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Quantification of human splenic blood flow (Quantitative measurement of splenic blood flow with $H_2{}^{15}O$ and a dynamic state method: 1)

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Positron emission tomography (PET) by means of a dynamic state method and $H_2{}^{15}O$ was performed to quantify splenic blood flow in 20 patients who had no hepatic functional disorders. Non-linear regression analysis was applied to determine splenic blood flow. In calculating arterial input function for the spleen, our original **exponential method** was used to facilitate computerization. Mean splenic blood flow per 100 g of spleen (SBF) was 168.0 m*l*/min/100 g with a standard error (SE) of 12.4 m*l*/min. The mean spleen-blood partition coefficient for water (ρ) was 0.767 with a SE of 0.020. Significant correlations were noted between the values for SBF obtained by the **exponential method** and **linear method** in which individual increasing values for arterial ^{15}O concentration were used rectilinearly ($r=0.96$, $p<0.005$) and also between the values for ρ obtained by the two methods ($r=0.95$, $p<0.005$). In order to validate the application of a one compartment model to an organ with a large blood volume such as the spleen, a further experiment was performed with a water flow model simulating splenic circulation.

We succeeded in quantifying regional splenic blood flow by PET. It was thought that the quantification of splenic blood flow by our method would be beneficial in the study of splenic circulation, which is expected to be altered under conditions of portal hypertension, liver dysfunction and shock, etc.

Key words: splenic blood flow, PET, $H_2{}^{15}O$

INTRODUCTION

SEVERAL TECHNIQUES are currently used to determine human splenic blood flow both semi-quantitatively and noninvasively. Examples including the inhalation of inert gasses such as ^{133}Xe and the subsequent monitoring of the clearance of the gas with an external scintillation counter,[1] measurement of the splenic uptake of ^{111}In-labeled platelets following their intravenous injection[2] and measurement of blood velocity in the splenic vein by Doppler Ultrasonography[3] have made it possible to determine splenic blood flow safely. However, because of the potency of the isotopes used, it is difficult to perform quantification or serial examinations. In addition, Doppler Ultrasonography sometimes fails in locating the splenic vein and measuring its diameter. Therefore, these methods of determining splenic blood flow are not considered totally satisfactory in spite of their non-invasive merit.

In the present study we applied positron emission tomography (PET) to quantifying human splenic blood flow with $H_2{}^{15}O$ in which it was possible to safely determine not only the splenic blood flow, but also the blood flow to all organs adjacent to the

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spleen. Generally organic blood flows measured by PET are blood flows in regional tissues which contain little blood volume. We ventured to measure splenic blood flow where there is a big blood volume and examined the validity of the measurement.

SUBJECTS AND METHODS

Mathematical model and theory

A one compartment model was adopted for the analysis of splenic blood flow. However, this model is suitable for organs in which blood volumes are negligibly small and the spleen is far from suitable. We therefore performed a further series of experiments with a blood flow model, details of which are shown in the section on *Model analysis*. The input function ($Ca(t)$) may be expressed as the time activity curve (TAC) for the aorta, and the flow of $H_2{}^{15}O$ into the splenic artery is determined from total splenic blood flow (F) with activity $Ca(t)$ (Fig. 1).

The radioactivity in the spleen ($Cs(t)$) is then washed out by the blood flow. The differential equation is:

$$\frac{dCs(t)}{dt} = \frac{F}{V} Ca(t) - \frac{F}{\rho V} Cs(t) \qquad \text{(a)},$$

where V is the volume of the spleen and ρ is the spleen-blood partition coefficient for water. Equation (a) is otherwise expressed as follows:

$$Cs(t) = \frac{F}{V} \int_0^t e^{-\frac{F}{\rho V}(t-x)} Ca(x)\,dx \qquad \text{(b)}.$$

In fact, a PET image measured between t_i and t_{i+1} can be expressed as

$$\frac{1}{t_{i+1}-t_i} \int_{t_i}^{t_{i+1}} Cs(t)\,dt \qquad \text{(c)}.$$

Two $Ca(t)$ functions were applied.[4,5]

$$Ca(t) = A_1\, e^{-B_1 t} + A_2\, e^{-B_2 t} \quad [t_0 \leq t] \qquad \text{(d)},$$
$$Ca(t) = C_1\, e^{D_1 t} + C_2\, e^{D_2 t} \quad [0 \leq t < t_0] \qquad \text{(e)},$$

where t_0 represents the time at which the input function is maximized. The left sides of both equations (d) and (e) are derived from the input function. Following determination of $Ca(t)$, equation (b) can be solved. Since the values in the expression shown in (c) are measurable by PET, F/V and ρ are determined in the same manner.

