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Original

Do ejection fraction and other gated stress rest myocardial perfusion parameters differ by age and gender?

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Abstract

BACKGROUND: We have studied the end-diastolic volume (EDV), the end-systolic volume (ESV), and the ejection fraction (EF) for patients who had normal results on treadmill exercise tests and perfusion scans. We also studied normal wall motion as diagnosed by gated myocardial perfusion imaging with the quantitative gated single photon emission tomography (QGSPECT) software set to launch a range of normal values. In addition, we evaluated differences based on age and gender.
MATERIALS AND METHODS: All subjects with normal results on Bruce exercise and myocardial perfusion imaging QGSPECT using the 2-days stress-rest technetium-99m (^{99m}Tc) sestamibi protocol were enrolled in the study. The quantitated functional data of EDV, ESV, and EF using the QGSPECT software were assessed in the rest and stress studies. The association of quantitated functional data with age and sex at both stress and rest was studied in 78 subjects with no symptoms from the cardiovascular system and normal QGSPECT imaging, 29 males (mean age: 58.41 ± 9.0 years) and 49 females (mean age: 58.18 ± 9.0 years). Also studied were differences between males and females.
RESULTS: Our results showed that in women compared with men only stress EF showed a significantly higher value (P = 0.02), whereas all other parameters including REF, SESV, SEDV, RESV, and REDV did not demonstrate a significant difference between men and women (P value > 0.05).
CONCLUSION: The study showed that EF as determined by the QGSPECT technique should be considered as gender-matched normative parameter.

KEY words: gated SPECT, ejection fraction, end diastolic volume, end systolic volume, myocardial perfusion imaging

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Background

An accurate and a reliable determination of the left ventricular ejection fraction (LVEF) is critical for prognosis, risk stratification, and therapeutic management of patients with myocardial disease [1–3]. Gated single-photon emission tomography (GSPECT) offers the unique ability to assess both myocardial perfusion and LV function [4, 5]. Previous studies demonstrated a high serial reproducibility of rest quantitative gated SPECT (QGSPECT) LVEF [6–8], end-diastolic volume (EDV), and end-systolic volume (ESV), as well as a high correlation of rest and stress QGSPECT measurements with those obtained by first-pass or exercise radionuclide angiography [8, 9], 2-dimensional echocardiography [9, 10], contrast ventriculography [11, 12], and magnetic resonance imaging [13].

Although the perfusion information acquired by the gated SPECT reflects perfusion at the time of injection, the ventricular function data occur at the time of the acquisition [14]. As a result, the ventricular function generally reflects the resting condition of the myocardium whether the patient is injected at rest or stress [15]. The time after stress when the SPECT acquisition is commenced is one factor that may enable a conclusion about whether the functional information is considered resting or post-stress [16].

A great number of nuclear medicine departments implement GSPECT only with the stress myocardial perfusion data. It has been reported that 58.8% of nuclear medicine departments in Australia do gating for the stress study only [17]. Moreover, a large body of evidence suggests that functional information acquired after

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stress is different from that acquired at rest [18]. Consequently, the American Society of Nuclear Cardiology recommends that gated SPECT should be performed on both stress and rest studies [19]. However, most of the abovementioned studies were conducted on patients with coronary artery disease who had a variable degree of LV dysfunction and lower EF values. The number of reports of normal studies is scarce [4, 17, 20–22].

The main objective of this study was to determine whether there are significant differences between age and gender in LV EF, EDV, and ESV for subjects with atypical symptoms and normal treadmill exercise tests, perfusion scans, and normal wall motion as determined by QGSPECT at rest and stress during a 2-days protocol and, if so, to determine whether subjects' characteristics such age and sex could predict such differences.

