Clinical Utility of a Slow 201Tl Washout Rate in the Detection of Multi-Vessel Coronary Artery Disease Using a Simultaneous Acquisition Rest 99mTc/Stress 201Tl Protocol and a Semiconducting Gamma Camera

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Background: The diagnostic accuracy of stress myocardial perfusion single-photon emission computed tomography (SPECT) to detect coronary artery disease (CAD) is reduced by the balanced reduction of myocardial perfusion in patients with multi-vessel or left main trunk CAD (multi-vessel group). This study investigated the diagnostic performance of a simultaneous acquisition rest 99mTc/stress 201Tl dual-isotope protocol for myocardial perfusion SPECT (MPS) in a multi-vessel group by examining the assessment of a slow 201Tl washout rate (WR) finding in comparison to the accuracy of perfusion assessments.

Methods and Results: This study enrolled 91 patients who had undergone angiography within 3 months after MPS. The diagnostic performances of perfusion assessments and a slow 201Tl WR parameter were compared using the area under the curve (AUC) in a multi-vessel group of patients with mild ischemia (2≤summed difference score [SDS]≤7). The AUC of a slow WR parameter was significantly larger compared with that for perfusion assessments, in patients with mild ischemia, (AUC, 0.736 vs. 0.504–0.558, P value: <0.01–0.05).

Conclusions: Among patients with mild ischemia, a slow 201Tl WR parameter improved the detection of CAD in a multi-vessel group.

Key Words: Cadmium-zinc-telluride; Myocardial perfusion; Single-photon emission computed tomography; 201Thallium (201Tl); Washout rate

S
tress myocardial perfusion single photon emission computed tomography (SPECT) has been established as a useful diagnostic modality for detecting significant coronary artery disease (CAD). The JCS 2018 Guideline on Diagnosis of Chronic Coronary Heart Diseases recommends confirmation of the presence of stress-induced ischemia before revascularization as class I evidence. In cases with multi-vessel or left main trunk CAD (multi-vessel group), a balanced reduction of myocardial perfusion can cause false-negative results on stress MPS. One reason for this phenomenon is that MPS is a relative flow assessment that can lead to underestimations of myocardial perfusion in patients with multi-vessel disease. 2 4

Sodium potassium channels deliver 201Tl into myocardial cells from the microvascular circulation. A fast delivery and a fast washout of 201Tl is observed in normal myocardium; however, a slow delivery and a slow washout of 201Tl is seen in ischemic myocardium. Therefore, calculating the washout rate (WR) of 201Tl in the multi-vessel group might assist diagnosis in these cases, and previous reports have reported the usefulness of a slow 201Tl WR parameter in assessments using conventional Anger-type gamma cameras. 1 5 8

D-SPECT, which is a dedicated cardiac gamma camera equipped with semiconductor detectors made of cadmium-zinc-telluride (CZT), is clinically used in limited hospitals, but the usefulness of a slow 201Tl WR for detecting CAD in the multi-vessel group using a simultaneous acquisition stress 201Tl/rest 99mTc dual-isotope MPS protocol (SDI protocol) and D-SPECT has not been previously reported. 9

The aims of this study were: (1) to define an appropriate 201Tl WR cut-off value for detecting CAD in the multi-vessel group; and (2) to determine the clinical usefulness of a slow 201Tl WR parameter in comparison to stress perfusion assessments for detecting CAD in the multi-vessel group. We focused on patients with mild ischemia (2≤SDS≤7) because a balanced reduction of MPS findings,
which could lead to false-negative results, is more likely in cases with mildly abnormal MPS findings. Conversely, in patients with severe and extensive ischemia, the observation of multiple perfusion defects would easily predict the presence of ischemia in multiple coronary arteries.

**Methods**

**Patient Population**

Ninety-one consecutive patients who underwent stress MPS for the diagnosis of CAD between April 2016 and December 2018 at Nihon University Hospital were enrolled. Each patient had undergone invasive coronary angiography (CAG) or coronary computed tomography angiography (CCTA) within 3 months after MPS to evaluate their CAD. Patients aged <20 years or with a history of prior myocardial infarction and coronary artery bypass graft surgery were excluded from the study. Caffeine intake was prohibited for 24 h before the study, and the patients were instructed fast before visiting the hospital. This study was approved by an independent review board committee of Nihon University Hospital (IRB No. 20210402).

