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Quantitative lung perfusion scintigraphy and detection of intrapulmonary shunt in liver cirrhosis

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Objective: Frequent association between liver cirrhosis and hypoxemia has been well documented. It is mostly attributable to intrapulmonary shunt due to dilation of pulmonary vasculature. We performed quantitative lung perfusion scintigraphy to detect an intrapulmonary shunt in cirrhosis patients. ***Methods:*** Prior to injection, Tc-99m MAA was applied to thin layer chromatography for quality control. Three cirrhosis patients who had hypoxemia were examined as well as 11 control subjects. After i.v. injection of Tc-99m MAA, whole body anterior and posterior images were taken at 5 min in patients with cirrhosis and at 8 time points up to 60 min in control subjects. Regions of interest were placed at the bilateral lungs and the whole body, and pulmonary accumulation was calculated. ***Results:*** All the control subjects demonstrated more than 90% of radioactivity in the lungs until 20 min. In contrast, all the patients showed values less than 80% at 5 min. In the cirrhosis patients with hypoxemia, the presence of intrapulmonary shunt was confirmed on quantitative lung perfusion scan. In control subjects, pulmonary accumulation of Tc-99m MAA dropped as a function of time and became less than 90% after 30 min. ***Conclusion:*** The timing of measurements is essential in evaluating intrapulmonary shunt.

Key words: liver cirrhosis, lung perfusion scintigraphy, technetium-99m MAA, intrapulmonary shunt, pulmonary vascular dilation

INTRODUCTION

In patients with liver cirrhosis, hypoxemia is often observed which may be attributable to the presence of intrapulmonary shunt due to dilated peripheral pulmonary vessels and small arteriovenous communications.[1–4] This intrapulmonary vascular dilation has been detected by Tc-99m macroaggregated albumin (MAA) scintigraphy.[4] Some Tc-99m MAA particles, when administered, pass through the pulmonary vasculature and lodge in the systemic capillary beds.

To detect and quantify an intrapulmonary shunt in cirrhotic patients with hypoxemia, we scintigraphically measured the percentage of Tc-99m MAA accumulation in the lung compared with whole body radioactivity by placing regions of interest. To make the quantification more precise, the quality of Tc-99m MAA was tested on thin layer chromatography (TLC) to evaluate the amount of unbound Tc-99m. We also studied control subjects to obtain normal values of lung uptake as a function of time after the administration of Tc-99m MAA. This was considered important because lung uptake dropped as MAA particles disintegrated and left the pulmonary vasculature for the extrapulmonary tissues.

MATERIALS AND METHODS

Subjects

Three patients who had hypoxemia associated with liver cirrhosis were enrolled in this study as well as 11 control adults (age 57 ± 15 yr, 8 males and 3 females). The control subjects were selected from among adult patients who underwent pulmonary perfusion scintigraphy on

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condition that 1) they received pulmonary perfusion scintigraphy to exclude pulmonary thromboembolism because of such symptoms as chest pain, shortness of breath, or dyspnea, 2) they did not have hypoxemia, evidence of any right-to-left shunt, cardiopulmonological abnormality, or liver disease, and 3) they were eventually diagnosed as normal.

Preparation of radiopharmaceutical and quality control
Tc-99m MAA kits (Daiichi Radioisotope Laboratories, Tokyo, Japan) were commercially obtained and labeled with Tc-99m pertechnetate eluted from a Mo-99/Tc-99m generator (Daiichi Radioisotope Laboratories) according to the manufacturer's instructions. Thin layer chromatography (TLC) was used to determine the labeling efficiency. ITLC-SG chromatography paper #61886 (Gelman Sciences, Ann Arbor, MI, USA) was cut into 1.5 × 10 cm strips and activated. The strips were stored dry at room temperature until use. Aliquots of labeled solution were taken and applied to TLC at 5 min and 60 min after labeling and the labeling efficiency was determined with phosphate buffered saline 1/15 M, pH 7.4 as a mobile phase. The unbound radioactivity migrated with the solvent front but the bound radioactivity remained at the origin. Fractions of strips were counted with a gamma counter, and the labeling efficiency was calculated.

