Nuclear Medicine Communications **12**, 235–242 (1991)

Measurement of hepatic blood flow by use of per-rectal portal scintigraphy with ^{133}Xe

S. SHIOMI*, T. KUROKI, T. UEDA, N. IKEOKA, K. KOBAYASHI, T. MONNA[1] and H. OCHI[2]

Third Department of Internal Medicine, [1]Department of Public Health, and [2]Department of Radiology, Osaka City University Medical School, Osaka, Japan

Received 14 August 1990, in revised form 15 October 1990 and accepted 17 October 1990

Summary

A relatively noninvasive method is needed to evaluate the hepatic blood flow of patients with liver disease. We used per-rectal portal scintigraphy with ^{133}Xe, and analysed the time–activity curves of the liver and portal vein. To do this, wash-out curves of the liver were plotted, and the hepatic blood flow and the ratio of the blood flow to the right lobe of the liver to that to the left lobe (R/L ratio) were calculated. The mean hepatic blood flow was 137 ± 23 ml/100 g/min for four patients with fatty liver, 139 ± 16 ml/100 g/min for seven patients with chronic persistent hepatitis, 120 ± 15 ml/100 g/min for ten patients with chronic aggressive hepatitis, and 75 ± 21 ml/100 g/min for 14 patients with cirrhosis. All seven patients with hepatic blood flow that was less than 100 ml/100 g/min and an R/L ratio less than 1.0 had cirrhosis. Only two of the 22 patients with hepatic blood flow that was greater than 100 ml/100 g/min and an R/L ratio greater than 1.0 had cirrhosis. Per-rectal portal scintigraphy can be used to measure the hepatic blood flow, but it was not useful for the diagnosis of fatty liver.

Introduction

In liver disease, and particularly in cirrhosis of the liver, a number of portal collaterals are formed as the disease progresses, and the decreased hepatic blood flow (HBF) that results is one cause of liver failure. For this reason, measurement of HBF would be useful for the diagnosis of liver disease and for the establishment of prognosis and plans for treatment.

^{133}Xe has been used in the measurement of the blood flow to various organs, including HBF. However, the methods that have been used are invasive, involving

*Author to whom correspondence should be addressed at Third Department of Internal Medicine, Osaka City University Medical School, Asahi-machi 1-5-7, Abeno-ku, Osaka 545, Japan.

the insertion of a catheter into the hepatic vein or injection of the radionuclide into the spleen, so they cannot be used routinely. Per-rectal portal scintigraphy with ^{133}Xe was used to obtain time–activity curves for the liver, and by using this relatively noninvasive method the HBF was calculated.

Patients and methods

Patients

Thirty-five patients with liver disease were diagnosed by inspection of a biopsy specimen taken during laparoscopy. Four had fatty liver (FL), seven had chronic persistent hepatitis (CPH), ten had chronic aggressive hepatitis (CAH), and 14 had cirrhosis of the liver.

Imaging

The patients fasted after the evening meal the day before the examination, and the rectum was emptied by the use of laxatives. The subject lay supine, and a polyethylene tube (Nelaton's catheter Fr. 18) was inserted 20 cm into the rectum, so that its tip was in the upper part of the rectum. Next, a camera for scintigraphy (Technicare-410S, Technicare, Solon, OH) was placed over the patient so that the heart and the liver were in the field of view. Then 370 MBq of ^{133}Xe in aqueous solution was injected via the tube into the upper part of the rectum, and the tube was flushed with 10 ml of physiological saline. A data processor for radionuclide studies (Sopha Simis 4, Baltimore, MD) was used to gather data starting at the time of this injection. One colour frame per 10 s was displayed for the 40 min of the test, after which the sum of the counts of these frames, called here the 40-min summed image, was displayed. The ^{133}Xe gas excreted by the lungs was collected by a gas-trap apparatus.

