

Simple scintigraphic parameters with Tc-99m galactosyl human serum albumin for clinical staging of chronic hepatocellular dysfunction

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Technetium-99m labeled diethylenetriaminepentaacetic acid (DTPA)-galactosyl human serum albumin (GSA) has been used for hepatocellular functional evaluation. This study proposed new and simple parameters to overcome the limitations of conventional parameters, and they were applied to the clinical staging of chronic liver dysfunction. The study group consisted of 93 patients including 81 with liver dysfunction and 12 control patients. In addition to the two conventional parameters, namely, receptor index (LHL15 = liver count divided by the sum of liver and heart counts at 15 minutes) and clearance index (HH15 = heart count at 15 minutes divided by the heart count at 3 minutes), 6 new parameters for Tc-99m GSA uptake and clearance were generated. The conventional receptor index of LHL15 showed a large variation depending on the size of region of interest (ROI) over the heart. The LHL15 normalized by the ROI size (nLHL15) showed more stable data and a better separation of mild liver dysfunction. A hyperbolic relationship between the LHL15 and HH15 changed to a linear relationship by using the nLHL15 index. The combination of the liver to heart average count ratio at 15 minutes (LH15) and T-half (minute) of the heart count also could differentiate each stage well. In conclusion, the use of the ROI-area normalized nLHL is recommended instead of the conventional LHL15. The indices of LH15 and T-half could be alternatively used as practical parameters for clinical staging in liver function.

Key words: Tc-99m galactosyl human serum albumin, asialoglycoprotein, receptor imaging, hepatocellular dysfunction, clinical staging

INTRODUCTION

TECHNETIUM-99m labeled diethylenetriaminepentaacetic acid (DTPA)-galactosyl human serum albumin (GSA) is a neoglycoalbumin generated for clinical hepatic imaging. Since asialoglycoprotein receptors on the hepatocellular membrane recognize and bind galactose-terminated glycoprotein and transport it into the hepatocytes, the function of this receptor has been demonstrated to reflect

a hepatocellular function.¹⁻³ After clinical trials in Japan,⁴⁻⁶ this radiopharmaceutical has become commercially available, and has been applied to evaluate various hepatocellular functional abnormalities, including the degree of hepatic dysfunction, hepatic functional reserve, hepatobiliary dysfunction and before and after treatment of hepatocellular carcinoma.⁷⁻¹⁷

In visual analysis, a characteristic finding of liver dysfunction is the reduction in hepatic Tc-99m GSA accumulation and increased background activity, reflecting a low clearance rate in the blood. Several functional indices with Tc-99m GSA have been used,⁴⁻¹⁰ but we have seen the limitations of these parameters. That is, the values seem to vary depending on the technologists and hospitals, and the differentiation of mild hepatic dysfunction was not always good. Therefore, the purpose of this

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study was to evaluate commonly used clinical parameters, and present some new parameters that reflect hepatic function more accurately. Considering clinical applicability, this study deals with relatively simple parameters rather than multi-compartmental analysis with computers.^{7,8}

MATERIALS AND METHODS

Patients

The study group consisted of 81 patients (48 males and 33 females) suspected of having chronic liver dysfunction, aged from 21 to 77 years with an average age of 60 ± 12 years (s.d.). The diagnosis included liver cirrhosis with or without hepatocellular carcinoma ($n = 51$), chronic active hepatitis ($n = 15$), chronic inactive hepatitis ($n = 2$), and mild liver injury including fatty liver ($n = 2$), alcoholic liver injury ($n = 1$), small focal nodular hyperplasia ($n = 1$) and non-specified liver dysfunction ($n = 9$). The number of patients with liver cirrhosis was 5, 12, 21 and 12 in stages 0 to III, respectively. The number of patients with chronic active hepatitis was 3, 6, 5 and 1 in stages 0 to III, respectively.

The control group used for calculating the standard value consisted of 12 patients with a low likelihood of liver dysfunction (8 males and 4 females, average age 54 ± 14 years). They were initially suspected of having liver dysfunction, but serial laboratory data showed no significant abnormalities in serum proteins or liver enzymes thereafter. All of the liver function test listed below showed normal values.