**Stress MPS Protocol**

An outline of the simultaneous acquisition dual-isotope (SDI) protocol for stress MPS reported by Makita et al is shown in Figure 1. Briefly, patients were injected with 125 MBq of $^{99m}$Tc-tetrofosmin (Nihon Medi-Physics, Tokyo, Japan) or $^{99m}$Tc-methoxy isobutyl isonitrile (MIBI; Fujifilm Toyama Chemical, Tokyo, Japan) to visualize myocardial perfusion during a resting state. Then, the patients underwent 6 min of vasodilator stress using an adenosine infusion (120 $\mu$g/kg/min; Fujifilm Toyama Chemical, Tokyo, Japan). At 3 min after the start of the adenosine infusion, 50–74 MBq of $^{201}$Tl was injected to visualize myocardial perfusion during stress. Subsequently, the first simultaneous rest $^{99m}$Tc/stress $^{201}$Tl acquisition performed in patients who were in an upright position was initiated using D-SPECT. After a meal break for 60–120 min to enable $^{201}$Tl redistribution, a second acquisition of the SDI protocol was performed. The acquisition time was determined based on the gamma-ray count for the left ventricle, and the target count values were set at more than 1 mega count.

**Photopeak Calibration**

The subtraction of photo-energy crosstalk between $^{99m}$Tc and $^{201}$Tl is a major problem in the SDI protocol; however, the higher energy resolution of CZT detectors compared with conventional Anger-type gamma cameras, enables the use of narrower energy windows to reduce the influence of down-scatter. Moreover, the iterative deconvolution method described by Kacperski et al has been used for down-scatter correction in D-SPECT. The method utilizes the triple energy window method and a scattering model based on the spatial and spectral distribution of projection counts in multiple photoelectric peak windows.

**Acquisition Protocol and Image Reconstruction**

A 10-s initial scan was performed to determine the location of the left ventricle and to define the range of the scan angles for each detector. The scan time was determined in accordance with the $^{201}$Tl count. Each image dataset consisted of 120 projections per detector. The reconstruction was performed using the successive approximation method and the proprietary Broadview reconstruction algorithm (Spectrum Dynamics Medical, Caesarea, Israel). Short axis, horizontal, and vertical long axis SPECT images were generated using Autoquant software (Cedars-Sinai Medical Center, Los Angeles, USA).

**Calculation of WR and Time Correction**

The absolute values of the mean count number in a 17-segment model of the left ventricle were obtained using Heart Risk View software (Nihon Medi-Physics, Tokyo, Japan). The calculation of the $^{201}$Tl WR using a conventional Anger-type gamma camera requires the use of a constant acquisition time (~15 min) and imaging interval (3–4 h) between the first and second acquisitions. However, the acquisition time and the imaging interval can vary because of the gamma ray count-based acquisition using D-SPECT. Therefore, the first and second acquisition times and the imaging interval had to be unified relative to the WR (%/h) obtained using a conventional Anger-type gamma camera using the following formulas.

\[
\text{WR (%/h)} = \frac{\text{mean stress }^{201}\text{Tl count} - \text{mean rest }^{201}\text{Tl count}}{\text{mean stress }^{201}\text{Tl count}} \times 100 / \text{imaging interval}
\]
Washout Rate to Detect CAD

The presence of myocardial ischemia was defined as SDS ≥ 2 in the corresponding coronary territory.

In patients with moderate to severely abnormal MPS findings (SDS ≥ 8), a perfusion assessment using MPS alone would be sufficient for the detection of multi-vessel disease; however, to determine the threshold of SDS at which a slow WR would be useful, we analyzed the patient groups with moderate to mild ischemia.

