A Noninvasive Method for Evaluating Portal Circulation by Administration of TI-201 per Rectum

Norihisa Tonami, Kenichi Nakajima, Kinichi Hisada, Nobuyoshi Tanaka, and Kenichi Kobayashi

Kanazawa University, Kanazawa, Japan

A new method for evaluating portal systemic circulation by administration of TI-201 per rectum was performed in 13 control subjects and in 65 patients with various liver diseases. In normal controls, the liver was visualized on the 0–5-min image whereas the images of other organs such as the heart, spleen, and lungs were very poor. In patients with liver cirrhosis associated with portal-systemic shunt, and in many other patients with hepatocellular damage, the liver was not so clearly visualized, whereas radioactivity in other organs, especially the heart, became evident. The heart-to-liver uptake ratio at 20 min after administration (H/L ratio) was significantly higher in liver cirrhosis than in normals and patients with chronic hepatitis (p < 0.001). The patients with esophageal varices showed a significantly higher H/L ratio compared with that in cirrhotic patients without esophageal varices (p < 0.001). The H/L ratio also showed a significant difference (p < 0.01) between Stage 1 and Stage 3 esophageal varices. Since there were many other patients with hepatocellular damage who had high H/L ratios similar to those in liver cirrhosis, the effect that hepatocellular damage has on the liver uptake of TI-201 is also considered. Our present data suggest that this noninvasive method seems to be useful in evaluating portal-to-systemic shunting.


The evaluation of portal circulation is essential to a full understanding of the pathological conditions in various liver diseases, and will allow more reasonable treatment of patients with portal hypertension. In order to study portal circulation, there have been many clinical reports by per-rectum administration of radioactive tracers such as Na-24 (1), Na 131I (2,3), Xe-133 (4), 99mTcO₄⁻ (5), and 13NH₄⁺ (6). However, none of these techniques has been widely applied routinely, because most of the radioactive tracers absorbed from the rectal lumen pass rapidly through the liver and do not remain there. This common biological behavior makes it complicated and difficult to obtain useful indices for the evaluation of a portal-to-systemic shunt.

While we have designed new clinical applications for tumor imaging using TI-201 chloride (7,8), we understood that TI-201 might be mainly distributed in its initial passage to a tumor according to the local blood flow and the cell viability. Consequently, we thought that if TI-201 is similarly subject to hepatic uptake, TI-201 might be an appropriate tracer to evaluate the rectum-to-hepatic vascular pathways when given rectally.

This paper will present images of the liver and other organs by this new technique, using TI-201 chloride in normal controls, in patients with hepatic cirrhosis with portal-systemic shunt, and in patients with other hepatocellular damage. The clinical results of the data are analyzed for the evaluation of portal-systemic shunt in various liver diseases.

Received April 9, 1982; June 23, 1982.

For reprints contact: Norihisa Tonami, MD, Dept. of Nucl. Med., School of Medicine, Kanazawa Univ., Takara-machi 13-1, Kanazawa City 920, Japan.
MATERIALS AND METHODS

A total of 78 patients (47 male and 31 female) were studied. These included 13 control patients with various disorders not related to the liver, heart, or gastrointestinal tract, 23 with liver cirrhosis, nine with liver cirrhosis accompanied by primary hepatic, 14 with chronic hepatitis, nine with acute hepatitis, two with subacute hepatitis, three with primary biliary cirrhosis, four with metastatic liver cancer, and one with primary hepaticoma without liver cirrhosis. Diagnosis of the liver diseases was confirmed by routine liver function tests, liver biopsy, laparoscopy, radionuclide colloid liver scan, computerized tomography, echography, or autopsy, as well as by clinical findings. In 21 out of 23 patients with liver cirrhosis, the presence or absence of esophageal varices was evaluated by fiber-optic endoscopy. Based on the endoscope findings, esophageal varices were classified into four stages as defined by the Japanese Society for the Study of Portal Hypertension (9). This classification is summarized in Table 1. Each patient received an enema one or two hours before the TI-201 examination, to empty the rectum. A polyethylene tube (2.2 mm i.d.) was inserted 20 cm up to the upper part of the rectum to avoid physiologic shunts to the systemic circulation in the lower rectum. In 47 patients, a dose of 2 mCi (74 MBq) of TI-201 chloride was given through the tube, followed by 10–20 ml of air to clear the tube. To find out whether 0.5 mCi (18.5 MBq) would be adequate (TI-201 is expensive), we repeated the test in six patients at 2 to 4 wk after the initial study, using the smaller dose. Since the result of the comparison was excellent, we used 0.5 mCi in the remaining 31 patients.

