Evaluation of Effective Portal Venous Flow in Chronic Liver Diseases Using Echo-Doppler Flowmetry Combined with Per Jejunal Portal Scintigraphy

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Portal circulation changes due to the progression of chronic liver disease and portal venous flow are also affected by pharmacotherapy. Thus, noninvasive measurement of effective portal venous flow (EPVF) is highly desirable. We evaluated EPVF under steady-state conditions using echo-Doppler flowmetry combined with per jejunal portal scintigraphy in 32 patients with chronic liver disease. After intraduodenal administration of 37 MBq (1 mCi) of ^{123}I-iodoamphetamine, scintigraphy of the pulmonary and hepatic regions was performed and a portosystemic shunt index (SI) calculated. EPVF was calculated as follows: EPVF = PVFx (1 − SI/100). EPVF in chronic hepatitis, compensated cirrhosis and decompensated cirrhosis was 12.0 ± 1.8 ml/min/kg, 10.3 ± 1.6 ml/min/kg and 8.0 ± 2.5 ml/min/kg, respectively. There were significant differences in EPVF between all groups, although PVF was similar in each group. EPVF correlated with liver function tests and was a better indicator of liver function than PVF. Measurement of EPVF may provide useful information in the management of patients with chronic liver disease.

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Portal venous flow may be one of the most important determinants of liver function because it accounts for most of the hepatic blood flow and carries nutrients and hormones from the splanchnic organs to the liver. Echo-Doppler flowmetry can provide information on portal hemodynamics under steady-state conditions (*1–3*). However, few studies have investigated the relationship between portal venous flow and liver function (*4,5*), and it remains unclear whether portal venous flow is lower in patients with liver cirrhosis than in those with chronic hepatitis (*4–6*). Since portal venous flow measured by echo-Doppler flowmetry is thought to include shunt flow which does not contribute to liver function, it appears more reasonable to evaluate the relationship between liver function and effective portal venous flow (EPVF). EPVF can be obtained by subtracting intrahepatic and extrahepatic portosystemic shunt flow from portal venous flow. We previously reported a scintigraphic method for assessing portosystemic shunt flow indices in patients with chronic liver disease (*7,8*). This study was designed to evaluate EPVF and to clarify whether or not this index was closely related to liver function.

Although there have been many studies on portal hemodynamics utilizing percutaneous transhepatic portography (*9–13*), the examination is invasive and is dangerous for patients with impaired hemostatic function or ascites. In contrast, echo-Doppler flowmetry combined with scintigraphy makes it possible to noninvasively evaluate EPVF under steady-state conditions. This method has the advantage of allowing multiple examinations to be performed for the monitoring of patients with chronic liver disease.

MATERIALS AND METHODS

Patients

Thirty-two patients with chronic liver disease were studied: 10 with chronic hepatitis (7 males and 3 females aged 42 ± 11 yr and weighing 66.3 ± 11.2 kg), 17 with compensated liver cirrhosis (14 males and 3 females aged 60 ± 7 yr and weighing 60.9 ± 8.6 kg) and 5 with decompensated liver cirrhosis (4 males and 1 female aged 62 ± 8 yr and weighing 64.4 ± 13.2 kg). The diagnosis was based on liver biopsy and/or laparoscopic, angiographic, laboratory and clinical findings. Decompensated liver cirrhosis was defined by the presence of jaundice, ascites and/or encephalopathy. The patients' laboratory data are listed in Table 1. Informed consent was obtained from each patient.

Measurement

After an overnight fast and resting for 15–20 min in the supine position, echo-Doppler flowmetry was performed and was immediately followed by portal scintigraphy.

