Optimal thallium-201 dose in cadmium-zinc-telluride SPECT myocardial perfusion imaging

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Abstract

Background. We aimed to determine the optimal thallium-201-chloride (thallium-201) dose using a novel ultrafast cardiac gamma camera with cadmium-zinc-telluride (CZT) solid-state semiconductor detectors (D-SPECT).

Methods and Results. The optimal thallium-201 dose for obtaining left ventricular (LV) myocardial counts was determined from a phantom study. Consecutive 292 patients underwent stress myocardial perfusion imaging with a thallium-201 injection. Stress test comprised exercise or pharmacological (adenosine) provocation. We calculated an optimal thallium-201 dose that resulted in better LV myocardial counts during 6 minutes of acquisition time. We corrected the respective values according to the patient's age, sex, body mass index (BMI), and type of stress test. The lowest thallium-201 dose for obtaining acceptable imaging was 1.2 million counts. Radiopharmaceutical doses showed a positive correlation with the patient's age ($P < .001$), sex ($P = .012$), BMI ($P < .001$), and type of stress test ($P < .001$). Multivariate analysis revealed that the patient's BMI and the type of stress test were statistically significant factors for determining the correct radiopharmaceutical dose ($P < .001$ for both).

Conclusions. For clinical use of the CZT SPECT system, the optimal individual

thallium-201 doses can be determined based on the patient's BMI and type of stress test.

Key Words: Myocardial Perfusion Imaging, SPECT, Thallium-201, Cadmium-zinc-telluride, Stress test

Abbreviations

MPI - Myocardial perfusion imaging

SPECT- Single-photon emission computed tomography

LV - Left ventricular

CZT - Cadmium-zinc-telluride

BMI - Body mass index

ROI - Region of interest

INTRODUCTION

Myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT) is widely used for assessing ischemia, viability, and scarring in the left ventricular (LV) myocardium.[1-4] Although thallium-201-chloride (thallium-201) has been used widely, it is considered suboptimal because of its low emission energy level (69–80 keV) and its long physical half-life of 73 hours. To circumvent the limitations of thallium-201, technetium-99m derivatives have been proposed as alternative perfusion tracers.[5-7] The higher emission energy of technetium-99m (140 keV) is better suited for conventional Anger gamma camera imaging, and the shorter half-life (6 hours) of this agent allows larger injectable doses, thereby improving image quality.[3]

Thallium-201, however, is a clinically important radiopharmaceutical for assessing both regional blood flow and myocardial viability. Redistribution images have been used as important markers of regional viability.[8,9] A high-quality redistribution image is key to an accurate diagnosis.[7,10] With MPI SPECT using a conventional Anger gamma camera, at least 100 counts in the hottest pixel of the left ventricle in the left anterior oblique 45° projection (acquisition time is 40–60 sec/step) are needed to ensure a diagnostic-quality image.[11,12] Therefore, the total acquisition time must be within 15–20

minutes.

Recently, dedicated cardiac systems with cadmium-zinc-telluride (CZT) detectors were introduced in Japan. This system uses stationary semiconductor technology. A nine-detector column is fixed in a mechanical mounting, no gantry rotation is necessary, and data acquisition is performed by rotating these columns in synchrony.[11] The improvements in efficiency and resolution allow low-dose imaging protocols and reduce the acquisition time.[13-15] However, the optimal dose of thallium-201 using the CZT detectors has not been determined. We aimed to determine the optimal thallium-201 dose using a new CZT cardiac scanner camera (D-SPECT).

MATERIALS AND METHODS

Myocardial Phantom Study

A myocardial phantom (model RH-2®; Kyoto-Kagaku, Kyoto, Japan) was developed in which we created a 10-mm defect in the anterior wall and a 20-mm defect in the inferior wall. The myocardium portion was filled with thallium-201 (28.5 kBq/mL). The mediastinum, left ventricle (LV), and right ventricle of the myocardial phantom were filled with water. A Teflon rod simulated the spine, and sawdust simulated the lungs (Figures 1 and 2). We obtained a total of 0.4–2.0 million counts. We

then assessed the image quality for each myocardial count, scoring it on a three-point scale (0, poor; 1, fair; 2, good) and examined the image uniformity, resolution, and contrast (e.g., myocardial endocardial and epicardial border definition) and the target/background ratio. Two experienced nuclear cardiologists and four radiology technologists individually performed the visual scoring. Average scores were calculated using quantitative analysis. We then compared them using a circumferential count profile curve with Prominence Processor Version 3.1® software (Conference for Nuclear Medicine Image Processing, Japan). Circumferential count profile curves are used for normalized maximum counts.

Patient Study

Population. The study population comprised 292 consecutive patients with suspected or known coronary artery disease who underwent stress/redistribution testing between March and July 2015 using a single injection of thallium-201 to assess myocardial viability. The Ethics Committee of Hyogo Brain and Heart Center at Himeji (Himeji, Japan) approved this retrospective study.

Imaging protocol. The imaging protocol is shown in Figure 3. In all, 85 patients (29.1%; 65 men, 20 women) with a body mass index (BMI) range of 15.0–30.0 kg/m^2)

underwent exercise stress in an upright position on a bicycle ergometer until one of the following endpoints was reached: ≥ 85% of predicted maximum heart rate (220 − age in years), physical exhaustion, leg fatigue, angina pectoris, ST depression > 2 mm, and sustained ventricular tachyarrhythmia. Thallium-201 was injected at peak exercise, and the patient was asked to continue at the same pace for an additional minute (1 min).

