Diagnostic Performance of a Cadmium-Zinc-Telluride Single-Photon Emission Computed Tomography System With Low-Dose Technetium-99m as Assessed by Fractional Flow Reserve

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Background: Although stress single-photon emission computed tomography (SPECT) using a cadmium-zinc-telluride (CZT) camera facilitates radiation dose reduction, only a few studies have evaluated its diagnostic accuracy in Japanese patients by applying fractional flow reserve (FFR) measurements.

Methods and Results: We prospectively evaluated 102 consecutive patients with suspected or known coronary artery disease with a low-dose stress/rest protocol (99mTc radiotracer 185/370 MBq) using CZT SPECT. Within 3 months, coronary angiography was performed and a significant stenosis was defined as ≥90% diameter narrowing on visual estimation, or as a lesion of <90% and ≥ 50% stenosis with FFR ≤0.80. To detect individual coronary stenosis, the respective sensitivity, specificity, and accuracy were 86%, 75%, and 82% for left anterior descending artery stenosis, 76%, 81%, and 79% for left circumflex artery stenosis, and 87%, 92%, and 90% for right coronary artery stenosis. When limited to 92 intermediate stenotic lesions in which FFR was measured, stress SPECT showed 77% sensitivity, 91% specificity, and 84% accuracy, whereas the diagnostic value decreased to 52% sensitivity, 68% specificity, and 58% accuracy based only on visual estimation of ≥75% diameter narrowing.

Conclusions: CZT SPECT demonstrated a good diagnostic yield in detecting hemodynamically significant coronary stenoses as assessed by FFR, even when using a low-dose 99mTc protocol with an effective dose ≤5 mSv. (Circ J 2016; 80: 1217 – 1224)

Key Words: Cadmium-zinc-telluride camera; Coronary artery disease; Diagnostic accuracy; Fractional flow reserve; Radiation dose reduction
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Methods

Subjects

We prospectively enrolled 102 consecutive patients with suspected or known CAD who had undergone stress myocardial SPECT using the CZT SPECT system with a low-dose 99mTc radiotracer (555 MBq) 1-day protocol, and who had also given written informed consent to participate in this study between July 2013 and December 2015. The clinical grounds for suspected or known CAD were based on clinical symptoms, coronary risk profiles, ECG findings, or past medical history. Patients requiring routine angiographic follow-up after successful percutaneous coronary intervention were also included. The exclusion criteria were as follows: (1) age <20 years, (2) acute myocardial infarction or unstable angina, (3) acute heart failure, (4) recent history of acute coronary syndrome within 1 month before the SPECT study, (5) history of coronary artery bypass grafting, (6) hypertrophic or dilated cardiomyopathy, (7) severe valvular heart disease requiring surgical operation, (8) bypass grafting, (9) history of drug allergy to 99mTc radiotracers, (10) serious coronary risk profiles, ECG findings, or past medical history.

Stress Myocardial SPECT Imaging

The study protocol during the 1-day schedule for stress myocardial SPECT is shown in Figure 1. This protocol, which is designed with a half-dose of 99mTc-labeled radiotracer and doubled scan time compared with the standard protocol using 1110 MBq of 99mTc-labeled radiotracer, has been validated in previous studies based on image quality and the myocardial counts of the radiotracer. Exercise stress using symptom-limited multistep exercise with a bicycle ergometer was performed by 42 patients. Technetium-99 m tetrofosmin or sestamibi (185 MBq) was given intravenously at 85% of age-adjusted predictive maximal heart rate (target heart rate), or when chest pain or ST-segment depression >0.1 mV or leg fatigue developed. Exercise was then continued for 1 min at the same previous level. At 1 h after the last exercise session, ECG-gated SPECT was performed and 4 h later, the patients were given 99mTc-tetrofosmin or sestamibi (370 MBq) while at rest. A further 60 min later, ECG-gated SPECT images at rest were obtained.

Adenosine triphosphate (ATP) loading SPECT with a half-dose of 99mTc-labeled radiotracer (99mTc-tetrofosmin or sestamibi) was performed in 60 patients. Anti-ischemic agents were withdrawn 24 h before the SPECT examination. Patients were also requested not to drink any beverage containing caffeine for at least 12 h before the test. ATP disodium (0.16 mg·kg⁻¹·min⁻¹) was administered intravenously for 6 min, and 3 min after its administration, 99mTc-tetrofosmin or sestamibi (185 MBq) was given intravenously. Image acquisition was started 60 min later. After 4 h, the patients were given 99mTc-tetrofosmin or sestamibi (370 MBq) while at rest and 1 h later, ECG-gated SPECT images were acquired at rest. The estimated total radiation exposure with this protocol was in the range of 4.24–4.79 mSv. The effective dose was determined on the basis of the data in ICRP publication 106.

