

1 **Abstract**

2 *Objective.* An iterative reconstruction method in combination with resolution recovery,
3 attenuation and scatter corrections (IR-RASC) can improve image quality. It, however,
4 is undetermined whether this technique can improve the detection of coronary artery
5 disease (CAD) when automated quantitative analysis is used. This study evaluated
6 diagnostic values of IR-RASC in combination with automated quantitative analysis in
7 stress myocardial perfusion imaging (MPI) in the CAD detection.

8 *Methods.* This study enrolled consecutive 64 patients (mean age 66.2 ± 17.3 years, 39
9 males) who had undergone both ^{99m}Tc -labeled tetrofosmin stress MPI and coronary
10 angiography within 3 months. Stress MPI abnormalities quantified as summed stress
11 score (SSS), summed rest score (SRS) and summed difference score (SDS) by Heart
12 Risk View-S (HRV-S) and Quantitative Perfusion SPECT (QPS) softwares using
13 IR-RASC images were compared with those by using conventional filtered
14 back-projection method (FBP) images and angiographic findings.

15 *Results.* Based on expert visual assessment, SSS and SRS by HRV-S/QPS softwares
16 with IR-RASC were significantly lower than those by HRV-S/QPS softwares with FBP

17 at mid- and basal left ventricular segments. Receiver-operating characteristics analysis
18 showed that areas under the curve assessed by HRV-S (0.687) and QPS (0.678) with
19 IR-RASC were nearly identical to those (0.717 to 0.724) by expert assessment with
20 FBP, and were significantly ($p < 0.05$) greater than those by HRV-S (0.505) and QPS
21 (0.522) with FBP. When HRV-S was used, the specificity and diagnostic accuracy of
22 IR-RASC in the CAD detection were significantly greater than those of FBP: 90.3%
23 versus 51.6%, $p < 0.0001$, and 79.7% versus 54.7%, $p = 0.0027$, respectively. Likewise,
24 when QPS was used, the specificity and diagnostic accuracy of IR-RASC in the CAD
25 detection were significantly greater than those of FBP: 80.6% versus 41.9%, $p < 0.0001$,
26 and 78.1% versus 51.6%, $p = 0.0018$, respectively. There, however, was no significant
27 differences in sensitivity between IR-RASC and FBP images.

28 *Conclusions.* IR-RASC can improve diagnostic accuracy of the CAD detection using an
29 automated scoring system compared to FBP, by reducing false positivity due to
30 artefactual appearance.

31

32 **Keywords:** Automated quantitation • Iterative reconstruction • Resolution recovery •

33 Attenuation correction • Scatter correction

34

35 **Introduction**

36 Stress myocardial perfusion single photon emission computed tomography (SPECT)

37 has robust clinical evidence to show clinical efficacies not only in the noninvasive

38 detection of coronary artery disease (CAD) but also in the risk-stratification of patients

39 with known or suspected CAD on future cardiovascular events [1-6]. Semi-quantitative

40 visual analysis (a 5-point, 17-segment model) has been widely utilized in the

41 assessment of stress myocardial SPECT imaging, but requires experienced experts to

42 maintain a reliable diagnostic accuracy and a high reproducibility by minimizing inter-

43 and intra-observer errors and by precisely identifying image artifacts. Instead of visual

44 quantitative analysis, there are several softwares developed for automated quantification

45 of myocardial perfusion abnormality and cardiac function [7-10]. These softwares are

46 basically applied for SPECT images reconstructed by a conventional filtered

47 back-projection method (FBP). FBP, however, has substantial limitations due to

48 attenuation artifacts and effects from an increased activity of adjacent organs, reducing

