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ABSTRACT

Aim: Myocardial perfusion imaging (MPI) with single photon emission computed tomography *(*SPECT) is widely adopted in clinical practice but is associated with a relatively high radiation dose. The aim of this study was to determine the minimum product of tracer dose and scan time, while maintaining diagnostic value for cadmium zinc telluride (CZT)-SPECT MPI.

Methods: 24 patients underwent clinically indicated stress MPI using CZT-SPECT and a body weight depending (3 MBq/kg) Tc-99m-tetrofosmin tracer dose. Data were acquired for 8 minutes in list mode. Next, images were reconstructed using 2, 4, 6 and 8 minutes time frames. Differences between the 8 minutes reference scan and the shorter scans were determined in segmental uptake values (using the 17 segment cardiac model), ejection fraction (EF) and end diastolic volume (EDV). A 5% difference in segmental uptake was considered to significantly influence the diagnostic value. Next, image quality of the 4, 6 and 8 minutes scans were scored by consensus of three experienced nuclear medicine physicians on a 4 point grading scale. Physicians were blinded for scan time and patient information.

Results: Differences in segmental uptake values, EF and EDV increased using shorter scans times as compared to the 8 minutes reference scan. On average, the diagnostic value was influenced in 7.7 segments per patient using the 2 minutes scans, in comparison to 2.0 and 0.8 segments per patient using the 4 or 6 minutes scans, respectively. In addition, the 4 minutes scans led to a significantly lower image quality compared to the 8 minutes scans ($p<0.05$). This was not the case for the 6 minutes scan.

Conclusion: Six minutes was the shortest acquisition time in stress MPI using CZT-SPECT that did not affect the diagnostic value when administrating a tracer dose of 3 MBq/kg. Hence, the patient-specific product of tracer dose and scan time can be minimized to 18 MBq·min/kg. This may lower the effective radiation dose for patients to values below 1 mSv.

INTRODUCTION

For patients with suspected stable coronary artery disease it is strongly recommended to test for ischemia prior to invasive coronary angiography (1,2). For this purpose, multiple tests are available of which myocardial perfusion imaging (MPI) with single photon emission computed tomography (SPECT) is the most validated non-invasive method (3).

MPI using SPECT is widely adopted in clinical practice. Yet, it is also known as a large contributor to the cumulative effective radiation dose from medical sources in the general population, accounting for more than 22% of the total effective dose in the United States (4). Despite the introduction of more sensitive gamma cameras, such as cadmium zinc telluride (CZT) based systems, as well as a general awareness of radiation burden, the tracer dose that should be administered remained largely unchanged in the last decade (5–7). Initially, research on these new cameras focused on decreasing the scan time while maintaining the image quality at a level similar to conventional sodium-iodide based cameras (8–10). Moreover, Nakazato et al. reported the minimum number of counts needed in CZT-SPECT that provides reproducible and similar results as compared to the number of counts acquired with a conventional camera (11). Furthermore, Einstein et al. recently validated a low-dose CZT-SPECT protocol by comparing it to conventional SPECT (12). However, these studies did not assess the minimum number of counts or scan time needed to maintain the diagnostic value acquired using CZT-SPECT. Therefore, the aim of our study was to determine the minimum product of tracer dose and scan time, while maintaining the diagnostic value of stress MPI using CZT-SPECT.

MATERIALS AND METHODS

Study population

We retrospectively included 24 consecutive patients who underwent clinically indicated stress MPI using CZT-SPECT (Discovery NM 570c, GE Healthcare). This study was approved by the local ethics committee and all patients signed a written informed consent for the use of their data for research purposes, including the collection of multiple patient-specific parameters and coronary artery disease risk factors.

