

Clinical need for both scintigraphy with technetium-99m GSA and per-rectal portal scintigraphy in some patients with chronic liver disease

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Scintigraphy with ^{99m}Tc -diethylenetriaminepentaacetate with galactosyl human serum albumin (^{99m}Tc -GSA) and per-rectal portal scintigraphy are useful for evaluating hepatic functional reserve and portal circulation, respectively. We did the procedures simultaneously in some patients to examine the relationship between hepatic functional reserve and portal circulation in chronic liver disease. Scintigraphy with ^{99m}Tc -GSA was done in 10 healthy subjects, 45 patients with chronic hepatitis, and 165 patients with cirrhosis. Fifty-seven patients (13 with hepatitis and 44 with cirrhosis) also underwent per-rectal portal scintigraphy with ^{99m}Tc -pertechnetate within two weeks. A receptor index was calculated by dividing the radioactivity of the liver region of interest (ROI) by that of the liver-plus-heart ROI at 15 min after the injection of ^{99m}Tc -GSA. The index of blood clearance was calculated by dividing the radioactivity of the heart ROI at 15 min by that of the heart ROI at 3 min. A solution containing ^{99m}Tc -pertechnetate was instilled into the rectum, and serial scintigrams were taken while radioactivity curves for the liver and heart were recorded sequentially. A per-rectal portal shunt index was determined by calculating the ratio of counts for the liver to counts for the heart integrated for 24 seconds immediately after the appearance of the liver time-activity curve. The median receptor index was lower for more severe liver disorders, increasing in the order of chronic hepatitis, compensated cirrhosis and decompensated cirrhosis, and the median index of blood clearance was higher. The median receptor index was significantly lower when a complication (varices, ascites, or encephalopathy) was present, and the median index of blood clearance was higher. The shunt index was correlated significantly with the two other indices, but these values for some one-third of the patients disagreed in either indices. Scintigraphy with ^{99m}Tc -GSA and per-rectal portal scintigraphy with ^{99m}Tc -pertechnetate are both needed for accurate assessment of the severity of chronic liver disease before treatment-making decisions, because in some patients, results are not correlated.

Key words: ^{99m}Tc -GSA, per-rectal portal scintigraphy, cirrhosis of the liver, portal circulation

INTRODUCTION

IN CIRRHOSIS with hepatitis virus, hepatocellular damage precedes and, after the necrotic hepatocytes have settled, fibrotic change progresses and portal pressure rises leading to the development of portosystemic shunt. This

portosystemic shunt reduces the portal blood flow and aggravates hepatocellular damage. Cirrhosis of the liver progresses in a vicious spiral of both parameters. Assessment of both the hepatic functional reserve and portal circulation is therefore necessary to grasp the severity of cirrhosis, but the degree of progress of both parameters differs according to the individual.

Ideally the results of one test should not interfere with those of the other. Some tests used at present for the evaluation of functional reserve, such as the indocyanine green retention test, are affected by the portal circulation. Hepatic receptor imaging with ^{99m}Tc -diethylenetri-

Received February 3, 1999, revision accepted April 16, 1999.

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aminepentaacetate with galactosyl human serum albumin (^{99m}Tc -GSA) is a new method for the diagnosis of hepatic disease by assessment of the specific binding of hepatocytes to asialoglycoprotein receptors.¹ Hepatic receptor imaging with ^{99m}Tc -GSA makes possible quantitative evaluation of hepatic functional reserve by a receptor index and an index of blood clearance.²⁻⁴ Results obtained by this method are not greatly affected by the portal circulation.

Per-rectal portal scintigraphy with ^{99m}Tc -pertechnetate makes possible relatively noninvasive measurement of the portal circulation via the inferior mesenteric vein.⁵ We used both methods to examine the relationship between hepatic functional reserve and the portal circulation in chronic liver disease. Furthermore, we examined how frequently these parameters disagreed and what treatments should be given in such cases.

