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• CLINICAL RESEARCH •

Evaluation of liver functional reserve by combining D-sorbitol clearance rate and CT measured liver volume

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Abstract

AIM: Our research attempted to evaluate the overall functional reserve of cirrhotic liver by combination of hepatic functional blood flow, liver volume, and Child-Pugh's classification, and to discuss its value of clinical application.

METHODS: Ninety two patients with portal hypertension due to hepatic cirrhosis were investigated. All had a history of haematemesis and hematochezia, esophageal and gastric fundus varices, splenomegaly and hypersplenia. A 2-year follow-up was routinely performed and no one was lost. Twenty two healthy volunteers were used as control group. Blood and urine samples were collected 4 times before and after intravenous D-sorbitol infusion. The hepatic clearance (CL_H) of D-sorbitol was then calculated according to enzymatic spectrophotometric method while the total blood flow (Q_{TOTAL}) and intrahepatic shunt (R_{INS}) were detected by multicolor Doppler ultrasound, and the liver volume was measured by spiral CT. Data were estimated by *t*-test, variance calculation and chi-squared test. The relationships between all these parameters and different groups were investigated according to Child-Pugh classification and postoperative complications respectively.

RESULTS: Steady blood concentration was achieved 120 mins after D-sorbitol intravenous infusion, which was (0.358±0.064) mmol· L^{-1} in cirrhotic group and (0.189±0.05) mmol· L^{-1} in control group (P<0.01). CL_H=(812.7±112.4) ml· min^{-1}, Q_{TOTAL}=(1280.6±131.4) ml· min^{-1}, and R_{INS}=(36.54±10.65) % in cirrhotic group and CL_H=(1248.3±210.5) ml· min^{-1}, Q_{TOTAL}= (1362.4±126.9) ml· min^{-1}, and R_{INS}=(8.37±3.32) % in control group (P<0.01). The liver volume of cirrhotic group was 1057±249 cm^3, 851±148 cm^3 and 663±77 cm^3 in Child A, B and C group respectively with significant difference (P<0.001). The average volume of cirrhotic liver in Child B, C group was significantly reduced in comparison with that in control group (P<0.001). The patient, whose liver volume decreased by 40 % with the CL_H below 600 ml· min^{-1}, would have a higher incidence of postoperative complications. There was no strict correspondent relationship between CL_H, liver volume and Child-Pugh's classification.

CONCLUSION: The hepatic clearance of D-sorbitol, CT measured liver volume can be reliably used for the evaluation of hepatic functional blood flow and liver metabolic volume. Combined with the Child-Pugh's classification, it could be very useful for further understanding the liver functional reserve, therefore help determine reasonable therapeutic plan, choose surgical procedures and operating time.

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INTRODUCTION

Accurate evaluation of the hepatic functional reserve is very important in the development of hepatobiliary surgery. Hepatic functional reserve means the whole functions of all hepatic parenchyma cells, which depend on the interaction between relatively healthy hepatic cells and blood perfusion. Based on Child-Pugh' s classification, we have established a new method to evaluate the liver functional reserve by D-sorbitol clearance rate indicating hepatic functional blood flow and CT measured liver volume indicating normal hepatic metabolic volume.

MATERIALS AND METHODS

Materials

Ninety two patients with portal hypertension due to hepatic cirrhosis, were selected in our hospital from March 1999 to January 2001, including 57 males and 35 females aged between 20-66 years, with a mean age 43.5±11.8 years. All of them had a history of haematemesis and hematochezia, and moderate esophageal varices were found in 41 patients and severe ones in 51 patients by gastroscopy. Porta-azygous devascularization was applied to all patients and the pathological diagnosis was confirmed by biopsy during the surgical procedure. According to Child-Pugh' s classification, 36 cases were scored as A, 39 as B and 17 as C. A 2-year follow-up was routinely performed. The healthy control group consisted of 20 volunteers, 11 males and 9 females, who had no abnormality in CT scan and related history of liver disease.

The postoperative data of operative complications and hepatic functions were carefully recorded and a routine follow-up was given. There was no operative mortality, severe complications occurred in 31 cases because of liver function deterioration after the operation, including 13 cases of long standing jaundice, 7 hepatic coma, 13 severe ascites, and 6 recurring hemorrhage of upper GI tract.

Methods

Intravenous infusion of D-sorbitol and collection of blood and urine samples Controlled by the peristalsis pump, 5 % D-sorbitol solution was continuously infused intravenously for 3 hours at a rate of 1 ml· min^{-1} (a dose of 50 mg· min^{-1}). The samples of blood (3 ml), urine and the volumes at the same time were collected and recorded once before infusion and 3 times at 120,150,180 min after infusion.