Patient preparation and acquisition

Patients were requested not to use any nicotine or caffeine containing beverages for 24h and to discontinue persantin for 48h prior to scanning. Pharmacological stress was induced by intravenous adenosine (140 µg/kg/min for 6 minutes) or regadenoson (5 ml with 400 µg for 15 seconds followed by a saline flush). Only pharmacologic stress was used due to logistic reasons, in particular the high patient throughput in our center (13). A body weight dependent tracer dose of 3 MBq/kg was administered intravenously at peak stress to minimize the influence of patients' physical characteristics on the image quality (7).

Patients were scanned in supine position, 45-60 minutes post injection, with their arms placed above their heads. Prior to scanning, the patient's chest was positioned in the center of the CZT-SPECT scanner using real time persistence imaging. Images were acquired during 8 minutes using a 20% symmetrical energy window centered at 140 keV. Data were acquired in list mode.

The dedicated heart CZT-SPECT system that we used has been described repeatedly in the literature (5,6,13,14). In short, the scanner uses 19 pinhole detectors centered around the myocardium containing 32x32 pixelated (2.46x2.46 mm^2) high sensitive CZT-elements.

Images were reconstructed using 2, 4, 6 and 8 minute time frames by applying an iterative reconstruction algorithm with maximum-likelihood expectation maximization (Xeleris software version 3.0562, GE Healthcare). The scans were displayed in traditional short, vertical long and horizontal long axes. Computed tomography (CT) based attenuation correction was not applied in this study to prevent additional reproducibility influences (15). In addition, the ejection fraction (EF) and end diastolic volume (EDV) were determined for all scans (Xeleris software version 3.0562, GE Healthcare).

Quantitative analysis

The measured numbers of photon counts in the 19 pinhole detectors were determined for each scan time. Next, we created circumferential polar plots for all MPI scans representing the percentage of tracer uptake in the 17 myocardial segments (16–18). In these polar plots, the segmental uptake values were normalised and presented as the percentage of the maximum myocardial regional uptake (16–18). For each segment the uptake differences between the 8 minutes scan (further referred to as the 8 minutes reference scan) and the 2, 4 and 6 minutes scans

(further referred to as shorter scans) were determined. Next, for each of the 17 segments, the percentage of patients with an absolute segmental uptake difference of more than 5% was determined. Furthermore, also the number of segments with an uptake difference of 5% was determined for each patient for all scans. An uptake difference of 5% is generally associated with possible ischemia and is considered to significantly influence the diagnostic value (19,20). In addition, a sub-analysis assessing only the outer (1-6) and only the inner (7-17) segments was performed to account for reproducibility errors (15). Furthermore, we calculated the mean absolute differences in EF and EDV between the 8 minutes reference and shorter scans.

Qualitative analysis

The image quality of the 4, 6 and 8 minutes MPI scans was assessed to determine possible non-inferiority of the shorter scans compared to the 8 minutes reference scan. Three experienced nuclear medicine physicians scored the reconstructed images by consensus by using a 4 point rating scale (1-poor, 2-fair, 3-good, 4-excellent). The following parameters were considered: myocardial shape, uptake density and uniformity, endocardial and epicardial edge definition and myocardium to noise ratio (7). In addition, each observer scored the diagnostic confidence in image interpretation as sufficient or insufficient, where sufficient indicates enough confidence to make a follow-up decision based on image quality. All readers were blinded for patient characteristics and scan times. Moreover, all scans were presented in random order.

Statistics

Patient-specific parameters and characteristics were determined as mean ± standard deviation (sd) using Stata (StataSE 12.0). The mean absolute differences in segmental uptake values, EF and EDV with the 8 minutes reference scans were compared between the 2, 4 and 6 minutes scans using Wilcoxon signed-rank test. The number of segments influencing the diagnostic value per patient was compared between the 2, 4 and 6 minutes scans using a Wilcoxon signed-rank test. Furthermore, the image quality between the 8 minutes reference scan and the 4 and 6 minutes scans was also compared using the Wilcoxon signed-rank test. To compare the mean diagnostic confidence in image interpretation between the 8 minutes reference scan and shorter scans, the Cochran's Q-test was used. The level of statistical significance was set to 0.05 for all statistical analyses.

