

# The validity of multi-center common normal database for identifying myocardial ischemia: Japanese Society of Nuclear Medicine working group database

Kenichi Nakajima · Shinro Matsuo · Masaya Kawano · Naoya Matsumoto · Jun Hashimoto · Keiichiro Yoshinaga · Junichi Taki · Koichi Okuda

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## Abstract

**Purpose** The Japanese Society of Nuclear Medicine (JSNM) working group has created a myocardial perfusion imaging database applicable to standard acquisition protocol. The aim of this study is to validate the diagnostic accuracy of the common normal database compared with the expert interpretation of each institute.

**Methods** Five institutions participated in this study and used different acquisition settings which included 360°/180° rotation, camera configuration and camera orbits. The

software and its version used in each institution also varied. The working group database was applied to detect the culprit coronary territory from a total of 166 patients with coronary artery disease (CAD) and 145 patients with low-likelihood of CAD.

**Results** When summed stress score  $\geq 4$  was defined as significant abnormality, overall sensitivity, specificity and accuracy of patient-based analysis were 77, 72 and 75%, respectively, based on quantitative analysis using the common database, whereas those by institutional visual expert reading were 72, 79 and 75%, respectively.

**Conclusion** The common database, which was created by a multi-center working group and separated between male/female with 180/360° acquisitions, demonstrated comparable diagnostic accuracy to expert interpretation by each institute, and it may be applicable to multi-center studies.

K. Nakajima (✉) · S. Matsuo · J. Taki  
Department of Nuclear Medicine,  
Kanazawa University Hospital, 13-1 Takara-machi,  
Kanazawa 920-8641, Japan  
e-mail: nakajima@med.kanazawa-u.ac.jp

M. Kawano  
Department of Radiology,  
Kanazawa Cardiovascular Hospital, Kanazawa, Japan

N. Matsumoto  
Department of Cardiology,  
Nihon University Surugadai Hospital, Tokyo, Japan

J. Hashimoto  
Department of Radiology, Keio University, Tokyo, Japan

K. Yoshinaga  
Department of Molecular Imaging, Hokkaido University  
Graduate School of Medicine, Sapporo, Japan

K. Okuda  
Department of Biotracer Medicine, Kanazawa University,  
Kanazawa, Japan

## Present Address:

J. Hashimoto  
Department of Radiology, Tokai University School of Medicine,  
Isehara, Japan

**Keywords** Myocardial perfusion imaging · Normal database · Japanese Society of Nuclear Medicine working group · Coronary artery disease · Quantification

## Introduction

Myocardial perfusion imaging has been applied to detect myocardial ischemia, therapeutic decision making and prognostic estimates, and is a well-established diagnostic tool. In the preceding studies, although visual evaluation of extent and severity of ischemia was essential, quantitative analysis aided or enhanced a diagnostic accuracy [1–3]. Since appropriate normal databases matching those of the acquisition parameters, genders and types of tracers were considered indispensable, we accumulated normal databases from multiple institutions as the working group

activity of the Japanese Society of Nuclear Medicine (JSNM) [4–6]. Our aim was to use one common standard database for multiple centers with nuclear medicine facilities. However, whether it was applicable to multiple centers and was comparable to expert interpretation of each institution were not clarified. Therefore, we hypothesized that the common database sets could be applied to different combinations of camera and software types. The results will also help with better understanding of the quantitative results from different institutions based on uniform or standard diagnostic criteria.

## Methods

### JSNM 2007 database

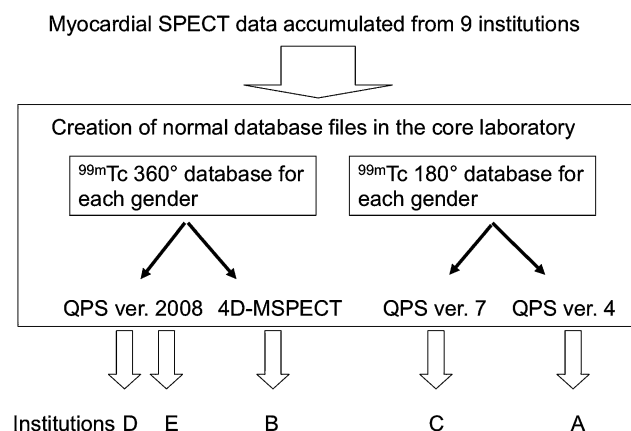
The JSNM working group database for myocardial perfusion tracers was created in 2007, and the characteristics of the database, backgrounds of a low-likelihood of coronary artery

