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# Functional hepatic flow and Doppler-assessed total hepatic flow in control subjects and in patients with cirrhosis

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**Functional hepatic flow and total hepatic flow were determined by non-invasive techniques in 32 patients with cirrhosis and in 32 paired control subjects. Functional hepatic flow was measured by the hepatic clearance of D-sorbitol, while total hepatic flow was determined by pulsed echo-Doppler, as the sum of portal and hepatic arterial blood flow.**

**Functional hepatic flow was significantly reduced in patients with cirrhosis (927±314 vs. 1287±315; $p<0.0001$), while total hepatic flow was slightly increased (1511±540 vs. 1261±321 in controls; $p=0.028$). In control subjects functional hepatic flow significantly correlated with total hepatic flow ($r=0.823$; $p<0.001$), while no correlation was observed in cirrhosis. Functional hepatic flow and the difference between total hepatic flow and functional hepatic flow significantly correlated with the Child-Pugh score in patients with cirrhosis.**

**The data obtained in control subjects support the measurement of functional hepatic flow and total hepatic flow by non-invasive techniques. The finding that in cirrhosis functional hepatic flow is significantly decreased, while Doppler-assessed total hepatic flow is preserved or even increased, confirms that a relevant part of blood flowing through the liver is diverted by intrahepatic shunts. The simultaneous assessment of these two parameters by non-invasive techniques may be proposed as a reliable tool for the study of functional shunting of cirrhosis.**

***Key words:*** **Cirrhosis; D-Sorbitol clearance; Echo-Doppler; Functional hepatic flow; Intrahepatic shunt; Total hepatic flow.**



TOTAL liver blood flow is the sum of the flow of the portal vein and the hepatic artery. In normal subjects, all the blood perfusing the liver is in close contact with functioning hepatocytes, which makes functional hepatic flow theoretically equivalent to total hepatic flow. In cirrhosis, part of the flow is diverted through intra- and extra-hepatic portal-systemic shunts; this blood becomes unavailable for metabolic exchanges and functional hepatic flow is consequently reduced.

Several methods have been described for the determination of hepatic perfusion (1). In most cases their use is limited to experimental studies because of extreme invasiveness, and they have no role in clinical hepatology.

In recent years new techniques have been proposed to measure, non-invasively, total hepatic flow (THF) and the functional hepatic flow (FHF). THF, i.e. the amount of blood circulating in the liver, independent of any metabolic activity, can be measured by pulsed echo-Doppler as the sum of portal blood flow and hepatic artery flow (2–5). FHF is the amount of blood perfusing the liver and making close contact with functioning hepatocytes leading to metabolic activity. The hepatic clearance of D-sorbitol has been found to give a reliable estimate of FHF, i.e. the flow through functioning sinusoids. Extensive studies have validated a non-invasive technique in comparison with invasive procedures based on the hepatic extraction of sorbitol and indocyanine green according to the Fick principle (6,7).

The aim of this study was to measure, in a series of

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control subjects and patients with cirrhosis, both FHF and THF and to define the significance of their simultaneous assessment in relation to the severity of liver disease.

## Patients and Methods

The study was carried out in 32 patients with biopsy-proven cirrhosis and 32 matched controls. Subjects with cirrhosis were selected from a group of 40 patients, without ascites at the time of examination. Eight patients had to be excluded because of inadequate echo-Doppler visualization of the hepatic vessels.

Seventeen patients with cirrhosis were males and 15 were females. They ranged in age from 30 to 78 years, median 60. The etiology of the disease was virus-related in 24 cases, and alcoholic in the remaining eight. Pertinent laboratory data were as follows: albumin, 3.38±0.45 g/dl; g-globulin, 2.14±0.71 g/dl; aspartate transaminase, 57±38 U/l; prothrombin activity, 65±18%; cholesterol, 141±53 mg/dl; total bilirubin, 2.51±2.28 mg/dl. Child-Pugh scores (8) ranged from 5 to 12, with a median of 7. All patients underwent endoscopic examination of the upper gastro-intestinal tract. Esophageal varices, graded according to Beppu et al. (9), were absent in nine patients, small in ten, medium in eight, and large in five.

Thirty-two subjects, without any clinical or laboratory evidence of liver disease, served as controls. They were matched with the patients with cirrhosis for sex, age and body surface. In our experience echo-Doppler study of splanchnic vessels, namely of the hepatic artery, is feasible in approximately 70% of healthy subjects, and this was a selection criterion.

