Evaluation of Postprandial Hyperemia in Superior Mesenteric Artery and Portal Vein in Healthy and Cirrhotic Humans: An Operator-blind Echo-Doppler Study

CARLO SABBÁ,[1,3]* GIOVANNA FERRAIOLI,[1,3]‡ PAUL GENECIN,[1] LUIS COLOMBATO,[1] PAOLO BUONAMICO,[1,3] EMANUEL LERNER,[2] KENNETH J. W. TAYLOR[3] AND ROBERTO J. GROSZMANN[1]

[1]Hepatic Hemodynamic Lab, Veterans Affairs Medical Center, Yale University School of Medicine, West Haven 06516; [2]Research Service, Veterans Affairs Medical Center, West Haven, 06516; and [3]Department of Diagnostic Radiology, Yale University, New Haven, Connecticut 06510

In an operator-blind design, we used an echo-Doppler duplex system to examine superior mesenteric artery and portal vein hemodynamics on two consecutive mornings in 12 fasting cirrhotic patients and 12 matched controls, randomized to a standardized 355 kcal mixed-liquid meal vs. water. Cross-sectional area and mean velocity were recorded from the portal vein and superior mesenteric artery at 30 min intervals, from 0 min to 150 min after ingestion. Flows were calculated. Pulsatility index, an index related to vascular resistance, was obtained for the mesenteric artery. Baseline flows did not differ between cirrhotic patients and control patients, but pulsatility index was reduced in the cirrhotic subjects. Maximal postprandial hyperemia was attained at 30 min. Cirrhotic patients showed a blunted hyperemic response to food. In normal controls, portal vein area increased significantly after the meal from 30 min to 150 min, whereas in cirrhotic patients a significant difference occurred only at 30 min. Pulsatility index in both groups was significantly reduced after eating, and this reduction persisted up to 150 min. No changes after ingestion of water were observed. Echo-Doppler was very sensitive in detecting postprandial splanchnic hemodynamic changes and differences between cirrhotic patients and normal subjects. Mesenteric artery pulsatility index was more sensitive than flow in detecting baseline hemodynamic differences. In cirrhotic patients, portal postprandial hyperemia was mainly related to the increase in mean velocity. (HEPATOLOGY 1991;13:714-718.)

Postprandial splanchnic circulatory response in cirrhosis could shed light on some of the hemodynamic derangements that characterize portal hypertensive liver disease. In fact, postprandial splanchnic hyperemia could be a risk factor for variceal bleeding in portal hypertensive patients.

Echo-Doppler flowmetry has been proposed as a noninvasive method for evaluating changes in the splanchnic circulation in portal hypertensive patients (1-7). However, until now no controlled studies using this technique have been conducted. The variability of blood flow measurements with the Doppler technique could be greater than the hemodynamic changes that the investigators intend to measure (8). Hence, controlled trials are needed to test the sensitivity of Doppler flowmetry in evaluating changes in splanchnic blood flow.

This study was undertaken to: (a) evaluate the sensitivity of echo-Doppler in detecting postprandial hyperemia under controlled conditions; (b) study postprandial hyperemia in cirrhotic patients in comparison with a matched noncirrhotic population; and (c) identify the echo-Doppler parameters best able to detect hemodynamic changes in cirrhotic patients.

MATERIALS AND METHODS

Patients

Thirteen male cirrhotic patients and 14 controls matched for sex, age and weight were enrolled in the study. One cirrhotic patient and two control subjects were excluded from the study (as described later in this section). Therefore only 12 cirrhotic patients (age 67 ± 6 yr; weight 86 ± 16 kg) and 12 controls (age 66 ± 7 yr; weight 83 ± 12 kg) were studied. The diagnosis of cirrhosis was based on liver biopsy in five subjects and on clinical grounds in the remaining patients. The cause of cirrhosis was alcohol in all patients; ethanol consumption in each patient was estimated to be more than 80 gm/day in the 5 yr before the diagnosis of alcoholic cirrhosis, and no other cause of liver disease was evident. According to Child-Turcotte classification (9), all patients were Class A. No one had reverse portal, splenic or mesenteric flow or portal vein thrombosis. No evidence of patent umbilical or paraumbilical vein or large splenorenal shunts was present. Seven of the 12 cirrhotic patients had a recent upper gastrointestinal endoscopy. Six of the 12 patients had esoph-

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*Current address: Istituto di Clinica Medica I, University of Bari, Bari 70100, Italy.