Materials and methods

Participants

A total of 1,647 patients were referred to our university diagnostic nuclear cardiology laboratory for the evaluation of chest pain and/or dyspnea between June 2011 and February 2012. Out of these patients, 78 were retrospectively included in this study as normals. Inclusion criteria were that exercise times on the Bruce protocol were normal and greater than 85% of the predicted maximum heart rate, calculated as 220-age, and that during the test, these subjects experienced neither chest pain nor ischemic changes on the recorded 12-lead stress electrocardiogram (ECG). All patients had normal perfusion scans and normal myocardial wall motion as determined by gated perfusion imaging. Furthermore, an attending physician supervised the stress tests, and ECG and images were analyzed by an experienced nuclear medicine physician and by cardiologists. Subjects were excluded if they had a history of myocardial infarction or of coronary artery disease, previous revascularization, clinically significant valvular heart disease, hypertension, hypertrophic or idiopathic dilated cardiomyopathy, diabetes mellitus, left bundle branch block, or paced ventricular rhythm or any abnormal ECG at rest or stress as well as atrial fibrillation, or frequent atrial or ventricular ectopy. In addition, individuals with any artifact at rest or stress were not enrolled.

All participants provided their written informed consent for the study protocol. This protocol was approved by the Isfahan University of Medical Sciences Review Board.

Study protocol

All subjects underwent stress/rest GSPECT using a 2-days protocol, which started with a GSPECT stress and continued next day with rest GSPECT images. A technetium-99m-methoxy-isobutyl isonitrile (^{99m}Tc-MIBI) dose of 740 MBq was intravenously (IV) administered at rest and during exercise.

Exercise stress protocol

All cardiovascular drugs were discontinued for at least two days and subjects fasted overnight before the study. All examined were asked to exercise on a treadmill under a standard Bruce protocol. A ^{99m}Tc-MIBI was injected as a bolus when the peak of the age-predicted maximum heart rate of more than 85% was achieved. The test started at the appearance of typical angina and/or at positive exercise ECG findings. The exercise test was considered to be positive if there was a horizontal or a downsloping ST segment depression more than 1 mm for 80 microseconds after the J point. Imaging was performed for 15–30 min after exercise. On the next day, 20 min after the injection of 740 MBq of ^{99m}Tc-MIBI, the patients were asked to eat a fatty meal to accelerate hepatobiliary clearance of ^{99m}Tc-MIBI. The resting SPECT was performed 90 min after ^{99m}Tc-MIBI administration.

Acquisition and processing protocols

A double-head SPECT scintillation camera (ADAC Forte, Malpitas CA, USA) was used to acquire 32 views over 180° using a step-and-shoot method, progressing from the 45° right anterior oblique to the 45° left posterior oblique projections. A symmetric 20% energy window over the 140 keV ^{99m}Tc photopeak and a low energy all-purpose (LEAP) collimator were used, and the data were stored in 64 × 64 matrices. Acquisition time was 25 sec per projection during rest and stress studies. The zooming factor was 1.46. An expert nuclear medicine specialist used the cine display of the rotating planar projections to evaluate sub-diaphragmatic activities and the attenuations and patients' motion to optimize the quality of the images. Processing was performed using a two-dimensional Butterworth prefilter and a ramp filter for back projection of transaxial tomographic images. The transaxial images were reoriented along the vertical long axis, the horizontal axis, and the short axis of the left ventricle. Acquisition parameters were identical for the rest and stress studies. For each patient, all three stress images were interpreted separately in comparison to the corresponding rest image.

For the ECG-gated acquisition, the *R-R* interval was divided into eight frames. On the ECG-gated short axis, images were processed for automatic LVEF and ventricular volumes quantification using the QGSPECT software (Cedars Sinai Medical Center, Los Angeles, CA). The quantitated functional data (EDV, ESV, and ejection fraction [EF]) for each patient's study were evaluated as rest and stress matched pairs.

Statistical analysis

The distribution of variables was assessed using probability plots and the Shapiro-Wilk test, with a P value < 0.05 indicating that the data varied significantly from normal. Confidence intervals (CI) were used with 95% confidence. A two-tailed t-test was used to compare the mean values between groups. The continuous variables were expressed as the mean ± SD, and categorical variables as the absolute values and percentages. The correlations of LVEF, EDV, and ESV between rest and stress in each patient were reported with regression analysis. Bland-Altman analysis was used to evaluate more thoroughly these relationships by relating the mean of matched pairs to the difference between matched pairs. The normal limits of LV volumes and EF were defined as the mean values +2SD for the LV volumes and the mean values –2SD for EF. A P value of < 0.05 was considered statistically significant. Statistical analysis was performed using an IBM computer and PASW software, version 18.0 (SPSS, Inc., Chicago, USA).

