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# Comparison of $^{99m}$Tc-tetrofosmin uptakes on planar images with those in excised rats organs

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The radioactivity in the organs adjacent to the heart causes interference with the quantitative assessment of myocardial uptake of tracer on scintigraphy. In order to investigate how much the functions of these organs affect myocardial uptake seen in imaging, we compared the myocardial uptake measured by means of a gamma camera with the actual activity in the excised organs. ***Methods:*** Thirty-three rats were imaged at 5, 10, 15, 30, 45, 60, 90 and 120 min after the administration of $^{99m}$Tc-tetrofosmin, and % injected dose per pixel (%ID/pixel) for each organ was assessed on planar images (PI measurement). Percent injected dose per gram of tissue (%ID/g) in the heart as well as lungs, liver, gastrointestines and blood was measured by means of a well scintillation counter (WC measurement). Comparison between PI and WC measurements was performed with % uptake, the PI-to-WC ratio and heart-to-organ ratios. ***Results:*** Our WC measurement showed an increase in cardiac uptake until 30 min (1.67 ± 0.31%) postinjection and subsequent gradual decrease, whereas PI measurement showed maximum activity of 1.81 ± 0.52% at 15 min postinjection. There was a prominent difference between the two measurements, particularly at 10 min, with a PI/WC ratio of about 1.6 times. Our WC measurement showed maximum pulmonary uptake at 15 min (0.87 ± 0.31%) and a gradual decrease over 15 min, whereas PI measurement showed maximum uptake at 10 min (1.14 ± 0.38%). There was hardly any variation in activity observed later than at 10 min. Our WC measurement showed hardly any variance in hepatic activity from 5 min (0.77 ± 0.19%) to 30 min (0.69 ± 0.27%) with a subsequent gradual decrease. The percent uptake in PI measurement was generally greater than that in WC measurement, and high values were found at 10 min and 15 min with PI/WC ratios of about 3.3 times and 2.3 times, respectively. ***Conclusion:*** Percent uptakes in PI measurement were greater than those in WC measurement. The difference between the two measurements was prominent in the early phases. The cardiac uptake in PI measurement was significantly greater than that in WC measurement at 10 min. It was considered that this discrepancy between the two measurements was caused by the Compton scatter from the organs adjacent to the heart.

**Key words:** $^{99m}$Tc-tetrofosmin, myocardial uptake, planar image, scintillation counter, rat

## INTRODUCTION

Thallium-201 myocardial perfusion imaging has been widely used for the diagnosis of coronary artery disease, but $^{201}$Tl has several disadvantages when compared with $^{99m}$Tc-labeled tracer because of its longer half-life and lower photon energy, which affects image quality. The cationic diphosphine complex $^{99m}$Tc-tetrofosmin has

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recently become available in a freeze-dried kit.[1–4] Electrocardiography gated SPECT with $^{99m}$Tc-tetrofosmin offers the potential for the simultaneous assessment of myocardial perfusion and left ventricular function, which has been used for quantification of perfusion abnormalities, global ejection fraction and regional systolic wall thickening.[5–8] In this imaging, however, significant amounts of tracer accumulate in the liver and the gastrointestines, and cause not only deterioration of the imaging quality in myocardial scintigraphy but also inaccurate quantification of uptake.[9–11] For accurate quantification, some problems should be solved including physical factors such as gamma ray absorption and Compton scatter. Improvements to remove this disadvantage have recently been devised[9,10] and some solutions have already been used clinically.[12–14] Nevertheless, we cannot obtain the actual uptake in patients' organs. Even if correction for the physical factors were done, we could not show how accurate the correction is accurate because it is impossible to clarify the actual uptake in a patient's myocardium in clinical practice. To the best of our knowledge, there is no report on comparison of % uptake measured by scintigraphy with the true values in organs. We therefore compared percent uptake in rats' organs with a gamma camera and a well scintillation counter.

The purpose of this study was to compare the uptake observed by scintigraphy with the actual value in excised organs, and to examine how much the liver and lung activities affect the observed myocardial uptake.

