

# The importance of population-specific normal database for quantification of myocardial ischemia: comparison between Japanese 360 and 180-degree databases and a US database

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**Objectives.** We aimed to develop a Japanese normal database for specific acquisition conditions, to compare US and Japanese normal populations, and to examine effects of camera rotation angle range on the normal limits.

**Methods and Results.** Stress-rest <sup>99m</sup>Tc myocardial perfusion databases for 360° (Jp360) and 180° (Jp180) acquisitions were created by the working group activity of the Japanese Society of Nuclear Medicine using Japanese patients. A standard 180° database (US180) had been previously generated by the Cedars Sinai Medical Center based on American patients. Additionally, 90 Japanese patients underwent coronary arteriography and stress-rest <sup>99m</sup>Tc perfusion study with 360° acquisition for validation purposes, and quantitative evaluation was performed by QPS software using the above three normal database sets. Major differences between US180 and Jp360 databases were found in the apex and in the anterior wall in females and in the inferior wall in males. When the diagnostic performance was evaluated by receiver-operating characteristic analysis, area under the curve was the highest for Jp360 (0.842), followed by Jp180 (0.758) and US180 (0.728) databases ( $P = .019$ , Jp360 vs US180;  $P = .035$ , Jp360 vs Jp180). The coronary territory score at stress was highest with the Jp360 database in male patients with right coronary artery stenosis ( $n = 26$ , Jp360:  $4.92 \pm 4.61$  [mean  $\pm$  SD], Jp180:  $4.23 \pm 4.29$ , US180:  $2.92 \pm 3.53$ ;  $P < .0001$  between Jp360 and US180) and in female patients with left anterior descending artery stenosis ( $n = 12$ , Jp360:  $6.33 \pm 4.76$ , Jp180:  $5.25 \pm 4.83$ , US180:  $4.50 \pm 4.15$ ;  $P = .0076$  between Jp360 and US180).

**Conclusion.** Because of the differences between US and Japanese normal databases, it is essential to use population- and acquisition-specific databases when using quantitative perfusion SPECT software. (J Nucl Cardiol 2009;16:422–30.)

**Key Words:** Myocardial perfusion imaging • quantification • normal database • Japanese Society of Nuclear Medicine database • coronary artery disease

## INTRODUCTION

Assessment of myocardial perfusion and function using myocardial single-photon emission computed

tomography (SPECT) has become an indispensable diagnostic tool for ischemic heart disease.<sup>1</sup> In particular, the diagnostic ability to detect inducible ischemia has been well validated for nuclear studies. Quantification of myocardial perfusion has objectified diagnosis by aiding visual interpretation and has allowed prognostic risk stratification.<sup>2-4</sup> Quantitative software for perfusion analysis typically employs normal databases with normal limits created from normal patient groups—since normal volunteers for the database are not usually available, databases are created from patients with a low likelihood of cardiac disease.<sup>5</sup> Although the selection criteria are not uniform among institutions, most laboratories tend to use a pre-installed database provided with the quantitative software package. However,

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Japanese and American populations may have substantial differences with respect to quantifiable cardiac parameters, and the use of an inappropriate database could influence the diagnostic performance of the quantitative software. Indeed, a recent report studying normal population in a Japanese multi-center study has indicated significant differences between Japanese and Western populations even in some fundamental parameters such as ejection fraction or cardiac volumes.<sup>6</sup>

In this study, we evaluate the effect of using databases from different ethnic populations (American vs Japanese) on quantitative perfusion SPECT results, and also we investigate differences in normal studies due to camera acquisition orbit length, since both 180° and 360° acquisition are common in Japan. Essentially, the database from the Japanese Society of Nuclear Medicine (JSNM) working group was compared with that from the US. Then, based on this comparison, we hypothesized that a Japanese-specific database has an advantage in quantitative diagnostic ability over the generic normal database from the US in patients with confirmed coronary artery disease.

