Comparison Between Ultrafast and Standard Single-Photon Emission CT in Patients With Coronary Artery Disease

A Pilot Study

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Background—A novel technology has been developed for ultrafast (UF) single-photon emission CT (SPECT) myocardial perfusion imaging by using a pinhole collimation design and multiple cadmium zinc telluride crystal arrays. The purpose of this study was to compare myocardial perfusion imaging obtained by UF-SPECT with standard (S) SPECT in patients with known or suspected coronary artery disease.

Methods and Results—A total of 34 patients underwent single-day $^{99m}$Tc-tetrofosmin stress/rest myocardial perfusion imaging. UF-SPECT was performed 10 minutes before S-SPECT. Images were qualitatively analyzed, and the summed stress score and summed rest score were calculated. The segmental tracer uptake value (percentage of maximum myocardial uptake) also was quantified for both UF- and S-SPECT. When only 29 of 34 patients with significant coronary lesions were analyzed, the summed stress score was $10.1 \pm 4.4$ versus $6.4 \pm 2.9$, respectively, for UF- and S-SPECT ($P=0.002$). Qualitative and quantitative per-patient analysis showed similar results in detection of coronary artery disease for UF- and S-SPECT. In contrast, per-vessel analysis demonstrated higher regional sensitivity of UF-versus S-SPECT. UF-SPECT showed higher sensitivity in detecting multivessel disease ($P=0.003$) versus S-SPECT.

Conclusions—This pilot study confirms that UF-SPECT provides high-quality fast myocardial perfusion imaging and suggests that it may allow a more-accurate evaluation of both extent and severity of myocardial ischemia in patients with coronary artery disease. (Circ Cardiovasc Imaging. 2011;4:51-58.)

Key Words: tomography emission-computed single-photon myocardial ischemia coronary artery disease

Over the past 2 decades, a number of technical innovations in nuclear cardiology have led to a mature technique that is widely used clinically. Single-photon emission CT (SPECT) imaging has replaced planar imaging, whereas technetium-based perfusion imaging agents have largely replaced thallium-201. The addition of ECG gating to myocardial perfusion imaging and the development of advanced quantitative tools have further improved diagnostic accuracy. Despite these technological advances, standard (S) SPECT myocardial perfusion imaging remains relatively inefficient because of the prolonged image acquisition time leading to long procedural time. In addition, the relatively large doses of radiopharmaceuticals required for S-SPECT increases radiation dosimetry. Editorial see p 5

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In an effort to overcome these limitations, a new, dedicated, ultrafast (UF), solid-state cardiac camera introducing a new design of both photon acquisition and image reconstruction has been developed. This new technology is based on a pinhole collimation design and multiple cadmium zinc telluride crystal arrays. Compared to the S-SPECT camera, this type of collimation provides a 3- to 5-fold increase in photon sensitivity, thereby reducing imaging times significantly, while providing a 1.7- to 2.5-fold increase in spatial resolution, thus enabling high-quality scans with a significant reduction in imaging time, radiation dose, or both. Recent studies have demonstrated that this new system shows excellent agreement in terms of uptake and clinical findings along with a substantial reduction of the minimal scan time for this solid-state detector. Similar results have been reported by another type of UF-SPECT camera based on the same new technology with a different design of collimation and using advanced reconstruction techniques that enable resolution recovery and noise reduction. We hypothesized that the increased photon sensitivity and spatial resolution of UF-SPECT would allow improved detection of coronary artery disease (CAD) compared to S-SPECT. The aim of this pilot clinical study was to assess the performance of UF-SPECT relative to S-SPECT with respect to image quality and detection of obstructive CAD as defined by coronary angiography.
Methods

Patients

We prospectively enrolled a group of 34 consecutive patients (27 men) with known or suspected ischemic heart disease who were referred to our institution for stress/rest SPECT and subsequently scheduled for invasive coronary or CT angiography within 1 month of the index SPECT study. Patients with acute or recent ST-segment elevation myocardial infarction (MI), unstable angina, or previous coronary artery bypass graft surgery were excluded from the study. The present patient cohort was selected from a total of 126 patients referred to stress/rest SPECT during a 3-month period. The study was approved by the local ethics committee, and all patients signed written informed consent to participate in the study.

