Binding rate constant of Tc-99m DTPA galactosyl human serum albumin measured by quantitative dynamic SPECT —Clinical evaluation as a total and regional liver function test—

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To evaluate the clinical utility of a new method with dynamic single photon emission computed tomography (SPECT) and scatter and attenuation compensation to estimate both total and regional liver function quantitatively. Five controls, 20 patients with chronic liver disease, and 2 patients with Budd-Chiari syndrome were studied. Dynamic liver SPECT data were acquired during 20 minutes after injection of Technetium (Tc)-99m diethylenetriaminepentaacetic acid (DTPA) galactosyl human serum albumin (GSA) with scatter and attenuation compensation. The binding rate constant of Tc-99m GSA (Kw) was derived quantitatively from the Patlak plot based on kinetic models for GSA receptor binding. The mean Kw was obtained by dividing the Kw value (total Kw) by the liver volume. Both total and mean Kw were significantly lower in patients with chronic liver disease than in controls (302 ± 112 vs. 523 ± 78 ml/min; p < 0.001, 0.26 ± 0.11 vs. 0.43 ± 0.03 ml/min/cm²; p < 0.001). In the patient group, both total and mean Kw were significantly correlated with the results of conventional liver function tests and the histological severity of chronic liver disease. In 2 patients with Budd-Chiari syndrome, the mean Kw was lower in the right lobe, where the hepatic veins were occluded, than in the left lobe, where draining veins were patent. In conclusion, this method is a reliable diagnostic technique for estimating total and regional liver function.

Key words: dynamic SPECT, Tc-99m DTPA galactosyl human serum albumin, liver function test, chronic liver disease, Budd-Chiari syndrome

INTRODUCTION

DIETHYLENEDIAMINEPENTACETIC ACID (DTPA) galactosyl human serum albumin (GSA) is an analog ligand to the asialoglycoprotein (ASGP) receptor, which resides on the plasma membrane of mammalian hepatocytes and is responsible for the metabolism of serum glycoproteins.1-3 Technetium (Tc)-99m GSA scintigraphy can help to probe ASGP receptor biochemistry and reflect the liver function.4,5 Vera et al. advocated the kinetic model for Tc-99m-galactosyl-neoglycoalbumin (NGA) receptor binding.6 This kinetic model is considered to be applied to Tc-99m GSA kinetics because NGA and GSA are almost the same pharmaceutical.7 The fundamental components that govern the rate of the receptor-binding process are the receptor and ligand concentrations, and the forward and reverse binding rate constants.3 Tc-99m GSA dynamic data provide valuable information in vivo regarding the receptor population density.8,9 Some investigators have reported the utility of Tc-99m GSA liver scintigraphy in evaluating total liver function.10-12 These studies were performed by acquiring Tc-99m GSA dynamic data by means of planar images. Recently, Hwang has reported
the clinical usefulness of Tc-99m GSA dynamic single photon emission computed tomography (SPECT) with Patlak plot to estimate hepatic functional reserve. On the other hand, we have developed and reported preliminary results for a new method for measuring the binding rate constant (Kd) with dynamic SPECT from the Patlak plot. The Kd is considered to represent the maximum removal rate of Tc-99m GSA that reflects receptor population density. Our method seems to have some advantages in evaluating liver function for the following reasons: a) since the time-activity curve of the liver can be acquired with scatter and attenuation compensation, the parameters obtained permit the quantitative evaluation of liver functions, b) both total and regional liver function can be evaluated quantitatively. In the present study, we evaluated the clinical usefulness of our method in the evaluation of liver function.