‡Current address: Divisione di Medicina, Ospedale Civile di Scafati, Scafati 84018, Italy.

Address reprint requests to: Roberto J. Groszmann, M.D., VA Medical Center, 950 Campbell Avenue, West Haven, Connecticut 06516.

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TABLE 1. Baseline studies in normal subjects and cirrhotic patients

Vessel	Area (mm^2)	Mean velocity (cm/sec)	Flow (ml/min)	PI
PV				
Normal subjects	133 ± 4[a]	13 ± 0.3[a]	1,066 ± 38	–
Cirrhotic patients	164 ± 8	12 ± 0.3	1,196 ± 81	–
SMA				
Normal subjects	45 ± 2	20 ± 1	522 ± 24	4.83 ± 0.17[b]
Cirrhotic patients	47 ± 2	21 ± 1	600 ± 45	4.26 ± 0.51

Baseline in absolute values (mean ± S.E.M. of the measurements over the 2 days).
Cirrhotic patients show a significant increase in PV cross-sectional area, a decrease in PV-V and a reduction in the SMA PI.
[a] $p < 0.005$.
[b] $p < 0.05$.

ageal varices. All patients were studied at the West Haven Veterans Affairs Medical Center. The study was approved by the Human Investigation Committee of the hospital and written, informed consent was obtained from each subject.

Equipment

A Toshiba sonolayer SSA-100A + SSD-100A B-mode and pulsed Doppler duplex system (Toshiba Corporation, Tustin, CA) with 2.5 MHz and 3.75 MHz sector electronic probes was used. Real-time and Doppler control settings were optimized in each case according to established techniques.

Methods

All subjects were studied in the early morning after an overnight fast. After 15 min of rest, baseline measurements were performed with the subject in a supine position. Subjects were randomized to a standardized mixed-liquid meal or water in a crossover design on two consecutive days. The meal (355 kcal, Ensure Plus, Abbott Laboratories, North Chicago, IL) was composed (gm/8 fl oz) of proteins (14.8), fat (11.8), carbohydrates (47.3) and water (182). Caloric distribution was protein (16.7%), fat (30%) and carbohydrate (53.3%). The placebo meal was an equivalent volume of water (8 oz). Measurements of the vessel parameters after either the meal or the placebo were obtained at 30 min intervals for 150 min. The operator did not know whether the patients received the meal or the placebo.

Two vessels of the splanchnic system were studied: the portal vein (PV) and the superior mesenteric artery (SMA). For each vessel, the cross-sectional area (A) (mm^2) and mean velocity (V) (cm/sec) were measured to calculate blood flow (F) (ml/min): $F = A \times V$. To calculate area, the transverse plane of the vessel was visualized, and the image was frozen. The axes of the vessel were defined, and A was calculated by the duplex system software using the ellipse formula: $A = \pi D_1 D_2/4$, where D_1 and D_2 are the diameters of the ellipse. Maximum velocity of blood flow was derived by the Doppler shift using the formula: $\Delta f = 2 f_0 V_{max} \cos\delta/c$. V was calculated from the maximum velocity using a correction factor for parabolic flow: $V = V_{max} \times 0.57$ (10). At each time period, A and V were obtained by averaging three consecutive measurements for each parameter.

In addition, the SMA pulsatility index (PI), an index related to vascular resistance (11), was calculated using the formula: $PI = (V_{max} - V_{min})/V_{mean}$.