Stress Protocols and Patient Preparation

Patients were instructed to discontinue \( \beta \)-blockers, calcium antagonists, and nitrates for 24 hours before testing. Twenty-five (73%) underwent exercise testing and 9 (27%) underwent dipyridamole stress testing. Bicycle exercise stress test (stepwise increments of 25 W every 2 minutes) or dipyridamole (0.56 mg/kg IV over 4 minutes) were chosen on the basis of the patient’s ability to exercise and to reach \( \geq 85\% \) of the maximal age-predicted heart rate. Of the 25 patients undergoing exercise stress testing, 19 reached \( 85\% \) of the age-predicted maximum heart rate, whereas 5 had a submaximal stress test. One patient was injected for significant ST-segment depression. Adverse events were defined according to international guidelines.

Acquisition Protocol

Each patient underwent \( \text{\textsuperscript{99m}} \text{Tc}\text{-tetrofosmin} \) stress/rest gated SPECT using a single-day standard protocol (370 MBq for stress, 740 MBq for rest). All patients with previous MI were injected at rest after sublingual administration of nitrates. UF-SPECT was performed before S-SPECT in all patients and initiated 5 to 15 minutes after the stress and rest injection of the radiopharmaceutical, respectively.

S-SPECT

Gated SPECT was performed using a dual-head gamma camera (E.Cam; Siemens Medical Solution; Hoffman Estates, IL, and Millennium MG; GE Medical Systems; Milwaukee, WI) equipped with a high-resolution collimator. Patients were imaged in the supine position with arms placed over the head. A 64\( \times \)64-matrix, 32-projections/head, 16-frames/cycle protocol was applied using a 20% energy window. All studies were reconstructed using a standard iterative algorithm with ordered-subset expectation maximization with 2 iterations and 10 subsets, without resolution recovery or attenuation correction. A Butterworth postprocessing filter (frequency, 0.50; order, 10) was applied to the reconstructed slices. Acquisition time was 20 minutes for the stress images and 18 minutes for the rest images. Standard short-axis, vertical and horizontal long-axis images, and polar maps of stress and rest myocardial perfusion were then created.

UF-SPECT

The UF camera (Discovery NM 530c; GE Healthcare; Haifa, Israel) is equipped with a multiple-pinhole collimator and 19 stationary cadmium zinc telluride detectors, simultaneously imaging 19 cardiac views. Each detector contains 32\( \times \)32 pixilated 5-mm-thick (2.46\( \times \)2.46 mm) elements. Patients were imaged in the supine position with arms placed over the head. Automated heart positioning in the field of view was assisted by using real-time persistence imaging. List files were acquired and stored. A 5-minute acquisition was performed within 10 minutes after stress injection, and a 4-minute acquisition was performed 15 minutes after rest injection. Although the UF-SPECT detector could be rotated by the gantry if required for positioning, no detector or collimator motion of any kind were allowed after starting the acquisition. Images were reconstructed on the same workstation as for the S-SPECT acquisition with a new dedicated iterative algorithm with integrated collimator geometry modeling, using maximum penalized likelihood iterative reconstruction to obtain perfusion images in standard axes. Fifty iterations were performed. A Butterworth postprocessing filter (frequency, 0.37; order, 7) was applied to the reconstructed slices. The tomographic studies also were reprojected into 60 planar projections to emulate the S-SPECT display. Images were reconstructed without scatter or attenuation correction.

Qualitative Analysis of Perfusion Images

Stress and rest myocardial perfusion images obtained with UF- and S-SPECT were semiquantitatively scored using a 17-segment model of the left ventricle (LV) and a 5-point scale (0=normal, 1=equivocal, 2=moderate, 3=severe reduction of radioisotope uptake, 4=absence of detectable tracer uptake). Visual scoring of UF- and S-SPECT images was performed by consensus of 2 experienced nuclear cardiology physicians. The summed stress score (SSS) and summed rest score (SRS) were calculated by adding the segmental scores in the stress and rest images, respectively.