diseases (CAD), type of tracers and acquisition conditions were described elsewhere [4]. Briefly, the perfusion databases consisted of 326 sets of short-axis images, and they were classified into male/female, 180°/360° and <sup>99m</sup>Tc-tracer/<sup>201</sup>Tl combinations. The data were collected from nine nuclear medicine centers, where standard acquisition protocols with multi-detector single-photon emission computed tomography (SPECT) were used. All the institutions used a gated SPECT study, but they did not use attenuation correction methods. The accumulation of data was approved by the ethical committee of each respective institution.

The method for creation and distribution of the databases in the present study was schematically shown in Fig. 1. The normal database files were created at Kanazawa University for QGS (Cedars Sinai Medical Center, USA) with different versions and 4D-MSPECT (Michigan University, USA), and sent to five institutions with different acquisition methods and software settings (Table 1) [1, 3]. The databases used in this study were based on <sup>99m</sup>Tc MIBI and tetrofosmin with 360° ( $n = 80$ ) and 180° ( $n = 56$ ) acquisition methods. Their ages, height, weight, heart rate and blood pressure at rest and exercise, ejection fraction (EF), left ventricular volumes and regional distribution of the tracers were precisely described elsewhere [4]. The common database was not modified in each institution thereafter.

### Patients

Two groups of patients were accumulated in five hospitals. Selection criteria for patients with CAD included (1) confirmed coronary artery stenosis  $\geq 75\%$  by coronary angiography (CAG), which was classified into single, double or triple-vessel diseases, (2) no history of old myocardial infarction and coronary revascularization, (3) no history of valvular heart disease, cardiomyopathy and severe arrhythmia, (4) no coronary intervention even if the patient underwent CAG before and (5) no changes of clinical signs



**Fig. 1** Normal database accumulation by JSNM working group and distribution of the databases to each institute

**Table 1** Data acquisition system and data processing

Institutions	A	B	C	D	E
Camera vendor	GE	Toshiba	Siemens	GE	Toshiba/Siemens
Number of detectors	2	3	2	2	2
Detector configuration (°)	79	Triangle	90	180	180
Acquisition parameters					
Rotation range (°)	180	360	180	360	360
Orbit	Circular	Circular	Non-circular	Circular	Circular
Pixel size (mm)	6.8	6.4	6.6	6.9	6.6
Step (°)	5.6	6.0	5.6	6.0	6.0
Quantification software					
Software type	QPS	4D-MSPECT	QPS	QPS	QPS
Version	4.0	2.1	7.0	2008	2008

**Table 2** Patient characteristics in five institutions

Institutions	A	B	C	D	E	Total
Number of patients	19	40	40	172	40	311
Age (years)	66 ± 10	73 ± 9	68 ± 10	67 ± 11	68 ± 13	
Male/female	8/11	25/15	30/10	107/65	27/13	197/114
BSA (m <sup>2</sup> )	1.57 ± 0.17	1.63 ± 0.21	1.73 ± 0.17	1.66 ± 0.20	1.70 ± 0.25	
Coronary stenosis						
No stenosis or low-likelihood	14	20	20	71	20	145
SVD	5	15	16	53	11	100
DVD	0	3	2	32	7	44
TVD	0	2	2	16	2	22
LV function						
EF (%)	69 ± 17	64 ± 9	64 ± 18	59 ± 10	67 ± 10	
EDV (ml)	74 ± 36	75 ± 22	87 ± 61	109 ± 35	75 ± 25	
ESV (ml)	29 ± 30	28 ± 14	41 ± 54	45 ± 23	26 ± 16	

