

Difference in regional hepatic blood flow in liver segments —Non-invasive measurement of regional hepatic arterial and portal blood flow in human by positron emission tomography with $H_2^{15}O$ —

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Organ blood flow can be quantitatively measured by positron emission tomography (PET). As the liver has dual blood supplies, arterial and portal, regional hepatic blood flow had not been measured quantitatively. However, we succeeded in simultaneously measuring both regional hepatic arterial and portal blood flow by PET in non-stressed patients. Mean regional portal hepatic blood flow in patients with normal liver and cirrhotic liver was 57.5 and 36.7 ml/minutes/100 g, respectively. Mean regional arterial blood flow was 42.5 and 30.7 ml/minutes/100 g, respectively. A significant difference between regional portal hepatic blood flows in normal and cirrhotic patients was noted. Mean regional portal hepatic blood flow in the lateral, medial, anterior, and posterior segments of the liver was 29.8, 43.4, 50.0, and 40.9 ml/minutes/100 g, respectively. Mean regional arterial blood flow in each liver segment was 37.6, 30.0, 28.2, and 31.6 ml/minutes/100 g, respectively. A significant difference between regional portal hepatic blood flows in lateral and anterior segment was noted. The p value was less than 0.025 and the 95% confidence interval of the difference between means was from -20.2 to -2.7 ml/minutes/100 g by ANOVA. These results showed that regional hepatic blood flow is not the same in all the liver segments.

Key words: regional arterial hepatic blood flow, regional portal hepatic blood flow, segmental hepatic blood flow, PET

INTRODUCTION

Organ blood flow can be quantitatively measured with positron emission tomography (PET)¹, for instance in the brain²⁻³ and heart.⁴ Although regional hepatic blood flow (rHBF) had not been measured by PET, because the liver has dual blood supplies, arterial and portal, we were able to measure regional hepatic arterial (rHBFa) and portal (rHBFp) blood flows by PET simultaneously, separately, non-invasively, and without stress.

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MATERIALS AND METHODS

Theory

If regional hepatic blood flow (rHBF) is expressed as shown schematically in Fig. 1 and a one compartment model⁶ is applied, the following simultaneous differential equations hold.

$$\frac{dCh(t)}{dt} = \frac{Fa}{Vh} \times Ca(t) + \frac{Fp}{Vh} \times \frac{Cp(t)}{Kp} - \frac{Fh}{Vh} \times \frac{Ch(t)}{Kh} \dots\dots\dots(A)$$

$$\frac{dCp(t)}{dt} = \frac{Fp}{Vh} \times Ca(t) - \frac{Fp}{Vh} \times \frac{Cp(t)}{Kp} \dots\dots\dots(B)$$

$$\frac{Fh}{Vh} = \frac{Fa}{Vh} + \frac{Fp}{Vh} \dots\dots\dots(C)$$

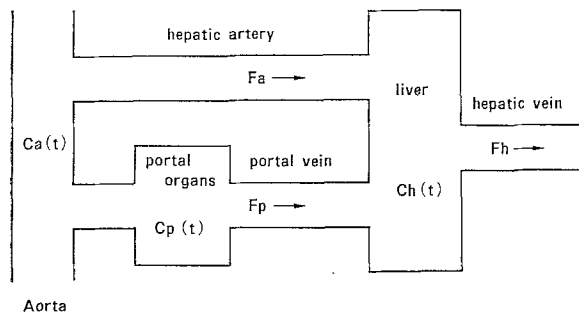


Fig. 1 Schema of the hepatic blood flow.

The rate of change of radioactivity in the liver can be expressed as equation (A), when organs which drain into the portal vein are considered as one organ called the portal organ. In this equation, F_a and F_p are the tracer flows into the liver by way of the hepatic artery and from the portal organ, respectively, $Ca(t)$ and $Cp(t)$ are the tracer concentrations in the arterial blood and portal organ, respectively, $Ch(t)$ is the radioactivity in the liver which is washed out by hepatic venous flow (F_h), V_h is the volume of the region of interest (ROI) in the liver, K_p is the constant for the portal organ, and K_h is the constant for the liver. If ROI for the portal organ is set to the same volume as for the liver, then the rate of change of radioactivity is represented by equation (B). From this condition, the tracer flow into the portal organ is F_p at a concentration equal to $Ca(t)$, and the radioactivity washes out of the portal organ at a rate defined by F_p . Consequently, hepatic venous flow is the sum of arterial and portal blood flow (equation (C)). Because F_a/V_h , F_p/V_h , and F_h/V_h are $rHBF_a(=fa)$, $rHBF_p(=fp)$, and $rHBF(=fh)$, respectively, equation (B) can now be expressed as follows:

$$Cp(t) = fp \times \int_0^t e^{-(fp/Kp) \times (t-x)} \cdot Ca(x) dx.$$

When this equation is substituted into equation (A), the solution of equation (A) becomes

$$Ch(t) = fa \times \int_0^t Ca(x) \cdot e^{-(fh/Kh) \times (t-x)} dx \\ + \frac{fp \times fp}{Kp} \times \int_0^t \left\{ \int_0^x Ca(y) \cdot e^{-(fp/Kp) \times (x-y)} dy \right\} \\ \cdot e^{-(fh/Kh) \times (t-x)} dx.$$

Since the PET radioactivity of the ROIs determined in the liver from t_n to t_{n+1} is

$$\frac{1}{t_{n+1} - t_n} \int_{t_n}^{t_{n+1}} Ch(t) dt,$$

the combination of serial measurements and non-linear multiple regression analysis permits the calcu-

lation of $rHBF_a$, $rHBF_p$, K_h , and K_p .

Materials

For eighteen (12 males and 6 females) patients, $rHBF$ was measured simultaneously in all 4 liver segments (lateral, medial, anterior, and posterior segments) by PET. They ranged in age from 32 to 74 with a mean age of 57.9 years. Five patients had normal liver function, 2 had chronic hepatitis, and 11 were cirrhotic, and had been diagnosed histologically.

Methods

Serial measurements were performed with the patients in the fasting state in a recumbent position on the bed of a whole body PET scanner (HEAD-TOME III SET-120W, Shimadzu Co., Kyoto, Japan). Following the intravenous injection of 20 to 30 mCi (370 to 740 MBq) of $H_2^{15}O$ produced by a medical cyclotron (BC-1710, Japan Steel Works, Muroran, Japan), twelve PET measurements were taken in the first minute and another 8 measurements were taken in the subsequent 4 minutes. Three PET scans 10 mm in width and spaced at 15 mm intervals were performed. ROIs were set on the liver segments of the PET images, always referring to the X-ray computed tomographic imagings on the same slices. From the PET images, the radioactivity in 4 liver segments was calculated. The $rHBF$ of the segments was determined by means of 3 scans, and the $rHBF$ in the whole liver was defined by means of 4 segments. Blood samples were taken from the left brachial artery for 5 minutes concurrent with PET measurements, at a rate of 1 every 5 seconds for the first 30 seconds and at intervals of 30 seconds thereafter, to give a total of 12 samples in 4 minutes. Radioactivity concentrations in the blood samples were measured immediately in a precalibrated well counter. They were approximated by non-linear multiple regression analysis with the following two equations.

$$Ca(t) = A_1 \times e^{B_1 \times t} - A_2 \times e^{B_2 \times t} (0 \leq t < t_{max})$$

$$Ca(t) = C_1 \times e^{-D_1 \times t} + C_2 \times e^{-D_2 \times t} (t_{max} \leq t)$$

where t_{max} was the time when the radioactivity concentration in the blood sample was maximal.

In the current study, the specific gravity of the liver, K_p , and K_h was assumed to be 1. Physical decay of ^{15}O was corrected every 2.5 seconds. The Simplex method⁶ was applied for non-linear multiple regression analysis and data processing was performed by means of a software newly produced by us with a personal computer (PC9801 RA2, NEC Co. Ltd., Tokyo, Japan). Statistical evaluation was performed with one way analysis of variance (ANOVA).

RESULTS

The result of non-linear multiple regression analysis is shown in Fig. 2. The dots and a line indicate the radioactivity concentrations in a hepatic ROI obtained by PET, and $y=Ch(t)$ obtained by the Simplex method, respectively.

