Cardiac Blood-Pool Scintigraphy Using Technetium-99m DTPA-HSA: Comparison with In Vivo Technetium-99m RBC Labeling

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We performed cardiac blood-pool scintigraphy using technetium-99m diethylenetriaminepentaacetic acid human serum albumin ([^{99m}Tc] DTPA-HSA), a newly developed blood-pool agent, in 31 patients with various heart diseases and evaluated its clinical usefulness in comparison with the conventional in vivo ^{99m}Tc red blood cell (RBC) labeling. Excellent cardiac blood-pool images were obtained by [^{99m}Tc]DTPA-HSA method. Biodistribution studies showed higher accumulation of [^{99m}Tc]DTPA-HSA than that of ^{99m}Tc RBC in the lungs and liver, but similar count ratios of the cardiovascular blood pool to whole body between the two methods. In ECG-gated end-diastolic images, no quantitatively significant difference was observed in left ventricular target-to-background ratios between these two methods. Left ventricular ejection fraction (LVEF) calculated by [^{99m}Tc]DTPA-HSA MUGA method was correlated well with that by contrast LVEF ($r = 0.91$). No side effects were observed in any patient. In conclusion, cardiac blood-pool scintigraphy using [^{99m}Tc] DTPA-HSA is readily performed by single i.v. injection and useful for the assessment of cardiac function.

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Cardiac blood-pool scintigraphy is an established noninvasive method that provides morphologic information as well as cardiac function. At present, in vivo technetium-99m red blood cell (^{99m}Tc RBC) is most frequently used (*1,2*). However, the labeling process in this method remains still unclarified, and two intravenous injections and waiting time of more than 30 min are needed. Another problem is the presence of free [^{99m}Tc]pertechnetate that do not bind to RBCs. On the other hand, ^{99m}Tc human serum albumin (HSA) (*3–5*) which had been widely used before the development of ^{99m}Tc RBC method, presents problems of the labeling and stability in the body after intravenous injection. By binding human serum albumin with diethylenetriaminepentaacetic acid (DTPA) with high chelating action (*6*), [^{99m}Tc]DTPA-HSA, a more stable ^{99m}Tc-labeled radiopharmaceutical as a new blood-pool agent, was developed (*7*). In the present study, we evaluated its clinical usefulness in comparison with the conventional ^{99m}Tc RBC labeling.

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MATERIALS AND METHODS

Patient Selection

Cardiac blood-pool scintigraphy using [^{99m}Tc]DTPA-HSA was carried out in 31 patients (21 males and ten females) with various heart diseases (13 with coronary artery disease (CAD), eight with valvular disease, three with aortitis syndrome, one with dilated cardiomyopathy, two with atrial septal defect, and four with other diseases). Their ages ranged from 27 to 77 yr (mean 58 ± 13 yr). The preparation composed of 20 mCi of [^{99m}Tc]pertechnetate at calibration time and 10 mg of DTPA-HSA in a vial (Nihon-Mediphysics). For comparison with [^{99m}Tc]DTPA-HSA labeling, cardiac blood-pool scintigraphy using ^{99m}Tc RBC labeling was carried out in 33 patients (22 males and 11 females) with various heart diseases (nine with CAD, ten with acquired valvular disease, three with dilated cardiomyopathy, two with aortitis syndrome, and nine with other heart disease). Their ages ranged from 28 to 70 yr (mean 53 ± 11 yr).

Cardiac Blood-Pool Scintigraphy

A scinticamera (Ohio-Nuclear Σ 410S) with low-energy, parallel hole collimator and online minicomputer system (DEC, PDP 11/60, 118 KB) was used. The first-pass method was performed by rapid i.v. injection of [^{99m}Tc]DTPA-HSA. Thus, data were collected in the equilibrium phase (5–10 min after intravenous injection) by the MUGA method, in which the R-R interval was divided into 20 by ECG gating, and data was collected at 64 × 64 matrix by the 2,000k count (500–1,000 heart beats-added) with image mode (100k count/frame). The left anterior oblique (LAO) view that provides good separation of the right and left ventricles was chosen for the MUGA method. The left ventricular ejection fraction (LVEF) was calculated by a varying region of interest counts methods (*8*).