All measurements were performed in fasting subjects, on the same morning. Functional hepatic plasma flow was determined on the basis of the hepatic clearance of D-sorbitol, as previously described by Molino and coworkers (6), with a 2 g intravenous bolus of sorbitol followed by a 2-h infusion at a rate of 54 mg/min. Total functional hepatic flow was calculated by multiplying the plasma flow by the hematocrit.

Echo-Doppler measurements of the portal vein and of the common hepatic artery were obtained using equipment which combines a real-time electronic sector scanner and a pulsed Doppler unit (Esaote-Hitachi AU 590). The echo-Doppler examination was always performed by the same investigator, who had more than 5 years' experience in Doppler examination of deep abdominal vessels, and who was unaware of the clinical diagnosis of the subject. Patients were examined in the supine position and, during the Doppler recording, were asked to hold their breath during normal respiration. According to recent experience (10), the measurements were repeated until three consistent values of blood velocity were consecutively obtained (maximum variability: portal velocity, 1 cm/s; hepatic artery velocity, 5 cm/s), and the mean values were considered for statistical purposes.

The portal vein was scanned longitudinally, and the sample volume was positioned in the middle of the portal trunk, in the tract just underneath the hepatic artery, as previously described (2).

The sectional area of the portal vein was determined by considering the vessel of circular shape ($\pi * r^2$). Mean portal blood velocity was calculated automatically by the equipment, while portal blood flow was calculated by multiplying blood velocity by the sectional area of the portal vein.

The hepatic artery measurements were taken where a straight stretch runs parallel to the portal vein, some centimeters away from the coeliac axis. In this position gastroduodenal and gastric arteries are expected already to have branched, so that only hepatic artery blood flow is measured. Care was taken to maintain the $\theta$ angle (the angle between the ultrasonic beam direction and the blood flow direction) at below 55°. Also, the sectional area of the hepatic artery was determined on the basis of its caliber, while mean blood velocity was calculated by multiplying the average maximum velocity by 0.62, as suggested by Nakamura et al. (11). Hepatic artery flow was determined by multiplying the mean blood velocity by the sectional area of the artery.

Total hepatic blood flow was calculated as the sum of portal flow and hepatic artery flow.

In a subgroup of subjects, day-to-day reproducibility of Doppler measurements was assessed by measuring each vessel, under the same conditions, on 2 consecutive days.

All subjects gave their informed consent to take part in the study, which was carried out according to the Helsinki Declaration. The protocol of the study was

TABLE 1

Functional hepatic flow and Doppler assessed flow in the portal vein, in the hepatic artery, and total hepatic flow in control subjects and in patients with cirrhosis

| | Controls | Cirrhosis | $p$ |
|---|---|---|---|
| Functional hepatic flow (FHF) | 1287±315 | 927±314 | <0.0001 |
| Portal blood flow | 978±307 | 1050±523 | =0.506 |
| Hepatic artery flow | 284±109 | 462±342 | =0.007 |
| Total hepatic blood flow (THF) | 1261±321 | 1511±540 | =0.028 |
| FHF per kg b.w. | 20.4±4.4 | 14.2±5.1 | <0.0001 |
| THF per kg b.w. | 19.8±3.8 | 23.4±8.6 | =0.045 |

The data are expressed as mean±SD in ml/min.

submitted to the Senior Staff Committee, who approved it.

The data in the text and in the tables are expressed as mean±SD. The statistical analyses were performed by means of Student's *t*-test for paired and unpaired data. The *r*-coefficients of linear correlation analysis were also determined by the least square method and by means of non-parametric analysis (Spearman rank test).

## Results

FHF, evaluated by means of the sorbitol clearance, was significantly reduced in patients with cirrhosis in comparison to controls (927±SD 314 ml/min vs. 1287±315; $p<0.0001$) (Table 1), ranging, respectively, from 353 to 1668 ml/min and from 837 to 1962. Reduced FHF in cirrhosis was related to the severity of hepatic disease, as expressed by significant correlation with the Child-Pugh score (r=−0.713; Fig. 1, left). FHF correlated significantly with body weight in controls (r=0.436; $p=0.013$), but not in cirrhosis (r=0.298).

