



Simulating dose reduction for myocardial perfusion SPECT using a Poisson resampling method

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Abstract

Purpose The purpose of this study was to determine the lowest Tl-201 dose that does not reduce the image quality of myocardial perfusion SPECT (MPS) by Poisson resampling simulation.

Methods One hundred and twelve consecutive MPS data from patients with suspected or known coronary artery disease were collected retrospectively. Stress and rest MPS data were resampled using the Poisson method with 33%, 50%, 67%, and 100% count settings. Two nuclear medicine physicians assessed the image quality of reconstructed data visually by giving grades from –2 to +2. The summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS) were obtained on the workstation. Image quality grades and semi-quantitative scores were then compared among these resampled images.

Results The proportions of “adequate” image quality were 0.48, 0.75, 0.92, and 0.96 for the groups of images with 33%, 50%, 67%, and 100% data, respectively. The quality of the resampled images was significantly degraded at 50% and 33% count settings, while the image quality was not different between 67 and 100% count settings. We also found that high body mass index further decreased image quality at 33% count setting. Among the semi-quantitative parameters, SSS and SRS showed a tendency to increase with a decline in count.

Conclusion Based on the simulation results, Tl-201 dose for MPS can be reduced to 74 MBq without significant loss of image quality. However, the SSS and SRS can be changed significantly, and it needs to be further verified under the different conditions.

Keywords Myocardial perfusion SPECT · Thallium-201 · Radiation dose · Poisson resampling

Introduction

Myocardial perfusion single-photon emission computed tomography (MPS) is a non-invasive diagnostic tool used to evaluate patients with ischemic cardiomyopathy. Two main types of radiopharmaceuticals are used for MPS: thallium-201 (Tl-201) chloride and technetium-99 m (Tc-99 m)-labeled agents such as Tc-99 m sestamibi and Tc-99 m tetrofosmin. Tl-201 decays by electron capture with a half-life of 73.1 h and emits X-rays primarily at 68–80 keV and γ -rays

at 135 and 167 keV [1]. The physical properties of Tl-201 make it sub-optimal for myocardial perfusion imaging compared to Tc-99 m-labeled agents, but it has a higher first-pass extraction rate (85%) and thus can maintain high coronary flow rates. Consequently, Tl-201 is still widely used for MPS in many institutions.

One of the concerns when using Tl-201 for MPS is the high radiation exposure of patients (1.4×10^{-1} mSv/MBq, International Commission on Radiological Protection publication 128) [2]. Working groups recommend 74–148 MBq of Tl-201 for MPS, which is approximately 10–20 mSv [3, 4]. Several studies have investigated reducing the radiation exposure from Tl-201 during MPS.

Some researchers have used advanced imaging devices such as cadmium-zinc-telluride (CZT) single-photon emission computed tomography (SPECT) [5–7]. Ishihara et al. reported that the optimal dose for obtaining acceptable images depends on the type of stress and body mass index (BMI) of patients. For adenosine stress, 74 MBq Tl-201 was

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the lowest optimal dose for those with BMIs ≤ 19.2 , during 6 min of acquisition [5]. CZT SPECT has a higher photon sensitivity compared to conventional gamma cameras, which means that Tl-201 doses as low as 0.5 MBq/kg body weight (≈ 37 MBq for 70 kg adult) can be used. In such cases, the radiation exposure from the radiopharmaceutical to patients decreases to 4.8 ± 0.9 mSv [6]. However, dedicated cardiac SPECT is not currently available in most institutions.

Another approach to reduce the Tl-201 dose is to use novel reconstruction algorithms. Jin et al. developed an advanced four-dimensional (4D) reconstruction method during gated acquisition and reconstruction for MPS [4]. The 4D reconstruction method can be used in combination with CZT SPECT to reduce the radiopharmaceutical dose to a quarter of that used by the conventional methods and to improve the consistency of quantitative parameters. Zafrir et al. utilized a resolution recovery software with an ordered-subset expectation maximization (OSEM) reconstruction algorithm, which led to good MPS image quality using a half-dose of Tc-99 m sestamibi [8].