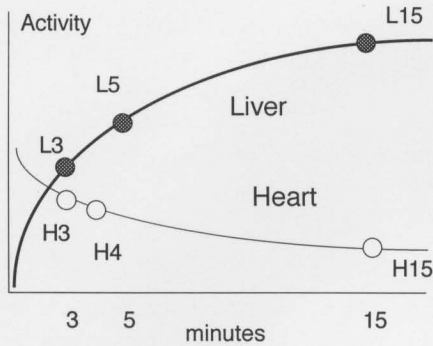
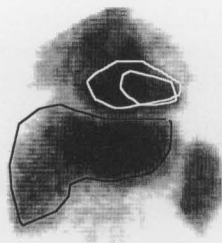


Fig. 1 Time-activity curves generated on the heart and liver. The Tc-99m GSA parameters are determined by heart count at 3, 4 and 15 minutes (H3, H4 and H15) and liver count at 3, 5, 15 minutes (L3, L5 and L15). See details in the text for calculation.



- Liver
- heart(large)
- △— heart(small)

Heart ROI size

	Large	Small
LHL15	0.65	0.82
HH15	0.80	0.81
LHL15/HH15	0.81	1.02
nLHL15	0.47	0.49
LH15	0.87	0.94
T-half (min)	38	40

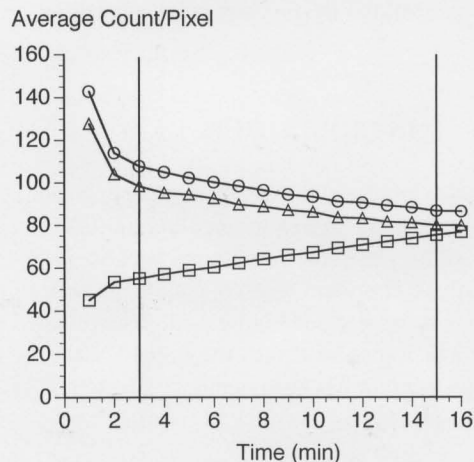
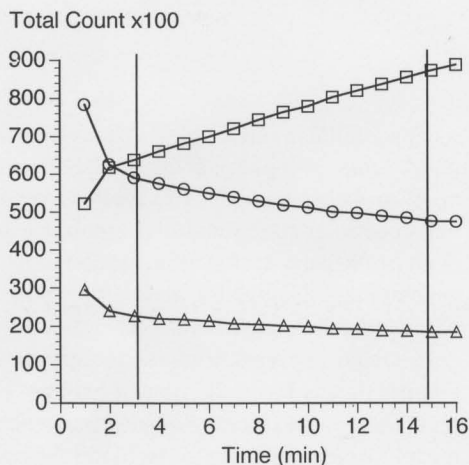


Fig. 2 Effect of ROI size on the time-activity curves and GSA parameters. The variation of the parameters is small when the average count per pixel is used. Total count in the ROI was used for calculating LHL15 and LHL15/HH15, and the average count per pixel was used for calculating nLHL15 and LH15. The parameters of HH15 and T-half were calculated by the heart count at 3-minute and 15-minute using the same ROI size, resulting in similar values for both large and small regions.

Table 1 Blood sampling data in patient's groups

Laboratory values from blood sampling	Normal values of our hospital	Stage				Statistical significance p < 0.05
		O	I	II	III	
N		17	24	26	14	
Albumin (g/dl)	3.9–4.9	4.52 ± 0.49	4.00 ± 0.50	3.68 ± 0.59	3.21 ± 0.45	O vs. I, O vs. II, O vs. III, I vs. III
Cholinesterase (IU/ml)	5.18–11.07	6.30 ± 1.20	4.9 ± 2.1	3.7 ± 1.8	2.7 ± 1.8	O vs. II, O vs. III, I vs. III
Bilirubin (mg/dl)	0.2–1.3	0.6 ± 0.2	0.8 ± 0.7	1.1 ± 0.7	2.6 ± 2.5	O vs. III, I vs. III, II vs. III
ICG retention at 15 min	< 10%	8 ± 2	13 ± 3	27 ± 8	45 ± 10	O vs. II, O vs. III, I vs. II, I vs. III, II vs. III

Statistical significance: "A vs. B" indicates significance between stages A and B.

