LIVER

The extent of the collateral circulation influences the postprandial increase in portal pressure in patients with cirrhosis

Agustín Albillos, Rafael Bañares, Mónica González, Maria-Vega Catalina, Oscar Pastor, Rosario Gonzalez, Cristina Ripoll, Jaime Bosch

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See end of article for authors' affiliations

Correspondence to: Professor A Albillos, Departamento de Medicina, Facultad de Medicina-Campus Universitario, Universidad de Alcalá, Carretera Madrid-Barcelona km 33.600, 28871 Alcalá de Henares, Madrid, Spain; aalbillosm@meditex.es

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Background: In cirrhosis, repeated flares of portal pressure and collateral blood flow provoked by postprandial hyperaemia may contribute to variceal dilation and rupture.
Aim: To examine the effect of the extent of the collateral circulation on the postprandial increase in portal pressure observed in cirrhosis.
Patients and methods: The hepatic venous pressure gradient (HVPG), hepatic blood flow and azygos blood flow were measured in 64 patients with cirrhosis before and after a standard liquid meal.
Results: Peak increases in HVPG (median+14.9%), hepatic blood flow (median+25.4%), and azygos blood flow (median+32.2%) occurred at 30 min after the meal. Compared with patients with marked postprandial increase in HVPG (above the median, n = 32), those showing mild (<15%, n = 32) increase in HVPG had a higher baseline azygos flow ($p<0.01$) and underwent a greater postprandial increase in azygos flow ($p<0.02$). Hepatic blood flow increased similarly in both groups. Postprandial increases in HVPG were inversely correlated ($p<0.001$) with both baseline azygos flow ($r=-0.69$) and its postprandial increase ($r=-0.72$). Food intake increased nitric oxide products in the azygos ($p<0.01$), but not in the hepatic vein. Large varices ($p<0.01$) and previous variceal bleeding ($p<0.001$) were more frequent in patients with mild increase in HVPG.
Conclusions: Postprandial hyperaemia simultaneously increases HVPG and collateral flow. The extent of the collateral circulation determines the HVPG response to food intake. Patients with extensive collateralisation show less pronounced postprandial increases in HVPG, but associated with marked flares in collateral flow. Collateral vessels preserve their ability to dilate in response to increased blood flow.

Splanchnic vasodilatation and increased portal blood flow is a physiological response to food intake.[1 2] Experimental studies have shown that endothelial cells lining the sinusoids of the normal liver produce nitric oxide (NO) when portal blood flow rises.[3] In response to this rise in NO, the hepatic microcirculation relaxes to accommodate the sudden increase in blood flow, maintaining portal pressure as normal.[3 4] By contrast, the experimental or human cirrhotic liver is unable to vasodilate when blood flow increases and postprandial hyperaemia provokes an increase in portal pressure.[3–11] The inability of the cirrhotic liver to relax in response to flow is partly due to an impaired capacity of the sinusoidal cells to release NO.[12] The postprandial rise in portal pressure noted in cirrhosis varies greatly among individuals[4–11] and the factors determining this variability remain unclear.

The portal-systemic collaterals, mainly oesophageal varices, that develop in cirrhotic portal hypertension constitute an attempt to decompress the portal venous system. Portal-collateral and portal-hepatic vessel networks run a parallel course, and their respective resistances are thought to determine the portal pressure response to blood flow increases,[13 14] such as those occurring in the postprandial period. Moreover, besides increasing portal blood flow, splanchnic hyperaemia might also enhance collateral flow[7 9 15] and thus contribute to the dilation and rupture of oesophageal varices.[16] The few studies examining the postprandial response of portal-collateral blood flow in patients with cirrhosis have yielded conflicting results.[5 7 9] This study aimed to establish whether the extent of the collateral circulation, estimated as blood flow in the azygos vein, could influence the postprandial increase in portal pressure that occurs in patients with cirrhosis.

