Original Article

Sex-specific reference limits of left ventricular ejection fraction and volumes estimated by gated myocardial perfusion imaging for low-risk patients in China: a comparison between three quantitative algorithms

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Background: Establishing appropriate reference value limits of left ventricular (LV) functional parameters is fundamental for the assessment of cardiac function. At present, there are no reports aimed at establishing reference limits using gated myocardial perfusion imaging (MPI) in mainland China.

Methods: A total of 175 consecutive patients who were defined as low-risk coronary artery disease patients underwent stress Technetium-99m sestamibi (^{99m}Tc-MIBI)-gated myocardial perfusion single-photon emission computed tomography (SPECT) imaging. The LV ejection fraction (EF), end-diastolic volume (EDV), and end-systolic volume (ESV) were obtained by 3 quantitative algorithms: quantitative-gated SPECT, emory cardiac toolbox, and 4-dimensional model SPECT, respectively. The threshold values were obtained using Gaussian distribution or percentiles. The influence of gender, age, and weight on cardiac functional parameters was analyzed by multiple regressions for linear models.

Results: For males, the lower reference limits of EF were 52%, 63%, and 58%, respectively; and the upper limits of EDV/ESV were 106/45, 152/55, and 135/55 mL, respectively. For females, the lower reference limits of EF were 58%, 66%, and 65%, respectively; and the upper limits of EDV/ESV were 73/27, 105/31, and 88/29 mL, respectively. Compared to females, males had greater cardiac volume values and lower mean EF values. Bland-Altman plots revealed that the cardiac function parameters calculated by the three quantitative algorithms were in high agreement.

Conclusions: In this study, the reference limits of cardiac parameters calculated by the 3 methods based on single-center data in China were preliminarily established. The threshold values determined by three quantitative algorithms were not interchangeable but were highly correlated.

Keywords: Gated SPECT; left ventricular function; sex; age; weight; reference limits

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Introduction

Left ventricular (LV) ejection fraction (EF) and end-diastolic and end-systolic volumes (EDV/ESV) are considered to be crucial factors in the diagnosis and treatment of heart disease (1,2). Establishing appropriate threshold values is extremely important for the evaluation of clinical significance. Numerous factors affect the precision of ventricular volume and EF determination. The reference limits of LV functional parameters likely vary across imaging modalities (3,4), populations (5,6), genders (7-10), and quantitative methods (11-13).

Imaging technologies, such as echocardiography, cardiovascular magnetic resonance imaging, and gated blood pool studies, are widely used in clinical practice. Gated myocardial perfusion single-photon emission computed tomography (SPECT) imaging is a state-of-the-art technique for the combined evaluation of myocardial perfusion and LV function within a single study in patients with coronary artery disease (14) and has demonstrated a high correlation with the outcomes of other modalities. SPECT quantification is based on myocardial radioactivity count densities, which could be influenced by attenuation, and numerous previous studies have confirmed the effect of gender, age, and analyzing methods. Considerable research has shown that US or European populations have a greater body mass index (BMI) and more significant soft tissue attenuation. In comparison, Asian populations have a greater incidence of small heart (5), which causes nonlinear underestimation of small hearts and amplifies the influence caused by acquisition and processing methods (15,16).

The purpose of this research was to establish normal reference limits of cardiac functional parameters using three quantitative methods based on the patients who were defined as low-risk coronary artery disease patients. We also aimed to analyze the influence of gender, age, weight, and body surface area (BSA) on cardiac functional parameters. These analysis results are necessary to establish more precise threshold values in clinical practice.

Methods

Study population

Between May 2009 and May 2011, we prospectively enrolled 175 patients (89 males and 86 females) who underwent exercise or adenosine stress myocardial perfusion SPECT imaging. All patients were defined as those with a low pretest likelihood of coronary artery disease (<10%). We defined the low likelihood for coronary heart disease (<10%) according to the patients' histories of illness, age, sex, symptoms, and the extent of ST-segment depression (17). This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval for this study was waived by the Ethics committee of Fuwai Hospital due to the following reasons: (I) the study was observational; (II) gated myocardial perfusion imaging (MPI) was conducted daily in the nuclear department; and (III) the participants did not receive interventions before and after MPI. Informed consent was obtained from all of the patients.

The inclusion criteria were as follows: (I) males or females (aged between 30 and 69) who complained of nonanginal chest pain and had no ST segment depression when undertaking electrocardiographic stress test, males (aged between 30 and 39) and females (aged between 30 and 59) who complained of nonanginal chest pain and had ST depression between 0.5 and 1.0 mm, females (aged between 30 and 49) who complained of nonanginal chest pain and had ST depression between 1.0 and 1.5 mm, and females (aged between 30 and 39) who complained of nonanginal chest pain had ST depression between 1.5 and 2.5 mm; (II) males (aged between 30 and 39) and females (aged between 30 and 59) who complained of atypical anginal and had ST depression between 0 and 0.5 mm, and females (aged between 30 and 39) who complained of atypical anginal and had ST depression between 0.5 and 1.0 mm; (III) females (aged between 30 and 39) who complained of typical anginal and had ST depression between 0 and 0.5 mm; and (IV) all participants with negative gated MPI results (normal myocardial perfusion and wall motion, no abnormal wall thickness).

Patients with any of the following were excluded: (I) hypertension, diabetes mellitus and hyperlipemia, valvular heart disease, myocarditis, arrhythmias (including atrial fibrillation and other significant arrhythmias), or cardiac failure (class III or higher according to New York Heart Association); (II) confirmed myocardial infarction or coronary heart disease; (III) electrocardiogram (ECG) abnormalities at rest, during exercise, adenosine stress test, or stress myocardial perfusion SPECT imaging; (IV) regional wall motion or thickening abnormality seen on gated SPECT; and (V) ECG-gated ^{99m}Tc-MIBI SPECT.