Table 2 Parameters derived from Tc-99m GSA study in each clinical stage of liver dysfunction

GSA Parameters	normal value (n = 12)	Stage				Statistical significance p < 0.05
		O (n = 17)	I (n = 24)	II (n = 26)	III (n = 14)	
<i>Receptor indices and modified parameters</i>						
"Receptor Index" LHL15	0.95 ± 0.02	0.93 ± 0.03	0.91 ± 0.07	0.83 ± 0.08	0.78 ± 0.09	O vs. II, O vs. III, I vs. II, I vs. III
Normalized LHL15	0.84 ± 0.04	0.84 ± 0.04	0.77 ± 0.09	0.66 ± 0.09	0.60 ± 0.11	O vs. II, O vs. III, I vs. II, I vs. III
LHL/HH	1.82 ± 0.33	1.70 ± 0.25	1.52 ± 0.40	1.19 ± 0.29	1.01 ± 0.22	O vs. II, O vs. III, I vs. II, I vs. III
LH15	5.47 ± 1.25	5.54 ± 1.39	3.98 ± 2.07	2.27 ± 1.33	1.75 ± 0.98	O vs. I, O vs. II, O vs. III, I vs. II, I vs. III
<i>Clearance indices</i>						
"Clearance Index" HH15	0.53 ± 0.08	0.56 ± 0.07	0.63 ± 0.11	0.72 ± 0.10	0.79 ± 0.08	O vs. II, O vs. III, I vs. II, I vs. III
Heart T-1/2 (min)	14 ± 4	15 ± 3	20 ± 9	30 ± 14	39 ± 14	O vs. II, O vs. III, I vs. II, I vs. III
<i>Slope indices</i>						
LL3	0.32 ± 0.07	0.32 ± 0.07	0.27 ± 0.05	0.23 ± 0.07	0.20 ± 0.07	O vs. I, O vs. II, O vs. III, I vs. II, I vs. III
LH3	0.53 ± 0.13	0.56 ± 0.18	0.38 ± 0.18	0.22 ± 0.14	0.17 ± 0.12	O vs. I, O vs. II, O vs. III, I vs. II, I vs. III

Statistical significance: "A vs. B" indicates significance between stages A and B.

Liver function tests

Blood sampling and conventional liver function tests were performed within two weeks of the nuclear studies, and cholinesterase albumin and bilirubin were measured (n = 81). The indocyanin green (ICG) retention rate at 15 minutes was also measured (n = 61). The normal values of these parameters are shown in Table 1.

Clinical stages for liver dysfunction

By referring to staging criteria according to the clinical and pathological study of primary liver cancer in Japan,¹⁹ the following classifications were used in this study.

Stage O (near normal, n = 17): All the abovementioned 4 laboratory data are within the normal limits for the standard values at our hospital. Because of slight abnormalities in other hepatic function tests, the diagnosis of liver disease was made clinically.

Stage I (slight dysfunction, n = 24): At least one of the abovementioned 4 laboratory data was outside the normal range, but the blood sampling data were: serum albumin > 3.5 g/dl, serum bilirubin < 2.0 mg/dl and ICG retention < 15%.

Stage II (moderate dysfunction, n = 26): Serum albumin 3.0–3.5 g/dl, serum bilirubin 2.0–3.0 mg/dl and ICG retention 15%–40%.

Stage III (severe dysfunction, n = 14): Serum albumin < 3.0 g/dl, serum bilirubin > 3.0 mg/dl and ICG retention

> 40%.

If the above laboratory data belonged to more than one stage, the worse stage was defined as the patient's clinical stage.

Data acquisition

Tc-99m GSA (185 MBq) was intravenously injected as a bolus in the supine position. A series of dynamic images including the heart and liver were obtained in a 128 × 128-pixel format from 0 to 16 minutes at 1 minute per frame. A large field-of-view camera was equipped with a low-energy parallel-hole collimator, and the energy was centered at 140 keV with a 20% window for Tc-99m.

Data analysis and parameters

With both 1-minute and 15-minute images as references, regions of interest (ROIs) were set over the heart and the liver. Usually the left and right ventricular ROIs were encircled for the heart ROI in a 3-minute image, and the liver ROI included the whole liver in a 15-minute image. Time-activity curves were generated for 16 minutes. The scheme of generated time-activity curves is shown in Figure 1.

