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Relationship between liver function and splenic blood flow (Quantitative measurement of splenic blood flow with $H_2{}^{15}O$ and a dynamic state method: 2)

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We measured splenic blood flow in 55 patients by means of quantitative splenic positron emission tomography (PET), a novel, dynamic state method with $H_2{}^{15}O$ as a tracer. Twenty-four of the 55 patients suffered from liver cirrhosis (LC), 25 showed no evidence of cirrhosis (NR) and 6 patients were diagnosed as having chronic hepatitis (CH). Splenic blood flow per 100 g weight of the spleen (SBF) was significantly correlated with splenic volume ($r=-0.39$, $p<0.005$). The indocyanine green retention test at 15 min ($r=-0.39$, $p<0.005$) and the hepaplastin test ($r=0.37$, $p<0.025$) also correlated significantly with SBF. The means and 95% confidence intervals for the LC, CH, and NR groups were 117.5 ml/min/100 g (96.6–138.4), 102.5 ml/min/100 g (60.6—144.4), and 160.3 ml/min/100 g (139.8–180.8), respectively. The differences in SBF between these 3 groups were significant ($p<0.01$). We conclude that regional splenic blood flow is not proportionate to splenic volume, although the splenic volume does increase with the progressive chronic changes observed in hepatic diseases.

Key words: splenic blood flow, PET, liver function

INTRODUCTION

IN A PREVIOUS STUDY, we quantified human splenic blood flow by positron emission tomography (PET) with $H_2{}^{15}O$ as a tracer. The spleen often increases in size according to the severity of compromised hepatic function, and the cause of this splenomegaly is generally considered to be simple congestion. However, no precise study on its pathophysiology has yet been performed. Although studies on splenic blood flow reported thus far have been semi-quantitative,[1–4] such studies can now be quantified with PET. We therefore investigated the relationship between splenic blood flow (SBF) and liver function by this method. Our operating hypothesis is that liver dysfunction is associated with portal hypertension and a decrease in portal venous flow, which in turn may alter splenic blood flow and splenic volume.

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SUBJECTS AND METHODS

Patients

Fifty-five patients were classified into three groups referred for liver biopsy or surgical specimen, who had been informed of the significance of the study and had consented to it. The first group (LC group) included 18 males and 6 females, ranging in age from 34 to 74 years (mean: 56.5 years), who had liver cirrhosis (LC): 20 of them were diagnosed as having hepatocellular carcinomas (HCC) but no liver tumors could be found in the other 4 patients. The CH group consisted of 5 males and a female ranging in age from 45 to 72 years (mean: 62.5 years) who

were diagnosed as having chronic hepatitis (CH): 4 of them had HCC as a complication and the other 2 patients had no detectable liver tumors. The final group (NR group) consisted of 16 males and 9 females with an age distribution of 32 to 77 years (mean: 56.4 years), and no history of any chronic liver disease. All but five patients in the NR group were found to have liver tumors: 12 metastatic liver tumors, 3 hemangiomas of the liver, 2 hepatic hilar bile duct carcinomas, 1 carcinoma of the gallbladder, 1 angiomyolipoma of the liver and 1 HCC. No liver tumors could be detected in the other 5 NR patients.

Methods

The PET system (HEADTOME III SET-120W, Shimadzu Co., Kyoto, Japan) was used with a whole body collimator and a cyclotron with a ^{15}O gas production system (BC-1710, Japan Steel Works, Muroran, Japan). Details of the performance characteristics of this PET system and the actual methods used in the PET-study have been described in a previous report.[5] The splenic blood flow per 100 g weight of the spleen (SBF) and the spleen-blood partition coefficient for water (ρ) were then calculated. The splenic volume (V) was calculated by analyzing serial splenic imagings by computed tomography (CT).[6] Total splenic flow (F) was obtained as SBF$\times$V. The indocyanine green retention test at 15 min. ($ICGR_{15}$), hepaplastin test (HPT), and the prothrombin elongation time (PT) were carried out in these patients. Correlations between these functional assays and splenic blood flow were then calculated.