Model analysis

Simulating the human splenic blood circulation, a water flow model was designed. As shown in Fig. 2, two pellucid acryl boxes (an imitation of lungs with a volume of 500 m*l*; pulmonary box and of spleen with a volume of 200 m*l*; splenic box) were connected by a silicon tube 52 cm long and with an internal diameter of 0.8 cm. Before the splenic box a flow meter was inserted (MODEL RK400, KOFLOC Co., Tokyo, Japan) and valves for sampling water were set up just before and behind the splenic box. A valve for infusion of indigocarmine (DAIICHI Pharmaceut., Tokyo, Japan) was set before the pulmonary box. Under the condition of regular water flow through the flow meter, 2 m*l* of indigocarmine was infused and 1 m*l* water samples were obtained from the both valves at 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 60, 120, 180, and 240 sec. after the infusion. With a spectrophotometer (HITACHI 220A), the indigocarmine concentration in each water sample was measured. Then Simplex method analysis determined the simulated $Ca(t)$ and $Cs(t)$. The water used was stored and the volume was counted for 240 sec. in order to estimate the error of the flow meter.

Patients

Twenty patients who were free of diseases causing chronic hepatic damage such as liver cirrhosis or chronic hepatitis were investigated. The patients included 11 males and 9 females whose ages ranged from 32 to 77 years (mean: 55.4 years). Eight of the patients were diagnosed as having metastatic liver tumors. The conditions of 8 other patients were as follows: 3 hemangiomas of the liver, 2 hepatic hilar

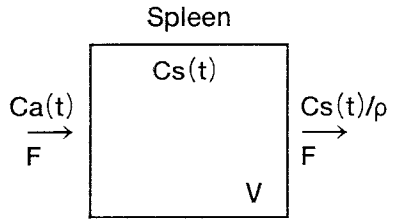

Fig. 1 Ingressing and egressing blood flow of the spleen based on the one compartment model. Ca(t): input function to the spleen, Cs(t): radioactivity in the spleen, F: total splenic blood flow, V: volume of the spleen, ρ: spleen-blood partition coefficient for water.

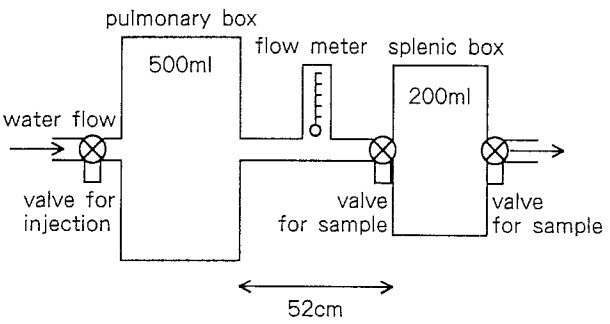

Fig. 2

bile duct carcinomas, 1 gallbladder carcinoma, 1 hepatocellular carcinoma, and 1 angiomyolipoma of the liver. Liver tumors could not be identified in the other 4 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). The performance characteristics of the PET system in this study were set as follows: an image resolution of 8.2 mm in full width at half-maximum (FWHM), and a slice thickness of 11 mm (direct) and 13 mm (cross plane) FWHM. The matrix size of the image was 128×128 with a 2 mm pixel size. The slice interval of the planes was 15 mm.

The scan position for each patient was determined by computed tomography. About 20–30 mCi of $H_2{}^{15}O$ was administered by intravenous bolus injection. Emission data for 3 slices in every 1.5 cm interval were collected simultaneously.

The patients had measurements taken every 5 sec. for one minute, followed by measurements at 30 sec. intervals for 4 min. The count data obtained from the brachial arterial blood samples were substituted for $Ca(t)$. Arterial blood samples were obtained from the left brachial artery at 10, 15, 20, 25, 30, 35, 60, 120, 180 and 240 sec. after the beginning of the emission scan. The values for A_1, A_2, B_1, B_2, C_1, C_2, D_1, and D_2 were then determined by the Simplex method[6] based on non-linear regression analysis. Regions of interest (ROIs) were placed on the spleen, and time-activity curves (TAC) were then obtained. Corrections for the physical decay of ^{15}O (half-life 123 seconds) were made every 2.5 seconds. In the present study, an average F/V for each slice derived from one scanning process was adopted as the splenic blood flow for the patient. Initially, the **linear method** was utilized, where individual values for the arterial ^{15}O concentration are used rectilinearly.[7] The **exponential method** was then added and the values for F/V and ρ calculated by the two methods were compared by paired t-testing. The value for V was calculated by the analysis of serial splenic imagings by computed tomography (CT).[8]

RESULTS

In the model analysis, when the water flow was set at 100, 200, 300, and 400 ml/min, the water flow in the splenic box was calculated as 121, 198, 370, and 398 ml/min, respectively, actual water flow being 118, 231, 330, and 440 ml/min, respectively (Fig. 3).

