ORIGINAL ARTICLE

Clinical Validation of Japanese Normal Myocardial Perfusion Imaging Databases Using Semi-conductor Gamma Camera (D-SPECT): Japanese Society of Nuclear Cardiology Working Group Reports

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Abstract

***Objective*: A working group (WG) of the Japanese Society of Nuclear Cardiology (JSNC) determined Japanese normal databases of myocardial perfusion single-photon emission computed tomography (SPECT) on semi-conductor gamma camera (D-SPECT), and the aim of this study was to validate its clinical utility.**

***Materials and methods*: The normal myocardial perfusion SPECT (MPS) databases of Japanese patients in the ^{201}Tl stress/redistribution protocol (^{201}Tl protocol), ^{99m}Tc stress/rest or rest/stress protocol (^{99m}Tc protocol), and rest ^{99m}Tc/stress ^{201}Tl simultaneous acquisition dual-isotope protocol (SDI protocol) were created by JSNC WG. The WG collected clinical cases for the ^{201}Tl protocol (male/female [m/f], 8/8), ^{99m}Tc protocol (m/f, 9/7), and SDI protocol (m/f, 10/10) from WG participating hospitals. Four WG members read those clinical cases on a 17-segment and 5-point scale (0–4). Using the most frequent values as the score for each segment, weighted κ values were calculated with the scores obtained from quantitative perfusion software (QPS).**

***Results*: Weighted κ values were as follows; ^{201}Tl stress/female, 0.77; ^{201}Tl rest/female, 0.74; ^{201}Tl stress/male, 0.81; ^{201}Tl rest/male, 0.68; ^{99m}Tc stress/female, 0.77; ^{99m}Tc rest/female, 0.62; ^{99m}Tc stress/male, 0.77; ^{99m}Tc rest/male, 0.75; SDI stress/female, 0.87; SDI rest/female, 0.82; SDI stress/male, 0.87; SDI rest/male, 0.85.**

***Conclusions*: The diagnostic accuracy of Japanese MPS normal databases on D-SPECT were comparable with nuclear cardiology expert reading and further clinical applications are expected.**

Keywords: Cadmium zinc telluride semiconductor, Coronary artery disease, D-SPECT, Myocardial perfusion SPECT, Normal database

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Stress myocardial perfusion single-photon emission computed tomography (SPECT) has been well validated as a useful diagnostic tool to detect significant coronary artery disease (CAD) (1–3). Semi-conductor gamma camera (D-SPECT, Spectrum Dynamics Medical, Israel) is one of paradigm shifts from conventional gamma camera including outstanding technical features of high spatial resolution, high sensitivity and high energy resolution.

Automatic scoring of myocardial perfusion SPECT (MPS) on polar map has clinically been used conveniently not only for beginners but also expert readers. Two methods of defect scoring have been utilized for myocardial perfusion analysis, one with the normal database (quantitative perfusion software; QPS, Cedars Sinai Medical Center, Los Angeles, CA, USA)

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Table 1 WG members and hospitals

Working group members	
Naoya Matsumoto	Nihon University Hospital, Chief of the working group
Yasuyuki Suzuki	Nihon University Hospital
Nobuo Iguchi	Sakakibara Heart Institute
Mamoru Nanasato	Sakakibara Heart Institute
Keisuke Kiso	Tohoku University
Yasuyo Taniguchi	Harima-Himeji General Medical Center
Tatsuya Yoneyama	Central Hospital of Matto Ishikawa
Koichi Okuda	Kanazawa Medical University
Kenichi Nakajima	Kanazawa University

Collaborative hospitals for data collections	
1	Harima-Himeji General Medical Center
2	Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital
3	Kobe University
4	Central Hospital of Matto Ishikawa
5	National Cerebral and Cardiovascular Center
6	Nihon University Hospital
7	Sakakibara Heart Institute
8	Kanazawa University

and the other without it (serial change analysis)(4–6). The latter, serial variation analysis, does not require a comparison of normal database, but QPS has the advantage that analysis using a normal database can be used with any version of on-board software. Usually, specific normal databases are established according to gender (male, female), radioisotope agents (^{201}Tl, ^{99m}Tc-sestamibi, ^{99m}Tc-tetrofosmin), conditions during SPECT imaging (stress, rest), and SPECT acquisition ranges (180° or 360° acquisition). However, normal MPS databases fitted for D-SPECT Japanese population had not been created and Japanese Society of Nuclear Cardiology (JSNC) Working Group (WG) was established in 2018 for the purpose of making Japanese normal perfusion databases including 1) ^{201}Tl stress-redistribution protocol, 2) ^{99m}Tc-sestamibi or tetrofosmin rest/stress or stress/rest protocol, and 3) simultaneous acquisition dual-isotope protocol (rest ^{99m}Tc/stress ^{201}Tl: SDI protocol). Regarding the SDI protocol, its clinical utility and validation detecting significant CAD has been already reported by Makita et al (7).