49 diagnostic reliability and clinical application of computerized quantitative analysis.
50 Iterative reconstruction, such as ordered-subset expectation maximization (OSEM), is
51 recently available for the improvement in signal-to-noise ratio of myocardial perfusion
52 count and for the reduction in artifacts due to reconstruction and radiation from liver or
53 gall bladder [11, 12]. This method is likely to improve visual assessment of CAD in
54 combination with resolution recovery, attenuation and scatter corrections compared to
55 FBP [13, 14]. It, however, is not determined whether an iterative reconstruction method
56 in combination with resolution recovery, attenuation and scatter corrections (IR-RASC)
57 can improve CAD detection when automated quantitative analysis is applied for stress
58 SPECT image. This study was designed to clarify diagnostic reliability of IR-RASC
59 when automated quantitative scoring system is applied to stress myocardial perfusion
60 SPECT for the detection of CAD by comparing with expert visual assessment using
61 FBP image without any correction.

62

63 **Materials and Methods**

64 **Subjects**

65 The study population consisted of consecutive 64 patients (mean age, 66.2 ± 17.3 years;
66 39 males and 25 females) who had undergone both stress ^{99m}Tc -tetrofosmin SPECT and
67 coronary angiography (CAG) within 3 months from May, 2012 to December, 2015 at
68 the nuclear medicine laboratory of the Sapporo Medical University Hospital, Sapporo,
69 Japan. The institutional ethics committee of Sapporo Medical University Hospital
70 approved the study protocol. The exclusion criteria were as followed; 1) prior
71 myocardial infarction, 2) a history of coronary revascularization, 3) multi-vessel CAD
72 and 4) cardiomyopathy.

73

74 **Stress-rest myocardial perfusion imaging**

75 Stress-rest myocardial SPECT imaging was performed using ^{99m}Tc -tetrofosmin with
76 296 MBq for a stress study and 740 MBq for a rest study. A dual-headed SPECT
77 system equipped with low-energy high-resolution collimator (Discovery NM/CT 670:
78 SPECT/CT scanner, GE Healthcare, Milwaukee, WI) was used for data acquisition with
79 a 180-degree acquisition. A photopeak window of ^{99m}Tc was set as a 15 % energy
80 window centered at 140 keV, and a high and low sub-window for scatter correction

81 (SC) was set as a 7 % of photopeak window. The acquisition pixel size was a 6.6 mm
82 for a 64 x 64 matrix. We acquired a low-dose computed tomography (CT) image for
83 attenuation correction (AC) using a 16-detector row CT on the SPECT/CT scanner. Tube
84 voltage and effective mAs for AC CT were 120 kVp and 10 mAs, respectively. We used
85 two reconstruction methods, FBP and IR-RASC. RASC algorithm was not incorporated
86 into the conventional FBP processing. An iterative reconstruction method used OSEM
87 with 12 iterations and 10 subsets. Reconstructed stress and rest images were smoothed
88 by use of a 3-dimensional Butterworth low pass filter with a critical frequency of 0.4
89 Nyquist with an order of 10 and a critical frequency of 0.5 Nyquist with an order of 10,
90 respectively.

91

92 **Automated quantitation of myocardial perfusion abnormality**

93 Automated quantification of myocardial perfusion abnormality was performed using
94 Heart Risk View-S (HRV-S, Nihon Medi-Physics Co Ltd, Tokyo, Japan) mounted on
95 AZE Virtual Place Hayabusa (AZE Co Ltd, Tokyo, Japan) and Quantitative Perfusion
96 SPECT (QPS) software (Cedars-Sinai Medical Center, USA) for the evaluation of

97 applicability of IR-RASC. Based on the 17-segment, 5-point scoring model
98 recommended by Cardiac Imaging Committee of the American Heart Association and
99 the American Society of Nuclear Cardiology (ASNC) guidelines [15], HRV-S
100 automatically measured a mean percent count at each 17-segment, scored with a 5-point
101 method from normal (0) to absent (4), then calculated summed stress score (SSS),
102 summed rest score (SRS) and summed difference (SDS). The threshold of a mean
103 percent uptake for the 5-point scoring system each segment was determined using the
104 gender-, tracer- and acquisition angle-based database developed by the Japanese Society
105 of Nuclear Medicine working group (JSNM WG) [16] (Table 1). Regional SSS, SRS
106 and SDS were also calculated separately at apical, mid- and basal left ventricular areas
107 to evaluate effect of each reconstruction method on automated scoring data.