MATERIALS AND METHODS

Patients

The subjects were 10 persons found to have healthy livers, 45 patients with chronic hepatitis, 119 patients with compensated liver cirrhosis, and 46 patients with decompensated liver cirrhosis. All subjects had been admitted to our hospital between April 1993 and September 1997. Chronic hepatitis and cirrhosis were diagnosed on the basis of the results of laparoscopic biopsy or needle biopsy done under ultrasonic guidance. Within 1 week of entering the hospital, all patients with suspected or confirmed cirrhosis underwent barium esophagography or endoscopy for detection of esophageal varices, and all patients had abdominal ultrasonography for detection of ascites. Decompensated liver cirrhosis was identified by the presence of jaundice, ascites and/or encephalopathy.

To evaluate the portal circulation, we selected 57 patients with an underlying hepatic viral infection without hepatocellular carcinoma for per-rectal portal scintigraphy. Thirteen had chronic hepatitis and 44 had cirrhosis. Informed consent was obtained. Both ^{99m}Tc -GSA scintigraphy and per-rectal portal scintigraphy were done within 2 weeks of admission.

Measurement of receptor index and index of blood clearance

^{99m}Tc -GSA (185 MBq) was injected intravenously, and dynamic images were recorded with the patient supine

under a gamma-camera with a large field of view and a low-energy multipurpose collimator with parallel holes (ZLC-3500, Shimadzu Corp., Kyoto, Japan). Computer acquisition of the gamma-camera data was started just before the injection of the ^{99m}Tc -GSA and was stopped 20 min later. The receptor index was calculated by dividing the radioactivity of the liver ROI by that of the liver-plus-heart ROI at 15 min after the injection. The index of blood clearance was calculated by dividing the radioactivity of the heart ROI at 15 min after the injection by that of the heart ROI at 3 min.⁴

Measurement of portal shunt index

Patients fasted after the evening meal of the day before the test. The rectum was emptied by administering a laxative. A polyethylene tube (Nélaton's catheter, French 18) was inserted 20 cm into the rectum, reaching the upper part. To generate the time-activity curves, we used the same gamma-camera and collimator as before, interfaced with a digital computer. The camera was positioned over the patient's abdomen so that the field of view included the heart, liver and spleen. 370 MBq of ^{99m}Tc -pertechnetate (2 ml) was first given through the tube, followed by 15 ml of air. Then time-activity curves for the heart and liver areas were obtained every 4 sec. At the end of the 5-min examination, the 5-min summed image displayed in color was recorded. To evaluate the extent of the portosystemic shunt by the shunt index, we calculated the ratio of counts for the liver to counts for the heart integrated for 24 seconds immediately after the appearance of the liver time-activity curve.⁵ The shunt indices ranged from 2.0% to 8.6% in normal subjects.⁶

Statistical Analysis

Results are expressed as medians with 25th and 75th percentiles. The significance of differences between medians was evaluated by the Mann-Whitney *U* test (two-tailed). Differences with $p < 0.05$ were considered to be significant. The correlation of the receptor index and index of blood clearance with the shunt index was analyzed by Spearman's rank correlation analysis.

RESULTS

The median (25th and 75th percentiles) of the receptor index and index of blood clearance in patients with chronic liver disease are shown in Table 1. The difference

Table 1 Receptor index and index of blood clearance in patients with chronic liver diseases

Diseases	n	Receptor index	Index of blood clearance
		Median (25%, 75%)	Median (25%, 75%)
Healthy subjects	10	0.95 (0.94, 0.96)	0.51 (0.42, 0.56)
Chronic hepatitis	45	0.94 (0.92, 0.95)	0.54 (0.48, 0.62)
Compensated liver cirrhosis	119	0.87 (0.82, 0.92)	0.66 (0.58, 0.73)
Decompensated liver cirrhosis	46	0.80 (0.71, 0.85)	0.75 (0.68, 0.81)

Table 2 Receptor index and the presence of varices, ascites, and encephalopathy in patients with cirrhosis

Group	Absent		Present	
	n	Median (25%, 75%)	n	Median (25%, 75%)
Varices	62	0.89 (0.85, 0.93)	103	0.83 (0.79, 0.88)**
Ascites	128	0.87 (0.81, 0.92)	37	0.80 (0.70, 0.84)***
Encephalopathy	156	0.86 (0.81, 0.91)	9	0.71 (0.66, 0.72)*

* $p = 0.0007$, ** $p = 0.0002$, *** $p < 0.0001$ compared with other group by Mann-Whitney U test.