## MATERIALS AND METHODS

*Materials*

Animals experiments were performed in compliance with the National Institutes of Health (NIH) guidelines on animal care and use. Thirty-three male Donryu rats (Charles River Ltd., Japan) weighing 150–267 g (average 208 ± 45.9 g) were used in this study. They were allowed to take food and water freely until anesthetized.

*Preparation of $^{99m}$Tc-tetrofosmin*

$^{99m}$Tc-tetrofosmin was prepared from a freeze-dried kit (Nihon Medi-Physics, Tokyo, Japan) by reconstitution with approximately 2 m*l* of a sterile pertechnetate solution containing 296 MBq of $^{99m}$Tc. This process does not require heating but only 15 min incubation at room temperature.

*Measurements of standard sample with gamma camera and scintillation counter*

Six $^{99m}$Tc-tetrofosmin standards with various specific activities of 13, 16.3, 27.0, 31.7, 42.8 and 49.5 MBq per 0.2 m*l* were prepared and measured with both a gamma camera (planar image, PI measurement) and a well scintillation counter (well counter, WC measurement). For PI measurement, injected by means of a 1 m*l* syringe approximately 0.2 m*l* of a standard was at a location corresponding to the center of the rat body and imaged for 15 seconds. Average counts per pixel were obtained from the counts and pixels within the regions of interest (ROIs). In WC measurement, standards were measured for 1 min.

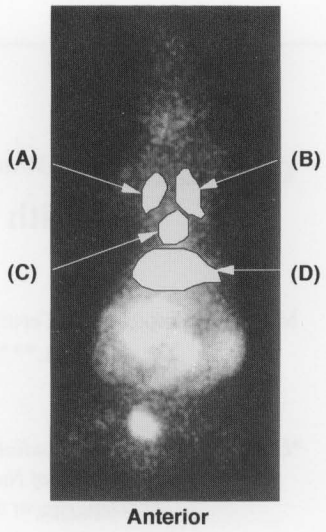


**Fig. 1** Regions of interest (ROIs) on the anterior view to obtain the total and average counts per pixel. (A); right lung, (B); left lung, (C); heart, and (D); liver.

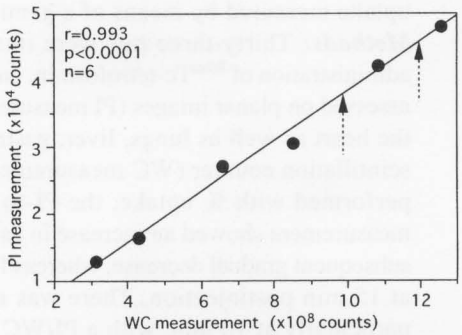


**Fig. 2** Correlation of radioactivity in the standards between WC and PI measurement. Arrow ( ↑ ) shows the range of injected dose used in this study.

*Biodistribution and imaging of $^{99m}$Tc-tetrofosmin*

Rats were anesthetized with intraperitoneal administration of pentobarbital (4.0 mg per 100 g). When necessary, ether anesthesia was added. After the injection of $^{99m}$Tc-tetrofosmin (30 MBq/0.2 m*l*) into the caudal vein, an anterior planar image was obtained with a gamma camera (Sigma 410S, Aloka, Tokyo, Japan) equipped with a parallel hole collimator (full width at half maximum; FWHM 5.2 mm). Time from injection to imaging was 5, 10, 15, 30, 45, 60, 90 and 120 min. Four rats were used at 5, 10, 15, 60 and 90 min, respectively, and five rats were used at 30 and 45 min, respectively. Three rats was used at 120 min. Data were acquired for 2 min with a 256 × 256