We took the specific gravity of the spleen to be 1 because the mean specific gravity of 13 surgically removed spleens was 1.004 (the mean specific gravity of spleens from 4 patients with liver cirrhosis was 0.966 and the mean specific gravity of spleens from 9 patients who had no hepatic functional disorders was 1.021). Blood flow data for the 20 patients produced by the **exponential method** are as follows.

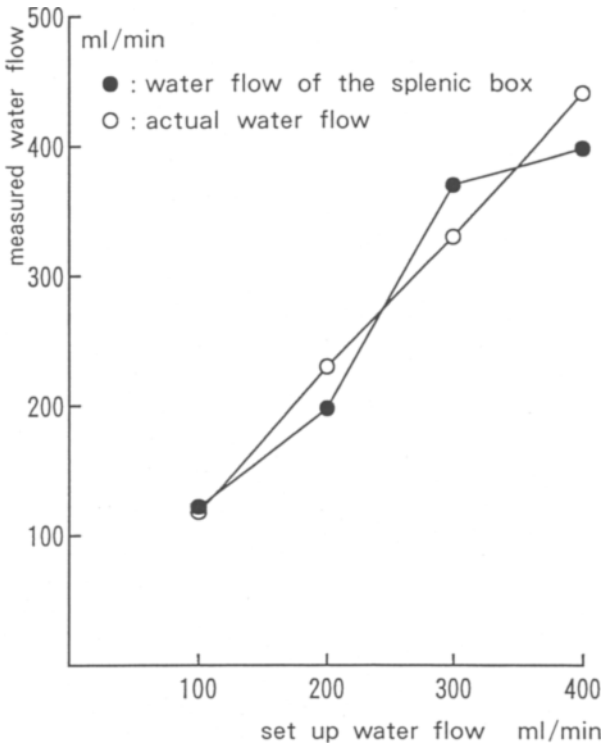

Fig. 3 Measured water flows (water flow of the splenic box and actual water flow) were plotted on the longitudinal axis versus set up water flows on the horizontal axis. Water flow of the splenic box showed similar values to actual water flow in the range of 100 to 400 ml/min of set up water flow.

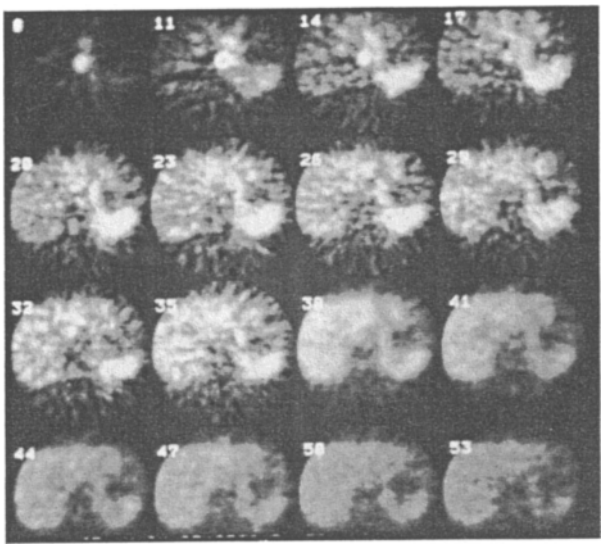

Fig. 4 Serial imaging of the upper abdomen of a patient without chronic liver disease.