CAG and CCTA Interpretation

All patients underwent CAG or CCTA within 3 months after the stress MPS examination. Significant coronary stenosis was defined as ≥75% stenosis in the main coronary artery and ≥50% stenosis in the left main trunk. Small vessels with a narrow perfusion area and peripheral lesions were excluded from the definition of significant CAD. We categorized significant CAD into 2 groups as follows: a

<WR calculation formula for use with D-SPECT>

WR (%/h) = \frac{\text{mean stress }^{201}\text{TI count} - \text{mean rest }^{201}\text{TI count}}{\text{1st acquisition time (min)}} \times \frac{\text{1st acquisition time (min)}}{\text{2nd acquisition time (min)}} \times 100 / \text{imaging interval}

Image Interpretation

MPS images were scored semi-quantitatively by 2 experienced readers using a 17-segment model of the left ventricle and a 5-point scale (0, normal uptake; 1, mildly reduced uptake; 2, moderately reduced uptake; 3, severe reduced uptake; 4, almost no uptake). When the image interpretation differed, a consensus was reached between the 2 doctors. In this model, the left anterior descending coronary artery (LAD) territory consisted of 7 segments (Segments 1, 2, 7, 8, 13, 14, and 17), the left circumflex coronary artery (LCX) territory consisted of 5 segments (Segments 5, 6, 11, 12, and 16), and the right coronary artery (RCA) territory consisted of 5 segments (Segments 3, 4, 9, 10, and 15). The summed stress score (SSS), the summed rest score (SRS), and the summed difference score (SDS) were calculated according to methods previously described by Berman et al. The presence of myocardial ischemia was defined as SDS ≥ 2 in the corresponding coronary territory.

A balanced reduction of myocardial perfusion is usually seen in patients with mild ischemia.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Multi-vessel group (n=25)</th>
<th>0–1 vessel group (n=66)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69±10</td>
<td>69±9</td>
<td>ns</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>19 (76.0)</td>
<td>49 (74.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>66±11</td>
<td>63±10</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.4±2.6</td>
<td>23.6±3.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HD (%)</td>
<td>6 (24.0)</td>
<td>6 (9.1)</td>
<td>ns</td>
</tr>
<tr>
<td>Coronary risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>19 (76.0)</td>
<td>45 (68.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17 (68.0)</td>
<td>21 (31.8)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>12 (48.0)</td>
<td>29 (43.9)</td>
<td>ns</td>
</tr>
<tr>
<td>Current smoking</td>
<td>2 (8.0)</td>
<td>7 (10.6)</td>
<td>ns</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>ARB (%)</td>
<td>14 (56.0)</td>
<td>29 (43.9)</td>
<td>ns</td>
</tr>
<tr>
<td>Ca blocker (%)</td>
<td>11 (44.0)</td>
<td>31 (47.0)</td>
<td>ns</td>
</tr>
<tr>
<td>β-blocker (%)</td>
<td>4 (16.0)</td>
<td>224 (36.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Statin (%)</td>
<td>14 (56.0)</td>
<td>21 (31.8)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD or n (%). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; HD, hemodialysis; ns, not significant.

Table 2. Parameters of Perfusion and Gated Assessment

<table>
<thead>
<tr>
<th></th>
<th>Multi-vessel group (n=25)</th>
<th>0–1 vessel group (n=66)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSS</td>
<td>7 [5, 11]</td>
<td>1 [0, 4]</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>SRS</td>
<td>0 [0, 1]</td>
<td>0 [0, 0]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SDS</td>
<td>7 [3, 9]</td>
<td>1 [0, 3.75]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stress LVEF (%)</td>
<td>66.7±11.7</td>
<td>64.5±13.5</td>
<td>ns</td>
</tr>
<tr>
<td>Rest LVEF (%)</td>
<td>68.9±13.4</td>
<td>68.3±14.0</td>
<td>ns</td>
</tr>
<tr>
<td>ΔEF (%)</td>
<td>2.24±4.80</td>
<td>3.85±4.62</td>
<td>ns</td>
</tr>
<tr>
<td>TID ratio</td>
<td>1.15±0.10</td>
<td>1.11±0.13</td>
<td>ns</td>
</tr>
</tbody>
</table>

Values are presented as the median [25th percentile, 75th percentile] or n (%) for SSS, SRS and SDS. LVEF and TID ratio data are expressed as mean±standard deviation. ΔEF, Δ ejection fraction; LVEF, left ventricular ejection fraction; ns, not significant; SDS, summed difference score; SRS, summed rest score; SSS, summed stress score; TID, transient ischemic dilatation.
Results

Patient Background Characteristics

The patient background characteristics of the multi-vessel and 0–1 vessel groups are shown in Table 1. The multi-vessel group had a significantly higher BMI and prevalence of diabetes mellitus than the 0–1 vessel group (25.4 ± 2.6 vs. 23.6 ± 3.1 kg/m², P<0.05; and 68.0 vs. 31.8%, P<0.05).