## METHODS

### Normal Patients. Japanese Society of Nuclear Medicine Standard Databases

The JSNM started a working group project for creating a myocardial perfusion SPECT standard database in 2006, and conducted that study over a 2-year period.<sup>7</sup> The <sup>99m</sup>Tc-labeled perfusion-imaging agents hexakis (2-methoxy-isobutyl isonitrile) (MIBI) and tetrofosmin were used. Nine hospitals collaborated on the acquisition of the myocardial SPECT images, and five SPECT camera vendors (GE Yokogawa Medical Systems, Toshiba Medical Systems Corporation, Siemens-Asahi Medical Technologies, Hitachi Medical Corporation, Shimadzu Corporation; Japan) and two radiopharmaceutical companies (FUJIFILM RI Pharma, Nihon Medi-Physics; Japan) were also involved. The selection criteria of subjects with low likelihood of cardiac disease are as follows: (1) Only patients with exercise stress were included; (2) Wall motion, determined by either echocardiography or gated SPECT, needed to be normal; (3) Patients who had normal coronary arteriography were included. Those who had closer clinical work-ups and were diagnosed as having no ischemic heart disease, therefore having no indication for coronary angiography, were also included.

In addition, exclusion criteria included underlying cardiac disease, ischemic electrocardiographic (ECG) changes, hypertension and diabetes mellitus that required medication, and arrhythmias compromising ECG gating. Gated SPECT was performed using <sup>99m</sup>Tc-MIBI or tetrofosmin, and the two perfusion agents were not separated when creating the standard database, because preliminary comparisons of MIBI and

tetrofosmin databases revealed no significant difference in all segments.

The methods for radiopharmaceuticals administration and data acquisition have been previously described.<sup>7</sup> The standard administration dose of <sup>99m</sup>Tc perfusion-imaging tracers depended on the institutions and ranged from 740 to 1300 MBq. However, the tracer dose and SPECT acquisition parameters were confirmed by each institute, and were judged to be reliable. The camera rotation range was set to 180° or 360° according to each institutional acquisition protocol, depending on the type of camera (dual- or triple-detector cameras, respectively). Both circular orbits (47%) and non-circular orbits (53%) were used. For 180° rotation dual-detector SPECT, 90° and 76° detector configurations were used. The angular step between projections was 4–6°. No attenuation correction method was used in any of the hospitals. The SPECT data format was modified to the appropriate DICOM (Digital imaging and communication in medicine) format for further processing. SPECT reconstruction was performed with a Butterworth pre-filter and a ramp filter using the same reconstruction parameters on all cases. The cut-off frequency of the Butterworth filter was 0.45 cycles/cm and 0.40 cycles/cm for non-gated and gated acquisitions, respectively. The same software (Xeleris, GE Yokogawa Medical Systems, Ltd., Tokyo, Japan) was used for generating gated and non-gated short-axis images. We also confirmed that the subjects had normal ejection fraction, wall motion, and volumes, using the QGS software (Cedars Sinai Medical Center, CA, USA).<sup>8</sup>

### Comparison between Japanese and US Databases

The JSNM databases for <sup>99m</sup>Tc-labeled perfusion tracer included 80 patients for 360° data and 56 patients for 180° data. The precise characteristics, including age, height, weight, heart rate and blood pressure at rest and peak exercise, EF, and volumes, are summarized elsewhere.<sup>7</sup> Comparative data of stress perfusion between US and Japanese databases are shown in Table 1. The database from the US was contained in the QPS software, which was previously validated by the Cedars Sinai Medical Center.<sup>9</sup> The database was created from 40 male and 40 female patients with a low-likelihood of coronary artery disease.

The QPS software algorithm<sup>10</sup> with the simplified normal limits generator<sup>5</sup> was used to generate perfusion polar maps and to characterize the mean and the mean deviation using a 17-segment model. An optimal normalization factor between patient studies and the databases was established by an iterative search for the minimal difference between the counts in the normal part of the myocardium and the corresponding count distribution in the normal database. Such scheme avoided normalization based on an arbitrary selection of pixels (maximum or percentile maximum). Subsequently, threshold of 3.0 average (mean absolute) deviations was applied, which is approximately equivalent to the 2.5 standard deviations (SD), is needed to estimate extent of hypoperfusion.

**Table 1.** Characteristics of subjects with low-likelihood of CAD used in creation of databases

	JSNM database		CSMC database
	360°	180°	180°
N	80	56	80
Age	61 ± 14	59 ± 13	56 ± 14
Females	40 (50%)	28 (50%)	40 (50%)
Body mass index	22 ± 3	24 ± 3	27 ± 5
Diabetes mellitus	0*	0*	n. a.
Hypertension	0*	0*	39 (49%)
Hypercholesterolemia	n. a.	n. a.	44 (55%)
Exercise stress	80 (100%)	56 (100%)	57 (71%)
EF at rest (%)	(M) 63 ± 7, (F) 68 ± 7	(M) 65 ± 6, (F) 71 ± 8	n. a.
EDV at rest (mL)	(M) 76 ± 14, (F) 60 ± 10	(M) 89 ± 16, (F) 70 ± 14	n. a.

