the consequence of a decrease in outflow resistance caused by a decrease in resistance in the hepatic or collateral vascular bed.[27-29] In the eight cases who became good responders to the association, the main effect was a decrease in RPBF, associated with a variable effect on PBF; in the only patient who remained a poor responder, the two mechanisms were balanced one against the other, the decrease in PBF exceeding the increase in RPBF by an insufficient amount. We have no clear explanation for the increase in RPBF after the addition of I5M seen in this patient.

A further observation may be derived from the present material. The variable and unpredictable degree of enhancement of portal resistance induced by β-blockers is the pathophysiological basis of the lack of correlation between changes in PBF and in HVPG. Because poor responders are likely to be the only patients who benefit from the additional therapy with nitrates, it appears that they must be investigated by repeat measurement of HVPG (which is the only validated method to predict clinical effectiveness of treatment[1-3]), and that this information cannot be surrogated by measuring PBF using duplex-Doppler ultrasonography. Further studies are needed to elucidate if different Doppler parameters are more strictly related to HVPG than PBF.

In conclusion, the association with I5M converts most poor responders to nadolol alone into good responders. As a group, good responders differ from poor responders in the fact that they keep RPBF rather constant after nadolol, while, in poor responders, a marked increase in RPBF occurs after nadolol. The beneficial effect of the addition of I5M is mainly caused by a decrease in outflow resistance.

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