The purpose of this study was to determine the lowest Tl-201 dose that does not significantly reduce MPS image quality. However, obtaining both full-count images and reduced-count images in the same patients has an ethical issue of high radiation exposure (more than 20 mSv). On the other hand, comparing two images from the different patients lacks reliability. Therefore, instead of conducting a clinical trial, we used a simulation method based on the Poisson resampling [9] that can produce reduced-count images from the full-count images in the same patients.

Materials and methods

Patient selection

We retrospectively enrolled 112 consecutive patients with suspected or known coronary artery disease who underwent stress/redistribution Tl-201 MPS between September 2018 and December 2018. No specific inclusion or exclusion criteria were used. Clinical information (including age, sex, BMI, and a history of smoking, diabetes, hypertension, and hyperlipidemia) was obtained from the medical record review. This study was approved by the Institutional Review Board (AJIRB-MED-MDB-21-071) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The Institutional Review Board waived the need for informed consent.

MPS imaging protocol

All anti-anginal medications were withheld from patients for 2 days before examination, and patients did not smoke on the day of imaging. Adenosine (140 $\mu\text{g}/\text{kg}/\text{min}$) was infused slowly over a period of 6 min. A fixed dose of 111 MBq Tl-201 was intravenously injected 4 min after the initiation of adenosine infusion. Stress images were acquired 5–10 min after the Tl-201 injection using dual-head SPECT with low-energy, high-resolution, and parallel-hole collimators (Discovery NM/CT 670, GE Healthcare, Milwaukee, USA). Redistribution images were acquired 3–4 h later. The acquisition parameters were as follows: collimators with 90° configuration (L-mode), 60 projections, 20 s per frame for stress and 25 s per frame for rest studies, 180° circular orbit, 64×64 matrix, $70 \pm 15\%$ keV, and $167 \pm 10\%$ keV photopeak energy window.

Simulation of dose reduction and visual/semiquantitative assessment of images

Raw data from both the stress and rest SPECT images were resampled using the Poisson method (Evolution toolkit, GE healthcare) on the Xeleris workstation (GE Healthcare). Count settings for resampling were 33%, 50%, 67%, and 100% of the original data. In Poisson resampling, each count in an original image is regarded as an independent variable, to which a random number is allocated. After the probability of selection (for example, 50%) is defined, the count to be included in the new image is determined according to principles of the Bernoulli trial [9, 10]. All SPECT images were then reconstructed using OSEM (2 subsets and 10 iterations) with a Butterworth filter (cut-off frequency = 0.4, power = 10). Attenuation correction was not applied to the image processing. The quality of the resampled SPECT images was then visually assessed and scored on tomographic and polar maps by two nuclear medicine physicians (23 and 3 years of clinical experiences in MPS). The grades were given individually for images, without comparison with other images, on a scale from -2 to $+2$, with $+2$ being the best grade (Table 1) [11, 12]. The image quality was regarded as “inadequate” for the interpretation in cases where the image was graded as -1 or -2 by at least one reader, while it was regarded as “adequate” in cases where the image was graded as 0 to $+2$ by both the readers. The percentage of resampling and patient information were blinded during the evaluation.

The summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS) were obtained automatically using QPS software on the Xeleris workstation from resampled images. The SSS, SRS, and SDS were

Table 1 Visual grades for the image quality of resampled SPECT images

Grade	Description
+ 2	Homogeneous perfusion of normal areas on tomography and polar map, Clear distinction between normal and defective regions
+ 1	Homogeneous perfusion of normal areas on tomography Subtle heterogeneity of normal area on a polar map Clear distinction between normal and defective regions
0	Partially heterogeneous perfusion of normal areas on tomography and polar map The distinction between normal and defective regions is possible
− 1	Heterogeneous perfusion of normal areas on tomography and polar map Poor distinction between normal and defective regions
− 2	Heterogeneous perfusion of normal areas on tomography and polar map Decreased perfusion of normal areas with a loss of continuity Poor distinction between normal and defective regions

calculated on a 17-segment myocardial model on a 5-point scale: 0, normal; 1, equivocal; 2, moderate reduction; 3, severe reduction; and 4, absent. Image processing was performed without the knowledge of patient information. MPS result was considered to be normal if the SSS was < 4 and abnormal if the SSS \geq 4. Meanwhile, ischemia on MPS was considered to be insignificant if the SDS was < 7 and significant if the SDS \geq 7 [13].