The aim of this study was to validate relationships between WG experts' reading scores and automated quantitative scores by QPS from the Japanese MPS normal database.

Materials and methods

JSNC WG

The members of JSNC WG and collaborated hospitals were depicted in Table 1.

Creating normal database

In determining the normal range for Japanese MPS normal database, patients between the ages of 20 and 90 years with suspected having CAD were included in the study. Patients in the normal subjects in the study are as defined, 1) apparently low pretest likelihood of CAD (<5%), 2) no electrocardiogram (ECG) abnormality suspected of having cardiac disease or ischemia, 3) neither hypertension nor diabetic mellitus requiring medical treatment, 4) no arrhythmia causing electrocardiography (ECG) -gating errors, 5) normal wall motion and ejection fraction (EF) of >50% on quantitative gated SPECT software (QGS, Cedars Sinai Medical Center, Los Angeles, CA, USA), 6) no stenosis on coronary computed tomography (CT) angiography or coronary angiography diagnosed as normal, 7) visual SPECT imaging determined to be normal, 8) no underlying cardiac diseases, 9) no chronic kidney disease (eGFR<45ml/min/1.73m^2) and 10) no significant body motion during acquisition.

The collected data from collaborative hospitals for creating Japanese MPS normal database were summarized in Table 2. Each normal database (^{201}Tl stress-redistribution protocol [^{201}Tl protocol], ^{99m}Tc rest/stress or stress/rest protocol [^{99m}Tc protocol] and simultaneous acquisition dual-isotope protocol [rest ^{99m}Tc/stress ^{201}Tl: SDI protocol]) was created by different number of cases. MPS findings were based on a comparison between stress and rest imaging using relative myocardial counts after the normalization; therefore, we treated equally ^{99m}Tc isotopes (^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin), stress

Table 2 Protocols and types of stress

Radioisotope protocol, hospital and patient number to create

	Number of cases
A. ^{201}Tl stress/ redistribution protocol (^{201}Tl protocol) (1, 2, 5, 7)	
Female	58
Male	72
B. ^{99m}Tc stress/ rest or rest/ stress protocol (^{99m}Tc protocol) (1–6, 8)	
Female	97
Male	127
C. Simultaneous acquisition rest ^{99m}Tc/ stress ^{201}Tl protocol (SDI protocol) (6)	
Female	34
Male	38

Hospitals and stress protocol

Hospital No.		Stress protocol
1	Harima-Himeji General Medical Center	exercise/adenosine
2	Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital	exercise/adenosine
3	Kobe University	adenosine
4	Central Hospital of Matto Ishikawa	adenosine
5	National Cerebral and Cardiovascular Center	exercise/adenosine
6	Nihon University Hospital	adenosine
7	Sakakibara Heart Institute	exercise
8	Kanazawa University	exercise/adenosine

protocols (rest/stress or stress/rest ^{99m}Tc protocol) and stress types (exercise or adenosine stress) in this study.

Clinical validation group

The number of validation cases was targeted to accumulate at least 2 male and 2 female cases for four categories of summed stress score (SSS) normal (0–3), mildly abnormal (4–8), moderately abnormal (9–13), and highly abnormal (13<) from each WG participating hospitals. Four WG members (NM, YS, NI, and MN) read all cases using a 17-segment and 5-point scale scoring system (0, normal; 1, mildly reduced; 2, moderately reduced; 3, severely reduced; and 4, nearly no uptake) (8, 9). Four WG readers of the MPS were all certified specialists of Japanese Society of Nuclear Medicine. However, weighted κ values in the SDI protocol were obtained from four WG readers to verify inter-reader variability. SDI protocol includes both ^{201}Tl and ^{99m}Tc images, therefore it would be appropriate to verify it. The most frequent score among 4 WG readers in each 17-segment was obtained from each case. Weighted κ values were calculated between the visual segmental scores by 4 WG readers and automated segment scores obtained from QPS software based on various kinds of Japanese MPS normal databases.

Statistical analysis

Numbers are expressed as mean ± SD. Statistical analyses were performed using MedCalc for Windows, version 19.2.1 (MedCalc Software, Ostend, Belgium). Inter-rater agreement of κ statistics was applied.

Approval of ethics committees

This retrospective study was registered as UMIN 000035757 and approved by an independent review board committee of the Nihon University Hospital (IRB No. 150102 for creating normal database and IRB No. 20190301 for this validation study). Ethics committees approved the study in all participating hospitals.

