Comparison Between Ultrafast and Standard SPECT in Patients with Coronary Artery Disease: A Pilot Study

Running Title: Gimelli et al: Ultrafast SPECT in CAD

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Abstract

Background—A novel technology has been developed for ultrafast (UF) single-photon emission computed tomography (SPECT) myocardial perfusion imaging by employing a pin-hole 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 ⁹⁹ᵐTc-Tetrofosmin stress/rest myocardial perfusion imaging. UF-SPECT was performed 10 min before S-SPECT. Images were qualitatively analyzed, the summed stress score (SSS) and summed rest score (SRS) were calculated. The segmental tracer uptake value (percentage of maximum myocardial uptake) was also quantified for both UF- and S-SPECT. When only 29/34 patients with significant coronary lesions were analyzed, SSS was 10.1 ± 4.4 versus 6.4 ± 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.

Key Words: ultrafast SPECT, myocardial ischemia, coronary artery disease
Over the past two decades, a number of technical innovations in nuclear cardiology have led to mature technique that is widely used clinically. Single photon emission computed tomography (SPECT) imaging has replaced planar imaging (1), while Technetium-based perfusion imaging agents have largely replaced Thallium-201 (2). The addition of ECG gating to myocardial perfusion imaging and the development of advanced quantitative tools have further improved diagnostic accuracy (3). 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 (4).

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 (5). This new technology is based on a pin-hole collimation design and multiple cadmium zinc telluride crystal arrays. Compared to the S-SPECT camera, this type of collimation provides a 3-5 fold increase in photon sensitivity, thereby reducing imaging times significantly, while providing a 1.7-2.5 fold increase in spatial resolution, thus enabling high quality scans with a significant reduction in imaging time, radiation dose, or both (6). Recent studies have demonstrated that this new system shows excellent agreement in terms of uptake and clinical findings (6-8), along with a substantial reduction of the minimal scan time for this solid-state detector (7). Similar results have also been reported by another type of UF-SPECT camera based on the same new technology with a different design of collimation (9, 10), and also using advanced reconstruction techniques that enable resolution recovery and noise reduction (11, 12). We hypothesized that the increased photon sensitivity and spatial resolution of UF-SPECT would allow improved
The detection of coronary artery disease (CAD) as compared to S-SPECT.
The aim of this pilot clinical study was to assess the performance of UF- 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 males) with known or suspected ischemic heart disease, who were referred to our Institute for stress/rest SPECT and subsequently scheduled for invasive coronary or computed tomography (CT) angiography within one 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. This 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 ethical 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 patients (73%) underwent exercise and 9 patients (27%) underwent dipyridamole stress testing. Bicycle exercise stress test (stepwise increments of 25 watts every 2 min) or dipyridamole (0.56 mg/Kg i.v. over 4 min) were chosen on the basis of the patient’s ability to exercise and to reach at least 85% of the maximal age-predicted heart rate. Of the 25 patients undergoing exercise stress testing, 19 patients reached
85% of the age-predicted maximum heart rate, whereas 5 patients had a submaximal stress test. One patient was injected for significant ST segment depression. Adverse events were defined according to international guidelines (13).

**Acquisition protocol.** Each patient underwent $^{99m}$Tc-Tetrofosmin stress/rest gated SPECT using a single-day standard protocol (370 MBq for stress and 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 5-15 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, USA and Millennium MG, GE Medical System, Milwaukee, WI, USA) equipped with a high resolution collimator. Patients were imaged in the supine position with arms placed over the head. A 64x64 matrix, 32 projections per 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 post-processing 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. Technology and acquisition protocol.** 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 32x32 pixilated 5-mm-thick (2.46 x 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-min acquisition was performed within 10 minutes post stress injection, and a 4 min acquisition was performed 15 minutes post 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 using 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 have been performed (7, 8). A Butterworth postprocessing filter (frequency, 0.37; order, 7) was applied to the reconstructed slices. The tomographic studies were also re-projected 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 semi-quantitatively scored using a 17-segment model of the left ventricle and a 5-point scale system (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 two 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 was also performed using normalized polar maps and the same 17-segment model. Segmental radiotracer uptake was then calculated for both the stress and 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, i.e. left anterior descending artery (LAD), circumflex artery (LCx), and right coronary artery (RCA), as previously described (14).

Analysis of gated images. The gated images were used to assess left ventricular volumes and ejection fraction, and were used as an aid to 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 using standard software (15).