RESULTS

The baseline characteristics of all included patients are summarized in Table 1.

Quantitative analysis

The mean measured photon counts was 303 ± 54, 604 ± 105, 902 ± 157 and 1196 ± 211 kilo counts using a scan time of 2, 4, 6 and 8 minutes, respectively. The mean absolute differences in tracer uptake between the 8 minutes reference and the shorter scan times in each of the 17 segments increased significantly using shorter scan times ($p<0.001$), as shown in Table 2. These differences decreased from 6.2 ± 4.8% to 3.4 ± 3.0% and 2.2 ± 2.1% using the 2, 4 or 6 minutes scans, respectively.

For each of the 17 segments, a decrease in scan time led to more patients in whom the diagnostic value was influenced, as illustrated in Figure 1 and 2. The outer segments (segments 1 to 6) showed far more patients in whom the diagnostic value was influenced than the inner segments (segments 7 to 17) did when using the 4 and 6 minutes scans.

The use of the 2 minutes scans led to more segments in which the diagnostic value per patient was influenced, as illustrated in Figure 3. The mean number of influenced segments compared to the 8 minute scan decreased significantly from 7.7 ± 5.4 to 2.0 ± 3.1 and 0.8 ± 1.7 using the 2, 4 and 6 minutes scans, respectively ($p\leq0.013$).

The mean absolute difference in EF and EDV comparing the 8 minutes reference scan to the shorter scans increased when decreasing scan time, as shown in Table 2. The absolute differences in EF differed significantly between the reference scan and the 2, 4 and 6 minutes scans ($p<0.04$). Yet, the absolute differences in EDV were only significant when comparing the 2 with the 6 minutes scans ($p<0.04$). No significant differences were found comparing the mean absolute difference of the 4 and 6 minutes scans for both EF and EDV.

Qualitative analysis

As the 2 minutes scans were found to be inferior to the 4, 6 and 8 minutes scans, they were not incorporated in the image quality assessment.

The image quality was scored good or excellent by the physicians for the 4, 6 and 8 minutes scans in 46%, 75% and 67%, respectively, as shown in Figure 4. No difference in image quality was found between the 6 and 8

minutes scans (p=0.43). However, the mean image quality of the 4 minutes scans was inferior to the 6 and 8 minutes scans (p<0.05).

The mean diagnostic confidence in image interpretation remained unchanged when using shorter scan times (p=0.93) as both the 4 and 6 minutes scans yielded adequate diagnostic confidence in 92% of all cases, versus 93% using the 8 minutes scans.

DISCUSSION

In this study we have demonstrated that 6 minutes was the shortest acquisition time that maintained the diagnostic value in terms of segmental uptake values, EF and EDV, in patients administered with 3 MBq/kg for stress MPI using CZT-SPECT. Scan times of 2 or 4 minutes led to a substantially lower diagnostic value and are therefore not recommended.

Our results can be compared with previous reported low-dose protocols using the tracer dose and scan time product (TDSTP). The TDSTP accounts for both the recommended tracer dose and the scan time, and therefore allows easy comparison between varying protocols. Assuming a patient of 80 kg, our proposed TDSTP is 1440 MBq·min for stress imaging (18 MBq·min/kg). This is even lower than the recently proposed low-dose protocol by Einstein et al. with a TDSTP of 1690 for an average patients (12). Yet, the minimal tracer dose to administer was not determined in this study and rest rather than stress images were used. Moreover, our proposed protocol is higher than the previously reported low-dose CZT-SPECT protocols using 1210 MBq·min, as suggested by Nakazato et al. (11), and 981 MBq·min, as suggested by Herzog et al. (8). Yet, both research groups determined the TDSTP to achieve the same image quality and/or diagnostic value as obtained with their conventional gamma camera instead of aiming for the minimum TDSTP needed to maintain the diagnostic value acquired using a CZT-based SPECT camera. Thereby, the TDSTP for a conventional camera differed between both studies, which might explain the differences in the recommended TDSTP using a CZT-camera. Furthermore, the dose regime proposed by Herzog et al. (8) is comparable to a scan time of 4 minutes in our study. Considering our results, this can thus be associated to an inferior diagnostic value and image quality in comparison to the use of a scan time of 6 or 8

