Validation of Automated Quantitation of Myocardial Perfusion and Fatty Acid Metabolism Abnormalities on SPECT Images

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Background: Myocardial perfusion and fatty acid imaging have played important roles in the risk stratification of patients with coronary artery disease (CAD). However, visual image assessment requires considerable experience and training. Therefore, an automated program has been developed that can quantify perfusion and fatty acid uptake on myocardial single emission computed tomography (SPECT). The present study aimed to validate the automated quantitative program.

Methods and Results: A total of 50 patients were studied with known or suspected CAD who underwent stress $^{201}$Thallium ($^{201}$Tl) and resting $^{123}$I-labelled $\beta$-methyl iodophenyl pentadecanoic acid (BMIPP) SPECT. The SPECT images were quantified in 17 segments visually and using our Heart Score View software. Values were compared with those in a normal Japanese database and calculated summed stress (SSS), summed rest (SRS), summed difference (SDS), and summed BMIPP scores for each modality. Summed scores obtained using standard visual analysis and Heart Score View significantly correlated ($^{201}$Tl: SSS: $r=0.934$; SRS: $r=0.827$; SDS: $r=0.743$ summed BMIPP score: $r=0.913$) (each $P<0.001$) and Bland-Altman analysis revealed good agreement between the 2 approaches.

Conclusions: Correlations between scores determined using Heart Score View software and standard visual interpretation were linear for both perfusion and fatty acid images. Thus, our new automated program might be useful for the risk stratification of patients with CAD in the clinical setting. (Circ J 2011; 75: 2187–2195)

Key Words: Coronary artery disease; Quantitative assessment; Risk stratification
A Flow chart of Heart Score View Analysis

- Selection of Short Axis SPECT Image
- Fitting two images with co-registration system

Image analysis
- Selection of analysis tools
  - Subtraction image
  - Washout
  - BMIPP-MPI Mismatch
  - Comparison with Database

B

<table>
<thead>
<tr>
<th>Segment No</th>
<th>Location</th>
<th>%Uptake of standard database</th>
<th>Defect scores in each segment (1, Slightly abnormal - 4, Absent uptake)</th>
<th>Adjustment factors</th>
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<tr>
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<td>Basal A</td>
<td>74.7</td>
<td>64 55 46 37</td>
<td>0.86</td>
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<td>Basal AS</td>
<td>61.6</td>
<td>53 46 38 30</td>
<td>0.74</td>
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<td>3</td>
<td>Basal LS</td>
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<td>50 43 36 29</td>
<td>0.61</td>
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<td>4</td>
<td>Basal L</td>
<td>62.1</td>
<td>53 46 38 30</td>
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<td>Basal IL</td>
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<td>61 52 43 35</td>
<td>0.48</td>
</tr>
<tr>
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<td>Basal AL</td>
<td>76.8</td>
<td>66 57 47 38</td>
<td>0.48</td>
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<tr>
<td>7</td>
<td>Mid A</td>
<td>85.9</td>
<td>74 64 52 42</td>
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<td>8</td>
<td>Mid AS</td>
<td>84.2</td>
<td>72 62 51 41</td>
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<tr>
<td>9</td>
<td>Mid LS</td>
<td>74.1</td>
<td>64 55 45 36</td>
<td></td>
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<td>10</td>
<td>Mid L</td>
<td>72.4</td>
<td>62 54 44 35</td>
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<td>Mid IL</td>
<td>80.0</td>
<td>69 59 49 39</td>
<td></td>
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<tr>
<td>12</td>
<td>Mid AL</td>
<td>89.1</td>
<td>77 66 54 44</td>
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<td>Apical A</td>
<td>85.9</td>
<td>74 64 52 42</td>
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<td>14</td>
<td>Apical AS</td>
<td>84.4</td>
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<td>15</td>
<td>Apical LS</td>
<td>76.7</td>
<td>66 57 47 38</td>
<td></td>
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<td>Apical L</td>
<td>87.6</td>
<td>75 65 53 43</td>
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<td>17</td>
<td>Apex</td>
<td>77.8</td>
<td>67 58 47 38</td>
<td></td>
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</tbody>
</table>

Average of six basal segments: 56 48 40 32
Average of 11 mid to apex segments: 70 60 50 40

Figure 1. (A) Concept of Heart Score View software. (B) Threshold settings based on normal database established by Japanese Society of Nuclear Medicine. Mid A, middle anterior; Mid AL, middle antero-lateral.
the automated program by comparison with standard expert visual interpretations of both $^{201}$Thallium ($^{201}$Tl) and BMIPP myocardial SPECT images.