108

109 **Visual assessment and CAD definition**

110 Visual interpretation of myocardial perfusion SPECT image reconstructed by FBP was
111 performed using a 5-point, 17-segment model by two nuclear cardiology experts (A.H.
112 and N.Y.) blinded to clinical data as follows: 0, normal; 1, mildly reduced; 2,

113 moderately reduced; 3, severely reduced; and 4, absent. SSS, SRS and SDS were
114 calculated. CAD was defined angiographically as a diameter stenosis of $\geq 50\%$ at any of
115 3 main coronary arteries or their major branches by visual assessment [17].
116 Scintigraphic CAD was defined as $SDS \geq 2$ in stress myocardial SPECT imaging,
117 because the pilot studies reporting a diagnostic capacity of automated quantitative
118 program software have proposed $SDS=2$ as the optimal cut-off value for identifying
119 angiographical CAD [18, 19]. A true positive was defined angiographically as a
120 diameter stenosis of $\geq 50\%$ and $SDS \geq 2$ in stress myocardial SPECT imaging. A true
121 negative was defined angiographically as a diameter stenosis of $< 50\%$ and $SDS < 2$ in
122 stress myocardial SPECT imaging.

123

124 **Statistical Analysis**

125 Continuous variables were expressed as mean \pm standard deviation and compared using
126 the paired two-tailed Student's t test. Multiple comparisons were analyzed using the
127 Scheffe test. Agreement among summed scores between two methods was evaluated by
128 Pearson's correlation coefficient for linear regression. The diagnostic accuracy of CAD

129 was evaluated using receiver-operating characteristics (ROC) curve analysis and area
130 under the curve (AUC) and Pearson's Chi-square test. A one-way ANOVA and post-hoc
131 analysis using Scheffe test were used to test for statistically significant differences
132 between two AUCs from the six different ROC curves. A p value <0.05 was considered
133 statistically significant. These analyses were performed by using MedCalc software
134 (MedCalc software, Mariakerte, Belgium, 2009).

135

136 **Results**

137 Angiographic CAD was identified in 33 (51.5%) of 64 patients; 15 lesions in left
138 anterior descending artery, 11 in left circumflex artery and 7 in right coronary artery.
139 There was no significant difference in clinical backgrounds between CAD and
140 non-CAD patients (Table 2). When FBP images were used, SSS and SRS assessed by
141 HRV-S and QPS were significantly greater than those assessed by visual interpretation
142 of Readers 1 and 2 (Table 3), particularly at mid- and basal left ventricular areas (Figure
143 1). When IR-RASC images were used, however, there was no significant difference in
144 SSS or SRS between the automated analyses (HRV-S and QPS) and the expert visual

145 assessment (Table 3). SSS, SRS and SDS more closely correlated between expert visual
146 assessment and automated analyses when IR-RASC images were used for the HRV-S
147 and QPS compared to those when FBP images were used (Figures 2-4).

148 Receiver-operating characteristics analysis showed that AUCs assessed by HRV-S
149 (0.687) and QPS (0.678) with IR-RASC were nearly identical to those (0.717 to 0.724)
150 by visual analysis (Readers 1 and 2) with FBP, and were significantly ($p<0.05$) greater
151 than those by HRV-S (0.505) and QPS (0.522) with FBP (Figure 5). When HRV-S was
152 used, the specificity and diagnostic accuracy of IR-RASC in the CAD detection were
153 significantly greater than those of FBP: 90.3% versus 51.6%, $p<0.0001$ and 79.7%
154 versus 54.7%, $p=0.0027$, respectively (Table 4). Likewise, when QPS was used, the
155 specificity and diagnostic accuracy of IR-RASC in the CAD detection were
156 significantly greater than those of FBP: 80.6% versus 41.9%, $p<0.0001$ and 78.1%
157 versus 51.6%, $p=0.0018$, respectively. There, however, was no significant difference in
158 sensitivity between IR-RASC and FBP irrespective of softwares used. These diagnostic
159 values of IR-RASC with HRV-S or QPS were nearly identical to those of visual
160 assessment; 66.7% for sensitivity, 87.1% for specificity and 76.6% for accuracy.

