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A new liver functional study using Tc-99m DTPA-galactosyl human serum albumin: Evaluation of the validity of several functional parameters

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Several parameters calculated with a new functional imaging agent for the liver, Tc-99m DTPA-galactosyl human serum albumin, were evaluated in 9 patients with liver cirrhosis, one with hepatocellular carcinoma, and five with both liver cirrhosis and hepatocellular carcinoma. LU3, which represents the cumulative uptake of the tracer from 3 to 4 minutes after injection, showed a strong correlation ($r=0.858$, $p=0.0001$) with LHL15, which represents the count ratio for the liver to sum for the liver and heart 15 minutes after injection of the tracer. It also showed a strong correlation ($r=-0.896$, $p=0.0001$) with the indocyanine green retention rate (ICGR15). Regional ICGR15 is therefore calculable from the regional LU3. GSAR15, which represents the radioactivity of the tracer retained in the blood 15 minutes after injection, showed a strong correlation ($r=0.878$, $p=0.0001$) with HH15, which represents the count ratio for the heart 15 minutes after injection of the tracer divided by the count for the heart 3 minutes after injection. In conclusion, LU3 and GSAR15 are interesting and promising parameters for assessing liver function.

Key words: Tc-99m DTPA-galactosyl human serum albumin, Tc-99m GSA, liver function

INTRODUCTION

TECHNETIUM-99m labeled DTPA-galactosyl human serum albumin (Tc-99m GSA) is a newly-developed receptor-binding ligand. It binds to the asialoglycoprotein receptors on the membrane of hepatocytes. The amount of this receptor in the hepatic tissues decreases in patients with liver cirrhosis.[1] Consequently, the serum asialoglycoprotein level increases in such patients.[2] Therefore, liver imaging with Tc-99m GSA reflects this receptor binding activity,[3,4] and parameters calculated from the images correlate well with the liver function.[5] Several different parameters calculated by Tc-99m GSA liver imaging in patients with liver cirrhosis and hepatocellular carcinoma were evaluated from a clinical point of view.

MATERIALS AND METHODS

Tc-99m GSA was supplied by Nihon Medi-Physics as a labeled agent, prepared by the following labeling procedure.

DTPA-galactosyl human serum albumin (GSA) synthesized by conjugating galactosyl human serum albumin with diethylenetriaminepentaacetic acid (DTPA) at a molecular ratio of 1 : 4–7. The molecular weight of GSA is about 76,000 daltons. GSA was labeled with Tc-99m using stannous chloride anhydride. Ascorbic acid was added to stabilize the labeled compound. The final radioactivity and amount of the agent for one injection to a patient was 185 MBq of Tc-99m (at the calibration time) and 3 mg of GSA.

A total of 15 patients (13 males and 2 females) were studied. They consisted of 9 patients with liver

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cirrhosis, one with hepatocellular carcinoma, and five with both liver cirrhosis and hepatocellular carcinoma. The study was repeated in five of these patients; therefore, the total number of cases studied was 20. The average age of these patients was 57.8 years (range; 37–76 years).

After a bolus intravenous injection of the radiotracer, sequential anterior abdominal 64×64 matrix size images, including the liver and heart, were acquired every 10 seconds for 20 minutes. Data analysis was done by creating a ROI for each liver and heart and then drawing their time-activity curves. The following parameters were calculated from the time-activity curves. An example is shown in Fig. 1.

HH15; parameter representing retention of the tracer in the blood

$$\text{HH15}=\frac{\text{count for the heart at 15 minutes}}{\text{count for the heart at 3 minutes}}$$

LHL15; parameter representing uptake of the tracer in the liver

$$\text{LHL15}=\frac{\text{count for the liver at 15 minutes}}{\text{sum of the counts for the heart and liver at 15 minutes}}$$

LU3; cumulative liver uptake of the tracer from 3 to 4 minutes after injection

$$\text{LU3}=\frac{\int_3^4 C(t)\,dt}{\text{total injected dose}}\times 100(\%)$$

C(t) is the time-activity curve for the liver. The total injected dose was measured by counting the radioactivity of the syringe with a gamma-camera located 30 cm from the syringe before and after injection and calculating the difference.

LU15; cumulative liver uptake of the tracer from 15 to 16 minutes after injection

$$\text{LU15}=\frac{\int_{15}^{16} C(t)\,dt}{\text{total injected dose}}\times 100(\%)$$

GSAR15; radioactivity of Tc-99m GSA retained in the blood 15 minutes after injection

GSAR15 was calculated by counting the radioactivity of the syringe with a Curiemeter before and after injection, withdrawing 1 m*l* of blood 15 minutes after injection, counting its radioactivity with a well-type scintillation counter, and calculating the percent radioactivity retained in the total blood volume. Cross calibulation factor between the Curiemeter and the well-type scintillation counter was determined beforehand. The total blood volume was determined by means of an equation based on the patient's body weight and height.