\* Based on selection criteria, patients with hypertension and diabetes mellitus who required medication were excluded. JSNM, Japanese Society of Nuclear Medicine; CSMC, Cedars Sinai Medical Center; n. a., not available.

In this manuscript, the databases from Japan with the 360° and 180° acquisition orbits are referred to as Jp360 and Jp180, respectively. The US database, with all studies acquired with 180° orbit is referred to as US180.

### Validation Study

A total of 90 consecutive patients (60 male and 30 female patients, aged 68 ± 10 years) who underwent both coronary arteriography and SPECT study within a month were selected at Kanazawa Cardiovascular Hospital. All patients with prior myocardial infarction, any type of coronary revascularization, non-ischemic cardiomyopathy, and valvular heart disease were excluded. Patients with changes in symptoms between coronary arteriography and SPECT were also excluded. Coronary arteriography revealed no significant stenosis (<75%) in 32 patients, one-vessel disease (1VD) in 26, two-vessel disease (2VD) in 21, and three-vessel disease (3VD) in 11. In the 1VD patients, left anterior descending artery (LAD) stenosis was observed in 16, left circumflex artery (LCX) stenosis in 4, and right coronary artery (RCA) stenosis in 6.

A <sup>99m</sup>Tc-MIBI 1-day protocol with a stress-rest sequence was performed. According to patients' conditions, both exercise and pharmacological stress with adenosine were included. The projection data over 360° were obtained using 64 × 64 matrices and a circular orbit. A dual-detector SPECT system equipped with low-energy high-resolution collimators was used (GE, Millennium VG, Tokyo, Japan).

The standard 17-segment model with 0- to 4-point scoring (0, normal; 1-3, slight, moderate, and severe decrease in uptake; 4 uptake absent) was used to evaluate myocardial perfusion. Computer-based automatic scoring, from 0 to 4, was performed using the QPS algorithm.<sup>11</sup> Summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS) were also calculated by the QPS algorithm. Coronary

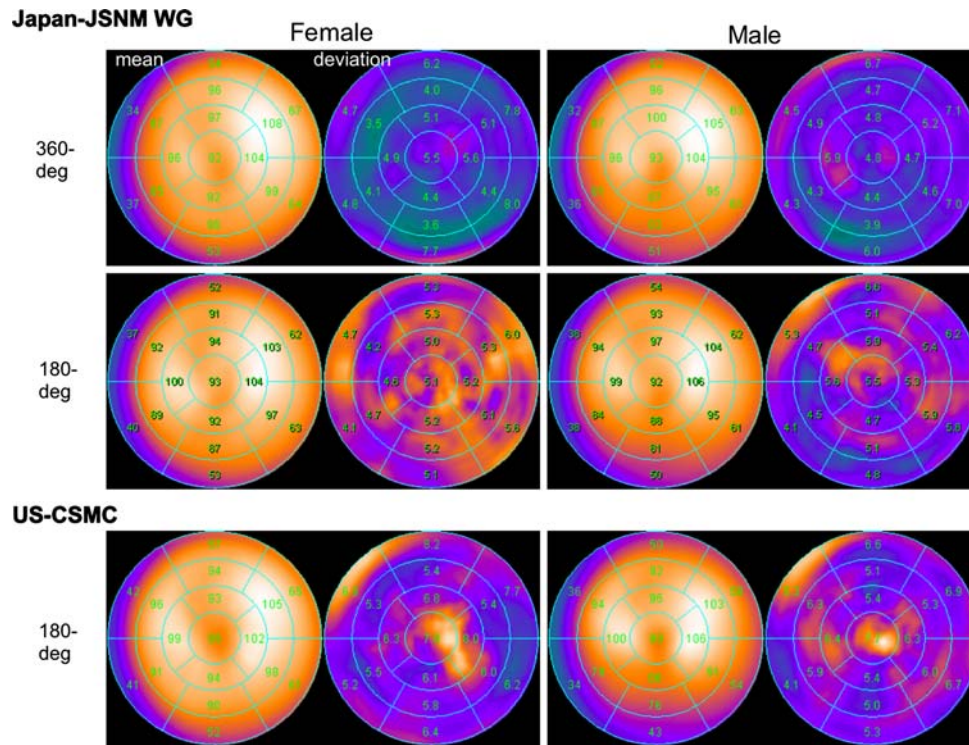
artery territories were defined as LAD to the anteroseptal and apical regions, LCX to the lateral region, and RCA to the inferior to inferoseptal regions. However, considering the normal variability of each coronary artery and the fact that 32 of 57 patients (56%) had multi-vessel disease, the coronary territory was manually adjusted in the border zones. Regional stress score (rSS) and rest score (rRS) were calculated as the sum of scores in each coronary artery territory. A patient-based SSS was used to evaluate the diagnostic performance of each normal database.