Statistics

Statistical analysis was performed using R software (version 3.6.3). The results are presented as mean \pm standard deviation for continuous variables and as percentages of total patients for categorical data. A chi-square test was used to compare the grades among resampled images. The Wilcoxon signed-rank test was used to measure changes in the SSS or SRS after low-dose simulation. Weighted Cohen's kappa statistics were used to measure the agreement between the two readers on image quality (grades) assessment. Kappa results were interpreted as poor ($k < 0.20$), fair ($k = 0.21–0.40$), moderate ($k = 0.41–0.60$), good ($k = 0.61–0.80$), very good ($k = 0.81–0.90$), or excellent ($k \geq 0.91$). Statistical significance was set at a level of < 0.05 .

Results

Patient characteristics

A total of 112 patients were included in this study (Table 2). Fifty-five patients (50.9%) underwent MPS for the follow-up evaluation of known coronary artery disease, while 52 patients (46.4%) underwent MPS due to suspected coronary artery disease. The mean age of the patients was 65 ± 11 years. Seventy patients (62.5%) were men. The percentages of patients with type 2 diabetes, hypertension, and hyperlipidemia were 39.3%, 72.3%, and 58.9%, respectively.

Table 2 Patients' characteristics

Parameters	Values*
Number of patients	112
Follow-up evaluation in patients with CAD	57 (50.9%)
Suspected coronary artery disease	52 (46.4%)
Preoperative evaluation	3 (2.7%)
Age	65 ± 11 years
Sex	
Male	70 (62.5%)
Female	42 (37.5%)
Diabetes	44 (39.3%)
Hypertension	81 (72.3%)
Hyperlipidemia	66 (58.9%)
BMI	24.3 ± 3.3 kg/m ²
Smoking	22 (19.6%)

CAD coronary artery disease; BMI body mass index

*Data except age and BMI are presented as number and percentage in parenthesis

The BMI was 24.3 ± 3.3 ; thus, the cutoff for high BMI used in further analysis was ≥ 25.0 . Twenty-two patients (19.6%) were current smokers.

Visual assessment for the full-data and resampled images

A total of 448 MPS images were assessed for image quality. Figure 1 shows representative tomographic and polar map images showing the gradual decline of the image quality by reducing counts. Inter-observer agreement on visual grades was moderate (weighted Cohen's kappa = 0.60). Figure 2 shows the proportions of "adequate" images for each count setting: 0.48, 0.75, 0.92, and 0.96 for the groups of images with 33%, 50%, 67%, and 100% data, respectively. There was no statistically significant difference in the proportion of "adequate" images between the 100% and 67% resampled data. However, the