Quantitative Analysis of Perfusion Images

Quantitative analysis also was performed using normalized polar maps and the same 17-segment model. Segmental radiotracer uptake was then calculated for both the stress and the rest scans and expressed as percentage of the peak tracer uptake. For the per-vessel analysis, the 17 segments were clustered into the 3 main coronary territories: left anterior descending artery (LAD), circumflex artery (LCx), and right coronary artery (RCA), as previously described.

Analysis of Gated Images

The gated images were used to assess LV volumes and ejection fraction (EF) as well as used as an aid in the interpretation of the tomographic myocardial perfusion images to troubleshoot attenuation artifacts. In each patient, LV volumes and EF were measured after stress and at baseline with standard software.

Photon Sensitivity and Image Quality

The photon sensitivity of UF- and S-SPECT was assessed as myocardial counts per minute from regions of interest encompassing the heart on the projection images. Image quality for UF- and S-SPECT images was assessed with a 5-point scale (1=poor, 2=fair, 3=good, 4=very good, 5=excellent).

Quantitative Coronary Angiography

Selective conventional coronary angiography was performed using standard techniques (Innova 2000 GE; GE Healthcare). Standard multiple projections were recorded for the left and right coronary arteries. Coronary angiograms were quantified with off-line computer software (MEDIS CMS version 6.0; MEDIS Imaging Systems; Leiden, The Netherlands) with an automatic edge-contour detection algorithm using previously validated quantitative and quantitative parameters and definitions. Obstructive CAD was defined as \( \geq 70\% \) diameter stenosis in the 3 major coronary arteries and \( \geq 50\% \) for the left main coronary artery.

CT Coronary Angiography

All the examinations were performed using a 64-slice CT scanner (GE Discovery VCT; GE Healthcare). An unenhanced scan was obtained first followed by the CT angiographic acquisition using the following parameters: slices per rotation, 64 (32\( \times \)2); detector collimation, 0.6-mm; gantry rotation time, 330 ms; effective temporal resolution, 165 ms; spatial resolution, 0.4 mm\(^2\); tube voltage, 120 kV; and tube current, 900 mA. Sublingual nitroglycerin 0.3 mg was administered to all patients before the examination. Patients with a heart rate \( >65 \) beats/minute received intravenous atenolol (5 to 10 mg). A dose of 80 to 100 mL of nonionic contrast material (Iomeron 400; Bracco; Milan, Italy) was administered in the antecubital vein. All the images were acquired during an inspiratory breath hold of 10 to 12 seconds, with simultaneous recording of the patient’s ECG. A prospective ECG gating with tube modulation was used.

The CT data sets were analyzed by 2 independent and experienced readers using an off-line workstation software package (CardiQ Xpress and VesselQ Xpress; GE Healthcare). The analysis was performed using multiplanar reconstruction of the original axial images. For each
coronary segment, a cross-sectional image was created perpendicular to the vessel centerline, and the vessel area at the proximal tract and 5 mm from the proximal point of measurement was calculated with the corresponding diameters. In the presence of coronary plaque, the percent stenosis was determined. The variable explored was the presence of a stenosis (≥70% luminal diameter reduction) in the main coronary arteries and ≥50% for the left main coronary artery.

Statistical Analysis
Continuous variables are presented as mean ± SD. Where indicated, differences were assessed by Student t test for paired data. Interobserver agreement was measured using percent agreement and κ values. Accuracy in coronary stenosis detection was assessed by the area under the receiver operating characteristic (ROC) curve. Analysis of agreement between the 2 methods was evaluated by Bland-Altman plots with respect to SSS and SRS territory percentage tracer uptake, stress EF, and stress end-diastolic volume (EDV) and end-systolic volume (ESV). P < 0.05 was used to define statistical significance. The analyses were carried out with STATA version 11 (StataCorp; College Station, TX).