Results

Creation of normal databases

Patient numbers from WG member's hospitals were as follows: ^{201}Tl protocol, female 58 and male 72; ^{99m}Tc protocol, female 97 and male 127; and SDI protocol, female 34 and male 38 (Table 2). ^{201}Tl data came from institutions 1, 2, 5 and 7. ^{99m}Tc data came from institutions 1–6 and 8. SDI data came from institution 6. Japanese MPS normal databases for various isotopes and gender were depicted in Figure 1. Figure 1A–C showed ^{201}Tl protocol, ^{99m}Tc protocol, and SDI protocol, respectively.

Validation group

Weighted κ values of SDI protocol at rest and stress among

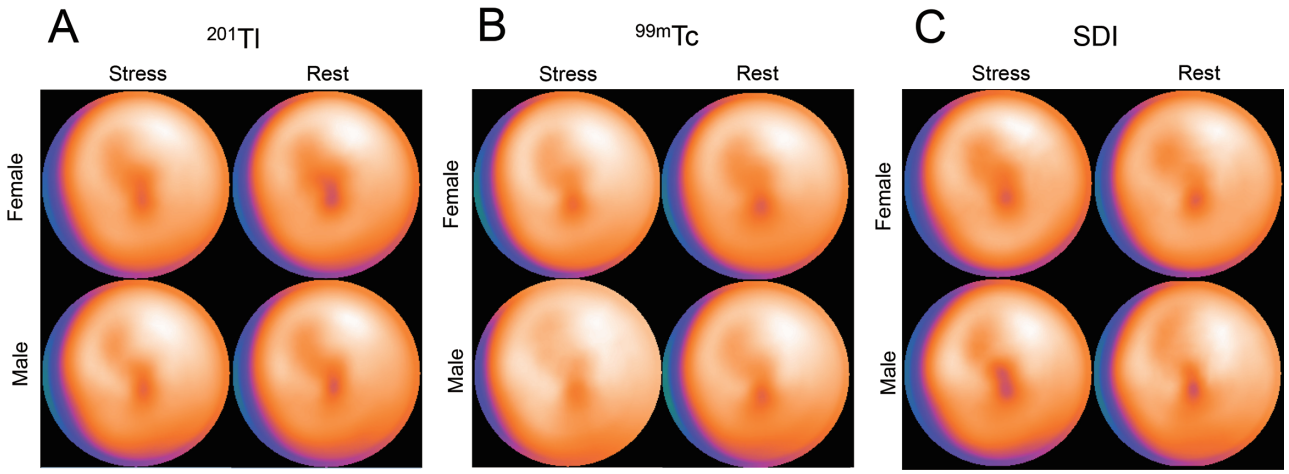

Figure 1 Polar map display of normal databases.

4 WG readers were as follows; MN-NI, 0.51; MN-NM, 0.69; MN-YS, 0.67; NI-NM, 0.57; NI-YS, 0.59; and NM-YS, 0.93 at resting ^{99m}Tc images. At stress ^{201}Tl images; MN-NI, 0.60; MN-NM, 0.75; MN-YS, 0.72; NI-NM, 0.66; NI-YS, 0.64; and NM-YS, 0.94 were observed. Patient population and background in validation group were depicted in Table 3. Table 3A–C showed ^{201}Tl protocol, ^{99m}Tc protocol, and SDI protocol, respectively. Weighted κ values for various combinations of methods and gender were as follows; ^{201}Tl stress/female, 0.77; ^{201}Tl rest/female, 0.74; ^{201}Tl stress/male, 0.81; ^{201}Tl rest/male, 0.68; ^{99m}Tc stress/female, 0.77; ^{99m}Tc rest/female, 0.62; ^{99m}Tc stress/male, 0.77; ^{99m}Tc rest/male, 0.75; SDI stress/female, 0.87; SDI rest/female, 0.82; SDI stress/male, 0.87; SDI rest/male, 0.85 (Figure 2).

Discussion

An appropriate normal database is one of the essential factors for reliable and reproducible quantification of MPS. The normal database is known to vary by gender, body size, tracer, and camera types. Since D-SPECT is a new generation gamma camera with a semiconductor detector, the normal database on board has been made only by foreign subjects. With the spread of D-SPECT in Japan, the normal database for Japanese subjects became necessary, as the type of population-specific databases significantly influenced the diagnostic accuracy (10). In comparison to the Japanese MPS normal databases created by Japanese Society of Nuclear Medicine WG, Japanese MPS normal database on D-SPECT showed basically uniform distribution of myocardial counts (11). Anger-type conventional gamma camera sometimes includes breast attenuation in the anterior wall in female patients and subdiaphragmatic attenuation in the inferior wall in male subjects. However, D-SPECT provides uniform count distribution compared with Anger camera, probably because effects of attenuation is relatively small using upright-position imaging. Moreover, the %count in the basal segments was relatively higher by D-SPECT compared with that by Anger camera (12). Figure 1A–C showed relatively reduced tracer uptake in the distal inferior wall to inferoapex in the left ventricle in each tracer.