Scintigraphy
Tc-99m MAA at a dose of 111 MBq was administered to patients and control subjects from a peripheral vein of the upper extremities in the supine position.

All the images were acquired with the examinees in the supine position. For control subjects, whole body anterior and posterior images were taken with a two-head gamma camera (PRISM-AXIS, Marconi Medical Systems, Inc., Cleveland, Ohio, USA) equipped with low-energy all-purpose collimators and a 1024 × 256 matrix at a speed of 100 cm/min in a single pass at 5, 10, 15, 20, 30, 45 and 60 min after intravenous injection of Tc-99m MAA. This high-speed whole body scanning was adopted to obtain images at these various time points with short intervals, and the image quality was felt to be adequate for the quantification of lung uptake. For the three patients with cirrhosis and hypoxemia, the examination was performed only at 5 min.

Regions of interest were placed at the bilateral lungs and the whole body, and then pulmonary accumulation was calculated as the geometric mean of the percentages of lung accumulations on both anterior and posterior whole body images. Planar lung images were obtained to confirm the absence of pulmonary perfusion defects. Additional planar images were taken on the head and the abdomen to visualize extrapulmonary accumulation of Tc-99m MAA.

RESULTS

Quality control of Tc-99m MAA
At 5 min and 60 min after the labeling of MAA with Tc-99m, greater than 99.5% of radioactivity was observed at the fraction of MAA on TLC in all examinations.

Control subjects versus cirrhosis patients
On planar images, all the control adults had homogeneous MAA distribution without any perfusion defects. Lung accumulation in normal adults was 96.9 ± 0.5, 95.3 ± 2.1, 94.9 ± 2.4, 93.2 ± 2.9, 92.4 ± 2.1, 91.3 ± 2.8 and 89.2 ± 3.4%, at 5, 10, 15, 20, 30, 45 and 60 min, respectively. All

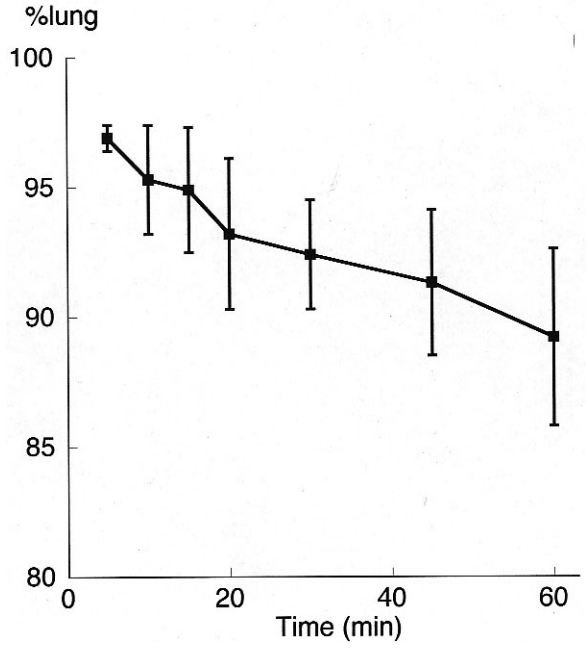


Fig. 1 Percentage of lung accumulation in control subjects (n = 11). Percentage of lung accumulation of Tc-99m MAA on whole body images was calculated and expressed as a geometrical mean of anterior and posterior images as a function of time.

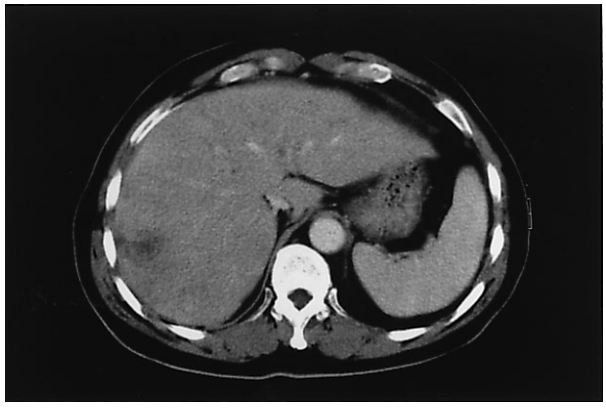


Fig. 2 Case 1. CT reveals a tumor in the right lobe of the liver with cirrhosis.