Results
Patient Characteristics
Table 1 summarizes clinical characteristics of the patient group. Mean age was 61 ± 9 years. Prescan likelihood of CAD on the basis of age, sex, risk factors of CAD, symptoms, and history of CAD was low in 6 (18%) patients and intermediate to high in 28 (82%).

Assessment of Coronary Anatomy
CT coronary angiography was used in 7 patients, who were identified at low clinical risk by their referring physicians, and invasive coronary angiography was used in 27 patients. Five patients showed no significant coronary artery stenosis, 9 had single-vessel disease, and the remaining 20 showed 2- (11 patients) or 3-vessel (9 patients) disease. Of the 29 patients with obstructive CAD, 20 (69%) showed a significant stenosis of the

Table 1. Clinical Characteristics of Patients (n = 34)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
<td>61 ± 9</td>
</tr>
<tr>
<td>Male sex</td>
<td>27 (80)</td>
</tr>
<tr>
<td>Angina on effort</td>
<td>21 (62)</td>
</tr>
<tr>
<td>Angina at rest</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Mixed (rest/effort) angina</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>18 (53)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>15 (44)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>12 (35)</td>
</tr>
<tr>
<td>Obesity</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>7 (20)</td>
</tr>
<tr>
<td>Previous coronary angioplasty</td>
<td>10 (29)</td>
</tr>
<tr>
<td>EF, %</td>
<td>52 ± 13</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or no. (%).

Table 2. Per-Patient Analysis of Qualitative Evaluation in Detection of CAD Obtained for UF- and S-SPECT

<table>
<thead>
<tr>
<th>Observation</th>
<th>Area</th>
<th>SE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSS (SPECT)</td>
<td>34</td>
<td>0.8621</td>
<td>0.0635 0.73762–0.98652</td>
</tr>
<tr>
<td>SSS (UF-SPECT)</td>
<td>34</td>
<td>0.9828</td>
<td>0.0181 0.94727–1.00000</td>
</tr>
</tbody>
</table>

P value for the difference, 0.078.
Table 3. Per-Vessel Analysis of Qualitative Evaluation in Detection of CAD Obtained for UF- and S-SPECT

<table>
<thead>
<tr>
<th>Observation</th>
<th>Area</th>
<th>SE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD‡</td>
<td>34</td>
<td>0.9339</td>
<td>0.0465</td>
</tr>
<tr>
<td>SSS (S-SPECT)</td>
<td>34</td>
<td>0.9196</td>
<td>0.0581</td>
</tr>
<tr>
<td>LCx†</td>
<td>34</td>
<td>0.8536</td>
<td>0.0645</td>
</tr>
<tr>
<td>SSS (S-SPECT)</td>
<td>34</td>
<td>0.9714</td>
<td>0.0270</td>
</tr>
<tr>
<td>RCA‡</td>
<td>34</td>
<td>0.8750</td>
<td>0.0589</td>
</tr>
<tr>
<td>SSS (UF-SPECT)</td>
<td>34</td>
<td>0.9931</td>
<td>0.0076</td>
</tr>
</tbody>
</table>

*P value for the difference, 0.35.
†P value for the difference, 0.039.
‡P value for the difference, 0.045.

LAD, 20 (69%) had a significant stenosis of the LCx, and 18 (62%) had a significant stenosis of the RCA.

Myocardial Count Rate and Image Quality
Myocardial count rate was significantly higher for UF-SPECT imaging than for S-SPECT imaging for stress (242±40 cpm·103 versus 45±12 cpm·103, respectively; P=0.0012) and rest (550±51 cpm·103 versus 105±25 cpm·103, respectively; P=0.0023). There were no equivocal studies on consensus interpretation. Moreover, the semiquantitative score was evaluated independently by the 2 interpreters. On a per-patient basis, the interobserver agreement rate for UF-SPECT was 95% (κ=0.81; 95% CI, 0.77 to 0.94) compared with 94% for S-SPECT (κ=0.78; 95% CI, 0.72 to 0.92). Stress images were graded good, very good, or excellent in 32 (94%) of the 34 patients for UF-SPECT and in 31 (91%) for S-SPECT (P=0.6). Rest images were graded good or better in 33 (97%) for UF-SPECT and in 32 (94%) for S-SPECT (P=0.6).