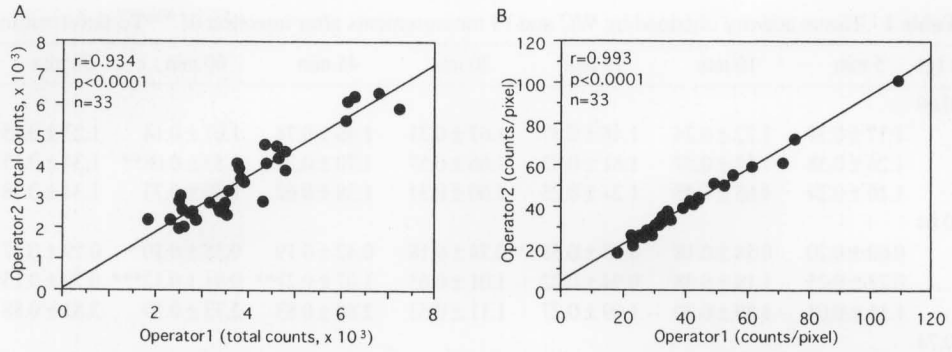


**Fig. 3** Interoperator reproducibility in ROIs setting. (A); total counts, and (B); average counts per pixel.

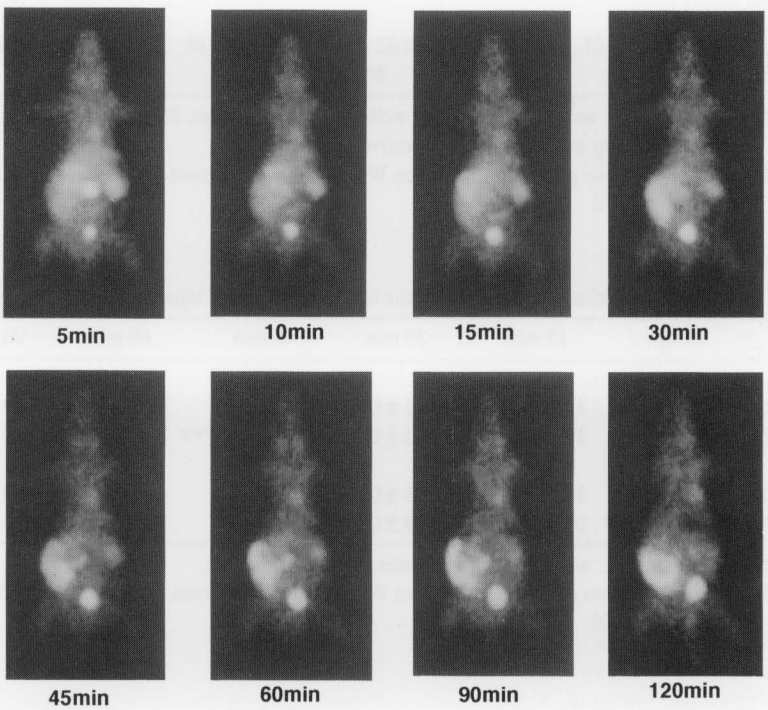


**Fig. 4** An example of serial images at 5 min to 120 min postinjection.

matrix (pixel size 1.0 mm) and a 20% (126–154 keV) energy window and recorded with a computer (MCS560, Aloka, Tokyo, Japan). Prior to the study, we investigated the effect of imaging by obtaining both the anterior and posterior views by moving a gamma camera. There was no discrepancy between the two views and we adopted the anterior view. After data acquisition, a rat was sacrificed by taking blood from the heart under ether anesthesia, and the organs were dissected and weighed. Activity was measured by means of a well scintillation counter (ARC-500, Aloka, Tokyo, Japan). Total activity in the organs was calculated by multiplying total weight by counts per gram of tissue.

*Data analysis*

*Data obtained by WC measurement.* Radioactivity in standards, organs and blood samples was counted one and two days after the experiment. Data were expressed as % injected dose per gram of tissue (%ID/g). Heart-to-lung and heart-to-liver ratios were obtained.

*Data obtained by PI measurement.* In order to examine the interoperator reproducibility in the ROI setting, two operators determined the ROIs of the heart, lung and liver on a planar image with a trackball to obtain the counts and pixels in the ROIs (Fig. 1). Data were expressed as % injected dose per pixel (%ID/pixel). PI-to-WC ratios were also obtained as well as those for heart-to-lung and heart-to-liver.