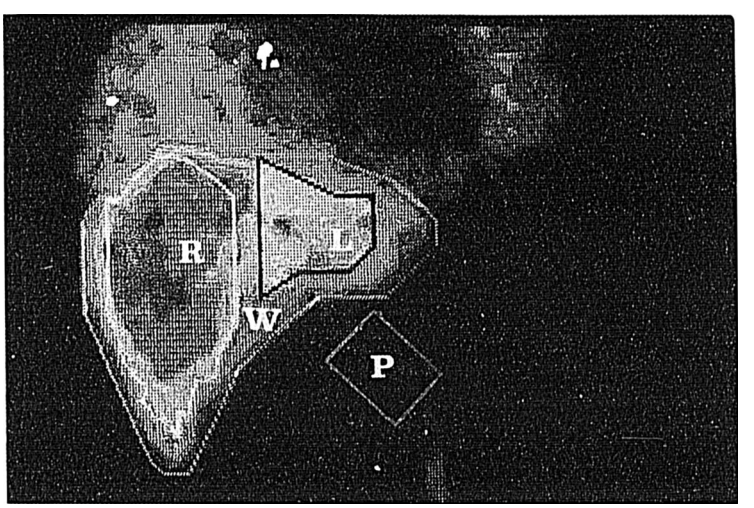

Fig. 1. Definition of regions of interest on a 40-min summed image for a patient with chronic persistent hepatitis. R, Right lobe of the liver; L, left lobe of the liver; W, whole liver; P, portal vein.

Calculation of hepatic blood flow

The ^{133}Xe in the rectum was absorbed quickly, and in time the portal vein and liver became clearly visible. On the 40-min summed images, the whole liver, the right lobe of the liver, the left lobe, and the portal vein were identified as regions of interest (Fig. 1 shows a patient with chronic persistent hepatitis and Fig. 2 a patient with cirrhosis). The count at each region for the 10-s periods was used to calculate the time–activity curves. Because much ^{133}Xe is excreted via the lungs, without flowing through the hepatic artery, it was assumed that the radionuclide that entered the liver arrived through the portal vein only. The count for ^{133}Xe that passed through the portal trunk at time n was P_n, and the count for the ^{133}Xe that reached the liver was defined as kP_n, where k was a coefficient that was different in different individuals.

kP_n decreases with time along the decreasing curve $e^{-\mu t}$, where e is the base of natural logarithms, μ is the coefficient of decrease in a particular patient, and t is the time after the injection of ^{133}Xe, and is $kP_n e^{-\mu t(i-n)}$ at time i. The liver count at time i is:

$$C_i = kP_1e^{-\mu t(n-1)} + kP_2e^{-\mu t(n-2)} + \ldots + kP_ne^{-\mu t0}$$
$$= k\sum_{j=1}^{n} P_j e^{-\mu t(n-j)} \quad (1)$$

where C_i is the liver count at time i.

Values from the time–activity curves for the liver and portal vein obtained for individuals were used in this equation, and an equation for the decreasing curve for the liver, $N=N_0e^{-\mu t}$, was obtained by solution of Equation 1 for μ. The results shown in Fig. 3 are for the same patient with chronic persistent hepatitis as in Fig. 1, and those in Fig. 4 are for the same patient with cirrhosis as in Fig. 2; in both figures, the time–activity curves shown on the left were used

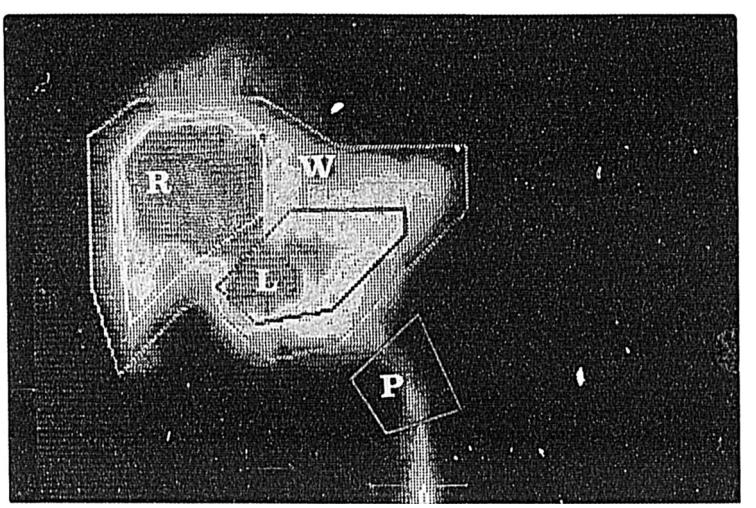

Fig. 2. Definition of regions of interest on a 40-min summed image for a patient with cirrhosis of the liver. R, Right lobe of the liver; L, left lobe of the liver; W, whole liver; P, portal vein.