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TABLE 1
Laboratory Data Profile of Patients

	Chronic hepatitis (n = 10)	Compensated cirrhosis (n = 17)	Decompensated cirrhosis (n = 5)
Serum albumin(g/dl)	4.1 ± 0.3*	3.6 ± 0.3*	2.7 ± 0.3*
Serum cholinesterase(U/liter)	3973 ± 798*	2164 ± 650*	1038 ± 164*
Prothrombin time(%)	89 ± 9*	77 ± 9*	58 ± 6*
Alanine aminotransferase(U/liter)	98 ± 53	83 ± 42	59 ± 42
Serum bilirubin(mg/dl)	0.7 ± 0.2	0.9 ± 0.3†	2.0 ± 0.8†
$ICGR_{15}$(%)	13 ± 8*	31 ± 14*†	48 ± 15†
ICGK	0.160 ± 0.026*	0.097 ± 0.042*	0.058 ± 0.021

*$p < 0.01$.
†$p < 0.05$.
$ICGR_{15}$ = indocyanine green 15-min retention rate and ICGK = indocyanine green plasma disappearance rate.

Echo-Doppler Flowmetry

By using an echo-Doppler flowmeter (EUB-515; Hitachi Medico, Tokyo, Japan) comprised of a 3.5-MHz, real-time, two-dimensional, ultrasonic scanner with a 3.5-MHz pulsed Doppler flowmeter, the portal trunk was scanned longitudinally and venous flow was measured at the middle of the portal trunk. After a sampling marker was set in the vessel lumen, care was taken to maintain the angle formed by the ultrasonic beam and the direction of venous flow at less than 60° (Fig. 1). The measurement was repeated until clear and reproducible spectrum patterns were obtained. Measurements were carried out with the patients holding their breath for approximately 3 sec after light expiration.

For each subject, the caliber of the portal vein and the maximum velocity of portal venous flow (in cm/sec) were determined. Portal venous flow then was calculated using the following equation:

$$\text{Portal venous flow} = \text{cross-sectional area} \times 0.57 \times \text{maximum velocity} \times 60 \text{ (ml/min)},$$

where the cross-sectional area of the portal vein (in cm^2) was calculated from the inner diameter by assuming circular geometry and 0.57 as the coefficient obtained by Moriyasu et al. in an experiment using bovine blood and a silicon tube (*14*). Portal venous flow was normalized by body weight to give results in ml/min/kg.

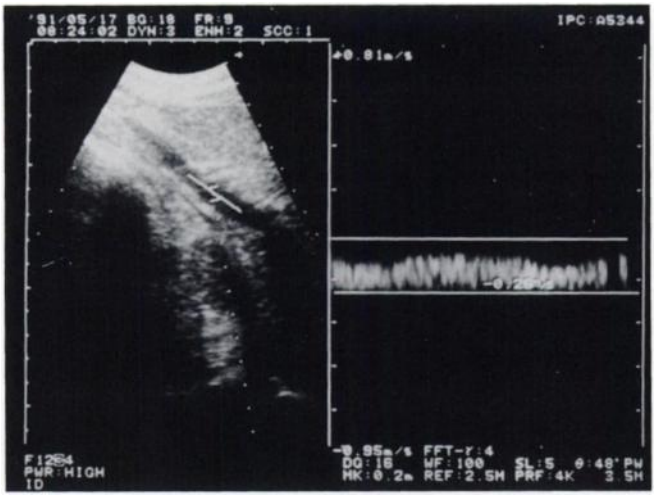

FIGURE 1. Portal venous flow measurement using an echo-Doppler flowmeter. The portal trunk was scanned longitudinally and the maximum velocity was measured at the middle of the portal trunk.