minutes. This might indicate that CZT-SPECT provides a higher diagnostic value and image quality than conventional cameras. This indication is in agreement with two previous studies. Mouden et al. compared the need for additional imaging and the 1-year outcome between CZT-SPECT and conventional cameras (13). In this study they showed that using CZT-SPECT resulted in more normal scans with identical clinical outcome after 1-year follow-up. Furthermore, although Einstein et al. did not find any diagnostic differences between conventional and CZT-SPECT when using a low-dose protocol, they did find an improvement in image quality using CZT-SPECT (12).

Although differences were observed in segmental uptake values, EDV and EF between the 6 and 8 minutes scans, the 6 minutes scans were considered to achieve the same diagnostic value as the 8 minutes scans. Koopman et al. showed that the diagnostic value was influenced in 18%-43% of all outer segments and 0%-16% of all inner segments due to reproducibility errors (15). Comparing these errors with our data shows that the observed differences in segmental uptake for the 6 minutes scans are likely due to reproducibility errors. The 2 or 4 minutes scans revealed higher differences than the reported reproducibility errors, indicating the loss in diagnostic value for these scan times. In addition, Cherck et al. reported a reproducibility error in determining the EF using CZT-SPECT of more than 5% in the sd of the differences (21). Although we did not determine the sd of the difference in EF in this study, the results of Cherck et al. suggest that a large part of our observed differences in EF will presumably be due to reproducibility errors.

Several assumptions were made in this study. Firstly, the 8 minutes reference scan (TDSTP of 24 MBq·min/kg) was considered to provide a sufficient diagnostic value in all patients. Although it was not tested whether a higher TDSTP would further improve diagnostic value, a TDSTP of 24 MBq·min/kg is almost twice as high as the TDSTP as previously suggested for CZT-SPECT (8,11). Moreover, the influence of patient's physical characteristics on the study outcomes was considered to be eliminated due to the use of a patient-specific dose protocol (7). Secondly, the diagnostic value was influenced in the quantitative assessment when using shorter scan times but this was not observed in the qualitative assessment, as illustrated in Figure 2 and 4. The random and blinded design of the qualitative image assessment resulted in the scoring of the appearance of the scans and not on the emerging of possible defects, corresponding with the diagnostic value. Therefore, the qualitative assessment should solely be interpreted as a measurement of scan appearance instead of diagnostic value. This might also explain the absence

of differences in the scored diagnostic confidence between the 4, 6 and 8 minutes scans. Thirdly, only the minimum TDSTP in stress MPI was determined. Yet, we recommend the same TDSTP for rest as for stress MPI when using a two-day protocol, as mentioned in EANM/ESC and ASNC procedural guidelines (16,17). When using a one-day stress-optional rest protocol, we assume that administering a rest dose of triple the stress tracer dose, as recommended in guidelines(16,17), would automatically lead to sufficient image quality in rest MPI. Finally, CT based attenuation correction was not applied in this study to prevent inclusion of additional errors (15). Yet, when attenuation correction is applied on (hypothetically) identical 6 and 8 minutes scans, they will still be identical after correction. Moreover, as indicated by Heller et al., attenuation correction will only lead to more reliable diagnosis when the original scans have a sufficient amount of photon counts (22). Hence, applying attenuation correction on the 2 or 4 minutes scans, associated with an insufficient amount of photon counts, would only introduce additional errors, possibly influencing the results.