For quantitative analysis, the percentages of the counts in anterior images of the cardiovascular system, lungs, liver, and spleen to the total anterior counts from the neck to the mid-thigh were calculated as % organ activity (present time, 1 min) by the method of Atkins et al. (*9*).

In the end-diastolic images, the ratios of the left ventricular counts to those of the total image counts were calculated. The ratios of the mean counts of the left ventricle to those of the background were also calculated by the method of Thrall et al. (*10*). Similar analysis was performed in the patients with ^{99m}Tc RBC labeling. In addition, three of the patients underwent both [^{99m}Tc]DTPA-HSA labeling and ^{99m}Tc RBC labeling at a 1-wk interval. The whole-body images were also taken at equibrium phase after the i.v. administration.

Left Ventriculography

Left ventriculography was carried out in 20 patients with [^{99m}Tc]DTPA-HSA labeling and in 22 patients with ^{99m}Tc RBC labeling. Left ventricular ejection fraction was calculated by area-length method by using right anterior oblique (RAO) 30° view. These two procedures were carried out within 1 wk in all patients.

Statistical Analysis

Data were expressed as mean ± 1 s.d. Data of these two labeling method were compared by paired and unpaired t-test.

RESULTS

Whole-body images at equilibrium phase were compared between ^{99m}Tc RBC and [^{99m}Tc]DTPA-HSA labeling in a 45-yr-old male after valve replacement. The whole-body images at equilibrium phase are shown in Figure 1. The liver activity as background was higher with [^{99m}Tc]DTPA-HSA labeling and that in the spleen was higher with ^{99m}Tc RBC labeling. However, clear cardiac blood-pool images were obtained by both methods. In ECG-gated images obtained by both methods in the same patient, the background with [^{99m}Tc]DTPA-HSA labeling was visually slightly higher but clinically comparable to that with ^{99m}Tc RBC labeling (Fig. 2).

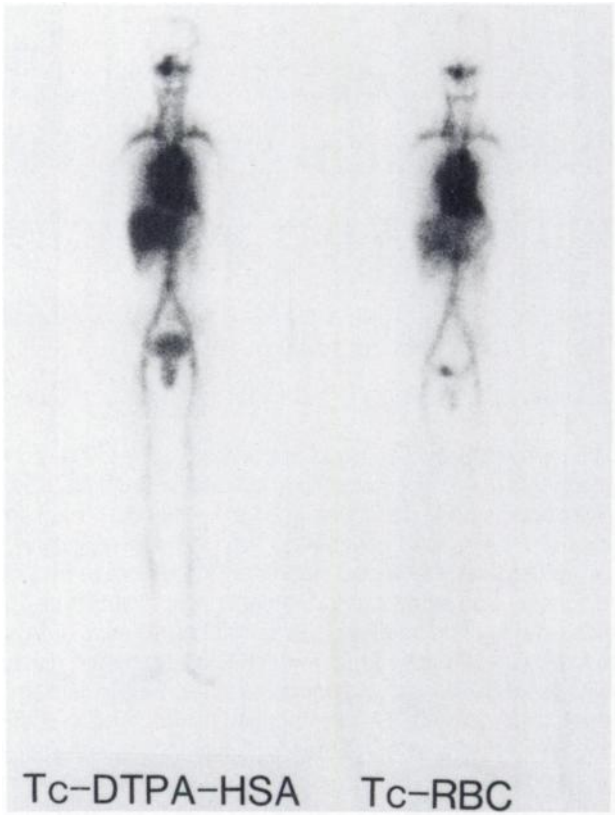

FIGURE 1
Anterior whole-body images by [^{99m}Tc]DTPA-HSA and ^{99m}Tc RBC labeling taken at equilibrium phase in the same patient.

For quantitative analysis, the % organ activities were compared between these two methods. No significant difference was observed in the % organ activity of cardiac blood pool (21.4 ± 3.6% vs. 20.4 ± 2.9%) between ^{99m}Tc RBC labeling and [^{99m}Tc]DTPA-HSA labeling. However, the % organ activity in the lungs and liver were higher with the latter method (lung; 10.7 ± 1.2% vs. 10.0 ± 1.2%, $p < 0.05$. liver; 12.9 ± 3.0% vs. 11.08 ± 2.8%, $p < 0.02$). On the other hand, the % organ activity in the spleen was higher with the former (1.31 ± 0.5 vs. 2.11 ± 0.9, $p < 0.01$) (Fig. 3). In the end-diastolic images, the LV counts in an image did not significantly differ between [^{99m}Tc]DTPA-HSA and ^{99m}Tc RBC labeling method (8.8 ± 2.8% vs. 7.2 ± 2.5%, p = N.S.) (Fig. 4A). The ratio of the mean counts of the LV to those of the background were calculated according to Thrall et al. (*10*) for quantitative comparison, but no significant difference was noted between the two methods (1.9 ± 0.3% vs. 2.0 ± 0.3%, p = N.S.) (Fig. 4B).