Statistical testing was performed by simple regression analysis, and one-way analysis of variance (ANOVA). A p-value less than 0.05 was considered significant.

RESULTS

Analysis of the blood flow data is summarized in Table 1. The mean SBF and spleen-blood partition coefficient (ρ) of patients in the LC group were 117.5 ml/min/100 g and 0.824, respectively. The mean SBF and ρ of patients in the CH group were 102.5 ml/min/100 g and 0.702, respectively. The mean SBF and ρ of patients in the NR group were 160.3 ml/min/100 g and 0.770, respectively.

Significant differences in SBF ($p<0.01$) were noted between all 3 groups, and differences in total splenic blood flow (F) between the 3 groups were also significant ($p<0.005$).

In addition, significant correlations were noted between SBF and V ($r=-0.39$, $p<0.005$), SBF and $ICGR_{15}$ ($r=-0.39$, $p<0.005$ as illustrated in Fig. 1), SBF and HPT ($r=0.37$, $p<0.025$), ρ and V ($r=0.36$, $p<0.01$), ρ and $ICGR_{15}$ ($r=0.38$, $p<0.005$), ρ and PT ($r=0.38$, $p<0.01$), ρ and HPT ($r=-0.42$, $p<0.01$) (Fig. 2), F and V ($r=0.79$, $p<0.005$), F and $ICGR_{15}$

Table 1 Data according to diagnosis

	SBF ml/min/100 g	F ml/min	ρ	V ml
LC	117.5	412.4	0.824	374.6
n=24	(96.6–138.4)	(345.6–479.1)	(0.789–0.859)	(307.1–442.1)
CH	102.5	171.4	0.702	202.1
n=6	(60.6–144.4)	(37.8–304.9)	(0.632–0.771)	(67.1–337.1)
NR	160.3	184.6	0.770	121.0
n=25	(139.8–180.8)	(119.1–250.0)	(0.735–0.804)	(54.9–187.2)

Splenic blood flow per 100 g of spleen, total splenic blood flow, spleen-blood partition coefficient for water and splenic volume of groups of patients with liver cirrhosis (LC), chronic hepatitis (CH) and showing no chronic liver disease (NR). Each value represents the mean and 95% confidence interval. SBF: splenic blood flow per 100 g of spleen, F: total splenic blood flow, ρ: spleen-blood partition coefficient for water, V: volume of the spleen.

Table 2 Correlation coefficients between splenic data and liver function

	SBF	ρ	F	V
$ICGR_{15}$	-0.39 ($p<0.005$)	0.38 ($p<0.005$)	0.34 ($p<0.025$)	0.38 ($p<0.005$)
PT		0.38 ($p<0.01$)	0.51 ($p<0.005$)	0.46 ($p<0.005$)
HPT	0.37 ($p<0.025$)	-0.42 ($p<0.01$)	-0.32 ($p<0.05$)	-0.33 ($p<0.05$)
V	-0.39 ($p<0.005$)	0.36 ($p<0.01$)	0.79 ($p<0.005$)	

SBF: splenic blood flow per 100 g of spleen, ρ: spleen-blood partition coefficient for water, F: total splenic blood flow, V: volume of the spleen, $ICGR_{15}$: indocyanine green retention test at 15 minutes, PT: prothrombin test time, HPT: hepaplastin test