161

162 **Case presentation**

163 Figure 6 shows typical stress and resting SPECT images reconstructed by FBP and
164 IR-RASC in a normal case. Because of artefactual appearance at anterobasal,
165 inferobasal and lateral segments of FBP images, SSS, SRS and SDS were overestimated
166 by HRV-S and visual analysis, but were reasonably estimated by using IR-RASC. In a
167 CAD patient with a 60% stenosis of left circumflex coronary artery, SSS, SRS and SDS
168 underestimated by HRV-S using FBP images were more precisely estimated by visual
169 analysis and HRV-S using IR-RASC images (Figure 7).

170

171 **Discussion**

172 The present study clearly demonstrated the diagnostic superiority of IR-RASC to
173 FBP in stress myocardial perfusion SPECT imaging to which automated quantitative
174 assessment using HRV-S and QPS is applied. The presented method using IR-RASC
175 can reduce overestimation of artefactual perfusion abnormalities particularly at mid-
176 and basal left ventricular areas, contributing to improvement in the specificity of

177 detection of CAD. Furthermore, the overall diagnostic accuracy of the
178 computer-assisted scoring systems using IR-RASC is nearly identical to expert visual
179 assessment.

180 Conventional automated scoring programs are based on self-normalized counts as
181 relative percent uptake and, therefore, tend to overestimate artefactual perfusion
182 abnormality inherent in SPECT imaging due to motion artifacts, attenuation artifacts
183 due to diaphragm or breast, selection error of basal segments and reconstruction
184 artifacts by FBP [9, 19]. Recently, a software package called Heart Score View (HSV;
185 version 1.5) (Nihon Medi-Physics, Japan), previous version of HRV-S, was developed
186 and widely used in Japan. The application of HSV software to stress myocardial
187 perfusion SEPCT studies with ^{99m}Tc-labeled tracers can improve specificity (80-88%)
188 and accuracy (75-81%), rather than sensitivity (71-75%), in the detection of CAD [7,8].
189 In these studies, however, the automated computerized analysis was used
190 complementarily when a low count-image or artefactual image makes visual assessment
191 difficult. IR-RASC in combination with automated scoring system improved the
192 specificity in the CAD detection significantly by reducing SSS and SRS overestimated

193 at anterobasal, inferobasal and lateral segments in FBP images in this study. IR-RASC
194 images can reduce spatial heterogeneity of SPECT counts and artefactual abnormality
195 and more precisely identify left ventricular wall contour when compared to FBP images.
196 This is because iterative reconstructions with resolution recovery and noise reduction
197 algorithms can significantly improve perfusion defect contrast and spatial resolution
198 [20]. Thus, IR-RASC can improve the quantitative assessment using HRV-S and QPS
199 as a full automated scoring system when compared to FBP.

200 Despite a robust evidence of quantitative visual analysis of stress perfusion
201 SPECT imaging, visual assessment requires nuclear cardiology training, experience and
202 expertise to reduce inter- and intra-observer errors among physicians with less
203 experience [21]. High-image quality and reliable automated quantitative analysis with
204 IR-RASC can contribute not only to better diagnostic performance, high interpretive
205 reproducibility and time-saving in a routine clinical practice of stress myocardial
206 perfusion study with ^{99m}Tc -labeled tracers but also to education of physicians and
207 nuclear cardiology staff with a wide range of training and experience in distinguishing
208 various sorts of artifacts from true myocardial perfusion abnormality or ischemia.