In conformity with the guidelines from the American Society of Nuclear Cardiology and the America Heart Association (1), exercise or adenosine stress ^{99m}Tc-MIBI SPECT imaging was performed. β-blockers were prohibited

24–48 hours prior to the exercise stress test, and no caffeine-containing beverages or medications were permitted at least 12 hours before the adenosine stress test. The Bruce treadmill test protocol was carried out; when a submaximum heart rate was reached, 25–30 mCi ^{99m}Tc-MIBI was injected intravenously. Adenosine (0.14 mg/kg/min) was intravenously infused over 6 minutes to trigger coronary hyperemia, and 3 minutes after the completion of the infusion, a dose of 25–30 mCi ^{99m}Tc-MIBI was injected. Image acquisition was conducted approximately 1 hour after the stress test.

Images were acquired on a dual-head SPECT scanner (Siemens e. Cam, Siemen Healthineers, Erlangen, Germany) equipped with low-energy high-resolution collimators, using a noncircular 180°-acquisition for 32 projections. Data were stored in a 64×64 matrix and a zoom factor of 1.45. Acquisition was gated for 8 frames per cardiac cycle, with a beat acceptance window set at 20% of the average R-R interval.

Image reconstruction and analysis

Images were reconstructed by filtered back projection using the Butterworth filter function (cutoff 0.45 cycles/pixel and order of 5). Attenuation or scatter correction and background subtractions were not performed. Cardiac functional parameters were derived by three quantitative methods: quantitative-gated SPECT (QGS; version 3.1, Cedars Sinai Medical Center, Los Angeles, CA, USA), emory cardiac toolbox (ECToolbox; version 3.0, Emory University, Atlanta, GA, USA), and 4-dimensional model SPECT (4D-MSPECT; version 4.2, University of Michigan Medical Center, Ann Arbor, MI, USA). These 3 algorithms were used in the automatic processing mode for the majority of the time; however, in rare cases when the automatic mode was confounded by liver/bowel or incorrect detection of the atrioventricular (AV) valve plane, manual processing was required. The quality of gated data was checked within 30 minutes after acquisition and during reporting.

All MPI results were analyzed independently by two experienced nuclear medicine physicians, and the senior physician's decision was adopted in cases of disagreement. The gated data were always checked when we suspected a decreased radioactivity uptake in the anterior wall caused by breast attenuation or decreased uptake in the inferior by diaphragmatic attenuation. If there was no wall motion abnormality (as confirmed by the two physicians), we considered the imaging results to be normal; however, if there was wall motion abnormality, then the patient was excluded.

Data analysis and statistics

We use MedCalc Version 19.7.4 (MedCalc Software Ltd, Ostend, Belgium) to construct Bland-Altman plots. Other statistical analyses were performed using SPSS version 19.0 for Windows (IBM Corporation, Armonk, NY, USA). Statistical test results were considered significant with a P value <0.05. Continuous normally distributed variables are reported as mean ± standard deviation (SD). The Kolmogorov-Smirnov (K-S) test and quantile-quantile (Q-Q) plot were used to assess the goodness of fit of a Gaussian distribution. Differences between mean values for each sex were evaluated using the Student's *t* test. Sex differences between mean ESV, EDV, and EF were investigated using unpaired and paired *t* tests, respectively. Analysis of variance (ANOVA) for the mean was performed according to sex, age, and body weight. A multiple linear regression analysis was performed using the standard and stepwise methods. ANOVA analysis was used to compare the cardiac parameter results of the 3 quantitative methods. EDV index (EDVI) and ESV index (ESVI) were defined as EDV and ESV divided by BSA (EDVI = EDV/BSA; ESVI = ESV/BSA). The Tukey test was used to compare the variables between age groups for both women and men.

The reference thresholds were obtained using Gaussian distribution or percentiles. The bounds of this range were the 95th centiles of the fitted Gaussian distribution. The cardiac function parameters, EF, EDV, EDVI, ESV, and ESVI, were 1-tailed cutoffs; an EF value that was too low was considered abnormal, in which case the lower limit was demanded. Meanwhile, EDV/ESV or EDVI/ESVI values that were too high were considered abnormal, in which case the upper limit was demanded. The lower limit was calculated as follows: lower limit = mean – 1.64 × SD; the upper limit was calculated as follows: upper limit = mean + 1.64 × SD. BSA was calculated as follows: male BSA = 0.0057 × height (cm) + 0.0121 × weight (kg) + 0.0882; female BSA = 0.0073 × height (cm) + 0.0127 × weight – 0.2106 for females.

Results

In this study, a total of 175 patients were selected as the study population, according to the criteria for a low risk of coronary heart disease. The demographic characteristics of the study population are listed in *Table 1*. The mean age was 49±10 years for women and 48±10 years for men (P=0.034).

Table 1 Baseline characteristics

Variable	Male (n=89)	Female (n=86)	P value
Age (years), mean ± SD	48±10	49±10	<0.05
Weight (kg), mean ± SD	75±9	61±7	<0.001
Height (cm), mean ± SD	172±5	160±4	<0.001
BMI (kg/m^2), mean ± SD	25.1±2.7	23.7±3.0	<0.005
BSA (m^2), mean ± SD	1.9±0.1	1.7±0.1	<0.001
HR and BP at rest			
Resting HR (bpm)	77±11	77±13	NS
Resting SBP (mmHg)	122±16	112±17	<0.001
Resting DBP (mmHg)	78±12	73±11	<0.01
HR and BP at exercise			
No.	75	57	<0.01
Peak HR (bpm), mean ± SD	143±14	138±13	NS
Peak SBP (mmHg), mean ± SD	169±21	168±23	<0.001
Peak DBP (mmHg), mean ± SD	92±17	83±14	<0.001
HR and BP at adenosine stress			
No.	14	29	
HR (bpm), mean ± SD	103±9	113±21	NS
SBP (mmHg), mean ± SD	121±27	101±27	<0.05
DBP (mmHg), mean ± SD	74±14	65±12	NS

BMI, body mass index; BP, blood pressure; SBP, systolic pressure; DBP, diastolic pressure; BSA, body surface area; HR, heart rate; bpm, beats per minute; NS, not significant.