Each patient was positioned supine under a large-field gamma camera with an all-purpose, medium-resolution collimator (42,000 holes) viewing the liver, heart, spleen, and the lower parts of the lungs. Images were obtained every 5 min up to 25 min at least. Data were recorded by computer for 25 min in 25 frames. Regions of interest (ROIs) were placed on the liver, heart, spleen, and right lung. Each such ROI contains about 100 points (one point = 5.2 mm × 5.2 mm). Areas of these ROIs were normalized. We then obtained time-activity curves in each normalized ROI, and time-ratio curves for heart to liver, spleen to liver, and lung to liver. In this study, however, we used the heart-to-liver ratios at 20 min (H/L ratio) after administration to evaluate the degree of portal-systemic shunt. A background correction was not made since backgrounds in this study result mainly from collateral circulation, and it is very difficult to estimate the backgrounds over the liver and heart, which might be quite different in the ROIs of the two organs.

In patients showing very low TI-201 activity in the liver even at 20–25 min, a liver scan with 0.2 mCi (7.4 MBq) of Tc-99m Sn colloid was performed before moving the patient, to locate the liver precisely.

We first investigated whether an H/L ratio can be affected by the selection of the ROI on the liver. In four patients, ROIs were placed on the liver at five different areas: the lower part of the right lobe, the upper part of the right lobe, the middle part of the liver, the left lobe, and the whole liver. Since the results suggested that, if one avoided the left lobe, the choice of ROI would make little difference to the H/L ratio (Table 2), we chose the middle of the liver for our standard ROI. H/L ratios in 21 of 23 patients with liver cirrhosis were investigated at each stage of esophageal varicosity, based on fiber-optic endoscopy. Two other patients were not included here because endoscopy was not performed. Also H/L ratios were compared with the results of indocyanine green retention at 15 min (ICG), performed in 42 patients with various diseases. To test for difference between the mean values, student’s t-test was used. Correlations were assessed by standard linear regression. Results were considered significant when p < 0.05.
RESULTS

In the normal controls the liver was visualized on the 0- to 5-min image and became clearer with time, while the accumulations in other organs (heart, spleen, and lung) were very small even on the 20-25-min image with 0.5 mCi TI-201 (Fig. 1). Time-activity curves for the normalized ROIs in each organ showed that the liver activity increased rapidly with time, but the activities of other organs increased much more slowly (Fig. 2). The heart-to-liver ratio curve became nearly constant after about 10 min and held there up to 25 min. (Fig. 3). Similarly constant time-ratio curves were observed in every patient. In contrast to the normal controls, in most of the patients with liver cirrhosis associated with portal systemic shunt, liver activity was low and did not increase much with time, whereas activity was seen in the heart, lungs, spleen, and stomach, probably related to collateral circulation. The patients with portal-systemic shunt showed prominent changes of TI-201 distribution, clearly different from the findings in normal controls (Fig. 4). As a matter of course, the activities of the heart, spleen, and lung increase rapidly with time (Fig. 5). A typical

FIG. 1. Sequential scintigrams after administration per rectum of 0.5 mCi TI-201 in a 66-year-old man without liver disease. Liver is observed on 0-5-min image and becomes clearer with time, whereas other organs are very faint even on the 20-25-min image.

FIG. 2. Time-activity curves in from normalized ROIs of liver, heart, spleen, and lung in control of Fig. 1. Liver activity increases rapidly with time, whereas activities of other organs increase much more slowly.

FIG. 3. Time-ratio curve for heart to liver in same control patient. Curve becomes relatively constant between 10 and 25 min. H/L ratio in this control is 0.13.

FIG. 4. Sequential scintigrams after administration per rectum of 0.5 mCi TI-201 in a 65-year-old woman with liver cirrhosis with portal-systemic shunt. Liver cannot be clearly visualized, whereas other organs such as heart, lungs, spleen, and stomach were observed, probably due to collateral circulation.
curve for the heart-to-liver ratio leveled off at 1.4 after 10 min (Fig. 6); the mean value for normal controls was 0.16 (Table 3).

