ORIGINAL ARTICLE

Normal Values and Gender Differences of Left Ventricular Functional Parameters with CardioREPO Software: Volume, Diastolic Function, and Phase Analysis

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Abstract

***Background*: Gated myocardial perfusion single-photon emission computed tomography (SPECT) has been used to evaluate quantitative cardiac functional parameters using a dedicated software program. The aim of this study was to measure normal values of left ventricular (LV) functional parameters for a cardioREPO software program (cREPO) and to evaluate gender differences in these parameters.**

***Methods*: The Japanese normal database consisted of 206 ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin myocardial perfusion SPECT images was used. The RR interval of the electrocardiogram was divided into 16 frames in the gated image. The cREPO can automatically calculate LV ejection fraction (EF), end-diastolic volume (EDV), end-systolic volume (ESV), peak filling rate, 1/3 mean filling rate (MFR), time to PFR (TTPF) as well as phase histogram parameters of 95% phase bandwidth, phase standard deviation (SD), and entropy.**

***Results*: Mean LVEF was slightly higher in females (71.7 vs. 69.6%, p=0.0018), and EDV and ESV were higher in males (92.5 vs. 70.9 mL for EDV, p<0.0001; and 27.5 vs. 19.9 mL for ESV, p<0.0001). Diastolic functions of 1/3 MFR, TTPF, and TTPF/RR interval significantly differed between males and females (1.46 vs. 1.62/sec, p=0.007; 171 vs. 153 ms, p=0.001; and 0.18 vs. 0.17, p=0.028, respectively). Gender differences were observed in 95% bandwidth (43° for males vs. 37° for females, p<0.0001), phase SD (10.6° vs. 9.2°, p<0.0001), and entropy (46% vs. 41%, p<0.0001).**

***Conclusions*: Normal mean values of LV functional parameters for cREPO were determined. These normal values for cREPO could be used as a basis for evaluation of a gated SPECT image in patients with cardiac diseases.**

Keywords: Cardiac diastolic function, CardioREPO, Gated SPECT, Japanese normal database, Left ventricular volume, Phase histogram distribution
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Gated myocardial perfusion single-photon emission computed tomography (SPECT) (GMPS) has been used to evaluate quantitative cardiac functional parameters including the left ventricular (LV) volume and ejection fraction (EF). It has also been used for calculating LV diastolic functions such as peak filling rate (PFR), 1/3 mean filling rate (MFR), and time to PFR (TTPF) (1). Furthermore, phase analysis of GMPS data has been used to diagnose LV mechanical dyssynchrony (2-4). Commercially available software programs are widely utilized to calculate LV volume, diastolic function, and phase histogram parameters.

We developed a software package that integrates myocardial perfusion and LV functional analyses: cardioREPO (cREPO; FUJIFILM RI Pharma, Tokyo, Japan, developed in collaboration with EXINI Diagnosis, Lund, Sweden, and Kanazawa University, Kanazawa, Japan) (5,6). The purpose

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Table 1 The patient characteristics of the JSNM-WG normal database

	Males	Females	p value
Number of patients	106	100	
Mean age (y)	63.5 ± 13.2	64.4 ± 11.9	n.s.
Height (cm)	165.8 ± 6.4	154.1 ± 6.0	<0.0001
Weight (kg)	62.8 ± 10.7	52.4 ± 9.0	<0.0001
BMI (kg/m^2)	22.8 ± 3.3	22.0 ± 3.3	n.s.
BSA (m^2)	1.69 ± 0.15	1.49 ± 0.13	<0.0001

Abbreviations: BMI, body mass index; BSA, body surface area by the DuBois formula; JSNM-WG, the Japanese Society of Nuclear Medicine working group.

of this study was to measure normal mean values of LV volume, diastolic function, and phase histogram parameters, and to evaluate gender differences in these parameters.

Methods

The Japanese normal database generated by the Japanese Society of Nuclear Medicine working group (JSNM-WG) in 2012 was used (1,7,8). A total of 206 sets of GMPS images were accumulated from patients with a low likelihood of cardiac diseases. These were retrospectively collected from eight hospitals in Japan. All patients underwent stress-rest ^{99m}Tc-sestamibi (MIBI) or ^{99m}Tc-tetrofosmin (TF) GMPS testing with a standard dose of 555-1110 MBq. The patient selection criteria for generating the normal database has been summarized elsewhere (7,8). The patient characteristics are shown in Table 1. The ethics committee in Kanazawa University hospital approved patient enrollment for JSNM-WG activity, and then the ethics committees in all hospitals also approved this study.