Determination of D-sorbitol concentration and calculation The enzymatic spectrophotometric method was used to determine the D-sorbitol concentration in blood and urine[1, 2]. The total D-sorbitol clearance rate (CL_{TOTAL}), renal D-sorbitol clearance rate (CL_{REN}) and liver D-sorbitol clearance rate (CL_H) were calculated according to the formula reported[3,4] as $CL_{TOTAL}=R\div Css$ and $CL_{REN}=U\div Css$. (R: D-sorbitol infusion rate; Css: homeostatic plasma concentration; U: average urinary excretion rate, ($C_{LH}=CL_{TOTAL}- C_{LREN}$).

Hepatic total blood flow (Q_{TOTAL}) and intrahepatic shunt rate (R_{INS}) and liver extraction rate (E) assay and calculation The angle between blood flow and Doppler ultrasound wave direction was controlled below 60 degrees, the mean blood flow rates of three main liver veins (left, middle, right hepatic vein) were carefully detected by ultrasonic equipment. Then, the accurate blood flow of each vein was calculated according to the formula as $Q=1/4\pi D^2\times 60\times V_{mean}$[5, 6], and their sum was the total blood flow (Q_{TOTAL}). The D-sorbitol hepatic clearance rate equaled to the liver functional blood flow (Q_{FUNC}), and $R_{INS}=(Q_{TOTAL}-Q_{FUNC})/Q_{TOTAL}$. According to Fick' s rule[7, 8], the hepatic extractive rate $E=CL_H/Q_{TOTAL}$.

Method for measuring liver volume change by CT Guided by the reported method[9], the cirrhotic liver volume was measured by CT (PQ6000), at the same time the expected "normal" liver volume of the patient was calculated according to the reported formula[10]. The volume change rate (R) was then calculated according to the formula : (CT measured LV-expected LV)/expected LV×100 %.

Statistical analysis

The relationship between liver functional blood flow, liver volume change rate, Child-Pugh' s classification, postoperative complication rate was investigated.Data were expressed as mean ±S. Statistical significance was estimated by *t*-test. The multiple means between various groups were estimated by variance calculation. The difference of percentage was estimated by chi-squared test.

RESULTS

Changes of D-sorbitol clearance index in two groups

Table 1 Indexes of D-sorbitol clearance (mean ±s)

Groups	n	Css (mmol·L^{-1})	R_{INS} (%)	$CL_H(Q_{FUNC})$ (ml·min^{-1})	E (%)	Q_{TOTAL} (ml·min^{-1})
Control	20	0.189±0.05	8.37±3.32	1248.3±210.5	91.6±6.5	1362.4±126.9
Cirrhotic	92	0.385±0.064^a	36.54±10.65	812.7±112.4^a	63.5±9.4^a	1280.6±131.4

$^a P<0.01$ in comparison between the two groups.

Table 1 shows that the D-sorbitol plasma concentration of each group could come to a stable level after continuous intravenous infusion for 120 minutes. The homeostatic plasma concentration of control group was (0.189±0.05) mmol· L^{-1}, and that of hepatic cirrhotic group was (0.358±0.064) mmol· L^{-1}. The difference between the two groups was significant ($P<0.01$). The total liver blood flow between the two groups had no significant difference. The D-sorbitol liver extraction rate and hepatic clearance rate decreased significantly while intrahepatic shunt flow increased significantly in the cirrhotic group. All reached statistical significance compared with that of the control group.

Relationship between Child-Pugh's classification and D-sorbitol liver clearance rate and liver volume change rate

Table 2 Relationship between Child-Pugh's classification and D-sorbitol liver clearance rate and liver volume change rate

Child-Pugh's classification	n	CL_H (ml·min^{-1})	Q_{INS} (%)	Mean cirrhotic liver volume (cm^3)
A	36	995.8±174.8	22.2±4.2	1057±249
B	39	783.4±120.6^a	38.8±7.3^a	851±148^a
C	17	548.6±32.8^b	57.8±6.6^b	663±77^b

$^b P<0.01$, $^a P<0.05$ in comparison between the two groups.

Table 2 shows that there was a clear correlation between each Child-Pugh's classification group and D-sorbitol liver clearance rate and liver volume,respectively. The higher the Child-Pugh' s classification degree, the lesser the liver functional blood flow, the more the intrahepatic shunt flow, and the smaller the mean liver volume. The difference had statistical significance between each group ($P<0.05$).