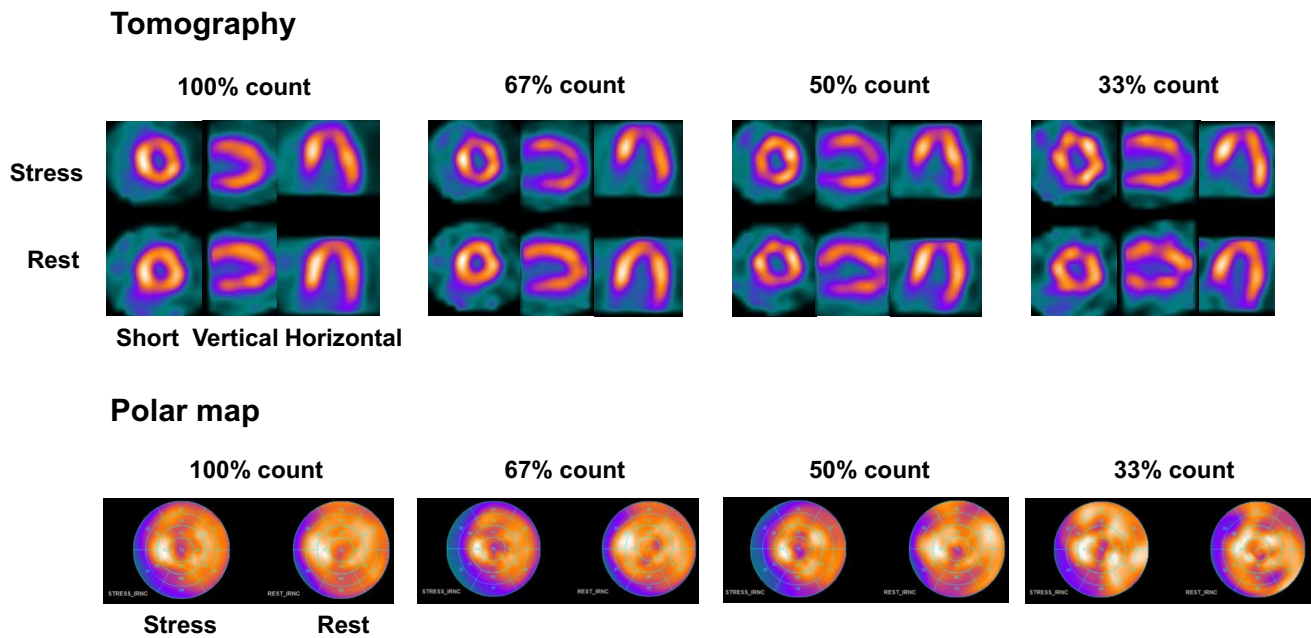


Fig. 1 The representative myocardial perfusion tomographic and polar map images showing the gradual decline in the image quality by reducing counts. All images were obtained from the same patient by the Poisson resampling method

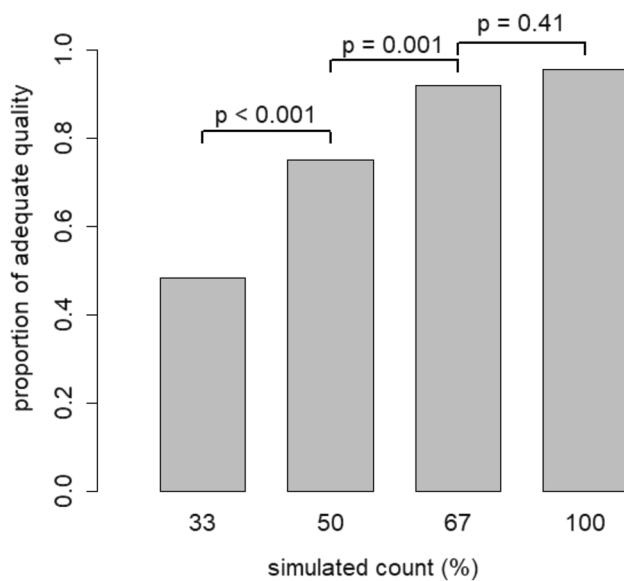


Fig. 2 The proportions of “adequate” images at each count setting. There was statistically significant difference between images with 33% and 50% counts, and between images with 50% and 67% counts. * $p < 0.05$

number of “adequate” images was significantly smaller in the 50% resampled data than in the 67% resampled data ($p = 0.001$). Likewise, there was a significant difference in the proportion of “adequate” images between the 33% and 50% count settings ($p < 0.001$).