PATIENTS AND METHODS

Patients

The study population comprised 64 patients with cirrhosis and oesophageal varices referred for evaluation of portal hypertension. Of these, 34 patients were studied at the Hospital Ramón y Cajal, Madrid, Spain, and 30 at the Hospital Gregorio Marañón, Madrid, Spain. Thirty six patients had previously undergone variceal bleeding; 15 patients had mild–moderate ascites, 11 were receiving treatment with spironolactone and 4 with spironolactone and furosemide. At the time of the study, no patient had clinical evidence of hepatic encephalopathy. The exclusion criteria were age <18 years or >70 years, treatment with β-blockers or band ligation for prophylaxis of variceal bleeding, hepatocellular carcinoma, portal vein thrombosis or advanced liver failure defined as bilirubin >5 mg/dl or prothrombin time <40%. The severity of liver disease was graded according to Child–Pugh's criteria. Oesophageal varices >5 mm or <5 mm were denoted large or small, respectively.[17] The study protocol was approved by the ethics committees of the participating centres. Patients participated after giving their informed consent according to the Helsinki II Declaration.

Abbreviations: AzBF, azygos blood flow; HBF, hepatic blood flow; HVPG, hepatic venous pressure gradient; ICG, indocyanine green; NOx, nitric oxide metabolites

Haemodynamic studies

After an overnight fast, two catheter introducers were placed in the right femoral vein using the Seldinger technique. One of these introducers was used to insert a balloon catheter (Medi-Tech, Boston Scientific Cork, Cork, Ireland) into the right hepatic vein to measure wedged and free hepatic vein pressures or a Swan–Ganz catheter into the pulmonary artery to measure cardiac output. The other vein introducer was used to advance a continuous thermal dilution catheter (Webster Laboratories, Baldwin Park, California, USA) into the azygos vein to measure azygos blood flow (AzBF), according to previously described methods.[18–20] Measurements were performed in triplicate, and permanent tracings were recorded on a multichannel recorder (Hellige, Friburgo, Germany).

Portal pressure was estimated from the hepatic venous pressure gradient (HVPG), as the difference between wedged and free hepatic vein pressures. Heart rate and mean arterial pressure were measured non-invasively every 10 min by an automatic electronic sphygmomanometer (Dinamap; Critikon, Tampa, Florida, USA). The cardiac index was obtained by dividing cardiac output by body surface area. Hepatic blood flow (HBF) was determined during continuous infusion of indocyanine green (ICG, 0.2 mg/min; priming dose 5 mg; ICG; Pulsion Medical Systems, Munich, Germany), as described previously.[19 20] Plasma concentrations of ICG were determined by spectrophotometry using Nielsen's method to correct for plasma turbidity. Measurements were made in three separate sets of simultaneous samples of peripheral and hepatic vein blood obtained at 2-min intervals after an equilibration period of 40 min. A hepatic extraction of ICG >0.1 was required to calculate HBF. The systemic vascular resistance index (in dyn s m^2/cm^5) was calculated as 80×(mean arterial pressure–right atrial pressure)/cardiac index.

Plasma glucagon immunoreactivity was analysed using a commercially available radioimmunoassay kit (Double Antibody Glucagon, DPC, Los Angeles, California, USA). The detection limit of the assay was 13 ng/l, and the coefficient of variation was 3.2–6.5% (Cayman, Ann Arbor, Michigan, USA). Serum concentrations of NO metabolites (nitrates+nitrites (nitric oxide metabolites (NOx))) were determined by chemiluminescence (Nitric Oxide Analyzer; NOA 280, Sievers Instruments, Boulder, Colorado, USA).