In addition, 207 patients (70.9%; 133 men, 74 women) were subjected to pharmacological stress that was achieved with adenosine 0.12 mg/kg/min (Adenoscan®; Astellas Pharma, Tokyo, Japan) administered for 6 minutes using an intravenous infusion pump. After 3 minutes of the infusion, thallium-201 [3–4 mCi (111–148 MBq)] was injected intravenously. Stress SPECT imaging was performed 5–10 minutes after the thallium-201 injection, and redistribution SPECT images were acquired 3–4 hours later.

CZT SPECT

The CZT SPECT (D-SPECT®; Spectrum Dynamics, Caesarea, Israel) uses nine pixilated solid-state CZT crystal detector columns, wide-angle tungsten collimators, and region of interest (ROI)-centric scanning. Each column consists of 1024 (16 × 64) 5 mm thick CZT elements (2.46 × 2.46 mm). The detectors, rotating in synchrony while

focusing on the ROI (the heart), produce the needed data.[13] Imaging was conducted with the patient upright in all cases. After 10-sec pre-scan acquisition and positioning the heart in the field of view according to previous reports,[16] 1.5 million LV myocardial counts were acquired for both post-stress and redistribution images, with an energy peak and energy window width of 71 keV ± 15%. We used an acquisition protocol based on total myocardial counts. The imaging myocardial volumetric ROI counts were of high order to obtain more than 1.2 million LV myocardial counts. The cardiac cycle was divided into 16 equally spaced intervals. Summed and gated projections were reconstructed with an iterative maximum likelihood expectation maximization algorithm (using a variant of the ordered-subset expectation maximization algorithm) using three and four iterations, respectively, and 32 subsets.[17]

We calculated an optimal thallium-201 dose that resulted in acceptable LV myocardial counts according to a patient-specific classification using redistribution images. We also examined the factors that influenced obtaining the optimal dose of thallium-201 and found three compounds that were commercially available: 2, 3, and 4 mCi (74, 111, and 148 MBq, respectively).

Statistical Analysis

Statistical analysis was performed with commercial software (StatView version 5.0® and JMP version 11.2.0®; SAS Institute, Inc., Cary, NC, USA). All continuous variables are expressed as means ± SD. Multiple regression analysis was used to investigate the possible influence of patient-specific factors regarding their relation with the radiopharmaceutical doses. Multivariate analysis was used to determine the predictive value of statistically significant patient-specific factors. The results are shown as linear regression plots. The decision coefficients were calculated. A value of $P < .05$ was considered to indicate statistical significance.

RESULTS

In the phantom study, we examined the minimum dose for appropriate imaging (Table 1). The lowest myocardial count for good-quality imaging detection was 1.2 million counts for the anterior wall (≤10 mm defect size) (Figure 4). We then calculated an optimal dose of thallium-201 that would result in 1.2 million myocardial counts during 6 minutes of acquisition time.

The patient's clinical characteristics are shown in Table 2. There were 292 consecutive patients [198 men (67.8%)] with a mean age ± SD of 72.4 ± 9.3 years. A

total of 109 (37.3%) patients had known coronary artery disease. The optimal radiopharmaceutical doses were calculated as the ratio of acquisition time (minutes)/myocardial counts (millions) based on the injected dose (mCi). It was then converted to the dose required for 1.20 million counts for 6 minutes of acquisition time. The calculating formula is as follows:

Optimal radiopharmaceutical dose (mCi)

= injected dose × (acquisition time/myocardial count)

× [1.2 (million)/6 (minutes)] (1)

The multiple regression analysis showed a positive correlation with age ($r^2 = 0.10$, $P < .001$), sex ($r^2 = 0.02$, $P = .012$), BMI ($r^2 = 0.25$, $P < .001$), and type of stress test ($r^2 = 0.40$, $P < .001$). The multivariate analysis showed that the patient's BMI ($P < .001$) and the type of stress test ($P < .001$) contributed to the estimation of injected radiopharmaceutical doses. The patient's age and sex were not statistically significant factors ($P = .440$ and $P = .113$, respectively). Based on these findings, we could predict the optimal radiopharmaceutical doses as follows.

For the exercise stress test, the optimal radiopharmaceutical doses (mCi) were calculated as

$6.85 \times \text{BMI} - 16.27$ ($r^2 = 0.28$, $P < .001$). (2)

For the adenosine stress test, optimal radiopharmaceutical doses (mCi) were calculated as

$$5.09 \times \text{BMI} - 22.9 \ (r^2 = 0.29, P < .001). \quad (3)$$

Linear regressions for the calculated radiopharmaceutical doses and the patient's BMI were compared using linear regression plots (Figure 5). According to the patient's BMI and the type of stress test (exercise, adenosine) the optimal doses were as follows (Figure 6).

2 mCi for adenosine with BMI $\leq$ 19.2 kg/m^2

3 mCi for exercise with BMI $\leq$ 17.4 kg/m^2 and for adenosine with BMI >19.2 but $\leq$ 26.0 kg/m^2, and

4 mCi for exercise with BMI < 17.4 but $\leq$ 24.2 kg/m^2 and for adenosine with BMI > 26.0 but $\leq$ 32.8 kg/m^2.

Representative cases are shown in Figure 7.