Figure 3 shows the proportions of “adequate” images in subgroups based on the presence of diabetes and BMI. The proportions of “adequate” images were 0.43, 0.77, 0.86, and 0.95, for patients with diabetes at 33%, 50%, 67%, and 100% count settings, respectively, while the proportions were 0.51, 0.74, 0.96, and 0.96, respectively, for patients without diabetes. There was no statistically significant difference in the proportions of “adequate” images between the diabetic and non-diabetic groups at all count settings (Fig. 3a). For BMI, the proportions of “adequate” images were 0.35, 0.67, 0.92, and 0.96 for patients with high BMIs at 33%, 50%, 67%, and 100% count settings, respectively, while the proportions were 0.58, 0.81, 0.92, and 0.95, respectively, for patients with low BMIs. In contrast to diabetes, there was a significant difference in the proportions of “adequate” images between the high and low BMI groups at 33% count setting ($p = 0.02$, Fig. 3b). Additionally, we performed a subgroup analysis with 6 obese patients ($BMI > 30$). Of 12 images with 67% or 100% count settings, 7 images were adequate, while of those with 33% or 50% count settings, 5 were adequate.

Semiquantitative assessment for the full-data and resampled images

The average scores by semiquantitative analysis were as follows: 7.54 ± 6.93 , 8.35 ± 6.91 , 8.85 ± 6.98 , and 9.39 ± 7.09 for the SSS; 5.09 ± 5.44 , 5.36 ± 5.94 , 5.49 ± 5.30 , and 6.50 ± 5.78 for the SRS; and 2.46 ± 5.72 ,

Fig. 3 The proportions of “adequate” images at each count setting. The patients with and without diabetes (A) and the patients with high BMIs and those with low BMIs (B). BMI, body mass index; * $p < 0.05$

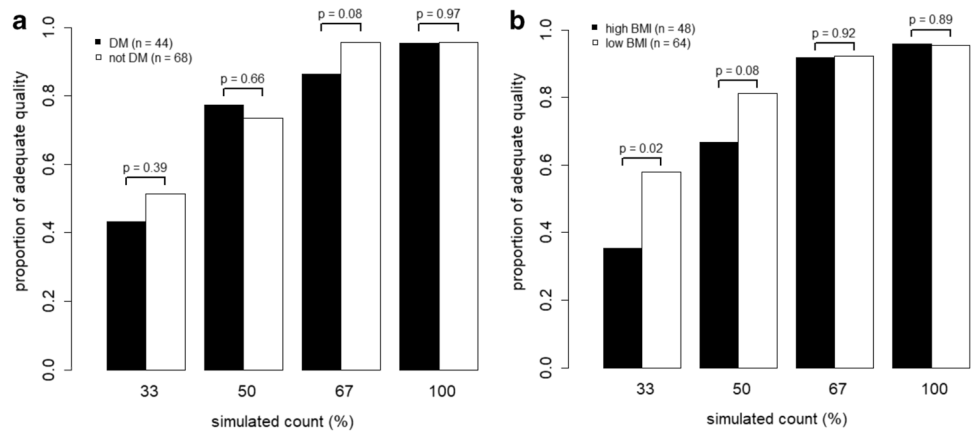
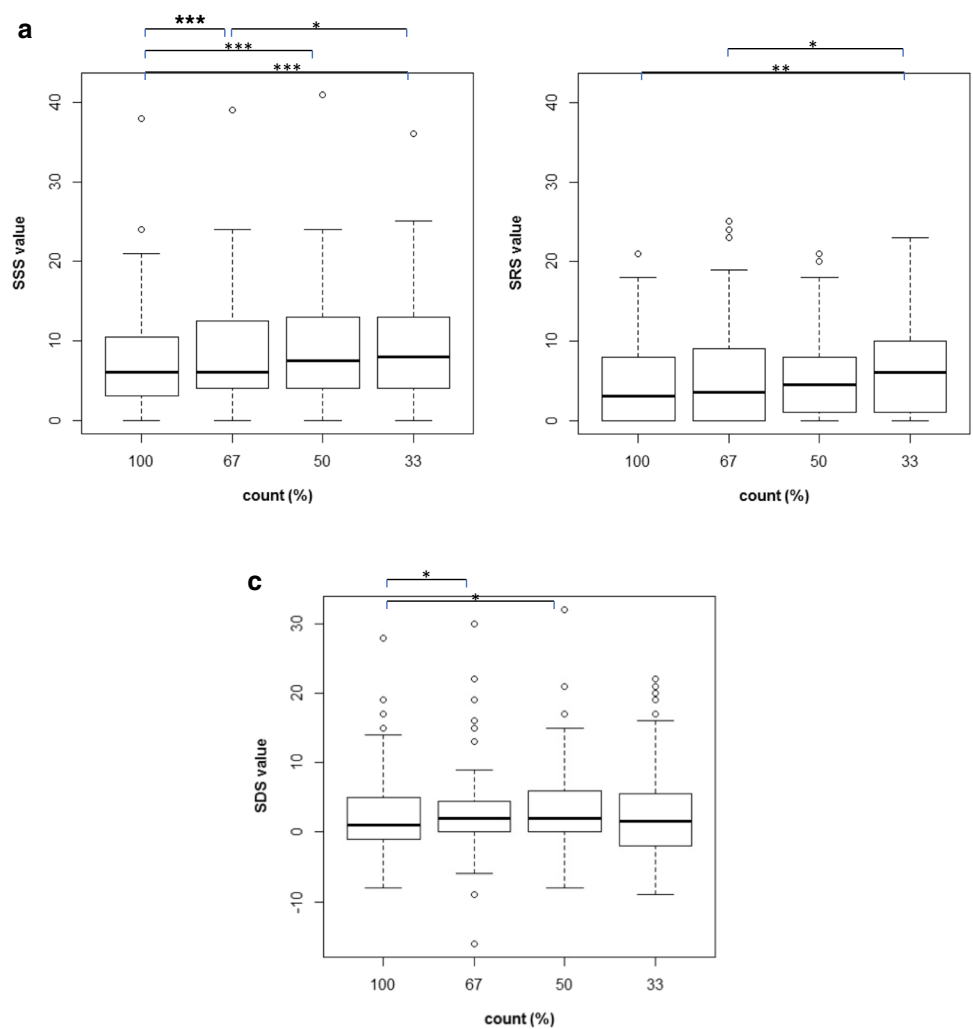


