

# Functional hepatic flow in patients with liver cirrhosis

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## Abstract

**AIM:** To evaluate hepatic reserve function by investigating the change of functional hepatic flow and total hepatic flow in cirrhotic patients with portal hypertension.

**METHODS:** HPLC method was employed for the determination of concentration of D-sorbitol in human plasma and urine. The functional hepatic flow (FHF) and total hepatic flow (THF) were determined by means of modified hepatic clearance of D-sorbitol combined with duplex doppler color sonography in 20 patients with cirrhosis and 10 healthy volunteers.

**RESULTS:** FHF, evaluated by means of the D-sorbitol clearance, was significantly reduced in patients with cirrhosis in comparison to controls ( $764.74 \pm 167.91$  vs  $1\ 195.04 \pm 242.97$  mL/min,  $P < 0.01$ ). While THF was significantly increased in patients with cirrhosis in comparison to controls ( $1\ 605.23 \pm 279.99$  vs  $1\ 256.12 \pm 198.34$  mL/min,  $P < 0.01$ ). Portal blood flow and hepatic artery flow all were increased in cirrhosis compared to controls ( $P < 0.05$  and  $P < 0.01$ ). D-sorbitol total clearance was significantly reduced in cirrhosis compared to control ( $P < 0.01$ ), while D-sorbitol renal clearance was significantly increased in cirrhosis ( $P < 0.05$ ). In controls FHF was similar to THF ( $1\ 195.05 \pm 242.97$  vs  $1\ 256.12 \pm 198.34$  mL/min,  $P = 0.636$ ), while FHF was significantly reduced compared with THF in cirrhosis ( $764.74 \pm 167.91$  vs  $1\ 605.23 \pm 279.99$  mL/min,  $P < 0.01$ ).

**CONCLUSION:** Our method that combined modified hepatic clearance of D-sorbitol with duplex doppler color sonography is effective in the measurement of FHF and THF. FHF can be used to estimate hepatic reserve function.

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## INTRODUCTION

The management of portal hypertension in patients with liver cirrhosis is still a therapeutic challenge<sup>[1]</sup>. Liver failure and variceal bleeding are the chiefly causes that lead to death in cirrhosis. Now surgical devascularization and shunting play an important role in treatment of portal hypertension. Though operation is useful in controlling variceal bleeding, the mortality of operation is very high. Some cirrhotic patients

can not bear the strike of operation and anaesthesia because of inadequate hepatic reserve function. So the evaluation of hepatic reserve function preoperatively is very important, in addition to proper perioperative management. At present the evaluation of clinical severity of cirrhosis is mostly based on the Child-Pugh score. However, such an approach can not directly provide reliable quantitative evaluations of the integrity and functional reserve of the hepatic parenchyma because the parameters are not very specific and test sensitivity is sometimes too low to detect mild liver alteration<sup>[2]</sup>. Recently several studies<sup>[3-10]</sup> have considered that hepatic clearance of D-sorbitol was a valid procedure in determination of FHF, by which hepatic reserve function could be estimated. The aim of this study was to measure THF and FHF of control subjects and patients with cirrhosis by means of duplex doppler color sonography combined with modified hepatic clearance of D-sorbitol and then to evaluate the hepatic reserve function.

## MATERIALS AND METHODS

### Patients

This study was carried out on 20 patients with cirrhosis and portal hypertension. The diagnosis of cirrhosis was established by liver biopsy intraoperatively. Fourteen patients with cirrhosis were males and six were females. They ranged in age from 35 to 73 years. The etiology of the disease was virus-related in 19 cases and drug-induced in the remaining one. The exclusion criteria were: patients with a variceal bleeding in the previous four weeks; those on portal-pressure-lowering drugs; those with portal and splenic vein thrombosis; those with severe ascites.

Ten subjects that 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 area. All patients gave their informed consent before participation in this study, which was performed according to the Helsinki Declaration.

### Measurement of THF

Duplex doppler measurements of the portal vein and common hepatic artery were obtained using a real-time electronic sector scanner and a pulsed doppler unit.

All the patients and controls were kept fasting overnight prior to the procedure. They were examined in the supine position and were asked to hold their breath during the doppler recording. The portal vein was scanned longitudinally, and the sample volume was positioned in the middle of the portal trunk. The hepatic artery measurements were taken where a straight stretch ran parallel to the portal vein, some centimeters away from the coeliac axis. Care was taken to maintain the angle at below 55°. Portal vein and hepatic artery flow were determined by multiplying the mean blood velocity (V mean) by the sectional area ( $\pi r^2$ ). Total hepatic flow was calculated as the sum of portal flow and hepatic artery flow.