The criterion for inclusion of a subject in the data analysis was feasibility of SMA, PV measurements by echo-Doppler or both. Adequate visualization of a vessel in two planes was required with a Doppler angle of insonation of less than 60 degrees. Both these conditions are necessary to calculate absolute blood flow by Doppler flowmetry. One of 13 cirrhotic patients and two of 14 control subjects were excluded from the study because of poor visualization of both PV and SMA. PV measurements were obtained in 12 cirrhotic patients and 12 control subjects, and SMA measurements were obtained in 6 cirrhotic patients and 7 control subjects.

Statistics

The baseline results for each group of patients were given as mean ± S.E.M. of absolute values. The changes over time (30 min intervals for 150 min) after either the meal or the placebo were expressed as percentage changes from baseline. Comparisons within one group (meal vs. placebo) and between groups (cirrhotic patients vs. control subjects) were made using Student's *t* test for unpaired data with the Bonferroni correction for multiple comparisons. p Values < 0.05 were considered significant.

RESULTS

Portal Vein

Baseline Absolute Values of A, V and F. Cirrhotic patients showed an increase in PV-A and a decrease in PV-V in comparison with normal subjects ($p < 0.005$). No statistical difference was found between cirrhotic patients and normal subjects in PV-F (Table 1).

Percentage Changes from Baseline (Fasting) after the Meal (Fig. 1). PV-F increased after the meal (in comparison with the placebo) in both groups. This difference was significant at all measurement intervals up to 150 min. The maximum postprandial hyperemia was attained at 30 min (189% ± 7% in normal subjects and 165% ± 6% in cirrhotic patients). However, the response of cirrhotic patients to the meal was significantly less than that of normal subjects at 30 min and 60 min. PV-A measurements after the meal (in comparison with the placebo) showed significant increase in normal subjects (from 30 to 150 min), whereas in cirrhotic patients a significant difference occurred only at 30 min. The increase in PV-V after the meal was maximal at 30 min for cirrhotic patients and normal subjects. This increase remained statistically significant at all mea-

