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## Creation and characterization of Japanese standards for myocardial perfusion SPECT: Database from Japanese Society of Nuclear Medicine working group activity

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### Abstract

**Objective:** Standards for myocardial single-photon emission computed tomography (SPECT) adapted for a Japanese population have not been available. The purpose of this project was to create standard files approved by the Japanese Society of Nuclear Medicine and to make known the characteristics of the myocardial perfusion pattern of this population.

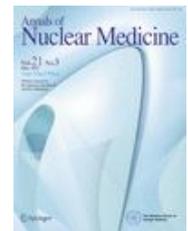
**Methods:** With the collaboration of nine hospitals, a total of 326 sets of exercise-rest myocardial perfusion images were accumulated from subjects with a low-likelihood of cardiac diseases. The normal database included a  $^{99m}\text{Tc}$ - MIBI/tetrofosmin myocardial perfusion study with 360-degree (n=80) and 180-degree (n=56) rotations,  $^{201}\text{Tl}$  study with 360-degree (n=115) and 180-degree rotations (n=54) and a dual-isotope study with 360-degree rotation (n=27). The projection images were transferred by DICOM (Digital Imaging and Communications in Medicine) format and reconstructed and analyzed with polar maps.

**Results:** The projection data from multiple centers were successfully transferred to a common format for SPECT reconstruction. When the average values were analyzed using a 17-segment model, myocardial counts in the septal segment differed significantly between 180-degree and 360-degree rotation acquisitions. Regional differences were observed between males and females in the inferior and anterior regions. A tracer difference between  $^{99m}\text{Tc}$  and  $^{201}\text{Tl}$  was also observed in some segments. The attenuation patterns differed significantly between subjects from the United States and Japanese populations.

**Conclusion:** Myocardial perfusion data that were specific for the Japanese population were generated. The normal database can serve a standard for nuclear cardiology work conducted in Japan.

#### Keywords:

Myocardial perfusion imaging, SPECT, Standard, Japanese population, Working Group of the Japanese Society of Nuclear Medicine



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### Introduction

Myocardial SPECT has been utilized as an important tool for optimal decision making in cardiology. The Guidelines for the Clinical Use of Cardiac Radionuclide Imaging were originally published in 1986 in the USA and updated in 1995. <sup>1</sup> In Japan, Nuclear Cardiology Guidelines were also summarized and published in 2005 by the task force of the Japan Circulation Society, Japanese Society of Nuclear Medicine (JSNM) and related societies, and the role of nuclear modalities has been recognized. <sup>2</sup> Among non-invasive technologies currently being developed in the fields of echocardiography, multi-detector x-ray computed tomography and magnetic resonance imaging, nuclear medicine plays a pivotal role in evaluating myocardial perfusion and metabolism.

To be accepted as a reliable technology, standard patterns of myocardial radiotracer distribution and

function should be defined. However, because myocardial distribution is known to be affected by factors of data acquisition methods, radiopharmaceutical types and gender, one of the most important issues is the standardization of myocardial SPECT studies. Moreover, since the differences in body habitus are not negligible, standards cannot be used interchangeably among populations.

In light of this background, the Japanese Society of Nuclear Medicine started working on a group project for creating myocardial standard based on a SPECT study from 2006 during a two-year period. The goal of the project was to create normal database and standard files for computer software and outline characteristics of a Japanese population with respect to perfusion, fatty acid and sympathetic imaging. This first report presents and provides data on the characteristics of a Japanese population with respect to myocardial perfusion SPECT.

## Methods

### *Participating institutions*

The members of the working group and those who cooperated with the accumulation and analysis of the SPECT data are listed in Table 1. Nine hospitals collaborated on the accumulation of the myocardial SPECT images. Five vendors of SPECT and two radiopharmaceutical companies were also involved. We also consulted the developers of the major myocardial SPECT quantification software, namely, Quantitative Gated SPECT and Perfusion SPECT (QGS/QPS, Cedars-Sinai Medical Center, Los Angeles, CA), the Emory Cardiac Toolbox (ECTb; Emory University, Atlanta, GA) and 4D-MSPECT (University of Michigan Medical Center, Ann Arbor, MI).<sup>3-10</sup> The data collection was approved in each hospital by the appropriate ethical committee or review board.