Study design

At baseline, splanchnic (HVPG, HBF and AzBF) and systemic haemodynamic variables (mean arterial pressure and cardiac output) were determined in each patient. For the determination of glucagon, blood samples were withdrawn from a peripheral vein. For the determination of NOx, blood samples were drawn from a hepatic vein, and in a subset of 29 patients from the azygos vein. Thereafter, patients received a liquid meal (400 ml) containing proteins (25 g), carbohydrates (80.8 g) and lipids (19.6 g) to obtain a total of 600 kcal (Ensure Plus; Abbott Laboratories BV, Zwolle, The Netherlands). The meal was ingested in about 5 min. The onset of meal ingestion was taken as time zero. Haemodynamic measurements and biochemical determinations in blood were repeated at 15, 30 and 45 mins after meal ingestion.

Statistics

Results are expressed as mean (standard deviation (SD) (range). Comparisons within patient groups were performed by analysis of variance for repeated measures and Student's t test for paired data. Student's t test for unpaired data was used for comparisons among groups. Associations between continuous variables were determined by linear regression analysis. A value of $p<0.05$ was taken as significant. Multivariate analysis by logistic regression was used to identify variables independently associated with the postprandial increase in HVPG. Variables were included in the analysis when they achieved a $p<0.05$ in the univariate analysis. Statistical analysis was performed using the StatView v5.0.1 package (Abacus Concepts, Berkeley, California, USA).

RESULTS

The 64 patients examined had clinically significant portal hypertension (range 12–22.6 mm Hg), and increased AzBF (range 488–961 ml/min). The patients studied at the Hospital Ramón y Cajal and Hospital Gregorio Marañón had similar clinical characteristics (Child–Pugh score, 8.8 (1.0) *v* 8.9 (1.1); oesophageal varices >5 mm, 65% *v* 60%; previous variceal bleeding, 53% *v* 60%)) and baseline haemodynamic values (HVPG, 19.1 (5.2) *v* 20.7 (6.6) mm Hg; AzBF, 617 (195) *v* 686 (184) ml/min).

HBF increased significantly 15 min after meal intake (from 992 (544) (range 834–1152) ml/min at baseline to 1152 (596) (range 996–1323) ml/min, $p<0.04$) and peaked at 30 min (1224 (648) (range 987–1437) ml/min; mean increase 22.8% (23.2%); $p<0.03$; fig 1). Postprandial changes in HVPG paralleled changes in HBF. HVPG increased significantly as early as 15 min after meal intake (from 20.2 (4.0) (range 18.7–21.9) mm Hg at baseline to 23.5 (4.2) (range 21.8–25.2) mm Hg), peaked at 30 min (23.9 (5.6) (range 21.5–26.1) mm Hg; absolute change 3.9 (4.0) mm Hg), and remained increased at 45 min (23.3 (6.4) (range 21.7–26.1) mm Hg, all $p<0.001$ *v* baseline). AzBF was also significantly increased at 15 min (from 654 (336) (range 560–757) ml/min at baseline to 795 (408) (range 683–927) ml/min, $p<0.03$ *v* baseline) and peaked at 30 min (834 (528) (range 694–985) ml/min, $p<0.02$). However, by 45 min after meal intake, AzBF was not significantly different from baseline (717 (352) (range 611–827) ml/min, $p = 0.3$). As HBF, HVPG and AzBF peaked at 30 min after food intake, in subsequent analysis, we focused on the 30-min time point.

The mean (SD) change in HVPG 30 min after the meal was 17.9% (14.4%) (range 0–52%). We then divided the patient population according to the median postprandial (30 min) increase in HVPG (14.9%) into two groups: one comprised 32 patients showing "mild" (below the median) postprandial increase in HVPG (mean (SD) increase 1.8 (0.5) mm Hg, 6.1% (5.0%)) and another group comprised 32 patients showing "marked" (>15%) postprandial increase in HVPG (5.9 (2.2) mm Hg, 28.7% (10.3%); fig 2).