CAD coronary artery disease, SVD single-vessel disease, DVD double-vessel disease, TVD triple-vessel disease, LV left ventricle, EF ejection fraction, EDV end-diastolic volume, ESV end-systolic volume

and symptoms between SPECT and angiography. The near-normal, namely low-likelihood of CAD, patient group was defined as (1) no significant coronary artery stenosis identified by CAG or (2) no indications for CAG because of low-likelihood of CAD after screening of ischemic heart disease. In this near-normal group, additional criteria were no baseline cardiac disease including valvular heart disease, cardiomyopathy and severe arrhythmia, no medically treated complications of diabetes and hypertension and no exercise ECG abnormality.

Based on these criteria, a total of 311 studies were accumulated, including single-vessel disease ( $n = 100$ ), double-vessel disease ( $n = 44$ ) and triple-vessel disease ( $n = 22$ ) (Table 2). No patients with left main trunk stenosis were included. Since CAG was performed in each institution, the angiographic method was not strictly regulated. However, the interpretation was performed by cardiology specialists according to the criteria of segmentation and stenosis of American Heart Association. The average age was  $68 \pm 11$  years (197 males, 114 females), and body surface area was  $1.67 \pm 0.20$  m<sup>2</sup>.

The low-likelihood of CAD ( $n = 145$ ) included no significant stenosis confirmed by CAG in 36% and CAD denied by clinical work-ups in the remaining patients. Checked items included no baseline cardiac diseases in 77%, no medically treated diabetes in 48%, no medically treated hypertension in 43% and no exercise ECG abnormality in 20%.

#### Myocardial perfusion imaging and data acquisition

Stress and rest myocardial perfusion SPECT was performed using <sup>99m</sup>Tc-MIBI or tetrofosmin. Standard multi-

stage exercise or pharmacological stress with adenosine or dipyridamole was used in each institute.

Table 1 summarizes the acquisition conditions and software types in five institutions. All institutions used multi-detector SPECT cameras. The rotation range was 180° in two institutions and 360° in three. The pixel size ranged from 6.4 to 6.9 mm, and the camera rotation step was from 5.6° to 6° per projection. The software used for gated SPECT analysis was QPS with different versions and 4D-MSPECT [1, 3, 7, 8].

#### Visual and quantitative analysis

Visual analysis was performed in each institution by the nuclear cardiology specialist independent of quantitative data analysis. Existence of ischemia was determined by original myocardial stress-rest images and judged as positive or not without quantitative data. The visual interpretation was confirmed independently by two experts in the core laboratory. The consensus was based on  $\geq 2$  of the 3 observers. A 17-segment model was applied in all institutions. Quantitative five-point scoring was performed as 0 = normal, 1 = slight decrease, 2 = moderate decrease, 3 = severe decrease and 4 = complete defect. The scoring was performed automatically based on summed stress score (SSS), summed rest score and summed difference score, in addition to EF, end-diastolic volume (EDV) and end-systolic volume (ESV) at rest. Since old myocardial infarction was excluded in this study, we only used SSS at the stress condition for diagnosis of abnormality. For patient-based analysis,  $SSS \geq 4$  of the whole segments was defined as the definite abnormality. For coronary artery-based analysis, the territory of the left anterior descending artery

(LAD) was defined as anterior, anteroseptal and apical regions, that of the left circumflex artery (LCX) as anterolateral and inferolateral regions, and that of right coronary artery (RCA) as inferior and inferoseptal regions. Only regional scores  $\geq 2$  of one principal culprit coronary artery territory was judged as abnormal. The principal culprit coronary artery was defined as the region of the severest stenotic artery even in patients with multivessel diseases.

### Statistics

Mean and standard deviation was used for all parameters. Sensitivity and specificity were calculated in each hospital. However, since one institution used only five patients with coronary stenosis and clinical background was variable among institutions, we mainly evaluated diagnostic ability of the total number of patients. The differences of the mean and variances were analyzed using statistics software JMP version 7 (SAS Institute, Inc. US and Canada Sales).  $P < 0.05$  was considered significant.