Portal caliber was larger in cirrhosis (14.6±2.6 mm and 11.0±1.6 in controls; $p<0.001$), as was hepatic artery caliber (5.6±1.0 vs. 4.8±0.7; $p<0.001$). Portal blood velocity was lower in cirrhosis (9.5±4.9 cm/s vs. 16.9±3.4; $p<0.001$). In a single case a reversed portal flow was observed. Hepatic artery velocity was similar in the two groups (41±11 cm/s in controls and 45±17 in cirrhosis).

Portal blood flow was similar in controls and in cirrhosis, while hepatic artery flow was nearly doubled in cirrhosis (Table 1). As a consequence, THF was increased by 20% in patients with cirrhosis. THF significantly correlated with body weight in controls (r=0.639; $p<0.001$), but not in cirrhosis (r=0.142).

Two patients had a patent umbilical vein; in these cases portal flow was 2870 and 2130 ml/min, respectively, and the Doppler-assessed hepatofugal flow in the umbilical vein was 910 and 630 ml/min. The patient with a reversed flow in the portal vein (323 ml/min) had an extremely increased arterial flow (1414 ml/min).

In control subjects sorbitol-assessed FHF overestimated Doppler-assessed THF by only 25±186 ml/min, whereas in cirrhosis it underestimated THF by 583±598 ml/min. The difference between THF and FHF in controls did not reveal any systematic deviation from random distribution, whereas in patients with cirrhosis it correlated with the Child-Pugh score (r=0.460; Fig. 1, right). This correlation increased remarkably when the two patients with a patent umbilical vein were excluded from the analysis (r=0.620; $p<0.005$).

In control subjects FHF correlated significantly with portal blood flow (r=0.785; $p<0.001$) and with the THF (r=0.823; $p<0.001$, Fig. 2, left), while no correlation was observed in patients with cirrhosis (r=0.190 and r=0.061 (Fig. 2, right), respectively).

Day-to-day variations in echo-Doppler measure-

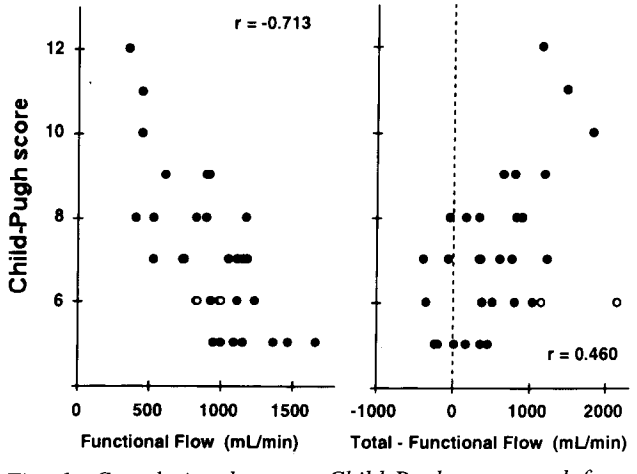


*Fig. 1. Correlation between Child-Pugh score and functional hepatic flow (left) or difference between total and functional hepatic flow (right) in cirrhosis. The equations of the curves are: Left, Y=10.875+(−0.004×X); Right, Y=6.262+0.001×X. The open circles identify the two patients with extrahepatic shunting due to patent umbilical vein. When these subjects are removed from the analysis, the correlation between Child-Pugh score and the THF−FHF difference gives a correlation coefficient of 0.620. The coefficients of Spearman rank correlation in the entire population are 0.663 (left) and 0.434 (right).*

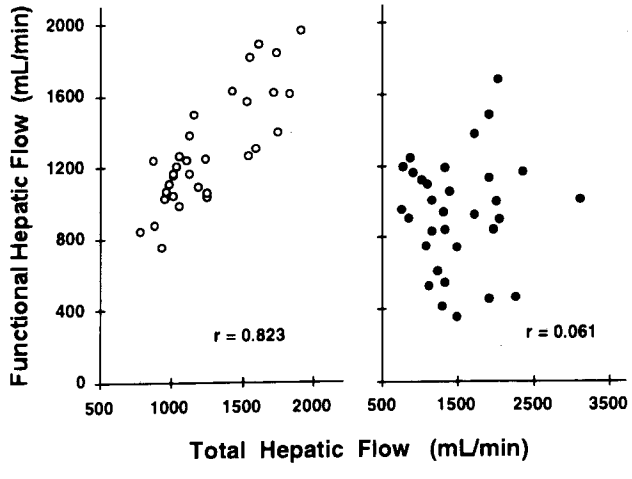


*Fig. 2. Correlation between Doppler-assessed total hepatic blood flow and functional hepatic flow in control subjects (left) and in patients with cirrhosis (right). The equations of the curves are: controls, Y=269.3+0.807×X; Cirrhosis, Y=873.9+0.035×X.*