In the patients with liver cirrhosis without esophageal varices, liver activity was evident and became clearer with time, while activities of other organs were lower relative to those in the patients with esophageal varices. Among the cirrhotics without varices, the highest H/L ratio was 0.49; the images (0.5 mCi Tl-201) are shown in Fig. 7. In other patients with hepatocellular damage showing abnormally high H/L ratios, Tl-201 images were similar to those of the patients with liver cirrhosis associated with portal-systemic shunt. However, image quality was somewhat different in each patient, since Tl-201 activity can be affected by the absorption rate from the rectum and also by the dosage. Sample images are shown in Fig. 8 (cirrhosis, Stage 3 esoph. var., 0.5 mCi Tl-201, H/L = 0.96); Fig. 9 (acute hepatitis, 0.5 mCi, H/L = 0.87); and Fig. 10 (subacute hepatitis, 2 mCi, H/L = 0.93). In the six patients who were given 0.5- and 2-mCi doses of Tl-201 2 to 4 wk apart, the H/L ratios correlated well (r = 0.98, p < 0.001, Fig. 11).

Table 3 lists the mean H/L values ± 1 s.d. found in the groups with various diseases, and in the 13 normal controls. In hepatic cirrhosis the mean H/L was significantly

---

**TABLE 3. RESULTS OF H/L RATIO IN VARIOUS LIVER DISEASES AND IN NORMAL CONTROLS**

<table>
<thead>
<tr>
<th>Disease</th>
<th>N</th>
<th>Mean ± s.d.</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>H/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>13</td>
<td>0.16 ± 0.07</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>23</td>
<td>0.92 ± 0.40</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Cirrhosis &amp; hepatoma</td>
<td>9</td>
<td>0.78 ± 0.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>14</td>
<td>0.25 ± 0.17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute hepatitis</td>
<td>9</td>
<td>0.43 ± 0.31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subacute hepatitis</td>
<td>2</td>
<td>0.89 ± 0.09</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliary cirrhosis</td>
<td>3</td>
<td>0.74 ± 0.30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic metastasis</td>
<td>4</td>
<td>0.72 ± 0.20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatoma &amp; cirrhosis</td>
<td>1</td>
<td>0.83</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**FIG. 6.** Time-ratio curve for heart to liver in same patient. Curve becomes constant between 10 and 25 min. H/L ratio is 1.40.
FIG. 7. Sequential scintigrams after administration per rectum of 0.5 mCi Tl-201 in a 35-year-old man with liver cirrhosis not associated with esophageal varices. Liver is visible but activities of heart and other organs are low. H/L ratio in this patient was 0.49.

FIG. 8. Sequential scintigrams after administration per rectum of 0.5 mCi Tl-201 in a 56-year-old man with liver cirrhosis associated with Stage 3 esophageal varices. Liver can not be seen clearly, whereas activities of heart and probably spleen become evident. Arrow indicates heart. H/L ratio in this patient was 0.96.

higher than normal (p <0.001) and also higher than in chronic hepatitis (p <0.001). In metastatic liver disease the H/L was also higher than normal (p <0.001). Table 4 lists the H/L ratios for the cirrhotic patients, subdividing them according to the severity of their esophageal varices as judged by endoscopy. The patients with esophageal varices showed a significantly higher mean value (1.06 ± 0.31) than those without (0.32 ± 0.19); even the lowest H/L ratio with varices (0.60) was greater than the highest nonvaricotic ratio (0.49). The mean H/L ratios were 0.71 ± 0.10 in Stage 1, 1.03 ± 0.36 in Stage 2, and 1.21 ± 0.20 in Stage 3. There was a sig-

FIG. 9. Sequential scintigrams after administration per rectum of 0.5 mCi Tl-201 in a 69-year-old man with acute hepatitis. Liver is not seen clearly, whereas cardiac activity becomes evident (arrow). Spleen is not visible. H/L ratio was 0.87.

FIG. 10. Sequential scintigrams after administration per rectum of 2 mCi Tl-201 in a 61-year-old man with subacute hepatitis. Liver can be seen but activities of heart (arrow) and other organs are also evident. H/L ratio was 0.93.
significant difference between stages 1 and 3 ($p < 0.01$). The relation between $H/L$ ratio and the results with indocyanine green in 42 patients is shown in Fig. 12; there was a relatively good correlation ($r = 0.71$, $p < 0.001$).