**Methods**

**Study Population**

This retrospective study included 196 consecutive patients with known or suspected CAD who underwent stress $^{201}$Tl and rest BMIPP myocardial SPECT at Shin-Nittetsu Muroran General Hospital between January 1995 and December 2000. Patients with known myocardial infarction were excluded. We randomly assessed 50 (25 males and 25 females) of these 196 patients. The Ethics Committee of Shin-Nittetsu Muroran General Hospital approved the study protocol.

**Myocardial Perfusion and Fatty Acid Imaging**

The data acquisition protocols have been described elsewhere. Briefly, patients fasted for >6 h before the studies. Forty-two and 8 patients underwent exercise and pharmacological stress-testing, respectively. The patients who underwent exercise symptom-limited treadmill stress testing were injected with $^{201}$Tl at peak exercise and then continued the exercise for 1 min. The patients who underwent dipyridamole stress testing were administered with dipyridamole (0.14 mg · kg$^{-1}$ · min$^{-1}$) and then injected with $^{201}$Tl at 3 min later. $^{201}$Tl and $^{99m}$Tc images were acquired starting from 15 min after tracer injection using a digital gamma camera (Shimazu 510R, Shimadzu CO, Kyoto, Japan). Rest images were acquired 4 h later. Patients were intravenously administered under both fasting and resting conditions with 111 MBq of BMIPP (Nihon Medi-Physics Co Ltd, Tokyo, Japan). We randomly assessed 50 (25 males and 25 females) of these 196 patients to evaluate the concordance of scores between the 2 assessment teams.

**Automated Quantitation of Myocardial SPECT Images Using Heart Score View Software**

We developed an automated program for myocardial SPECT called Heart Score View software (Nihon Medi-Physics Co Ltd, Tokyo, Japan) that was designed for use with the Windows operating system. It has multiple analytical tools including SSS and $^{201}$Tl washout, as well as perfusion and fatty acid mismatch. The algorithm for generating a polar map was a hybrid 2-part sampling method that operates in 3-dimensional space and uses short axis images to generate count profiles from a 3-dimensional sampling scheme of short-axis slices. Images were co-registered and fused using a fully automated and mutual information algorithm. The software requires manual setting of the left ventricular cavity and then it generates polar maps from myocardial SPECT data that are divided into 17 segments based on ASNC guidelines to calculate the mean count in each segment. These mean counts were compared with the normal stress/rest $^{201}$Tl, $^{99m}$Tc MPI, and rest BMIPP database developed for Japanese patients by the Japanese Society of Nuclear Medicine working group. The mean % uptake in each segment was derived, converted to scores using a 5-point scale ranging from normal to absent and then described on polar maps (Figures 1A, B). The % uptake was usually lower in the basal septum due to the membranous septum. Therefore, we excluded the 6 basal segments when determining threshold values.

We based the following definitions for scoring parameters based on various degrees of abnormal perfusion.

**Table 1. Clinical Characteristics of the Study Population**

| Age (years) | 66.0±10.3 |
| Gender (male) | 25/50 (50.0%) |
| Unstable angina pectoris | 5/50 (10.0%) |
| LVEF (%) | 67.9±9.2 |
| Coronary risk factors | |
| Current smoker | 15/50 (30.0%) |
| Diabetes mellitus | 10/50 (20.0%) |
| Hypertension | 30/50 (60.0%) |
| Dyslipidemia | 17/50 (34.0%) |

LVEF, left ventricular ejection fraction.