Data were acquired in the list mode using the CZT SPECT system (Discovery NM 530c; GE Healthcare, Haifa, Israel). This new gamma camera system is equipped with a multipinhole collimator and 19 stationary CZT semiconductor detectors, which simultaneously focus on the heart to maximize the efficiency of SPECT imaging. The CZT elements were 2.46×2.46 mm in size, and each detector contained 32×32 pixelated 5-mm thick elements. The stationary-arrayed semiconductor detectors simultaneously acquire all the views necessary for tomographic reconstruction, saving the time required by conventional cameras for acquisition while rotating around the subject. Image acquisition was performed in the supine and prone positions after stress for 10 min and 6 min, respectively, and in the supine position at rest for 6 min. For prone position imaging, patients lay prone on the table and the detectors were positioned underneath the table. Interpretation of perfusion abnormality in the inferior wall was judged by the combination of supine and prone position images, which can decrease the frequency of attenuation artifacts in the inferior wall.

SPECT images were reconstructed on a workstation (Xeleris; GE Healthcare) that utilizes a new dedicated iterative algorithm with integrated collimator geometric modeling, using maximum penalized likelihood iterative reconstruction to obtain perfusion images in standard axes. For both stress and rest image reconstructions, 70 iterations were performed. A Butterworth filter (order 15; cut-off frequency 0.28 cycles/cm) was applied to the reconstructed slices. When obtaining ECG-gated images, the R-R interval was divided by the R wave trigger into 8 equal portions. End-diastolic and end-systolic myocardial perfusion images were obtained using this method. All the patients were in sinus rhythm during image acquisition. No scatter or attenuation corrections were applied.

Table 1. Clinical Characteristics of the Study Patients With CAD

<table>
<thead>
<tr>
<th>n</th>
<th>102</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69±10</td>
</tr>
<tr>
<td>Sex (M/F [%])</td>
<td>80/22 [78/22]</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162±8</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>64±11</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24±3</td>
</tr>
<tr>
<td>Coronary risk factors</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>81 (79)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>46 (45)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>64 (63)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td>β-blocker</td>
<td>50 (49)</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>49 (48)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Nicorandil</td>
<td>23 (23)</td>
</tr>
<tr>
<td>Statin</td>
<td>57 (56)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>30 (29)</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>59 (58)</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Type of stress (exercise/ATP [%])</td>
<td>42/60 [41/59]</td>
</tr>
<tr>
<td>Radiotracer for SPECT study</td>
<td></td>
</tr>
<tr>
<td>99mTc-tetrofosmin</td>
<td>68 (67)</td>
</tr>
<tr>
<td>99mTc-sestamibi</td>
<td>34 (33)</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD or n (%). ATP, adenosine triphosphate disodium; CABG, coronary artery bypass grafting; CAD, coronary artery disease; PCI, percutaneous coronary intervention.

The study protocol during the 1-day schedule for stress myocardial SPECT is shown in Figure 1. This protocol, which is designed with a half-dose of 99mTc-labeled radiotracer and doubled scan time compared with the standard protocol using 1110 MBq of 99mTc-labeled radiotracer, has been validated in previous studies based on image quality and the myocardial counts of the radiotracer. Exercise stress using symptom-limited multistep exercise with a bicycle ergometer was performed by 42 patients. Technetium-99 m tetrofosmin or sestamibi (185 MBq) was given intravenously at 85% of age-adjusted predictive maximal heart rate (target heart rate), or when chest pain or ST-segment depression >0.1 mV or leg fatigue developed. Exercise was then continued for 1 min at the same previous level. At 1 h after the last exercise session, ECG-gated SPECT was performed and 4 h later, the patients were given 99mTc-tetrofosmin or sestamibi (370 MBq) while at rest. A further 60 min later, ECG-gated SPECT images at rest were obtained.

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Low-Dose Technetium SPECT

Image Analysis
In accordance with a previous method, each SPECT image was divided into 17 segments. Radiotracer accumulation in the myocardium was visually rated according to the criteria of the American Heart Association (AHA), and intracoronary pressure was measured in cases of intermediate lesions on CAG, which were defined as lesions of <90% and ≥50% diameter narrowing by visual estimation. A 0.014-in guidewire with a mounted pressure sensor (PressureWire™, St. Jude Medical Inc, St. Paul, MN, USA) was placed across the lesion. To induce a maximal hyperemic vascular response, 8 mg and 12 mg of papaverine hydrochloride, a vasodilator of resistance vessels, were injected into the right and left coronary arteries, respectively. Under conditions of maximal hyperemia, simultaneous recording of aortic pressure and distal coronary pressure was performed. FFR was calculated as the ratio of hyperemic mean distal coronary pressure to mean aortic pressure. A significant coronary stenosis was defined as ≥90% diameter narrowing on visual estimation or as a lesion of <90% and ≥50% stenosis with an FFR of ≤0.80.