### Statistics

All parameters were expressed as average and standard deviation. For polar map quantification, the average and mean deviations were calculated by the Database Editor function in the QPS software. The differences in segmental values among Jp360, Jp180, and US180 databases were calculated with one-way analysis of variance, after converting the mean deviation to the standard deviation assuming a normal distribution. The Bonferroni multiple comparison test was applied for comparing all pairs. Receiver operating characteristics (ROC) analysis was performed for comparing diagnostic accuracy by the three databases. For comparison of regional scores from the three databases in the corresponding territories, a paired *T* test was applied. A *P* value of less than .05 was considered significant.

### RESULTS

Figure 1 compares the database polar maps among the US180, Jp180, and Jp360 data. Major differences between genders were observed in the apical anterior and apical segments in females and in the inferior wall in males. The average segmental values for the US180,



**Figure 1.** Comparison of US180, Jp180, and Jp360 normal databases in polar map format. Average and mean deviation values are overlaid on the 17-segment model.

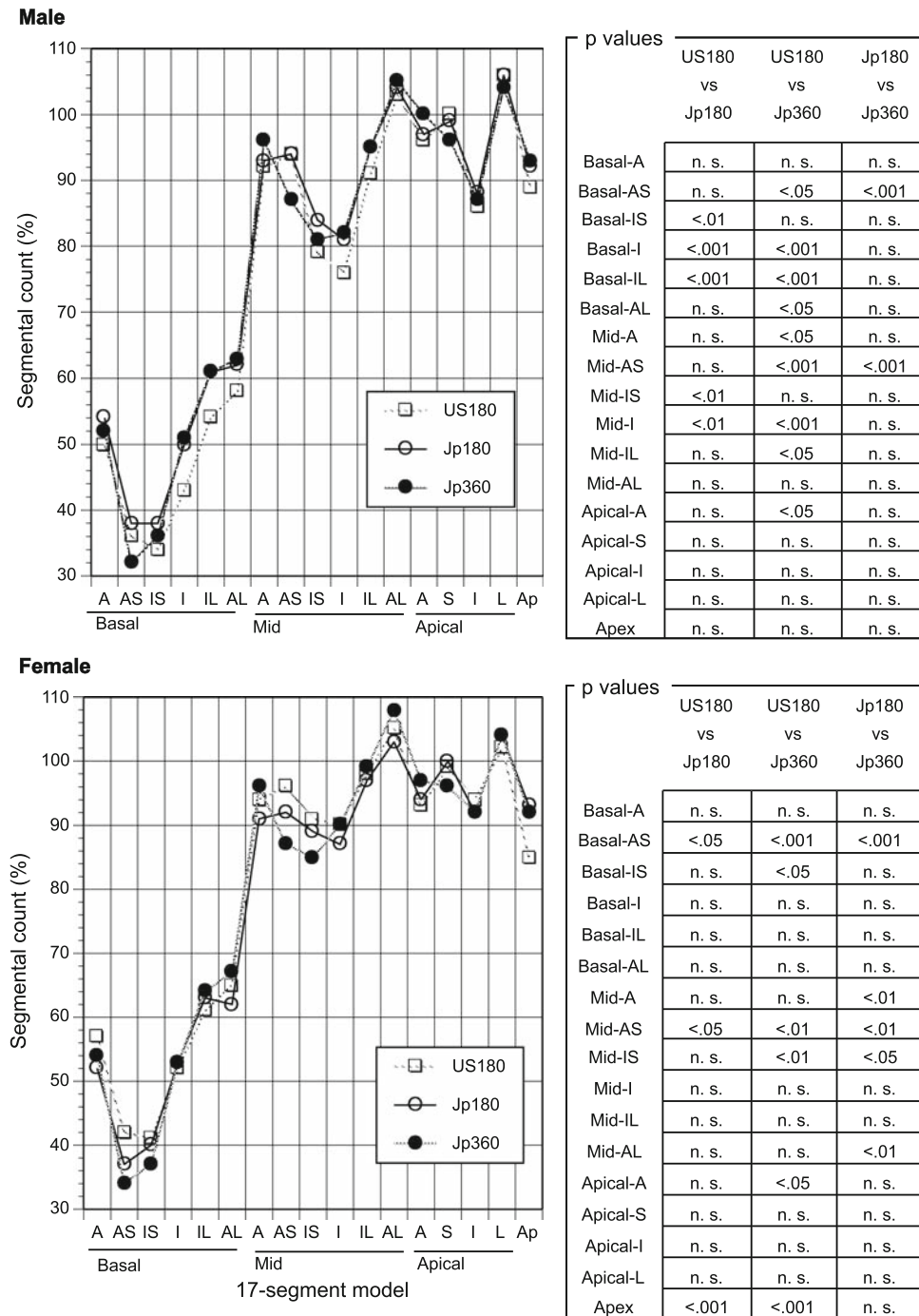
Jp180, and Jp360 database are summarized in Figure 2. When the mid-inferior segmental values are observed, male patients showed a lower uptake than female patients (76% vs 90% in US180,  $P < .0001$ ; 81% vs 87% in Jp180,  $P = .0010$ , 82% vs 90% in Jp360,  $P < .0001$ ). The apical-anterior and apical segments showed slightly lower counts for females than those for males in the US180 database, but the difference was not significant. The Japanese databases showed similar values in the apex between both genders (92% vs 93%, n. s.).