Photon sensitivity and image quality. The photon sensitivity of UF- and S-SPECT was assessed as myocardial counts/min from ROIs encompassing the heart on the projection images. Image quality for UF- and S-SPECT images was assessed using a 5-point scale system (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, General Electric). Standard multiple projections were recorded for the left and right coronary arteries.
Coronary angiograms were quantified using an off-line computer-based software (MEDIS CMS version 6.0; MEDIS Imaging Systems) with an automatic edge-contour detection algorithm using previously validated qualitative and quantitative parameters and definitions (16). Obstructive CAD was defined as ≥ 70% diameter stenosis in the three major coronary arteries, and ≥50% for the left main coronary artery.

**CT Coronary Angiography.** All the examinations were performed using a 64-slice CT scanner (GE Discovery VCT, General Electric). An unenhanced scan was first obtained. This was followed by the CT angiographic acquisition using the following parameters: 64 (32x2) number of slices per rotation, 0.6-mm detector collimation, gantry rotation time 330 ms, effective temporal resolution 165 ms, spatial resolution 0.4 mm³, tube voltage 120 kV, tube current 900 mAs. Sublingual nitroglycerin 0.3 mg was administered to all patients before the examination. Patients with a heart rate >65 bpm received intravenous atenolol (5 to 10 mg). A dose of 80-100 ml of non-ionic contrast material (Iomeron 400, Bracco, Milan, Italy) was administered in the antecubital vein. All the images were acquired during an inspiratory breath hold of approximately 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 VessellQ Xpress, General Electric 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 ± standard deviation. Where indicated, differences were assessed by Student t test for paired data. Interobserver agreement was measured using percent agreement and kappa values. Accuracy in coronary stenosis detection was assessed by the area under the receiver-operating-characteristic (ROC) curves. Analysis of agreement between the two methods was evaluated by Bland–Altman plots with respect to SSS and SRS territory percentage tracer uptake, stress ejection fraction (EF), stress end diastolic volume (EDV) and end systolic volume (ESV). A P value <0.05 was used to define statistical significance. The analyses were carried out with Stata version 11 (Statacorp, College Station, TX).

Results

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

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 patients had single vessel disease, and the remaining 20 patients showed two (11 patients) or three (9 patients) vessel disease. Of the 29 patients with obstructive CAD, 20 patients (69%) showed a significant stenosis of the left anterior descending (LAD) coronary artery, 20 (69%) patients had a significant stenosis of the left circumflex coronary artery (LCx), and 18 (62%) patients had a significant stenosis of the right coronary artery (RCA).

Myocardial count rate and image quality. Myocardial count rate was significantly higher for UF- than S-SPECT for stress (242 ± 40 cpm*10^3 versus 45 ± 12 cpm*10^3, p = 0.0012) and rest (550 ± 51 cpm*10^3 versus 105 ± 25 cpm*10^3, p = 0.0023) imaging. There were no equivocal studies on consensus interpretation. Moreover, the semiquantitative score was evaluated independently by the two interpreters. On a per-patient basis, the interobserver agreement rate for UF-SPECT was 95% (kappa = 0.81, 95% CI: 0.77-0.94) compared to 94% for S-SPECT (kappa = 0.78, 95% CI: 0.72-0.92). Stress images were graded “good,” “very good,” or “excellent” in 32/34 patients (94%) for UF-SPECT and in 31/34 patients (91%) for S-SPECT (p = 0.6). Rest images were graded “good” or better in 33/34 patients (97%) for UF-SPECT and in 32/34 patients (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 vs UF-SPECT) and SRS was 1.2 ± 1.2 (p = 0.26 versus UF-SPECT). When only 29/34 patients with significant coronary artery
disease were analyzed, the SSS was 10.1 ± 4.4 versus 6.4 ± 2.9 for UF- 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 coronary arteries.

Finally, when 20/34 patients with multivessel disease were analyzed, UF-SPECT correctly identified all significant coronary stenosis in 17/20 patients versus 6/20 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 it was 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 it was 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- than with S-SPECT (i.e., 60 ± 2 % versus 70 ± 3 % in the LAD territory; 65 ± 4 % versus 73 ± 4 % in the LCx territory; and 63 ± 5 % versus 71 ± 2 % in the RCA territory, respectively, p < 0.001 for all comparisons). Bland-Altman plots indicated significative differences for all the examined variables (Figure 4).