There were significant differences in the patients' demographic characteristics, except for resting heart rate, heart rate at peak, and mean diastolic blood pressure in the adenosine stress test. The number of male patients who underwent an exercise stress test was greater than that in women (P=0.008).

The EF, EDV, EDVI, ESV, and ESVI values derived from the quantitative gated SPECT (QGS) algorithm were in accordance with normal distribution. The K-S test results revealed that the ESV and EF values derived from the ECToolbox and the EDV value from the 4D-MSPECT did not fit the normal distribution. However, the Q-Q plot suggested they were approximately normally distributed, and we also observed that the ESV and EF values derived from ECToolbox and the EDV value from the 4D-MSPECT were approximately normally distributed. As shown in *Table 2*, the reference limits of cardiac functional parameters from the three algorithms were established.

The differences in cardiac functional parameters between men and women were compared (*Table 3*). The mean EF values for women and men were 74.7%±10.0% and 65.1%±7.6%, respectively (P<0.0001). Also, the EDV and ESV values were lower in women than in men. Likewise, the EDVI and ESVI values were also lower in women than in men. When a small heart was defined as ESV <20 mL, the incidence of small heart was significantly higher in women (76%) than in men (22%; P<0.0001).

As shown in *Table 4*, the influence of gender, age, and weight on EDV, ESV, EF, EDVI, and ESVI was assessed via

Table 2 Normal reference limits of EF, volume, and volume indices by the 3 methods

Parameters	QGS		ECToolbox		4D-MSPECT	
	Male	Female	Male	Female	Male	Female
EF (%)	≥52	≥58	≥63	≥66	≥58	≥65
EDV (mL)	≤106	≤73	≤152	≤105	≤135	≤88
EDVI (mL/m^2)	≤53	≤42	≤74	≤57	≤67	≤43
ESV (mL)	≤45	≤27	≤55	≤31	≤55	≤29
ESVI (mL/m^2)	≤28	≤16	≤26	≤17	≤26	≤17

EF, ejection fraction; EDV, end diastolic volume; EDVI, end diastolic volume index; ESV, end systolic volume; ESVI, end systolic volume index; EDVI = EDV/BSA; ESVI = ESV/BSA; BSA, body surface area; QGS, quantitative-gated single-photon emission computed tomography ECToolbox, emory cardiac toolbox; 4D-MSPECT, 4-dimensional model single-photon emission computed tomography.

Table 3 Comparison of EF, volume, and volume indices between men and women by QGS algorithm

Parameters	Male (n=89)	Female (n=86)	P value
EDV (mL), mean ± SD	75±18	53±11	<0.0001
EDVI (mL/m_2), mean ± SD	38±9	30±7	<0.0001
ESV (mL), mean ± SD	27±10	14±7	<0.0001
ESVI (mL/m_2), mean ± SD	19±5	8±4	<0.0001
EF (%), mean ± SD	65±7	74±10	<0.0001

EF, ejection fraction; EDV, end diastolic volume; EDVI, end diastolic volume index; ESV, end systolic volume; ESVI, end systolic volume index; EDVI = EDV/BSA; ESVI = ESV/BSA; BSA, body surface area; QGS, quantitative-gated single-photon emission computed tomography.

Table 4 Multiple linear regression analysis of EF, volume, and volume indices by forward stepwise method (EDV, EDVI, ESV, ESVI, and EF in this table are from QGS)

Parameters	Variables	Estimate of coefficient	P value
EDV (mL)	R^2=0.41, adjusted R^2=0.40		
	Gender (women-men)	−17.40	<0.001
	Age	−0.32	<0.005
	Body weight	0.33	<0.05
EDVI (mL/m^2)	R^2=0.20, adjusted R^2=0.18		
	Gender (women-men)	−5.83	<0.005
	Age	−0.21	<0.005
	Body weight	−0.16	<0.05
ESV (mL)	R^2=0.40, adjusted R^2=0.38		
	Gender (women-men)	−10.67	<0.001
	Age	−0.27	<0.001
	Body weight	0.12	NS
ESVI (mL/m^2)	R^2=0.73, adjusted R^2=0.72		
	Gender (women-men)	15.7	<0.001
	Age	−0.16	<0.005
	Body weight	−0.38	<0.001
EF (%)	R^2=0.33, adjusted R^2=0.32		
	Gender (women-men)	8.86	<0.001
	Age	0.30	<0.001
	Body weight	0.001	NS

EF, ejection fraction; EDV, end diastolic volume; EDVI, end diastolic volume index; ESV, end systolic volume; ESVI, end systolic volume index; EDVI = EDV/BSA; ESVI = ESV/BSA; BSA, body surface area; QGS, quantitative-gated single-photon emission computed tomography.

multiple regression analysis. Gender and age were identified as significant variables for EF based on a forward stepwise regression model, and gender, age, and body weight were all found to be significant variables for EDV and ESVI. When EDV was normalized by BSA, body weight was not a significant predictor for EDVI.

In order to evaluate age-related differences in EF, volumes and volume indices, three age groups were defined: ≤40, 41–49, and ≥50 (*Table 5*). In men, LVEF, EDV, ESV, EDVI, and ESVI did not differ significantly among the three age groups. The percentage of patients with a small heart did not differ among the male age groups although it was slightly higher (29%) in the ≥50 years group. In women, the EDV did not differ significantly among the three age groups. Meanwhile, the ESV, ESVI, and EF differed significantly among the three age groups; ESV and ESVI decreased with age (P<0.005; *Figure 1*), and EF increased with age (P<0.001; *Figure 2*). Also, the percentage of patients with a small heart varied among the female age groups, reaching as high as 86% in the ≥50 years group.