Portal Scintigraphy

A tube was introduced orally into the duodenum after local anesthesia of the pharynx, and 37 MBq (1 mCi) of ^{123}I-iodoamphetamine (IMP; Nihon Medi-Physics Corp, Takarazuka, Japan) was administered intraduodenally. The patient was kept supine for 60 min to allow good absorption by the intestine, and a 10-min image of the liver and lungs was obtained using a large field of view gamma camera (150DT; Hitachi Medico, Tokyo, Japan) with a low-energy, high-resolution collimator. Data were collected on a 256 × 256 matrix and stored in a computer (HARP II; Hitachi Medico, Tokyo, Japan). In six patients, five sequential 10-min exposures from 40 to 90 min were obtained after ^{123}I-IMP administration. Regions of interest (ROIs) were set over the liver and lungs (Fig. 2). The portosystemic shunt index (SI) was estimated using the following formula (*7*):

$$SI = (\text{Lung counts}/[\text{Liver counts} + \text{Lung counts}]) \times 100\%,$$

where the counts were corrected by subtracting the background counts along the outer border of the lower left lung.

Reproducibility was assessed by placement of another ROI and subsequent calculations. The first calculation (X) and the second calculation made on another day (Y) exhibited a significant correlation ($Y = 0.932X + 1.25$; $r = 0.990$; $n = 32$; $p < 0.0001$).

Effective Portal Venous Flow

EPVF was determined by subtracting portosystemic shunt flow from portal venous flow calculated by the formula:

$$EPVF = \text{Portal venous flow} \times (1 - SI/100) \text{ (ml/min/kg)}.$$

Statistics

Data were expressed as mean ± standard deviation. Comparisons were made using the unpaired Student's t-test, and correlations between groups were examined using linear regression analysis. Significant differences were considered to be present at $p < 0.05$.

RESULTS

Portal Scintigraphy

The calculated SI remained constant in all six patients undergoing sequential examination from 40 to 90 min after

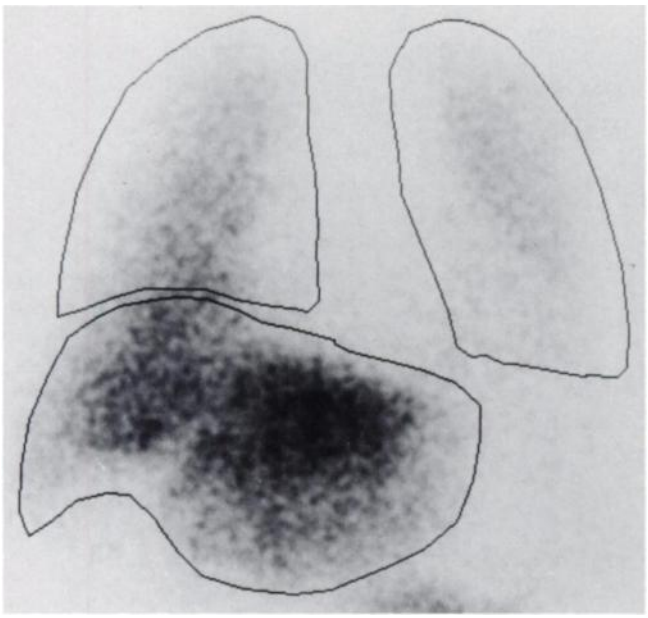

FIGURE 2. Selection of ROIs over the liver and lungs.

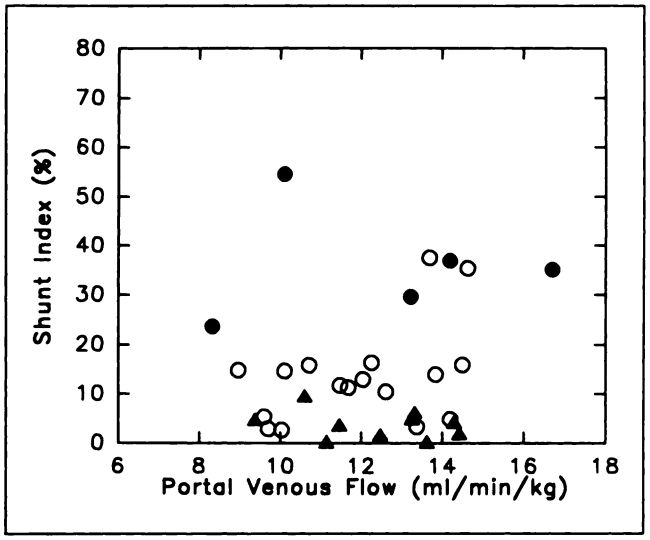

FIGURE 4. Distribution of SI and portal venous flow values. (▲)chronic hepatitis; (○)compensated cirrhosis; (●)decompensated cirrhosis. There was a tendency for patients with high portal venous flow to also have a high SI.