Results

The study included 29 male (mean age: 58.41 ± 9.0 years) and 49 female subjects (mean age: 58.18 ± 9.0 years). As shown

Table 1. Left ventricular ejection fraction and volumes values measured by GSPECT

Variable	Overall group (n = 78)	Men (n = 29)	Women (n = 49)	P value
SEF (%)	68.08 ± 5.91	64.76 ± 6.71	70.04 ± 4.38	0.01
SESV [mL]	21.36 ± 7.88	27.17 ± 8.86	17.92 ± 4.60	0.01
SEDV [mL]	65.12 ±15.76	74.28 ± 18.35	59.69 ± 11.01	0.01
REF (%)	58.78 ± 4.21	57.28 ± 4.79	59.67 ± 3.59	0.02
RESV [mL]	27.14 ± 7.99	32.31 ± 9.88	24.08 ± 4.46	0.01
REDV [mL]	74.10 ± 66.39	77.28 ± 18.00	60.53 ± 10.65	0.00

Table 2. Gated myocardial functional SPECT parameters assessed by QGS in rest and stress sets

Variable	Stress phase (Mean ± SD)	Rest phase (Mean ± SD)	P value	Difference (Mean ± SD)
EDV [mL]	65.12 ± 15.76	66.76 ±15.96	0.00	1.64 ± 6.57
ESV [mL]	21.36 ± 7.88	27.14 ± 7.99	0.00	5.78 ± 3.64
EF (%)	68.08 ± 5.91	58.78 ± 4.21	0.00	9.29 ± 3.57

in Table 1, ESV and EDV values were smaller in women compared to men whereas the EF was higher. The lower value for ESV was in females in the rest phase (24.08 ± 4.46 mL) and the highest EDV value was in males in the stress (74.28 ± 18.35 mL). In addition, the maximum EF in both stress and rest phases was in females. In the rest phase, the maximum parameter in males was in the EDV (Table 1).

From the gated parameters, only stress EF showed a significant difference with age (P = 0.02) while all other parameters: REF, SESV, SEDV, RESV, and REDV did not demonstrate a significant difference (P values > 0.05).

In terms of differences between stress and rest views of gated parameters, all three parameters demonstrated a significant difference (P value < 0.05) (Table 2). As shown in Table 2, the maximum EF was in the stress phase but the maximum of EDV and ESV were in the rest phase.

Overall, the lower limits of normal stress EF and rest EF were 56.26% and 50.36%, respectively. The lower limits of normal stress ESV and rest ESV were 5.6 mL and 11.16 mL, respectively. The lower limits of normal stress EDV and rest EDV were 33.6 mL and 61.32 mL, respectively.

In addition, just the rest EF did not show a significant correlation with stress and rest EDV (P value > 0.05). In contrast, the stress EF showed a significant correlation with all parameters (P value < 0.05).

The overall correlation between QGS for LVEF at rest and stress was quite good (R2 = 0.64; P < 0.05) (Figure 1). Bland-Altman analysis (Figure 2) showed a considerable agreement throughout the different measurements of EF. The stress EF could be calculated based on the rest EF as follows: Stress EF = 1.943 + 1.125 Rest EF.

Rest and stress gated ESV had a very good correlation (R2 = 0.80; P < 0.05) (Figure 3). Bland-Altman analysis (Figure 4) showed a considerable agreement throughout the different measurements of ESV. Five patients had ESV that exceeded 2SD from the study population mean ESV. In contrast, rest and stress gated EDV did not show a considerable correlation (P > 0.05).