Difference in cardiac functional parameters from the 3 quantitative algorithms was compared using ANOVA (*Table 6*). Liner regression analysis was used to test the correlation of the values from the three methods (*Figures 3-8*) Bland-Altman plots were used to test the agreement between the three algorithms (*Figures 9-17*). We found excellent correlations between the three methods for EF, EDV, and ESV. For LVEF and EDV, significant differences were noted among the three methods (P<0.001). Furthermore, the 4D-MSPECT values were significantly lower than those of the ECToolbox. Likewise, the QGS values were lower than those of the 4D-MSPECT. For ESV, there were no significant differences among the QGS, ECToolbox, and 4D-MSPECT (P=0.602).

Discussion

The present study was performed with a series of consecutive patients who routinely underwent myocardial perfusion SPECT imaging, which reflects the daily practice in Beijing. The key outcome of this research was the preliminary establishment of normal reference limits of cardiac functional parameters derived from three

Table 5 Age-related differences in EF, volume, and volume indices from QGS

Parameters	Age group (years)			Tukey test P value
	≤40	41–49	≥50	
Women				
No.	20	23	43	
HR (bpm), mean ± SD	79±14	75±9	77±15	NS
RSP (mmHg), mean ± SD	107±15	107±19	117±16	<0.05
RDP (mmHg), mean ± SD	73±11	72±10	74±11	NS
Height (cm), mean ± SD	162±5	162±4	159±3	<0.05
Weight (kg), mean ± SD	59±7	62±8	61±7	NS
BSA (m^2), mean ± SD	1.7±0.1	1.7±0.1	1.7±0.1	NS
BMI (kg/m^2), mean ± SD	22.5±3.2	23.6±3.3	24.4±2.7	NS
EDV (mL), mean ± SD	57±12	55±10	50±11	NS
EDVI (mL/m^2), mean ± SD	33±6	31±5	29±6.4	NS
ESV (mL), mean ± SD	18±8	15±8	11±6	<0.01
ESVI (mL/$m^{2)}$, mean ± SD	10±4	8±4	7±4	<0.05
EF (%)	69±10	73±9	78±9	<0.005
Small heart	55% (11/20)	74% (17/23)	86% (37/43)	0.028*
Men				
No.	29	36	24	
HR (bpm), mean ± SD	77±12	78±13	75±9	NS
RSP (mmHg), mean ± SD	119±13	124±16	123±19	NS
RDP (mmHg), mean ± SD	79±8	81±12	74±15	NS
Height (cm), mean ± SD	174±5	171±5	171±4	NS
Weight (kg), mean ± SD	75±9	77±9	71±9	NS
BSA (m^2± SD)	2.0±0.1	2.0±0.1	1.9±0.1	NS
BMI (kg/m^2), mean ± SD	25.0±3.2	26.0±2.5	24.0±2.2	NS
EDV (mL), mean ± SD	80±19	76±18	69±15	NS
EDVI (mL/m^2), mean ± SD	40±10	38±9	36±7	NS
ESV (mL), mean ± SD	30±11	27±10	23±9	NS
ESVI (mL/m^2), mean ± SD	20±5	19±5	19±4	NS
EF (%)	63±6	65±7	68±8	NS
Small heart	14% (4/29)	22% (8/36)	29% (7/24)	0.391*

*, stands for rates comparison. RSP, resting systolic blood pressure; RDP, resting diastolic blood pressure; BSA, body surface area; BMI, body mass index; HR, heart rate; bpm, beats per minute; EF, ejection fraction; EDV, end diastolic volume; EDVI, end diastolic volume index; ESV, end systolic volume; ESVI end systolic volume index; EDVI = EDV/BSA; ESVI = ESV/BSA; QGS, quantitative-gated single-photon emission computed tomography.

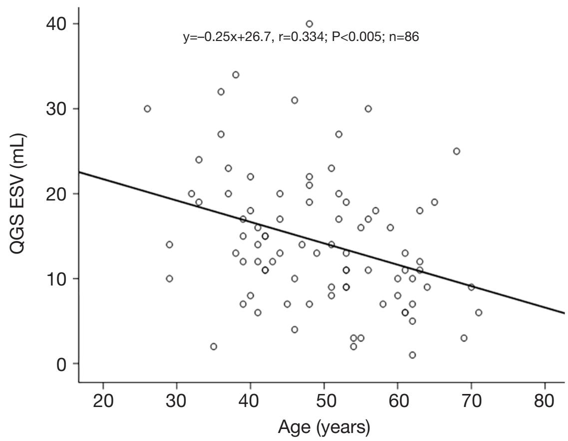

Figure 1 Scatter plot of age and ESV by QGS in women. ESV, end systolic volume; QGS, quantitative-gated single-photon emission computed tomography.

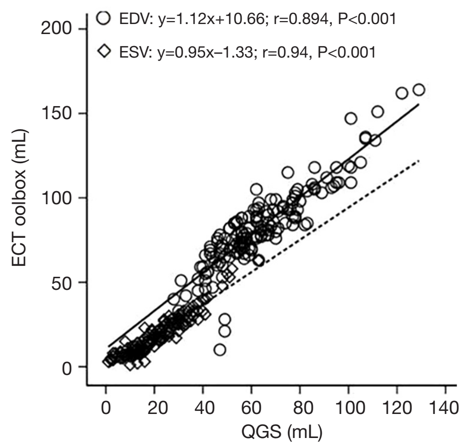

Figure 3 Scatter plot of EDV and ESV by QGS and ECToolbox methods (N=175). EDV, end diastolic volume; ESV, end systolic volume; QGS, quantitative-gated single-photon emission computed tomography; ECToolbox, emory cardiac toolbox.