### Results

Figure 2 shows an example, patient with a three-vessel disease, involving 75% stenosis of the segment 1 (RCA, proximal), 75% stenosis of the segment 6 (LAD, proximal) and 90% stenosis of the segment 11 (LCX, proximal). Induced ischemia was judged in the LCX territory, and quantitative scoring was 16 points including LCX and RCA territories. In this case, only the LCX territory with the severest stenosis was used for evaluating diagnostic ability, although quantitative analysis seemed to detect ischemia in the RCA territory. Table 2 summarizes the accumulated patient profiles. Mean EF was  $63 \pm 13\%$ , and EDV and ESV were  $89 \pm 41$  and  $36 \pm 31$  ml, respectively. The lowest EF and the highest EDV in the institution D depended on a higher inclusion rate of CAD.

In the patient-based analysis, sensitivity ranged from 0.40 to 0.80 by visual analysis and from 0.60 to 0.85 by quantitative analysis (Table 3). Specificity ranged from 0.72 to 0.95 by visual analysis and from 0.70 to 1.00 by quantitative analysis. Overall sensitivity, specificity and diagnostic accuracy were 0.72, 0.79 and 0.75, respectively, by visual detection of ischemia. Based on quantitative analysis with  $SSS \geq 4$  used for the abnormal stress study, overall sensitivity, specificity and diagnostic accuracy were 0.77, 0.74 and 0.75, respectively ( $p = ns$  between visual vs. quantitative analyses). Coronary artery-based analysis demonstrated similar diagnostic performance of sensitivity, specificity and diagnostic accuracy of 0.71, 0.79 and 0.75, respectively, by visual analysis, and those of 0.70, 0.75 and 0.73 by quantitative analysis, respectively ( $p = ns$ ).

Regarding the lower specificity of quantitative analysis compared to that of visual analysis, we found 12 patients without CAD who showed abnormality in quantitative results, but were visually judged as normal. Of 12 patients, 11 were females, and 10 of these 11 had false-positive score (score 1 or 2 for each segment) in the anterolateral regions, which was caused by breast attenuation (Fig. 3). One male patient also showed an abnormal score in the anterior (score 2) and lateral (scores 2 and 1).

### Discussion

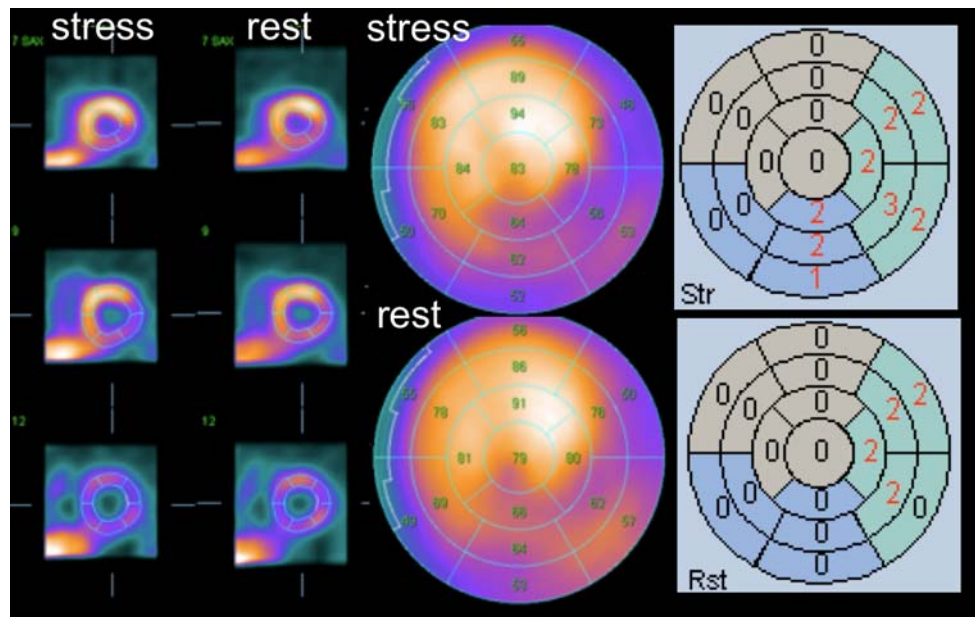
The hypothesis of this study was that a single common database created by multiple institutions with similar acquisition parameters could be applied to any hospital under the terms of similar acquisition and processing. This study demonstrated comparable diagnostic ability between the institutional expert visual interpretation and the quantitative analysis using different software types and versions.

