Asialoglycoprotein Receptor Scintigraphy in Evaluation of Auxiliary Partial Orthotopic Liver Transplantation

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The purpose of this study was to evaluate asialoglycoprotein receptor scintigraphy in the post-transplant monitoring of liver graft and native liver functions in recipients of auxiliary partial orthotopic liver transplantation (APOLT) from living donors. **Methods:** We performed 36 asialoglycoprotein receptor scintigraphies on 13 patients who had undergone APOLT for noncirrhotic metabolic liver diseases or for small-for-size grafts. The portal vein of the native liver was separated in 12 patients. Anterior dynamic images including the heart and both livers were obtained for 16 min after intravenous injection of ^{99m}Tc-diethylenetriamine pentaacetic acid-galactosyl human serum albumin (GSA), and thereafter static SPECT images of both livers were obtained. Uptake rates from the blood to the graft and to the native liver were determined separately by Patlak plot graphical analysis. Relative uptake of GSA by the graft was calculated from transverse SPECT images. The relative volume of the graft liver was determined by CT. **Results:** The relative uptake of GSA by the graft was higher or increased more rapidly than the relative volume of the graft in 8 of 11 patients with no severe complications concerning the graft. The relative uptake by severely damaged graft liver in 2 patients was much lower than the relative volume. The uptake rate of GSA by the graft was low in these 2 patients. The uptake rate by the native liver decreased when the portal vein was separated. **Conclusion:** The relative uptake of GSA was a better indicator of graft liver function than was anatomic volume. The uptake rate provided additional independent information of each liver. Asialoglycoprotein receptor scintigraphy is useful for distinguishing and monitoring the graft and native liver functions in patients who had undergone APOLT.

Key Words: asialoglycoprotein receptor scintigraphy; auxiliary partial orthotopic liver transplantation; ^{99m}Tc-galactosyl serum albumin

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The asialoglycoprotein receptor on hepatocytes is responsible for the metabolism of serum glycoproteins (*1*). The number of receptors decreases in patients with chronic liver disease (*2*). The usefulness of asialoglycoprotein receptor scintigraphy in liver diseases has been reported (*3,4*). Galactosyl human serum albumin (GSA) is an analog ligand to the asialoglycoprotein receptor. GSA labeled with ^{99m}Tc by chelation with diethylenetriamine pentaacetic acid has been used to evaluate liver functions and image the liver (*5–7*).

Auxiliary partial orthotopic liver transplantation (APOLT), in which the native liver is left partially in place and a donor liver fragment is added orthotopically, has been developed as therapy for patients suffering from fulminant hepatic failure (*8*). APOLT has also been performed in patients with noncirrhotic metabolic liver disease (*8–11*). Separate assessment of the graft and native liver functions is necessary for patients who undergo APOLT. Biochemical tests are of limited clinical value because they do not distinguish between the functions of two different livers. The only definitive method with which to assess respective liver function is liver biopsy. However, this is invasive and cannot be repeated easily.

The primary usefulness of hepatobiliary scintigraphy has been demonstrated for the postoperative monitoring of graft function in recipients of liver transplants including APOLT (*12–16*). We performed asialoglycoprotein receptor scintigraphy in the post-transplant monitoring of the graft and native liver functions in patients who had undergone APOLT for noncirrhotic metabolic liver diseases or for small-for-size grafts.

MATERIALS AND METHODS

Patients

We performed 36 studies on 13 patients (3 males, 10 females; age range 5–52 y, mean age 25.5 y) who had undergone APOLT from living related donors. Four patients had noncirrhotic metabolic liver disease, and 9 patients had cirrhosis of variable etiology. The patients underwent resection of the native left lobe or left lateral segment and orthotopic replacement of a donor left lobe or left lateral segment. The portal vein of the native liver was separated at the time of transplantation in 10 patients and later in 2

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patients to increase the portal blood flow of the graft. The interval of APOLT and the ^{99m}Tc-GSA study ranged from 12 d to 32 mo.