**Table 2. Profiles of Regression Coefficients of Summed Scores Between Visual Interpretation and Heart Score View Analysis**

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition 1</th>
<th>R</th>
<th>Equation</th>
<th>Definition 2</th>
<th>R</th>
<th>Equation</th>
<th>Definition 3</th>
<th>R</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSS</td>
<td>0.953</td>
<td>Y=1.554x+0.415</td>
<td>0.934</td>
<td>Y=1.065x–0.447</td>
<td>0.852</td>
<td>Y=0.691x–1.712</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRS</td>
<td>0.906*</td>
<td>Y=1.448x–0.001</td>
<td>0.827</td>
<td>Y=0.915x–0.236</td>
<td>0.716*</td>
<td>Y=0.537x–0.769</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SDS</td>
<td>0.850*</td>
<td>Y=1.388x+0.569</td>
<td>0.743</td>
<td>Y=0.903x+0.187</td>
<td>0.593*</td>
<td>Y=0.437x+0.175</td>
<td></td>
<td></td>
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<tr>
<td>BMIPP score</td>
<td>0.953</td>
<td>Y=0.660x–0.227</td>
<td>0.913</td>
<td>Y=0.916x+0.016</td>
<td>0.882</td>
<td>Y=0.673x–0.860</td>
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</table>

*SSignificant difference in regression coefficients for SRS between thresholds 1 and 3, P<0.01 as well as in SDS between definitions 1 and 3, P<0.01. NS between thresholds 1 and 2.

R, regression coefficient; SSS, summed stress score; SRS, summed rest score; SDS, summed difference score; BMIPP, $^{11}$C-labelled $\beta$-methyl iodophenyl pentadecanoic acid; $^{201}$Tl, $^{201}$Thallium; SPECT, single photon emission computed tomography.
Figure 2. Correlations and Bland-Altman plot of data generated from visual interpretation (VI) and Heart Score View software using 201Tl Thallium (201Tl) MPI. (A) Summed stress scores (SSS). (B) Summed rest scores (SRS). (C) Summed difference scores (SDS). (D) Representative images of 66-year-old diabetic woman with effort angina pectoris. 201Tl images show moderately sized, moderate intensity of perfusion defect in inferolateral wall that improved at rest, indicating moderate ischemia in LCX territory. Visual and automated SSS were 9 and 8, respectively.
Table 3. Profiles of Correlations of Regional Summed Scores Between Visual Interpretation and Heart Score View Calculation

<table>
<thead>
<tr>
<th>Score</th>
<th>LAD territory</th>
<th>LCX territory</th>
<th>RCA territory</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSS</td>
<td>r=0.903</td>
<td>r=0.911</td>
<td>r=0.778</td>
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<tr>
<td></td>
<td>(P&lt;0.001)</td>
<td>(P&lt;0.001)</td>
<td>(P&lt;0.001)</td>
</tr>
<tr>
<td>SDS</td>
<td>r=0.793</td>
<td>r=0.501</td>
<td>r=0.530</td>
</tr>
<tr>
<td></td>
<td>(P&lt;0.001)</td>
<td>(P&lt;0.001)</td>
<td>(P&lt;0.001)</td>
</tr>
</tbody>
</table>

LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery. Other abbreviations see in Table 2.

Definition 1 All segments with a mean uptake of <70% on images were defined as abnormal.\(^a\) Segments with mild, moderate, or severe reduction were defined as 60 to 70%, 50 to 60%, and 40 to 50% uptake, and scored as 1, 2, and 3, respectively. Segments with absent uptake were defined as <40% uptake and scored as 4. Normal segments were scored as 0.

Definition 2 All segments with a mean uptake of <75% on images were defined as abnormal.\(^b\) Mild, moderate, and severe reduction was defined using the same approach. Absent uptake was defined as <45% uptake.

Definition 3 Segments with a mean uptake of <80% on images were defined as abnormal.\(^c\) Mild, moderate, and severe reduction was defined using the same approach. Absent uptake was defined as <50% uptake.