TABLE 2

Day to day variation of echo-Doppler measurements in 13 patients (Case 1–5: control subjects; Case 6–13: patients with cirrhosis)

| Case no. | Day | Portal blood flow (ml/min) | Hepatic artery flow (ml/min) | Total hepatic flow (ml/min) | Variability in THF (%) |
|---|---|---|---|---|---|
| 1. | 1 | 850 | 136 | 986 | |
| | 2 | 902 | 158 | 1060 | +7.5 |
| 2. | 1 | 1323 | 218 | 1541 | |
| | 2 | 1352 | 244 | 1596 | +3.6 |
| 3. | 1 | 1289 | 308 | 1597 | |
| | 2 | 1224 | 276 | 1500 | −6.0 |
| 4. | 1 | 1659 | 274 | 1933 | |
| | 2 | 1542 | 252 | 1794 | −7.2 |
| 5. | 1 | 1143 | 344 | 1487 | |
| | 2 | 1084 | 298 | 1382 | −7.1 |
| 6. | 1 | 1273 | 276 | 1549 | |
| | 2 | 1360 | 238 | 1598 | +3.2 |
| 7. | 1 | 1483 | 422 | 1905 | |
| | 2 | 1451 | 448 | 1899 | −0.3 |
| 8. | 1 | 1604 | 445 | 2049 | |
| | 2 | 1491 | 504 | 1995 | −2.6 |
| 9. | 1 | 1035 | 642 | 1677 | |
| | 2 | 1001 | 723 | 1724 | +2.8 |
| 10. | 1 | 2966 | 170 | 3136 | |
| | 2 | 2752 | 186 | 2938 | −6.3 |
| 11. | 1 | 1154 | 570 | 1724 | |
| | 2 | 1218 | 518 | 1736 | +0.7 |
| 12. | 1 | 1397 | 674 | 2071 | |
| | 2 | 1422 | 582 | 2004 | −3.2 |
| 13. | 1 | 678 | 455 | 1133 | |
| | 2 | 732 | 397 | 1129 | −0.4 |

ments were within 8% for portal blood flow and within 15% for hepatic artery flow (Table 2). Doppler-assessed total blood flow was remarkably similar on repeated measurements, the maximum variation being from −7.2 to +7.5% in controls and from −6.3 to +3.2% in cirrhosis.

## Discussion

The data obtained in control subjects support the measurement of FHF and THF by non-invasive techniques. The finding that in cirrhosis FHF is significantly decreased, while Doppler-assessed THF is preserved, confirms that a relevant part of the portal flow is diverted through intrahepatic shunts, with defects in the hepatic handling of substrates. In this case the simultaneous assessment of these two non-invasive parameters could be useful to quantify functional shunting in cirrhosis.

Changes in hepatic blood flow are a relevant feature in chronic liver diseases, where altered hepatic microcirculation, with ensuing portal hypertension and formation of portal systemic collaterals, results in progressive impairment of liver perfusion. Unfortunately, the study of splanchnic hemodynamics has so far been limited by the invasiveness of the techiques (1).

THF can be studied by means of indocyanine green clearance (12). The relatively high hepatic intrinsic clearance of indocyanine green and absence of extrahepatic elimination make indocyanine green suitable for the measurement of total hepatic blood flow in control subjects. Unfortunately, the correct measurement of indocyanine green clearance requires hepatic vein catheterization (12,13), and invasiveness is not counterbalanced by precision, since large variability was demonstrated by repeated measurements (14).

We utilized pulsed echo-Doppler, a non-invasive technique which is increasingly being used in clinical practice (2–4). The technique cannot be used with severe ascites and meteorism, but in experienced hands a valid measurement is feasible in approximately 80% of cases. Many studies have also focused on the reproducibility of the echo-Doppler parameters (15–17), and the sources of errors in their determination have been well defined (18). They stem from uncertainty in the measurement of blood velocity, uncertainty in vessel caliber measurement and finally the possible non-circular shape of the cross-sectional area of the vessel. To minimize these errors, we examined only patients in whom the vessels could easily be visualized. In addition, in agreement with a recent study aimed at improving the reproducibility of the technique (10), Doppler data were obtained by the same well-trained operator, with the use of the same equipment, and following strict guidelines in the measurement of blood velocities. We accepted a variability in blood velocity in the order of 10% during three repeated measurements, which leads to a variability lower than 5% in blood flow. Variability may be amplified by uncertainty in vessel caliber, particularly in the small hepatic artery, but well-trained operators may limit the error to less than 15%. Finally, the error inherent in the assumption of circular cross-sectional area is probably lower than that which would ensue from the actual measurement of vessel area. Adherence to a strict protocol in echo-Doppler examination is possibly the reason for the good day-to-day reproducibility we observed, particularly for portal blood flow determination.