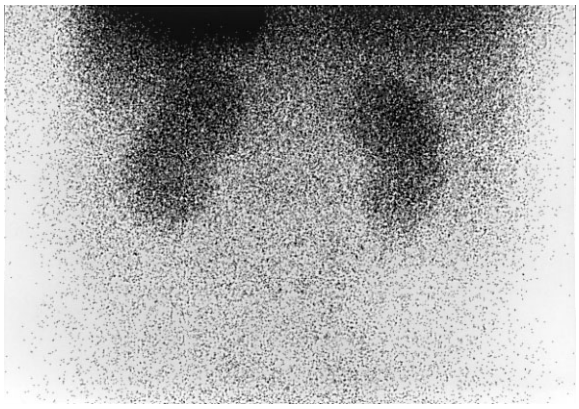


Fig. 3 Case 1. Posterior view. Extrapulmonary accumulation of Tc-99m MAA is marked.

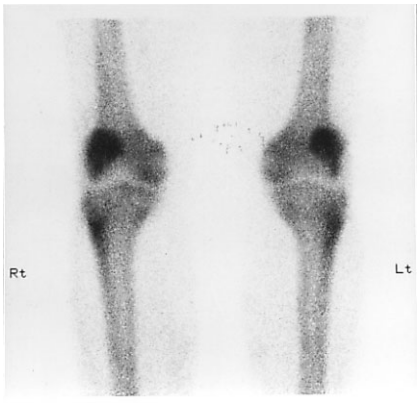


Fig. 4 Case 1. On bone scan (anterior view), increased subcortical accumulation is depicted at the bilateral lower extremity bones, which represents hypertrophic pulmonary osteoarthropathy.

the control adults demonstrated greater than 90% of radioactivity in the lung until 20 min (Fig. 1).

The three patients with hypoxemia had values less than 80% at 5 min (mean 70.1%, range 66–75%, $p < 0.0001$ versus normal subjects).

Case 1

A 64-year-old male had hepatitis-C virus positive cirrhosis. The Child-Pugh class[5] was B with a serum total bilirubin of 2.4 mg/d*l*, a serum albumin of 3.2 g/d*l*, no ascites, no encephalopathy and a normal prothrombin time. Abdominal CT revealed a tumor in the right lobe of the liver (Fig. 2). Arterial blood gas analysis showed a PaO_2 of 55 mmHg and a $PaCO_2$ of 28 mmHg at room air. On lung perfusion scan, the percentage of lung uptake was 69% at 5 min and extrapulmonary accumulation of Tc-99m MAA was marked (Fig. 3). Thus, an intrapulmonary shunt was detected. No perfusion defect was observed in the lungs. On bone scan, increased subcortical accumulation was depicted in the bilateral lower extremity bones

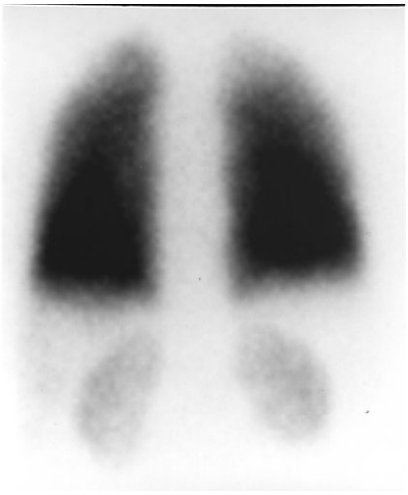


Fig. 5 Case 2. Posterior view. Tc-99m MAA scan shows conspicuous renal uptake.