Table 3 Correlative relationship between hepatic D-sorbitol clearance rate and liver volume change rate and Child-Pugh's classification

Child-Pugh's classification	CL_H (mL·min^{-1})			Liver volume change rate		
	>800	600-800	<600	R≥-20 %	-40 %<R<-20 %	R ≤-40 %
A(case)	21	11	4	20	13	3
B(case)	8	24	7	9	26	4
C(case)	0	6	11	2	5	10

Table 3 shows in view of individual patient, there was not any complete correlation between the D-sorbitol liver clearance rate and liver volume change rate or liver function status in cirrhotic patients. Even in the same Child-Pugh' s classification group, the D-sorbitol clearance rate and liver volume change rate varied remarkably. It was found that a mild Child' s classified patient could have a low D-sorbitol clearance rate and a small liver volume, and *vice versa*.

Relationship between postoperative complications and D-sorbitol clearance rate and liver volume change rate

Table 4 shows that severe postoperative complications increased steadily as the D-sorbitol clearance rate and/or liver volume decreased. When the CL_H was below 600 /ml· min^{-1}, R below -40 %, the incidence of severe complications was higher than 70 % ($P<0.05$).

Table 4 Relationship between hepatic D-sorbitol clearance rate and liver volume change rate and postoperative complications

Postoperative complications	CL_H / mL·min^{-1}			Liver volume change rate		
	>800	600-800	<600	R≥-20 %	-40 %<R<-20 %	R ≤-40%
Case number	29	41	22	31	44	17
Complication cases	1	14	16	3	16	12
Rate (%)	3.4	34.2^a	72.7^b	9.7	36.4^a	70.6^b

$^b P<0.01$, $^a P<0.05$ in comparison between each groups.

Table 5 shows that 22 cases had a D-sorbitol clearance rate lower than 600/ml· min^{-1}. 8 of them had their liver volume change rate between -20 % and -40 %, 14 below -40 %, and the incidences of postoperative complications were 62.5 % (5/8), and 78.6 % (11/14), respectively.

Table 5 Correlation between hepatic D-sorbitol clearance rate and liver volume change rate and operation complications

CL_H (ml·min^{-1})	-40 %<R<-20 %			R≤ -40%		
	Number	Complication case	Complication rate	Number	Complication case	Complication rate
600-800	35	12	34.3(%)	3	1	33.3(%)
<600	8	5	62.5(%)	14	11	78.6(%)

DISCUSSION

It is essential in the surgical treatment of portal hypertension, to evaluate accurately the patient' s preoperative liver functional reserve and to make a reasonable peri-operative therapeutic plan in order to choose the best surgical procedures and to increase its efficacy. The Child-Pugh' s classification is still the most important method to determine the type and time of operation, and is widely accepted for the patients who are in stage I or II. But there are relatively high-risks for post-operative complications and mortality[11-13]. This is because the present classification cannot completely reflect the injured and whole hepatic function, besides the technical factors[14-16]. What condition would go worse with the operative burden is another factor that is difficult to tell. It is therefore necessary to find more objective criteria for the evaluation of hepatic functional reservation.

The liver inherent metabolic volume and blood flow determine its functions in most occasions, which also depend on the relative ratio and mutual influence of the two factors[17-20]. When cirrhosis and portal hypertension occur, necrosis of liver cells, hyperplasia of fibrous tissue, formation of pseudo lobules and abnormality of liver microcirculation will result in decrease of liver inherent metabolic volume, increase of anatomical and physiological intrahepatic shunt and change of their relevant ratio[21]. Therefore, measurement of liver inherent metabolic volume and functional blood flow can provide more information on the understanding of physiological changes and functional reserve of the cirrhotic liver, and help to make individualized and reasonable therapeutic decisions.