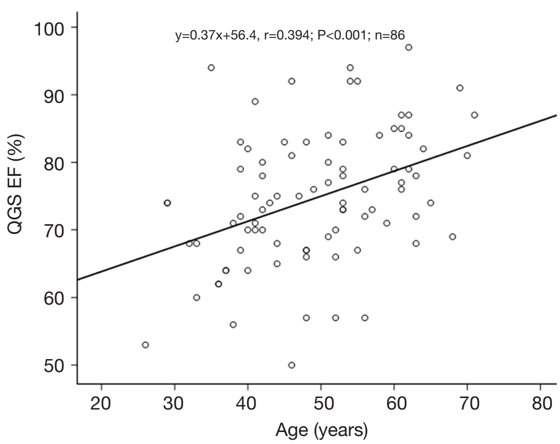

Figure 2 Scatter plot of age and EF by QGS in women. EF, ejection fraction; QGS, quantitative-gated single-photon emission computed tomography.

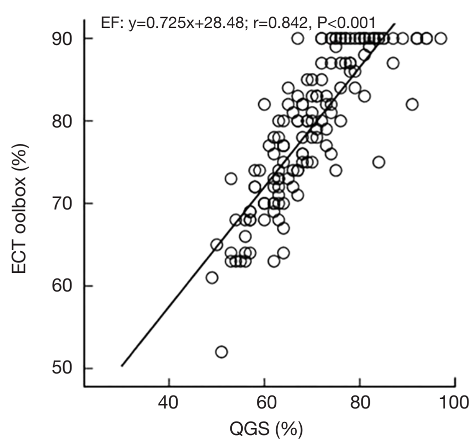

Figure 4 Scatter plot of EF by QGS and ECToolbox methods (N=175). EF, ejection fraction; QGS, quantitative-gated single-photon emission computed tomography; ECToolbox, emory cardiac toolbox.

Table 6 Comparison of EF and volumes between the 3 quantitative algorithms

Parameters	QGS	4D-MSPECT	ECToolbox	Δ_1	Δ_2	Δ_3	P value
EF (%), mean ± SD	71±10	75±8	79±10	−4	−8	−4	<0.005
EDV (mL), mean ± SD	61±18	70±21	81±24	−9	−19	−11	<0.005
ESV (mL), mean ± SD	19±11	18±11	18±12	1	1	0	0.602

Δ_1 = QGS-(4D-MSPECT); Δ_2 = QGS-ECToolbox; Δ_3 = (4D-MSPECT) – ECToolbox. EF, ejection fraction; EDV, end diastolic volume; ESV, end systolic volume; QGS, quantitative-gated single-photon emission computed tomography ECToolbox, emory cardiac toolbox; 4D-MSPECT, 4-dimensional model single-photon emission computed tomography.

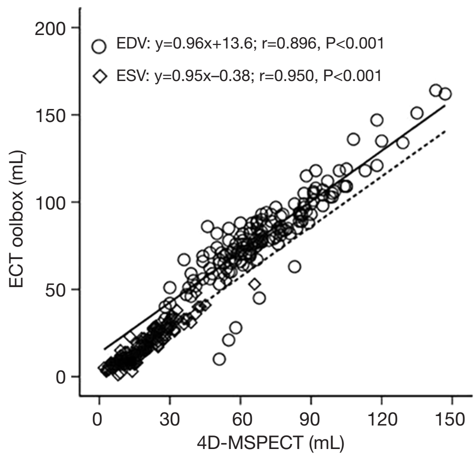

Figure 5 Scatter plot of EDV and ESV by 4D-MSPECT and ECToolbox methods (N=175). EDV, end diastolic volume; ESV, end systolic volume; ECToolbox, emory cardiac toolbox; 4D-MSPECT, 4-dimensional model single-photon emission computed tomography.

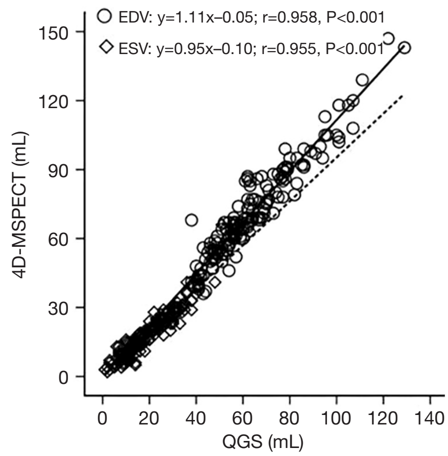

Figure 7 Scatter plot of EDV and ESV by QGS and 4D-MSPECT methods (N=175). EDV, end diastolic volume; ESV, end systolic volume; QGS, quantitative-gated single-photon emission computed tomography; 4D-MSPECT, 4-dimensional model single-photon emission computed tomography.

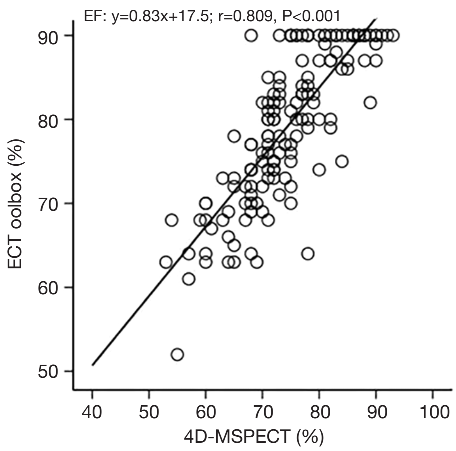

Figure 6 Scatter plot of EF by 4D-MSPECT and ECToolbox methods (N=175). EF, ejection fraction; ECToolbox, emory cardiac toolbox; 4D-MSPECT, 4-dimensional model single-photon emission computed tomography.