The segmental uptake was compared for males and females (Figure 2). In males, the basal and mid-inferior and inferolateral segments showed lower values in the US180 database compared to the Jp180 and Jp360 databases ( $P$  values ranged from  $<.001$  to  $<.01$ ). In females, the anteroseptal and inferoseptal segments showed lower values in the Jp360 database when compared with the US180 and Jp180 databases. In the apical segments, US180 database showed a lower value (85%) than the Jp180 (93%) and Jp360 (92%) databases ( $P < .01$  for both). In both males and females, septal regions showed lower values in the Jp360 database than in Jp180 database

Sensitivity and specificity for detecting significant coronary artery disease were analyzed by ROC curves (Figure 3). The diagnostic accuracy of the Jp360 database was comparable for  $SSS \geq 2$ ,  $\geq 3$ , and  $\geq 4$  (73%, 76%, and

74%, respectively). When  $SSS \geq 3$  was used as the threshold of abnormality, sensitivity, specificity, and accuracy were 79%, 72%, and 76% for the Jp360 database; 78%, 56%, and 70% for the Jp180 database; and 71%, 53%, and 64% for the US180 database. The area under the curve from ROC analysis was 0.842, 0.758, and 0.728 for Jp360, Jp180, and US180 databases, respectively ( $P = .019$  between Jp360 and US180,  $P = .035$  between Jp360 and Jp180,  $P = n. s.$  between Jp180 and US180).