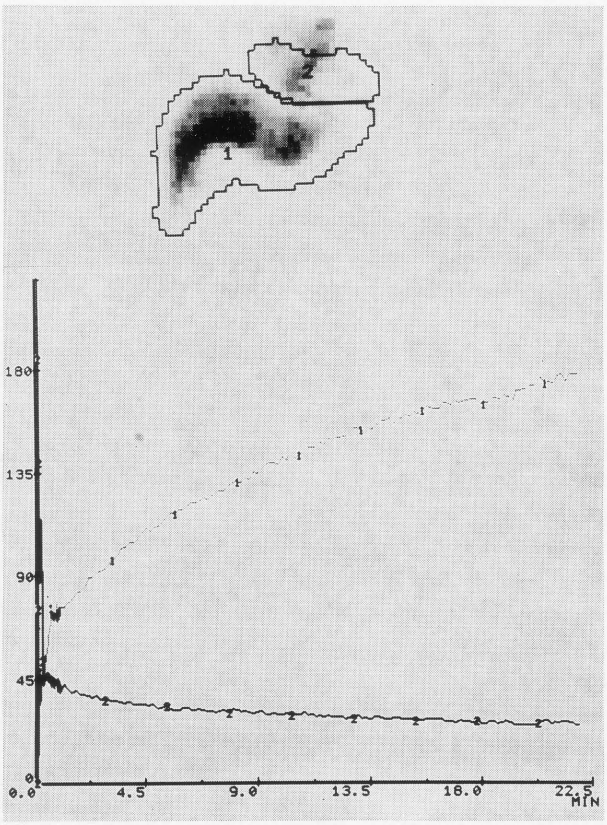

Fig. 1 ROIs drawn over the liver and heart and typical time-activity curves of the regions.

Table 1 Correlation coefficients between two parameters

	Blood retention parameters			Liver uptake parameters		
	HH15	GSAR15	ICGR15	LHL15	LU3	LU15
HH15		0.894	0.574	−0.753	−0.763	−0.814
GSAR15	0.878		0.469	−0.720	−0.694	−0.756
ICGR15	0.653	0.411		−0.752	−0.896	−0.866
LHL15	−0.887	−0.782	−0.717		0.813	0.848
LU3	−0.851	−0.730	−0.868	0.858		0.986
LU15	−0.875	−0.772	−0.863	0.859	0.992	

The values above the diagonal line are Pearson correlation coefficient (r_p), while those below the diagnonal line are Spearman correlation coefficients (r_s).

ICGR15; indocyanine green (ICG) retained in the blood 15 minutes after injection measured by the standard method

Correlations between these parameters were evaluated on the basis of both Pearson (r_p) and Spearman (r_s) correlation coefficients.

RESULTS

The correlation coefficients for these parameters are summarized in Table 1. The parameters are divided into two groups; blood retention parameters and liver uptake parameters. The former includes HH15, GSAR15 and ICGR15, while the latter includes LHL15, LU3 and LU15. The correlation coefficients in the same group are positive, while those between the different groups are negative if they correlate well. The largest positive correlation coefficient was observed between LU3 and LU15, while the largest negative correlation was between ICGR15 and LU3. Both LU3 and LU15 showed good correlation with LHL15, HH15 and ICGR15. In particular, correlation between ICGR15 and LU3 or LU15 was better than that between ICGR15 and LHL15 or HH15. The correlation between ICGR15 and GSAR15 was not so good. Several important and interesting scatter diagrams of these parameters are shown in the figures and are described below.

The correlation between LHL15 and HH15 is shown in Fig. 2. These two parameters show a strong inverse correlation. However, the regression line is not linear, and LHL15 and HH15 seem to have plateau values of 1.0 and 0.9 respectively. On the other hand, Fig. 3 and Fig. 4 show that there is no

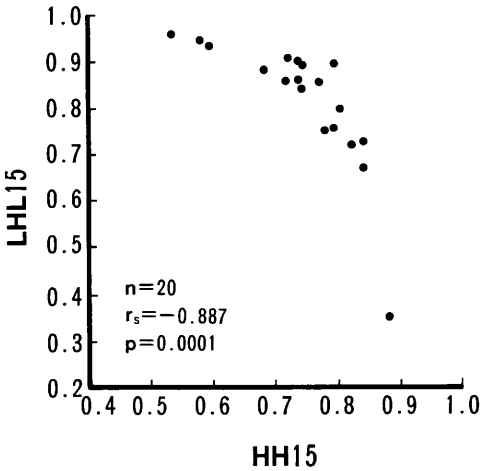

Fig. 2 Scatter diagram of LHL15 and HH15. These two parameters show quite a good nonlinear, inverse correlation.