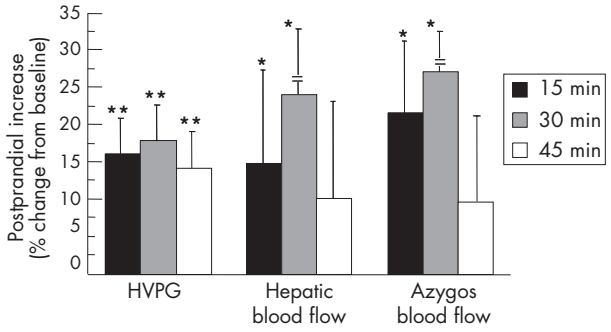

Figure 1 Changes in the hepatic venous pressure gradient (HVPG), hepatic blood flow (HBF) and azygos blood flow (AzBF) estimated 15, 30 and 45 min after food intake. Data represent percentage changes from baseline (mean (SD)). Asterisks indicate a significant difference from baseline (*$p<0.05$, **$p<0.001$), and crosses indicate significant differences from the change at 15 min (*$p<0.05$).

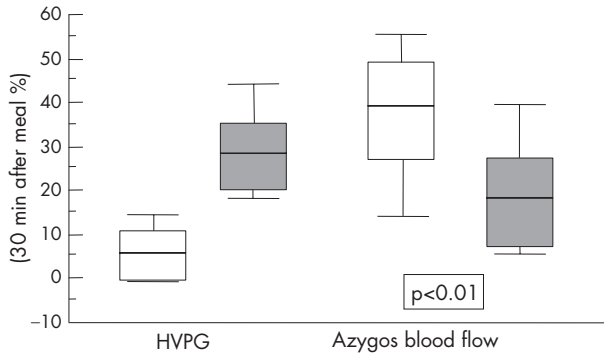

Figure 2 Postprandial (30 min) changes in the hepatic venous pressure gradient (HVPG) and azygos blood flow. The median (14.9%) postprandial change in the HVPG was used to divide the 64 patients with cirrhosis into those with mild (n = 32; white boxes) or marked (n = 32; grey boxes) postprandial increase in HVPG. The box plots represents the 10th, 25th, 50th (median), 75th and 90th centiles of the variables.

Our two patient groups were well-matched in terms of the aetiology and severity of liver disease, as assessed by Child–Pugh score and the presence of ascites (table 1). In addition, both groups had similar baseline HVPG and HBF values. Extents of systemic hyperaemia and peripheral vasodilatation, as assessed by cardiac index and systemic vascular resistance values, were also comparable in the two groups of patients. However, the group with mild increase in postprandial HVPG showed greater baseline values of collateral blood flow, as measured by AzBF (739 (316) (range 614–876) *v* 561 (186) (range 452–661) ml/min, $p<0.01$) than the group with marked increase in postprandial HVPG. Accordingly, the patients with mild increase in postprandial HVPG showed a significantly higher prevalence of large oesophageal varices and previous variceal bleeding (table 1).

At 30 min, the test meal induced similar increases in HBF (22.1 (32.2) *v* 23.0 (28.6) %, $p = 0.98$) and serum glucagon concentrations (28.1 (45) *v* 28.6% (51%), $p = 0.96$) in patients with mild and marked postprandial increase in HVPG (table 1). Despite this similar HBF response to the meal in both groups, the postprandial increase in AzBF was significantly greater in patients showing mild compared with marked increase in HVPG (35.7% (34%) *v* 17.1% (23%), $p<0.01$; fig 2). For the entire patient set, postprandial increase in HVPG was inversely related to the extent of portal-collateral circulation, as assessed by AzBF, both in terms of baseline values ($r = -0.69$, $p<0.001$) and postprandial increases ($r = -0.72$, $p<0.001$; fig 3). AzBF showed a marked increase in all 10 patients in whom HVPG failed to change 30 min after food intake (mean (SD) change 56.6% (28.3%); range 45.2–64.3%).

Postprandial hyperaemia caused a significant increase in serum concentrations of NOx in the azygos vein in both patient groups (table 2). By contrast, the postprandial increase in HBF did not significantly modify NOx levels in the hepatic vein of either group.