In 20 patients with [^{99m}Tc]DTPA-HSA labeling, LVEF calculated from MUGA method correlated well with that from left ventriculography (r = 0.91), on the other hand, in 22 patients with ^{99m}Tc RBC labeling,

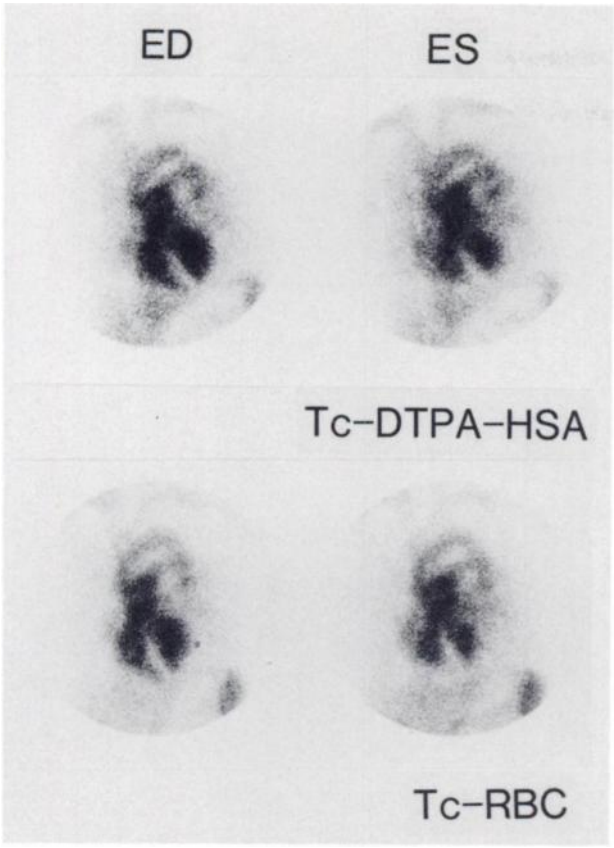

FIGURE 2
End-diastolic (ED) and end-systolic (ES) images in LAO projection from MUGA method by [^{99m}Tc]DTPA-HSA and ^{99m}Tc RBC in the same patient.

LVEF calculated from MUGA method was correlated well with that from left ventriculography (r = 0.92) (Fig. 5).

DISCUSSION

Cardiac blood-pool scintigraphy is an established noninvasive method, and in vivo or in vitro ^{99m}Tc RBC labeling (*1,2,11*) is most frequently performed. On the other hand, ^{99m}Tc HSA prepared by direct labeling of ^{99m}Tc to HSA is not widely used at present because of instability in the blood (*3–5*). However, in vitro RBC labeling requires a complicated procedure and two injections. In in vivo RBC labeling, in addition to two injections, the site of binding of ^{99m}Tc remains unclarified, ^{99m}Tc RBC labeling is not always constant, and uptake by the thyroid glands and stomach is sometimes observed. Though ^{99m}Tc RBC labeling with two injections is routinely used at our institution, the 30-min waiting time after administration of $SnCl_2$ is frequently a burden on patients with any circulatory abnormality.