Myocardial Perfusion and Gated Assessment

The median SSS, SRS and SDS values, mean stress left ventricular ejection fraction (LVEF), rest LVEF, ∆EF and transient ischemic dilatation (TID) ratio are shown in Table 2. The SDS was higher in the multi-vessel group than in the 0–1 vessel group (7 vs. 1, P<0.0001).

CAG and CCTA Findings

All the patients underwent invasive CAG or CCTA because of significant ischemia or at the decision of their physician. The number of cases with significant CAD and the frequency are shown in Table 3. Thirty-eight patients did not have significant coronary stenosis. Twenty-eight patients (LAD, 42.9%; LCX, 25.0%; RCA, 32.1%) had 1-vessel disease, 12 patients (LAD and RCA, 16.7%; LAD and LCX, 25.0%; LCX and RCA, 58.3%) had 2-vessel disease, and 13 patients had 3-vessel disease or left main trunk lesions.

Acquisition Time and Imaging Interval

Regarding the median acquisition time and imaging interval, no significant differences in the first acquisition time, the second acquisition time, or the imaging interval were seen between the multi-vessel group and the 0–1 vessel group (≥2 significant stenoses or a left main trunk lesion) and a 0–1 vessel group (no significant stenosis or stenosis in 1 vessel).

Statistical Analysis

EZ-R software was used for the statistical analysis. Continuous variables were expressed as the mean±SD or the median [25th percentile, 75th percentile]. An unpaired t-test, Mann-Whitney U-test, and Fisher’s exact test were used to compare the multi-vessel group and the 0–1 vessel group. Statistical significance was defined as P<0.05. A receiver operating characteristic (ROC) curve was used to describe the WR cut-off value for the diagnosis of CAD in the multi-vessel group. The ROC analysis for the detection of CAD in the multi-vessel group was performed in patients with moderate to mild ischemia, and the area under the curve (AUC) was compared between a slow WR and perfusion assessments. The range of SDS was varied as 2≤SDS≤4, 2≤SDS≤5, 2≤SDS≤6, 2≤SDS≤7, 2≤SDS≤8, 2≤SDS≤9, 2≤SDS≤10, 2≤SDS≤11 and 2≤SDS≤12. The results were compared with perfusion assessments in each range and a slow WR.

Figure 2. Comparison of 201Tl WR between the 0–1 vessel and multi-vessel groups. WR, washout rate.

Figure 3. Cut-off value for 201Tl WR for the detection of CAD in the multi-vessel group disease using a receiver operating characteristic curve (ROC) analysis. AUC, area under the curve; WR, washout rate.
Washout Rate to Detect CAD

To the best of our knowledge, this is the first study to confirm the usefulness of a slow WR parameter in the SDI protocol for D-SPECT. A slow 201Tl WR parameter in comparison to perfusion assessments of ischemic myocardium successfully improved the detection of CAD in the multi-vessel group in patients with mild ischemia. Furthermore, a perfusion assessment alone might be insufficient to detect CAD in the multi-vessel group in patients with mild ischemia, as suggested by the lower AUCs for the SDS alone findings (ranging from 0.504 for 2 ≤ SDS ≤ 4 to 0.558 for 2 ≤ SDS ≤ 7), as shown in Table 4.

The median 201Tl WR of the multi-vessel group was 2.8%/h in the present study, which was lower than that of the 0–1 vessel group (11.7 vs. 2.8%/h, P<0.001) (Figure 2). Because the WR cut-off value for discriminating the multi-vessel group using a ROC analysis was calculated to be 6.2%/h, we defined <7%/h as indicating a slow 201Tl WR suggestive of the multi-vessel group (Figure 3). The sensitivity and specificity for the WR being <7%/h in diagnosing the multi-vessel group was 76% and 71%, respectively.