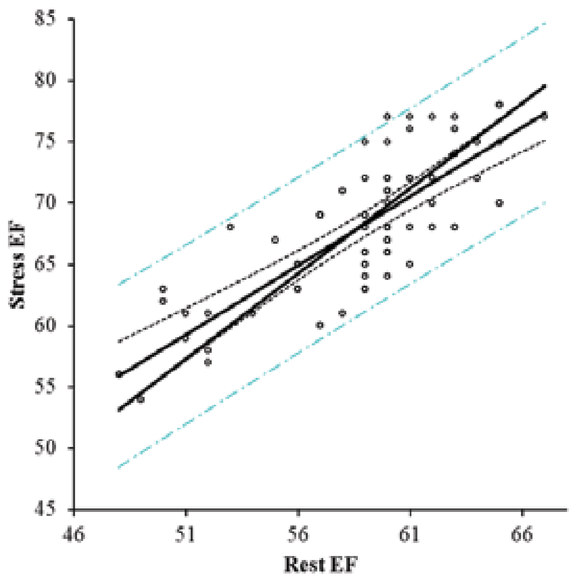

Figure 1. Correlation between LVEF determined by gated myocardial perfusion SPECT in the stress and rest sets

Discussion

Gated SPECT is often used in myocardial perfusion imaging examinations because of its unique advantage of providing information on both myocardial perfusion and function by a single test [23]. Quantitative functional data including gated EF, EDV, and ESV are extremely reproducible [20, 24, 25]. The accuracy of EF, EDV, and ESV measurements with QGS is comparable to measurements obtained with other imaging modalities such as MRI and echocardiography [20, 25, 26]. In a large investigation of 514 patients with suspected or known coronary artery disease, a good agreement was seen in the assessment of LVEF between GSPECT and radionuclide angiocardiography. Nevertheless, in abnormal perfusion group patients, a slight underestimation in post-stress LVEF was

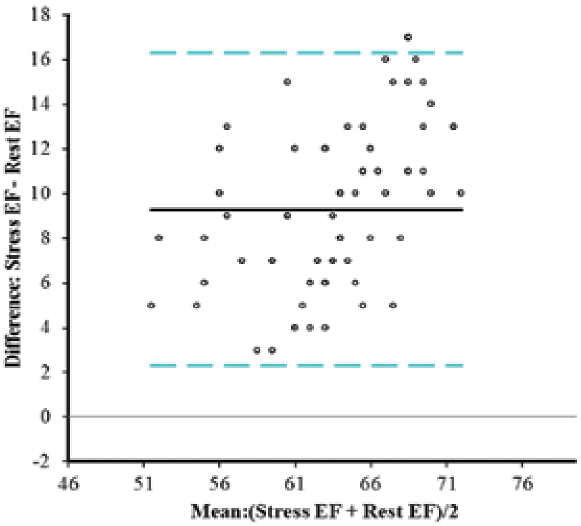

Figure 2. Bland-Altman analysis of mean of stress/rest matched pairs vs. ΔEF shows no trend toward under- or overestimation of stress EF. Mean stress EF was 68.08%, mean rest EF was 58.78%, and mean difference in EF indicated by the solid horizontal line was 9.29%. Outer dashed lines represent 95% limits of agreement, whereas inner dotted lines represent 95% CI of EF difference

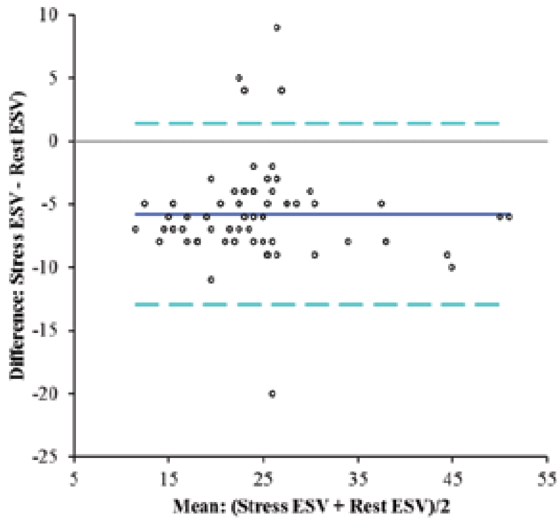

Figure 4. Bland-Altman analysis of the mean of the stress/rest matched pairs vs. ΔESV shows no trend toward under- or overestimation of stress ESV. Mean stress ESV was 21.36 mL, mean rest ESV was 27.14 mL, and mean difference in ESV, which is indicated by a solid horizontal line, was 5.78 mL. Outer dashed lines represent 95% limits of agreement, whereas inner dotted lines represent 95% CI of ESV difference