### *Definition of study population*

Selection criteria of subjects with a low likelihood of cardiac disease are as follows. Regarding stress type, only subjects who had taken part in exercise were included, while subjects who underwent pharmacological stress were not. The subjects had no electrocardiographic abnormalities indicative of ischemia and no underlying cardiac diseases. Subjects with hypertension and diabetes mellitus that required medication were excluded. Subjects with inappropriate arrhythmia for electrocardiography (ECG)-gated SPECT data collection were excluded. Gated SPECT was required for <sup>99m</sup>Tc-hexakis(2-methoxy-isobutyl isonitrile) (MIBI) and tetrofosmin and if possible for <sup>201</sup>Tl. The data of MIBI and tetrofosmin were not separated. Wall motion determined by gated SPECT should have been normokinetic. Both patients who had normal coronary arteriography and those who were not indicated for coronary arteriography because of a low possibility of ischemic heart disease were included. The standard administration dose of <sup>99m</sup>Tc perfusion tracers and <sup>201</sup>Tl depended on the institutions. However, the tracer dose and SPECT acquisition parameters were confirmed in each institute, and were judged appropriate for reliable results. Either low-energy high-resolution (LEHR) or general-purpose (LEGP) collimators were used. A projection set of 360-degree rotation derived from dual- (n=17) or triple-detector (n=205) cameras, and a projection set of 180-degree rotation from dual- (n=90) or triple-detector (n=14) cameras with rectangular or 76-degree rotation range were used. A circular orbit was used in 153 patients and a non-circular orbit in 173 patients. The acquisition angle for each projection was 4-6 degrees per step. No attenuation correction method was used

in any of the hospitals. For gated acquisition, division of RR interval was 16 (n=79), 10 (n=49) and 8 (n=8) frames for <sup>99m</sup>Tc tracers, while it was 16 (n=100) and 8 (n=69) frames for <sup>201</sup>Tl study.

### *Data transfer and reconstruction*

The data included exercise and rest imaging for <sup>99m</sup>Tc tracers, and exercise and delayed imaging for <sup>201</sup>Tl, in which <sup>201</sup>Tl reinjection studies (17 of 169 patients, 10%) were also included. The SPECT projection data with gated and ungated (or sum of the gated images) were anonymously transferred by the original or DICOM formats. All the data were accumulated at Kanazawa University. The SPECT data format was modified, if necessary, to the appropriate format for further processing. The SPECT reconstruction was performed with a Butterworth prefilter and a ramp filter using the same reconstruction parameters. The cut-off frequency of the Butterworth filter was 0.45 and 0.40 cycles/cm for gated and ungated acquisition, respectively. The same software (Xeleris, GE Yokogawa Medical Systems, Ltd.) was used for generating gated and ungated short-axis images.

### *Polar map and segment-based analysis*

The QGS/QPS, ECTb and 4D-MSPECT software were available to us for results.<sup>3-10</sup> In this manuscript, a QPS software algorithm was used to generate perfusion polar maps and to characterize the mean and the mean deviation of 17 segments. The QPS algorithm used the normalization of the maximal values so that normal segments had 100% values to eliminate errors due to maxima located in small hot spots.<sup>11, 12</sup> Gated SPECT quantification was used to confirm normal ejection fraction, wall motion and volumes using the QGS software.

### *Statistics*

The parameters were expressed as the average and standard deviation. For the polar map quantification, the average and mean deviations were calculated based on the database editor of the QPS software. The differences in segmental values were calculated based on unpaired T test after converting the mean deviation to standard deviation assuming normal distribution. A p value of less than 0.05 was considered significant. p values between 0.05 and 0.1 were considered borderline significant.