Summed BMIPP Scores The same 3 definitions were also applied to BMIPP images and summed BMIPP scores were obtained using the automated program.

Regional Analysis
The LV wall was divided into 17 segments that were subdivided into 3 coronary artery territories according to the ASNC imaging guidelines, and then SSS and SDS were evaluated.\(^d\)

Inter- and Intra-Operator Variability of Heart Score View Software
Inter- and intra-operator variability in stress \(^{201}\)TI MPI and rest BMIPP values was analyzed using the datasets. Two datasets analyzed by 1 operator were compared to determine intra-operator agreement and datasets analyzed by different operators were compared to assess inter-operator agreement.

Coronary Angiography (CAG)
Among the 50 patients, 7 underwent CAG using a standard technique within 2 months of the index \(^{201}\)TI stress/retest SPECT study. The presence or absence of CAD was determined from clinical CAG reports. The presence of significant CAD was a visually determined diameter stenosis of ≥75% for the 3 main coronary arteries or their major branches.\(^e\) Reversible myocardial ischemia was defined as SDS ≥2.\(^f\)

Statistical Analysis
Continuous values are expressed as means±SD. Categorical measures are presented as frequencies with percentages. Pearson’s correlation coefficients were calculated. Agreement among summed scores between visual interpretations and the automated program was determined using the Bland-Altman method. The optimal cut-off value for \(^{201}\)TI SDS was determined using receiver operating characteristics (ROC) curve analysis with the automated software. Concordance between the SDS and CAG was evaluated using the \(\kappa\) statistic. All data were statistically analyzed using MedCalc Software (Version 9.4.2.0, Medcalc Software, Mariakerke, Belgium). A P-value of <0.05 was considered significant.

Results

Patients' Characteristics
Table 1 shows the patients’ characteristics. Five of them had unstable angina pectoris but this stabilized by the time of the SPECT studies.

Correlations Among Summed Scores From MPI Between Visual Interpretation and Automated Software
Table 2 shows the correlation coefficients and the results of the Bland-Altman analysis of results using visual and automated modalities.

Definition 1 (Abnormal Uptake Defined as <70% Uptake) Values closely correlated (SSS: \(r=0.953\), \(P<0.001\); SRS: \(r=0.906\), \(P<0.001\); SDS: \(r=0.850\), \(P<0.001\)) and Bland-Altman analysis revealed good agreement in the comparison of SSS, SRS and SDS between the 2 modalities.

Definition 2 (Abnormal Uptake Defined as <75% Uptake) Values closely correlated (SSS: \(r=0.934\), \(P<0.001\); SRS: \(r=0.827\), \(P<0.001\); SDS: \(r=0.743\), \(P<0.001\)) (Figures 2A–D) and Bland-Altman analysis revealed good agreement in the comparison of SSS, SRS, and SDS between the 2 modalities with a mean difference near 0 (Figures 2A–C).

Definition 3 (Abnormal Uptake Defined as <80% Uptake) Values closely correlated (SSS: \(r=0.852\), \(P<0.001\); SRS: \(r=0.716\), \(P<0.001\); SDS: \(r=0.593\), \(P<0.001\)) and Bland-Altman analysis revealed good agreement for all summed scores between the 2 modalities.

Correlations Among Regional Summed Scores From MPI Between Visual and Automated Interpretation
Table 3 shows the correlation coefficients of the visual and automated modalities with regional analysis. Correlations between the 2 approaches were good for stress perfusion defects. Summed difference scores also correlated between the 2 methods.

Assessment of Anatomical CAD Using SDS Value of Heart Score View Software
Using definition 2, the exact agreement between myocardial ischemia, SDS ≥2 by \(^{201}\)TI SPECT, and CAG in assessing the anatomical extent of CAD was 85.7% (Table 4). The \(\kappa\) value was 0.695, indicating substantial agreement. The sensitivity and specificity were 80% and 100%, respectively, using \(^{201}\)TI SDS with definition 2.