Statistical Analysis
Results are expressed as mean±SD, or number and frequency. Student’s t-test was used to compare the means of the continuous variables, and the chi-square test was used to analyze the contingency tables. The sensitivity, specificity, and accuracy of the CZT SPECT system using a low-dose 99m Tc radiotracer in detecting significant coronary restenosis were analyzed on a per-vessel basis. A P-value <0.05 was considered to indicate a statistically significant difference. Statistical analyses were performed using the SPSS-PC+ computation program (version 22.0, IBM SPSS Statistics, New York, NY, USA).

Results
Patients Characteristics
The clinical characteristics of the patients, including medications at the time of the study, are summarized in Table 1. The mean age of the patient population was 69 years, and 78% were men. The mean body mass index was 24.5 kg/m². Previous myocardial infarction had occurred in 30 patients (29%). Remote percutaneous coronary intervention was performed in 59 patients (58%). Of the classical coronary risk factors, the prevalence of hypertension was the highest, and that of diabetes mellitus was 45%.

All of the 102 patients successfully underwent both stress myocardial SPECT using CZT SPECT and CAG. Of these 102 patients, 57 (56%) had intermediate lesions in at least one of the 3 major coronary arteries. In the per-vessel analysis, 92 coronary vessels out of the 306 coronary arteries were regarded to have intermediate lesions and were measured with myocardial FFR. Of these 92 intermediate lesions, the average FFR was 0.79±0.11, with 48 lesions having an FFR ≤0.80. The remaining 214 arteries were judged to have either a severe stenosis with ≥90% diameter narrowing (n=85) or a mild stenosis with <50% diameter narrowing (n=129) by visual estimation. Based on these anatomic and physiologic analyses of coronary arteries, left main or 3-vessel CAD was
Among the 102 patients, the 99m Tc radiotracers used were CZT SPECT Findings

Table 2

<table>
<thead>
<tr>
<th>Angiographic findings</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insignificant lesion</td>
<td>27 (27)</td>
</tr>
<tr>
<td>1-vessel disease</td>
<td>31 (30)</td>
</tr>
<tr>
<td>2-vessel disease</td>
<td>30 (29)</td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>14 (14)</td>
</tr>
</tbody>
</table>

Stenotic coronary arteries

<table>
<thead>
<tr>
<th>Diameter narrowing ≥80%</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Left anterior descending</td>
<td>34 (33)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>26 (26)</td>
</tr>
<tr>
<td>Right coronary</td>
<td>25 (25)</td>
</tr>
<tr>
<td>Intermediate lesion (n=92) and FFR ≤0.80</td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>32 (31)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Right coronary</td>
<td>13 (13)</td>
</tr>
<tr>
<td>Diameter narrowing ≥90% or FFR ≤0.80</td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>66 (65)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>29 (28)</td>
</tr>
<tr>
<td>Right coronary</td>
<td>38 (37)</td>
</tr>
</tbody>
</table>

Data are expressed as n (%). CAD, coronary artery disease; FFR, fractional flow reserve.

observed in 14 patients (14%), 2-vessel CAD in 30 (29%), 1-vessel CAD in 31 (30%), and insignificant lesions in the remaining 27 (27%). Patients with left main CAD were considered to have stenosis in both the left anterior descending (LAD) and left circumflex (LCx) coronary arteries. The distribution of significant stenoses was 66 in the LAD, 29 in the LCx, and 38 in the right coronary artery (RCA) (Table 2).