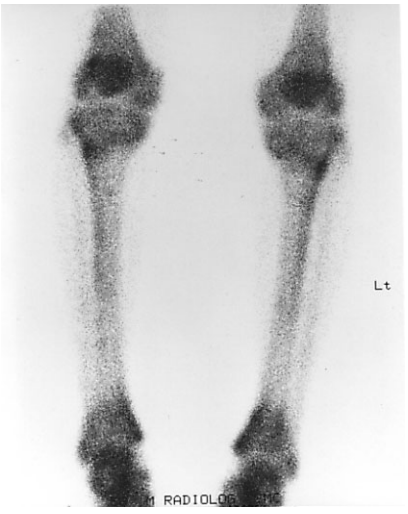
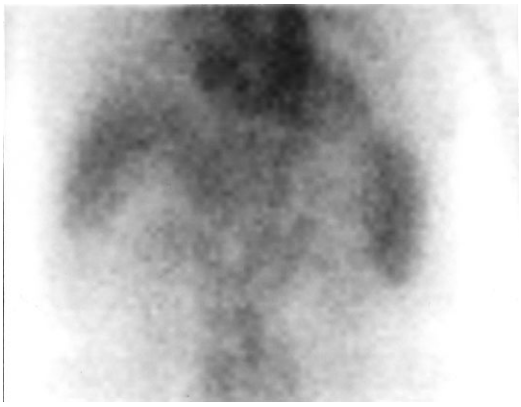


Fig. 6 Case 2. On bone scan (anterior view), increased subcortical accumulation is observed at the bilateral lower extremity bones similar to that of case 1.

(Fig. 4) which represented hypertrophic pulmonary osteoarthropathy probably attributable to hypoxemia.[6]

Case 2

A 58-year-old male with known advanced esophageal cancer in the abdominal esophagus was undergoing curative radiation therapy combined with chemotherapy. He had alcoholic liver cirrhosis. The Child-Pugh class was B with a serum total bilirubin of 1.2 mg/d*l*, a serum albumin of 2.7 g/d*l*, no ascites, no encephalopathy and a normal prothrombin time. During the radiation therapy, he was found to have hypoxemia with a PaO_2 of 61 mmHg and a $PaCO_2$ of 24 mmHg at room air. Therefore, radiation pneumonitis and malignant invasion had to be ruled out. Tc-99m MAA scan showed conspicuous renal uptake



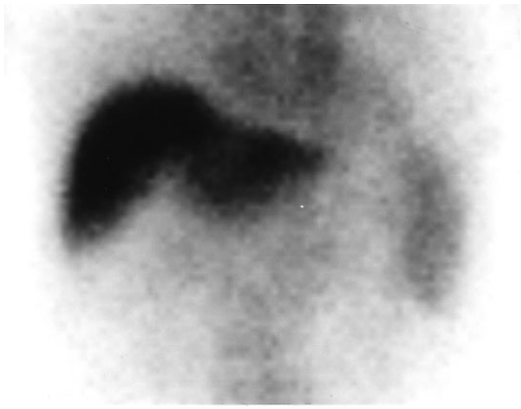


Fig. 7 **Fig. 8**

Figs. 7 and 8 Case 3. On Tc-99m galactosyl human serum albumin (GSA) liver scintigraphy, the clearance of GSA from the blood is delayed and the accumulation of GSA in the liver is low (Fig. 7 at 3 min and Fig. 8 at 15 min after administration). Morphologically, hypertrophy of the lateral segment of liver and splenomegaly are observed.

(Fig. 5). The percentage of lung uptake was 66% at 5 min; so an intrapulmonary shunt was confirmed. Increased subcortical accumulation was observed on bone scan in the bilateral lower extremity bones (Fig. 6), which represented hypertrophic pulmonary osteoarthropathy similar to that in case 1.