Gated images. The analysis of LV function demonstrated comparable stress LV ejection fraction, end diastolic and end systolic volumes between UF- and S-SPECT
(Figure 5). However, Bland-Altman plots showed significant differences between the
same variables measured at rest (Figure 6).

Discussion

This is the first clinical study comparing UF- and S-SPECT for detection of
obstructive CAD as defined by coronary angiography. In this pilot study, single-day
$^{99m}$Tc-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 coronary artery disease.

Comparison to prior studies. Our findings regarding image quality are consistent
with recent studies (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 (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.

Previous published studies focused on the reduction of imaging time with good
agreement versus standard SPECT approaches (6-10). The 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 non-
significant trend towards 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 coronary arteries. The improved per-vessel detection of CAD corresponded with a significant improvement in the delineation of multivessel CAD with UF- than S-SPECT.

There were two 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. A 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 coronary artery disease by UF SPECT was highly improved mostly through this mechanism.

This result is not in contrast with previous published studies, but should be considered as a new data obtained in a sample of selected and well characterized population.

Study limitations. The results of this study are likely affected by the highly selected nature of the enrolled criteria of the protocol that included patients already scheduled for coronary angiography. For this reason, the conclusions can be considered clinically reliable only to patients with high CAD likelihood or known CAD and not in the more general group of patients who undergo SPECT who 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 29/34 or 20/34 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 as a second limit of this study.
The scintigraphic protocol shows a limit in the study design because UF SPECT was always performed first and not in a random order. Since 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.

Our patients showed a low occurrence of previous myocardial infarction and ventricular dysfunction, and thus the identity of volumes and ejection fractions between UF 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, providing fast imaging with increased sensitivity and higher resolution than S-SPECT. This pilot study demonstrated that UF SPECT acquired with a super-fast 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 are superior to S-SPECT especially in the LCx and RCA territories, and that this results in better delineation of multivessel CAD.
Acknowledgments

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Disclosures

None.
References


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<tr>
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<td>27 (80%)</td>
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<tr>
<td>Angina on effort</td>
<td>21 (62%)</td>
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<tr>
<td>Angina at rest</td>
<td>5 (15%)</td>
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<td>Mixed (rest/effect) angina</td>
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<tr>
<td>Diabetes mellitus</td>
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<td>Previous myocardial infarction</td>
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<td>Previous coronary angioplasty</td>
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</tr>
<tr>
<td>Ejection fraction %</td>
<td>52 ± 13</td>
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Table 2. Per-patients analysis of qualitative evaluation in detection of CAD obtained for UF- and S-SPECT. SSS: Summed Stress Score; Obs: Observation; Std. Err.: Standard Error.

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<td>Obs</td>
<td>Area</td>
<td>Std. Err</td>
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<td>SSS (S SPECT)</td>
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<td>0.8621</td>
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<td>SSS (UF SPECT)</td>
<td>34</td>
<td>0.9828</td>
<td>0.0181</td>
<td>0.94727 - 1.00000</td>
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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. SSS: Summed Stress Score; Obs: Observation; Std. Err.: Standard Error. LAD = left anterior descending coronary artery, LCx = left circumflex coronary artery, RCA = right coronary artery.

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<td>Obs</td>
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<td>SSS (S SPECT)</td>
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P-value for the difference: 0.35

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P-value for the difference: 0.039

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<td>34</td>
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P-value for the difference: 0.045
Figure Legends

Figure 1. Overall qualitative analysis of UF- versus S-SPECT: ROC curves.

Figure 2. Per-patient qualitative analysis of UF- versus S-SPECT: ROC curves.

Figure 3. Comparison between UF (on the right side, stress and rest bull’s eyes) and S SPECT (on the left side, stress and rest bull’s eyes) in a patient with three vessel disease. UF SPECT correctly identifies all diseased vessels while S SPECT shows a lower agreement between reversible perfusion defects and coronary anatomy.

Figure 4. Linear regression analysis (left) and Bland–Altman plots (right) for per-territory percentage tracer uptake in UF and S SPECT.

Figure 5. Linear regression analysis (left) and Bland–Altman plots (right) for stress ejection fraction (EF), stress end diastolic volume (EDV) and end systolic volume (ESV) in UF and S SPECT.

Figure 6. Linear regression analysis (left) and Bland–Altman plots (right) for rest ejection fraction (EF), rest end diastolic volume (EDV) and end systolic volume (ESV) in UF and S SPECT.
S SPECT

20 min Stress  18 min Rest

UF SPECT

5 min Stress  4 min Rest

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