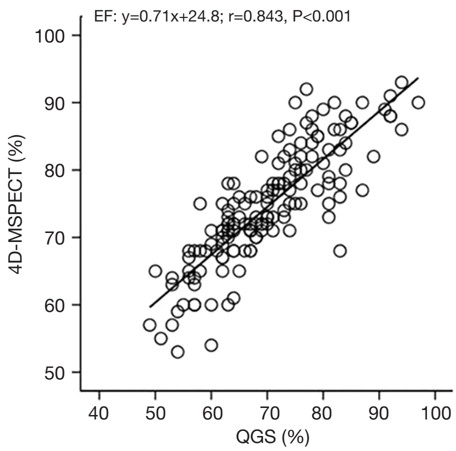

Figure 8 Scatter plot of EF by QGS and 4D-MSPECT methods (N=175). EF, ejection fraction; QGS, quantitative-gated single-photon emission computed tomography; 4D-MSPECT, 4-dimensional model single-photon emission computed tomography.

algorithms, and analysis of the influence of sex, age, and weight on these parameters.

In clinical practice, the quantitative analysis results of gated myocardial SPECT imaging are influenced by numerous factors (13). For example, men may differ from women, and the differences between different algorithms have been confirmed by previous studies. The results of this study also highlight the importance of establishing a population-specific standard.

Characteristics of the Chinese population

In this study, the mean age of the participants were 10–15 years younger than that reported in similar previous studies conducted in the United States (7), Europe (8), Japan (6),

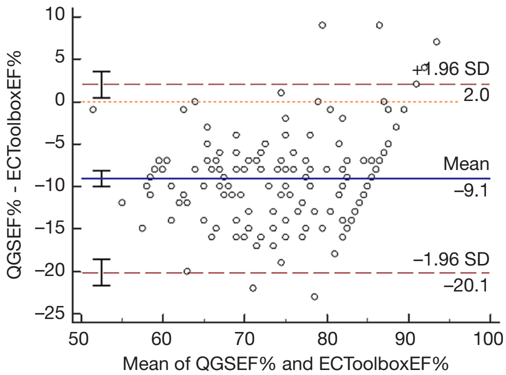

Figure 9 Bland-Altman plot comparing the EF from QGS and ECToolbox (N=175). EF, ejection fraction; QGS, quantitative-gated single-photon emission computed tomography; ECToolbox, emory cardiac toolbox.

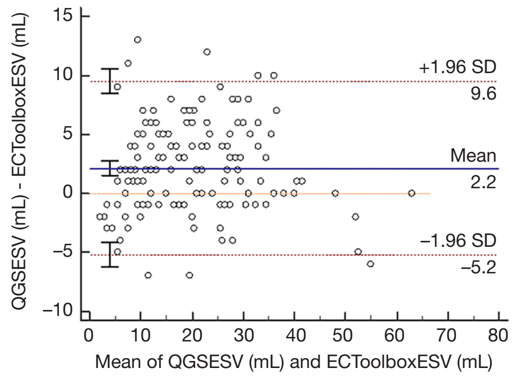

Figure 11 Bland-Altman plot comparing the ESV from QGS and ECToolbox (N=175). ESV, end systolic volume; QGS, quantitative-gated single-photon emission computed tomography; ECToolbox, emory cardiac toolbox.

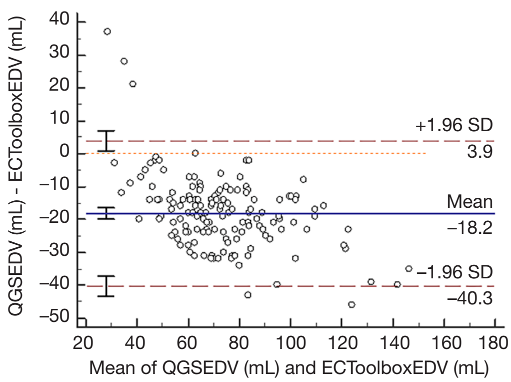

Figure 10 Bland-Altman plot comparing the EDV from QGS and ECToolbox (N=175). EDV, end diastolic volume; QGS, quantitative-gated single-photon emission computed tomography; ECToolbox, emory cardiac toolbox.

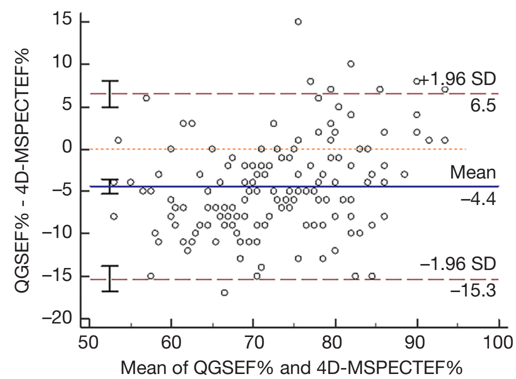

Figure 12 Bland-Altman plot comparing the EF from QGS and 4D-MSPECT (N=175). EF, ejection fraction; QGS, quantitative-gated single-photon emission computed tomography; 4D-MSPECT, 4-dimensional model single-photon emission computed tomography.

and Taiwan (18). Another feature of this population was the incidence of patients with a small heart. Akincioglu *et al.* excluded patients with a small heart (defined as ESV <20 mL) (19) because the major objective of their research was the evaluation of diastolic function. It is recognized that the values determined by QGS are less precise for patients with small LV volumes (20-22). Given the high incidence of small heart in our study, especially in the female population, we decided to include all of the small heart patients. Thus, this study reflects the real-word situation when we perform gated SPECT imaging in China to some extent, and other normal populations in East Asian could also be analogous.

Dependency on sex

Sex-specific discrepancies have been discussed in previous studies with gated SPECT (6-8,23), as well as in a larger scale magnetic resonance imaging (MRI) investigation in the probability-based Dallas heart study (9). After normalization of cardiac functional parameters by BSA, differences between men and women were still present, implying a dependency on the intrinsic physiological

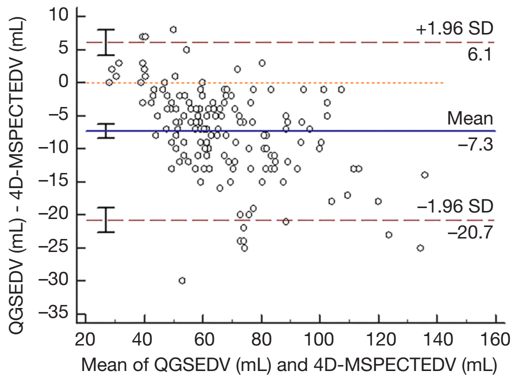

Figure 13 Bland-Altman plot comparing the EDV from QGS and 4D-MSPECT (N=175). EDV, end diastolic volume; QGS, quantitative-gated single-photon emission computed tomography; 4D-MSPECT, 4-dimensional model single-photon emission computed tomography.

