Clinical Feasibility of Simultaneous Acquisition Rest 99mTc/Stress 201Tl Dual-Isotope Myocardial Perfusion Single-Photon Emission Computed Tomography With Semiconductor Camera

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Background: The aim of this study was to evaluate the clinical feasibility of simultaneous acquisition of rest 99mTc-tetrofosmin/stress 201Tl dual-isotope single-photon emission computed tomography with a semiconductor gamma camera.

Methods and Results: Ninety-four patients with known or suspected coronary artery disease (CAD) were enrolled in the study. First, patients were injected with 99mTc-tetrofosmin (296 MBq) for rest imaging, followed by 201Tl (74 MBq) injection during 6 min of vasodilator stress test. Immediately after the stress test, the patients underwent the first electrocardiogram (ECG)-gated simultaneous acquisition including rest and stress perfusion scans. Patients were brought back for the second simultaneous acquisition for the comparison of ECG-gated wall motion between stress and rest scan 30 min later. Coronary angiography was performed in all the patients within 3 months of this protocol. Sensitivity, specificity and accuracy on a per patient basis to detect significant coronary artery stenosis (≥75%) were 88.6%, 79.2% and 86.2%, respectively. Per coronary vessel, sensitivity, specificity and accuracy were as follows: 84.9%, 80.5% and 83% in the left anterior descending coronary artery; 75%, 93.1% and 86.2% in the left circumflex coronary artery; and 74.2%, 85.7% and 81.9% in the right coronary artery.

Conclusions: Simultaneous acquisition of rest 99mTc-tetrofosmin/stress 201Tl dual-isotope protocol had high diagnostic accuracy for significant CAD. (Circ J 2016; 80: 689–695)

Key Words: Cadmium-zinc-telluride; Dual isotope; Myocardial perfusion; Simultaneous acquisition; Single-photon emission computed tomography
They used 92–133 MBq $^{201}$Tl for rest and 740–1,110 MBq labelled tracer and $^{201}$Tl is smaller in the resting condition than conversely, the difference in extraction fraction between $^{99m}$Tc-tetrofosmin/stress $^{201}$Tl is a major problem. The much lower extraction fraction (54–62%) of $^{201}$Tl in vasodilator stress would be ideal to visualize myocardial perfusion in the area of hyperemic condition. Therefore, $^{201}$Tl may be slightly more effective in identifying mild coronary stenosis. Combination of vasodilator stress and $^{201}$Tl is physically compatible and clinically useful for effective time management. $^{99m}$Tc-labelled myocardial perfusion tracers such as sestamibi and tetrofosmin have a low extraction fraction (54–62%), potentially causing a mild myocardial perfusion defect that could be missed. Conversely, the difference in extraction fraction between $^{99m}$Tc-labelled tracer and $^{201}$Tl is smaller in the resting condition than in the hyperemic condition. Previously, Berman et al carried out a sequential acquisition of rest $^{99m}$Tc-tetrofosmin/stress $^{201}$Tl dual-isotope protocol in 1993, which could visualize the combined assessment of stress perfusion and myocardial viability. They used 92–133 MBq $^{201}$Tl for rest and 740–1,110 MBq $^{99m}$Tc-sestamibi for stress imaging. The higher radiation exposure and lower cost-effectiveness of this protocol were not conducing to good cost containment. Recently, they proposed sequential acquisition rest $^{99m}$Tc-sestamibi/stress $^{201}$Tl dual-isotope MPS with semiconductor gamma camera. In that recent study, they proposed the utilization of low-dose tracers (74–92.5 MBq $^{201}$Tl for stress and 296–370 MBq $^{99m}$Tc-sestamibi for rest), followed by the sequential scanning.

In the present study, we developed a novel MPS protocol using low-dose rest $^{99m}$Tc-tetrofosmin/stress $^{201}$Tl with simultaneous acquisition of dual-isotope protocol (SDI protocol) using D-SPECT and validated its clinical application.

**Methods**

**Patients**

We enrolled 94 consecutive patients with known or suspected CAD between 1 April and 30 June 2015, who had invasive coronary angiography (CAG) due to the SPECT results or physician recommendation. Patients with high-grade atrioventricular block or bronchial asthma were excluded. Patients were asked to discontinue nitrates and caffeine for 24 h prior to the study.