Our findings show a possible reduction of 25% in tracer dose or scan time when applying a dose regimen of 24 MBq·min/kg (7). Using a 10 minutes acquisition time, the administered dose for stress MPI will be 1.8 MBq/kg, associated with an effective dose of approximately 1 mSv for an average patient of 80 kg (23). In comparison, the mean effective dose associated with a CT angiography can be as low as 3 mSv whereas a diagnostic cardiac catheterization can be associated with a mean effective dose of 7 mSv (4,24). Consequently, when this proposed dose reduction will be widely adopted in clinical practice, MPI might not be the largest contributor to the effective dose in the general population anymore (4).

CONCLUSION

A scan time of 6 minutes is the shortest acquisition time that does not affect the diagnostic value when applying a tracer dose of 3 MBq/kg for CZT-SPECT stress MPI. Hence, the product of tracer dose and scan time can be minimized to 18 MBq·min/kg. This may lower the effective radiation dose for patients to values below 1 mSv.

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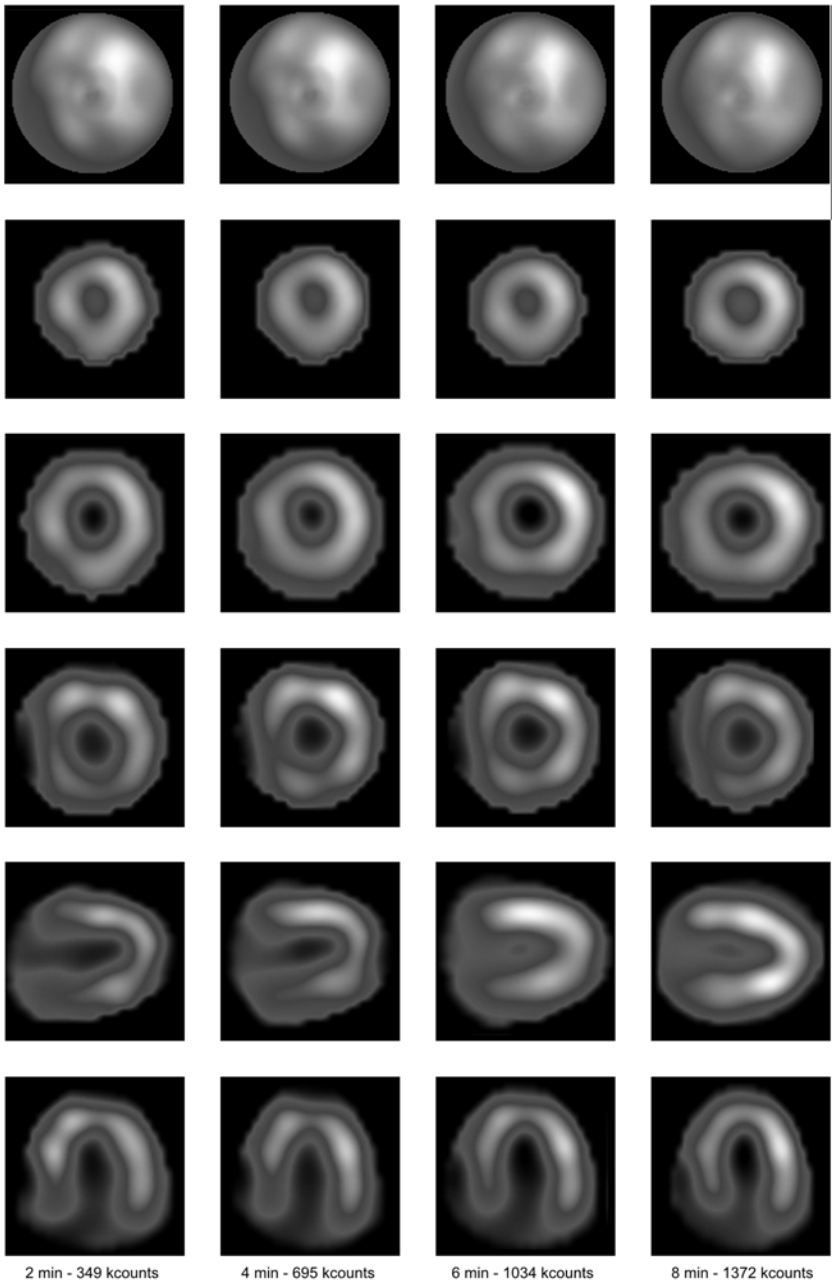