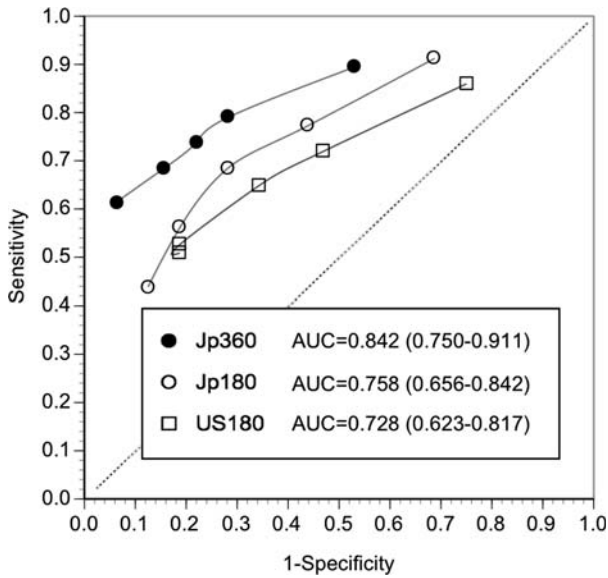
Figure 4 shows two examples of polar maps and scores, showing differences in the regional scores due to the use of different databases. Since significant differences between the databases were observed in the anterior region in female patients and in the inferior region in male patients, the regional scores corresponding to the coronary territory were evaluated (Table 2). In male patients with RCA stenosis as a culprit ischemic lesion ( $n = 26$ ), the rSS values in the inferior segments were  $2.92 \pm 3.53$ ,  $4.23 \pm 4.29$ , and  $4.92 \pm 4.61$  for the US180, Jp180, and Jp360 databases, respectively. When both coronary territory score of rSS and rRS were added, the differences were significant between three database combinations. The rSS was highest in the Jp360 database, which was matched to the 360° acquisition study. In female patients with LAD stenosis as a culprit ischemic lesion ( $n = 12$ ), the rSS values were  $4.50 \pm 4.15$ ,  $5.25 \pm 4.83$ , and



**Figure 2.** Detailed comparison of normal stress segmental values for each database obtained from the QPS data generator. The average values are shown for Jp360 (solid circle), Jp180 (open circle), and US180 (open square) databases. P values in the right table are based on the Bonferroni multiple comparison test. US, United States; Jp, Japan; A, anterior; AS, anteroseptal; IS, inferoseptal; I, inferior; IL, inferolateral; L, lateral; AL, anterolateral; deg., degrees; n. s., not significant.

6.33 ± 4.67 for the US180, Jp180, and Jp360 databases, respectively. The rSS was highest in the Jp360 database for the female anterior region. The difference in rSS was significant between the US180 and Jp360 databases, and

that in rRS was significant between the US180 and Jp180 databases. When both rSS and rRS were added, the differences were significant for combinations of US180 vs Jp180 and US180 vs Jp360.

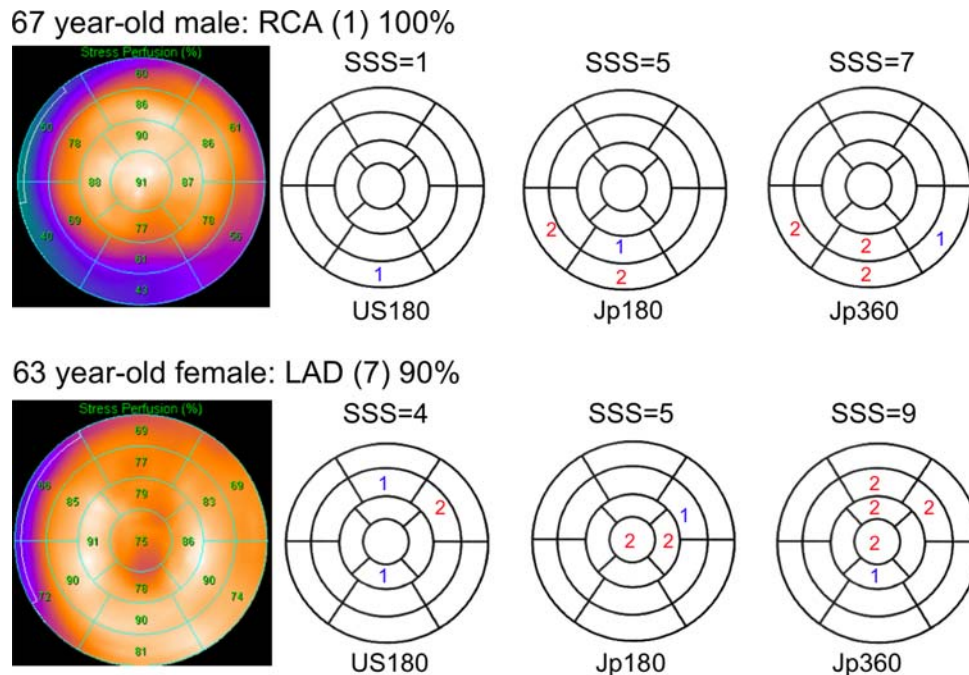


**Figure 3.** ROC analysis for the diagnostic performance of the Jp360 (solid circle), Jp180 (open circle), and US180 (open square) databases. Each point indicates threshold points of SSS  $\geq 2$  to  $\geq 6$ . Area under the curve (AUC) are shown with 95% confidence interval in the parentheses.