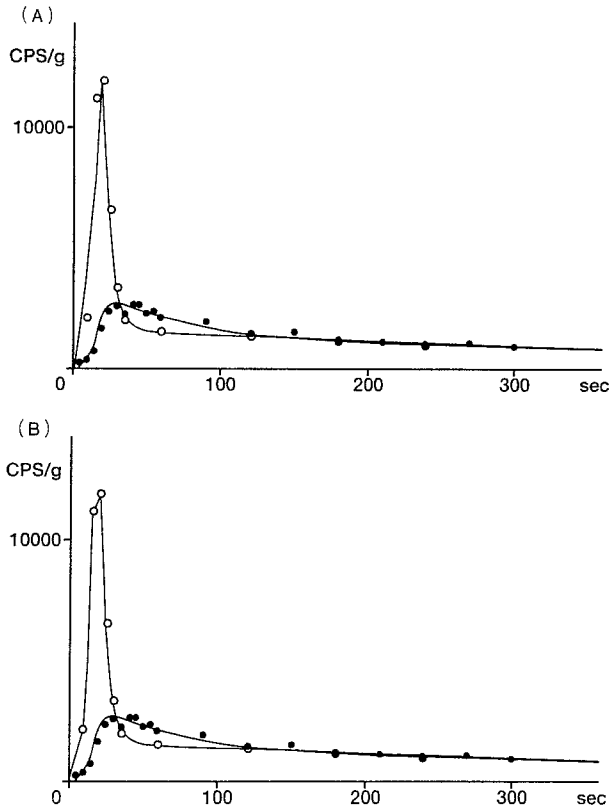

Fig. 5 Open circles are individual values of arterial ^{15}O concentration and closed circles are mean values of radioactivity in the spleen during individual time sections measured by PET. Each line is Ca(t) or Cs(t) determinated by nonlinear regression analysis. Fig. 5A gives an example by **exponential method** and Fig. 5B presents the same one by **linear method.** CPS: count per second, Ca(t): input function to the spleen, Cs(t): radioactivity in the spleen.

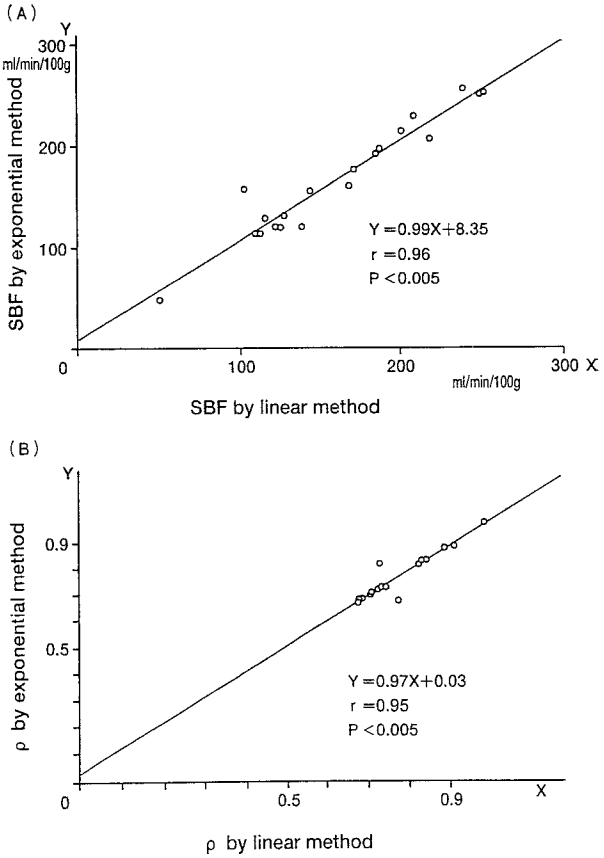

Fig. 6 The relationship between values of SBF by the **exponential method** and by the **linear method** was presented in Fig. 6A and the same relationship for ρ was shown in 6B. The values of SBF and ρ by the **exponential method** were correlated well with them by the **linear method.** SBF: splenic blood flow per 100 g of splenic tissue, ρ: spleen-blood partition coefficient for water.

Splenic blood flow per 100 g of splenic tissue (SBF= F/V) ranged from 48.0 to 258.9 m*l*/min/100 g (mean: 168.0, standard error (SE): 12.4); F ranged from 71.9 to 333.7 m*l*/min (mean: 196.8, SE: 20.1); ρ ranged from 0.680 to 0.981 (mean: 0.767, SE: 0.020); and V ranged from 46.0 to 243.1 m*l* (mean: 125.2, SE: 13.5). SBF and ρ calculated by the **linear method** ranged from 47.5 to 236.0 (mean: 160.7, SE: 12.0) and from 0.681 to 0.979 (mean: 0.765, SE: 0.019). An actual image of the spleen is shown in Fig. 4 and an example of the determination of $Ca(t)$ and $Cs(t)$ by the **exponential method** and the **linear method** are presented in the Fig. 5A and 5B.

Significant correlations were noted between the values for SBF derived by the two methods ($r=0.96$, $p<0.05$) (Fig. 6A) and also between the values of ρ determined by the two methods ($r=0.95$, $p<0.005$) (Fig. 6B).