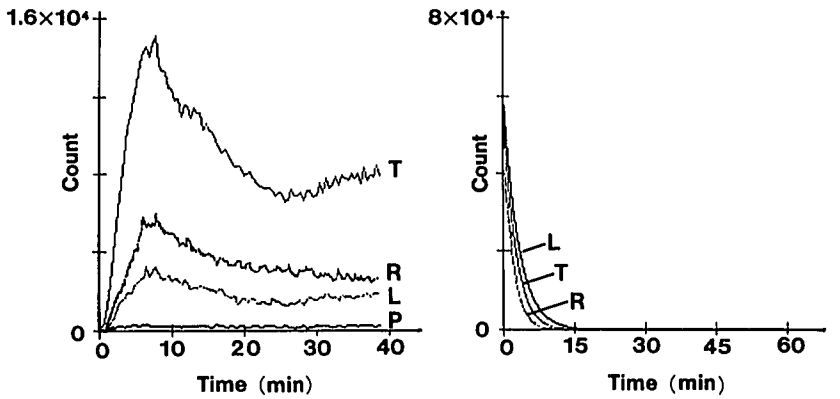

Fig. 3. Calculation of wash-out curves for the same patient as in Fig. 1. Time–activity curves were generated from the regions of interest (left). Wash-out curves are shown for the right lobe of the liver, left lobe of the liver, and the whole liver (right). These curves were calculated from values obtained from curves on the left and Equation 1. T, Total hepatic blood flow; R, flow to right lobe of the liver; L, flow to left lobe of the liver; P, portal blood flow.

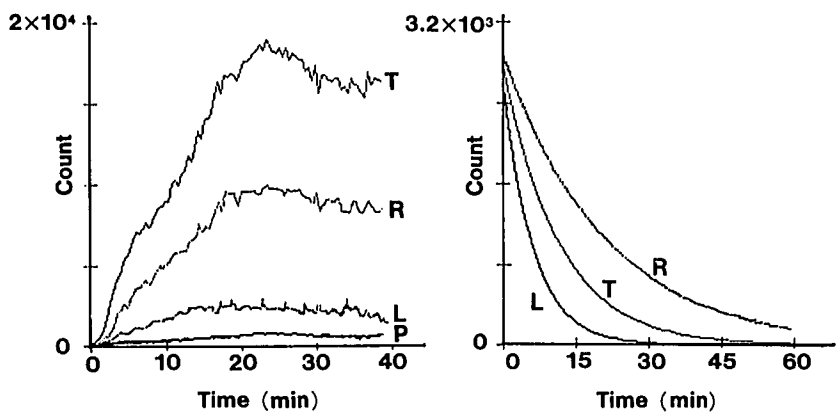

Fig. 4. Calculation of wash-out curves for the same patient as in Fig. 2. Time–activity curves were generated from the regions of interest (left). Wash-out curves are shown for the right lobe of the liver, left lobe of the liver, and the whole liver (right). These curves were calculated from values obtained from curves on the left and Equation 1. T, Total hepatic blood flow; R, flow to right lobe of the liver; L, flow to left lobe of the liver; P, portal blood flow.

to calculate the decreasing curves for the liver shown on the right. By the height-over-area method [1], the HBF can be calculated per 100 g of liver by the following equation:

$$HBF = 100\lambda q_0/\rho A \text{ (ml/100 g/min)} \quad (2)$$

where the area under the curve, A, and the initial count, q_0, are obtained from such decreasing curves, λ is the distribution coefficient between the blood and the liver, taken to be 0.74 [2], and ρ is the specific gravity of the liver, taken to be 1.02 [3].

Statistics

Results are expressed as mean ± S.D. The significance of differences between median values was tested by the Mann-Whitney U test. A P value less than 0.05 was considered to be significant.

Results

The mean total HBF (Table 1) was 137 ± 23 ml/100 g/min in FL, 139 ± 16 ml/100 g/min in chronic persistent hepatitis (CPH), 120 ± 15 ml/100 g/min in CAH, and 75 ± 21 ml/100 g/min in cirrhosis of the liver. The HBF for cirrhosis was significantly lower. In the right lobe, the mean blood flow was 151 ± 32 ml/100 g/min in FL, 152 ± 18 ml/100 g/min in CPH, 128 ± 22 ml/100 g/min in CAH, and 72 ± 31 ml/100 g/min in cirrhosis. Again, the value for cirrhosis was significantly lower. In the left lobe, these values were 117 ± 12, 117 ± 18, 112 ± 12 and 77 ± 15 ml/100 g/min, respectively. For cirrhosis, these differences were significant. As the liver disease progressed from hepatitis to cirrhosis, the ratio of the blood flow to the right lobe to that of the left lobe (R/L ratio) tended to decrease. The relationship between HBF and the R/L ratio was examined (Table 2). All seven patients with an HBF of 100 ml/100 g/min or less and a R/L ratio of 1 or less had cirrhosis. Of the 22 patients with an HBF higher than 100 ml/100 g/min and a R/L ratio higher than 1, only two had cirrhosis of the liver.