Two conventional parameters, receptor and retention indices, were as follows: (1) Receptor index (LHL15). This parameter was calculated with a 15-minute image as $L15/(H15 + L15)$, where the L15 and H15 were the liver

and heart count at 15 minutes. (2) Retention index of the heart count at 15 minutes relative to that at 3 minutes (HH15). This was calculated as a H15/H3 ratio, where the H15 and H3 were calculated based on the heart count at 15 and 3 minutes.

The following parameters were also generated. (3) The ratio of LHL15 to HH15 (LHL15/HH15). This ratio was proposed by Ha Kawa, et al.,¹⁸ to better separate the stages of hepatic dysfunction.

The following parameters were originally made. (4) LHL15 normalized by ROI pixels (nLHL15). Since both the liver and heart counts were considered to be influenced by the ROI size, we used count densities (count/pixel) of the liver and heart at 15 minutes (LD15 and HD15, respectively). The nLHL15 index was calculated as the formula LD15/(HD15 + LD15). (5) Liver uptake relative to heart blood activity at 15 minutes (LH15). The ratio of liver and heart densities, LD15/HD15 was calculated.

The following 2 parameters were related to the slope of the hepatic curve at the initial 3 to 5 minutes. (6) The initial slope of hepatic time-activity curve (LL3). This parameter was calculated by the formula (L5 - L3)/L3, where the L5 and L3 were liver counts at 5 minutes and 3 minutes. (7) Change in liver count relative to heart count (LH3). This parameter was defined as a change in liver count density from 3 to 5 minutes (LD5 - LD3) divided by the average blood activity at 4 minutes (LH4), that is, the formula (LD5 - LD3)/HD4.

Finally, (8) a half-time (T-half) in the heart count corresponding to blood clearance was calculated. This parameter was determined from 2 time points at 15 minutes and 3 minutes, namely, $k = \{\ln(H15) - \ln(H3)\} / (15 - 3)$ and $T\text{-half} = -\ln 2/k$. Since this clearance parameter was essentially derived from H15 and H3 as in the HH15 calculation, the relationship between the parameters T-half and HH15 was theoretically on an exponential function.

Considering the equations mentioned above, the values seem to be influenced by the ROI size and location. In our experience, the liver ROI was set on the whole liver, and the border could be easily determined, but the heart ROI may vary. Then we set small and large ROI sizes on the heart, and their effects on the parameters were compared.

Interobserver and intraobserver reproducibility of the parameters were calculated in the first 18 patients. The intraobserver variation was tested by the same operator 1 month later. The operators were asked to draw cardiac ROIs on both of the ventricles to avoid large variation in setting them.

Statistics

Values were expressed as a mean \pm standard deviation (s.d.). The differences in the variance and mean values were examined by a multiple comparison test following a significant finding in the one-way analysis of variance (ANOVA). Scheffé's test and Bonferroni/Dunn's test

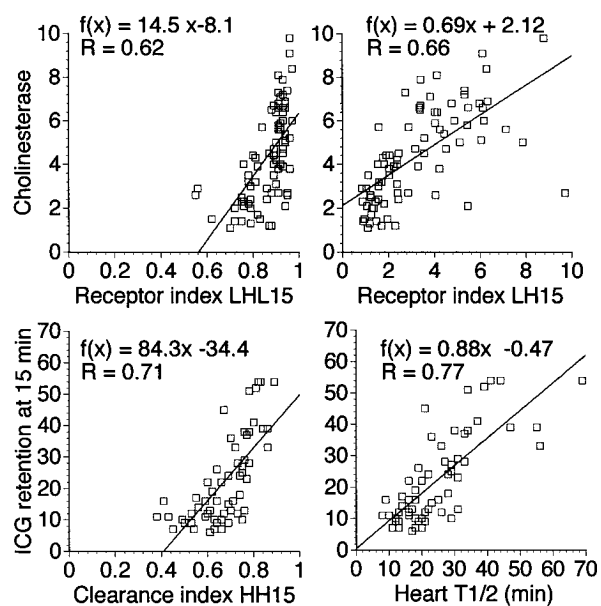


Fig. 3 Relationship between cholinesterase and the LHL15 or LH15, and that between ICG retention at 15 minutes and the LHL15 or LH15.

were applied. Linear regression analysis was performed for the two parameters by a least square method. Curve fitting of the datapoints on the scattergram was performed with an iterative algorithm of Deltagraph 4.0 (Delta Point, Inc.). A p value less than 5% was considered significant.