## Results

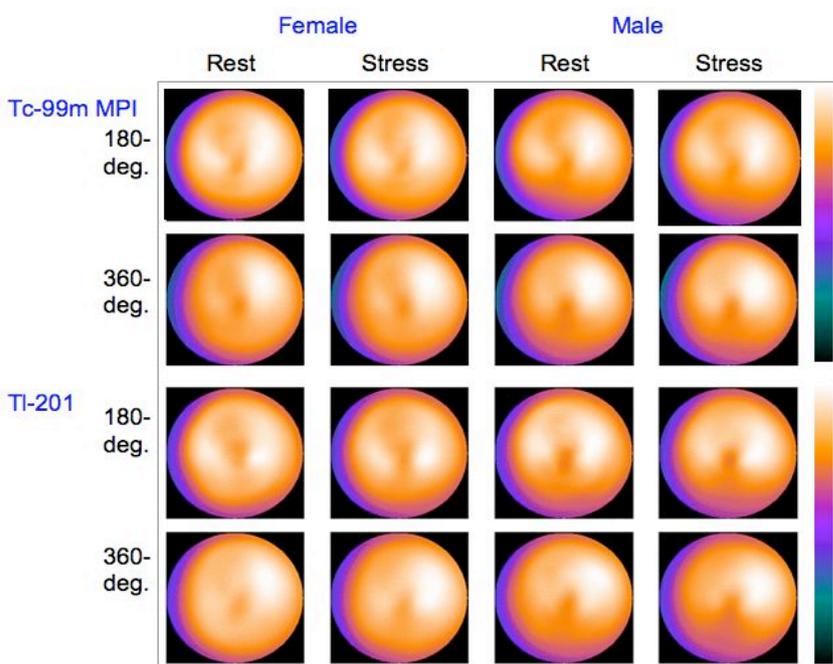
### Background of subjects

The patient background regarding age, height, weight, heart rate, blood pressure, ejection fraction and left ventricular volumes is summarized in Table 2. Left ventricular volumes divided by body surface area are shown as volume index (mL/m<sup>2</sup>). For <sup>201</sup>Tl SPECT studies, all 180-degree data were acquired by ECG gating, and no significant difference was observed between tracers in terms of age, stature, heart rate or blood pressure. When EFs for the 180-degree data from <sup>201</sup>Tl and <sup>99m</sup>Tc studies were compared, the <sup>201</sup>Tl study showed lower EF than the <sup>99m</sup>Tc study in females (p=0.016) and males (p=0.038). However, the <sup>201</sup>Tl 360-degree data were ungated and precise information for ventricular function was not available.

### Statistical differences in polar map analysis

Average segmental values were calculated based on 17-segment models for post-stress and resting conditions. The polar maps were compared as shown in Figure 1. Table 3 shows the average values of mid and apical segments for females and males with <sup>99m</sup>Tc and <sup>201</sup>Tl tracers in resting condition. Since the segment of the normal regions was adjusted to 100% in the QPS algorithm, values greater than 100% were included.

When the 360-degree and 180-degree rotation methods were compared, septal segments showed higher values in the 180-degree rotation for both <sup>99m</sup>Tc and <sup>201</sup>Tl. Gender differences were significant in the mid and apical inferior segments, showing lower values in males. Mid anterior segments showed significant differences between the 360 and 180-degree rotations for <sup>99m</sup>Tc but not for <sup>201</sup>Tl. Apical anterior segments showed gender differences, namely, values were lower in females in <sup>201</sup>Tl but not in <sup>99m</sup>Tc. Apical segments showed lower values in the 180-degree rotation than in the 360-degree rotation. Differences in radionuclide were observed regarding the segments of statistical significance in the mid anterior segment and the apex.



**Table 1. Working group members and participating institutes for JSNM myocardial standards**

Chief	Kanazawa University Hospital: Kenichi Nakajima*
Medical Institutes	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*, Junichi Yamazaki Toranomon Hospital: Hiroataka Maruno* Kanazawa University Hospital: Koichi Okuda, Tatsuya Yoneyama, Nasima Akhter, Junichi Taki* Kanazawa Cardiovascular Center: Masaya Kawano
Manufacturers of SPECT systems	GE Yokogawa Medical Systems: Masami Ogawa* Toshiba Medical Systems Corporation: Masahiro Kubota*, Nobutoku Motomura Siemens-Asahi Medical Technologies: Tetsuro Odagawa* Hitachi Medical Corporation: Koichi Yokotsuka* Shimadzu Corporation: Munehiro Takahashi*, Yuichi Inaoka
Radiopharmaceutical Companies	FUJIFILM RI Pharma: Takehiro Ishikawa, Katsunori Yoshioka Nihon Medi-Physics: Junichi Kato, Hideharu Niida
Acknowledgement for creating standards	Cedars-Sinai Medical Center: Guido Germano, Piotr Slomka, Geoff Pollard Emory University Hospital: Ernest Garcia University of Michigan Medical Center: Edward Ficaro
* Working group members	