Gated and non-gated short-axis (SA) myocardial perfusion images composed the JSNM-WG normal database. The rest gated SA image was used to measure cardiac functional parameters. The acquisition matrix was 64. There were 16 RR intervals in the gated SA image. The cREPO can automatically compute LVEF, LV volume (end-diastolic volume (EDV) and end-systolic volume (ESV)), diastolic function (PFR, 1/3 MFR, TTPF, and TTPF/RR interval), and phase parameters (95% phase bandwidth, phase standard deviation (SD), and entropy). The cREPO has a small-heart compensation algorithm fitted for Japanese population－particularly for some of the female patients (6).

After outliers were excluded using Tukey outlier detection method (9), all values were expressed as mean ± SD. The differences in continuous variables were analyzed using the Student's t-test. All statistical tests were two-tailed; p values < 0.05 were considered significant. These analyses were performed using the JMP version 11.2.1 (SAS Institute Inc., Cary, NC, USA) software.

Results

Normal values for cardiac functional parameters are shown in Table 2. Although the mean LVEF was slightly higher by 2.1% in females (p=0.0018), EDV, ESV, EDVI, and ESVI were significantly higher in males (p<0.0001).

Diastolic functions of 1/3 MFR, TTPF, and TTPF/RR significantly differed between genders (p=0.007, 0.001, and 0.028, respectively). No gender differences were observed in any diastolic parameters when image datasets derived from patients aged ≤ 65 years were selected from the normal database. Next, the diastolic parameters derived from image datasets of patients aged ≤ 65 years and > 65 years were compared. The PFR and 1/3 MFR showed significantly higher values in patients ≤ 65 years (female PFR: 2.78 vs. 2.43/sec, p=0.0049, male PFR: 2.78 vs. 2.12/sec, p< 0.0001, female MFR: 1.70 vs. 1.52/sec, p=0.031, and male MFR: 1.62 vs. 1.30/sec, p=0.0003).

There were significant gender differences in 95% bandwidth (42.9° for males vs. 36.8° for females), phase SD (10.6° vs. 9.2°), and entropy (45.6% vs. 41.1%) in Table 2. The normal mean and upper limit of phase histogram distribution were consistently higher in males than in females (p<0.0001). When 44 females and 34 males who showed the EDV of 65-85 mL were selected from the normal database to normalize the effect of volume difference between genders, both 95% bandwidth and phase SD did not differ significantly. However, entropy still showed significant difference between genders (40.9 ± 5.4 for females and 43.3 ± 6.6 for males, p=0.040). Subsequently, the relationships between phase parameters and LV volumes were analyzed in Fig. 1. Significant correlations were observed in all combinations: between 95% bandwidth and EDV (r=0.279, p<0.0001), 95% bandwidth and ESV (r=0.418, p<0.0001), phase SD and EDV (r=0.330, p<0.0001), phase SD and ESV (r=0.471, p<0.0001), entropy and EDV (r=0.335, p<0.0001), and entropy and ESV (r=0.537, p<0.0001).

Discussion

Using the JSNM-WG normal database, we measured mean values for the normal LV volumes, diastolic parameters, and phase parameters derived from the cREPO software program. Nakajima et al. have already reported normal values derived from the quantitative gated SPECT (QGS) program (8). Although the normal ranges of diastolic parameters by cREPO were equivalent to those by QGS, the normal ranges of EDV and ESV showed higher values in cREPO. Moreover, the upper limits of phase parameters by cREPO were higher than those by QGS. The calculation algorithm for gated SA myocardial perfusion images might cause these differences.