**MPS and Stress Protocol**

This novel protocol is shown in Figure 1. First, patients were injected with 296 MBq $^{99m}$Tc-tetrofosmin (Nihon Medi-Physics, Tokyo, Japan) at the time of calibration for visualizing resting perfusion. After the injection of $^{99m}$Tc-tetrofosmin, patients then underwent 6 min of adenosine stress (120 μg · kg$^{-1}$ · min$^{-1}$; Adenoscan injection, Daiichi Sankyo, Tokyo, Japan). Seventy-four MBq $^{201}$Tl was injected 3 min after the start of adenosine infusion. Prior to the first acquisition, patients were asked to drink 100 ml of soda in order to produce the space between the heart and subdiaphragmatic activity. The first simultaneous rest $^{99m}$Tc-tetrofosmin/stress $^{201}$Tl acquisition (10 min) was started after the end of adenosine stress in an upright position. The second simultaneous rest $^{99m}$Tc-tetrofosmin/redistribution $^{201}$Tl acquisition (10 min) was then done 30 min after the first acquisition (Figure 1). Calculated total protocol time was 1 h. This novel protocol was approved by the hospital’s ethics committee, and informed consent was given by all patients.

**Photopeak Calibrations**

To carry out simultaneous acquisition of rest $^{99m}$Tc-tetrofosmin/stress $^{201}$Tl MPS, the subtraction of photo-energy cross-talk between $^{99m}$Tc-tetrofosmin and $^{201}$Tl is a major problem. Although down-scatter of the 140 keV $^{99m}$Tc photons into the main $^{201}$Tl window (70 keV) is a major problem, the much better energy resolution of CZT detectors as compared with the conventional anger camera allows the use of narrower energy windows, thereby reducing down-scatter contribution and effective scatter correction. Briefly, the iterative deconvolution method developed by Kacperski et al was used for the calibrations of D-SPECT, which was a hybrid between the triple energy window method and scatter modelling based on spatial and spectral distribution of projection counts in multiple selected energy windows. The selected photopeak windows of $^{99m}$Tc and $^{201}$Tl were as follows: 130–150 keV for $^{99m}$Tc, and 64–77 keV and 157.4–177.4 keV for $^{201}$Tl, respectively. Scatter correction via the iterative deconvolution method was applied to the $^{201}$Tl images.

**Acquisition Protocol and Image Reconstruction**

Sixteen-frame electrocardiogram (ECG)-gated MPS data were acquired using D-SPECT. A 10-s prescan was performed to...
set the heart position and define limits of scanning angle for each detector. Each image dataset was acquired with 120 projections per detector. Transaxial images were reconstructed using the proprietary Broadview reconstruction algorithm (Spectrum Dynamics), which is based on the maximum likelihood expectation maximization method.16 SPECT images (short axis, horizontal and vertical long axis) were generated using Autoquant (Cedars-Sinai Medical Center, Los Angeles, CA, USA).29

Image Interpretation
The SPECT images were scored semi-quantitatively by 2 experienced readers using a 17-segment model of the LV on a 5-point scale (0, normal uptake; 1, mildly reduced uptake; 2, moderately reduced uptake; 3, severely reduced uptake; 4, almost no uptake).14,21 Discordance in image interpretation was resolved by consensus. In this model, the left anterior descending coronary artery (LAD) territory consists of 8 segments (segments 1, 2, 5–7, 11, 12, 17), the left circumflex coronary artery (LCX) consists of 5 segments (segments 4, 9, 10, 15, 16) and the right coronary artery (RCA) consists of 4 segments (segments 3, 8, 13, 14). Summed stress score (SSS), summed rest score (SRS) and summed difference score (SDS) were calculated as previously defined by Berman et al.22 Jeopardized myocardium was defined as SDS ≥2 in the relevant coronary vessels.23 Summed regional wall motion score (SWMS) was derived from a 6-point scale scoring system (0, normal; 1, mildly reduced; 2, moderately reduced; 3, severely reduced; 4, akinesia; and 5, dyskinesia) at both rest and stress.24 Transient ischemic dilation (TID) ratio was also calculated using the following equation: end-diastolic LV volume at stress divided by that at rest.25

Image Quality Score
$^{99}$Tc-tetrofosmin concentration at rest imaging located below the diaphragm may cause an artificial perfusion defect in the inferior wall by adjacent liver uptake.

Statistical Analysis
Continuous variables are expressed as mean±SD. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy in detecting significant CAD on a per patient or coronary vessel basis were calculated using the usual equations. Receiver operating characteristic (ROC) curve analysis for detection of significant CAD was performed, and ROC area under the curve (AUC) was calculated. Unpaired t-test was used for the evaluation for TID ratio between the normal coronary group and the multi (2 or 3)-vessel group. Paired t-test was used for the evaluation of end-diastolic volume (EDV), ejection fraction (EF) and SWMS between stress and rest.

CAG
All patients underwent invasive CAG within 3 months after MPS. Significant CAD was defined as stenosis (≥75%) in one or more coronary arteries or ≥75% in the left main coronary artery (LMCA).