**Figure 1**  
Standard polar maps of the average values for <sup>99m</sup>Tc myocardial perfusion imaging (MPI) and <sup>201</sup>Tl. Note the difference in the septal count between 180-degree and 360-degree acquisition protocols. Gender differences in the anterior and inferior regions are also demonstrated.

**Table 2. Background of patients with myocardial perfusion gated SPECT**

Tracer	Tc-99m MIBI and tetrofosmin				Tl-201	
	180-deg.		360-deg.		180-deg.	
Gender	Female	Male	Female	Male	Female	Male
No. of patients	28	28	40	40	27	27
Age	61 ± 10	57 ± 15	59 ± 16	63 ± 12	64 ± 10	66 ± 9
Height (cm)	155 ± 7	168 ± 6	155 ± 6	164 ± 6	155 ± 6	165 ± 7
Weight (kg)	60 ± 8	68 ± 12	51 ± 7	63 ± 9	56 ± 8	64 ± 8
BSA(m <sup>2</sup> )	1.55 ± 0.12	1.71 ± 0.16	1.44 ± 0.12	1.64 ± 0.14	1.50 ± 0.09	1.66 ± 0.12
<i>HR and BP at rest</i>						
HR (/min)	75 ± 13	67 ± 12	63 ± 10	67 ± 11	74 ± 12	71 ± 12
SP (mmHg)	145 ± 30	135 ± 16	125 ± 15	133 ± 14	152 ± 23	138 ± 16
DP (mmHg)	82 ± 11	84 ± 15	71 ± 10	79 ± 10	86 ± 15	84 ± 14
<i>HR and BP at peak exercise</i>						
HR (/min)	129 ± 20	122 ± 21	129 ± 23	132 ± 18	131 ± 22	129 ± 15
SP (mmHg)	188 ± 39	203 ± 33	192 ± 25	205 ± 25	206 ± 22	220 ± 26
DP (mmHg)	90 ± 17	96 ± 34	97 ± 23	98 ± 23	102 ± 21	113 ± 23
<i>Rest condition</i>						
EF (%)	71 ± 8	65 ± 6	68 ± 7	63 ± 7	65 ± 8	62 ± 5
EDV (mL)	70 ± 14	89 ± 16	60 ± 10	76 ± 14	62 ± 11	73 ± 15
ESV (mL)	21 ± 7	31 ± 9	20 ± 6	28 ± 8	22 ± 7	28 ± 8
EDVI(mL/m <sup>2</sup> )	45 ± 8	52 ± 8	41 ± 6	47 ± 9	41 ± 8	44 ± 9
ESVI(mL/m <sup>2</sup> )	14 ± 5	19 ± 5	13 ± 4	17 ± 5	15 ± 5	17 ± 5
<i>Post-stress condition</i>						
EF (%)	71 ± 8	66 ± 7	69 ± 6	63 ± 7	67 ± 7	64 ± 8
EDV (mL)	69 ± 15	82 ± 15	59 ± 10	72 ± 14	59 ± 13	69 ± 14
ESV (mL)	21 ± 8	28 ± 8	19 ± 6	27 ± 7	20 ± 6	25 ± 8
EDVI(mL/m <sup>2</sup> )	44 ± 8	48 ± 7	40 ± 6	44 ± 9	40 ± 8	42 ± 8
ESVI(mL/m <sup>2</sup> )	14 ± 5	16 ± 4	13 ± 4	16 ± 5	13 ± 4	15 ± 5