DISCUSSION

In this study, we sought to assess whether the extent of the portal-collateral circulation, as estimated by AzBF, could affect the portal pressure response to food intake in patients with cirrhosis. We hypothesised that patients with extensive development of portal-systemic collaterals would be able to accommodate the large increase in blood flow caused by postprandial hyperaemia without markedly increasing the perfusion pressure (ie, the portal pressure). By contrast, we predicted that patients with mild collateralisation would show a marked increase in portal pressure, because of the known impaired capacity of the cirrhotic liver to undergo flow-mediated vasodilatation due to intrahepatic endothelial dysfunction.[3 12] To test this working hypothesis, we compared basal and postprandial AzBF in a cohort of patients with cirrhosis showing marked or mild postprandial increases in portal pressure, as estimated by HVPG measurement.

Our findings indicate that the splanchnic hyperaemia that follows meal ingestion in patients with cirrhosis leads to increases in both portal pressure and portal-collateral blood flow (collateral hyperaemia). As in other vascular beds, the endothelial cells of the hepatic sinusoids augment NO production in response to shear stress, which allows the normal liver to accommodate increases in portal blood flow.[3 4] Confirming previous experimental and clinical studies,[4 8 11 21] the livers of our patients with cirrhosis failed to show a vasodilatory NO-mediated adaptive response to postprandial hyperaemia, as indicated by the increases recorded in portal pressure after the test meal and the lack of changes in NOx levels observed in the hepatic vein.

Besides increasing portal pressure, postprandial hyperaemia led to pronounced increases in collateral blood flow. The finding of a marked increase in AzBF in the group of patients with mild increase in HVPG indicates that collateral resistance decreases in response to blood flow load after food intake. In addition, hyperaemia was associated with a selective increase in serum NOx in the azygos vein, suggesting flow-induced up regulation of endothelial NO production in the collaterals. Thus, contrary to the situation in the hepatic circulation, flow-dependent relaxation is preserved in portal-collateral vessels in cirrhosis. This finding has not been previously reported in patients with cirrhosis. In effect, in situ collateral perfusion experiments have shown that the portal-collateral vessels dilate in response to isoproterenol, a β-adrenoceptor, or acetylcholine, a NO agonist, and contract in response to endothelin-1 and vasopressin.[22–24] We postulate that the shear stress caused by postprandial hyperaemia promotes NO release and relaxation at the level of the collateral vessels.

The degree of postprandial hyperaemia is influenced by the type of meal and host characteristics. The timing and intensity of hyperaemia have been related to the caloric content and composition of the meal, with carbohydrates inducing the earliest and fat the greatest intestinal blood-flow response.[1] All our patients received the same meal containing similar proportions of proteins, fats and carbohydrates as those of a standard diet. Variations in the response shown by patients with cirrhosis to such a meal include a lesser degree of postprandial splanchnic hyperaemia in those with alcoholic disease, advanced (Child C) cirrhosis or severe peripheral vasodilatation and hyperdynamic circulation.[7 25 26] None of these factors was, however, able to predict the postprandial increase in HVPG shown by our patients.

The only difference we found between patients with marked or mild postprandial increase in HVPG was related to the extent of collaterals. In keeping with our hypothesis, patients with extensive portal-collateral circulation, high AzBF, large varices and previous variceal bleeding showed a less pronounced postprandial increase in portal pressure despite exhibiting marked increases in collateral blood flow. Greatest increases in portal pressure were noted in patients with mild collateralisation, suggesting that the extent of the portal-collateral circulation largely determines the portal pressure response to food intake. This idea is further supported by the inverse correlation shown between postprandial changes in HVPG and AzBF, whether we considered baseline or postprandial changes in AzBF. Moreover, these results were reinforced by our logistic regression analysis, which indicated that baseline AzBF and

Table 1 Basal and postprandial (30 min after meal intake) clinical, haemodynamic and biochemical variables in the groups of patients showing mild or marked increase in postprandial hepatic venous pressure gradient