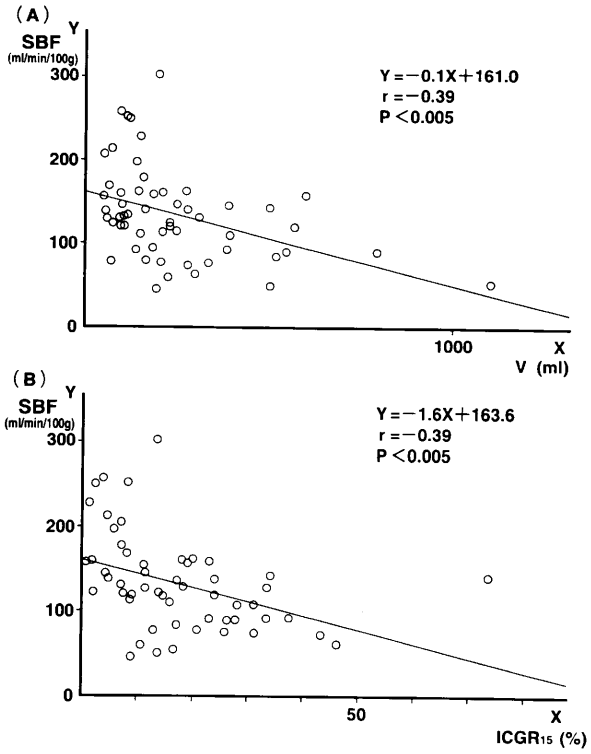

Fig. 1

(A) Correlation between splenic blood flow per 100 g of spleen and splenic volume, SBF: splenic blood flow per 100 g spleen, V: splenic volume.

(B) Correlation between splenic blood flow per 100 g of spleen and $ICGR_{15}$, SBF: splenic blood flow per 100 g of spleen, $ICGR_{15}$: indocyanine green retention test at 15 minutes.

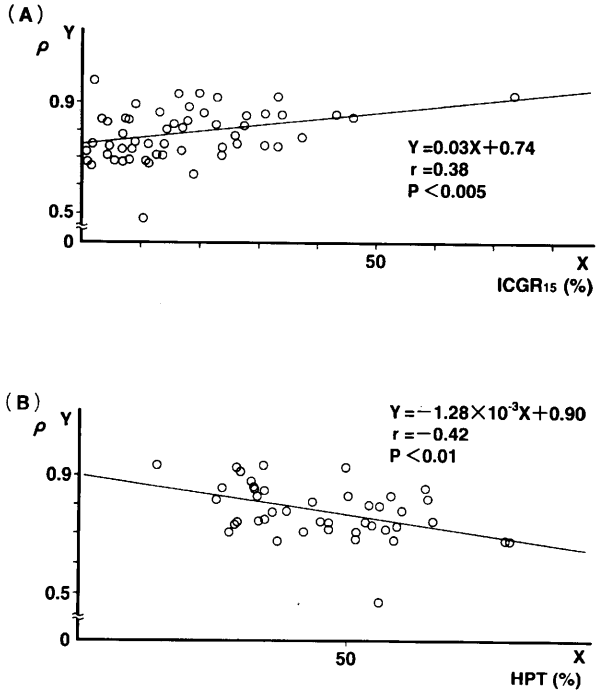

Fig. 2

(A) Correlation between spleen-blood partition coefficient for water and $ICGR_{15}$, ρ: spleen-blood partition coefficient for water, $ICGR_{15}$: indocyanine green retention test at 15 minutes.

(B) Correlation between spleen-blood partition coefficient for water and hepaplastin test, ρ: spleen-blood partition coefficient for water, HPT: hepaplastin test.

($r=0.34$, $p<0.025$), F and PT ($r=0.51$, $p<0.005$), F and HPT ($r=-0.32$, $p<0.05$), V and $ICGR_{15}$ ($r=0.38$, $p<0.005$), V and PT ($r=0.46$, $p<0.005$) and between V and HPT ($r=-0.33$, $p<0.05$), these correlation coefficients being arranged in Table 2. There were no other significant correlations between any of the markers.