^{123}I-IMP administration (Fig. 3). The standard deviation of the SI in each of these patients was less than 3%. Thus, the SI values in this study were determined from data obtained between 60 and 70 min.

The SI was 3.5% ± 2.9% in chronic hepatitis, 13.5% ± 9.9% in compensated cirrhosis and 35.9% ± 11.6% in decompensated cirrhosis. There were significant differences in SI between all patient groups ($p < 0.01$).

Echo-Doppler Flowmetry

Portal venous flow was 12.4 ± 1.7 ml/min/kg in chronic hepatitis, 12.0 ± 1.9 ml/min/kg in compensated cirrhosis and 12.5 ± 3.3 ml/min/kg in decompensated cirrhosis. There was no significant difference between any of the groups.

Distribution of SI and Portal Venous Flow Values

The distribution of SI and portal venous flow values is shown in Figure 4. There was a tendency for patients with a high portal venous flow to also have a high SI. Some of these patients, however, had decompensated liver cirrhosis.

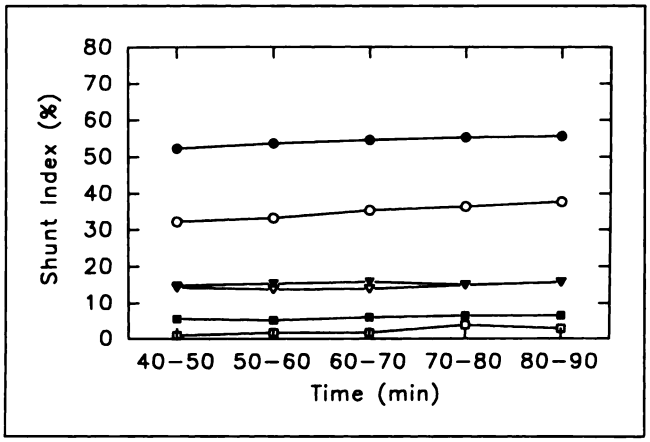

FIGURE 3. Changes in SI from 40 to 90 min in six patients. The standard deviation of the SI in each patient was less than 3%.

Effective Portal Venous Flow

EPVF had a significant correlation with indocyanine green plasma disappearance rates (ICGK), serum albumin levels and prothrombin time (PT), but portal venous flow did not correlate with any of these parameters (Fig. 5).

EPVF in chronic hepatitis, compensated cirrhosis and decompensated cirrhosis was 12.0 ± 1.8 ml/min/kg, 10.3 ± 1.6 ml/min/kg and 8.0 ± 2.5 ml/min/kg, respectively. There were significant differences in EPVF between all groups (Table 2, Fig. 6).

DISCUSSION

The current study demonstrates that noninvasive echo-Doppler flowmetry combined with per jejunal portal scintigraphy can be used to assess portal shunt flow and eliminate it from portal venous flow. It also demonstrates that EPVF obtained by this method is closely related to liver function.