Liver functional blood flow is a part of total liver blood flow that enters the hepatic sinusoid involved in the metabolic process[1]. Currently it can only be measured by assay of its clearance rate. D-sorbitol is the first substance suitable for noninvasive evaluation of hepatic blood flow, and is widely used to observe the normal and pathologic perfusion of the liver outside China[22]. Molino, Susanne *et al*, reported that the normal liver had a very high D-sorbitol extraction rate of around 94 %, and CL_H could be used to represent the liver total blood flow (Q_{TOTAL}), and its variation could reflect the change of liver blood flow[8,23]. In our research, D-sorbitol clearance rate and color Doppler ultrasonography were used to study the liver blood flow. It was found that D-sorbitol plasma concentration of the healthy control group always came to homeostasis by continuously intravenous infusion after 120 minutes (0.189±0.05 mmol/l), CL_H was 1 248.3±210.5/ml.min^{-1}, Q_{TOTAL} was 1 362.4±126.9/ml·min^{-1} and the D-sorbitol extraction rate of the liver was 91.6±6.5 %. The D-sorbitol extraction rate decreased dramatically to 63.5±9.4 % in the cirrhotic group, which was statistically significant compared with that of control group (P<0.01). The CL_H, reflecting the liver functional blood flow[1,11,24], was 812.7±112.4/ml.min^{-1} significantly different from that of the control group (P<0.01). The R_{INS} was 8.37±3.32 % in control group and was 36.54±10.65 % in cirrhotic group (P<0.01). The intrahepatic shunt consisted of anatomical shunt and physiological shunt, and the latter had no help to hepatic function even passing through hepatic sinusoid[25]. Therefore, the combination of D-sorbitol clearance rate and color Doppler ultrasonography can show the liver functional blood flow and the conditions of intrahepatic shunt which are so meaningful for the evaluation of liver blood flow in the liver functional reserve before proper medication is given[26, 27]. Our conclusion is that D-sorbitol clearance rate can be widely used in clinical practice, which is safe, economical, practicable, and noninvasive.

The liver inherent metabolic volume and liver functional blood flow are complementary to each other, especially their matching. It is a mature and repeatable method to use CT in measuring liver volume[28-30]. Liver volume is considered as a liver function index as important as the Child-Pugh' s classification because it can partly represent the hepatic parenchyma cell volume[31-33]. Combining liver volume measured by CT scanning and an expected "normal" liver volume calculated according to a standard liver volume formula[8], the cirrhotic liver volume change rate has been measured quantitatively. The Child-Pugh' s liver function classification is a classic liver function index and is widely used in clinical practice. Our research results demonstrated that the indexes for liver inherent metabolic volume and liver functional blood flow could be used as a complement to Child-Pugh' s classification to gain overall and objective data of liver functional reserve. The CL_H, R_{INS} and liver volume change rate had some correlations with the Child-Pugh' s classification. The higher the Child-Pugh' s classification, was the less the liver functional blood flow existed, the more the intrahepatic shunt occurred, the smaller the liver volume was. This result is comparable with other reports[34, 35]. It was also found that variation of CL_H and liver volume change rate did not always correlate with each other even the Child-Pugh' s classification was the same. There was an overlap among different groups, indicating that a patient classified as Child A might have a smaller CL_H and liver volume than a patient classified as Child B or C. This may explain why some deadly complications such as severe ascites or hepatic coma might occur in Child-Pugh' s A patients but not in Child-Pugh' s B or C patients after operation. In conclusion, the functional blood flow and cirrhotic liver volume are two critical indexes which are complementary to Child-Pugh' s classification and can help the evaluation of the overall status of cirrhotic liver and the establishment of individualized therapeutic plan[17,18,30,31].

The CL_H and liver volume change rate had a close relationship with the postoperative complications in cirrhotic patients. The complication incidence increased as the CL_H or liver volume change rate decreased. The complication rate exceeded 70 % (P<0.05) when CL_H was below 600/ml.min^{-1} or R below 40 %. This can be explained by the theory that the liver can not stand anesthesia and operative risks when decreased metabolic volume and functional blood flow have already put the liver at the edge of collapse. The CL_H and liver volume change rate could be complementary to each other when postoperative complications were to be predicted. 22 cases had D-sorbitol clearance rate lower than 600/ml·min^{-1}. 8 of them had their liver volume change rate between -20 % and -40 %, 14 below -40 %. The incidence of postoperative complications was 62.5 % (5/8) and 78.6 % (11/14), respectively. Therefore, the Child-Pugh' s classification complemented by CL_H and liver volume change rate should be used to determine the surgical time and type. When the liver has a better functional blood flow with liver volume compensated, the portal-systemic shunt or combination operation can be performed. When the functional blood flow and /or liver volume are decreased dramatically, the treatment of perioperative period should be strengthened to increase the tolerance of the cirrhotic liver, and porta-azygous devascularization would be more suitable. When CL_H <600/ml· min^{-1}, R<-40 %, conservative therapy should be recommended. If no improvement of these indexes is achieved after that, the patients should be considered as the end stage of liver cirrhosis and liver transplantation should be possibly considered.

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