As expected, reproducibility was lower for the hepatic artery flow, due to a lower vessel caliber. According to our data, the hepatic artery contributed 6–37% to THF in controls (mean 23±SD 8) and 6–62% in cirrhosis (mean 28±13), after exclusion of the patient with reversed portal blood flow. The observed error in hepatic artery flow up to 15% makes up an error in THF determination in the order of less than 10%, which is exactly what we found. It is worth noting that

in cirrhosis, where the contribution of hepatic artery flow to THF is higher, hepatic artery caliber is larger, which makes the echo-Doppler measurement more accurate and limits the error in THF to the same order of magnitude of controls.

The above calculation does not take into account the possible error due to the presence of a supernumerary hepatic artery, whose presence was excluded on the sole basis of US examination. Anatomical variations in the hepatic artery are rather common (19), but the most common variants concern the origin or course of its branches (20), past the area where blood flow is measured by Doppler. Variants with origin in the coeliac axis are easily identified by ultrasound, and we excluded any case with proven or suspected variation of hepatic artery origin. Only small supernumerary hepatic arteries originating from a vessel other than the coeliac axis might have passed undiagnosed. They would lead to underestimation of THF to an unpredictable extent, which does not fit with the data obtained in controls.

By measuring the portal flow past the origin of the left gastric vein, and the arterial flow at the common trunk of the hepatic artery, we theoretically measured, quantitatively, all the blood flowing through the liver. In the same patients, FHF was measured by means of the hepatic clearance of D-sorbitol (6). This non-invasive method has previously been tested against indocyanine green clearance in controls and patients with cirrhosis (7,21), and proved useful for this purpose.

The strict correlation we observed in control subjects between FHF and THF validates the use of these non-invasive techniques for the evaluation of hepatic flow. The differences between values obtained by the two methods are not systematic, and are most likely due to technical imprecision. However, it should be noted that two studies reported that the hepatic clearance of sorbitol is larger than indocyanine green clearance, assumed to equal THF (6,7). In any case, improvements in echo-Doppler equipment could also contribute to levelling out the differences observed: in a few control cases differences were as large as $\pm 360$ ml/min.

In patients with cirrhosis, in agreement with previous studies, we found that the portal flow was very close to that of control subjects (2,22,23) and that the arterial flow was increased, as expected on the basis of the well-known arterialization of the cirrhotic liver (24). On the other hand, in the same patients the functional flow was significantly reduced. We suggest that the difference between THF and FHF represents the amount of blood that undergoes intrahepatic shunting or reduced hepatic extraction by the damaged liver cells in the functioning sinusoids (24,25).

This hypothesis is confirmed by the data obtained in the two patients with a patent umbilical vein. In these patients the portal flow was exceedingly high (2870 and 2130 ml/min) and the difference between THF and FHF was very high as well, and mostly due to the hepatofugal flow measured in the patent umbilical vein.

Intrahepatic portal-systemic functional shunting might well play a role in the reduction of liver function, in patients with cirrhosis. FHF was inversely related to the Child-Pugh score (8), a semi-quantitative measure of liver function (26), while the amount of intrahepatic functional shunting (THF−FHF) was linearly correlated with the score, especially after excluding the two patients with a patent umbilical vein, where extrahepatic portal-systemic shunting was erroneously computed as intrahepatic shunt. These results suggest that FHF decreases with the progression of liver disease when a large intrahepatic functional shunt develops, and the two parameters could help the staging of cirrhosis and may have prognostic value.

In conclusion, the simultaneous determination of FHF and THF by means of non-invasive techniques, sorbitol clearance and Doppler flowmetry, give a comprehensive picture of the hemodynamic and functional changes which occur in the course of liver diseases. Such studies might be relevant both for pathophysiological and/or clinical purposes.

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