The use of radioisotopic tracers for imaging is noninvasive and easy to perform (*15–17*). Iodine-123-IMP, a tracer widely used for brain imaging, has a high first-pass extraction by a number of organs and has slow washout, which are particularly favorable imaging properties (*18–20*). Yen et al. reported a kinetic study and validation of a method for quantifying portosystemic shunts using ^{123}I-IMP (*21*). Kashiwagi et al. investigated patients with chronic liver disease and determined a portosystemic SI using portal scintigraphy with per rectally or intraduodenally administered ^{123}I-IMP (*7,8*). Thallium-201 has also been reported to be useful for the evaluation of portosystemic shunting on the basis of the heart-to-liver uptake ratio (*22–24*). How-

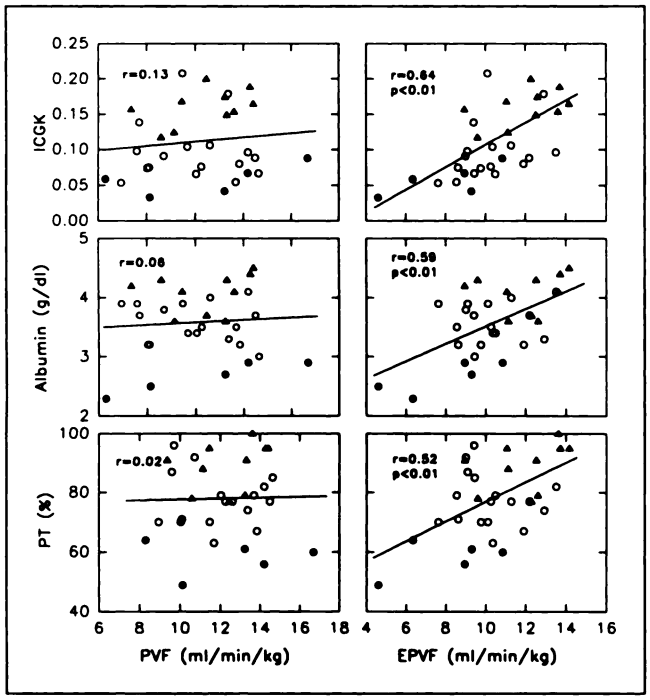

FIGURE 5. Correlations between serum liver function tests and PVF or EPVF. (▲)chronic hepatitis; (○)compensated cirrhosis; (●)decompensated cirrhosis. ICGK = indocyanine green plasma disappearance rate and PT = prothrombin time.

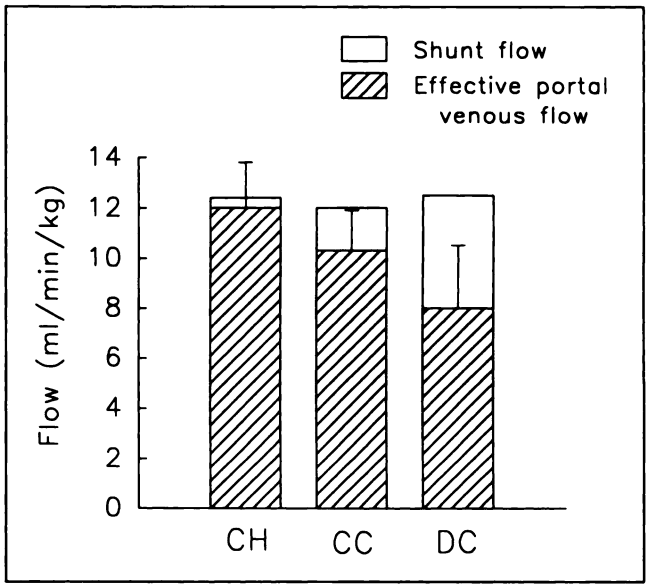

FIGURE 6. Portal venous flow in chronic hepatitis (CH), compensated cirrhosis (CC) and decompensated cirrhosis (DC). Portal venous flow equals EPVF plus shunt flow. There were significant differences in EPVF between the CH and CC groups ($p < 0.02$) and between the CC and DC groups ($p < 0.05$).

ever, ^{201}Tl is likely to underestimate the actual shunt because only a small fraction of thallium passing through the liver is taken up by the heart.