Semiquantitative Analysis and Correlation With Coronary Angiography
A good clinical agreement between nuclear and angiographic data was observed by both techniques. The mean SSS for UF-SPECT was 8.7±5.3, and the SRS was 1.3±1.3. The mean SSS for S-SPECT was 5.8±3.0 (P<0.001 versus UF-SPECT), and SRS was 1.2±1.2 (P=0.26 versus UF-SPECT). When only 29 of the 34 patients with significant CAD were analyzed, the SSS was 10.1±4.4 versus 6.4±2.9 for UF-SPECT and S-SPECT, respectively (P<0.001). The ROC curves are depicted in Figures 1 and 2, and the ROC areas are reported in Tables 2 and 3. The ROC area was 98% for UF-SPECT and 86% for S-SPECT (P=0.078). In the per-vessel analysis, UF-SPECT had larger ROC areas than S-SPECT for detection of coronary stenosis in the LCx and RCA. Finally, when 20 of the 34 patients with multivessel disease were analyzed, UF-SPECT correctly identified all significant coronary stenosis in 17 versus 6 patients identified with S-SPECT (P=0.003) (Figure 3).

Quantitative Analysis and Correlation With Coronary Angiography
Mean tracer uptake during stress was 70±15%, 73±12%, and 74±13% in the LAD, LCx, and RCA territories, respectively, for UF-SPECT and 75±10%, 78±7%, and 77±9% in the LAD, LCx, and RCA territories, respectively, for S-SPECT. At rest, mean tracer uptake was 87±7%, 86±4%, and 84±5% in the LAD, LCx, and RCA territories, respectively, for UF-SPECT and 84±6%, 83±3%, 83±5% in the LAD, LCx, and RCA territories, respectively, for S-SPECT. In patients with CAD, the mean tracer uptake in each vascular territory was consistently lower with UF-SPECT than with S-SPECT (LAD, 60±2% versus 70±3%; LCx, 65±4% versus 73±4%; RCA, 63±5% versus 71±2%; P<0.001 for all comparisons). Bland-Altman plots indicated significant differences for all the examined variables (Figure 4).

Gated Images
The analysis of LV function demonstrated comparable stress LV EF, EDV, and ESV between UF- and S-SPECT (Figure 5). However, Bland-Altman plots showed significant differences among the same variables measured at rest (Figure 6).

Discussion
To our knowledge, this clinical study is the first to compare UF- and S-SPECT for detection of obstructive CAD as defined by coronary angiography. In this pilot study, single-day 99mTc-tetrofosmin UF-SPECT was found to be superior to S-SPECT for detecting ischemia on a global and regional basis, identifying a higher number of vessels with obstructive CAD.
Comparison With Prior Studies
Our findings regarding image quality are consistent with recent studies\textsuperscript{6–10} and confirm the feasibility of assessing myocardial perfusion by UF-SPECT at a fraction of the time required to perform S-SPECT. Despite the shorter acquisition times, image quality is maintained owing to improvements in camera design (small field of view focusing on the heart), sensitivity, and improved reconstruction methods.\textsuperscript{17–19} Patient motion during acquisition was not evaluated in this study. However, the short imaging time is expected to reduce the occurrence of significant patient motion and frequency motion artifacts.

Previously published studies focused on the reduction of imaging time with good agreement versus S-SPECT approaches.\textsuperscript{6–10} The present study findings extend the results of prior studies by comparing UF- and S-SPECT with respect to detection of obstructive CAD, as defined angiographically. Our per-patient analysis showed a nonsignificant trend toward higher diagnostic accuracy for UF-SPECT than S-SPECT. In the
per-vessel analysis, we found a higher accuracy of UF- than S-SPECT for detecting obstructive CAD in the LCx and RCA. The improved per-vessel detection of CAD corresponded with a significant improvement in the delineation of multivessel CAD with UF-SPECT than with S-SPECT.