Table 3 Index of blood clearance and the presence of varices, ascites, and encephalopathy in patients with cirrhosis

Group	Absent		Present	
	n	Median (25%, 75%)	n	Median (25%, 75%)
Varices	62	0.63 (0.56, 0.71)	103	0.71 (0.66, 0.77)**
Ascites	128	0.66 (0.58, 0.73)	37	0.75 (0.69, 0.80)***
Encephalopathy	156	0.68 (0.60, 0.75)	9	0.83 (0.77, 0.84)*

* $p = 0.0011$, ** $p = 0.0004$, *** $p < 0.0001$ compared with other group by Mann-Whitney U test.

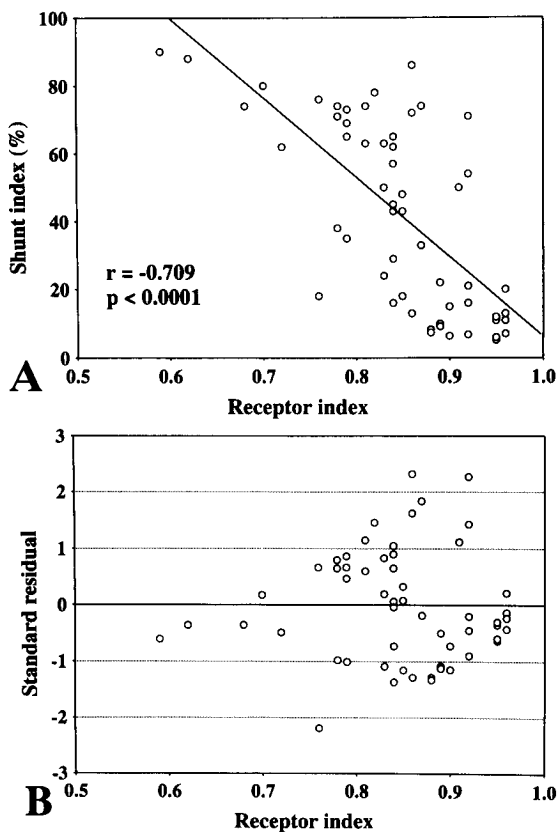


Fig. 1 A. Correlation between the receptor index and shunt index. B. Correlation between the receptor index and standard residual. There were 20 out of 57 patients with the absolute values of the standard residual above 1.0.

between the receptor index of patients with cirrhosis and healthy subjects or patients with chronic hepatitis was significant ($p = 0.0007$ and $p = 0.0065$, respectively). That between the receptor index of patients with compensated cirrhosis and decompensated cirrhosis was significant