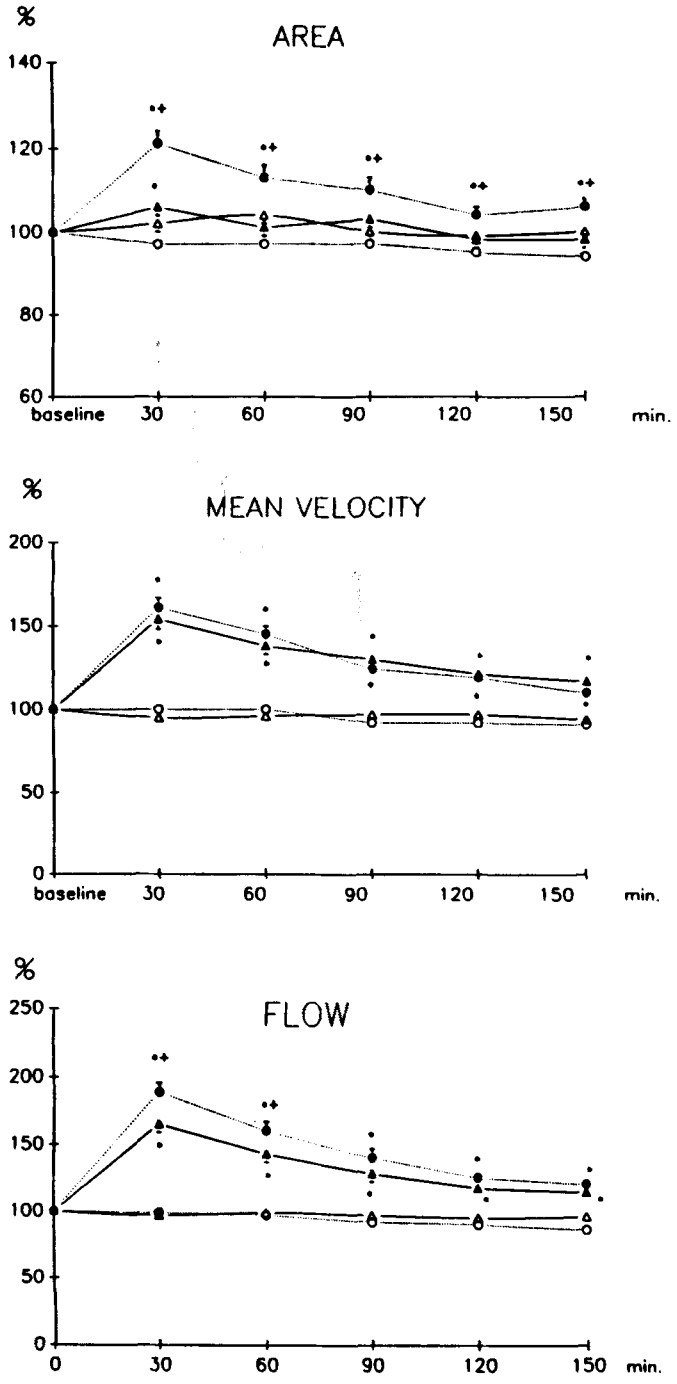

FIG. 1. Portal vein. Percentage changes from baseline in PV area, velocity and flow after meal or placebo in normal subjects and cirrhotic patients. (Normal subjects: o----o water; •----• meal. Cirrhotic patients: o—o water; •—• meal). Statistical significance: water vs. meal: • = $p < 0.05$; meal: normal subjects vs. cirrhotic patients: + = $p < 0.05$. In cirrhotic patients, the postprandial increase in PV blood flow was mainly related to an increase in blood velocity, whereas in normal subjects, an increase of both area and mean velocity occurred.

surement intervals up to 150 min. In both groups all patients responded to the meal with an increase in portal velocity in comparison with the administration of the placebo.

Superior Mesenteric Artery

Baseline Absolute Values of A, V, F and PI. No significant differences were found between the two groups when measuring SMA-A and SMA-V. The SMA-F increased slightly in cirrhotic patients, but compared with normal subjects, this difference was not significant. Nevertheless, a significantly lower SMA-PI was observed in cirrhotic patients in comparison with normal subjects ($p < 0.05$) (Table 1).

Percentage Changes from Baseline (Fasting) after the Meal (Fig. 2). A postprandial increase in flow occurred in normal subjects, peaking at 30 min and remaining significant at all measurement intervals up to 150 min. Likewise, in cirrhotic patients the SMA-F increased, although this increase tended to be less dramatic and was statistically significant compared with the placebo only up to 60 min. The postprandial hyperemia in normal subjects at 30 min was higher than in cirrhotic patients at 30 min (114% ± 10% vs. 71% ± 32%), although this difference did not reach statistical significance. In both populations, SMA-A did not change after either the meal or the placebo with the exception of SMA-A in normal subjects at 30 min. SMA-V increased after the meal (compared with the placebo) in both groups. This difference was significant at all time intervals up to 150 min in normal subjects and up to 90 min in cirrhotic subjects. SMA-PI was significantly reduced after the meal (in comparison with the placebo) in both groups, and this difference persisted up to 150 min. However, this reduction was significantly less pronounced in cirrhotic patients.

DISCUSSION

Noninvasive quantitation of portal blood flow under fasting and postprandial conditions has previously been studied (6, 7, 12, 13). However, it has been reported that the echo-Doppler technique is subject to many possible errors (14) and that differences in Doppler measurements caused by intraobserver and interobserver variability do exist (8). Therefore in contrast to previous studies, this study was undertaken in a blinded fashion (i.e., the operator did not know whether the subject had the meal or the placebo). The study was designed to monitor two splanchnic blood vessels for 150 min after ingestion of either the meal or the placebo. Its goal was to identify the most useful echo-Doppler parameters for assessing SMA and PV hemodynamic changes under physiological (meal vs. placebo) and pathological (cirrhotic vs. noncirrhotic) conditions.