The estimated extensions of the acquisition times were 8 and 10 minutes for lower radiation doses (Figures 8, 9). With the 10-minute acquisition time, for the exercise stress test, 2 mCi was administered in 11 patients (12.9 %) and 3 mCi in 74 patients (87.1 %). For the adenosine stress test, 2 mCi was administered in 204 patients (98.6 %) and 3 mCi in 3 patients (1.4 %).

DISCUSSION

We calculated an optimal thallium-201 dose for use with CZT SPECT that resulted in 1.2 million counts during 6 minutes of acquisition time. The optimal dose was calculated according to the patient's BMI and the type of stress test. For the exercise stress test, optimal radiopharmaceutical doses (mCi) were calculated as 6.85 × BMI – 16.27 (r^2 = 0.28, P < .001). For the adenosine stress test, the optimal radiopharmaceutical doses (mCi) were calculated as 5.09 × BMI – 22.9 (r^2 = 0.29, P < .001).

MPI is a well-established noninvasive method for identifying regional abnormalities in coronary artery blood flow and determining their physiological relevance to myocardial function and viability.[18] Thallium-201 has been in use since approximately 1980 and was responsible for much clinical evidence that accumulated during the decade that followed. Technetium 99m-labeled sestamibi, however, was approved in 1990.[19-21] Despite the fact that technetium-99m offers superior image quality (because of lower scatter) and a lower radiation count per unit of injected dose,[6,19-21] thallium-201 (compared with technetium-99m tracers) has a longer half-life and requires a lower injection dose. It is provided in a radiolabeled syringe (fixed at 2,

3, or 4 mCi). Therefore, it is rather difficult to modify the injected dose of thallium-201. However, thallium-201 still has many advantages. It is administered as a single injection for imaging during a stress/rest MPI protocol, and it provides higher first-pass myocardial extraction and lower extra-cardiac activity.[7,18]

CZT image quality with thallium-201 was reported to be superior to that achieved with the conventional Anger gamma camera,[15] and its diagnostic accuracy was not inferior to that of conventional SPECT. In a preliminary study, we produced data showing that thallium-201 MPI SPECT image quality provided by the CZT system had better-quality images than those found with technetium-99m because of the lower extra-cardiac activity.[7,18]

Technetium-99m used with a CZT gamma camera may allow LV myocardial counts as low as one million for stress MPI while maintaining excellent agreement regarding quantitative perfusion and functional parameters with those determined from higher counts.[22] In our phantom study, the lowest thallium-201 dose to obtain an appropriate image was 1.2 million counts based on the image quality and circumferential count profile curve. We then determined the thallium-201 dose needed to accumulate 1.2 million LV myocardial counts.

Our results indicated that different types of stress test (exercise versus adenosine in

this study) require different radiopharmaceutical doses for imaging. Coronary blood flow during a pharmacological stress test study was reported to be lower with dobutamine or exercise than with adenosine or dipyridamole.[23] Our study showed major differences in count rates between exercise- and adenosine-induced stress (Figure 5). The myocardial perfusion count rate was higher for the adenosine stress test than for the exercise stress test [23, 24] in regard to both stress and redistribution, allowing us to reduce the injection dose. Other studies have shown that there are sex-related differences regarding the myocardial blood flow and the injected pharmaceutical radiation dose,[25,26] whereas we found no statistically significant correlation.

Reducing the injection radiation dose is important. The most commonly used procedure involves administering 3 mCi of thallium-201 (the maximum administered dose was 4 mCi). Almost all patients with a 10-minute acquisition time who undergo the adenosine stress test have a 33% decreased radiation dose (2 mCi vs. 3 mCi).

These results suggest that the optimal dose could be lowered depending on the patient's BMI. However, this study was based on a Japanese population using a D-SPECT camera. Another population and another CZT camera system (Discovery NM 530c camera; GE Healthcare) could produce somewhat different results.

NEW KNOWLEDGE GAINED

The optimal dose of thallium-201 for MPI SPECT using CZT detectors has not been determined. Our results suggest how to determine an optimal dose of thallium-201 that could contribute to reducing the radiation dose.

CONCLUSIONS

We determined the optimal dose of thallium-201 for MPI SPECT using a dedicated cardiac system with CZT detectors. We suggest tailoring the dose according to the patient's BMI and the method of stress testing, with a lower dose needed for pharmacologically induced stress.

Acknowledgments

The authors thank all of their coworkers—radiological technologists and cardiologists—of Hyogo Brain and Heart Center at Himeji.

Disclosures

MS Masaru Ishihara, Dr. Yasuyo Taniguchi, Professor Masahisa Onoguchi, and MS Takayuki Shibutani have nothing to disclose.

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Figure Legends

Figure 1. Photograph shows the configuration of the myocardial phantom. (**A**) Front view. (**B**) Top view.

Figure 2. Median short-axis and vertical long-axis slice images of a myocardial phantom. A 10-mm defect is set in the anterior wall and 20-mm defect in the inferior wall.

Figure 3. Study protocol for stress/redistribution myocardial perfusion imaging with thallium-201.

Figure 4. Circumferential count profile curve analysis of the myocardial phantom. The lowest myocardial counts for quality-approved imaging detection were 1.2 million counts for the anterior wall (≤10 mm defect size).

Figure 5. Linear regression plots for radiopharmaceutical doses and body mass index (BMI) [1.2 million left ventricular (LV) counts during 6 minutes of acquisition time]. Differences in the stress test types: (**A**) Exercise. (**B**) Adenosine.