Technetium-99m DTPA-HSA used in this study was developed as a more stable ^{99m}Tc-labeled cardiac blood-pool agent by interposing DTPA, a bifunctional chelating agent, between HSA and ^{99m}Tc. The ^{99m}Tc labeling in this radiopharmaceutical is more than 95% (*7*). If clinical results similar to those with RBC labeling are obtained with [^{99m}Tc]DTPA-HSA, the examination time and burdens on the patient and operator can be decreased with this agent because of only one injection. Thus, we compared [^{99m}Tc]DTPA-HSA labeling and ^{99m}Tc RBC labeling to determine whether the latter can be replaced by the former. To obtain excellent blood-pool images, the background counts should be lower. Labeled HSA compounds are known to produce higher background counts than ^{99m}Tc RBC. In this study, the % organ activity in the lungs and liver were higher with [^{99m}Tc]DTPA-HSA. However, the % organ activity in cardiac blood pool did not differ between the two agents, and the blood-pool images with [^{99m}Tc]DTPA-HSA seem to be adequate for clinical application. Thrall et al. (*10*) reported count ratios of cardiac blood pool to whole body of 24% with ^{99m}Tc RBC labeling. Our value (21.4 ± 3.6%) with [^{99m}Tc]DTPA-HSA did not differ quantitatively from that with in vivo ^{99m}Tc RBC labeling (20.4 ± 2.9%).

In ^{99m}Tc RBC labeling, the pharmaceutical remains in the blood for a relatively long period compared to [^{99m}Tc]DTPA-HSA. These findings are consistent with the observations that [^{99m}Tc]DTPA-HSA escaped from the circulatory system into the extracellular fluid system (*1,12*). Since the extracellular fluid system of the liver is relatively large compared with other organs (*13*), the uptake of [^{99m}Tc]DTPA-HSA in the liver is high. Visualization of bone in some patients also seems to be due to the extracellular fluid system. Though comparison in the same patients showed higher uptake by the liver, retention in the cardiac blood pool was adequate, suggesting clinical applicability of this agent. In data processing, determination of the margins of the left ventricle also affects calculation of indices of cardiac function such as left ventricular ejection fraction. Separation of the right and left ventricles was very good with both methods. Therefore, the effects of the background on the left ventricular cavity were evaluated. The LV counts in each image and the ratio of the mean left ventricular counts to those of the background showed no significant differences between these methods. In addition, the correlation between [^{99m}Tc]DTPA-HSA and contrast LVEF was excellent and similar to that between ^{99m}Tc RBC and contrast LVEF. These results also support clinical applicability of [^{99m}Tc] DTPA-HSA.

One characteristic of ^{99m}Tc RBC labeling is visualization of the spleen. This method is not effective for evaluating lateral images overlapping with the spleen and seems to be not useful for evaluating blood-pool

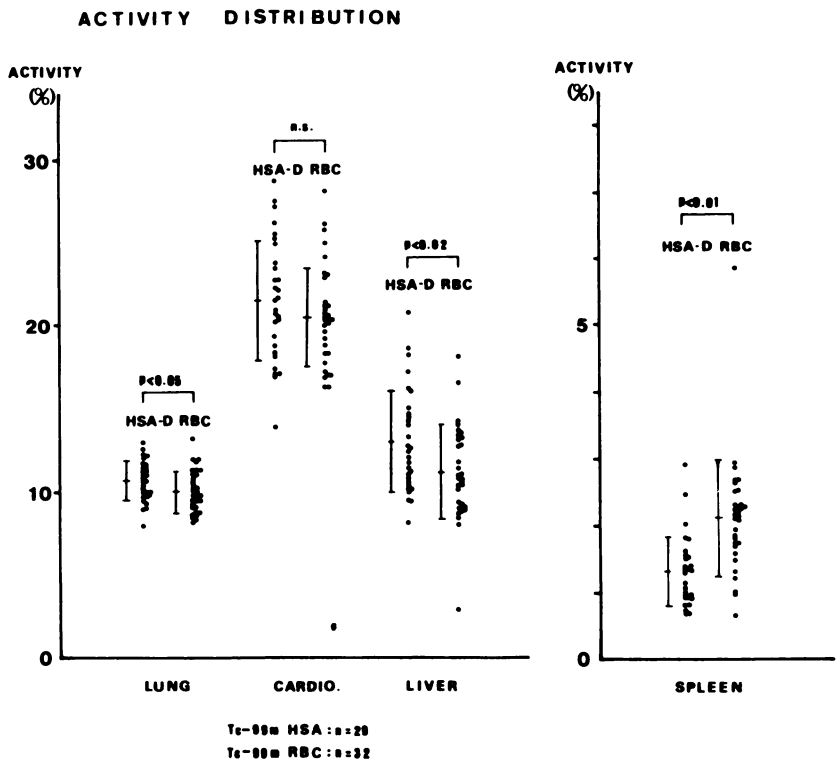

FIGURE 3
Comparison of % organ activity with [^{99m}Tc]DTPA-HSA and ^{99m}Tc RBC labeling.

images in cases with dilated right ventricle such as atrial septal defect. On the other hand, we obtained very clear cardiac blood-pool images with [^{99m}Tc]DTPA-HSA in these patients because of lower spleen uptake.