FIGURE 1. *An example of stress MPI using CZT-SPECT scans with varying scan times: from left to right, images of the 2, 4, 6 and 8 minute scan with their corresponding measured photon counts. The scans are from a typical patient (55 year-old female, 61 kg, BMI 21.1 kg/m^2, administered with 187 MBq). The corresponding bull's-eye, three slices of the short axes (from apical to basal),the vertical long and horizontal long axes are shown from top to bottom. For all axes, the same locations are shown for each scan time.*

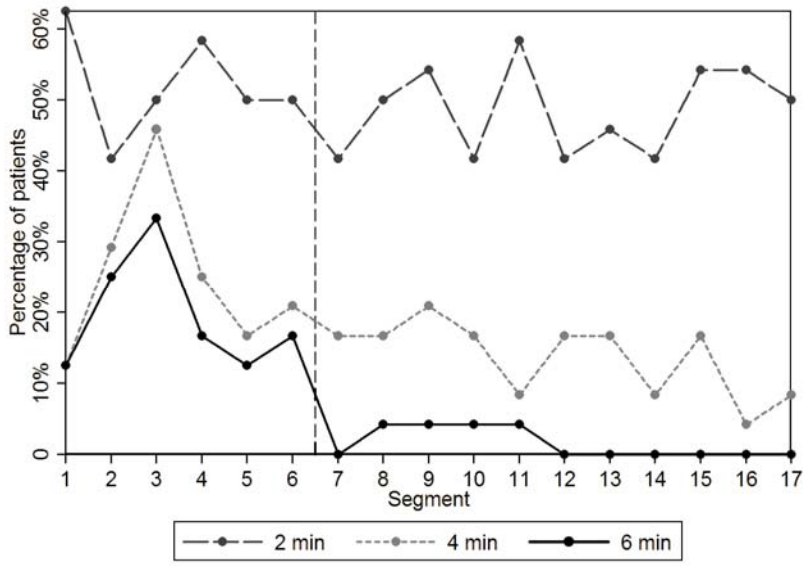

FIGURE 2. *The percentage of patients in whom the absolute difference in segmental uptake value between the 8 minutes reference scan and 2, 4 and 6 minutes scans was more than 5%, for each of the 17 segments. For example, in 42% of the patients segment 7 was affected when reducing scan time to 2 min, whereas this was 17% and 0% for 4 and 6 minutes scans, respectively. The vertical dashed line represents the separation between the inner and outer segments.*