	Mild increase in HPVG (n = 32)	Marked increase in HPVG (n = 32)	p Values
Clinical data			
Age (years)	55 (22) (44–66)	58 (23) (46–68)	NS
Sex (males/females)	26/6	28/4	NS
Aetiology of cirrhosis (alcoholics/non-alcoholics)	18/14	19/13	NS
Child–Pugh score	9.1 (1.1) (7–10)	8.8 (1.1) (6–10)	NS
Body weight (kg)	66 (28) (52–78)	65 (22) (53–76)	NS
Ascites (%)	8/24	7/25	NS
Oesophageal varices >5 mm (yes/no)	26/6	14/18	<0.01
Previous variceal bleeding (yes/no)	28/4	8/24	<0.0001
Splanchnic haemodynamics			
Baseline HVPG (mm Hg)	20.4 (6.7) (15.1–24.2)	19.8 (6.2) (22.2–29.7)	NS
Postprandial HVPG (mm Hg)	21.8 (5.1) (18.3–25.6)*	25.5 (5.1) (18.3–25.6)**	
Postprandial change in HVPG (%)	6.1 (5.0) (3.6–8.4)	28.7 (10.2) (24.0–33.5)	
Baseline HBF (ml/min)	986 (320) (853–1122)	1006 (401) (843–1215)	NS
Postprandial HBF (ml/min)	1203 (446) (962–1419)***	1234 (487) (985–1427)***	NS
Postprandial change in HBF (%)	22.1 (21) (9.4–34.7)	23.0 (20) (11.3–35.1)	NS
Baseline AzBF (ml/min)	739 (316) (614–876)	561 (186) (452–661)	<0.01
Postprandial AzBF (ml/min)	980 (429) (804–1182)***	659 (237) (543–769)*	<0.001
Postprandial change in AzBF (%)	35.7 (28) (23.1–48.2)	17.1 (16) (8.2–26.6)	<0.01
Systemic haemodynamics			
Baseline mean arterial pressure (mm Hg)	82 (16) (62–90)	84 (16) (75–91)	NS
Postprandial mean arterial pressure (mm Hg)	80 (22) (range 70–89)	81 (17) (range 72–88)	NS
Postprandial change in mean arterial pressure (%)	2.4 (1.1) (1.8–2.9)	3.5 (1.1) (2.6–4.1)	NS
Baseline cardiac index (l/min m^2)	4.32 (1.7) (3.5–5.0)	4.24 (1.7) (3.4–4.9)	NS
Postprandial cardiac index (l/min m^2)	4.66 (2.2) (3.7–5.7)	4.55 (2.2) (3.6–5.4)	NS
Postprandial change in cardiac index (%)	8.1 (3.3) (6.5–9.9)	7.8 (2.8) (6.5–9.2)	NS
Baseline systemic vascular resistance (dyne s m^2/cm^5)	1527 (526) (1321–1784)	1604 (605) (1344–1876)	NS
Postprandial systemic vascular resistance (dyne s m^2/cm^5)	1386 (418) (1202–1594)*	1410 (459) (1217–1609)*	NS
Postprandial change in systemic vascular resistance (dyne s m^2/cm^5)	9.3 (4.5) (7.4–11.8)	11.6 (5.6) (9.2–14.1)	NS
Biochemical data			
Baseline serum glucagon (ng/l)	93 (49) (72–112)	91 (53) (69–121)	NS
Postprandial serum glucagon (ng/l)	121 (67) (94–153)***	117 (62) (89–141)***	NS
Postprandial change in serum glucagon (%)	28.1 (45) (11.2–44.4)	28.6 (51) (10.1–46.9)	NS

AzBF, azygous blood flow; HBF, hepatic blood flow; HVPG, hepatic venous pressure gradient.
Values are mean (SD) (range).
*p<0.05, **p<0.001 and ***p<0.01 *v* baseline.

postprandial changes in AzBF were independently associated with the postprandial change in HVPG. In cirrhosis, portal blood flows through two parallel vascular networks: the liver sinusoids and the portal-collateral vessels, the second network including the oesophageal varices. The resistance posed by the collateral vessels to portal flow is greater than that of the normal hepatic microcirculation, but lower than the resistance offered by the sinusoids of the cirrhotic liver.[13] In consequence, the different resistance shown by each of these vascular networks to portal flow influences portal pressure.