In this study, no side effects or abnormal values on clinical examinations were observed. However, since development of granulomatous interstitial pneumonia following repeated i.v. administration of HSA was reported in animals (*14*), further studies on this problem are needed.

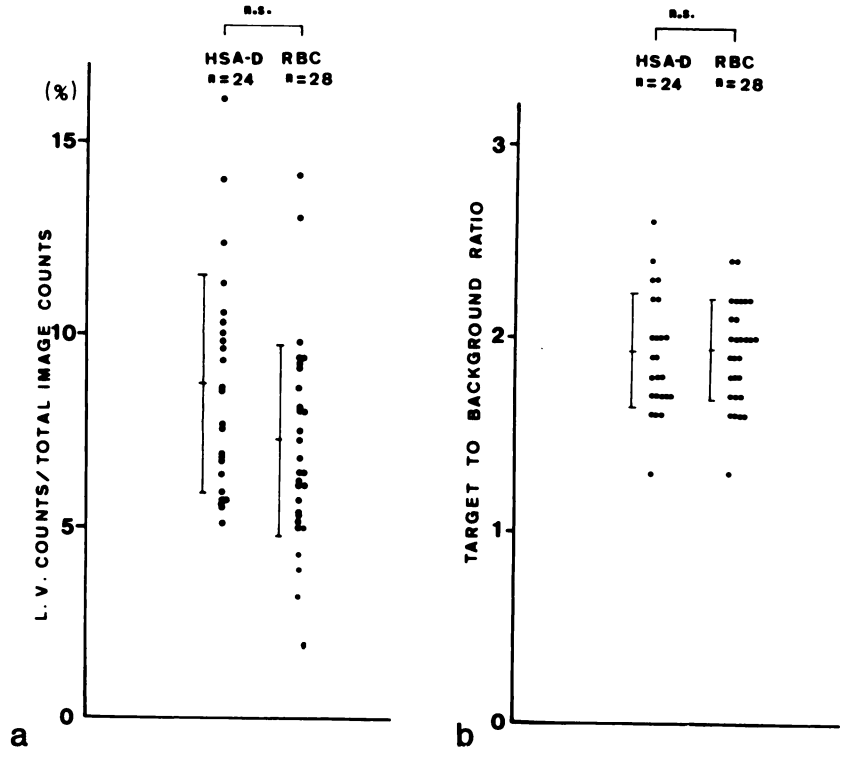

FIGURE 4
Technetium-99m DTPA-HSA and ^{99m}Tc RBC left ventricular distribution at end-diastolic image. (A) Net end-diastolic activity in the left ventricle, as a percentage of total image counts. (B) Left ventricular target-to-background ratios.

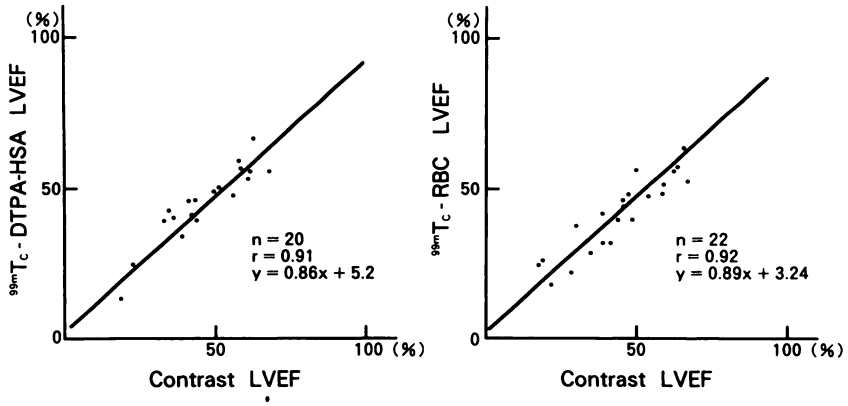

FIGURE 5
Comparison of radionuclide LVEF ([^{99m}Tc]DTPA-HSA and ^{99m}Tc RBC) and contrast LVEF. LVEF = left ventricular ejection fraction.

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