HR, heart rate; SP, systolic pressure; DP, diastolic pressure

EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume

**Table 3. Segmental average values in the polar map at resting condition**

Sgments	Average values				P values			
	180 deg.	360 deg.	180 deg.	360 deg.	180 vs 360 deg.		Female vs Male	
	Female	Female	Male	Male	Female	Male	180 deg.	360 deg.
<b>Tc-99m MIBI/Tetrofosmin</b>								
Mid A	92	96	92	96	0.008	0.007	ns	ns
Mid AS	92	87	94	87	0.0003	<0.0001	ns	ns
Mid IS	89	85	84	82	0.009	ns	0.002	0.024
Mid I	89	91	81	84	ns	0.024	<0.0001	<0.0001
Mid IL	99	99	96	97	ns	ns	ns (0.06)	ns
Mid AL	104	108	106	108	0.016	ns	ns	ns
Apical A	93	97	96	100	0.025	0.010	ns (0.078)	ns (0.05)
Apical S	99	95	98	95	0.016	ns (0.0822)	ns	ns
Apical I	92	92	88	87	ns	ns	0.009	0.0004
Apical L	104	105	106	105	ns	ns	ns	ns
Apex	92	91	93	92	ns	ns	ns	ns
<b>Tl-201</b>								
Mid A	94	94	97	96	ns	ns	ns	ns (0.10)
Mid AS	95	90	96	89	0.002	<0.0001	ns	ns
Mid IS	90	91	86	84	ns	ns	0.039	<0.0001
Mid I	90	92	82	83	ns	ns	<0.0001	<0.0001
Mid IL	97	97	94	95	ns	ns	ns	ns
Mid AL	101	105	104	107	0.028	ns (0.07)	ns	ns
Apical A	93	97	98	100	0.021	ns	0.020	0.012
Apical S	100	97	100	95	ns (0.07)	0.0034	ns	ns (0.10)
Apical I	95	93	87	87	ns	ns	0.0002	<0.0001
Apical L	102	100	103	102	ns	ns	ns	ns
Apex	90	93	88	92	0.043	0.010	ns	ns

**Abbreviations**

A, anterior; AS, anterosseptal; IS, inferoseptal; I, inferior; IL, inferolateral; AL, anterolateral; deg., degrees; ns, not significant

## Discussion

As a working group activity of the Japanese Society of Nuclear Medicine from 2006 to 2007, standards for myocardial perfusion SPECT were generated. The major conclusion of this study is that normal patterns were specific for genders, rotation angles and radionuclide used in the study. The importance of population specific standards should be emphasized. Normal perfusion files can serve as standards for clinical examinations as well as for multicenter studies.

### *Necessity of creating standards as working group activity*

Quantification of myocardial perfusion as well as ventricular function is considered important for the detection of myocardial ischemia and defect size. These standards created from a normal database can also serve as appropriate guides for treatment and predicting prognosis of patients after acute and chronic ischemic syndromes.<sup>1, 2</sup> Although standard perfusion patterns have been determined by some institutions and used for clinical practice, they may not be readily applicable to users' own institutions. Application of standards made for the US population to a Japanese population may also create inaccuracies in quantification. However, no authorized myocardial standards have been established by Nuclear Medicine Societies. Therefore, this working group was started to create common standard files that would be fitted to a Japanese population.

### *Need for specific population and technology*

Appropriate standards that are specific to the population should be used. The precision of gated SPECT results were examined in the current multicenter study and found to be excellent.<sup>13</sup> Near-normal patients were selected and analyzed from a J-ACCESS study (Japanese investigation for prognosis based on gated SPECT, Tsunehiko Nishimura as the chief investigator).<sup>14</sup> A total of 268 patients were selected from candidates with no baseline cardiac diseases and with no cardiac events over a three-year period. Ejection fractions for women and men were

$74\% \pm 9\%$  and  $63\% \pm 7\%$  ( $p < 0.0001$ ). The present working group study also showed higher EF in females than in males by 5-6%. Left ventricular volumes were significantly smaller in women than in men. Important factors for the studies in a Japanese population included a high incidence of small hearts in women and the relatively advanced age of the population. As for the regional perfusion patterns, similar differences due to differences in body habitus and ethnicity may be anticipated. The major SPECT technology and preference may also differ among countries. Approximately half of SPECT acquisition is performed with 360-degree rotation in Japan, while 180-degree rotation is more commonly used in the US. Some institutions prefer  $^{201}\text{Tl}$  studies to  $^{99\text{m}}\text{Tc}$  imaging agents. Considering the diversity of preferences in myocardial perfusion studies, individual data catering to the need in this country should be provided.