Figure 6. Bar graph of the BMI classifies the three dose groups (2, 3, and 4 mCi) compared with the types of stress test. It shows the radiopharmaceutical doses needed to acquire 1.2 million LV counts during 6 minutes of acquisition time.

Figure 7. Mildly abnormal myocardial perfusion (high-BMI patients) under two conditions (*top*: stress; *bottom*: redistribution). (**A**) A 68-year-old man with BMI 26.6 kg/m^2. The stress test was exercise, during which a dose of 3 mCi was injected. Redistribution imaging shows 1.3 million myocardial counts during 9.6 minutes of acquisition time. (**B**) A 78-year-old man with BMI 28.8 kg/m^2. The stress test was adenosine, and the injected dose was 3 mCi. Redistribution imaging show 1.3 million myocardial counts during 8.2 minutes of acquisition time.

Figure 8. Linear regression plots for radiopharmaceutical doses and various body mass indexes (BMIs) [1.2 million left ventricular (LV) counts during 8 minutes and 10 minutes of acquisition time]. (**A**) Exercise stress test (8 minutes of acquisition time). (**B**) Adenosine stress test (8 minutes of acquisition time). (**C**) Exercise stress test (10 minutes of acquisition time). (**D**) Adenosine stress test (10 minutes of acquisition time).

Figure 9. Bar graph of the BMI classifies the three dose groups (2, 3, and 4 mCi) compared with the types of stress test. It shows the radiopharmaceutical doses needed to acquire 1.2 million LV counts. (**A**) 8 minutes of acquisition time. (**B**) 10 minutes of acquisition time.