There are 2 possible explanations for these findings. The first one relates to the higher spatial resolution of UF-SPECT and, consequently, to the better identification of smaller and less-severe defects within individual coronary territories. The second possibility is that the increased sensitivity with UF-SPECT may have reduced attenuation artifacts, especially in the LCx and RCA territories. Indeed, the identification of multivessel CAD by UF-SPECT was highly improved mostly through this mechanism. This result is not in contrast with previously published studies but should be considered as new data obtained in a sample of a selected and well-characterized population.

Study Limitations
The results of this study are likely affected by the highly selective nature of the protocol enrollment criteria, which in-

Figure 5. Linear regression analysis (left) and Bland-Altman plots (right) for stress EF and stress EDV and ESV in UF- and S-SPECT.
cluded patients already scheduled for coronary angiography. For this reason, the conclusions can be considered clinically reliable only for patients with high CAD likelihood or known CAD and not in the more-general group of patients who undergo SPECT and do not have CAD and in whom the results of SPECT imaging are normal. Moreover, from a statistical point of view, the small sample, especially analyses in subgroups of 29 or 34 or 20 of 34 patients, does not provide much precision or power for comparing different imaging methods. The absence of a normal control population studied with UF-SPECT combined with new or updated automatic algorithms could be considered a second limitation of this study.

The scintigraphic protocol shows a limit in the study design because UF-SPECT was always performed first. Because newer data on tetrofosmin washout\(^{20,21}\) suggest that defect detection improves with early imaging, the comparison with S-SPECT performed second in every patient could be a model bias. As it stands, this pilot study should be considered a validation of UF-SPECT plus early imaging versus S-SPECT plus standard imaging.

Figure 6. Linear regression analysis (left) and Bland-Altman plots (right) for rest EF and rest EDV and ESV in UF- and S-SPECT.
Our patients showed a low occurrence of previous MI and ventricular dysfunction, and thus, the identity of volumes and EFs between UF-SPECT and S-SPECT was not examined in dilated hearts. Finally, no comparison of extent of viable myocardium was possible in our study group. Further studies will necessarily focus on multicenter analysis of a larger patient group, comparing UF-SPECT with S-SPECT perfusion imaging with normal limits specific for UF-SPECT images.

**Conclusions**

UF-SPECT is a new technology that provides fast imaging with increased sensitivity and higher resolution than S-SPECT. This pilot study demonstrated that UF-SPECT acquired with a superfast protocol resulted in high-quality images and an equivalent level of diagnostic confidence on a per-patient basis. On a per-vessel basis, our findings suggest that UF-SPECT is superior to S-SPECT, especially in the LCx and RCA territories, resulting in better delineation of multivessel CAD.

**Acknowledgments**

We thank Claudio Marcassa, MD, and Michele Coceani, MD, for their excellent help in reviewing the paper and Ilaria Citti for editing the manuscript.

**Disclosures**

None.

**References**


**CLINICAL PERSPECTIVE**

This pilot study compared the diagnostic accuracy of myocardial perfusion imaging assessed by ultrafast (UF) single-photon emission CT (SPECT) and standard (S) SPECT in a population of patients undergoing coronary or CT angiography. We evaluated regional myocardial ischemia in a head-to-head comparison using qualitative and quantitative analysis. On a per-patient basis, our results showed similar diagnostic accuracy between the 2 approaches. On a per-vessel analysis, UF-SPECT resulted in a higher sensitivity for identifying obstructive coronary artery disease (CAD) than S-SPECT. Consequently, UF-SPECT resulted in a more-accurate delineation of multivessel CAD. If confirmed in larger studies, these findings may have important implications for diagnosis and for risk stratification of patients with known or suspected CAD.
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*Circ Cardiovasc Imaging*. 2011;4:51-58; originally published online November 10, 2010; doi: 10.1161/CIRCIMAGING.110.957399
*Circulation: Cardiovascular Imaging* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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