MATERIALS AND METHODS

Subjects
Tc-99m GSA studies were performed in 5 volunteers with normal livers, 20 patients with chronic liver disease and 2 patients with Budd-Chiari syndrome. The control group consisted of 5 men with a mean age of 36 years (range, 24–60 years). All control subjects had normal liver function tests and had no history of liver disease. The chronic liver disease group consisted of 5 women and 15 men with a mean age of 54 years (range, 27–75 years). The diagnosis of chronic liver disease was histologically confirmed by laparoscopic biopsy in 13 patients. In the other 7 patients, the diagnosis was based on ultrasonographic findings, laboratory tests, and evidence of viral infection (hepatitis C viral antibody positive: 18 patients, hepatitis B viral antigen positive: 2 patients). Two patients with Budd-Chiari syndrome were a 38-year-old woman and a 55-year-old man. The inferior vena cava and all hepatic veins were occluded before percutaneous trans catheter angioplasty (PTA) in both patients. PTA was performed, and both the inferior vena cava and left hepatic vein was re-occluded, but, the right and middle hepatic veins were still occluded in both patients when Tc-99m GSA studies were done.

Tc-99m GSA study
Before injection of Tc-99m GSA, a tomographic transmission study was done to obtain the attenuation coefficient map: 60 images were acquired over a 360-degree orbit over 20 minutes in continuous scanning mode (four rotations at 5 minutes/rotation). Attenuation and scatter compensation was done with the flood source method for transmission computed tomography (TCT) with a dual-head SPECT system (GCA-7200A, Toshiba, Nasu, Japan). The projection data were subjected to Butterworth filter processing before reconstruction. The TCT images were reconstructed by filtered backprojection with a Shepp & Logan filter and a slice thickness of 8.6 mm (1 pixel).

Patients received 148 MBq (4 mCi) of Tc-99m GSA by intravenous injection. Forty sequential 30-second SPECT data were acquired in the first 20 minutes after the injection. For triple energy window (TEW) scatter correction, SPECT data and scatter rejection data were acquired with 141 ± 14 keV and 117.2–127 keV energy windows, respectively. Projection data were acquired with an acquisition time of 1 sec per view (30 sec per scan).

Ten minutes after intravenous Tc-99m GSA injection, a blood sample was collected from a contralateral antecubital vein. The whole blood radioactivity was measured with a well-type scintillation counter (ATC-301, Aloka, Tokyo, Japan). The reference sample was washed and diluted in 1,000 ml of water, and the radioactivity of 1 ml of the diluted reference tracer was measured. Based on the radioactivity of the reference, the blood radioactivity was measured in units of µCi/ml. SPECT images were reconstructed with a Shepp & Logan filter. The projection data were subjected to Butterworth filter processing before reconstruction. Attenuation compensation was performed with a 2-iteration Chang algorithm that was modified to incorporate a measured nonuniform attenuation map. The SPECT value (count) was converted to activity with the cross-calibration factor, pixel length, slice thickness, and acquisition time. Measured activity (µCi) = Cross calibration factor (µCi·sec/count)·SPECT value (count)/acquisition time (sec).

A region of interest (ROI) was specified over the heart on a summed image of a few selected 1-minute SPECT slices. The time-activity curve (TAC) of the heart was generated by plotting the counts in the ROI over the serial summed images against the respective mid-points in time during the serial SPECT data collection periods. The cardiac TAC [Hspectrum(t)] was approximated by the least-squares fitting method on the basis of the biexponential function with data from 2 to 20 minutes after injection.

An ROI for the entire liver was specified over a series of the summed images of the respective slices covering the liver by cutting off a fixed count. The SPECT images were rearranged to create serial summed liver SPECT images, in each of which all slices covering the liver were summed. The serial total liver counts were then measured over 20 minutes. The TAC of the entire liver [L(t)] was generated by plotting the total liver counts against the midpoints in time during the respective SPECT data collection periods. Five-minute SPECT data, the midpoint in time of which was a 15-minute injection, were merged from the serial SPECT data. In the 2 patients with Budd-Chiari syndrome, each ROI for the entire liver, right lobe and left lobe was specified referring to the CT images, and the same data analysis was performed for each ROI.