Among the 3 definitions, diagnostic accuracy was best for definition 2. However, the area under the curve did not significantly differ among the 3 definitions of an abnormal threshold in \(^{201}\)TI SDS based on ROC analysis (Figure 3).
Correlations for Summed Scores From BMIPP Between Visual and Automated Interpretation

Definition 1 (Abnormal Uptake Defined as <70% Uptake)
Values closely correlated (Summed BMIPP score: r=0.953, P<0.001) and Bland-Altman analysis revealed good agreement for summed BMIPP scores between the 2 modalities.

Definition 2 (Abnormal Uptake Defined as <75% Uptake)
Values closely correlated (summed BMIPP score: r=0.913, P<0.001) (Figures 4A, B) and Bland-Altman analysis revealed good agreement for summed BMIPP scores between the 2 modalities with a mean difference near 0 (Figure 4A).

Definition 3 (Abnormal Uptake Defined as <80% Uptake)
Values closely correlated (summed BMIPP score: r=0.882, P<0.001) and Bland-Altman analysis revealed good agreement for summed BMIPP scores between the 2 modalities.

Comparison of 3 Levels of Abnormal Uptake
Linearity was the best among the 3 definitions for abnormal uptake defined as <75% uptake (Definition 2) with near y=x linearity between the 2 modalities (Table 2). Furthermore, Bland-Altman analysis showed that the mean of the difference between the 2 methods was near 0 for this state.

Concordance of Visual Interpretations Between 2 Groups of Assessors
Correlations coefficients and the results of Bland-Altman plot analysis of standard visual interpretations between 2 teams (n=12) were evaluated. Summed scores between assessor teams A and B closely correlated (SSS: r=0.895, P<0.001, SDS: r=0.950, P<0.001, summed BMIPP score: r=0.981, P<0.001). Only SRS did not significantly correlate between the 2 teams (SSS: r=0.559, P=0.059). However, actual SRS did not significantly differ between them (1.1±1.2 vs. 0.3±0.7, NS).

Bland-Altman plot analysis revealed good agreement between the 2 assessor teams for all variables (bias indicating mean difference between the 2 groups of assessors and 95% limits of agreement for SSS: 1.1 and −3.0 to 5.2; SRS: 1.1 and −2.0 to 4.1; SDS: 0.0 and −2.8 to 2.8; summed BMIPP score: −0.1 and −3.3 to 3.1, respectively).

Inter- and Intra-Operator Variability of Heart Score View Software
Intra-operator correlations were significantly higher in SSS (r=0.995, P<0.001) and in BMIPP summed score (r=0.995, P<0.001), as was inter-operator agreement (r=0.976, P<0.001 and r=0.986, P<0.001, respectively).

Discussion
Myocardial perfusion and fatty acid abnormalities generated by the Heart Score View software and standard visual interpretations closely correlated and agreed between both stress/rest 201TI and rest BMIPP myocardial imaging protocols. Thus, the program could objectively assess myocardial perfusion and metabolism that play important roles in the accurate diagnosis and risk assessment of patients with CAD.

Risk Assessment Using MPI
Stress MPI has excellent prognostic value. The ASNC guidelines recommend semi-quantitative analysis of myocardial perfusion images and calculations of SSS, SRS, and SDS for risk stratification. Although the established scoring system is relatively simple, visual assessment of SPECT MPI is subjective and thus repeatability is lower than that of quantitative analysis. Quantitation of MPI has enhanced the reliability of interpretation. However, accuracy has been validated in very few automated programs that generate defect scores using a North American database. The North American physique is quite different from that of Asians in terms of breast size, lateral fat pad, and diaphragm, all of which could attenuate perfusion defects. Thus, automated programs should be designed considering target populations. Our automated Heart Score View software evaluates regional perfusion based on a Japanese database of normal values. Other studies have defined abnormal perfusion as relative % uptake <70%, 75%, and 80%. Therefore, we applied 80%, 75%, and 70% relative uptake as cut-off values in the present study and found good correlations between the scores generated visually and by the software. Thus, Heart Score View software was validated like the North American program. The closest correlation at 75% relative uptake among the 3 cut-off values agrees with previous findings. Quantitative perfusion SPECT and Heart View Software have similar functions, but the latter can also calculate SSS, SRS, SDS, and BMIPP summed score using cut-off values.