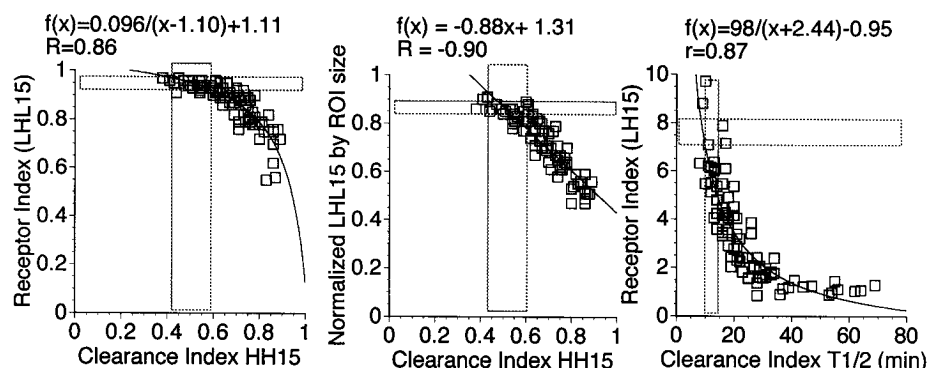
RESULTS

In Stage 0 the hepatic activity was high and the heart activity was negligible. In the higher stages, the blood activity in the heart became increasingly high. The high background activity was a characteristic of severe hepatic dysfunction. Figure 2 shows variations in time-activity curves and the parameters depending on the ROI size. The LHL15 index was significantly influenced by the ROI size, but the HH15 was relatively stable. The ratio LHL15/HH15 was also influenced by the ROI size, corresponding to the variation in LHL15. On the other hand, when the values were normalized by the ROI areas, the cardiac time-activity curve became similar, as shown in the right panel. Therefore the nLHL15 value did not vary greatly. LH15 was slightly higher when a small left ventricular heart ROI was used. The T-half value was similar in both ROIs.

The mean laboratory data from blood sampling are shown in Table 1. The standard values used at our hospital are also listed. The average albumin and cholinesterase levels were significantly lower in the higher clinical stages, whereas serum bilirubin and ICG retention at 15 minutes were higher in the higher clinical stages. Table 2 shows the average and standard deviation of the Tc-99m GSA parameters. The receptor indices and the modified

Table 3 Correlation coefficients of GSA parameters to laboratory data

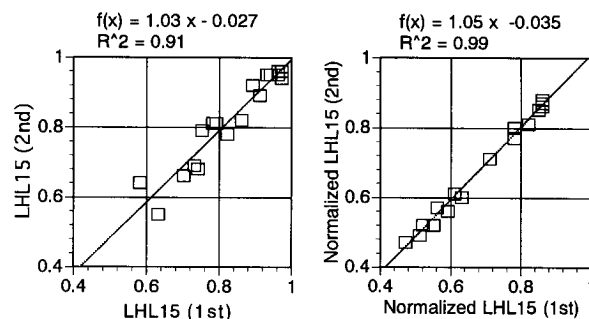
	Receptor indices				Clearance indices		Slope indices	
	LHL15	nLHL15	LHL/HH	LH15	HH15	T1/2	LL3	LH3
Albumin	0.51	0.58	0.49	0.48	-0.48	-0.49	0.53	0.50
Cholinesterase	0.62	0.72	0.68	0.66	-0.68	-0.65	0.60	0.63
Bilirubin	-0.37	-0.40	-0.31	-0.29	0.34	0.43	-0.39	-0.31
ICG Retention 15 min	-0.75	-0.75	-0.67	-0.63	0.71	0.77	-0.54	-0.65

**Fig. 4** Scattergrams among the LHL15 versus HH15, nLHL15 versus HH15 and LH15 versus T-half. The range of the mean \pm s.d. for the control patients is shown.