Results
Patient Characteristics
Patient characteristics are given in Table 1. All patients completed the protocol. Classical coronary risk factors and clinical symptoms were as follows: hypertension, 81%; dyslipidemia, 64%; diabetes, 55%; current smoking, 21%. Average body mass index was 24.1±3.8 kg/m². ECG at rest is also listed in Table 1.

Perfusion and ECG-Gated Parameters
Averaged SSS, SRS and SDS were as follows: 7.0±6.1, 2.3±4.3 and 4.6±4.4, respectively. LVEF was lower at stress (57.8±15.8%) than at rest (60.5±16.5%, P<0.0001), and EDV was larger at stress (99.3±48.6 ml) than at rest (94.4±49.4 ml, respectively.18

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics</th>
<th>Mean ± SD or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>94</td>
</tr>
<tr>
<td>Age</td>
<td>69.5±9.8</td>
</tr>
<tr>
<td>Male</td>
<td>77 (82)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.5±8.9</td>
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<tr>
<td>Body weight (kg)</td>
<td>65.6±13.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.1±3.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>77 (81)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>61 (64)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>52 (55)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>20 (21)</td>
</tr>
<tr>
<td>CKD</td>
<td>30 (31)</td>
</tr>
<tr>
<td>Prior AMI</td>
<td>29 (31)</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>46 (49)</td>
</tr>
<tr>
<td>Abnormal Q wave</td>
<td>14 (15)</td>
</tr>
<tr>
<td>ST-T change</td>
<td>19 (20)</td>
</tr>
<tr>
<td>AF</td>
<td>7 (7)</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; AMI, acute myocardial infarction; BMI, body mass index; CKD, chronic kidney disease; PCI, percutaneous coronary intervention.

<table>
<thead>
<tr>
<th>Table 2. Myocardial Perfusion and ECG-Gated Parameters</th>
<th>Mean ± SD or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>94</td>
</tr>
<tr>
<td>SSS</td>
<td>7.0±6.1</td>
</tr>
<tr>
<td>SRS</td>
<td>2.3±4.3</td>
</tr>
<tr>
<td>SDS</td>
<td>4.6±4.4</td>
</tr>
<tr>
<td>EF at stress (%)</td>
<td>57.8±15.8*</td>
</tr>
<tr>
<td>EF at rest (%)</td>
<td>60.5±16.5</td>
</tr>
<tr>
<td>EDV at stress (ml)</td>
<td>99.3±48.6**</td>
</tr>
<tr>
<td>EDV at rest (ml)</td>
<td>94.4±49.4</td>
</tr>
<tr>
<td>TID ratio in all subjects</td>
<td>1.06±0.10</td>
</tr>
<tr>
<td>TID ratio in normal coronary group</td>
<td>1.02±0.10</td>
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<tr>
<td>TID ratio in single vessel group</td>
<td>1.07±0.07</td>
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<tr>
<td>TID ratio in multi (2 or 3)-vessel group</td>
<td>1.08±0.11***</td>
</tr>
<tr>
<td>SWMS at stress</td>
<td>6.37±1.6****</td>
</tr>
<tr>
<td>SWMS at rest</td>
<td>5.98±1.1</td>
</tr>
</tbody>
</table>

*P<0.0001, paired t-test between stress and rest EF; **P<0.0001, paired t-test between stress and rest EDV; ***P=0.0609, unpaired t-test of TID ratio between normal coronary group vs. multi-vessel group; ****P=0.0602, paired t-test between stress and rest SWMS. ECG, electrocardiogram; EDV, end-diastolic volume; EF, ejection fraction; SDS, summed difference score; SRS, summed rest score; SSS, summed stress score; SWMS, summed wall motion score; TID, transient ischemic dilation ratio.
MAKITA A et al.

Accuracy were as follows: 88.6%, 79.2%, 92.5%, 70.4% and 86.2%, respectively. With regard to coronary vessels, the data were as follows: 84.9%, 80.5%, 84.9%, 80.5% and 83.0% for LAD; 75.0%, 93.1%, 87.1%, 85.7% and 86.2% for LCX; and 74.2%, 85.7%, 71.9%, 87.1% and 81.9% for the RCA (Figure 2). ROC AUC was 0.908 on a per patient basis; and with regard to the coronary arteries, it was 0.848 for the LAD; 0.835 for the LCX; and 0.813 for the RCA (Figure 3). Sensitivity to detect significant stenosis in 36 patients with multi-vessel disease was 97%.

Representative Cases

A 71-year-old man with dyspnea on exertion was referred for adenosine stress SDI protocol. The patient had a history of dyslipidemia and hypertension. MPS on SDI protocol showed a moderate amount of jeopardized myocardium in the mid-distal anteroseptal wall extending to the apex in the LAD territory (Figure 4). Invasive CAG then showed 75% stenosis in the proximal LAD coronary artery.