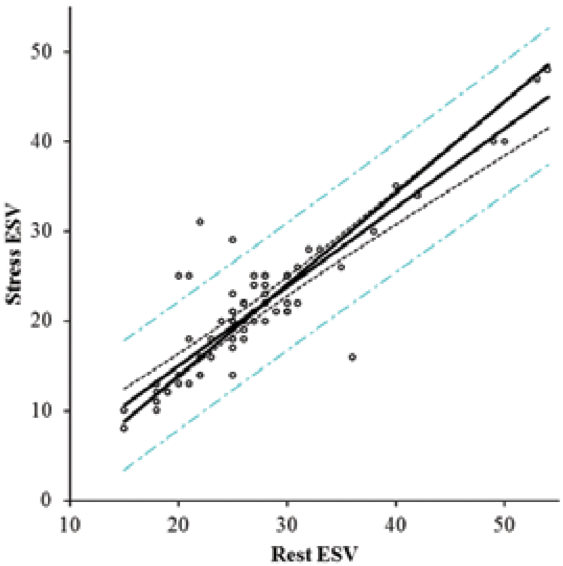

Figure 3. Correlation between ESV determined by gated myocardial perfusion SPECT in the stress and rest sets

visualized using GSPECT as compared to equilibrium radionuclide angiocardiography [26]. EF and volume measurements obtained from myocardial perfusion imaging tests provide important information beyond that obtained by perfusion images alone [27].

In our study, for the gender-related values in normal women for EF and ESV, both at stress and rest, and also for stress EDV, they had smaller values, whereas both stress and rest EF were higher in comparison to men ($P < 0.05$). Higher EF and smaller ES and ED volumes in women may arise from inaccurate estimates of volumes in small hearts [20]. However, Nakajima et al., presented the volume-dependent edge correction algorithm, which was able to decrease successfully the effects on ESV and EF of a small heart [28]. Such uniform normal values could be used in both genders and also for both small and normal-sized hearts [28].

In line with the study of other researchers [21], the aforementioned point in our study may indicate that measurement of EF in either stress or rest could be a more reliable index rather than ESV and EDV for assessment of the LV function.

As in our study, Peace et al., studied the effect of sex, age, and weight on LVEF and ESV reference limits in 127 patients with normal GSPECT [29]. The lower normal limits of LVEF were 46.2% and 55.6% for men and women, respectively [29]. The upper normal limits of ESV (indexed to BSA) were 30.4 mL and 21.4 mL, and 15.7 mL/m^2 and 11.1 mL/m^2, for men and women, respectively. In addition, they did not correlation between EF and age, weight, or BSA ($P > 0.05$) [29].

Normal limits of LV volume and EF, as measured by GSPECT, in women and men, were previously defined by other investigators [20, 30]. Among patients with a low likelihood of CAD, women had significantly smaller EDV and ESV values and higher EF than men.

Other researchers reported that the normal limits for LVEF estimated with GSPECT in patients with a normal exercise test in 884 patients examined with stress 99mTc-MIBI [20] was 63 ± 9%. The mean EF for women was 66 ± 8% ($n = 519$), and for men it was 58 ± 8%, $n = 365$, $P < 0.0001$ [20].

Gender-specific normal limits of poststress volumes and ejection fraction (EF) were obtained by other researchers in 597 women and 824 men with a low likelihood of coronary artery disease and normal perfusion and were applied in a prognostic evaluation of 6713 patients (2735 women and 3978 men) [2]. Patients underwent rest ^{201}Tl/stress ^{99m}Tc-MIBI gated myocardial perfusion SPECT. The normal limits of post-stress LVEF were higher in women than in men (67 ± 8% and 59 ± 8%, respectively). The normal limits of post-stress ESV were lower in women than in men (22 mL ± 12 mL and 41 mL ± 17 mL, respectively). The normal limits of post-stress EDV were 64 mL ± 19 mL in women and 95 mL ± 27 mL in men [2]. However, because of the difference in the method of stress induction (exercise or adenosine) a reliable comparison with findings of other studies cannot be conducted. These data provide further supportive evidence for the development of gender-specific guidelines for drawing the normal diagnostic levels for the above values.