209 The presented study includes limitations to be resolved in a future study. Because
210 of a lack of a normal database incorporated into resolution recovery, attenuation and
211 scatter corrections used here, automated quantification of myocardial perfusion
212 abnormality was performed using the conventional database created without any
213 correction. In this study, FBP images without any correction were used to compare with
214 IR-RASC images created by full corrections available at present time. Therefore, this
215 study showed no data derived from each correction or combinations rather than the
216 whole process of IR-RASC. Nevertheless, Narayanan MV, et al [13] showed
217 incremental improvements in the overall detection of CAD by adding attenuation
218 correction, scatter correction and resolution compensation to OSEM in the visual
219 assessment of FBP reconstructed images. Finally, a larger-scale study is required to
220 clarify prognostic values of automated quantitative system using IR-RASC as shown by
221 multicenter studies using automated quantitative analysis with FBP [10, 22].

222

223 **Conclusion**

224

225 IR-RASC can improve diagnostic accuracy of stress myocardial perfusion imaging
226 using an automated scoring system such as HRV-S and QPS in the CAD detection when
227 compared to FBP, by reducing false positivity due to artefactual appearance.

228

229 **Conflict of interest** The authors have declared no conflicts of interest.

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231 **References**

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313

314 **Figure legends**

315

316 Figure 1 Comparison of regional summed stress score (SSS), summed rest score (SRS)

317 and summed difference score (SDS) at apical, mid- and basal left ventricular areas

318 between automated quantitative analysis (HRV-S and QPS) using FBP or IR-RASC

319 images and expert (Readers 1 and 2) visual interpretation using FBP images.

320 HRV-S: Heart Risk View-S, QPS: Quantitative Perfusion SPECT, FBP: filtered

321 back-projection method, IR-RASC: iterative reconstruction method in combination with
322 resolution recovery, attenuation and scatter corrections

323 *P<0.05 versus HRV-S with FBP, **P<0.05 versus QPS with FBP

324

325 Figure 2 Correlations of summed stress score (SSS) between automated quantitative
326 analysis (HRV-S and QPS) with FBP/IR-RASC and visual (Readers 1 and 2)
327 interpretation with FBP.

328 Please see the abbreviations in Figure 1.

329

330 Figure 3 Correlations of summed rest score (SRS) between automated quantitative
331 analysis (HRV-S and QPS) with FBP/IR-RASC and visual (Readers 1 and 2)
332 interpretation with FBP.

333 Please see the abbreviations in Figure 1.

334

335 Figure 4 Correlations of summed difference score (SDS) between automated
336 quantitative analysis (HRV-S and QPS) with FBP/IR-RASC and visual (Readers 1 and

337 2) interpretation with FBP.

338 Please see the abbreviations in Figure 1.

339

340 Figure 5 Receiver operating curve analysis of the diagnostic accuracy of HRV-S with

341 FBP or IR-RASC, QPS with FBP or IR-RASC and expert (Readers 1 and 2) visual

342 interpretation with FBP in the detection of coronary artery disease.

343 Please see the abbreviations in Figure 1.

344

345 Figure 6 FBP images (left panels) from a patient without a coronary stenosis

346 overestimate scores by HRV-S and expert analysis due to artefactual perfusion

347 abnormalities at anterobasal, inferobasal and lateral segments, but IR-RASC images

348 (right panels) are significantly improved, contributing to more appropriate assessment

349 of summed stress score (SSS), summed rest score (SRS) and summed difference (SDS).

350 Please see the abbreviations in Figure 1.

351

352 Figure 7 FBP images (left panels) from a patient with a 60% stenosis of left circumflex

- 353 coronary artery underestimated lateral-wall perfusion abnormality but HRV-S using
- 354 IR-RASC images (right panels) precisely score the perfusion abnormality, resulting in
- 355 increases in summed stress score (SSS) and summed difference (SDS).
- 356 Please see the abbreviations in Figure 1.