CZT SPECT Findings

Among the 102 patients, the 99mTc radiotracers were tetrofosmin in 68 patients and sestamibi in 34 (Table 1). The average SSS, SRS, and SDS in all the patients was 12.9±9.2 (range 20–77), 7.5±8.2 (range 8–183), and 5.0±4.79 mSv, which is less than the effective dose estimation of ≥99 mTc 1-day protocol for myocardial perfusion SPECT imaging in a patient with normal myocardial perfusion (Figure 1).11,20 as cardiac imaging procedures have come under increasing scrutiny because of the potential risks attributable to ionizing radiation.1,2 The present study demonstrated good diagnostic performance of CZT SPECT using 555 MBq of a 99mTc radiotracer, with sensitivities of 76%, 86%, and 87%, specificities of 75%, 81%, and 92%, and accuracies of 79%, 82%, and 90% in detecting an individual coronary artery stenosis defined by anatomic and physiologic assessments with FFR measurements (Figure 2). With this low-dose 99mTc protocol, the estimated total radiation exposure is in the range of 4.24–4.79 mSv, which is less than the effective dose estimate of 8 mSv related to conventional chest computed tomography.30

### Diagnostic Performance of CZT SPECT

The diagnostic performance of the CZT SPECT myocardial imaging on a per-vessel basis is shown in Figure 2. To detect individual coronary stenosis, by applying a cut-off value of 0.80 in FFR, the respective sensitivity, specificity, and accuracy were 86%, 75%, and 82% for LAD stenosis, 76%, 81%, and 79% for LCx stenosis, and 87%, 69%, and 76% for RCA stenosis (Figure 2A). The combination of supine and prone imaging resulted in a higher specificity for RCA disease than supine imaging alone (92% vs. 69%) with an improvement in accuracy from 76% to 90% (Figure 2B). When the diagnostic value of CZT SPECT imaging was limited to 92 intermediate stenotic lesions in which FFR was measured, stress SPECT showed 77% sensitivity, 91% specificity, and 84% accuracy, whereas the diagnostic value decreased to 52% sensitivity, 68% specificity, and 58% accuracy based only on visual estimation of ≥75% diameter narrowing derived from the AHA criterion (Figure 3). Figure 4 shows an example of CZT SPECT imaging in a patient with normal myocardial perfusion on SPECT imaging but intermediate coronary lesions in the LAD and RCA on invasive CAG, which were functionally insignificant by FFR measurement.

### Discussion

**Major Findings**

To achieve radiation dose reduction, we recently developed a low-dose 99mTc 1-day protocol for myocardial perfusion SPECT imaging for Japanese patients, in which the acquisition time is still shorter than that of the conventional Anger camera system (Figure 1).11,20 as cardiac imaging procedures have come under increasing scrutiny because of the potential risks attributable to ionizing radiation.1,2 The present study demonstrated good diagnostic performance of CZT SPECT using 555 MBq of a 99mTc radiotracer, with sensitivities of 76%, 86%, and 87%, specificities of 75%, 81%, and 92%, and accuracies of 79%, 82%, and 90% in detecting an individual coronary artery stenosis defined by anatomic and physiologic assessments with FFR measurements (Figure 2). With this low-dose 99mTc protocol, the estimated total radiation exposure is in the range of 4.24–4.79 mSv, which is less than the effective dose estimate of 8 mSv related to conventional chest computed tomography.30

**Radiation Dose Reduction**

Considerable attempts have been made in reducing the ionizing radiation associated with cardiac imaging procedures.2-4 In 2012, a meeting of experts was organized by the International Atomic Energy Agency (IAEA), and they developed criteria for best practice in nuclear cardiology laboratories such as avoidance of 201Tl stress imaging protocols, avoidance of excessive 99mTc administration, and utilization of camera-based dose-reduction strategies, among others.5 The ASNC also recommends that 50% or more patients undergoing myocardial SPECT receive a total effective dose of ≤9 mSv.2

Despite these recommendations, recent surveillance has revealed disappointing results. In the United States, the Inter-societal Accreditation Committee data showed that the
Low-Dose Technetium SPECT

The average effective dose in 1,074 laboratories was 14.9±5.8 mSv, and only 1.5% of the participating laboratories met current recommendations for an average laboratory radiation exposure ≤9 mSv. By contrast, almost half of the participating laboratories in Europe fulfilled the aforementioned radiation dose reduction, although only 102 institutions were involved in the report. In 2012, the 7th Nationwide Survey was conducted to investigate the status of nuclear medicine practice in Japan. In contrast to the IAEA criteria for best practice, 52.4% of myocardial SPECT studies were performed using 201Tl in Japan. Regarding the dose of 99mTc radiotracers, a large Japanese multicenter study involving 4,629 patients disclosed that almost two-thirds of the registered patients were exposed to ionizing radiation ≤9 mSv, and a 99mTc-tetrofosmin dose ≤700 MBq was administered only in 1.3% of the patients. Although these reports are informative for the accumulation of data on radiation exposure from myocardial perfusion imaging, the quality of SPECT imaging and the diagnostic accuracy of the individual study protocols were not evaluated in those surveys. In other words, to assure a good diagnostic yield of stress myocardial SPECT, the recommendations issued by the ASNC and IAEA may be too difficult to achieve. The present results showing good diagnostic performance of CZT SPECT applying a low-dose 99mTc protocol with a radiation exposure ≤5 mSv is encouraging.