**DISCUSSION**

It is obvious that the rectal administration of TI-201 chloride allows us to understand the portal systemic circulation from the peripheral part of the inferior mesenteric vein, and the $H/L$ ratio can be a useful index revealing the degree of portal-systemic shunt. When TI-201 is delivered at the upper part of the rectum in a normal control, it can be absorbed from the rectal lumen and the greater part of the radioactivity will proceed to the liver through the superior rectal vein, the inferior mesenteric vein, and the portal vein in that order. Part of the radioactivity passes through the liver and flows into the hepatic veins. Some TI-201 also enters the inferior vena cava through the middle and inferior rectal veins and will be distributed to the whole body. However, usually the accumulation of TI-201 in each organ through this route is extremely small compared with that in the liver through the portal system. On the other hand, the patients with portal hypertension show that TI-201 can be distributed to the whole body through complex collateral routes. The major such routes are (a) collaterals from the middle and inferior rectal veins, or the inferior mesenteric vein, to the inferior vena cava, and (b) from the portal vein to the superior vena cava. Thallium-201 trapped in an organ remains there at least for a couple of hours and can not readily be washed out. This characteristic of TI-201 is quite important: it provides a constant $H/L$ ratio for a short time and this seems to be a valuable and reliable index for evaluating the amount of shunting from the rectal veins to the systemic circulation.

A number of substances have been given rectally to

---

**TABLE 4. H/L RATIO AND STAGE OF ESOPHAGEAL VARICES IN 21 PATIENTS WITH LIVER CIRRHOSIS**

<table>
<thead>
<tr>
<th>Esophageal Varices</th>
<th>N</th>
<th>Mean±s.d.</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>H/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>4</td>
<td>0.32±0.19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>3</td>
<td>0.71±0.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>6</td>
<td>1.03±0.36</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>8</td>
<td>1.21±0.20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The mean value ± s.d. of the patients with esophageal varices is 1.06 ± 0.31

Esophageal Varices (H) vs (N) $p < 0.001$

Stage I vs II n.s.

Stage I vs III $p < 0.01$

Stage II vs III n.s.
evaluate the portal systemic circulation. Newman and Cohen (10) reported that “the rectum-to-lung time” required to detect intrarectally administered ether in a patient’s expired air was longer in patients with cirrhosis than in normal subjects. However, Giges (11) and Waldstein (12) indicated that this method did not demonstrate a significant difference in portal circulation time between normal subjects and patients with liver cirrhosis. Deterling et al. (1) described a test of portal circulation time using the appearance of radioactivity over the brachial artery after administering Na-24 rectally. Castell et al. (4) presented a method using Xe-133 given rectally with monitoring of radioactivity over the precordium. In this method the portal circulation time was estimated “visually” from the initial tracing or calculated from a semilogarithmic plot of precordial radioactivity against time. The slope of appearance of precordial radioactivity was also obtained. However, these findings can vary with the availability of absorbing areas from the rectum. Xenon-133 diffuses easily into the descending or transverse colon as well as the lower part of the rectum, making it difficult to establish the circulation route. Blondheim et al. (2) monitored the time-activity curve over the liver after administering radiiodine rectally and evaluated portal hypertension by the shape and equilibration of the curve obtained. This equilibration over the liver is achieved after I-131 absorbed from the rectum has circulated several times through the portal and systemic circulations and the analysis of the curve is therefore complicated and difficult. To overcome this shortcoming, Kurki et al. (5) used [99mTc]pertechnetate as a radiotracer and obtained a relatively useful index of the liver-to-heart uptake ratio from the initial rising slope. Technetium-99m has very good physical characteristics for imaging and thus can provide visual information of portal systemic circulation. However, since the main factor affecting the rise of radioactivity over the liver is different in each disease (e.g., liver flow from portal vein in patients without portal hypertension vs. liver flow from systemic circulation in patients with portal hypertension), this index is not strictly reliable.

Caride (13) studied the dynamics of rectal absorption of pertechnetate in dogs and concluded that pertechnetate is not the ideal tracer for studying portal circulation using rectal entry, because a significant amount of radioactivity remains in the abdominal area following administration and induces considerable error. Nitrogen-13 ammonia has been also applied to such studies (6). This radiotracer can accumulate in the liver as well as the heart and stays for a while, thus affording a relatively good index of the heart-to-liver uptake ratio for evaluation of the portal circulation. Its disadvantage is that a cyclotron must be near the hospital for clinical use, so it is not widely suitable for routine study. An ideal radioactive tracer for studying portal circulation by rectal administration has to be rapidly absorbed and to accumulate in each organ according to its blood flow, preferably without recirculation. The main advantage of TI-201 over the other radiotracers studied is the comparatively prolonged cellular retention of thallium, as is seen in myocardial imaging. Bradley-Moore et al. (14) reported the tissue distribution of TI-201 given intravenously in goats, in which the greatest concentration is in the kidneys, heart, and liver; the concentration remains high in these organs for at least the first two hours. This characteristic of TI-201 makes possible a reliable index of portal-systemic shunt, such as the H/L ratio in our study. From this point of view, TI-201 chloride seems to be a reasonable tracer.