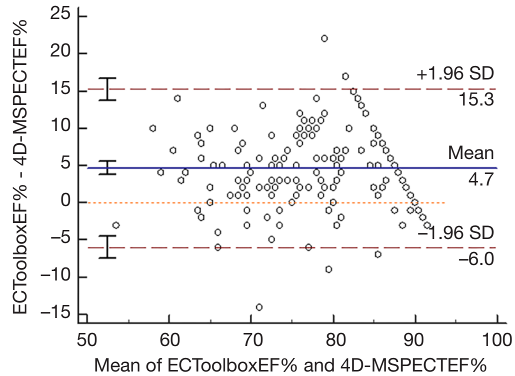

Figure 15 Bland-Altman plot comparing the EF from ECToolbox and 4D-MSPECT (N=175). EF, ejection fraction; ECToolbox, emory cardiac toolbox; 4D-MSPECT, 4-dimensional model single-photon emission computed tomography.

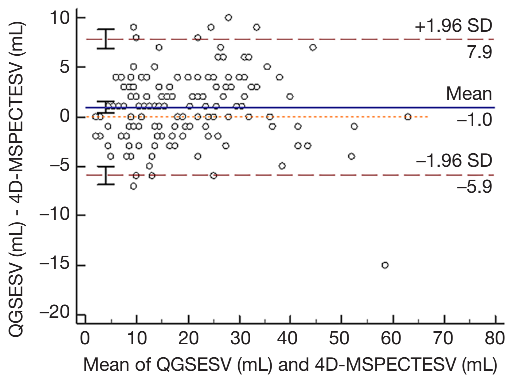

Figure 14 Bland-Altman plot comparing the ESV from QGS and 4D-MSPECT (N=175). ESV, end systolic volume; QGS, quantitative-gated single-photon emission computed tomography; 4D-MSPECT, 4-dimensional model single-photon emission computed tomography.

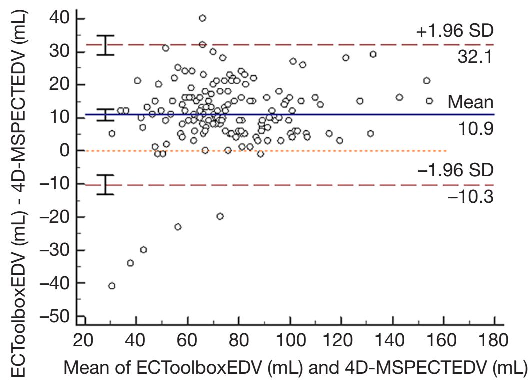

Figure 16 Bland-Altman plot comparing the EDV from ECToolbox and 4D-MSPECT (N=175). EDV, end diastolic volume; ECToolbox, emory cardiac toolbox; 4D-MSPECT, 4-dimensional model single-photon emission computed tomography.

difference between the genders. Women had lower EDV/EDVI and ESV/ESVI and higher EF than men. This finding appears to support evidence that higher EF and lower cardiac volumes are related to the female gender and not just a small body or heart size.

Dependency on age

In this study, age-related discrepancies were observed in women but not in men in the three age groups in this study. This differs from Nakajima *et al.*'s study based on the J-ACCESS database (6). They found that LV volumes decrease significantly as age increased in men but not in women, and that the LVEF did not correlate with age in men or women. One of the reasons for the difference between the two studies may be attributable to the different mean age of the study population; the mean age of Nakajima *et al.*'s study population was 64 years for women and 61 for men, which was markedly older than that of our study. Additionally, De Bondt *et al.* (8) reported differences

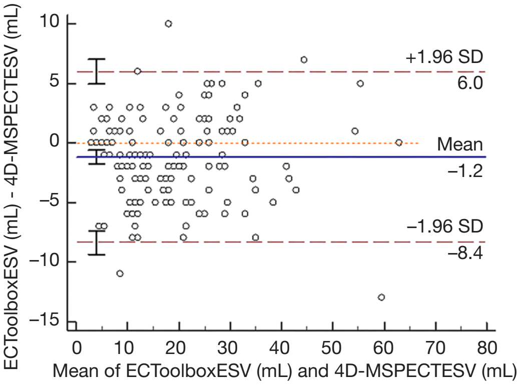

Figure 17 Bland-Altman plot comparing the ESV from ECToolbox and 4D-MSPECT (N=175). ESV, end systolic volume; ECToolbox, emory cardiac toolbox; 4D-MSPECT, 4-dimensional model single-photon emission computed tomography.

in the LVEF or volumetric parameters between the different age groups in women, including the >65 years age group, who had significantly higher EFs and lower volumes. This finding was similar to ours to some extent. Rozanski *et al.* (23) found that age was only weakly correlated with LVEF and did not correlate with LV volume. The age-related characteristics differed among studies; however, the statistical significance was weak in each study. Age-related differences may be associated with the patient populations studied. Multiple regression analysis in the present study showed age to be a crucial contributing factor of cardiac functional parameters for both genders, but it was a significant variable only in women.

Dependency on body weight

Body weight was considered as an important factor determining EDV as shown by the multiple regression analysis. However, after normalization by BSA, weight was not identified as a significant determinant, except with respect to ESVI. This indicated that the effects of body weight on EDV and ESV are different. Additionally, weight was not a significant determinant of LVEF. Considering the marked difference of body weight and BSA between men and women in this study, we recommend a volume index with the unit mL/m^2 as a reference criterion, rather than volume itself.