### Measurement of FHF

All tests were carried out at rest after an overnight fast. The sterile pyrogen-free 5% water solution of D-sorbitol (Fluka,

US) was intravenously infused at a constant rate of 50 mg/min. The steady-state regimen would be achieved after 2-h of continuous infusion<sup>[11]</sup>. Three blood samples were taken from peripheral vein at about 15-min intervals between 135 and 165 min after the start of the infusion. Urine samples were spontaneously collected for a 1-h period between 120 and 180 min during the infusion. FHF was determined on the basis of the hepatic clearance of SOR, as previously described by Molino<sup>[8]</sup>.

### Analyses

Blood and urine samples were centrifuged at 2 500 r/min for 15 min and the supernatants were stored at -40 °C until analysis. All samples were thawed before concentration measurement, then deproteinized by means of super-filter.

HPLC method was employed for the determination of concentration of D-sorbitol in human plasma and urine. The HPLC system (Waters) consisted of a pump, an injector and a fluorescence-detection (4210). The extracts of samples were chromatographed on a CORGEL-87P column that was kept at 85 °C and monitored by fluorescence-detection. The mobile phase was H<sub>2</sub>O at a flow-rate of 1.0 mL/min. All data were treated according to the formula described by Molino<sup>[8]</sup>.

### Statistical analysis

All the data are expressed as mean±SD. The statistical analyses were performed by means of two-sample *t*-test and paired *t*-test.

## RESULTS

The results are shown in the Table 1. All the tests were performed on 20 patients with cirrhosis and 10 healthy controls and all subjects tolerated the procedure without complications or side effects. As expected, FHF, evaluated by means of the D-sorbitol clearance, was significantly reduced in patients with cirrhosis in comparison to controls (764.74±167.91 vs 1 195.05±242.97 mL/min, *P*<0.01). While THF was significantly increased in patients with cirrhosis in comparison to controls (1 605.23±279.99 vs 1 256.12±198.34 mL/min, *P*<0.01).

Portal blood flow and hepatic artery flow were increased in cirrhosis compared to controls (*P*<0.05 and *P*<0.01). D-sorbitol total clearance was significantly reduced in cirrhosis compared to control, while D-sorbitol renal clearance was significantly increased in cirrhosis (*P*<0.01).

In controls FHF and THF were similar (1 195.05±242.97 vs 1 256.12±198.34 mL/min, *P*=0.636), while FHF was significantly reduced compared to THF in cirrhosis (764.74±167.91 vs 1 605.23±279.99 mL/min, *P*<0.01).

## DISCUSSION

Liver cirrhosis is the final pathologic and clinical expression of a wide variety of chronic liver diseases. The commonest causes of cirrhosis are chronic hepatitis B or C virus infection (nearly 90% of the total cases of cirrhosis in China). Pathophysiologically, the clinical manifestation of liver cirrhosis arises from the occurrence of two major events: hepatocellular insufficiency and portal hypertension<sup>[12]</sup>. In cirrhosis, portal hypertension develops as a result of an increased sinusoidal or post-sinusoidal portal resistance to blood flow, due to the loss of normal hepatic architecture and collagenization of the space of Disse<sup>[13,14]</sup>. The major pathophysiologic consequences of portal hypertension include portal-systemic collaterals formation, ascites and splenomegaly. The gastric and esophageal varices constitute the major cause of life-threatening digestive tract bleeding in cirrhosis. Now surgical devascularization and shunting play an important role in management of the complications of portal hypertension. Though operation is effective in controlling bleeding, the mortality of operation is still higher as some patients can not bear the strike of operation and anaesthesia due to inadequate hepatic reserve function. Recently some study discovered that the patients whose liver volume was decreased by 40% and the hepatic clearance of D-sorbitol was below 600 mL/min would have a higher incidence of postoperative complication<sup>[15]</sup>. Therefore it is of much importance to evaluate the hepatic reserve function preoperatively for the selection of operation approaches and the timing of operation.

FHF may be defined as the blood perfusing the liver that makes contact with functioning hepatocytes. The most widely used procedures to assess FHF are based on the clearance technique. But the test compound must not be eliminated by any organ other than the liver, must not re-enter the circulation once it has been eliminated, and has relatively high hepatic intrinsic clearance. To date, no compound has fulfilled these requirements completely. D-sorbitol, a naturally occurring polyol with prevailing hepatic metabolism, is almost completely extracted by the liver during the first-pass, and extrahepatic elimination is negligible<sup>[16]</sup>. Reproducible first-order kinetics and flow-dependent principle were demonstrated for D-sorbitol in previous studies<sup>[2,10,11,17]</sup>. D-sorbitol had an exceptionally high extraction ratio in the normal liver (approaching 100%)<sup>[16,17]</sup>, even in the presence of a severely impaired liver function, so we might consider that hepatic clearance of D-sorbitol very closely approximates total hepatic flow. While in cirrhosis, the hepatic clearance of D-sorbitol is less than total hepatic flow due to intrahepatic shunting. The