DISCUSSION

The binding of ICG to albumin after an intravenous injection was found to be rapid, with greater than 90% of the complex being taken up by hepatocytes, followed by its subsequent removal in the bile. Thus the administration of ICG is often used to measure hepatic blood flow,[7-9] and to evaluate liver function or the degree of chronic hepatic damage.[10] However, we should be careful not to adopt its value if a patient has congenital ICG retention. Similarly we must take care to deal with PT because deficiency of vitamin K makes elongates prothrombin time even when there is no hepatocellular damage. In the current study, there were no patients corresponding to such special cases. HPT eliminates the inhibitory effects of proteins (induced by the absence of vitamin K) on factor X and the test reflects the ability of the liver to synthesize proteins such as prothrombin, factor VII, and factor X.[11] In Owren's description of the assay,[12] HPT was identified as a marker which enables the evaluation of chronic liver diseases and hepatic function.[11,13]

Several conclusions are suggested by the present results. First, increasing spleen volume was due to an aggravation of hepatic function. Second, a decrease in regional splenic blood flow was accompanied by increasing hepatic dysfunction. However, in fact, SBF in the CH group was lower than SBF in the LC group. The small number ($n=6$) in the CH group may contribute to the inversion of the data for the two groups, and it is possible that patients in the LC group have more chance of obtaining a venous shunt, such as a splenorenal shunt, than patients in the CH group, and so the SBF of LC becomes greater than the SBF of CH in

spite of its worse liver function than that of CH. Further examination will be necessary to find the reason for this inversion. Third, total splenic blood flow does not correlate with increasing splenomegaly although an apparently significant correlation was noted between F and V. This third idea cannot be proven conclusively because the splenic volume and the total splenic blood flow could not be measured separately in our study.

With regard to the relationship between splenic volume and various markers of liver function, the splenic volume tended to increase with the progressive chronic changes found in hepatic diseases; statistically significant correlations were obtained between V and $ICGR_{15}$, V and PT, and V and HPT. Moreover, we noted from our analyses that F also increased significantly with advancing chronic changes when compared to the $ICGR_{15}$, PT and HPT results. However, such an increase in SBF is not necessarily accompanied by an increase in V, because the relationship between SBF and V can be expressed as SBF=F/V. Therefore, SBF is not proportionate to its V. Huchzermeyer[1] reported that the total splenic blood flow increased as the weight of the spleen increased in spite of low specific blood flow. Furthermore, Williams[2] noted that the total splenic flow calculated by intraarterial injections of radioactive xenon increased even in patients where the flow/100 g tissue was clearly reduced and Wadenvic[3] reported that splenic perfusion (the percentage of total blood volume entering 100 cm^3 of splenic tissue per minute) measured by intravenous injections of ^{111}In was found to decrease as the size of the spleen increased. These results were similar to our results and suggest that these increases in splenic size result from tissue expansion caused by congesting static blood due to portal hypertension, and from aggravating chronic changes observed in hepatic diseases. Moreover, Garnet[4] reported that the spleen behaved as an arteriovenous shunt. In order to demonstrate the existence of splenic phenomena indicating an arteriovenous shunt or congestive swelling, it is necessary to determine the blood flow in the regional splenic tissue minus the flow in the intrasplenic vascular space (real SBF). In this study, we obtained a SBF value that includes the intrasplenic vascular flow but in the future we will be developing a method for the quantification of the real SBF. PET scanning is suitable for performing such studies, because repeated measurements can be done by using ^{15}O, which has a very short half-life (123 sec). However, we analyzed the splenic blood flow by calculating an apparent SBF which included the flow in the intrasplenic vascular space, because the quantification of the real SBF was theoretically so complicated that it could not be applied clinically and the apparent SBF could be easily compared to splenic blood flow measured by other methods.

In the current study, the physiologic relevance of ρ is not clear, but its significance may be proven if a method for the quantification of the real SBF becomes established. There are some reports recording the structure of splenic vessels in the case of liver cirrhosis which suggest that they are different from the vessels found in a normal liver.[14,15] These difference in the structure of splenic vessels may contribute to the change in the ρ value. The application of PET will also solve this problem.

In conclusion regional splenic blood flow is not proportionate to splenic volume, although the splenic volume increases with the progressive chronic changes characteristic of hepatic diseases.

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