Fig. 4 Boxplots of the SSS (a), SRS (b) and SDS (c) at each count setting. SSS, summed stress score; SRS, summed rest score; SDS, summed difference score. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$



2.99 ± 5.85, 3.36 ± 6.28, and 2.89 ± 6.81 for the SDS at 100%, 67%, 50%, and 33% count settings, respectively (Fig. 4a–c). Both SSS and SRS showed a tendency to increase with a decline in resampled counts.

Paired Wilcoxon signed-rank test results comparing the SSS, SRS, and SDS between MPS images with different count settings are shown in the box plots. SSSs of 33%, 50%, and 67% resampled images were significantly larger than

those of the 100% count images ($p < 0.001$). In addition, a significant difference in the SSS was found between the 67% and 33% count groups ($p = 0.01$). In contrast, the SRS of 33% resampled images was larger than those of the 100% count images ($p = 0.001$) and 67% count images ($p = 0.01$). For the SDS, there was a significant difference between the 100% and the 67% ($p = 0.03$) or 50% ($p = 0.02$) count groups.

The proportions of abnormal MPS by SSS (≥ 4) were 0.66, 0.77, 0.76, and 0.79 for 100%, 67%, 50%, and 33% count settings, respectively. The proportion of abnormal MPS increased from 0.66 at 100% to 0.77 at 67% count settings, although there was no significant difference between 2 groups ($p = 0.10$). The proportions of ischemia on MPS by SDS (≥ 7) were 0.17, 0.17, 0.23, and 0.23 for 100%, 67%, 50%, and 33% count settings, respectively. There was no significant difference in pairwise comparison.