**Table 1** Results of Duplex doppler and D-sorbitol clearance in 20 patients with liver cirrhosis and 10 healthy controls

	Controls	Cirrhosis	<i>P</i>
Portal blood flow (mL/min)	960.35±220.86	1 181.10±279.79	<0.05
Hepatic artery flow (mL/min)	295.77±82.59	424.13±116.89	<0.01
Total hepatic flow (THF) (mL/min)	1 256.12±198.34	1 605.23±279.99	<0.01
THF per kg b.w. (mL/min)	20.14±3.51	25.12±4.40	<0.01
D-sorbitol concentration in blood (mg/dL)	4.15±0.81	6.05±1.22	<0.01
D-sorbitol total clearance (mL/min)	1 246.72±242.59	857.22±167.61	<0.01
D-sorbitol urinary elimination rate (mg/min)	2.16±1.0	5.58±2.76	<0.01
D-sorbitol renal clearance (mL/min)	51.67±19.96	92.48±48.66	<0.05
Functional hepatic flow(FHF) (mL/min)	1 195.05±242.97	764.74±167.91	<0.01
FHF per kg b.w. (mL/min)	19.18±4.28	12.07±2.40	<0.01

The data are expressed as mean±SD.

difference between THF and FHF can be assumed to be a parameter reflecting intrahepatic shunting.

Generally THF was measured by means of the hepatic extraction of D-sorbitol and indocyanine green, according to the Fick's principle<sup>[4,10]</sup>. But the procedure, which needs hepatic vein catheterization is invasive and difficult to popularize. In addition, direct measurements of total hepatic flow through the hepatic artery and the portal vein have been achieved with electromagnetic flow probes or laser doppler flow meter<sup>[18]</sup>. But the technique is applicable only during surgical procedures, which severely limits its usefulness. Recently the technique of duplex doppler color sonography has been gaining increasing popularity in the measurement of hepatic blood flow and found to be a safe, reproducible, noninvasive and fairly accurate method<sup>[19-22]</sup>.

There are still large variabilities in determination of FHF and THF by means of hepatic clearance of D-sorbitol and duplex doppler color sonography because of limitation of techniques and operations. To the former, the measurement of concentration of D-sorbitol is difficult. A small error of D-sorbitol concentration will lead to a large variability of final outcome. The concentration of D-sorbitol in plasma and urine used to be determined by an enzymatic-spectrophotometric method. It needs an enzymatic oxidation and deoxidization reaction since there is no absorption of ultraviolet for D-sorbitol. The concentration of D-sorbitol is determined indirectly following the measurement of fluorescence intensity of NADH1 that produced in reaction. While the attenuation of fluorescence and the incompleteness of reaction will result in certainty errors. To minimize these errors, we first established the method that measured the concentration of D-sorbitol by the use of HPLC and made the standard concentration curve. The data obtained in our study are in agreement with previous observations<sup>[2,3,9]</sup>. Moreover, there is smaller standard error than that of other studies due to absence of extremely big or small data. In the latter, the errors stem from uncertainty in the measurement of blood velocity, vessel caliber and the possible non-circular shape of the cross-sectional area of the vessel. To minimize these errors, the examination was always performed by the same investigator, who had more than 5 years' experience in doppler examination of deep vessels and was unaware of the clinical diagnosis of the subject, and following strict guidelines during the operation.

The results of our study showed that THF was similar to FHF in controls ( $1\,256.12 \pm 198.34$  vs  $1\,195.05 \pm 242.97$  mL/min,  $P=0.636$ ), which support the measurement of FHF and THF by non-invasive techniques. However, since D-sorbitol hepatic extraction was never completed, the FHF slightly underestimated THF in controls. In cirrhosis, the FHF was significantly decreased, while doppler-assessed THF was increased, indicating that a part of the portal flow was diverted through intrahepatic shunts or a substantial impairment of the functional integrity of hepatocytes<sup>[23]</sup>. In this case simultaneous assessment of these two non-invasive parameters could be useful to quantify functional shunting in cirrhosis. As expected, portal vein and hepatic artery blood flow were increased in cirrhosis in comparison to controls respectively, suggesting a hyperkinetic systemic circulation with a high cardiac output and decreased total peripheral vascular resistance. Though the THF was preserved or increased, the FHF was still reduced. This is thought to be due to reduced FHF and a compensatory increase in THF to maintain hepatic perfusion. In addition, we measured the FHF and THF in six patients with liver cirrhosis before and after transjugular intrahepatic portosystemic shunt (TIPS). We discovered that the THF measured one week after TIPS was more than that of before TIPS, while FHF was reduced significantly in all subjects. It may be considered that the reduction of portal vein pressure and increase in

portosystemic shunting caused by TIPS are associated with the reduction of hepatic perfusion, which can partly explain the high incidence of hepatic encephalopathy in patients with liver cirrhosis<sup>[24-26]</sup>.

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