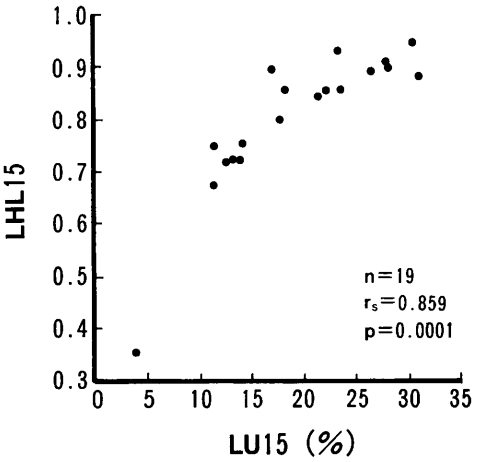

Fig. 4 Scatter diagram of LHL15 and LU15. These two parameters correlate quite well, and there is no plateau in the LU15 values.

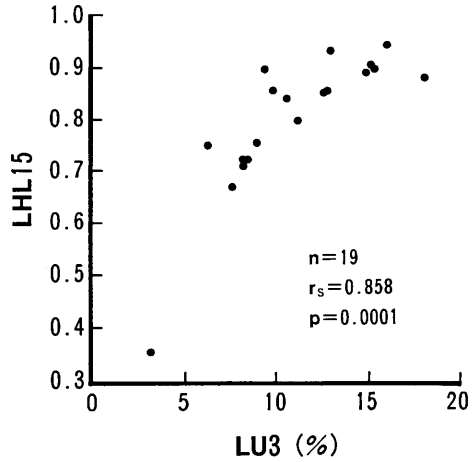

Fig. 3 Scatter diagram of LHL15 and LU3. These two parameters correlate quite well, and there is no plateau in the LU3 values.

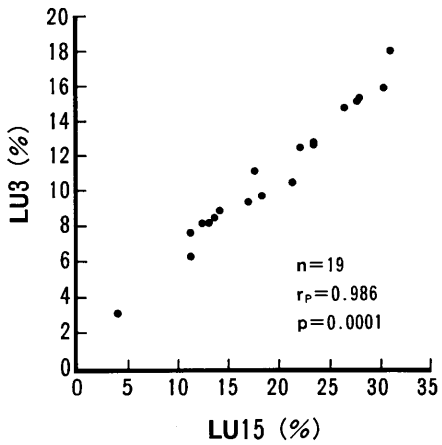

Fig. 5 Scatter diagram of LU3 and LU15. Very good correlation is seen.

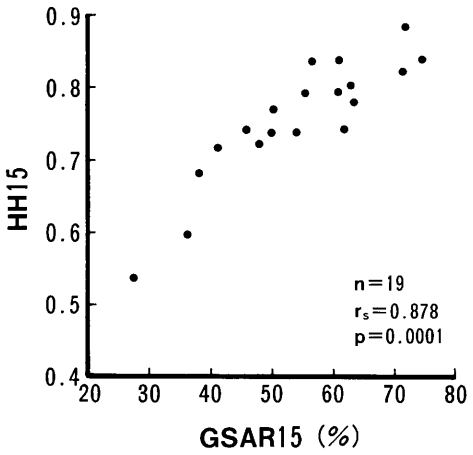

Fig. 6 Scatter diagram of HH15 and GSAR15. Good correlation is seen.

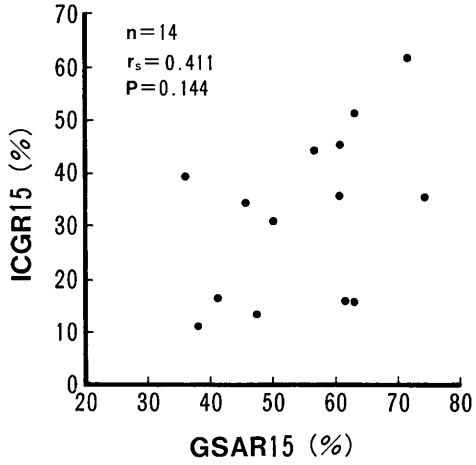

Fig. 7 Scatter diagram of ICGR15 and GSAR15. Poor correlation is seen.