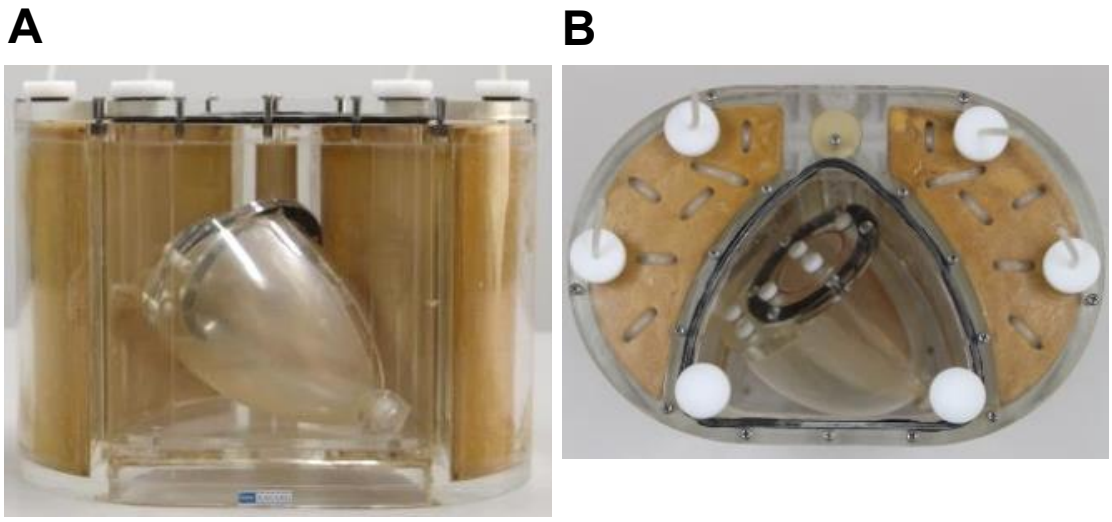


Figure 1

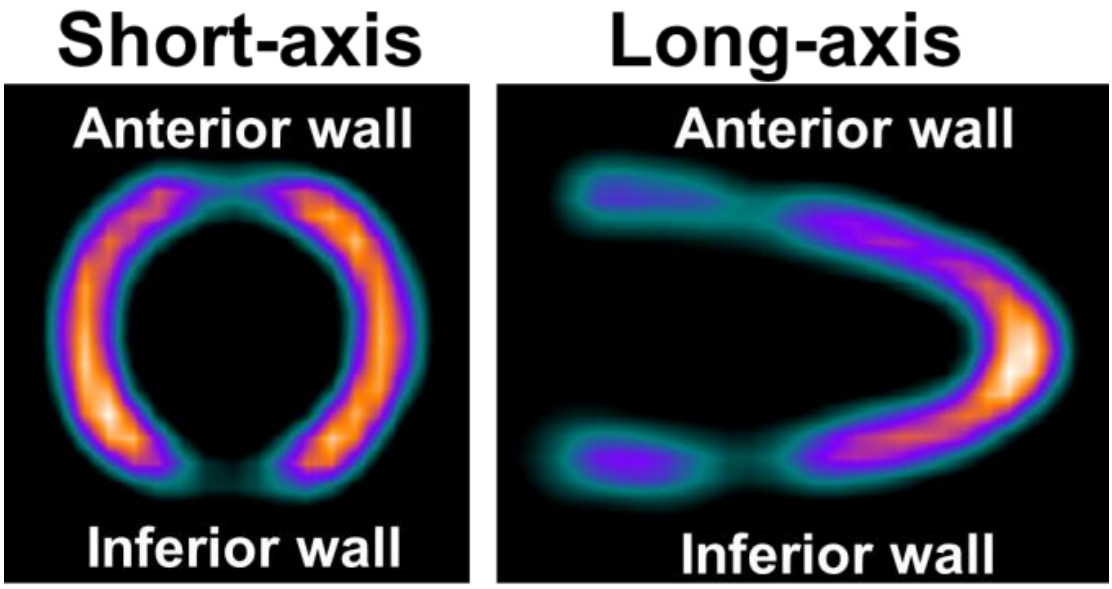


Figure 2

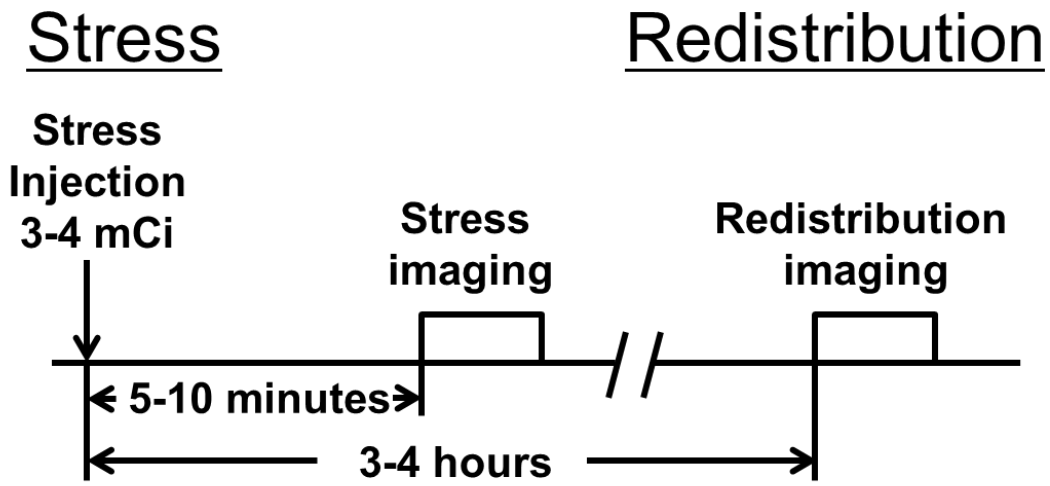
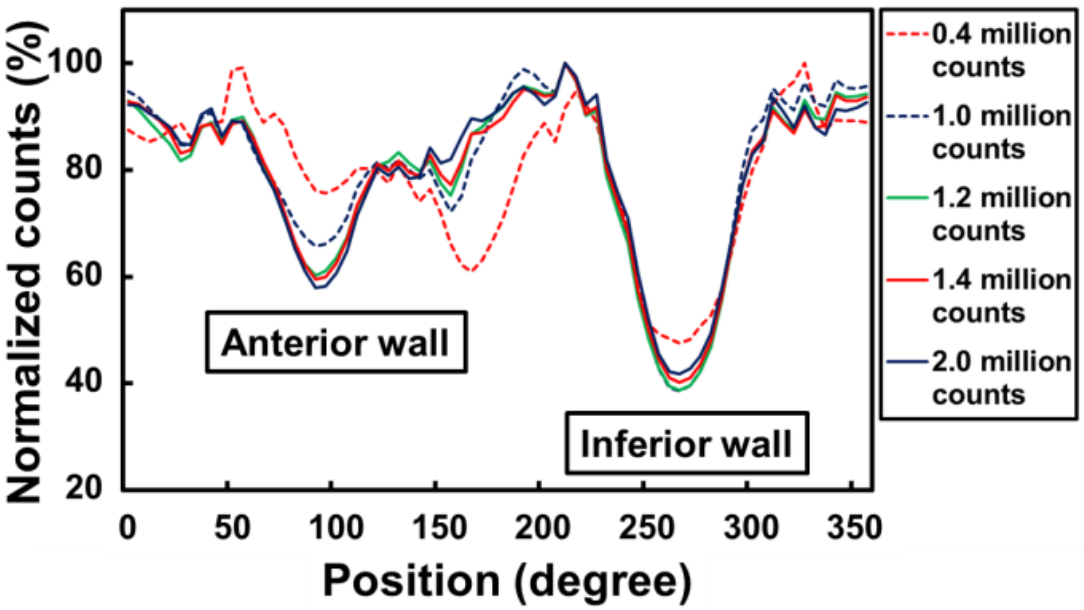


Figure 3



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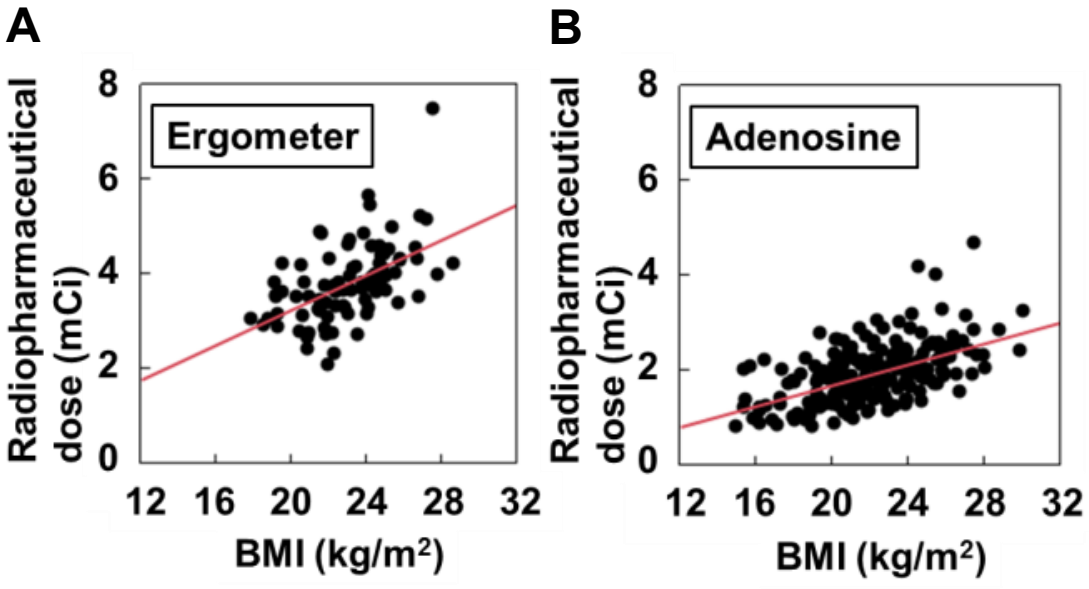