Furthermore, in our study, age was not significantly related with EDV, ESV, and EF in the rest phase or with EDV and ESV in the stress phase. This suggests that the measurement of EF at stress phases is the most appropriate indicator for judgment regarding other indices such as ESV and EDV, especially with consideration with age, for assessing myocardial function.

In addition, we found a good agreement between stress and rest EF and also rest and stress ESV while EDV did not show such an agreement. However in a study similar to ours, the study aimed to evaluate the above indices with GSPECT in 99 eligible patients, rest and poststress LVEF ($r = 0.89$), EDV ($r = 0.78$), and the ESV ($r = 0.93$) were highly correlated ($P < 0.001$) [26].

Other researchers also reported that ESV could be a good indicator for the assessment of LV function [2].

Different protocols were used for the study of possible differences in cardiac parameters during rest or stress GSPECT [2, 20, 31]. Other researchers investigated the difference in LVEF and ESV measured by GSPECT in 129 patients with normal dipyridamole stress myocardial perfusion imaging (MPI). They reported a significant difference between rest and stress EF (70.08% vs. 73.74%) and also rest and stress ESV (20.72 mL vs. 17.88 mL) [27].

In our study population, there was a 1.64 ± 6.57% EF unit difference between rest and poststress measurements as there was also 5.78 mL ± 3.64 mL in the ESV unit. Thus, poststress LVEF and ESV were rational surrogates for rest LVEF and ESV in our patients. The Bland-Altman plots of the difference of LVEF vs. mean LVEF and the difference between ESV vs. mean ESV demonstrated a reasonable reproducibility across the range of LVEF and ESV.

Our study is in line with other previous reports [18, 31] and provides additional evidence to suggest that functional information acquired after stress is different from that acquired after rest tests. On the other hand, other investigations demonstrated no statistical difference between stress and rest in terms of functional information ($P = 0.15$ for EF) [14].

The QGS normal limits for rest EF in this material were close to those presented by other researchers [28], while others reported lower stress EF limits for both men and women and lower EDV and ESV limits for both women and men relative to our study [2, 23].

The different cameras they used could in part explain the differences between our QGS limits and those of others [2, 23]. In addition, Sharir et al., used both exercise and pharmacologic stressors while we used only exercise stress [2]. Moreover, Ababneh et al. [20] included patients with diabetes mellitus, hypertension, previous revascularization or a combination of these factors, whereas we excluded such patients. These factors could, however, hardly explain why Ababneh et al., found lower EDV and ESV values for both women and men [20].

On the basis of findings in this study, we believe that gated MPI SPECT is a reliable, accurate method for measuring LV function, but it is necessary to have similar databases as to age, type of stress, gender, kind of camera, and software used.

Limitations of the study

One of the most important limitations is the relatively small sample size; however, it was quite homogenous in terms of cardiovascular risk factors. In this study we did not include patients with hypertension, diabetes, coronary artery disease previous revascularization, cardiomyopathy, LBBB, and pre-excitation abnormal ECG at rest. However, patients with other known and unknown risk factors for coronary artery disease were included in this study. Thus, the parameters reported here should not be construed to be from healthy patients. Furthermore, this study was conducted with a 2-day ^{99m}Tc-MIBI QGS GSPECT protocol ,and, thus, the findings might not apply to other protocols. What is more, it would be interesting if we could answer the questions how the heart beat in men and women and the higher EF in women, if present, was related to the faster heart beat in this group. However, the inclusion and exclusion criteria in this study and the vast variety among the GSPECT parameters should be taken into account in future well-designed studies.

Conclusions

We found that the assessment of cardiac function and the volumes for patients determined by the GSPECT-QGS technique should consider age- and gender-matched normative parameters. In addition, parameters from any individual nuclear medicine center may need to be validated by means of specific radiotracers, acquisition, reconstruction, and analysis protocols.

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