*Statistical analysis*

Data were presented as the mean ± S.D. Differences between PI and WC measurements were compared by means of Paired t-test. Differences among the organs were evaluated by means of Two-factor factorial ANOVA

**Table 1** Tissue activity obtained by WC and PI measurements after injection of $^{99m}$Tc-tetrofosmin

| Tissue | Weight (g) | 5 min | 10 min | 15 min | 30 min | 45 min | 60 min | 90 min | 120 min |
|---|---|---|---|---|---|---|---|---|---|
| Heart | 1.03 ± 0.09 | | | | | | | | |
| WC | | 1.17 ± 0.39 | 1.22 ± 0.24 | 1.48 ± 0.37 | 1.67 ± 0.31 | 1.46 ± 0.74 | 1.07 ± 0.14 | 1.23 ± 0.25 | 1.18 ± 0.11 |
| PI | | 1.26 ± 0.38 | 1.67 ± 0.57 | 1.81 ± 0.52 | 1.66 ± 0.57 | 1.70 ± 0.25 | 1.53 ± 0.08** | 1.34 ± 0.15 | 1.32 ± 0.07 |
| PI/WC | | 1.10 ± 0.24 | 1.65 ± 0.45 | 1.24 ± 0.25 | 1.00 ± 0.31 | 1.38 ± 0.62 | 1.80 ± 0.73 | 1.34 ± 0.28 | 1.55 ± 0.73 |
| Lung | 1.02 ± 0.04 | | | | | | | | |
| WC | | 0.62 ± 0.20 | 0.54 ± 0.18 | 0.87 ± 0.31 | 0.74 ± 0.18 | 0.42 ± 0.19 | 0.35 ± 0.10 | 0.29 ± 0.17 | 0.15 ± 0.01 |
| PI | | 0.73 ± 0.25 | 1.14 ± 0.38$^{\dagger}$ | 0.94 ± 0.22 | 1.01 ± 0.63 | 1.07 ± 0.27** | 0.91 ± 0.12*** | 0.79 ± 0.13* | 0.90 ± 0.11*** |
| PI/WC | | 1.16 ± 0.04 | 1.89 ± 0.20 | 1.09 ± 0.27 | 1.11 ± 0.63 | 2.80 ± 0.83 | 2.73 ± 0.59 | 3.81 ± 0.88 | 5.94 ± 0.96 |
| Liver | 10.4 ± 0.74 | | | | | | | | |
| WC | | 0.77 ± 0.19 | 0.59 ± 0.12 | 0.67 ± 0.45 | 0.69 ± 0.27 | 0.36 ± 0.11 | 0.21 ± 0.07 | 0.17 ± 0.04 | 0.12 ± 0.04 |
| PI | | 1.43 ± 0.43$^{\dagger}$ | 1.95 ± 0.60** | 1.85 ± 0.64$^{\dagger}$ | 1.32 ± 0.42$^{\dagger}$ | 0.95 ± 0.11$^{\dagger}$ | 0.97 ± 0.43$^{\dagger}$ | 0.73 ± 0.36$^{\dagger}$ | 0.72 ± 0.29$^{\dagger}$ |
| PI/WC | | 1.86 ± 0.30 | 3.30 ± 0.71 | 2.25 ± 0.61 | 2.04 ± 0.63 | 2.73 ± 0.39 | 3.07 ± 0.29 | 4.32 ± 1.51 | 4.23 ± 1.02 |
| Blood | 1.00 ± 0.00 | | | | | | | | |
| WC | | 0.04 ± 0.01 | 0.03 ± 0.01 | 0.03 ± 0.01 | 0.02 ± 0.00 | 0.02 ± 0.01 | 0.01 ± 0.00 | 0.01 ± 0.00 | 0.01 ± 0.00 |
| PI | | ND | ND | ND | ND | ND | ND | ND | ND |

Values were expressed as the mean ± s.d. ND: not determined. WC: well scintillation counter, PI: planar imaging.
Values of WC and PI were expressed as %ID/g and %ID/pixel, respectively.
There was no statistical difference ($p > 0.05$ two group t-test) between WC and PI measurement except where indicated.
$^{\dagger}p < 0.05$, *$p < 0.01$, **$p < 0.005$, ***$p < 0.001$