The cREPO program has a unique feature of LV delineation

Table 2 Normal values for LV volume, diastolic function, and phase parameters

	Males Mean ± SD (Mean -2SD to +2SD)	Females Mean ± SD (Mean -2SD to +2SD)	p value
LV volume			
EF (%)	69.6 ± 6.0 (58.2-85.2)	71.7 ± 6.7 (57.5-81.7)	0.018
EDV (mL)	92.5 ± 18.8 (54.8-130.1)	70.9 ± 14.6 (41.6-100.2)	<0.0001
ESV (mL)	27.5 ± 6.9 (13.7-41.4)	19.9 ± 5.7 (8.4-31.4)	<0.0001
EDVI (mL/m^2)	53.7 ± 8.4 (37.0-70.5)	47.6 ± 7.7 (32.3-63.0)	<0.0001
ESVI (mL/m^2)	16.3 ± 3.5 (9.2-23.3)	13.5 ± 3.4 (6.7-20.2)	<0.0001
Diastolic parameters			
PFR (per s)	2.44 ± 0.67 (1.31-3.90)	2.60 ± 0.65 (1.10-3.78)	n.s.
1/3 MFR (per s)	1.46 ± 0.45 (0.55-2.36)	1.62 ± 0.44 (0.75-2.50)	0.007
TTPF (ms)	171 ± 46 (80-263)	153 ± 38 (78-228)	0.001
TTPF/RR interval	0.18 ± 0.05 (0.08-0.28)	0.17 ± 0.04 (0.10-0.24)	0.028
Age ≤ 65 years			
N	55	56	
PFR (per s)	2.78 ± 0.62 (1.54-4.01)	2.78 ± 0.59 (1.61-3.95)	n.s.
1/3 MFR (per s)	1.62 ± 0.47 (0.68-2.55)	1.70 ± 0.39 (0.92-2.47)	n.s.
TTPF (ms)	165 ± 35 (94-235)	151 ± 32 (88-215)	n.s.
TTPF/RR interval	0.17 ± 0.03 (0.11-0.24)	0.17 ± 0.02 (0.12-0.21)	n.s.
Phase parameters			
Bandwidth (degree)	42.9 ± 12.2 (18.4-67.4)	36.8 ± 9.1 (18.6-55.0)	<0.0001
Phase SD (degree)	10.6 ± 2.6 (5.4-15.9)	9.2 ± 2.1 (5.0-13.4)	<0.0001
Entropy (%)	45.6 ± 6.4 (32.8-58.3)	41.1 ± 5.6 (29.8-52.4)	<0.0001
65 mL ≤ EDV ≤ 85 mL			
N	34	44	
Bandwidth (degree)	38.9 ± 11.0 (16.9-60.9)	36.3 ± 8.7 (18.9-53.7)	n.s.
Phase SD (degree)	9.65 ± 2.36 (4.93-14.3)	9.02 ± 1.97 (5.08-13.0)	n.s.
Entropy (%)	43.3 ± 6.6 (30.1-56.5)	40.9 ± 5.4 (30.1-51.7)	0.04

Abbreviations: EDV: end-diastolic volume, EF: ejection fraction, ESV: end-systolic volume, LV: left ventricular, MFR: mean filling rate, PFR: peak filling rate, SD: standard deviation, TTPF: time to PFR

for small heart (5,6). The LV contour is automatically detected based on the active shape model when the cardiac model simulated with an ellipsoid shape is adjusted to the myocardium. This process is continuously performed in all apical to basal MPS slices. Consequently, the endocardial and epicardial contours are shifted to the epicardial direction to compensate the underestimation of the LV volume. When the mid-ventricular volume is calculated as 0 mL, the endocardial and epicardial surfaces are shifted by 3.5 mm. When the mid-ventricular volume is calculated as 85 mL, the cREPO program do not apply this compensation method to volume calculation.

The cREPO program can avoid the underestimation of LV EDV and ESV using both the active shape model and LV volume compensation method even in the patients with a small heart. Female Asian patients frequently have a small heart (ESV ≤ 20 mL) in GMPS testing, and thus 24% and 41% of the female patients in this study were determined to have a small heart by cREPO and QGS, respectively. With regard to the male patients with ESV ≤ 20 mL, 6% and 12% of the male patients were also determined to have a small heart by cREPO and QGS, respectively. The cREPO program might be superior to QGS in LV volume calculation for patients with a small heart. Furthermore, cREPO is helpful in assessing pediatric LV volume (10).