![Figure 2](image1.png)

**Figure 2.** Diagnostic yield of CZT SPECT in detecting a significant coronary stenosis. (A) Sensitivities, specificities, and accuracies for the detection of significant coronary artery disease on a per-vessel basis, by applying a cut-off value of 0.80 in fractional flow reserve. (B) Comparison of sensitivity, specificity, and accuracy of supine only vs. combined supine and prone imaging for the detection of RCA disease. CZT, cadmium-zinc-telluride; LAD, left anterior descending coronary artery; LCx, left circumflex artery; RCA, right coronary artery; SPECT, single-photon emission computed tomography.

![Figure 3](image2.png)

**Figure 3.** Comparison of diagnostic accuracy of CZT SPECT in limiting to 92 intermediate stenotic coronary lesions. CZT, cadmium-zinc-telluride; FFR, fractional flow reserve.
Apart from another type of CZT SPECT (D-SPECT; Spectrum Dynamics, Caesarea, Israel), several studies have evaluated the relation of stress SPECT imaging using Discovery NM 530c with invasive CAG, although only a few reports have addressed individual vessel detection with this new CZT SPECT.

Nishiyama et al and Duvall et al have reported respective sensitivities and specificities of 53–56% and 66–81% for LAD stenosis, 66–72% and 66–74% for LCx stenosis, and 64–74% and 68–70% for RCA stenosis, but radiation dose reduction was not attempted in those studies.

Using low-dose $^{99m}$Tc-tetrofosmin myocardial perfusion CZT SPECT, Esteves et al reported 68% sensitivity and 69% specificity for RCA stenosis, and 76% to 90% accuracy for detecting LCx and RCA stenosis.

Diagnostic Value of CZT SPECT

In the present study, CZT SPECT with a low-dose $^{99m}$Tc protocol showed the highest sensitivity of 87% in detecting RCA stenosis, and the highest specificity of 81% was observed in detecting LCx stenosis based only on SPECT imaging performed while the patient was supine. Although the diagnosis of coronary stenosis in the RCA based only on data acquired in the supine position was problematic for the CZT SPECT system, owing to the presence of hepatic and bowel isotope activity, prone image acquisition helped to improve the diagnostic specificity and accuracy from 69% to 92% and from 76% to 90%, respectively (Figure 2).

Apart from another type of CZT SPECT (D-SPECT; Spectrum Dynamics, Caesarea, Israel), several studies have evaluated the relation of stress SPECT imaging using Discovery NM 530c with invasive CAG, although only a few reports have addressed individual vessel detection with this new CZT SPECT.

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Using low-dose $^{99m}$Tc-tetrofosmin myocardial perfusion CZT SPECT, Esteves et al reported 68% sensitivity and 69% specificity for RCA stenosis, and 76% to 90% accuracy for detecting LCx and RCA stenosis.
specificity for LAD stenosis, 63% sensitivity and 81% specificity for LCx stenosis, and 58% sensitivity and 78% specificity for RCA stenosis, and with their protocol, the estimated effective radiation dose was 6.0 mSv. Using a low-dose 99mTc-tetrofosmin protocol with an effective dose range of 4.55–6.84 mSv, Gimelli et al reported a higher sensitivity of 92% and a specificity of 85% for LAD stenosis, 88% and 74% for LCx stenosis, and 86% and 73% for RCA stenosis, respectively. In line with that report, the current study demonstrated high diagnostic accuracy of a low-dose 99mTc protocol, although the gold standard for CAD diagnosis was different: by anatomic analysis only in the previous study vs. by combined anatomic and physiologic analyses with FFR measurements in the current study.

Importance of FFR Measurements for CAD Diagnosis
Using a prospective approach to invasive coronary evaluation, more than half of the patients in the present study had intermediate lesions in at least one of the 3 major coronary arteries. This is in contrast to the study by Gimelli et al in which only mediate lesions in at least one of the 3 major coronary arteries. Using a prospective approach to invasive coronary evaluation, importance of FFR measurements for CAD diagnosis

Conclusions
CZT SPECT imaging demonstrated good diagnostic yield in detecting a hemodynamically significant coronary stenosis as assessed by FFR even with the use of a low-dose 99mTc (185/370 MBq) 1-day protocol with an effective dose ≤5 mSv.

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Disclosures
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