Galactosyl Human Serum Albumin Scintigraphy

^{99m}Tc-GSA was supplied by Nihon Mediphysics (Nishinomiya, Japan). Three milligrams and 185 MBq ^{99m}Tc-GSA were injected intravenously. The dose was decreased to one half for children younger than 10 y. Images, including those of the heart and both livers, were obtained immediately after injection of ^{99m}Tc-GSA. Patients were in the supine position under a dual-head, large-field-of-view gamma camera (Hitachi RC-2600I or Hitachi RC-2500IV; Hitachi Medical Corp., Tokyo, Japan) equipped with a low-energy, high-resolution, parallel-hole collimator. Digital images with a matrix size of 64 × 64 pixels were fed into an on-line nuclear data processor (Hitachi RW3000) at 10- or 20-s frames for 16 min after injection. After the dynamic study, static SPECT was performed. Data were collected in a 64 × 64 matrix with 1.5 zoom through 360° (180° for each head, 64 projections, 20 s/step). SPECT projections were spatially smoothed with a Butterworth filter and were reconstructed using a filtered backprojection technique with a ramp filter.

Data Analysis

To assess the whole liver function, the receptor index was calculated. Regions of interest (ROIs) were placed over the whole liver and precordium. Time-activity curves for the whole liver and heart were generated. The receptor index was calculated by dividing the radioactivity of the liver ROI by the sum of the radioactivity of the liver and heart ROIs at 15 min postinjection (*6*).

To avoid the superimposition of two livers, smaller ROIs were drawn in the graft and native liver, respectively, with reference to CT images. Smaller ROIs were also drawn in the heart. Time-activity curves for each organ were generated on a pixel basis. Uptake rates from blood to the graft liver and from blood to the native liver were calculated using Patlak plot graphical analysis (*17*). Assuming unidirectional transfer process of ^{99m}Tc-GSA from the blood to liver, liver activity, L(t), can be expressed as:

$$L(t) = k_u \int_0^t H(\tau)d\tau + V \times H(t),$$

where H(t) represents heart activity, k_u is the rate constant and V is the initial distribution volume. Dividing this equation by H(t) provides the following:

$$L(t)/H(t) = k_u \int_0^t H(\tau)d\tau/H(t) + V.$$

Plotting of L(t)/H(t) versus

$$\int_0^t H(\tau)d\tau/H(t)$$

provides k_u as the slope of a straight line. Therefore, the graph of the ratio of liver activity to heart activity versus the ratio of heart activity-time integral to heart activity at the respective times was composed. Using points between 1 and 5 min after injection, the slope of a straight line fitted by a least squares routine was determined (*17*).

In each transverse SPECT image, ROIs were placed over each liver with reference to CT images. Counts of radioactivity in the graft and native liver were obtained by integration of counts in all transverse SPECT images. Relative uptake by the graft liver was calculated by dividing counts in the graft liver by counts in both livers.

Volumetry

The relative uptake by the graft was compared with the relative volume of the graft. The volume of the graft liver and native liver was measured by CT within 8 d before or after ^{99m}Tc-GSA scintigraphy. The relative volume of the graft liver was calculated by dividing its volume by the volume of whole liver.

RESULTS

The results are summarized in Table 1. Patients 1, 2, 5 and 7 had noncirrhotic metabolic liver disease. In patients 1 and 2, the portal vein of the native liver was separated between the first and the second GSA study. The portal vein of the native liver was not separated in patient 3. The other patients underwent separation of the native liver portal vein at the time of transplantation.

The relative uptake by the graft liver correlated well with the relative volume of the graft (n = 33, $r = 0.715$, $P < 0.0001$, Fig. 1). However, in 8 of 11 patients without severe complications from the graft, the relative uptake was higher or increased more rapidly than the relative volume by a difference of more than 15% (patients 2, 5 and 8–13). A representative case is shown (Fig. 2). The relative uptake was almost the same as the relative volume in 3 of 11 patients (patients 1, 6 and 7). The relative uptake by the severely damaged graft liver was much lower than the relative volume (patients 3 and 4). In patient 3, in whom massive necrosis of the graft was demonstrated by biopsy, and in patient 4, who died of hepatic failure 1 mo after the GSA study, the relative uptake was less than 10%, but the relative volume was more than 30%. These findings suggest that the relative uptake of GSA is a better indicator of graft liver function than is anatomic volume.

Figure 3 shows an example of Patlak plot graphical analysis for the determination of the uptake rate. The uptake rate of GSA by the graft increased gradually after the transplantation (patients 5, 6, 8, 10 and 11) or the separation of the native liver portal vein (patient 1), but it was low in patients 3 and 4, whose graft liver was severely damaged. In patients 1 and 2, who had noncirrhotic metabolic disease, the portal vein of the native liver was separated more than 1 y after APOLT. The uptake rate by the native liver decreased after the separation of the portal vein, but the uptake rate by the noncirrhotic native liver, except in patient 5, still seemed higher than by the cirrhotic liver. In patient 3, who had cirrhosis and whose portal vein of the native liver was not separated, the uptake rate by the native liver was relatively high as among the other patients with cirrhosis.