Figure 5

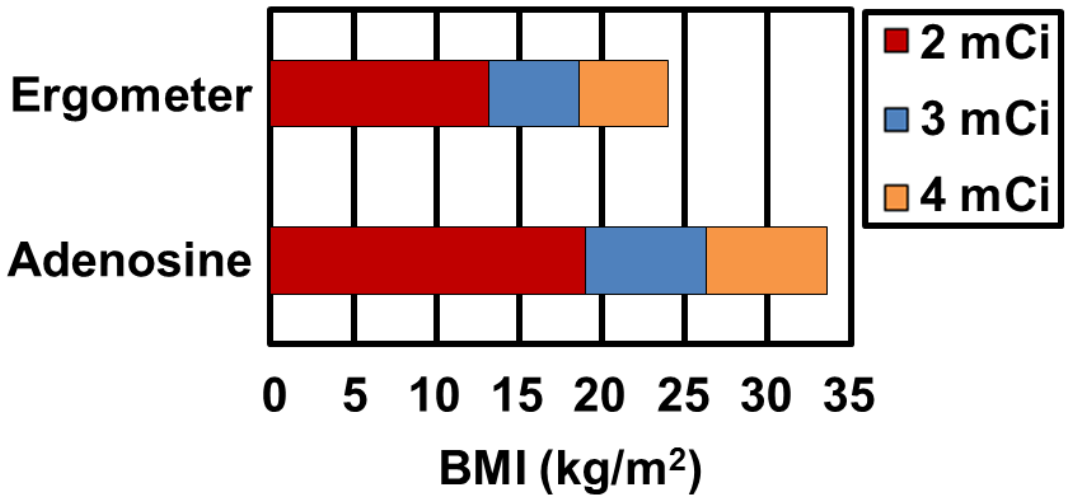
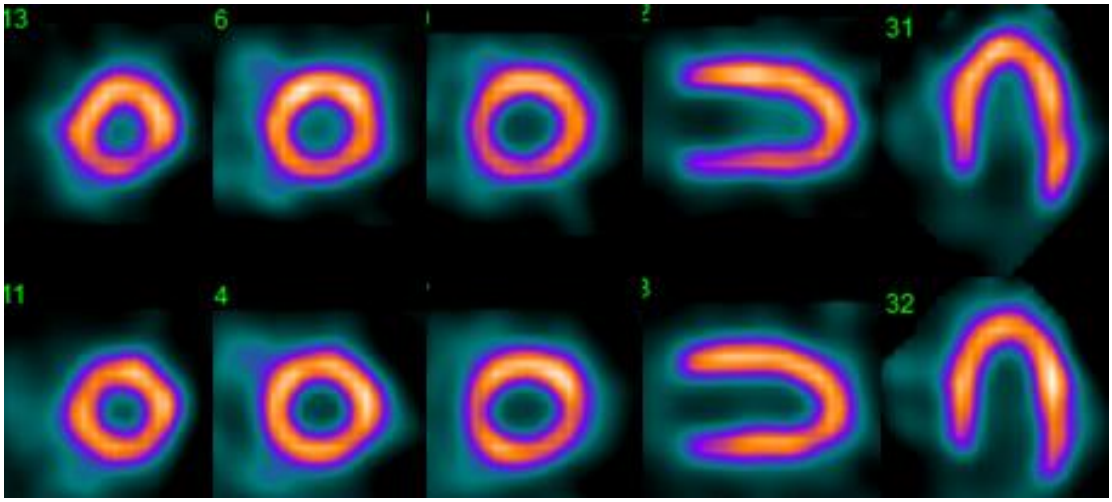


Figure 6

A



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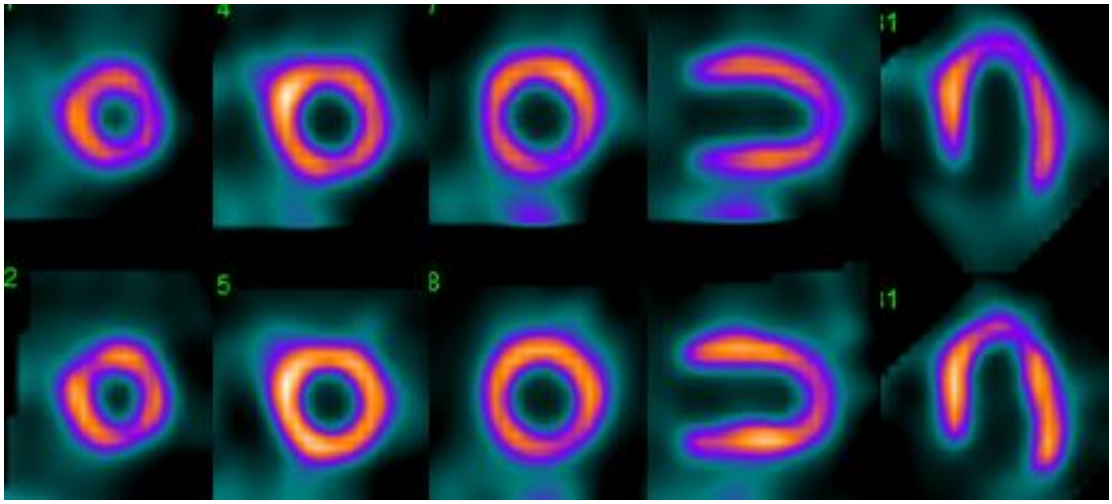