In ideal conditions, standard databases should be generated based on individual institutional conditions of the SPECT system and population. By comparing manufacturer databases and institutional databases, Knollmann et al. [9] found some differences in quantitative scores between software algorithms as well as between manufacturer databases. The merit of an individualized database is its specificity to camera types, camera rotation ranges, orbits, multi-detector configuration, and therefore higher diagnostic performance would be expected. The best-fitted databases to a specific study population might also be created separately. In contrast, the demerits of an institution-specific normal database involve not only the cumbersome procedures to make the databases, but also the use of different institutional normal databases in a multi-center study. In addition, normal databases adapted for each software and version should be created from different control subjects if the data could not be transferred successfully.

In a precedent study using the same normal database, we found that the American database and Japanese database demonstrated significant differences in scores, and the best diagnostic performance was observed by  $180^\circ/360^\circ$ -arc rotation matched and nationality-matched databases [10]. In a Japanese population, although the JSNM database was generated by the compilation of multiple hospitals, application of the pre-installed American normal database supplied by the manufacturer degraded the diagnostic ability compared with that of the Japanese database.

The variability of sensitivity and specificity among institutions could be explained by the patient selection

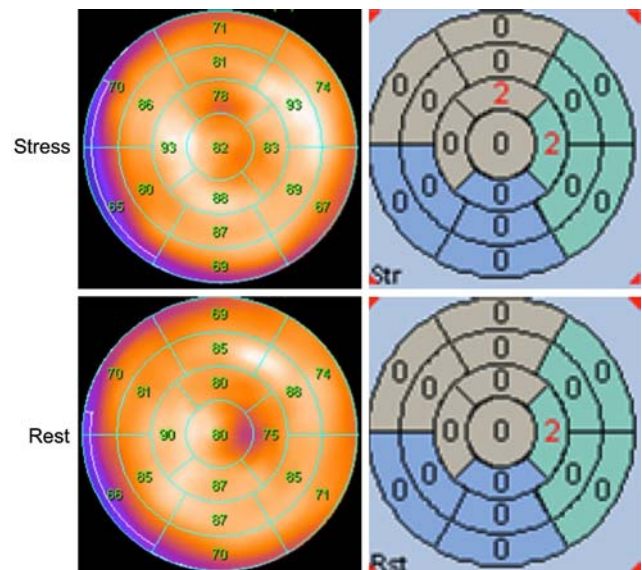
**Fig. 2** A patient with three-vessel disease. Hypoperfusion areas were observed in the lateral to inferolateral regions and ischemia was positively diagnosed. The culprit lesion was judged in the LCX territory both by visual and quantitative analyses



rather than by the diagnostic ability of each institute. In fact, some institutions examined relatively low-risk patient groups, and others had a number of CAG in the same period and a higher incidence of CAD. It should be noted that quantitative and visual analyses showed comparable values in all institutions. Slightly lower specificity for quantitative analysis was caused mainly by female breast attenuation. The breast attenuation artifact was judged correctly by visual analysis due to the non-coronary low count distribution. Moreover, attenuation artifacts could be judged by projection images and individual patient's breast size. Another option might be attenuation correction method, which was not used in this study. Comprehensive understanding is always required to avoid this sort of misinterpretation by artifacts.