Discussion

Software that can generate reduced-count images from existing data are useful tools for simulating low-dose images without the additional acquisition of patient data. Re-acquisition of MPS images is associated with problems related to a longer scan time, positional change of patients, and radioactive decay. In this study, MPS images with four different count settings were generated from the original data of patients using the Poisson resampling method [9, 14]. Using these resampled images, we investigated whether the dose of Tl-201 during MPS could be reduced without deteriorating the quality of images. Our results show that the quality was similar between 67 and 100% count images, but it was significantly reduced for images with 50% or 33% counts of the original Tl-201 MPS data. These results indicate that the dose of Tl-201 used for MPS can be reduced to 67% of the original dose without worsening the image quality. To our knowledge, this is the first study to report the effect of dose reduction simulated by Poisson resampling in Tl-201 MPS.

Before this study, Lawson et al. evaluated the effect of half-count acquisition on the image quality obtained through Tc-99 m tetrofosmin or sestamibi MPS [14]. Their multicenter trial used the Poisson resampling method and resolution recovery software. They found that results from half of the institutions did not show significant image deterioration after simulation; thus, at those institutions, a half-dose could be used for Tc-99 m MPS. On the contrary, results from the other half of the institutions showed clinically relevant discrepancies or poor images that were insufficient for reporting. Further adjustment to the protocol was recommended for the latter institutions.

Subgroup analysis was performed to determine whether the quality of low-dose MPS images is affected by diabetes, which is a well-known risk factor for coronary artery

disease. We found that the quality of MPS images did not differ significantly between patients with and without diabetes at all count settings. Kang et al. also evaluated the effect of diabetes on the detectability of MPS and demonstrated that the sensitivities and specificities of exercise dual-isotope MPS for $\geq 50\%$ and $\geq 70\%$ coronary artery stenosis were comparable between patients with and without diabetes [15]. Although a different study protocol was used, this result was in accordance with our results. Our study also showed that a high BMI had a negative effect on the quality of MPS images. In the 33% count setting, the proportion of “adequate” images was only 0.35% for the high-BMI (≥ 25.0 kg/m²) group, as compared with 0.58 for the low-BMI group. Hansen et al. also reported that the diagnostic accuracy of exercise Tl-201 MPS for coronary artery disease was significantly lower in obese than in non-obese patients, even though the maximal coronary blood flow and disease severity were similar between them [16]. Soft tissue attenuation by adipose tissue leads to false-positive perfusion defects in MPS [17]. Various techniques have been developed to overcome this problem, such as attenuation correction and upright scanning. In this study, the image quality of MPS was not affected at 67% count setting; thus, dose reduction to 67% could be applied to both high- and low-BMI patients. However, unfortunately, we have only 6 obese patients in this study population, which is too low a number to assess the influence of obesity to the image quality. Therefore, we should be careful in applying these results to obese patient, and a further evaluation is required.

To date, no comparative study has been published regarding the effect of half-count on semi-quantitative parameters in MPS. We observed that the SSS and SRS tended to increase as the count decreased. The SSSs of 50% and 33% count images were significantly higher than those of 100% count images. In addition, the SSS of 67% count images was also higher than that of 100% count images, although the image quality assessed by visual analysis was similar between them. The proportion of abnormal MPS by SSS (≥ 4) increased from 0.66 at 100% to 0.77 at 67% count settings, although it didn't reach a statistical significance ($p = 0.10$). Therefore, care must be taken when these semi-quantitative parameters are used in the interpretation of MPS images. On the other hand, the proportion of ischemia on MPS by SDS (≥ 7) was not significantly different among 4 groups. This is probably because both SSS and SRS increase with the decrement of count.