parameters LHL15, nLHL15, LHL15/HH15 and LH15 were generally lower in the higher stages (P values are shown in the table), but the difference between Stages O and I was not statistically significant in LHL15, although the latter stages showed lower values. On the other hand, nLHL15 and LH15 showed a significant separation between Stages O and I. For Stages O to III, nLHL15 was 0.84 ± 0.04 , 0.77 ± 0.09 , 0.66 ± 0.09 and 0.60 ± 0.11 , respectively. The clearance index HH15 was higher in the higher clinical stages. The T-half expressed in minutes was also significantly higher in the higher stages, i.e., 15 ± 3 , 20 ± 9 , 30 ± 14 and 39 ± 14 minutes for Stages O to III, respectively. The LH15 was also significantly different, i.e., 5.54 ± 1.39 , 3.98 ± 2.07 , 2.27 ± 1.33 , and 1.75 ± 0.98 , respectively. The slope indices of the LL3 and LH3 were lower in the higher stages indicating lower hepatic accumulation velocity in more severe dysfunction.

The relationship between cholinesterase and LHL15 or LH15 is shown in Figure 3. The correlation between cholinesterase and LHL15 (x) showed a regression line of $f(x) = 14.5x - 8.1$ ($R = 0.62$, $p < 0.0001$). In this graph, many data points were around $LHL = 0.9$. LH15 had more scattered distribution and a regression of $f(x) = 0.69x + 2.12$ ($R = 0.66$, $p < 0.0001$). The correlation between the ICG retention and HH15 (x) was $f(x) = 84.3x - 34.4$ ($R = 0.71$, $p < 0.0001$), and the correlation between ICG retention and T-half (x) was $f(x) = 0.88x - 0.47$ ($R = 0.77$, $p < 0.0001$).

The correlation coefficients of the GSA parameters and laboratory data are shown in Table 3. The ICG retention showed the highest coefficient for all the GSA parameters

**Fig. 5** Interobserver reproducibility of the parameters of LHL15 (left) and area-normalized LHL15 (right).

except for the LL3. The nLHL15 parameters had higher coefficients for all the laboratory data than the LHL15 values did.

The scattergrams for LHL15, HH15, nLHL15, LH15 and T-half are shown in Figure 4. The relationship between LHL15 and HH15 (x) was not linear, but fitted the hyperbolic curve $f(x) = 0.096/(x - 1.10) + 1.11$ ($R = 0.86$). In contrast, after normalizing the count divided by the ROI areas, the relationship between the nLHL15 and HH15 (x) changed to linear: $f(x) = -0.88x + 1.31$ ($R = -0.90$). The relationship between LH15 and T-half (x) was also fitted by a hyperbolic curve $f(x) = 98/(x + 2.44) - 0.95$ ($R = 0.87$).

The intraobserver reproducibility of parameters (n = 18) for LHL15, nLHL15, LH15, HH15 and T-half was very high: $R^2 = 0.97$, 0.99 , 0.98 , 0.99 and 0.99 ($p < 0.0001$ for all parameters), respectively. The interobserver repro-

ducibility was $R^2 = 0.91, 0.99, 0.98, 0.98$ and 0.96 ($p < 0.0001$ for all parameters), respectively, and nLHL15 had a higher correlation coefficient than LHL15 did (Fig. 5).

DISCUSSION

Tc-99m GSA has been used in Japan since the phase 2 (81 patients) and phase 3 (460 patients) studies were conducted.^{5,6} The mean values for the retention index (HH15) that have been presented by the Japanese clinical trials were $0.54 \pm 0.04, 0.63 \pm 0.08, 0.74 \pm 0.08$ and 0.83 ± 0.05 for normal, mild, moderate and severe liver dysfunction, respectively, based on the clinical staging by the liver cancer study group in Japan.¹⁹ The values for the receptor index LHL15 were $0.94 \pm 0.02, 0.91 \pm 0.04, 0.84 \pm 0.07$ and 0.70 ± 0.11 , respectively. Since then these two parameters have been used as useful parameters for liver dysfunction.⁷⁻¹⁷ Our results for the LHL15 and HH15 were comparable to these previously reported, but we have noticed that when LHL15 was calculated, the heart ROI was not strictly defined, and could have been a source of calculation errors. Since each chamber is not clearly separated in the anterior view, the activity from atria and great vessels might be included to various degrees, depending on the operators (usually technologists) and hospitals. The ROI setting with various ROI sizes in this study clearly indicated that the parameter without area normalization varied. Particularly when the heart count was high and the liver count was low in the 15-minute image in severe liver dysfunction, the variation in these parameters would be higher. In this study, however, the reproducibility of the indices was high, because the operators were in the same hospital and instructed the ROIs to be set only on both ventricles.