The ROC analyses used to discriminate the multi-vessel group according to a slow WR or perfusion assessment (SDS) are shown in Table 4. A slow WR parameter in comparison to the SDS results was useful for the diagnosis of multi-vessels in patients with mild ischemia (2 ≤ SDS ≤ 7, P<0.05); however, its diagnostic performance was not statistically significant in another subset. In addition, a slow WR parameter consistently showed high diagnostic performance for the diagnosis of multi-vessels in the patient group.

Representative Case

A 70-year-old woman with angina pectoris showed mild ischemia (SDS=3) in the mid-to-distal anteroseptal wall extending to the apex (Figure 4, arrows). Her WR of 201Tl was as low as 4.9%/h, and CAG revealed disease in 3 vessels (LAD segment seg. 6, 90% stenosis; LCX seg. 13, 99% stenosis; and RCA seg. 4AV, 90% stenosis).

Discussion

Table 4. AUCs in ROC Analyses

<table>
<thead>
<tr>
<th>WR cutoff</th>
<th>AUC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7%/h vs. 2 ≤ SDS ≤ 4</td>
<td>0.736 vs. 0.504</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&lt;7%/h vs. 2 ≤ SDS ≤ 5</td>
<td>0.736 vs. 0.508</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&lt;7%/h vs. 2 ≤ SDS ≤ 6</td>
<td>0.736 vs. 0.513</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&lt;7%/h vs. 2 ≤ SDS ≤ 7</td>
<td>0.736 vs. 0.558</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>&lt;7%/h vs. 2 ≤ SDS ≤ 8</td>
<td>0.736 vs. 0.583</td>
<td>ns</td>
</tr>
<tr>
<td>&lt;7%/h vs. 2 ≤ SDS ≤ 9</td>
<td>0.736 vs. 0.623</td>
<td>ns</td>
</tr>
<tr>
<td>&lt;7%/h vs. 2 ≤ SDS ≤ 10</td>
<td>0.736 vs. 0.643</td>
<td>ns</td>
</tr>
<tr>
<td>&lt;7%/h vs. 2 ≤ SDS ≤ 11</td>
<td>0.736 vs. 0.663</td>
<td>ns</td>
</tr>
<tr>
<td>&lt;7%/h vs. 2 ≤ SDS ≤ 12</td>
<td>0.736 vs. 0.695</td>
<td>ns</td>
</tr>
</tbody>
</table>

AUC, area under the curve; ns, not significant; ROC, receiver operating characteristic; WR, washout rate.

To the best of our knowledge, this is the first study to confirm the usefulness of a slow WR parameter in the SDI protocol for D-SPECT. A slow 201Tl WR parameter in comparison to perfusion assessments of ischemic myocardium successfully improved the detection of CAD in the multi-vessel group in patients with mild ischemia. Furthermore, a perfusion assessment alone might be insufficient to detect CAD in the multi-vessel group in patients with mild ischemia, as suggested by the lower AUCs for the SDS alone findings (ranging from 0.504 for 2 ≤ SDS ≤ 4 to 0.558 for 2 ≤ SDS ≤ 7), as shown in Table 4.

The median 201Tl WR of the multi-vessel group was 2.8%/h in the present study, which was lower than that found in a previous report (10.6%/h). A 201Tl WR cut-off value of <7%/h was capable of clinically discriminating the