The receptor index reflected the whole liver function. In patient 3, the index was high during the 3 mo after APOLT but decreased when the function of the graft liver decreased.

DISCUSSION

In APOLT, the separate assessment of two different livers is necessary. GSA scintigraphy provided valuable information on the graft and native liver function. We calculated two

TABLE 1.
Parameters for Graft and Native Liver Determined by ^{99m}Tc-GSA Scintigraphy

Patient no.	Age (y)	Sex	GSA study		Graft liver		Native liver	Receptor index
			No.	Days after APOLT	Relative uptake (%)	Uptake rate (min^{-1})	Uptake rate (min^{-1})	
1*	5	F	1	775	7.5	0.234	0.537	0.970
			2	803	26.4	0.257	0.304	0.955
			3	825	35.7	0.310	0.300	0.966
			4	886	39.6	0.392	0.380	0.966
			5	970	49.7	0.453	0.352	0.948
2*	5	F	1	403	49.5	0.442	0.406	0.969
			2	416	67.9	0.495	0.266	0.973
			3	446	72.6	0.362	0.235	0.970
			4	518	67.2	0.352	0.251	0.900
3	24	M	1	38	61.3	0.159	0.203	0.929
			2	90	62.9	0.260	0.374	0.965
			3	208	11.0	0.059	0.260	0.848
			4	242	8.0	0.055	0.252	0.820
			5	277	5.2	0.042	0.263	0.803
			6	325	2.0	0.027	0.243	0.830
4	19	M	1	27	9.0	0.013	0.041	0.502
5*	52	F	1	27	55.4	0.202	0.135	0.942
			2	45	68.5	0.286	0.151	0.953
			3	189	77.7	0.374	0.180	0.960
6	50	F	1	25	27.4	0.160	0.166	0.928
			2	53	41.5	0.203	0.191	0.959
			3	151	40.0	0.305	0.203	0.949
7*	5	M	1	18	39.5	0.392	0.619	0.979
			2	234	34.1	0.245	0.385	0.934
8	15	F	1	12	45.6	0.194	0.197	0.962
			2	26	57.1	0.339	0.260	0.981
			3	41	67.2	0.339	0.210	0.973
			4	159	84.9	0.285	0.157	0.942
9	13	F	1	20	72.0	0.138	0.084	0.832
10	20	F	1	17	62.7	0.288	0.161	0.908
			2	27	74.6	0.353	0.151	0.975
11	44	F	1	19	82.0	0.121	0.038	0.850
			2	82	93.0	0.224	0.047	0.930
			3	112	93.6	0.288	0.036	0.948
12	50	F	1	32	54.5	0.222	0.133	0.938
13	30	F	1	19	57.9	0.113	0.083	0.832

*Patients with noncirrhotic metabolic liver disease.
GSA = galactosyl human serum albumin; APOLT = auxiliary partial orthotopic liver transplantation.

kinds of parameters, relative uptake by the graft and uptake rate of GSA by the graft and native liver.

The relative uptake of GSA by the graft was a simpler, better indicator than the relative volume for the function and growth of the graft. Its decrease was in accordance with the pathological outcome of the graft. In studies using hepatobiliary scintigraphy, a similar parameter has been proposed (*16,18*). The relative uptake by the graft or the native liver was calculated from anterior planar images. One problem with using planar images is the superimposition of two livers. Buyck et al. (*16*) performed a preliminary colloid liver scan just before hepatobiliary scintigraphy, so that the superimposition of the native liver and the graft was minimal. In this study, however, the well-regenerated graft overlapped the native liver in anterior planar images, and it was not possible to draw ROIs separately over the two livers. Another problem is attenuation correction. The left lobe or the left lateral segment from a donor was transplanted orthotopically in these patients. Thus the graft liver was more anterior than the native liver. In our preliminary study, the relative uptake by the graft that was calculated from anterior planar images without attenuation correction was 5%–20% higher than that calculated from SPECT images. Attenuation correction is difficult for large organs such as the liver. SPECT is a more practical and accurate method for evaluating counts in each liver.

SPECT may be possible in hepatobiliary scintigraphy. However, the hepatobiliary agent is excreted rapidly from the liver to the biliary tract, and the acquisition time of SPECT in each step is limited, resulting in images with low