**Table 2** Tissue activity ratios of the heart versus lung or liver after injection of $^{99m}$Tc-tetrofosmin

| | 5 min | 10 min | 15 min | 30 min | 45 min | 60 min | 90 min | 120 min |
|---|---|---|---|---|---|---|---|---|
| Heart-to-Lung | | | | | | | | |
| WC | 1.89 ± 0.16 | 1.93 ± 0.34 | 1.73 ± 0.11 | 2.31 ± 0.56 | 3.48 ± 0.66 | 3.19 ± 0.46 | 5.50 ± 1.01 | 7.65 ± 0.51 |
| PI | 1.81 ± 0.41 | 1.41 ± 0.11$^{\dagger}$ | 1.92 ± 0.11 | 1.82 ± 0.38 | 1.62 ± 0.20*** | 1.62 ± 0.20** | 1.65 ± 0.24*** | 1.46 ± 0.08** |
| Heart-to-Liver | | | | | | | | |
| WC | 1.51 ± 0.12 | 2.09 ± 0.36 | 1.78 ± 0.17 | 2.66 ± 0.90 | 3.34 ± 1.74 | 4.35 ± 0.82 | 6.68 ± 1.23 | 8.82 ± 0.42 |
| PI | 0.89 ± 0.06** | 1.04 ± 0.24** | 0.89 ± 0.15*** | 1.33 ± 0.53$^{\dagger}$ | 1.84 ± 0.46 | 1.99 ± 0.27** | 2.39 ± 0.26* | 2.49 ± 0.18*** |

Values were expressed as the mean ± s.d. WC: well scintillation counter, PI: planar imaging.
There was no statistical difference ($p > 0.05$ two group t-test) between WC and PI measurement except where indicated.
$^{\dagger}p < 0.05$, *$p < 0.01$, **$p < 0.005$, ***$p < 0.001$

and Scheffe's F. Correlation of the injection doses for PI and WC measurement was evaluated by means of Pearson's correlation coefficient. Statistical significance was defined as $p < 0.05$.

## RESULTS

*Comparison of standard activity in WC and PI measurement*

Total counts obtained by PI measurement correlated well with those by WC measurement with a correlation coefficient of $r = 0.993$ ($p < 0.0001$) (Fig. 2).

*Interoperator reproducibility in ROIs setting*

Total counts in the ROIs and average counts per pixel correlated well between two operators with a correlation coefficient of $r = 0.934$ ($p < 0.0001$) and $r = 0.993$ ($p < 0.0001$), respectively (Fig. 3).

*Tissue activities obtained by WC and PI measurement*

Figure 4 shows an example of serial images from 5 to 120 min postinjection. Hepatic activity in early phases was much more than cardiac activity. In the late phase, small intestinal activity increased as hepatic activity decreased. The gastrointestinal activity at 45 min became much greater than the cardiac activity. Tables 1 and 2 show tissue activity, and heart-to-organ ratios, respectively.

*Cardiac uptake.* Our WC measurement showed an increase in cardiac uptake until 30 min (1.67 ± 0.31%) with a subsequent gradual decrease. The % uptake at 60 min was 1.07 ± 0.14%. On the other hand, PI measurement showed the maximum uptake at 15 min (1.81 ± 0.52%) with a high uptake of 1.53 ± 0.08% at 60 min (Fig. 5A), so that the difference between both measurements was the greatest at 10 min, with a PI/WC ratio of about 1.6 times (Fig. 5B).

*Pulmonary uptake.* Our WC measurement showed maximum activity of 0.87 ± 0.31% at 15 min with a subsequent gradual decrease. On the other hand, PI measure-