## DISCUSSION

This study demonstrated the importance of using separate myocardial perfusion normal limits for 360° and 180° rotations, as well as for US and Japanese populations. The use of population-specific and orbit-specific normal limits significantly influenced the quantification of perfusion defects. Although the importance of population-specific standards and methodology-specific standards have been previously implied, we confirmed the impact of database selection on the final diagnostic results with the use of the widely available QPS software and the JSNM working group database.

The JSNM working group compiled nation-specific normal databases for myocardial perfusion for common radiopharmaceuticals, as well as  $^{123}\text{I}$  labeled radiopharmaceuticals used in fatty acid and sympathetic imaging.<sup>7</sup> The perfusion data were classified by genders, 360° and 180° acquisition orbits,  $^{201}\text{Tl}$ ,  $^{99\text{m}}\text{Tc}$ -tracers, or dual isotope studies. The goal was to provide the databases in the appropriate format for clinical work and software developers. From the experience of multi-center studies in Japan, important factors characterizing



**Figure 4.** Examples of polar maps and scores for two abnormal patients, showing diagnostic differences in the regional stress score. In the upper panel, coronary arteriography revealed 100% stenosis in the RCA. Corresponding inferior defect is more clearly detected when the appropriate Jp360 database is applied. In the lower panel, a female patient with LAD stenosis showed apical anterior to apical hypoperfusion. Similarly, the segmental score showed the highest value in the Jp360 map.

**Table 2.** Regional stress and rest scores in the coronary territories

	Type of database			P values (paired)		
	US180	Jp180	Jp360	US180 vs Jp180	US180 vs Jp360	Jp 180 vs Jp360
Regional scores on QPS perfused by RCA in male patients (n = 26)						
<i>rSS and rRS</i>						
Mean	2.62	3.27	3.65	.0008	.0002	.0153
SD	3.33	3.86	4.19			
<i>Stress (rSS)</i>						
Mean	2.92	4.23	4.92	.0004	<.0001	.0096
SD	3.53	4.29	4.61			
<i>Rest (rRS)</i>						
Mean	1.31	2.31	2.38	.0014	.0016	n. s.
SD	2.33	3.16	3.34			
Regional scores on QPS perfused by LAD in female patients (n = 12)						
<i>rSS and rRS</i>						
Mean	2.46	3.83	4.21	.0049	.0021	n. s.
SD	3.60	4.15	4.54			
<i>Stress (rSS)</i>						
Mean	4.50	5.25	6.33	n. s.	.0076	n. s. (.084)
SD	4.15	4.83	4.76			
<i>Rest (rRS)</i>						
Mean	0.42	2.42	2.08	.0096	n. s. (.080)	n. s.
SD	0.90	2.88	3.26			

rSS, Regional stress score; rRS, regional rest score.

a Japanese population included a high incidence of small hearts in females and the relatively advanced age of the population, which significantly influenced EF, ventricular volumes, and wall thickening.<sup>6,12</sup> As for regional perfusion patterns, analogous differences due to differences in body habitus were anticipated. Commonly used standards were generated based on the prevalence of imaging preferences in Japan, namely <sup>201</sup>Tl or <sup>99m</sup>Tc and 360- or 180-degree acquisitions.

A normal database pre-installed by the manufacturer may not be optimal for a specific population and acquisition protocol, but sometimes it is used due to the difficulties in collecting local data or the inability of the quantification software package to accept/generate user-specific normal-limits. Knollmann et al<sup>13</sup> compared summed scores using the manufacturer-based and institution-based normal database. Both QPS and 4D-MSPECT yielded higher scores when the institutional database was used as opposed to the manufacturer's database, but the authors did not compare the characteristics and differences between the databases. The JSNM database was derived from data originating from several institutions, and therefore it was not institution-specific; however, it represented averaged data for the most common acquisition conditions. Therefore, the

primary merit of using multi-center JSNM-authorized standards is that they can be utilized safely in most of the institutions where standard SPECT acquisition and processing protocols are used. This type of validated database may also be utilized for multi-center studies, in which common databases are used for quantification.