Table 1. Hepatic blood flow (HBF) in liver diseases.

	n	*Total HBF*	*Flow to right lobe*	*Flow to left lobe*	*Right/left ratio*
Fatty liver	4	137 ± 23^{a1}	151 ± 32^{a2}	117 ± 12^{a3}	1.27±0.21
Chronic persistent hepatitis	7	139 ± 16^{b1}	152 ± 18^{b2}	117 ± 18^{b3}	1.32±0.23
Chronic aggressive hepatitis	10	120 ± 15^{c1}	128 ± 22^{c2}	112 ± 12^{c3}	1.14±0.15
Liver cirrhosis	14	75 ± 21^{d1}	72 ± 31^{d2}	77 ± 15^{d3}	0.94±0.35

Significant differences between a1 and d1, $P<0.05$; b1 and d1, $P<0.01$; c1 and d1, $P<0.01$; a2 and d2, $P<0.05$; b2 and d2, $P<0.01$; c2 and d2, $P<0.05$; a3 and d3, $P<0.05$; b3 and d3, $P<0.05$; c3 and d3, $P<0.05$. Differences in the right/left ratio were not significant.

Table 2. Numbers of patients with different liver diseases grouped by hepatic blood flow (HBF) in ml per 100 g of liver per minute and by the right/left lobe ratio.

	Numbers with R/L <1 and HBF <100	*Numbers with R/L >1 and HBF <100*	*Numbers with R/L <1 and HBF ≥100*	*Numbers with R/L ≥1 and HBF ≥100*
Fatty liver	0 (0%)	0 (0%)	0 (0%)	4 (100%)
Chronic persistent hepatitis	0 (0%)	0 (0%)	0 (0%)	7 (100%)
Chronic aggressive hepatitis	0 (0%)	1 (10%)	0 (0%)	9 (90%)
Liver cirrhosis	7 (50%)	5 (36%)	0 (0%)	2 (14%)

Discussion

The liver, which is the largest intraperitoneal organ, receives about a quarter of the total cardiac output. Many studies have measured HBF, the earliest being the report by Burton-Opitz [4] in which the HBF of dogs was measured with the use of a stromuhr. The earliest measurements in humans were reported by Bradley *et al.* [5], who used bromsulphalein and a catheter in the hepatic vein in a method based on the Fick principle. Problems with this method have been its complexity and invasiveness.

The inert gases ^{133}Xe and ^{85}Kr are fat-soluble, and are able to disperse freely through tissues. When injected in the form of an aqueous solution into an organ for which blood flow is to be measured, more than 95% is trapped in the alveoli of the lungs at the time of its first passage, and is rapidly excreted by that route. Thus, there is almost no recirculation. Also, because the amount of inert gas that is excreted from tissue is dependent on the blood flow to that tissue, it is possible to find the amount of blood flow to a tissue from the decreasing curve for the tissues. This method was used by Iio *et al.* [6], who injected ^{85}Kr or ^{133}Xe into the splenic vein or the spleen of dogs. Methods used for measurement of HBF in humans include direct injection into the parenchyma of the liver [7] and direct injection into the parenchyma via a catheter placed in the hepatic vein [8]. Kashiwagi *et al.* [9] used scintiphotosplenoportography and ^{133}Xe to measure HBF. However, the invasiveness of these methods prevents their routine use.

We have suggested the use of $^{99}Tc^{m}$-O_4 in per-rectal portal scintigraphy. Using this method the portal circulation can be evaluated continuously. Here, we tried using ^{133}Xe in such scintigraphy [10]. Ueda *et al.* [11] have reported the mean HBF of healthy adults to be 184 ml/100 g/min, and Schmitz-Feuerhake *et al.* [12] have reported a very different value of 91 ml/100 g/min. We found a mean HBF of 75 ml/100 g/min in patients with cirrhosis, and a mean of 128 ml/100 g/min in patients with chronic hepatitis. Compared to the mean value for healthy persons reported by Ueda *et al.*, the mean HBF reported here was not particularly low for the patients with chronic hepatitis, but it was low for the patients with cirrhosis. Earlier methods have involved the injection of a radionuclide or measurements made during surgery, in which, because of the use of anaesthesia etc., physiological conditions were abnormal. In our