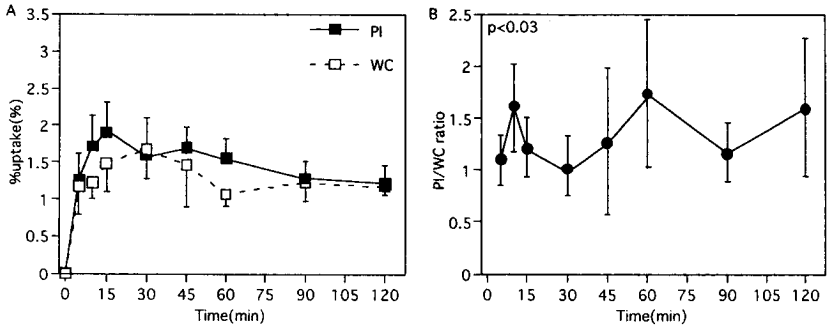


**Fig. 5** (A); cardiac % uptake by PI and WC measurements, and (B); PI-to-WC ratios.

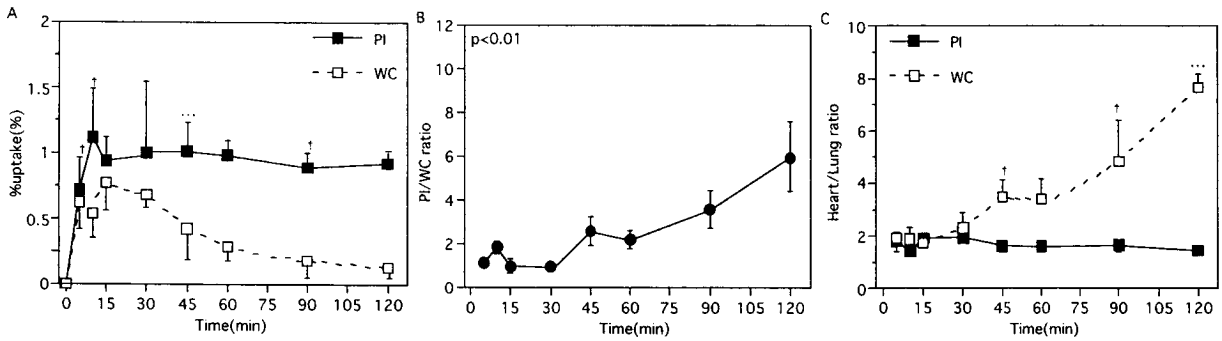


**Fig. 6** (A); pulmonary % uptake by PI and WC measurements, (B) PI-to-WC ratios, and (C); heart-to-lung ratios.

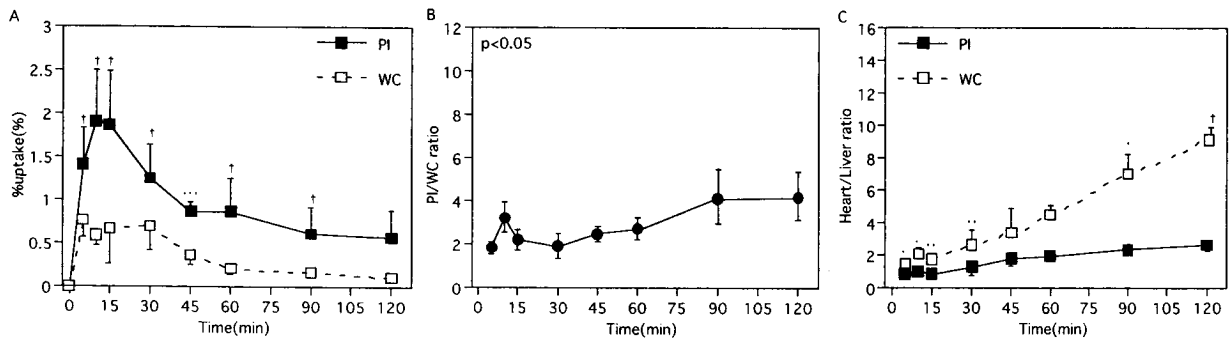


**Fig. 7** (A); hepatic % uptake by PI and WC measurements, (B); PI-to-WC ratios, and (C); heart-to-liver ratios.

ment showed a maximum activity of 1.14 ± 0.38% at 10 min, and there was hardly any change in activity later than 10 min (Fig. 6A). The PI-to-WC ratio was approximately 1.9 at 10 min, and increased significantly after 30 min (Fig. 6B, $p < 0.01$).

*Heart-to-lung ratios.* Our PI measurement showed heart-to-lung ratios of 1.81 ± 0.41 and 1.62 ± 0.20 at 5 and 60 min, respectively. The heart-to-lung ratios in WC and PI measurements were 2.31 ± 0.56 and 1.82 ± 0.38 at 30 min, respectively, and there was no significant difference, but the WC measurement was significantly greater than the PI measurement at 90 min (5.50 ± 1.01 versus 1.65 ± 0.24, $p < 0.001$). Our WC measurement showed an increase in the heart-to-lung ratio with time, whereas the PI measurement was stable (Fig. 6C).