Several practical and pathophysiological implications can be drawn from our results. Considerable attention has been devoted in recent years to develop drugs (ie, vasodilators) that lower portal pressure by modulating the dynamic component of the increased vascular resistance of the cirrhotic liver.[4 11 21 27] These studies have taken advantage of the portal pressure response to meal ingestion to test the adaptive vasodilatory efficiency of the intrahepatic circulation. The results of this study indicate that the postprandial increase in portal pressure in patients with cirrhosis is determined not only by intrahepatic vascular resistance but also by the extent of portal venous system collateralisation. We propose that future studies in which postprandial hyperaemia is used to test the dynamic component of intrahepatic vascular resistance should stratify

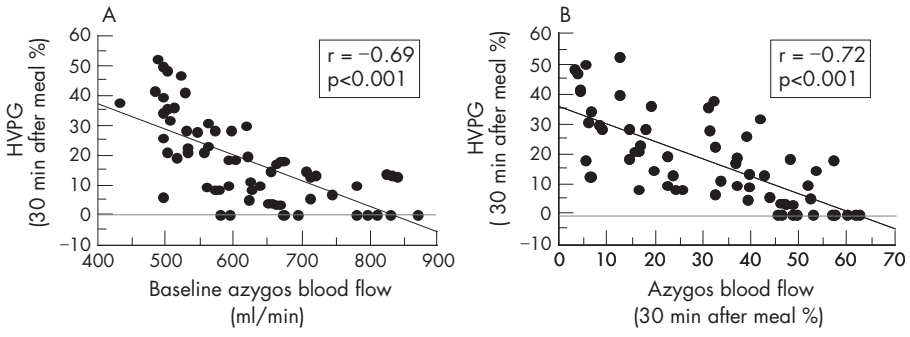

Figure 3 Inverse correlation between the postprandial (30 min) change in the hepatic venous pressure gradient (HVPG) and baseline azygos blood flow (A) or postprandial increase in azygos blood flow (B).

Table 2 Basal and postprandial (30 min after meal intake) serum levels of nitric oxide metabolites in the azygos and hepatic veins of patients with mild or marked postprandial increase in hepatic venous pressure gradient

	NOx in azygos vein (nmol/ml)		NOx in hepatic vein (nmol/ml)	
	Mild increase in HPVG, n = 14	Marked increase in HPVG, n = 15	Mild increase in HPVG, n = 32	Marked increase in HPVG, n = 32
Baseline	31.5 (15.3) (21.9–41.8)	30.6 (13.9) (22.1–39.6)	30.9 (18.6) (23.9–38.5)	31.7 (20.3) (23.3–41.7)
Postprandial	38.3 (16.4) (28.2–48.1)*	35.4 (13.5) (27.4–45.6)**	32.6 (26.0) (22.2–43.9)	33.5 (25.1) (23.2–43.6)
Postprandial change (%)	21.7 (14.2) (12.4–30.7)	15.1 (10.1) (9.5–21.7)	5.3 (2.2) (4.1–6.9)	5.8 (2.8) (4.3–7.2)

AzBF, azygous blood flow; HVPG, hepatic venous pressure gradient; NOx, nitric oxide metabolites.
Values are mean (SD) (range).
Significant differences compared with baseline: *$p<0.001$, **$p<0.04$.
To explore the variables independently associated with the postprandial change in HVPG, we performed a logistic regression analysis including four variables: baseline HVPG, baseline AzBF, postprandial change in AzBF and a history of variceal bleeding. On multivariate analysis, only baseline AzBF ($p<0.001$) and postprandial change in AzBF ($p<0.01$) were independently associated with the postprandial change in HVPG.

patients according to their degree of portal-systemic collateralisation. As measurement of AzBF by thermodilution is not yet available in most centres, stratification could be based on surrogate variables, such as variceal size and a history of variceal bleeding. Both these factors were found to be related to the magnitude of the postprandial increase in HVPG in our study. Indeed, variceal size and previous variceal bleeding showed accuracies of 69% and 81%, respectively, for classifying the patients by extent of portal-systemic collateralisation.