Discussion

To our knowledge, this is the first study of simultaneous...
Simultaneous Dual-Isotope Protocol

201Tl and 740 MBq 99mTc-sestamibi) resulted in an effective dose of almost 30 mSv. This SDI protocol using 74 MBq 201Tl and 296 MBq 99mTc-tetrofosmin, however, delivers an effective dose <12 mSv, which is similar to the regular 1-day 99mTc-sestamibi protocol. We propose a reduced dose of 1 MBq/kg for 201Tl and 3 MBq/kg for 99mTc-tetrofosmin isotope when used with the sensitive D-SPECT camera. This may lower radiation exposure and should be confirmed in the future.

Second, the short examination time increases patient throughput and facilitates high satisfaction. All the patients were able to follow the SDI protocol without any complaints. A total examination time of 60 min is acceptable in the regular clinical setting. Six SDI protocols are routinely available from 9 to 12 o’clock in the laboratory. We used a second simultaneous acquisition for the calculation of TID ratio and observation of LV wall motion.

TID ratio is a well known marker of severe and extensive myocardial ischemia or jeopardized myocardium. We believe that TID ratio and stress-induced myocardial stunning, reflected by SWMS, would be useful to diagnose the presence of ischemic or jeopardized myocardium. Regarding these variables, there was a tendency toward a difference between the normal coronary group and multi-vessel group. The reasons for this are as follows: (1) the relatively short waiting time between the first and second acquisition; and (2) the lack of myocardial stunning due to the lower severity of SDS, compared with the previous study.

Conversely, Emmett et al reported that the TID phenomenon with vasodilator stress was not associated with stunning of wall motion or ventricular enlargement, but was more likely a function of...

Figure 3. Receiver operating characteristic curve analysis for detection of significant coronary artery disease. AUC, area under the curve; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery.
subendocardial hypoperfusion and impaired coronary flow reserve. This supports the present unexpected results regarding both TID ratio and SWMS in the SDI protocol with vasodilator stress. Moreover, if physicians did not need TID ratio or changes of wall motion between stress and rest scan in clinical reading, the second acquisition might not be necessary. A simple first simultaneous acquisition only protocol may contribute to reduce total examination time to 20 min. (The total examination time for sequential acquisition dual-isotope protocol [stress 201TI and rest 99mTc-sestamibi] with D-SPECT documented by Berman et al was estimated at 24 min.)

In addition, completely identical attenuation due to body position is guaranteed with simultaneous acquisition. If the heart drifts during the acquisition, the same artifactual perfusion defect would be created in the same location of the heart. This phenomenon suggests the need for clinical reading in order to cancel out the motion artifacts.

Third, regular MPS includes supine and prone position imaging, reducing attenuation of inferior walls. Given the much lower image attenuation with D-SPECT, single position imaging in the upright position would be useful. Upright imaging would also be appropriate to separate the heart and subdiaphragmatic activity (eg, liver or bowel uptake) with assistance of gastric bubble using soda. Single position imaging would therefore reduce total examination time and increase patient satisfaction.

Fourth, the image quality score of 201TI at stress was sufficient in the SDI protocol, but the 99mTc-tetrofosmin images were sometimes disturbed by extracardiac uptake of liver. In these cases, comparison between first and second acquisition of 99mTc-tetrofosmin images would be helpful to eliminate the extracardiac uptake, but further analysis is required.

Comparison of Diagnostic Performance

Although the hardware and protocol were different, diagnostic performance in the detection of significant CAD using another CZT gamma camera (Discovery NM 530c, GE healthcare, Haifa, Israel) was reported by Tanaka et al as follows: 76–85% sensitivity, 69–85% specificity and 74–81% accuracy on a per vessel basis. Of course, the subject group was also completely different between the 2 studies. Diagnostic performance is similar, but the advantages of the SDI protocol and D-SPECT are as follows: shorter total examination time (<1 h with the SDI protocol vs. 4 h with 201TI scan with NM 530c) and single position imaging (upright only scan with D-SPECT vs. supine and prone position scans with NM 530c).

Study Limitations

Although the TID phenomenon is associated with jeopardized myocardium or impaired coronary flow reserve, the relatively short waiting time (30 min) between the first and second acquisitions in the SDI protocol is not sufficient to show a difference in this between the 2 acquisitions. Further validation of the threshold for TID ratio in the SDI protocol is therefore needed.

Conclusions

Simultaneous acquisition rest 99mTc-tetrofosmin/stress 201TI dual-isotope protocol with D-SPECT facilitates high-speed MPS, lower radiation exposure and precise diagnostic accuracy compared with sequential dual-isotope scans.

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References

Simultaneous Dual-Isotope Protocol

695