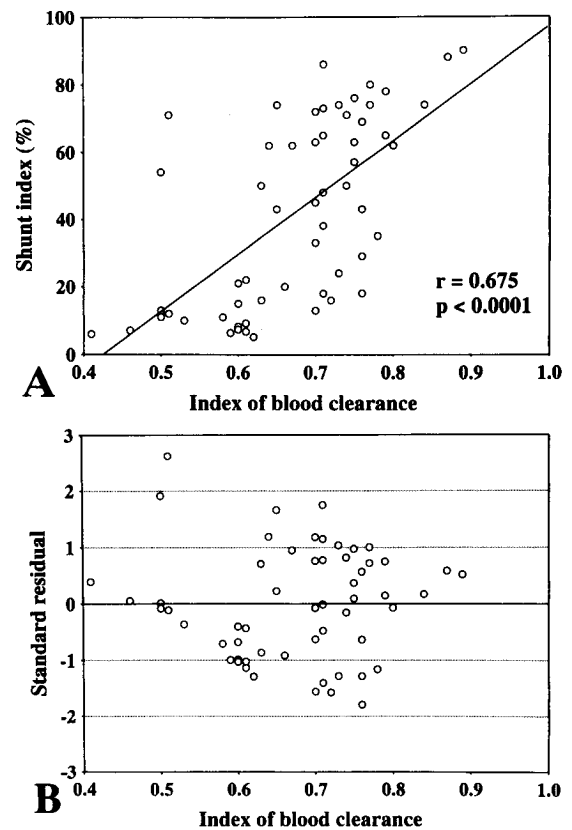


Fig. 2 A. Correlation between the index of blood clearance and shunt index. B. Correlation between the index of blood clearance and standard residual. There were 21 out of 57 patients with the absolute values of the standard residual above 1.0.

($p < 0.0001$). The difference between the index of blood clearance of patients with cirrhosis and healthy subjects or patients with chronic hepatitis was significant ($p = 0.0008$ and $p < 0.0001$, respectively). That between the index of blood clearance of patients with compensated cirrhosis

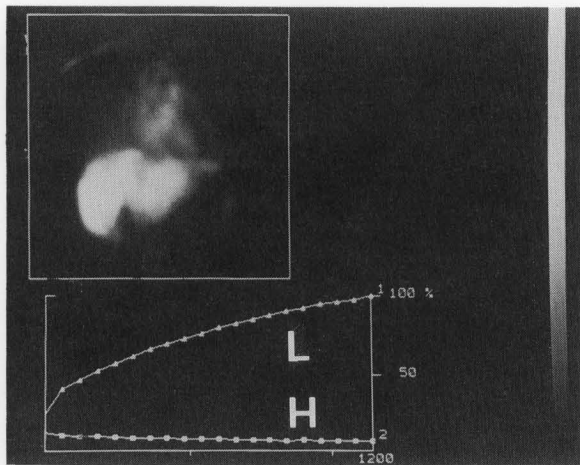


Fig. 3 Patient 1. Image summed over a 20-min period and time-activity curves for the heart and liver after injection of ^{99m}Tc -GSA. H = heart; L = liver. The liver image is more distinct than the heart image, showing liver function to be almost normal.

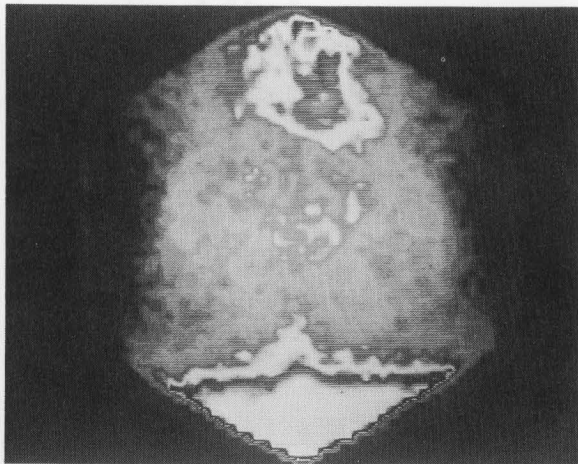


Fig. 4 Patient 1. Per-rectal portal scintigram with ^{99m}Tc -pertechnetate. The liver image is less distinct than the heart image, showing portal circulation to be abnormal. Because of the findings from Figures 3 and 4, the patient underwent transjugular intrahepatic portosystemic shunt, with good results.

and decompensated cirrhosis was significant ($p = 0.0002$).

The medians of the receptor index in cirrhotic patients with complications (varices, ascites or encephalopathy) were lower than those in cirrhotic patients without complications ($p = 0.0002$, $p < 0.0001$ and $p = 0.0007$, respectively; Table 2). The medians of the index of blood clearance in cirrhotic patients with complications (varices, ascites or encephalopathy) were higher than those in cirrhotic patients without complications ($p = 0.0004$, $p < 0.0001$ and $p = 0.0011$, respectively; Table 3).