Only SRS did not significantly correlate between the 2 visual assessment teams. This was due to the small range of...
distribution in rest scores because none of the patients had prior myocardial infarction. In fact, SRS values did not significantly differ between the 2 teams.

Correlations between the 2 approaches were also good for regional SSS (Table 3) and SDS. Thus, Heart Score View software might be able to detect regional perfusion abnormalities at stress and regional ischemia as well as the global approach. The correlation for SDS seems lower than that for SSS. The SDS is the result of subtracting the SSS from the SRS. Thus, the magnitude of the SDS is usually lower than that of the SSS, which would affect the results. However, the correlation remained significant and the present data agree with previous findings.15

We further applied the automated program to detect ischemia location and culprit lesions. Although the number of study patients with CAG was limited, but when applied together with the ischemic parameter, SDS, the automated program substantially agreed with coronary stenosis and seemed to accurately detect culprit lesions because the diagnostic accuracy was comparable with previous reports.9,34,35 Thus, the automated program also has the potential to detect culprit lesions. However, this requires further investigation.

Experts in visual analysis usually consider the characteristics of given tracers and soft tissue attenuation. Mild defects related to soft tissue attenuation are usually considered normal. Thus, summed stress and rest scores might be lower

Figure 4. Correlations and Bland-Altman plot of data generated from visual interpretation (VI) and Heart Score View software using β-methyl iodophenyl pentadecanoic acid (BMIPP) imaging. (A) Summed BMIPP scores. (B) Representative images of 66-year-old diabetic woman with effort angina pectoris. Rest BMIPP images show moderately sized, moderate intensity of perfusion defect in inferolateral wall that improved at rest, indicating moderate ischemia in LCX territory. Visual and automated summed stress scores were both 8.
than those generated by the automatic program. Correlations between the 2 approaches were good in the present study, but the SDS and SRS were slightly higher in the automatic approach. However, differences between them were not significant. One solution for reducing this discrepancy might be to use an appropriate normal database as in the present study. However, further technical improvements are required to overcome this issue.

### Risk Assessment Using Myocardial Fatty Acid Imaging

Because abnormal fatty acid metabolism can persist after myocardial ischemia, fatty acid imaging at rest might identify ischemic history.36–38 We, Matsuki et al and others have reported that summed scores obtained from BMIPP images have prognostic value for cardiac events.16–18 However, automated quantitative BMIPP imaging has not been validated. The approach used in the present study was the same that used for SPECT MPI. Heart Score View closely correlated with visual interpretations. Thus, this automated method of quantitative measurement might enhance the reliability of BMIPP imaging as well as of SPECT MPI.

### Study Limitations

Although the current study population was small, the sample size was similar to that of a previous validation study.17 Our sample data represented a relatively larger CAD cohort of 196 patients and thus we consider it to have sufficient power to validate the new program.

Although we found close correlations between the visual and automated modalities, we did not have outcome data for the patients. Outcomes should be evaluated and a follow-up study is underway.

Only a few patients had CAG. The diagnostic accuracy of detecting the location of myocardial ischemic based on CAG data in the present study was relatively good, but further investigations are required with a larger population.

We validated the automated program using 201Tl, but we did not evaluate reliability using a technetium-labeled tracer of myocardial flow. This should also be addressed in further studies.

### Conclusion

Myocardial perfusion and fatty acid abnormalities closely correlated and agreed between Heart Score View and standard visual interpretations both in stress/rest 201Tl and rest BMIPP myocardial imaging protocols.

This automated program might be useful for risk stratification in patients with CAD in the clinical setting.

### Acknowledgments

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### Disclosure

None to disclose.

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Quantitative Assessment of Myocardial SPECT Images