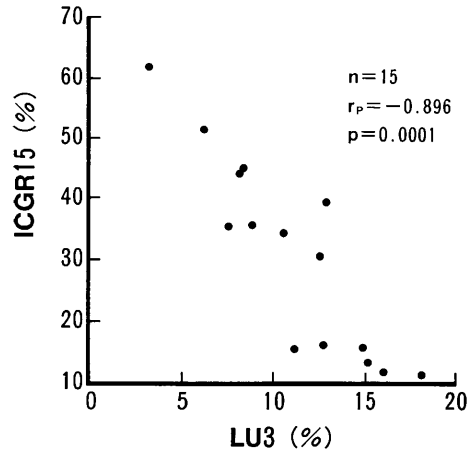

Fig. 8 Scatter diagram of ICGR15 and LU3. Good correlation is seen.

plateau in the LU3 and LU15 values; that is, even after the values of LHL15 approach 1.0, the values of LU3 and LU15 continue to increase. Nevertheless, the correlation coefficient between LHL15 and LU3 or LU15 is very large and significant.

The correlation between LU3 and LU15 is shown in Fig. 5. These two parameters show a strong linear correlation. Figure 6 shows that there is good correlation between HH15 and GSAR15; that is, both parameters reflect fairly well the degree of retention of the tracer in the patients' blood pool. Figure 7 shows the correlation between ICGR15 and GSAR15. Although both parameters reflect the retention of the agents which are cleared from the blood by the liver, the correlation coefficient is not very good, probably due to different blood clearance mechanisms for Tc-99m GSA and ICG. In spite of this poor correlation between ICGR15 and GSAR15, the correlation between ICGR15 and LU3 is fairly good, as shown in Fig. 8.

DISCUSSION

Mathematical models and compartmental analysis were proposed by several authors for quantitative evaluation of the liver function with radiolabeled liver binding proteins.[6–9] Although the receptor binding parameters estimated by these methods are quite accurate and fascinating, the method is rather complicated and impractical for routine clinical studies. Two parameters initially investigated, LHL15 and HH15,[10] can be easily obtained and reflect fairly well the functional status of patients. Moreover, the correlation coefficient for these two parameters is very large. However, if two parameters correlated quite well, they would generally not be used together; that is, one parameter would be considered to be sufficient. However, based on the equation for calculating LHL15, this parameter reaches a plateau as the liver function improves and it does not exceed 1.0; therefore, precise functional discrimination among cases with almost normal liver function may not be possible. On the other hand, HH15 also seems to reach a plateau value in cases of severe liver dysfunction. Therefore, these two parameters, LHL15 and HH15, should be used together as complementary indicators of liver function.

We investigated several different parameters in this study. LU3 and LU15 did not seem to have plateau values in the cases studied, and the values of LU3 and LU15 continued to increase even after the value of LHL15 approached 1.0, as seen in Fig. 3 and Fig. 4. The correlation between LU3 and LU15 is linearly very strong as seen in Fig. 5; therefore, only one of them would be considered to be sufficient. However, it is controversial which of the two

parameters, LU3 or LU15, is better. LU3 has the advantage of shorter acquisition time and better correlation with ICGR15. On the other hand, LU15 has the advantage of a wider range and a higher level of the value and better correlation with the other parameters except ICGR15.

The regional or segmental LU3, such as the LU3 of the right lobe or the left lobe, can be calculated. LU3 correlates well with ICGR15; therefore, the expected ICGR15, such as ICGR15 of the postoperative residual liver, can be calculated by means of a regression equation. In our cases, the linear regression equation, $ICGR15 = -3.48 \times LU3 + 70.0$, was obtained. Of course a more precise technique, such as dynamic SPECT, must be applied to evaluate residual liver function of the right lobe because gammarays from the right lobe are especially attenuated on the planar anterior image.

GSAR15 is also an interesting parameter. It correlates well with HH15; that is, it is a good indicator of blood retention of the tracer. Moreover, there seems to be no plateau in the GSAR15 values compared with the HH15 values. Interestingly, GSAR15 does not correlate well with ICGR15 probably because the clearance mechanism for Tc-99m GSA from the blood is different from that for ICG. Therefore, the hepatic functional status evaluated by GSAR15 might be different from the status evaluated by ICGR15. Unfortunately, troublesome venous blood sampling and counting of the blood are required to determine GSAR15. However, a method to estimate the quantitative dose of Tc-99m GSA in whole blood without blood sampling was reported,[11] and it might be helpful to determine GSAR15.

Though there was a rather poor correlation between ICGR15 and GSAR15, ICGR15 correlated well with LU3 or LU15. That is, LU3 or LU15 might well reflect the hepatic functional status represented by ICGR15. However, LU3 or LU15 might not accurately reflect the hepatic functional status represented by GSAR15. Of course it is not well understood what kind of hepatic functional status is represented by GSAR15. That is, GSAR15 might not purely and simply represent the hepatic functional status. Further evaluation and clarification of GSAR15 will be required.

In conclusion, LU3 and GSAR15 appeared to be interesting and promising parameters for the quantitative assessment of the liver function with Tc-99m GSA. Further clinical experience is required.

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