One of the problems with TI-201 is the influence of radioactivity distributed to the liver through the hepatic artery. It arises because TI-201 is partly cleared from the liver through hepatic veins and some enters into the systemic circulation through various collaterals. According to the study of the biological behavior of TI-201 by Bradley-Moore et al. (14), the heart-to-liver uptake ratio is 1.6 at 25 min after intravenous injection. This means that the distribution of TI-201 through the hepatic artery should be considered in patients with portal-systemic shunt, and the H/L ratio calculated in our study may be higher than the real one. However, the H/L ratio may also be raised by decreased TI-201 accumulation in the injured liver cells of patients with various hepatic diseases. Although the real condition is uncertain, there seem to be opposing errors in patients with hepatic disease. Another problem is the variation of myocardial uptake of TI-201 between patients, which should be considered in those with heart disease. There is also a possibility that other diseases may affect TI-201 distribution.

In our study, the mean H/L ratio was significantly higher than normal in liver cirrhosis and in chronic hepatitis. The cirrhotic patients with esophageal varices showed a significantly higher H/L ratio compared with that in patients without esophageal varices, and there was a significant difference between Stages 1 and 3 of the endoscopy findings. In spite of some problems, then, this technique seems quite useful in evaluating noninvasively the degrees of portal-systemic shunt. However, the effects of hepatocellular damage on liver uptake of TI-201 should be considered, since there was relatively good correlation between the H/L ratio and ICG, and the high ratios found in cirrhosis also occurred in three of nine patients with acute hepatitis, two of two with subacute hepatitis, three of three with biliary cirrhosis, four of four with hepatic metastases, and in one case of primary hepatoma without cirrhosis. It can be said that the H/L ratio is the result of portal blood flow and hepatic cell viability, assuming a normal myocardial uptake. Since there were many cirrhotic patients showing TI-201 images similar to those in patients with hepato-
cellular damage and high H/L ratios, it seems to be difficult to separate them on the TI-201 images. In subacute hepatitis and metastatic liver cancer, we assume that intrahepatic shunt formation may also account for the high H/L ratio. Although all of the patients with metastatic liver cancer showed clear focal defects on the Tc-99m Sn colloid liver scans, high H/L ratio in these patients indicates that this method may also have a useful diagnostic value to suggest the presence of diffuse small metastatic liver tumors. In the comparison study regarding H/L ratio between the use of 0.5 mCi and 2.0 mCi of TI-201 chloride, the dosage of 0.5 mCi gave a satisfactory result. This encourages us to perform this method routinely with less expense in patients with various liver diseases.

ACKNOWLEDGMENTS

We wish to thank Mr. M. Matsudaaira, M. Yamada, H. Tsuji, and Y. Kurata for their technical assistance and Nihon Medi-Physics Co., Ltd., for kindly supplying the radionuclide.

REFERENCES


George Simon Memorial Fellowship Award

The Fourth Annual George Simon Memorial Fellowship Award, given by the Fleischner Society for the best submitted work relating to the imaging of the respiratory system, has been given to H. Dirk Sostman of Yale University for his paper "Experimental Studies with "Indium Labeled Platelets in Pulmonary Embolism."

Entries for the Fifth George Simon Award are now being accepted. The paper can represent the work of more than one investigator, but the senior author should be the applicant and responsible for the majority of the work. Applicants should be no older than 40 years. Papers which have been published or submitted elsewhere are not eligible. The award consists of an all-expense-paid trip to the 1983 Fleischner Society Meeting, New York City in May, plus a cash prize. All submissions must be in the form of a complete scientific paper, not longer than 25 pages (double spaced) and should be sent in triplicate to:

Richard H. Greenspan, MD
Dept. of Diagnostic Radiology
Yale University School of Medicine
333 Cedar Street
New Haven, CT 06510

Papers must be sent on or before January 1, 1983