Figure 7

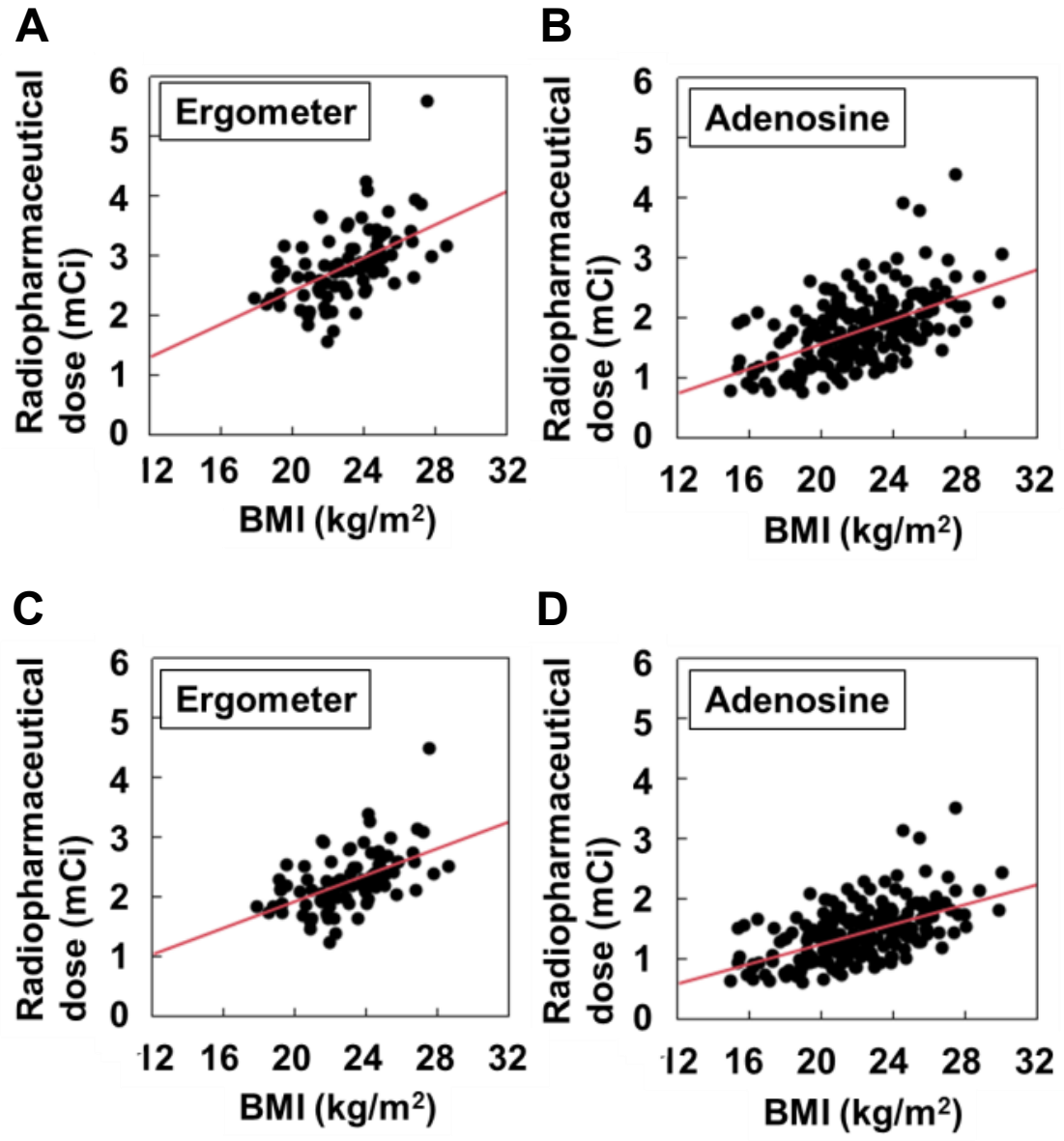
A
B
C
D
Ergometer
Adenosine
Radiopharmaceutical dose (mCi)
BMI (kg/m²)
0
1
2
3
4
5
6
12
16
20
24
28
32