We used relatively strict criteria for the selection of normal patients because several centers were involved. The database generated by Cedars Sinai Medical Center included diabetic and dyslipidemic patients. In contrast, in the JSNM database, patients who required medication due to diabetes and hypertension were excluded from both the Jp180 and the Jp360 databases. The body mass index was also smaller in the Japanese database, including only one subject with a BMI >30. It is noteworthy that the standard deviation of the segmental uptake was generally smaller in the Japanese population as shown in Figure 1. Although there are several types of patient body sizes in Japan, this finding might reflect a relatively uniform nature of the Japanese database. When comparing each segment between US and Japanese databases, the attenuation in the anterior wall and apex was greater in females in the US population than in Japanese females by 8% unit in the apex (US180 vs Jp180). The inferior wall also showed lower uptake

values in males in the US population compared to Japanese males. Consequently, gender differences were more pronounced in the US population than in the Japanese population. These differences seem to reflect the difference in attenuation effects from female breasts and male diaphragms.

Different attenuation patterns related to genders have been noticed for both  $^{201}\text{Tl}$  and  $^{99\text{m}}\text{Tc}$  tracers.<sup>14,15</sup> The combined use of supine and prone acquisitions in women increased specificity and normalcy rate with the appropriate normal databases,<sup>9,16</sup> and also enhanced diagnostic accuracy in obese patients.<sup>17</sup> Attenuation correction may also be applicable to both genders and specifically to obese population, enhancing diagnostic accuracy.<sup>17-20</sup> However, the clinical efficacy of attenuation correction has not been validated in Japan and attenuation corrected databases were not available at this time.

There have been studies comparing the use of 180° and 360° rotations since the 1980s.<sup>21-25</sup> Most of the previous studies were performed to compare the detectability of defects and image distortion. In contrast, the present study demonstrates the differences in normal databases and the final effect on the diagnostic accuracy of perfusion quantification. Presently, approximately half of SPECT acquisition is performed with 360° rotation in Japan, while 180° rotation is almost exclusively used in the US. The characteristics of 360° rotation are a relatively low count in the inferior to septal regions, and these differences should be kept in mind as well for the qualitative assessment of SPECT images.

This study demonstrated that the database derived from several centers was successfully applied to one institution's 360° protocol. The differences in radiopharmaceuticals and rotation angles should be fitted to achieve proper diagnostic ability. Considering differences between US and Japanese populations, the major differences in the databases might be related to body habitus, rather than ethnicity. Therefore, when a database of another institute was used for the individual institute, the attenuation characteristics of the body as breast size and diaphragm should be considered.

The JSNM database was compiled from various institutions with some variations in imaging protocols. Although standard acquisition was used in each institute, minor differences in acquisition and preference for MIBI and tetrofosmin were permitted. Using a specific database for each institute could conceivably result in slightly better diagnostic performance, although the detectability of coronary artery disease was acceptable in this particular study. Although we used the CSMC database as a reference US standard, there are also

various types of normal data files generated for the US population. However, we assumed that the characteristics of both databases included typical situations in both countries. Furthermore, the differences in algorithms, such as Emory Cardiac Toolbox and 4DM might also yield different diagnostic performances.<sup>3,4,26</sup> We are considering applying these newly created Japanese databases to various clinical situations in further studies.

## CONCLUSION

Databases created for a Japanese population with 360° and 180° rotations were compared with a US database with 180° rotation. When the database was applied to patients with coronary artery disease with 360° rotation, Jp360 data yielded the best diagnostic ability. The best diagnostic accuracy is obtained by the quantitative software when the population- and orbit-specific normal databases are used.

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## APPENDIX

Participating hospitals and researchers for database accumulation are as follows:

Nippon Medical School Hospital (Shinichiro Kumita\*, Yoshimitsu Fukushima), National Cardiovascular Center (Yoshio Ishida\*), Keio University Hospital (Jun Hashimoto\*), Tokyo Women's Medical University (Mitsuru Momose\*), Hokkaido University Hospital (Koichi Morita\*, Masayuki Inubushi, Keiichiro Yoshinaga\*), Toho University Omori Medical Center (Shohei Yamashina\*), Toranomon Hospital (Hirotaka Maruno\*), Nihon University School of Medicine (Naoya Matsumoto\*), Kanazawa University Hospital (Koichi Okuda, Shinro Matsuo, Tatsuya Yoneyama, Junichi Taki\*), Kanazawa Cardiovascular Center (Masaya Kawano)

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