The SRS was significantly different only between 100% count and 33% count images. This is a fully anticipated result. As the dose decreases, the noise increases owing to the limited count statistics, resulting in an inaccurate diagnosis. Although attenuation correction was not performed in this study, it could be one of the factors that influenced the semi-quantitative parameters. Giubbini et al. evaluated

whether attenuation correction affected the infarct size determined by the SSS, SRS, and SDS [18]. The SSS and SRS of the inferior wall and total myocardium were significantly higher in the uncorrected images than in the corrected images. As the low count statistics may increase the effect of soft tissue attenuation, the SSS and SRS could increase in low-dose settings. On the contrary, the results of the SDS comparison were inconsistent throughout the count settings. The SDS of 100% count images was not statistically different from the SDS of 33% count images. We hypothesize that the impact on the SDS values in the low count setting was offset by the increase in both the SSS and SRS values.

Several groups have experimented with various dose reduction methods in MPS studies. DePuey et al. compared filtered back projection and OSEM with resolution recovery (OSEM-RR) and wide beam reconstruction (WBR) on Tc-99 m sestamibi MPS [19]. They found on visual analysis that the image quality was slightly better for 7-min OSEM-RR and WBR images compared with 15-min filtered back projection images. They also compared half-time, half-dose Tc-99 m sestamibi images processed with WBR and full-time images processed with OSEM. They concluded that images obtained through both half-time and half-dose MPS with WBR were superior in image quality compared to those obtained through full-time MPS with OSEM [20]. The WBR method, developed by UltraSPECT, is based on a depth-dependent resolution recovery algorithm that improves image quality by modeling the geometry of the collimator and the detector's distance from patients [20, 21]. Depth-dependent resolution recovery algorithms are also incorporated in reconstruction software provided by various vendors: Evolution for Cardiac (GE Healthcare), Astonish (Philips Medical System), and 3D Flash (Siemens Medical Solutions). These software programs were validated by several groups, and they successfully reduced the Tc-99 m sestamibi or Tc-99 m tetrofosmin dose by 1/3 to 3/4 [22, 23].

A limitation of this study is that attenuation correction was not applied to the current data sets. Owing to the longer scan time, we do not routinely perform attenuation correction for MPS in daily clinical practice. Attenuation-corrected images were available for only a portion of the patients. As long as gated acquisition data are available, volumetric parameters are very useful in interpreting MPS. As low dose Tl-201 may decrease the image quality of MPS, particularly in obese patients, myocardial thickening would be very helpful in discriminating true perfusion defect from attenuation artifact. Unfortunately, volumetric parameters are not available in this study population. Another limitation is that this study was conducted at a single institution. According to the study by Lawson et al., even with the same simulation method, results may differ among institutions because of the diversity of scanners and scanning protocols [14]. Therefore,

the results of this study need to be validated by and adjusted for other institutions.

Conclusion

Based on the simulation results of the Poisson resampling method, MPS images with 67% of the original data did not induce a significant loss of image quality. Therefore, the dose of Tl-201 for MPS can be reduced to 74 MBq. In such cases, however, it must be considered that the SSS and SRS can be changed significantly. Reducing the dose of Tl-201 required for MPS will reduce the exposure of patients to radiation during the process and may therefore avoid long-term radiation-related health problems. In order to be generally applicable, it needs to be further verified under the different imaging conditions.

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Author contribution The study was designed by Il-Hyun Kim and Joon-Kee Yoon. Material preparation and data collection were performed by Il-Hyun Kim, So-Yeon Choi, and Joon-Kee Yoon. The data analysis was performed by Il-Hyun Kim, Su Jin Lee, Young-Sil An, and Joon-Kee Yoon. The first draft of the manuscript was written by Il-Hyun Kim, and Joon-Kee Yoon, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Availability of data and materials Please contact author for data requests.

Declarations

Competing interests Il-Hyun Kim, Su Jin Lee, Young-Sil An, So-Yeon Choi, and Joon-Kee Yoon declare no competing interests.

Ethics approval and consent to participate This study was approved by the Institutional Review Board (AJIRB-MED-MDB-21-071) and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The institutional review board waived the need to obtain informed consent.

Consent for publication The institutional review board waived the need to obtain informed consent because of the anonymity and the retrospective nature of the study.

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