Normalization of LHL15 by ROI area

Because of the hyperbolic relationship between LHL15 and HH15, the mild liver dysfunction could not be separated well, particularly by LHL15. This point has already been noted in clinical trials and studies.^{6,10,11,18} We could also find that many data points were clustered around the high LHL15 in Figures 3 and 4. On the other hand, the normalization by ROI size improved the variability. Since nLHL15 was determined by the average ROI count per pixel, slight changes in the ROI setting would not influence the results significantly. This is a merit when standardizing the parameters in many hospitals. By using nLHL15, the effect of hepatic size as in hepatomegaly and atrophy may disappear, but the clearance value for the whole liver is not influenced if the same ROI is used in both 3- and 15-minute images. Moreover, the relationship between nLHL15 and HH15 became linear, and even clinical stages of mild dysfunction could be separated.

The LH15 and T-half parameters

The conventional receptor index LHL15 is defined as

$L15/(L15 + H15)$. In this formula, it was implicitly assumed that H15 was a representative of the amount of Tc-99m GSA in the circulating blood. This was certainly a rough approximation of Tc-99m GSA distribution. We therefore thought that the simple parameter for the L15 to H15 ratio may be sufficient as an index to reflect receptor function regarding the clinical staging. Both the T-half and HH15 parameters were derived from the heart count of H3 and H15. Then the relationship was on the exponential function, and the capability for staging was essentially the same, but by using T-half expressed in minutes, severe dysfunction was emphasized. In Figure 4, the relationships between LHL15 and HH15 and between LH15 and T-half were both hyperbolic, but we noticed that the former scattergram showed a lumping of datapoints in the upper portion, whereas the latter scattergram showed more discrete datapoints on the fitted curve. If we use the latter combination of LH15 and T-half, slight liver dysfunction will be reflected in a decrease in the L15/H15 ratio. When the dysfunction becomes more severe, the T-half value will show a significant increase. Approximate T-half values for normal, mild, moderate and severe dysfunction were 15, 20, 30 and 40 minutes, respectively. In addition, the scatter of the LH15 and cholinesterase on the graph showed the same range of values, and the T-half (minute) and ICG retention (%) also showed a similar range of values. The similarity between standard values would be convenient for physicians.

Limitations

This study dealt with rather simple parameters derived from 16 serial dynamic images for 16 minutes. More physiological parameters such as the maximal binding rate, hepatic blood flow, rate of excretion from the liver and distribution volumes may be desirable.^{2,3,7-11} One of the studies by means of compartmental analysis showed that the hepatic blood flow and maximal receptor binding rate correlated closely to the semiquantitative ratio indices of HH15 and LHL15.¹¹ Nevertheless, most of these parameters require computer modeling for compartment analysis with non-linear least square fitting, and are complex for routine clinical application. Since the major area of interest in this study was clinical staging by Tc-99m GSA studies, the simple parameters are rather important and useful. A comparative study of modeling parameters and these simple values should be undertaken. The other sources of error in these parameters included an increase in background activity with increasing severity of liver dysfunction and a decreased blood clearance rate in patients with heart failure. To solve these problems may also require dynamic SPECT studies with modeling of parameters.

CONCLUSION

Clinical parameters with Tc-99m GSA for classifying

patients into hepatic dysfunction staging were reevaluated. The conventional receptor index of LHL15 varied with the ROI size, so that the normalization by ROI size should be performed. The linear relationship between nLHL15 and HH15 was an advantage with this parameter. Another good option is using a combination of LH15 and T-half. These parameters correlated well with clinical hepatic functional staging. The application of these parameters to the follow-up studies and response to treatments is indicated.

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