Case 3

A 71-year-old female had hepatitis-C virus positive liver cirrhosis. The Child-Pugh class was B with a serum total bilirubin of 1.5 mg/d*l*, a serum albumin of 3.4 g/d*l*, moderate ascites, no encephalopathy and a normal prothrombin time. On Tc-99m galactosyl human serum albumin (GSA) liver scintigraphy,[7] the clearance of GSA from the blood was delayed and the accumulation of GSA in the liver was low (Figs. 7 and 8). She had hypoxemia with a PaO_2 of 72 mmHg and a $PaCO_2$ of 38 mmHg at room air. On Tc-99m MAA scintigraphy, the percentage of lung uptake was 75% at 5 min.

DISCUSSION

Hypoxemia associated with liver cirrhosis has previously been well described.[1–4] Several physiological mechanisms including portopulmonary anastomoses,[8] decreased diffusion capacity,[9,10] dilated peripheral pulmonary vessels and small arteriovenous communications[1] have explained the association between liver cirrhosis and hypoxemia. Among them, dilated peripheral pulmonary vessels and small arteriovenous communications, that is, intrapulmonary vascular dilations, have been suggested as the most important cause of hypoxemia.[4,11,12]

The systemic distribution of Tc-99m MAA particles can be used to determine the shunt fraction because they do not normally traverse the pulmonary capillary bed. The right-to-left shunt fraction can be obtained by comparing radioactive counts in the kidney to counts in the injected dose.[13] A shunt index calculated as brain activity/lung activity was also reportedly useful.[14] In this study, we used whole body scanning and calculated the amount of lung activity/whole body activity.

On quantitative lung perfusion scan, a quality control is indispensable prior to administration of Tc-99m MAA. Incomplete labeling leads to false low lung uptake and visualization of extrapulmonary tissues. We determined the labeling efficiency of Tc-99m MAA by a simple TLC. Labeling efficiency proved to be greater than 99.5% in all the examinations.

In the control subjects, pulmonary accumulation of Tc-99m MAA dropped as a function of time and became less than 90% after 30 min. Therefore, it is essential to consider the timing of measurement for pulmonary accumulation when we determine whether a patient has a low pulmonary accumulation.

The quantitative lung perfusion scan may be recommended in cirrhosis patients with hypoxemia regardless of the severity of liver dysfunction. The correlation between the extent of intrapulmonary shunt and oxygenation has previously been reported.[4] In the present three patients with liver cirrhosis, this method confirmed the presence of intrapulmonary vascular dilation as the cause of hypoxemia. The three patients were in a moderate stage of liver cirrhosis on the Child-Pugh classification. No pulmonary arteriovenous fistula or cardial right-to-left shunt was found in any of the patients. The quantitative lung perfusion scan made further examinations for hypoxemia unnecessary. Case 2 of esophageal carcinoma was undergoing curative radiotherapy in combination with chemotherapy. The cause of hypoxemia had to be clarified because in such cases, eventual pulmonary diseases with hypoxemia, like radiation pneumonitis, chemotherapy-induced pneumonitis, opportunistic infection,

and pulmonary lymphangitis carcinomatosa, often result in mortality. The quantitative lung perfusion demonstrated that hypoxemia was due to liver cirrhosis not pulmonary complications of chemo-radiation therapy for esophageal carcinoma.

Krowka et al. reported that intrapulmonary right-to-left shunt was detected in 13.2% of patients with advanced liver disease on contrast echocardiography.[15] Meanwhile, Hopkins et al. reported that intrapulmonary right-to-left shunt occurred in 43% of patients with end-stage liver disease on contrast echocardiography, and moreover, patients with a shunt unexpectedly showed better short-term survival than those without a shunt after liver transplantation.[16] The quantitative lung perfusion scan may also serve in predicting prognoses for patients with advanced liver diseases.[17]

CONCLUSION

The findings of the present study suggested that the described method with the quality-controlled radiopharmaceutical allowed the quantitative detection of intrapulmonary vascular dilation.

Pulmonary accumulation of Tc-99m MAA dropped as a function of time after administration. Therefore, the time points of measurement should be strictly considered for accurate evaluation of a shunt. In the present patients with liver cirrhosis, intrapulmonary shunt was confirmed to be a most likely cause of hypoxemia and further examinations were avoided.

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