Data analysis
We calculated the Kd value for the total liver (total Kd)
with dynamic Tc-99m GSA SPECT as described below. The cardiac TAC of Hspret(t) (μCi) can be converted to the radioactivity concentration in the blood H(t) (μCi/ml) as follows. The radioactivity concentration in venous blood obtained 10 minutes after tracer injection is expressed as H. The 10-minute value is measured from the above-mentioned approximated cardiac TAC [Hspret (10)]:

\[
H(t) (\mu Ci/ml) = \frac{Hspret(t) (\mu Ci) \times H(10) (\mu Ci/ml)}{Hspret(10) (\mu Ci)}
\]

The \( K_a \) is obtained with equation (2):

\[
L(t)/H(t) = \frac{1}{K_a} \int_0^t H(t) dt + V_h
\]

where \([L(t)]\) is the hepatic radioactivity concentration measured by SPECT, and \( V_h \) is the hepatic blood volume in a unit volume of the liver. The liver TAC of L(t) is expressed in units of [mCi]; H(t), the blood concentration curve is expressed in units of [mCi min/ml]; and \( V_h \), the hepatic blood pool volume, is expressed in units of [ml]. Using measured L(t) and H(t) data, \( L(t)/H(t) \) was plotted against \( \int H(t) dt/H(t) \) and linear approximation was performed at points from 86 s to 400 s. \( K_a \) and \( V_h \) values were determined as the slope and intercept, respectively, by this linear approximation.

**Volume measurement of the liver and calculation of mean \( K_a \)**

To calculate the mean \( K_a \), the volume of the whole liver was obtained. Volume measurement was performed with the CT system in 5 controls, 16 patients with chronic diseases, and 2 patients with Budd-Chiari syndrome because it was difficult to identify the edges of the liver on SPECT images in some patients with poor liver profiles (Fig. 3b). CT images were obtained covering the whole liver with a helical CT system (X-vigor, Toshiba, Nasu, Japan). Helical CT scans were acquired during a single breath hold. Parameters for helical CT were 5–10 mm collimation and 5–10 mm/sec table sliding. Contiguous axial sections 5 or 10 mm thick were reconstructed from the volumetric data. The total liver area was measured by tracing on each CT image. The volume of the whole liver was then automatically calculated by multiplying each area by the slice thickness. In 2 patients with Budd-Chiari syndrome, the volumes of the right and left lobes were measured. The mean \( K_a \) value was calculated by dividing the total \( K_a \) value by the volume of the whole liver (ml/min/cm²). The total and mean \( K_a \) values were calculated in the right and left lobes, respectively.

**Liver functional imaging**

The mean TAC of the liver L(t) was generated by plotting the liver counts for each pixel in the SPECT slice against the respective midpoint in time of the serial SPECT data. By the same data processing as mentioned above, the \( K_a \) values for each voxel were obtained and the respective distribution images corresponding to the original SPECT images were generated. This functional image displays the distribution of \( K_a \) per voxel (ml/min/voxel) values.

**Assessment of clinical significance**

The severity of chronic liver disease was classified into three groups, based on the Child-Pugh classification. Twenty-two patients had grade A liver profiles, 4 patients had grade B liver profiles, and 4 patients had grade C liver profiles. The total and mean \( K_a \) values were evaluated in controls and in patients with various degrees of chronic liver disease.

Relationships between the total and mean \( K_a \) values and the following conventional liver function tests were
evaluated: aspartate aminotransferase (AST) (IU), alanine aminotransferase (ALT) (IU), the serum albumin level (g/dl), serum bilirubin level (mg/dl), serum cholinesterase activity (APH), prolongation of prothrombin time (%), normoest (%), and plasma retention rate for indocyanine green at 15 minutes (ICG R15) (%).

The total $K_u$ value was evaluated and compared with the histological severity of chronic disease in 13 patients who underwent biopsy. The relationship between the mean $K_u$ value and histological severity was also compared in 12 patients. Histological severity was assessed with the histological activity index score (HAI score).

**Statistical analysis**

Data are expressed as the mean ± standard deviation. The total and mean $K_u$ values in the controls and in patients with liver disease were compared statistically by Student’s t test. Correlation of total and mean $K_u$ values with each liver function test and the HAI score was analyzed by standard Pearson correlation analysis. A p value of less than 0.05 was considered statistically significant.