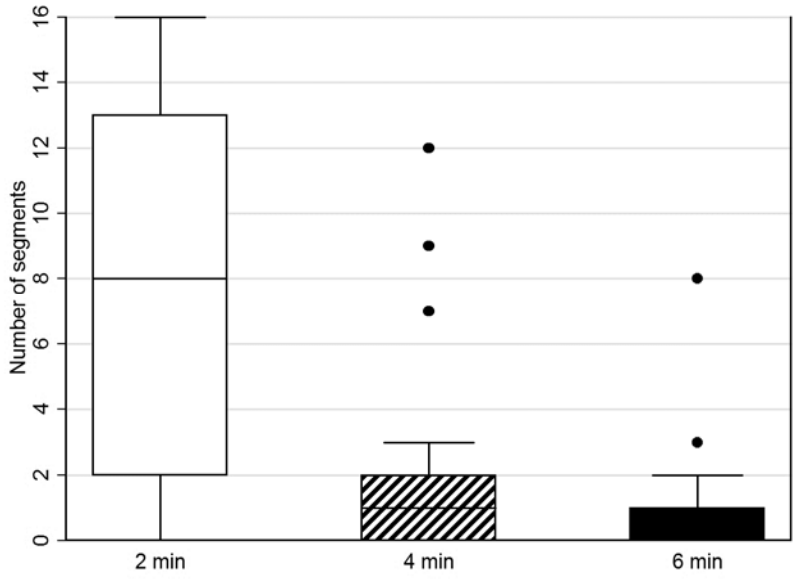

FIGURE 3. *Boxplot of the number of segments per patient that showed a segmental uptake difference of 5% or more compared to the 8 minute reference scan for the 2, 4 and 6 minutes scans. The black lines in the box represent the median, the box demarks the 25th and 75th percentile (interquartile range) and the whiskers the highest and lowest number of segments that are no outliers. Values that are more than 1.5 times the interquartile range are represented by the dots.*

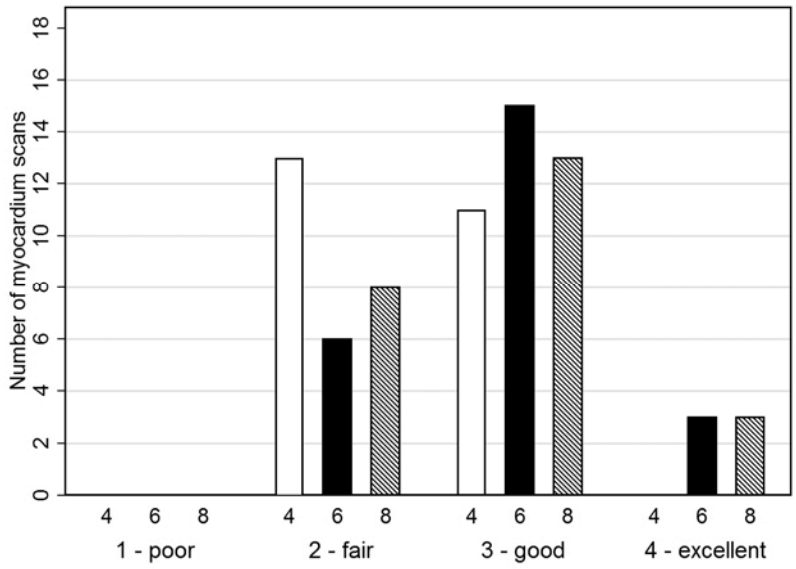

FIGURE 4. *Scored image quality for the myocardial scans for all 24 patients using scan times of 4, 6 and 8 minutes. Image quality was scored blinded on a four point grading scale by consensus of three experienced nuclear medicine physicians. The image quality using the 4 minutes scans was significantly lower than when using the 6 or 8 minutes scans ($p<0.05$).*

TABLES

TABLE 1. *Baseline characteristics of all 24 stable patients with suspected coronary artery disease referred for CZT-SPECT imaging including the reported scan results.*

Data are presented as percentages or mean ± sd

Characteristic	
Age (years)	65.2 ± 12.6
Male gender (%)	41.7
Body weight (kg)	78.3 ± 15.6
Height (cm)	171 ± 10
BMI (kg/m^2)	26.7 ± 4.6
Normal MPI scan (%)	75.0
Ischemic defect (%)	16.7
Non reversible defect (%)	25.0

TABLE 2. *Mean absolute differences and sd in segmental uptake values, ejection fractions and end diastolic volumes comparing the 8 minutes reference scan to the shorter 2, 4 and 6 minutes scans.*

	2 versus 8 min	4 versus 8 min	6 versus 8 min
Uptake values of all segments (%)	6.2 ± 4.8	3.4 ± 3.0	2.2 ± 2.1
Uptake values of inner segments (%)	6.0 ± 4.3	2.9 ± 2.4	1.7 ± 1.4
Uptake values of outer segment (%)	6.7 ± 5.5	4.2 ± 3.7	3.2 ± 2.7
Ejection fraction (%)	6.1 ± 4.8	4.3 ± 4.7	3.6 ± 3.2
End diastolic volume (ml)	6.4 ± 5.4	4.0 ± 2.3	3.8 ± 3.9