The original JSNM working group database was prepared using a DICOM format of short-axis images, and it can be installed on any computer software. We have successfully installed the same normal databases into QPS with the latest and previous versions, 4D-MSPECT, Emory cardiac toolbox (Emory University, USA) and other currently developed software [1–3]. Since each software program has a different calculation algorithm, regional mean and deviation values on a polar map were not exactly identical. However, they were generated from the same sets of short-axis images, and therefore have common background characteristics. Although we admit significant differences in regional counts among genders and camera rotation ranges [10–15], the institutional differences in the Japanese population seemed to be less critical if these factors were in agreement.

The principal culprit coronary artery was evaluated for detection of ischemia, although additional ischemia could



**Fig. 3** Polar maps from a female patient showing anterior and lateral scores. By visual analysis, the small regional decrease was explained by breast attenuation and its movement at resting map. Based on quantitative scores, small segmental scores were calculated

be detected as shown in Fig. 2. Even in multivessel disease, the induced ischemia may not be detected in all of the stenotic artery territories [16, 17]. Myocardial perfusion imaging has rather been used to identify the culprit lesion for ischemia in multiple stenotic lesions. To detect multivessel high-risk patients, additional information, such as multiple defects more than coronary supply region, transient ischemic dilatation after stress, post-stress ventricular dysfunction, multiple areas of abnormal regional wall motion and thickening, increased volume and high lung uptake, might have incremental values.

**Table 3** Diagnostic accuracy by visual and quantitative analyses

Institution	Visual			Quantitative		
	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy
Patient-based						
A	0.40	0.86	0.74	0.60	0.93	0.84
B	0.80	0.95	0.88	0.75	1.00	0.88
C	0.75	0.80	0.78	0.85	0.80	0.83
D	0.70	0.72	0.71	0.76	0.62	0.70
E	0.75	0.80	0.78	0.75	0.70	0.73
Total	0.72	0.79	0.75	0.77	0.74	0.75
Number	119/166	114/145	233/311	127/166	107/145	234/311
Coronary artery-based						
A	0.40	0.86	0.74	0.40	0.93	0.79
B	0.80	0.95	0.88	0.75	1.00	0.88
C	0.70	0.80	0.75	0.80	0.85	0.83
D	0.70	0.72	0.71	0.71	0.63	0.68
E	0.75	0.80	0.78	0.60	0.70	0.65
Total	0.71	0.79	0.75	0.70	0.75	0.73
Number	118/166	114/145	232/311	117/166	109/145	226/311

Number of patients with coronary artery disease in 5 institutions was 5 of 19 for A, 20 of 40 for B, 20 of 40 for C 101 of 172 for D and 20 of 40 for E. In the coronary artery-based analysis, only principal culprit coronary artery was analyzed for detection of ischemia

This study has some limitations. Visual analysis was performed only to judge positive and negative ischemia in each coronary territory. Since visual scoring criteria of each physician could not be completely unified, we accepted ordinary decision criteria of each institution, and visual analysis was compared with the institutional quantitative analysis based on JSNM standards. For the 180° rotation method, the rotation orbit included both circular and non-circular orbits, and the camera configuration was not specific to 90° and 79° rotations. In addition, the 180° camera setting included various preferences for acquisition parameters including centering of heart and a variable camera-heart distance according to the orbit. Since specific databases that included all these factors would increase the number of database types, the JSNM working group decided to simplify the database type to only include the combinations of radiopharmaceuticals (<sup>99m</sup>Tc perfusion tracers, <sup>201</sup>Tl, <sup>123</sup>I BMIPP and <sup>123</sup>I MIBG), rotation range (180° and 360° rotation acquisitions) and genders. The software was not the latest version in some institutes including QPS and 4D-MSPECT, although we understood that the algorithm had been updated by the software developers. Therefore, better diagnostic yields might be expected by the unified computer algorithm with the newest versions.

In conclusion, a common database created by the JSNM working group activity provided comparable diagnostic performance to expert interpretation of the institutes despite variations of acquisitions and software programs.

The precision of quantitative gated SPECT results for EF and volumes was generally good, even if the same data were separately processed in each institution [18]. This study further suggested that the common normal databases for myocardial perfusion might be used as part of a multi-center study.

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