**RESULTS**

**Correlation of total and mean $K_u$ with conventional liver function tests**

The total and mean $K_u$ values according to the Child-Pugh classification are shown in Figure 1. Both values were lower in patients with chronic liver disease than in the controls. For the total $K_u$, the value in the controls was $523 ± 78$ ml/min and that in patients with chronic liver disease was $302 ± 112$ ml/min (p < 0.001). The mean $K_u$ value in the controls was $0.43 ± 0.33$ ml/min/cm$^2$ and that in patients with chronic liver disease was $0.26 ± 0.11$ ml/min/cm$^2$ (p < 0.001). In patients with chronic liver disease, both total and mean $K_u$ values clearly reflected the severity of the liver profile. The total $K_u$ values according

**Table 1** Correlation of total and regional effective hepatic blood flow with conventional liver function tests

<table>
<thead>
<tr>
<th>Liver function tests</th>
<th>Total EHBF</th>
<th>Regional EHBF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation coefficient ($r$)</td>
<td>p value</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>0.564</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>0.62</td>
<td>&lt; 0.0001</td>
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<td>Albumin</td>
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<td>&lt; 0.0001</td>
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<tr>
<td>Bilirubin</td>
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<td>&lt; 0.0001</td>
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<td>Cholinesterase</td>
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<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Prothrombin time</td>
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<td>0.062</td>
</tr>
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<td>Normo test</td>
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<td>&lt; 0.0001</td>
</tr>
<tr>
<td>ICG R15</td>
<td>-0.772</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

ICG R15: plasma retention rate of indocyanine green at 15 minutes

EHBF: effective hepatic blood flow

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Fig. 3  

a: Liver functional image of mean $K_u$ in a control subject. The maximum $K_u$ value per voxel is displayed as 0.55 ml/min/cm$^3$, and the minimum value as 0 ml/min/cm$^3$. The mean $K_u$ is diffuse throughout the entire liver parenchyma. The total $K_u$ is 479 ml/min and the mean $K_u$ is 0.40 ml/min/cm$^3$ in this control subject. 
b: Functional image of mean $K_u$ in a patient with a severe liver profile (Child-Pugh grade C). The maximum $K_u$ value per voxel is displayed as 0.05 ml/min/cm$^3$, and the minimum value as 0 ml/min/cm$^3$. Atrophy of both the right and left lobes and hypertrophy of the caudate lobe are seen. The mean $K_u$ is markedly decreased and its distribution is irregular compared with the controls. Note the increased mean $K_u$ in the caudate lobe. The total $K_u$ is 65 ml/min and the mean $K_u$ is 0.06 ml/min/cm$^3$ in this patient.  
c and d: Computed tomography (c) and functional (d) image in a patient with Budd-Chiari syndrome. The inferior vena cava and left hepatic vein are patent after transcatheter angioplasty (arrows). The right and middle hepatic veins are still occluded (arrowheads) (c). The functional image shows hypertrophy of the left lobe and atrophy of the right lobe, and clearly demonstrates a lower mean $K_u$ in the right lobe compared with the left lobe. The mean $K_u$ is 0.31 ml/min/cm$^3$ in the right lobe and 0.44 ml/min/cm$^3$ in the left lobe, respectively, in this patient.

to Child-Pugh classification were as follows: Grade A ($n = 12$); 362 ± 75 ml/min, Grade B ($n = 4$); 280 ± 63 ml/min, and Grade C ($n = 4$): 144 ± 83 ml/min. The mean $K_u$ values were as follows: Grade A ($n = 8$); 0.32 ± 0.08 ml/min/cm$^3$, Grade B ($n = 4$); 0.25 ± 0.08 ml/min/cm$^3$, and Grade C ($n = 4$): 0.15 ± 0.09 ml/min/cm$^3$. Correlations between total and mean $K_u$ values and conventional liver function tests are shown in the Table 1. The total $K_u$ value was significantly correlated with conventional liver function tests except for percent prothrombin time. The mean $K_u$ value was significantly correlated with those except for AST, ALT and albumin.