DISCUSSION

In this report, we have examined a technique for quantifying splenic blood flow by PET. The merits of scanning by PET include very little tissue invasion, with the exception of two intraluminal insertions, one into a vein for the infusion of $H_2{}^{15}O$ and the other into the brachial artery in order to monitor and sample arterial blood. The method of scanning the spleen is technically simple and failure is rare since the areas scanned enable the easy location of target organs. In addition, repeated measurements by means of this method can be performed as ^{15}O has a very short half-life (123 seconds). Local blood flow measurements by PET with ^{15}O has been previously employed in the examination of cerebral blood flow.[9] However, we modified this technique by adopting the input function derived from the fitting by the **exponential method** during the time period

$0 \leq t < t_0$, which altered the calculation to the sum of two exponents. This proved successful in determining input functions. This formula expresses the increase in arterial ^{15}O activity following the intravenous injection of $H_2{}^{15}O$ and makes possible the computerization of calculations based on non-linear regression analysis. This makes the analysis quicker and simpler than using individual increasing values of the arterial ^{15}O concentration rectilinearly (**linear method**). Although the **exponential method** has the disadvantage that $Ca(t)$ never begins from (0,0), unless the absolute values of C_1 and C_2 are equal as a result of minimization based on non-linear regression analysis, there was very little difference between the values for SBF and ρ obtained by means of our **exponential method** and those obtained by means of the **linear method**. It is these findings which further validate the application of the modified system. In another study, Herscovitch adopted the following as the arterial input function.[10]

$$Ca(t) = At\, e^{-\frac{t}{t_0}} \qquad (f).$$

Because equation (f) automatically has the peak $Ca(t_0)$, there is no need to separate calculations for the time period $0 \leq t < t_0$ from those for the period $t_0 \leq t$. However, although equation (f) makes the calculations much simpler, it could not be used in our analysis because minimization could not be carried out with the Simplex method.

In the current study, the accuracy of the SBF values obtained is based on the hypothesis that the spleen can be represented by the single compartment model originally described by Ketty;[11] blood perfusion in a small volume of local splenic tissue is uniform and the tracer concentration in this volume is also assumed to be uniform. In addition to the problem of assuming that the compartment describes the system, there is one other problem with the spleen. Because the spleen behaves as a major blood volume reservoir,[12–14] the SBF obtained by our method is apparent blood flow per 100 g of splenic volume consisting of blood flow not only in the white pulp but also in the red pulp, both of which consist of blood cells. Although the value obtained with this method is not the blood flow in the splenic tissue except for the vascular space, it can be easily compared with values for total splenic blood flow measured by other methods.

In the spleen the blood volume in the splenic artery and capillaries cannot be distinguished from the blood volume in the red and white pulp. It is therefore impossible to correct the splenic blood flow in consideration of the blood volume. Furthermore, white pulp forms another compartment because this does not contain erythrocytes. If these problems are negligibly small, a single compartment model can be adopted as a model of splenic blood flow. In the experiment with the water flowing model, the splenic box behaved as if all the space in the spleen had been occupied by the blood volume and there was no tissue volume. In spite of a lack of minuteness, almost similar values were obtained for the water flows in the splenic box and the actual water flows. Needless to say, the spleen has not only a solid space but also a fluid space, so this experiment does not solve all the problems relating to the adoption of a one compartment model for a spleen. However, this examination showed the possibility of quantifying the blood flow of an organ which contains a large blood volume. Further studies will be necessary to determine whether the one compartment model is suitable for use with the spleen. However, our results, which are similar to those of previous studies, suggest that the one compartment model can indeed be applied to the spleen. To illustrate the similarity in results, the use of radioactive rare gases has demonstrated a splenic blood flow of 170 m*l*/min in healthy persons.[1] Moreover, Peters[2] showed the flow to be about 200 m*l*/min in normal healthy individuals following the administration of ^{111}In-labeled platelets. Finally, Doppler Ultrasonography has recorded flows of 155–435 m*l*/min, which is considered normal.[3] In our results splenic blood flow per 100 g of splenic tissue ranged widely from 48.0 to 258.9 m*l*/min/100 g. As the reason for this great variation, technical error derived from improper arterial samples, and the movement of ROIs by the patients' respiration can be considered. Moreover, the error produced by the adoption of a single compartment model may play a part in the great variation in blood flow.

The blood flow in the spleen is an important constituent of portal circulation, especially in abnormal states such as liver cirrhosis and portal hypertension.[15,16] Therefore, the quantification of normal splenic blood flow by our method with PET should further the study of portal circulation.

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