Inter reader agreement using inter-rater agreement (κ statistics) among 4 WG readers showed moderate to good reproducibility. This would be explained by only MPI assessment without the information of ECG-gated wall motion study. Usually, the fixed perfusion defects without wall motion abnormality are considered to be attenuation. However, WG member evaluated MPS with only severity of tracer uptake without QGS study. Therefore, use of the frequent scores in each segment should be appropriate.

Relationship between semiquantitative visual scoring by WG readers on Japanese MPS normal database and automated segmental scores obtained from QPS software showed good to excellent association in all 3 protocols ($0.62 \leq \kappa \leq 0.87$). Notably, SDI protocol showed excellent association (all $\kappa > 0.8$). There are two possible reasons for this good association. SDI protocol uses ^{201}Tl which has higher extraction fraction than ^{99m}Tc without subdiaphragmatic activity. This might lead a good to excellent correlation between two scores. Another reason is the possibility of patient selection bias. Conversely, ^{99m}Tc rest/female showed a little bit lower κ value (0.62). Subdiaphragmatic extracardiac accumulation of ^{99m}Tc tracer in close proximity to the inferior wall of the left ventricle might affect the scoring of the inferior wall (13). Therefore, we mention to pay attention to the interpretation of the inferior wall in the right coronary artery territory. Since the diagnostic accuracy depends on the selection of patients for validations, we suppose these results were reasonable concordance with nuclear cardiology experts, and further clinical applications are expected.

Conclusions

The Japanese MPS normal databases on D-SPECT created

Table 3A ^{201}Tl protocol

	Female	Male
n	8	8
Age	69 ± 12.0	66 ± 15.5
Height (cm)	153 ± 6.5	164 ± 6.0
Body weight (kg)	54.7 ± 12.4	61.5 ± 5.7
Diabetes mellitus	2 (25%)	2 (25%)
Hypertension	6 (75%)	2 (25%)
Dyslipidemia	5 (62.5%)	4 (50%)
Smoking	0 (0%)	1 (12.5%)
Chronic kidney disease	1 (12.5%)	4 (50%)

Table 3B ^{99m}Tc protocol

	Female	Male
n	7	9
Age	75 ± 11.3	67 ± 8.3
Height (cm)	147 ± 7.2	169 ± 6.0
Body weight (kg)	48.8 ± 10.8	67.2 ± 15.7
Diabetes mellitus	2 (28.5%)	4 (44%)
Hypertension	5 (71.4%)	6 (66.6%)
Dyslipidemia	4 (57.1%)	4 (44%)
Smoking	0 (0%)	0 (0%)
Chronic kidney disease	1 (14.2%)	0 (0%)

Table 3C SDI protocol

	Female	Male
n	10	10
Age	70 ± 11.3	67 ± 9.5
Height (cm)	157 ± 7.9	168 ± 9.7
Body weight (kg)	57.3 ± 6.97	79.1 ± 21.7
Diabetes mellitus	3 (30%)	7 (70%)
Hypertension	6 (60%)	9 (50%)
Dyslipidemia	6 (60%)	5 (50%)
Smoking	0 (0%)	0 (0%)
Chronic kidney disease	2 (20%)	4 (40%)

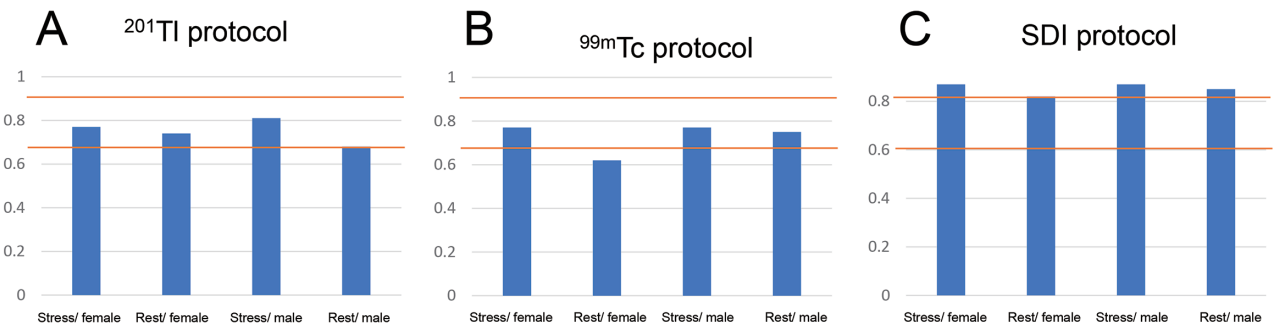

Figure 2 Weighted κ value in each protocol.

by JSNC WG were verified and found to be comparable to expert readings.

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Conflicts of interest

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