As previously reported (15), PV-A was greater at baseline in cirrhotic patients, probably as a consequence of portal hypertension. Other investigators, however, have observed that in advanced portal hypertension the PV diameter can be reduced because of the opening of many portosystemic shunts with the consequent reduction in portal flow. This is frequently associated with retrograde flow in at least one of the primary afferent vessels of the PV (splenic or mesenteric veins), a reduced retrograde flow in the main PV or both (16). Our

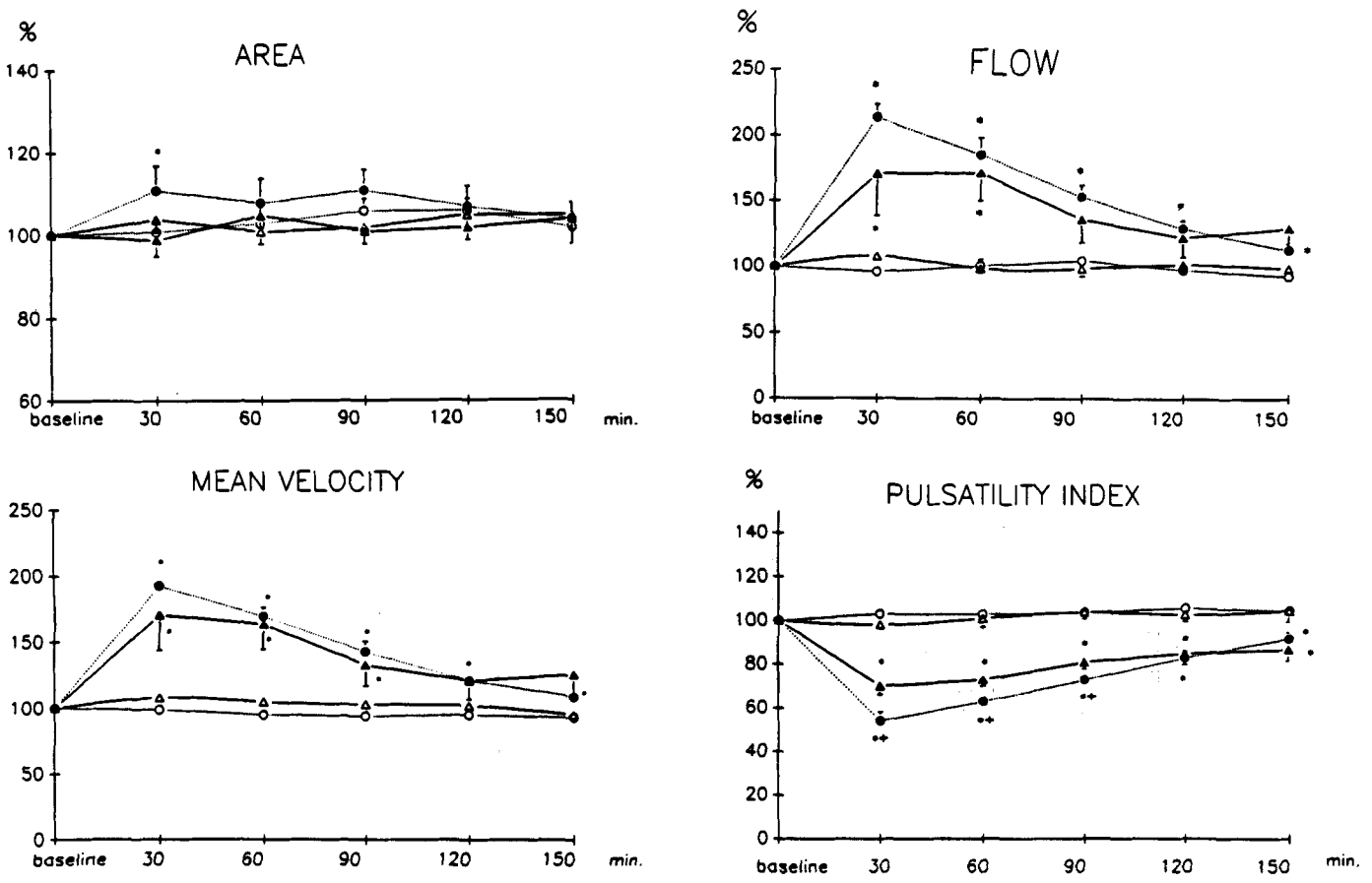

FIG. 2. Superior mesenteric artery. Percentage changes from baseline in SMA area, velocity, flow and pulsatility index after meal or placebo for normal subjects and cirrhotic patients. (Normal subjects: o----o water; •----• meal. Cirrhotic patients: o—o water; •—• meal). Statistical significance: water vs. meal: • = $p < 0.05$; meal: normal subjects vs. cirrhotic patients: + = $p < 0.05$. In both populations, postprandial changes in flow are caused by increases in blood velocity. Pulsatility index is significantly reduced after meal in both groups. However, the reduction is significantly less pronounced in cirrhosis.

patients were all Child class A with moderate portal hypertension as seen by the relatively high portal velocities observed. PV-F in cirrhotic patients was not significantly different from that observed in normal subjects because the increased PV-A was accompanied by a reduction in PV-V. We did not find any difference in SMA-F between normal subjects and cirrhotic patients in baseline fasting measurements. On the other hand, in comparison with normal subjects, our cirrhotic patients showed a reduced SMA-PI under fasting conditions. PI has been proposed as an index of vascular resistance in the study of arterial vessels by echo-Doppler; higher PI values correspond to greater impedance to flow in the resistance vessels (11, 17). In the cirrhotic patients, PI was more sensitive than flow in detecting baseline hemodynamic differences. SMA-PI was reduced in cirrhotic subjects, reflecting a reduced SMA vascular resistance, a situation similar to that observed in experimental models of portal hypertension (18). PI has never before been applied to the study of circulatory abnormalities observed in portal hypertension. Because determination of PI is not affected by the angle between the direction of the Doppler beam and the blood vessel (angle of insonation), PI may be preferable to flow in evaluating subtle hemodynamic changes in the superior mesenteric arterial bed (19).