Correlation of total and mean $K_u$ with histological activity index
The results are shown in Figure 2. Both total and mean $K_u$ values were significantly correlated with the histological severity of chronic liver disease (HAI score) (total $K_u$: $r = -0.63$, $p < 0.0002$, mean $K_u$: $r = -0.63$, $p < 0.003$).
Total and mean $K_u$ in patients with Budd-Chiari syndrome
The total $K_u$ values were lower in 2 patients with Budd-Chiari syndrome than in the controls (324 and 335 ml/min, respectively). A difference in the mean $K_u$ value was seen between the right and left lobes in both patients. Although the mean $K_u$ value was lower in the right lobe, it was similar to that in the control subjects in the left lobe. The mean $K_u$ was 0.29 ml/min/cm$^3$ in the right lobe and 0.39 ml/min/cm$^3$ in the left lobe in one patient, and 0.31 ml/min/cm$^3$ in the right lobe and 0.44 ml/min/cm$^3$ in the left lobe in the other patient.

Liver functional imaging
Liver functional images provided visual display of both anatomical and functional information. As chronic liver disease progressed, a change in liver shape was observed: hypertrophy of the left and/or caudate lobe and atrophy of the right lobe. The $K_u$ was homogeneous in the liver parenchyma in the controls (Fig. 3a). On the other hand, the $K_u$ was reduced and its distribution became more irregular with progression of the underlying liver disease in the patient group. In patients with severe liver profiles (Grade C), hypertrophy of the caudate lobe and a higher $K_u$ in the caudate lobe were demonstrated compared with other liver parenchyma (Fig. 3b). In 2 patients with Budd-Chiari syndrome, the functional images showed hypertrophy of the left lobe and atrophy of the right lobe and clearly demonstrated higher $K_u$ in the left lobe than in the right lobe (Fig. 3c and d).

DISCUSSION

Scatter and attenuation compensation
Scatter and nonuniform attenuation in the body are the most important factors degrading the accuracy of counts toward the interior of the organ in SPECT images of the liver. The usefulness of a TFW scatter and attenuation compensation technique for dynamic studies with Tc-99m sheet line source transmission data has been reported.

Regional liver function
The present method makes it possible to evaluate regional liver function quantitatively. Evaluation of regional liver function provides useful information in patients with many types of liver disease. In patients with Budd-Chiari syndrome, the mean $K_u$ value in the left lobe, where the draining veins were patent was similar to that in the controls, but that in the right lobe, where draining veins were occluded, was reduced. It is known from histological studies that the degree of liver congestion, fibrosis and liver cell necrosis differs depending on the site of hepatic vein occlusion in Budd-Chiari syndrome. It was thought that fibrosis and congestion were severe in the right lobes but that histological changes were minimal in the left lobe. Measurement of regional liver function will also be useful in surgical planning. Estimation of remnant liver function is very important in patients with liver tumors who are scheduled to undergo heptectomy. It may be possible to predict remnant liver function by measuring the $K_u$ of the remnant liver. If we can determine the minimum value for $K_u$ needed to meet metabolic requirements, the $K_u$ value for the remnant liver will be a useful index for determining the degree of surgical intervention.
Liver functional image
Liver functional images clearly reflected the results of total and mean Ks measurements and made it possible to visually assess the severity of chronic liver disease and regional dysfunction of the liver parenchyma. These functional images provided both anatomical and functional information. In patients with chronic liver disease, functional images depicted changes in liver shape and differences in the regional Ks in the liver parenchyma. In patients with severe liver dysfunction, hypertrophy of the caudate lobe and higher Ks in the caudate lobe were demonstrated. In the 2 patients with Budd-Chiari syndrome, functional images demonstrated hypertrophy of the left lobe, and atrophy of the right lobe, and differences in Ks between the right and left lobes. Functional images seem be useful in evaluating the pathophysiology and severity of chronic liver disease. Both anatomical and functional information provided by functional images will be of great value in monitoring regeneration of the remnant liver after hepatectomy, in evaluating transplanted livers, and in following the clinical course after interventional radiology procedures (PTA or transscatheter hepatic arterial chemoembolization).

CONCLUSIONS
In conclusion, receptor imaging with Tc-99m GSA by means of Patlak plot and dynamic SPECT makes it possible to observe total and regional hepatic functional parameters in vivo. These data can be obtained qualitatively by attenuation and scatter compensation. Our results suggest that the proposed technique provides unique and diagnostic information that is not available with any other method.

REFERENCES