The shunt index was correlated significantly with the

receptor index ($r = -0.709$, $p < 0.0001$; Fig. 1) and the index of blood clearance ($r = 0.675$, $p < 0.0001$; Fig. 2). To find the patients falling out of the correlation of the shunt index and receptor index or index of blood clearance (disagreeing cases), the standard residual (standardization of the distance between the sample and the regression curve) was calculated. The patients with the absolute values of the standard residual above 1.0 were defined as disagreeing cases. There were 20 out of 57 patients with the absolute values of the standard residual above 1.0 in terms of receptor index, and 21 out of 57 patients had the absolute value of the standard residual above 1.0 in terms of the index of blood clearance. Fourteen of those patients were in both groups with values that were disagreeing cases.

Case Report

Patient 1. A 51-year-old man was admitted to hospital and found to have cirrhosis and esophageal varices. Scintigram with ^{99m}Tc -GSA showed the left lobe of the liver to be swollen, and the heart was less clearly defined than the liver (Fig. 3). The receptor index and the index of blood clearance were slightly abnormal (0.89 and 0.50, respectively). A per-rectal portal scintigram (Fig. 4) showed high radionuclide activity in the heart, but the liver image was less clear than that of the heart, and the shunt index was high (72%). These values were not correlated. For this patient, the seriously abnormal shunt index showed that a transjugular intrahepatic portosystemic shunt (TIPS) was indicated. The treatment was successful.

DISCUSSION

Both the hepatic functional reserve and the portal circulation are necessary to evaluate the degree of cirrhosis when decisions about treatment are being made. TIPS is indicated in cases which have developed portosystemic shunt with a slightly decrease in hepatic functional reserve. Nevertheless, cases with a severe decrease in hepatic functional reserve fall into liver failure if TIPS is performed, and therefore they are excluded from TIPS indication. In contrast, cases with a severe decrease in hepatic functional reserve detected by GSA scintigraphy are indicated to require liver transplantation.

The per-rectal approach for the measurement of the portal circulation via the inferior mesenteric vein is a relatively noninvasive method. Sodium iodine-131⁷ and ^{13}N -ammonia⁸ have been used as the radiopharmaceuticals in this approach, but these nuclides are not absorbed well by the rectum, making it difficult to make a detailed analysis of the portosystemic shunt. Per-rectal measurement with $^{201}\text{TlCl}$,^{9,10} ^{99m}Tc -pertechnetate⁵ or ^{123}I -iodoamphetamine^{11,12} has been used in recent years. With $^{201}\text{TlCl}$ or ^{123}I -iodoamphetamine, calculation of an index is easy by dividing of the radioactivity of the heart or lungs by the radioactivity of the liver, but the half-time is long

and the cost is high.¹³ We have been doing per-rectal portal scintigraphy with ^{99m}Tc-pertechnetate routinely because of its shorter half-time and low cost, although calculation of an index is difficult, involving a more complex equation.^{5,6}

We found significant differences between patients with ascites and those without ascites in both the receptor index and the index of blood clearance. These differences were greater than those depending on the presence or absence of varices. These findings suggest that scintigraphy with ^{99m}Tc-GSA reflects hepatic functional reserve more than the portal circulation (reserve has already declined when ascites appears). In contrast, with per-rectal portal scintigraphy, the shunt index was significantly affected by the presence or absence of varices but not by the presence or absence of ascites.⁶ Fifty-seven of our patients with chronic liver disease had both kinds of scintigraphy done simultaneously, and the shunt index was correlated significantly with both the receptor index and the index of blood clearance.

Development of portosystemic shunt and a decrease in hepatic functional reserve are considered to seriously affect the prognosis of patients with cirrhosis. We have reported a significant relation between the data obtained by per-rectal portal scintigraphy and prognosis.⁶ It is also considered that the hepatic functional reserve obtained by GSA scintigraphy is related to the prognosis of cirrhosis, and will be a useful tool for the assessment of the indication of liver transplantation in future. We found however that these values for one or both tests were not correlated for a total of 27 patients. In these patients, most with cirrhosis of the liver, the decrease in hepatic functional reserve and the increase in the abnormality of the portal circulation did not proceed at the same rate. Both examinations are necessary for accurate assessment of the severity of the liver disease in such patients.

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