In both normal and cirrhotic groups, the ingestion of food was a powerful physiological stimulus (20-24). In fact, in this operator-blind study we were able to detect dramatic hyperemic changes in the splanchnic circulation after ingestion of the meal in both groups. Our data demonstrate a maximum increase in splanchnic blood flow at 30 min, whereas other authors (7, 13) have described a peak at 60 min. This discrepancy could be caused by the type of meal our patients received. The meal was liquid, with a relatively high content in carbohydrates, rather than the solid meal that was used previously (13).

In this study, cirrhotic subjects demonstrated a significant postprandial hyperemia, although it was less than that observed in normal subjects. Normal subjects and cirrhotic patients showed different hemodynamic responses to the stimulus of food, suggesting that the already dilated splanchnic vascular bed of cirrhotic patients cannot dilate as much as that of normal subjects.

Postprandial hyperemia may exaggerate the hemodynamic derangements that characterize the splanchnic circulation in portal hypertension. In fact, in cirrhosis, the hepatic vascular resistance is not only increased but also relatively fixed; therefore in the presence of portosystemic shunts, any further increase in portal venous inflow could be diverted directly into the systemic circulation through collateral vessels. This situation may not only aggravate the metabolic derangement of liver disease but also may increase the risk for variceal rupture.

In cirrhotic patients, the postprandial increase in PV-F was mainly related to an increase in blood velocity, whereas in normal subjects, an increase of both A and V occurred. In both groups, the hemodynamic changes in SMA-F depended on changes in SMA-V. These results suggest that velocity measurement, especially in cirrhotic patients, is a reliable parameter in monitoring acute changes in blood flow by echo-Doppler in physiological and/or pathological conditions.

In conclusion, in this operator-blind, crossover study, Doppler flowmetry was very sensitive in detecting postprandial splanchnic hemodynamic changes. In cirrhosis, the pulsatility index is more sensitive than flow in detecting baseline hemodynamic differences in the mesenteric arterial bed as a result of reduced vascular resistance.

Additional studies on larger number of patients are needed to confirm this finding.

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