The JSNM-WG normal database consists of GMPS images derived from both 180° and 360° SPECT image acquisitions (n=93, 113, respectively). However, the excellent correlation and agreement between 180° and 360° SPECT acquisitions have been reported in LVEF and EDV measurements (11). Different SPECT acquisition conditions would not affect LV diastolic function and phase distribution. We have measured normal LV functional parameters, and thus clinical validation would be required using these normal LV parameters.

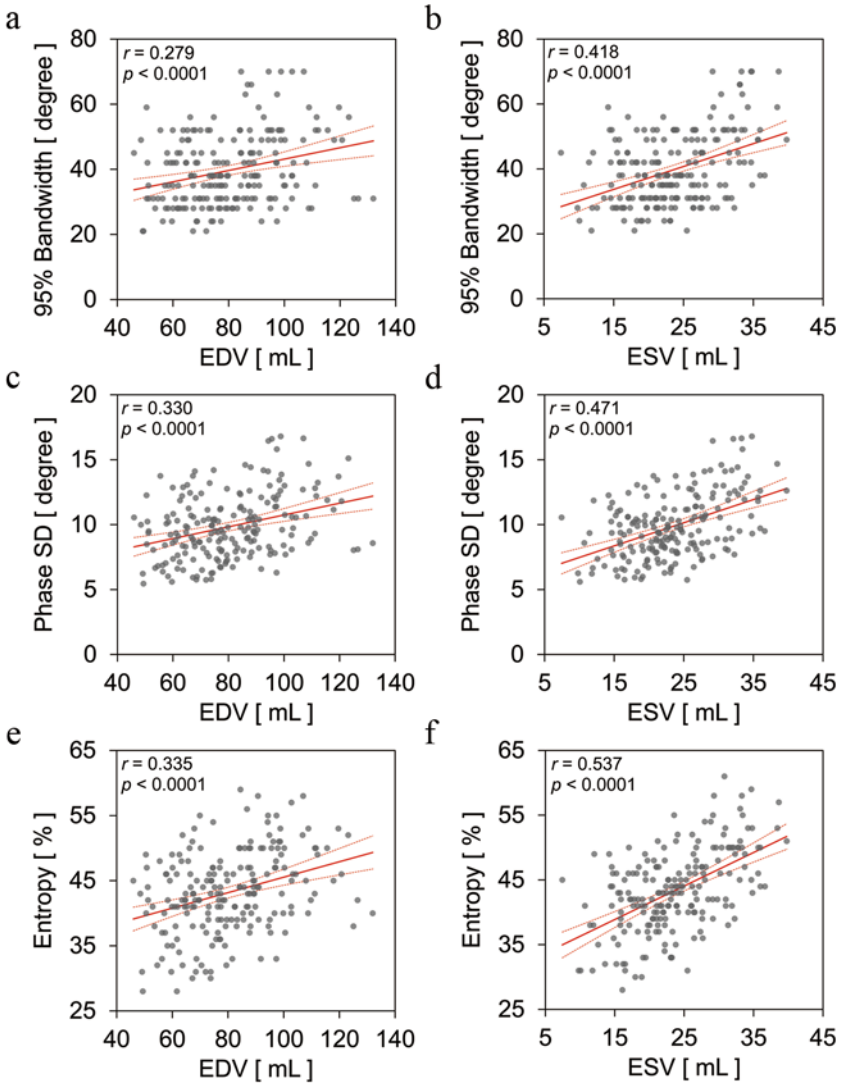

Fig. 1　The relationship between 95% bandwidth and EDV (**a**), that and ESV (**b**), phase SD and EDV (**c**), that and ESV (**d**), entropy and EDV (**e**), and that and ESV (**f**). The red solid lines indicate the regression lines. The dashed lines indicate 95% upper and lower limits for the regression lines.

Conclusions

Normal mean values of cardiac functional parameters were determined by using the cREPO software program. Gender differences in these parameters were clearly exhibited, and the normal ranges were different in male and female patients. The normal mean values and ranges of the LV volume, diastolic function, and phase histogram parameters for cREPO could be used as a basis for evaluating GMPS images in various cardiac diseases.

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Conflicts of interest

K Nakajima has a collaborative research work with FUJIFILM RI Pharma Co., Ltd., Tokyo, Japan, which developed the cREPO software program.

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