|Figure 4. Representative case. (A) Stress-induced ischemic myocardium in the left anterior descending coronary artery (white arrows) in short, vertical long and horizontal slices. (B) Upper, stenosis in the left anterior descending coronary artery and left circumflex coronary artery stenosis; Lower, stenosis in the right coronary artery stenosis (red arrows).
multi-vessel group from the 0–1 vessel group. Because overlooking the presence of multi-vessel CAD and left main trunk stenosis is a common concern, we recommend the use of a slow \(^{201}\)Tl WR parameter in comparison to perfusion assessments, as this measure can be easily calculated in the SDI protocol. Berman et al previously reported the utility for detecting left main trunk CAD.\(^{17}\) A low ejection fraction of the left ventricle, multiple perfusion defects, increased lung uptake of isotopes, abnormal wall motion and TID were significant parameters for the detection of left main trunk lesions in their study. Of note, Berman et al assessed the lung uptake of \(^{201}\)Tl at rest using rest \(^{201}\)Tl/stress \(^{99m}\)Tc-MIBI planar imaging. In the present study, however, we examined the usefulness of a slow \(^{201}\)Tl WR parameter for the detection of multi-vessel CAD as well as left main trunk stenosis.

This difference in the median \(^{201}\)Tl WR between the present and previous reports can be explained by: (1) the difference in SPECT protocols (the SDI protocol requires cross-talk correction from the \(^{99m}\)Tc to \(^{201}\)Tl windows); (2) the difference in the imaging interval (a shorter imaging interval might cause a smaller \(^{201}\)Tl WR between the first and second acquisitions); (3) the absence of decay correction for \(^{99m}\)Tc using iterative deconvolution correction; and (4) the application of vasodilator stress only in the present study (exercise and vasodilator stress were both included in the previous report).\(^{8,10,19}\) Exercise stress tests can be difficult for elderly patients to undergo, and so vasodilator stress tests might be more appropriate for elderly patients. Therefore, the \(^{201}\)Tl WR during vasodilator stress tests might be more important than in situations where exercise stress tests are also performed. In addition, the WR is reportedly correlated with the coronary flow reserve (CFR) during vasodilator stress tests, possibly making vasodilator stress more suitable than exercise stress for the prediction of CFR.\(^{7}\)

In a previous study, Sharir et al reported that reducing stress LVEF and TID are useful in diagnosing multi-vessel CAD and left main trunk stenosis, but none of these measures were found to be significant in the present study.\(^{20}\) There were no significant differences in stress LVEF, rest LVEF, ΔEF and TID ratio between the multi-vessel and 0–1 vessel groups. The reason for this may be that all patients in this study underwent vasodilator stress using an adenosine infusion. Although vasodilator stress increases coronary blood flow, it does not necessarily induce myocardial ischemia or post-stress myocardial stunning instead of CFR. Xu et al reported that TID was more frequently observed in patients with moderate to severe perfusion abnormality in comparison to our population that had observed in patients with moderate to severe perfusion abnormality in comparison to our population that had moderate to severe perfusion abnormality.\(^{21}\) Therefore, measurement of WR may be a more favorable indicator for diagnosis of multi-vessel CAD than ΔEF or TID ratio in cases of vasodilator stress.

In Table 2, there was a significant difference in the median SRS between the multi-vessel and 0–1 vessel groups, even though the median SRS was 0. Fourteen out of 25 patients (56%) in the multi-vessel group and 61 out of 66 patients (92%) in the 0–1 vessel group had SRS=0, which may be due to the significantly lower number of patients in the multi-vessel group. This may be because there were significantly fewer cases of CAD in the multi-vessel group.

In this study, there were a total of 12 patients with a WR <9%/h, 4 of which were in the 0–1 vessel group and 8 of which were in the multi-vessel group. Regarding the 8 patients in the multi-vessel group, previous reports have shown that a negative WR suggests severe stenosis of the coronary arteries and is useful as an adjunct diagnosis for multi-vessel disease. Therefore, it is usually possible to have a negative WR in the multi-vessel group. In 2 of the 4 patients in the 0–1 vessel group, \(^{99m}\)Tc-MIBI was used as a tracer at resting perfusion, and extracardiac accumulation was observed. The problem with \(^{99m}\)Tc-MIBI is that it has been reported to cause extracardiac accumulation at rest. As the \(^{99m}\)Tc agent is excreted from the hepatobiliary system, it may cause a high extracardiac accumulation adjacent to the heart. The extracardiac uptake of \(^{99m}\)Tc-MIBI in the liver at rest may disrupt the stress count of \(^{201}\)Tl in the SDI protocol. Actually, Johansen et al documented that changes between the first and second perfusion assessment with and without extracardiac uptake of \(^{99m}\)Tc may affect the \(^{201}\)Tl WR.\(^{22}\)