Figure 8

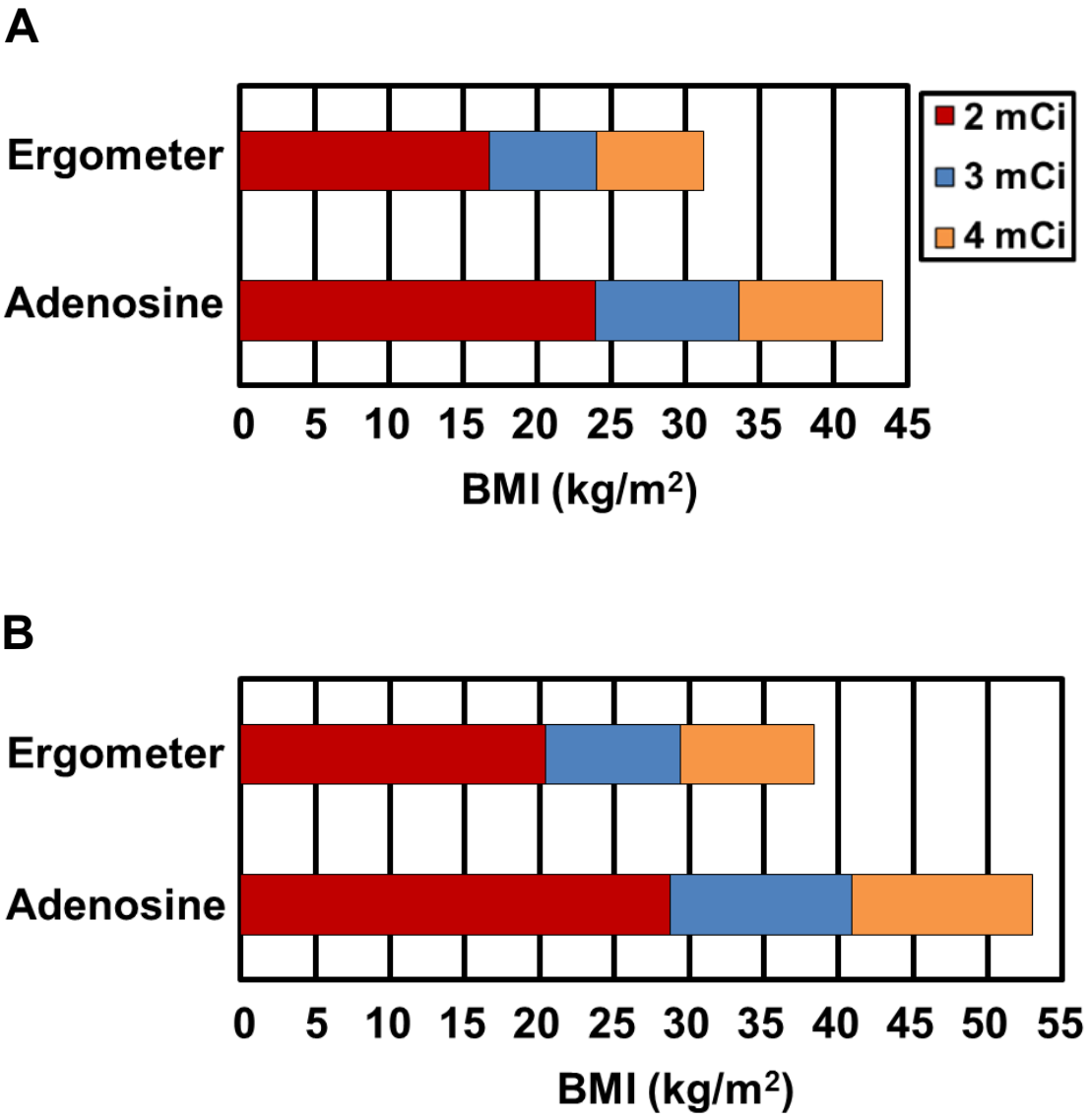
A
Ergometer
Adenosine
2 mCi
3 mCi
4 mCi
0 5 10 15 20 25 30 35 40 45
BMI (kg/m2)
B
Ergometer
Adenosine
0 5 10 15 20 25 30 35 40 45 50 55
BMI (kg/m2)

Figure 9

Table 1. Image quality in the myocardial phantom study image quality

Myocardial counts (millions)	**Average score**
0.4	0.0 ± 0.0
0.6	0.0 ± 0.0
0.8	0.0 ± 0.0
0.9	0.2 ± 0.4
1.0	0.5 ± 0.5
1.1	0.8 ± 0.4
1.2	1.0 ± 0.0
1.3	1.0 ± 0.0
1.4	1.0 ± 0.0
1.5	2.0 ± 0.0
1.6	2.0 ± 0.0
1.8	2.0 ± 0.0
2.0	2.0 ± 0.0

Data are given as means ± SD

Table 2. Patients' characteristics

Characteristic	Value
Age (years)	72.4 ± 9.3
Men sex, *n* (%)	198 (67.8)
BMI (kg/m^2)	22.3 ± 2.9 (range 15.0–30.0)
LV stress counts (millions)	1.7 ± 0.3 (range 1.0–2.7)
LV redistribution counts (millions)	1.7 ± 0.3 (range 1.1–2.7)
Stress acquisition times (minutes)	4.2± 1.4 (range 2.0–8.3)
Redistribution acquisition times (minutes)	7.2 ± 2.4 (range 2.6–15.2)
Prior myocardial infarction	57 (19.5)
Prior revascularization	67 (23.0)
Co-morbidities	
Diabetes	102 (34.9)
Hypertension	195 (66.8)
Hypercholesterolemia	131 (44.9)
Chronic kidney disease	110 (37.2)
Smoking	87 (29.8)

Data are given as mean ± SD or the number (%)

BMI, body mass index; *LV*, left ventricular