The portosystemic SI obtained by portal scintigraphy includes both intrahepatic and extrahepatic shunt flow. The SI obtained by per rectal administration has a different meaning from that obtained by intraduodenal administration because of the vascular anatomy of the portal venous system. The former procedure is affected by extrahepatic shunt flow in the coronary veins as well as gastrorenal and/or splenorenal shunts. Furthermore, the lower part of the inferior mesenteric venous system communicates with the hemorrhoidal plexus, which provides portosystemic collaterals in patients with portal hypertension. The latter procedure primarily indicates intrahepatic shunt flow because the superior mesenteric vein does not usually interact with the systemic circulation (*9–12*). We therefore used intraduodenal administration to estimate EPVF in this study.

There are some technical limitations to the accuracy of echo-Doppler flowmetry (*25–28*). However, we took care to maintain the angle formed by the ultrasonic beam and venous flow at under 60° and the diameter of the portal trunk was always much larger than 4 mm, which is the reported resolution limit (*29*). Acceptable levels of intraobserver and interobserver variability of less than 8%–10% have been reported for this method (*30–32*), although variability exceeded 10% in some reports (*26,33*). Repeated measurements, however, can substantially reduce observer variability (*34*).

Intrahepatic shunt flow may be overestimated and EPVF may be underestimated when collaterals arise from the portal trunk or superior mesenteric vein. However, few authors have reported collaterals arising from the superior mesenteric vein (*9–12*). If a coronary vein arising from the portal trunk is detected by ultrasound, the patient should not be assessed with our methods.

TABLE 2
Portal Venous Flow and EPVF

	Portal venous flow (ml/min/kg)	EPVF (ml/min/kg)
Chronic hepatitis (n = 10)	12.4 ± 1.7	12.0 ± 1.8*†
Liver cirrhosis (n = 22)	12.1 ± 2.2	9.8 ± 2.0*
Compensated (n = 17)	12.0 ± 1.9	10.3 ± 1.6†‡
Decompensated (n = 5)	12.5 ± 3.3	8.0 ± 2.5‡

*$p < 0.01$; †$p < 0.02$; ‡$p < 0.05$.

In the relationship between portal venous flow and liver function, there is controversy about the data obtained by echo-Doppler flowmetry. It has been reported that portal venous flow was similar for cirrhosis patients and healthy subjects (*6*), but another paper reported that portal venous flow was significantly higher in cirrhosis patients (*5*). In this study, liver function was found to be related to EPVF but not to uncorrected portal venous flow. Portal venous flow did not differ between patients with chronic hepatitis, compensated cirrhosis and decompensated cirrhosis, whereas EPVF decreased as liver function worsened in all three groups (Fig. 6).

Kawasaki et al. suggested that portosystemic shunting might reduce EPVF in patients with liver disease even though they had large portal venous flow (*4*). Our study indicated that some cirrhosis patients with large portal venous flow had low EPVF due to extensive shunting and correspondingly poor liver function (Fig. 4). Patients with high portal venous flow may have high shunt flow due to the following two mechanisms: (1) increased portal venous flow due to a hyperdynamic state associated with cirrhosis may cause portal hypertension and intrahepatic shunting or (2) intrahepatic shunting due to posthepatitic regeneration may reduce EPVF, with secondary compensation or reduced hepatic vascular resistance subsequently increasing portal venous flow.

Treatments such as surgical portosystemic shunting or pharmacotherapy (*31,32,35*) are often used to prevent hemorrhage from esophageal varices in patients with portal hypertension. Such treatments, however, may reduce portal venous flow, and a reduction in EPVF may lead to hepatic encephalopathy or liver failure (*36,37*). Thus, there is a need to determine EPVF before treatment and to provide subsequent follow-up. Further studies will elucidate the clinical usefulness and significance of this method in the management of patients with chronic liver disease.

In conclusion, EPVF under steady-state conditions was evaluated by noninvasive echo-Doppler flowmetry combined with per jejunal portal scintigraphy. EPVF appeared to be closely related to liver function in patients with chronic liver disease and was a better indicator of liver function than portal venous flow.

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