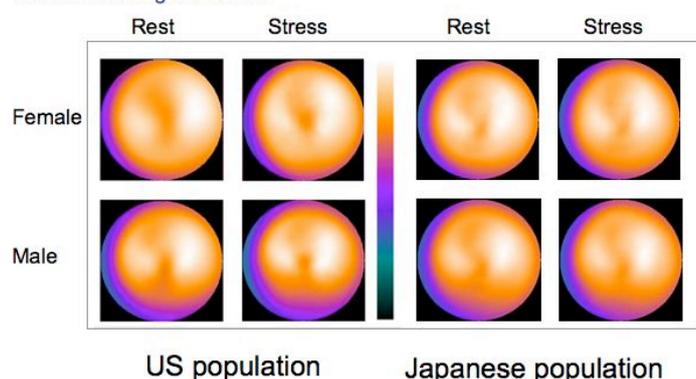
### *Benefits and limitations based on multicenter data*

The standards established by the working group contained various acquisition conditions with standard protocols but with minor differences. The standards provided an average pattern from several institutions, which have benefits as well as drawbacks. Strictly speaking, the database generated by each of the institutions would be more specific when considering the differences in technology, study protocol and targets of each study. However, accumulation of near-normal subjects based on strict criteria may be difficult for all institutions. The major merit of using authorized standards is that they can be utilized safely in most of the institutions where standard SPECT protocols are used. A common database can also be used for multicenter studies including nuclear cardiology techniques. However, as shown in this study, differences in rotation angle range, gender and tracers are important determinants affecting standard patterns. The factors ignored in this standard included differences in LEHR and LEGP collimators, differences in  $^{99\text{m}}\text{Tc}$  MIBI and tetrofosmin, and differences in noncircular and non-circular orbit. The last factor might be re-considered when a sufficient number of data have been accumulated. The dual nuclide study may be an option for some hospitals and the database could be of additional benefit.

**Figure 2**

Standard polar map patterns made by US population (Cedars Sinai Medical Center, CA, USA) with 40 males and 40 females<sup>11</sup>. The maps were obtained by 180-degree rotation in the supine position. The maps from a Japanese population are shown for comparison (right).

Tc-99m 180-degree rotation



### *Differences of standards between the United States and Japan*

When the normal databases from the US and Japan were compared, some differences should be noted. Figure 2 shows an example of maps based on US and Japanese standards. In the comparison, attenuation in the anterior wall seemed to be greater in females in the US population than in the Japanese population (93-85% vs. 93-92% in the apical anterior segment to the apex).<sup>11</sup> The inferior wall also showed lower values in males in the US population than in the Japanese population (76% vs. 81% in the mid inferior segment). The gender difference was considered to be larger in the US population than in the Japanese population. The differences seem to reflect the difference in attenuation from female breasts and male diaphragm. In addition, the difference in the same gender could not be explained by body weight alone. Thus, transferring application of the US standards to a Japanese population is considered inappropriate.

### *Future direction*

The standards are prepared to offer the normal database and computer files to nuclear medicine institutions. Their validity and diagnostic accuracy should be examined in subsequent studies. The parameters derived from a gated study could be calculated for standardization using these compiled studies. Considering the current use of an attenuation correction method, new sets of standards may be required in the near future. Additional important fields requiring a standard database are <sup>123</sup>I-BMIPP and <sup>123</sup>I-MIBG. SPECT data accumulation for <sup>123</sup>I tracers is in progress and will be completed soon.

## **Conclusion**

Myocardial perfusion data specific for the Japanese population were generated by the JSNM working group for standardization of myocardial SPECT. Significant segmental differences were observed based on the SPECT rotation angles, gender and tracers. The normal database can serve as a standard for common myocardial stress protocols and for multi-center comparative studies involving myocardial SPECT.

## **Acknowledgment**

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