Another important finding of this study was that a slow \(^{201}\)Tl WR parameter was useful for the diagnosis of CAD in the multi-vessel group in patients with mild ischemia. Patients with moderate to severe ischemia sometimes exhibit multiple perfusion defects, which naturally suggests the presence of multi-vessel disease. To avoid understimating the presence of CAD in the multi-vessel group, however, other information on the presence of a slow \(^{201}\)Tl WR might be necessary for patients with mild ischemia, and might play a more important role than it would in patients with moderate to severe ischemia (SDS ≥8).

Dual-isotope imaging is not usually recommended for MPS because of the higher radiation exposure; however, the high sensitivity to gamma ray counts of semi-conductor gamma cameras allows the SDI protocol to be used with a lower radiation exposure and a shorter imaging time, compared with conventional Anger-type gamma cameras. According to a survey conducted in 2016, the ratio of the utilization of \(^{201}\)Tl and \(^{99m}\)Tc in Japan was approximately 1:1, and the utilization of \(^{201}\)Tl was higher in Japan than it was in Europe or the United States.\(^{23}\) Both \(^{201}\)Tl and \(^{99m}\)Tc agents are unique, but \(^{201}\)Tl has a long half-life and an increased exposure, compared with \(^{99m}\)Tc. In contrast, the detection sensitivity in the ischemic myocardium is known to be higher because of good myocardial blood flow tracking and a high myocardial extraction fraction.\(^{24}\)

According to the IAEA Nuclear Cardiology Protocols Cross-Sectional Study (INCAPS) study, to optimize radiation exposure, \(^{201}\)Tl should not be used for patients aged <70 years.\(^{25}\) In addition, the American College of Cardiology has proposed that an exposure dose of >50% for all examinations be ≤9 mSv per test.\(^{26}\) However, semi-conductor gamma cameras enable radiation exposure from \(^{201}\)Tl to be reduced because of their high sensitivity. The minimum usage is 50 MBq of \(^{201}\)Tl and 125 MBq of \(^{99m}\)Tc in the SDI protocol, for a total of 8.0 mSv/test; this exposure dose is <9 mSv. In future, if the \(^{201}\)Tl dose can be adjusted according to body weight, it might be possible to further reduce the radiation exposure dose in some cases.

**Study Limitations**

Regarding the time correction for the WR (%/h), the conventional imaging protocol using \(^{201}\)Tl used a 3- to 4-hour imaging interval; however, the imaging interval of the SDI protocol is shortened to approximately 1.3–1.7 h. The transfer of \(^{201}\)Tl from the circulatory blood flow to the myocardium is regulated by sodium/potassium channels; however, this relatively short imaging interval might not be sufficient...
to fully investigate the effect of $^{201}$Tl WR in ischemic myocardium. The $^{201}$Tl WR in ischemic myocardium is delayed and may have a negative WR value. Functional coronary stenosis evaluated using the fractional flow reserve during invasive CAG can sometimes differ from anatomical stenosis. However, Di Carlo et al reported an association between anatomical coronary stenosis and CFR, as evaluated in a vasodilator and a positron emission tomography study. Therefore, anatomical coronary stenosis is still used for evaluating functional ischemia.

The rate of $^{99m}$Tc-MIBI use at rest perfusion was in 4 of 25 patients in the multi-vessel group and 25 of 66 patients in the 0–1 vessel group (16% vs. 38%, P = ns). Extra cardiac accumulation of $^{99m}$Tc might disrupt the $^{201}$Tl WR in the 0–1 vessel group patients and a cause larger variation of WR (Figure 2).

**Conclusions**

A slow $^{201}$Tl WR parameter in comparison to perfusion assessments improved the diagnostic accuracy of detecting multi-vessel CAD and left main trunk stenosis in patients with mild ischemia.

**Disclosures**

The authors have no conflicts of interest to declare.

**Sources of Funding**

This study received no specific funding.

**IRB Information**

This study was approved by an independent review board committee of the Nihon University School of Medicine (IRB No. 20210402).

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