The rHBFp in the whole liver ranged from 17.9 to 110.5 with a mean value of 41.0 ml/minutes/100 g. The mean rHBFa in the whole liver was 31.9 ml/minutes/100 g, ranging from 16.1 to 70.3. The rHBF in the whole liver ranged from 40.6 to 135.6 ml/

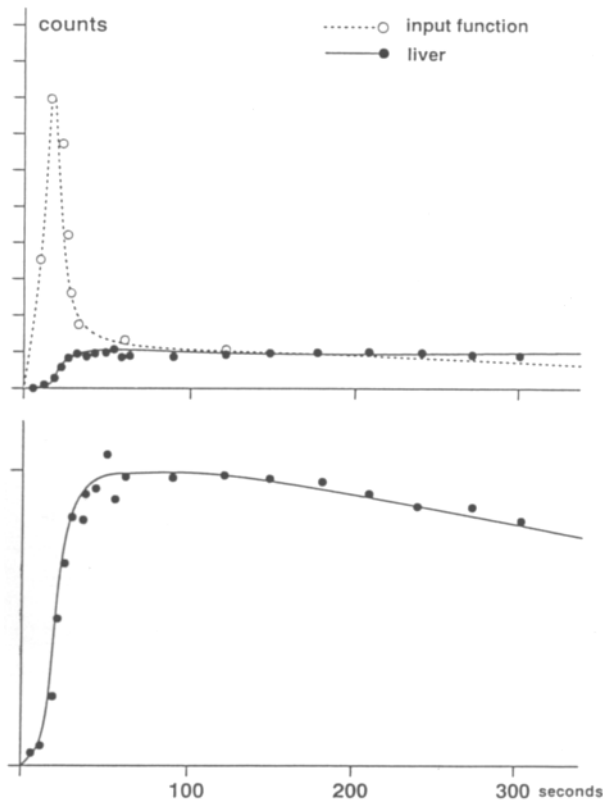


Fig. 2 An example of radioactivity of concentration of a ROI (closed circle) and input function (radioactivity of concentration of arterial blood), and results of minimization [solid line: $Ch(t)$, perforated line: $Ca(t)$] (top). They are magnified in the bottom.

Table

	rHBF	rHBFp	rHBFa
normal liver [n=5]	100.0	57.5	42.5
cirrhotic liver [n=11]	67.4	36.7	30.7
all patients [n=18]	72.9	41.0	31.9

All patients includes two chronic hepatitis.

rHBF: regional hepatic total blood flow
 rHBFp: regional hepatic portal blood flow
 rHBFa: regional hepatic arterial blood flow

minutes/100 g, and mean rHBF in the whole liver (Table). The mean rHBFp/rHBF ratio in the whole liver was 0.56. There was a significant correlation between rHBF in the whole liver and the 15 minute indocyanine green clearance test ($p < 0.03$, $R = 0.53$, $y = 1.12x + 93.7$) (Fig. 3).

The mean rHBFps in the lateral, medial, anterior, and posterior segments of the liver were 29.8, 43.4, 50.0 and 40.9 ml/minutes/100 g, and 95% confidence intervals for the segments were 17.5–42.1, 31.2–55.7, 37.7–62.3, 28.6–53.2, respectively. The mean rHBFas for the liver segments were 37.6, 30.0, 28.2, and 31.6 ml/minutes/100 g with 95% confidence intervals being 31.2–44.1, 23.5–36.4, 21.7–34.6, and 25.2–38.1, respectively. The mean rHBFs for the segments were 67.4, 73.4, 78.2, and 72.5 ml/minutes/100 g, and 95% confidence intervals were 54.5–80.4, 60.4–86.4, 65.2–91.2, and 59.5–85.5, respectively (Fig. 4).

There was no significant difference among the 4 segment of the liver in the rHBFp, rHBFa, or rHBF. However, a significant difference between lateral and anterior segment rHBFps was noted. The p value

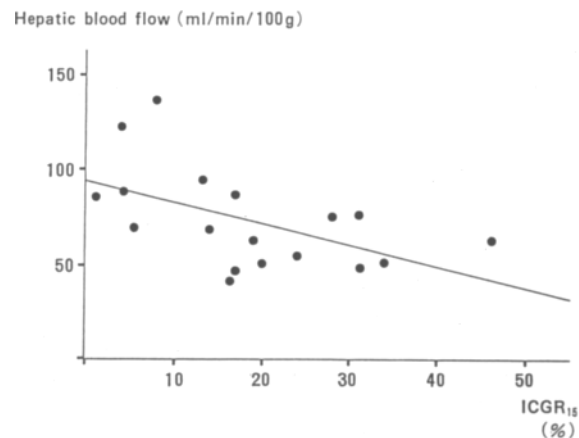


Fig. 3 There was a significant correlation between regional total hepatic blood flow and 15 minutes indocyanine green clearance test ($r = 0.53$, $P < 0.03$).