*Hepatic uptake.* Our WC measurement hardly varied at all in hepatic activity between 5 (0.77 ± 0.19%) and 30 min (0.69 ± 0.27%), but decreased greatly after 30 min. On the other hand, PI showed significantly greater hepatic activity than WC ($p < 0.05$). Hepatic activities at 10 and 15 min were 1.95 ± 0.60% (PI/WC ratio: about 3.3 times) and 1.85 ± 0.64% (PI/WC ratio: about 2.3 times), respectively (Fig. 7A–B).

*Heart-to-liver ratios.* Our WC measurement showed an increase in the heart-to-liver ratio with time, with values of 1.51 ± 0.20 and 4.35 ± 0.82 at 5 and 60 min,

respectively, whereas the PI measurement was stable (Fig. 7C).

## DISCUSSION

*Interoperator reproducibility in ROIs setting*

An accurate ROI setting is essential for the quantification of tracer uptake in scintigraphy. Prior to the study we evaluated interoperator reproducibility in a ROI setting. Since the results showed good correlation between two operators, we concluded that relatively high reproducibility could be obtained if only reasonable operations were performed.

*Comparison of WC and PI measurements*

As shown in Figure 4, it was possible to observe the biodistribution of tracer from planar images. Imaging showed description of liver, gastrointestine, kidney, and heart.

*Heart.* Our WC measurement showed cardiac uptakes (%ID/g) of 1.17 ± 0.39%, 1.59 ± 0.28% and 1.13 ± 0.09% at 5, 30, and 60 min post injection, respectively. Kelly et al.[2] reported that the cardiac uptake (%ID) in Wister rats was 1.58 ± 0.09% and 1.53 ± 0.13% at 2 and 60 min, respectively. We cannot easily compare the two results because of the difference between units used (%ID and %ID/g), but our results seemed to be compatible with their results after correction for organ weight. As shown in Figure 5, PI measurement showed greater uptake than WC measurement, particularly at 10 min (PI/WC ratio: about 1.6 times) and 60 min (PI/WC ratio: about 1.8 times). This disagreement seems to be attributable to the high cardiac activity and slow washout of $^{99m}$Tc-tetrofosmin. Decreased blood clearance is thought to affect the results of PI measurement, but we have concluded that the PI/WC ratios greater than 1.0 may be induced by the Compton scatter from the organs adjacent to the heart.

*Lung.* Our WC measurement showed pulmonary uptake (%ID/g) of 0.62 ± 0.20%, 0.87 ± 0.31% and 0.35 ± 0.10% at 5, 15, and 60 min, respectively. Kelly et al.[2] reported pulmonary uptakes (%ID) of 1.51 ± 0.35% and 0.59 ± 0.19% at 2 and 60 min, respectively. Their results showed greater pulmonary uptake than ours.

*Heart-to-lung ratio.* In our WC measurements, the heart-to-lung ratios increased with time and were 1.89 ± 0.16 and 3.19 ± 0.46 at 5 and 60 min, respectively. In contrast, heart-to-lung ratios in PI measurements decreased gradually with time and were 1.81 ± 0.41 and 1.62 ± 0.20 at 5 and 60 min, respectively. By using a canine with dynamic planar imaging, Sinusas et al.[15] evaluated the myocardial uptake and clearance of $^{99m}$Tc-tetrofosmin. They reported that the heart-to-lung ratio at 10 min in PI measurements was 3.57 ± 1.01. It was higher than our 1.41 ± 0.11. Jain et al.[3] investigated 20 patients to determine the biokinetics of $^{99m}$Tc-tetrofosmin. They reported that heart-to-lung ratios on planar images hardly changed from 5 to 180 min and were 1.8 ± 0.2, 2.0 ± 0.4 and 2.1 ± 0.3 at 5, 30, and 60 min, respectively. Similarly, Munch et al.[16] reported that heart-to-lung ratios in 12 patients were 2.49 ± 0.43 and 2.66 ± 0.55 at 5 and 60 min, respectively, and the values hardly changed from 5 to 60 min. On the other hand, Higley at al.[17] reported that heart-to-lung ratios in 12 healthy volunteers increased with time and were 3.1 ± 1.8, 4.5 ± 1.5 and 7.3 ± 4.4 at 5, 30 and 60 min, respectively. In order to explain the disagreement, Munch et al. proposed the difference between the subjects: Higley et al. investigated young and healthy volunteers, whereas Munch et al. investigated a mixed population of older patients. Our results are consistent with the results of Jain et al.[3] and Munch et al.[16] Rapid clearance of $^{99m}$Tc-tetrofosmin from the lungs is one of the possible causes of the difference between PI and WC in the heart-to-lung ratios. Moreover, slow clearance from the blood affects PI measurement rather than WC measurement. In the clinical cases, it has reported that the heart-to-lung ratio was useful for the diagnosis of coronary artery disease.[21,22]