Our study has several limitations. Firstly, we evaluated changes in the intrahepatic circulation in response to food intake by the combined measurement of HVPG, to estimate portal pressure, and fractional clearance of ICG, to estimate HBF. The latter evaluates the sum of arterial and portal hepatic blood flow. Thus, the possibility exists that after a meal, portal and total hepatic blood flow could behave differently. In such a case, HBF measured by the ICG constant infusion technique would underestimate the postprandial increase in portal inflow. Nevertheless, using this technique, we were able to detect a significant increase in HBF of similar magnitude in patients with mild or marked postprandial increases in HVPG. Secondly, to investigate the factors underlying the great variability of the portal pressure response to meal ingestion, we divided our patients into two groups according to the extent of the postprandial rise in HVPG. The 15% discriminating value selected was based on the following criteria:

- this number is the median of the distribution of the postprandial change in HVPG;
- a variation of at least 10% is considered a measurable change in HVPG[18 28 29]; and
- a longitudinal study has shown the prognostic value of a 15% change in HVPG in patients with alcoholic cirrhosis.[30]

Taken together, our results implicate postprandial increases in portal pressure and collateral flow in the pathophysiology of the variceal enlargement that precedes variceal bleeding and predisposes the patient to this complication. In the early stages of portal hypertension, when the portal-collateral system is not yet fully developed, postprandial hyperaemia leads to pronounced increases in HVPG. Hence, repeated postprandial flares in portal pressure could promote the opening and growth of collaterals. Recent experimental studies have shown that increased portal pressure activates vascular endothelial growth factor expression,[31] which might promote new vessel formation.[32] In advanced stages, when portal-systemic collateralisation is extensive, the resistance of the collateral vessels becomes an important determining factor for overall portal resistance. In consequence, postprandial hyperaemia results in less pronounced increases in HVPG, but in marked increases in collateral blood flow (collateral hyperaemia). Hyperaemia-driven shear stress stimulates vascular endothelial growth factor and NO production by the endothelium of the collateral vessels, which enhances portal-collateral development and distension independently of portal pressure.[23 31] At this stage, the measurement of portal pressure changes might underestimate the potential effect of postprandial hyperaemia on variceal dilation. This situation is the opposite of the response to propranolol, in which the reduction in HVPG and AzBF caused by the drug results in a decrease in the transmural pressure, radius and wall tension of the varix.[33] In a patient with large oesophageal varices, the postprandial increase in HVPG is blunted, but associated with intense collateral flow, possibly aggravating variceal distension, thus leading to variceal enlargement and an increased risk of bleeding.

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Authors' affiliations

Agustín Albillos, Mónica González, Rosario Gonzalez, Servicio de Gastroenterología, Hospital Universitario Ramón y Cajal, Universidad de Alcalá, Madrid, Spain
Rafael Bañares, Maria-Vega Catalina, Cristina Ripoll, Servicio de Gastroenterología, Hospital Universitario General Gregorio Marañón, Universidad Complutense, Madrid, Spain
Oscar Pastor, Servicio de Bioquímica Clínica, Hospital Universitario Ramón y Cajal, Madrid, Spain
Jaime Bosch, Servicio de Hepatología, Hospital Clinic IDIBAPS, Universidad de Barcelona, Barcelona, Spain

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Agustín Albillos, Rafael Bañares, Mónica González, et al.

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