Dependency on the algorithm

The QGS, 4D-MSPECT, and ECToolbox algorithms have widespread clinical uses (24,25) and have been validated by the current gold standard of cardiac MRI (25,26). Our study suggested that all cardiac function parameters between these three software packages had good consistency; however, further analysis of EF and EDV showed that the mean values obtained by QGS were lower than those obtained by 4D-MSPECT, and the mean values obtained by 4D-MSPECT were still lower than those obtained by ECToolbox although they correlated well (*Table 6*; *Figures 3-8* illustrate their good correlation). Many previous studies have demonstrated that the cardiac functional parameters from the three methods are not interchangeable (18,25,26). Several studies have also shown a tendency to underestimate LVEF when using QGS compared with equilibrium radionuclide angiography (27,28), echocardiography (22), and cardiac MRI (26), although this was less pronounced when using 4D-MSPECT (26). Faber *et al.* (29) reported a good correlation between QGS and ECToolbox, and there was an underestimation of LVEF using QGS, but no underestimation when using ECToolbox. Schaefer *et al.* (25) found that there was no difference in the EDV between ECToolbox and 4D-MSPECT, but the LVEF obtained by ECToolbox was greater than that by 4D-MSPECT. It is necessary to establish algorithm-specific reference limits according to the findings of all of related studies.

Significance of population-specific criteria

This present research confirms the importance of establishing normal reference values for specific nationalities or ethnicities. Since the backgrounds of patients referred to nuclear department studies may differ in terms of their ethnicity, physicians should always be cautious when applying results from other countries. *Table 7* illustrates the variability of normal EF, EDV, and ESV in several studies that we have mentioned in this discussion.

The differences in EF and volumes for various nationalities are probably dependent on combinations of body weight, age, and patient background. Taking these factors into consideration, the present study demonstrated the necessity for population-specific standards.

Study limitations

There were some limits to our study that should be noted. First, all of the patients underwent stress myocardial perfusion SPECT imaging, and none received rest myocardial perfusion SPECT imaging; thus, whether

Table 7 Comparisons with other studies for left ventricular functional parameter determination

Author	De Bondt (8)	Ababneh (7)	Nakajima (6)	Jiajun Li (this study)
Population	European	American	Japanese	Chinese
Radiopharmaceuticals	^{99m}Tc-tetrofosmin	^{99m}Tc-MIBI	^{99m}Tc-tetrofosmin	^{99m}Tc-MIBI
Algorithm	QGS	QGS	QGS	QGS
Women				
No.	59	60	149	86
Age (years), mean ± SD	59±12	60±12	64±10	49±10
Weight (kg), mean ± SD	–	–	53±8	61±7
BMI (kg/m^2), mean ± SD	27±5	–	–	24±3
BSA (m^2), mean ± SD	1.7±0.2	–	1.5±0.1	1.7±0.1
EF (%), mean ± SD	66±9	65±9	74±9	74±10
EDV (mL), mean ± SD	75±23	58±20	59±17	54±11
ESV (mL), mean ± SD	27±14	20±13	17±10	14±7
EDVI (mL/m^2), mean ± SD	43±11	32±8	39±11	30±7
ESVI (mL/m^2), mean ± SD	16±7	10±5	11±6	8±4
Small heart	–	–	74%	76%
Men				
No.	43	53	119	89
Age (years), mean ± SD	56±13	60±12	61±12	46±10
Weight (kg), mean ± SD	–	–	65±10	75± 9
BMI (kg/m^2), mean ± SD	28±6	–	–	25±3
BSA (m^2), mean ± SD	2.0±0.2	–	1.7±0.2	1.9±0.1
EF (%), mean ± SD	59±6	57±7	63±7	65±7
EDV (mL), mean ± SD	106±25	81±22	88±22	75±18
ESV (mL), mean ± SD	44±14	35±11	33±13	27±10
EDVI (mL/m^2), mean ± SD	53±14	38±9	51±12	38±9
ESVI (mL/m^2), mean ± SD	23±8	15±6	19±7	19±5
Small heart	–	–	13%	22%

–, no data. EF, ejection fraction; EDV, end diastolic volume; EDVI, end diastolic volume index; ESV, end systolic volume; ESVI, end systolic volume index; EDVI = EDV/BSA; ESVI = ESV/BSA; BSA, body surface area; BMI, body mass index; QGS, quantitative-gated single-photon emission computed tomography; ^{99m}Tc, Technetium-99m; ^{99m}Tc-MIBI, Technetium-99m sestamibi.

there the same findings would be found for stress and rest imaging is unclear. Second, QGS software underestimates LV volumes, and in our study there was a high incidence of small heart, especially among the female patients. This underestimation could not be readily corrected by a brief correction formula and thus represented an unavoidable defect of our study. Third, the sample size was relatively small for establishing a reference range and was based on a population of participants with a low likelihood of coronary artery disease. Thus, the cutoffs proposed can only be considered as approximates. Also, some of our results are consistent with other reports, so they are not particularly novel. Additionally, none of patients in our study population underwent echocardiography or cardiac MRI, and therefore, we could not compare the cardiac functional parameters with other imaging modalities.

Conclusions

In this study, population- and algorithm-specific reference limits of cardiac functional parameters based on the Chinese population were preliminarily established. Sex and age were significant determining factors for EF and LV volumes. Body weight was a third predictor when the ESV was normalized by BSA. A higher frequency of small hearts was characteristic of our study participants, and the importance of population-specific standards needs to be emphasized.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/qims-21-347). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval was waived by the Ethics committee of Fuwai Hospital for the following reasons: (I) the study was observational; (II) gated MPI is a daily routine in the nuclear department; and (III) the participants did not receive interventions before and after MPI. We selected the participants from a number of patients according to strict criteria. Additionally, informed consent was obtained from all the patients.

Disclaimer: The views expressed in this article are the authors' own and do not represent the views of other individuals and organizations.

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