The results of this study indicated that PI measurement of the heart-to-lung ratio should be punctual to avoid the effect of sequential changes in the count ratio.

*Liver.* Our WC measurements showed stable hepatic uptake (%ID/g) from 5 (0.77 ± 0.19%) to 30 min (0.69 ± 0.27%), but it had decreased greatly later than 60 min (0.21 ± 0.07%). Kelly et al.[2] reported that hepatic uptake (%ID) was 13.5 ± 3.0% and 2.99 ± 0.51% at 2 and 60 min, respectively. If correction for liver weight is performed, our results seem to be consistent with their results because average liver weight was 10.4 ± 0.74 g in our study. On the other hand, PI measurement showed greater uptake at 10 (1.95 ± 0.60%) and 15 min (1.85 ± 0.64%) than WC measurement, with a PI/WC ratio of about 3.3 times and 2.3 times, respectively. Therefore, it was guessed that such great activity in liver at 10 and 15 min should probably affect the cardiac activity. Sinusas et al.[15] reported that the heart-to-liver ratio in a canine was 0.58 ± 0.04 at 10 min in planar imaging. Jain et al.[3] reported that heart-to-liver ratios in 20 patients were 0.8 ± 0.2, 1.0 ± 0.2 and 1.3 ± 0.4 at 5, 30 and 60 min, respectively. Munch et al.[16] reported that heart-to-liver ratios in 12 patients slightly increased from 5 to 60 min, with values of 1.04 ± 0.24 and 1.51 ± 0.44 at 5 and 60 min, respectively. On the other hand, Higley et al.[17] reported that heart-to-liver ratios in 12 healthy volunteers increased with time, with values of 0.4 ± 0.1, 0.6 ± 0.3 and 1.2 ± 0.8 at 5, 30 and 60 min, respectively. Similarly, Matsunari et al.[18] reported that heart-to-liver ratios in 13 healthy volunteers were increased at 10 min (about 0.58) and 60 min (about 1.7). Our results are compatible with those obtained clinically. Heart-to-liver ratios were significantly greater in WC measurement than in PI measurement. These results suggested that real clearance from the liver must be rapid in human subjects. Higher hepatic uptake found with PI than

WC seems to result from photons emitted and scattered in the liver, and the partial volume effect due to limited spatial resolution of the camera.

We compared organ uptake by using units of %ID/g and %ID/pixel in WC and PI measurements, respectively. Since these units differ from each other, we cannot compare absolute values, but it is possible to catch the trends of changes. We adopted these units in this study because some authors[2,16,17] have reported uptake in animals and patients with %ID/g and %ID/pixel. An accurate ROI setting is essential for the quantification of tracer uptake from scintigraphy. Weber[19] and Ishizu et al.[20] reported pinhole SPECT systems with excellent spatial resolution in a small animal study, but its use is limited. To the best of our knowledge, none evaluated the biodistribution of tracer from rat planar images. One of the reasons may be that the ROI settings in this procedure are very difficult in rats because of their small size.

## CONCLUSION

Our PI measurement gave greater observed activity in each organ than WC measurement. The difference was particularly significant in the early phases post injection. Some causes of this disagreement are considered that only the excised organ is subjected to WC measurement, whereas the activity from the background such as blood, scatter from the liver and small intestine, and the partial volume effect may affect organ activity in PI measurement. Therefore, it was indicated that data obtained clinically with planar images do not always represent the true values.

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