method, ^{133}Xe was absorbed by the body, so the slight increase in the flow to the liver caused by injection of a liquid by the use of pressure is avoided. However, the portal count is probably underestimated by this method. The extraportal ^{133}Xe (that which passes through the lungs and then through the hepatic artery to the liver) probably cannot be completely ignored. Another possible source of error is the haematocrit. None of our patients had anaemia but correction for a low haematocrit should be made as described elsewhere [8]. It is difficult to measure the specific gravity and the distribution coefficient of the liver of human subjects, so the values obtained in studies of dogs were used. Because ^{133}Xe is fat-soluble, the removal of ^{133}Xe from the liver of patients with FL was slow, which probably caused the values calculated for the hepatic blood flow to be lower than the actual values. This would suggest that FL might be diagnosed by this method. However, the hepatic blood flow of the four patients with FL was not significantly lower than that of the patients with chronic hepatitis. The reason seems to be that the solubility of ^{133}Xe in fat had a larger effect on the results of this test than predicted, or perhaps that there was large variation in the values found for chronic hepatitis, so that the relatively small change caused by FL gave values in the same range. If this method is used clinically, patients with FL should be excluded for these reasons.

Our results showed that there is a significant decrease in the HBF in cirrhosis of the liver, accompanied by a tendency for the blood flow to the left lobe relative to the amount of blood flow to the right lobe to increase. Our results are similar to those of Kashiwagi *et al.* [9]; liver scintigraphy showed that with the progress to cirrhosis, morphological changes include atrophy of the right lobe of the liver, with hypertrophy of the left lobe. The different blood flow to the right and left lobes might arise because of differing needs for blood in these different parts. Whether portal streaming, in which blood from the splenic and inferior mesenteric vein flows mainly into the left lobe of the liver, and blood from the superior mesenteric vein mainly flows into the right lobe [13], has any effect on this difference is an important issue in measurements of HBF.

References

1. Mathew NT, Meyer JS, Bell RL, Johnson PC, Neblett CR. Regional cerebral blood flow and blood volume measured with the gamma camera. *Neuroradiology* 1972; **4**: 133.
2. Conn JR. Equilibrium distribution of radioxenon in tissue: xenon-hemoglobin association curve. *J Appl Physiol* 1961; **16**: 1065.
3. Rees JR, Redding VJ, Ashfield R. Hepatic blood-flow measurement with xenon 133. *Lancet* 1964; **ii**: 562.
4. Burton-Opitz R. The vascularity of the liver. VIII. The influence of adrenalin upon the arterial inflow. *Q J Exp Physiol* 1912; **5**: 309.
5. Bradley SE, Ingelfinger FJ, Bradley GP, Curry JJ. The estimation of hepatic blood flow in man. *J Clin Invest* 1945; **24**: 890.
6. Iio M, Wagner HN, Rose RS, Ueda K, Lichtlen PR, Jude JR, Knickerbocker GG, Bourne HR. Radioactive krypton and xenon in the measurement of coronary, hepatic and cerebral blood flow. *J Nucl Med* 1963; **4**: 213.

7. Birtch AG, Casey BH, Zakheim RM. Hepatic blood flow measured by the krypton-85 clearance technique. *Surgery* 1967; **62**: 174.
8. Lundbergh P, Strandell T. Hepatic wash-out curves of ^{85}Kr and ^{133}Xe after retrograde hepatic venous injections in patients with infectious hepatitis and in controls. *Scand J Clin Lab Invest* 1974; **33**: 277.
9. Kashiwagi T, Kamada T, Kimura K, Suematsu T, Abe H, Okagawa K. Studies on the portal circulation by scintiphotosplenoportography: measurement of regional hepatic blood flow with ^{133}Xe in man. *Acta Hepatol Jpn* 1976; **17**: 749.
10. Shiomi S, Kuroki T, Kurai O, Kobayashi K, Ikeoka N, Monna T, Ochi H. Portal circulation by technetium-99m pertechnetate per-rectal portal scintigraphy. *J Nucl Med* 1988; **29**: 460.
11. Ueda H, Unuma T, Iio M, Kameda H. Measurement of hepatic arterial and portal blood flow and circulation time via hepatic artery and portal vein with radioisotope. *Jpn Heart J* 1962; **3**: 154.
12. Schmitz-Feuerhake I, Huchzermeyer H, Reblin T. Determination of the specific blood flow of the liver by inhalation of radioactive rare gases. *Acta Hepato- Gastroenterol* 1975; **22**: 150.
13. Gates GF, Dore EK. Streamline flow in the human portal vein. *J Nucl Med* 1973; **14**: 79.