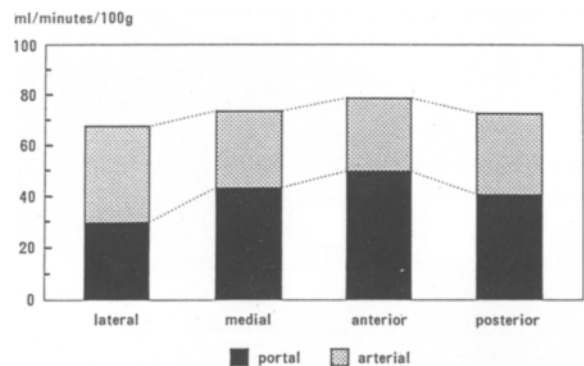


Fig. 4 Segmental regional hepatic arterial and portal blood flow. Regional blood flow was not similar elsewhere in the liver.

was less than 0.025 and the 95% confidence interval of difference of means was from -20.2 to -2.7 ml/minutes/100 g as determined by ANOVA.

DISCUSSION

There are several ways of measuring of hepatic blood flow, such as the dye clearance method with indocyanine green,⁷ the ultrasonic doppler method,⁸ electromagnetic flowmetry,⁵ laser doppler method,¹⁰ and reflectance spectrophotometry.¹¹ However, the first three methods cannot measure rHBF, and the last three methods require laparotomy.

Scintiangiography with radioactive colloid¹²⁻¹³ can measure rHBFa and rHBFp separately and simultaneously, but semi-quantitatively. Nevertheless, because ROI is restricted by the other organs such as the lungs, the concentration of radioactivity in the whole liver cannot be measured. If single photon emission computed tomography (SPECT) is used, this problem is solved, but it is still semi-quantitative measurement because of the dispersion of single photons. Another problem with this method is that it requires curve analysis of the arterial phase and the portal phase. There are several methods of curve analysis, and the best method has not been determined. Scintiphotography with rare gases such as ¹³³Xe¹⁴⁻¹⁵ and ⁸⁵Kr¹⁶ takes only a short time, and if the arterial catheter technique is used, rHBFa and rHBFp can be measured separately.¹⁵ However, ¹³³Xe is soluble in fatty tissue and some invasions are carried out in a patient with a catheter. Moreover, if the hepatic artery is occluded with a balloon catheter to measure portal blood flow, this flow is thought to increase due to hepatic arterial buffer response.¹⁷

Because the position tracer is used, accurate quantification by means of PET is much better than by SPECT. And PET in which a biological radio-tracer is used can perform physiological measurements are possible and radiotoxicity is limited, as the tracer has a short half life. In spite of these many merits,¹⁸ quantitative measurement of rHBF by PET has not been performed, primarily because of the complexity of the hepatic blood supply. However, we succeeded in measuring segmental rHBF by PET; both rHBFa and rHBFp simultaneously, separately, and easily. Besides, we found that rHBF is not the same to all liver segments.

Nevertheless, a few problems are associated with this method. The first relates to choosing values for the constants Kp and Kh. These constants are considered to relate to the organ blood equilibrium partition coefficients for the tracer. The liver, especially chronically damaged liver, had portosystemic shunts. And there is the time delay between the radioactivity of a radiotracer in the portal organ and that in the

liver. The latter must be considered when the tracer has a very short half life. These factors should be included in Kp, too. However, in the present study, Kp and Kh were assigned values of 1. As a result, rHBFp, and the rHBFp/rHBF ratio were estimated to be lower than the values for them that have been commonly known. Moreover, it is thought that Kh may change with the progress of chronic liver disease. An analysis of these constants will be needed.

The second problem, which is the most important one, stems from the assumption that water distribution is defined by a one compartment model. Although this assumption can be tested for an organ that has a single blood supply, such as the brain and the heart,^{4,19} it nevertheless remains extremely difficult. If a two or more compartment model is used, the analysis is of no practical value since it becomes very complicated. A final problem arises from the cost of the PET systems,²⁰ although they undoubtedly will become cheaper as they become more widely used.

With the demonstration of a new non-invasive technique for the quantitative measurement of both rHBFa and rHBFp simultaneously, a new tool has become available for studying the pathophysiology of liver disorders.

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