Development and Application of Normal Limits for Left Ventricular Ejection Fraction and Volume Measurements from ^{99m}Tc-Sestamibi Myocardial Perfusion Gated SPECT

Alan Rozanski, Kenneth Nichols, Siu-Sun Yao, Sanjay Malholtra, Randy Cohen, and E. Gordon DePuey

Division of Cardiology, Department of Medicine, and Division of Nuclear Medicine, St. Luke's-Roosevelt Hospital Center, New York; and Departments of Medicine and Radiology, Columbia University College of Physicians and Surgeons, New York, New York

Gated SPECT is a reproducible method for assessing left ventricular volume (LVV) and left ventricular ejection fraction (LVEF) from ^{99m}Tc-sestamibi myocardial perfusion imaging studies. LVV and LVEF measurements by this approach correlate well with those obtained from other cardiovascular imaging techniques. Nevertheless, the lack of criteria for abnormal test findings has limited the potential clinical application of this new imaging technique. **Methods:** Gated SPECT measurements were evaluated for 214 patients with a low Bayesian likelihood (<10%) of coronary artery disease (CAD) before performance of ^{99m}Tc-sestamibi stress–rest myocardial perfusion SPECT. The patients were grouped into normotensive patients (n = 98), hypertensive patients without left ventricular hypertrophy (LVH) (n = 80), and hypertensive patients with LVH on resting electrocardiography (n = 36). Gated SPECT measurements for left ventricular end-diastolic volume (LVEDV) index, left ventricular end-systolic volume (LVESV) index, and LVEF were obtained according to a published method, using a modified Simpson's rule technique. **Results:** Similar results were obtained for mean LVV and LVEF measurements between normotensive patients and hypertensive patients without LVH. Hence, these groups were combined (as group 1). By contrast, hypertensive patients with LVH (group 2), had significantly lower LVEF values (P = 0.01) and higher mean LVESV index values than normotensive patients (P = 0.03). Sex differences were marked: women had significantly higher mean resting LVEF values than men (P < 0.0001) and significantly lower mean resting LVEDV index values (P < 0.0001). A significant relationship was seen between LVEDV index and LVEF (r = −0.60; P < 0.0001) and between LVEDV index and heart rate (r = −0.26; P < 0.001). The normal limits were LVEF ≥ 41% in men and ≥ 49% in women, LVEDV index ≤ 76 mL/m^2 in men and ≤ 57 mL/m^2 in women, and LVESV index ≤ 38 mL/m^2 in men and ≤ 26 mL/m^2 in women. Among hypertensive patients, 22% with LVH had an abnormally low LVEF and 19% had an increased LVEDV index according to these test criteria. By contrast, no hypertensive patients without LVH had an abnormally low LVEF, and only 6% had volume abnormalities. **Conclusion:** Using a cohort of low-likelihood patients, we generated sex-specific normal limits for LVV and LVEF for myocardial perfusion gated SPECT. Application of these findings resulted in the detection of occult left ventricular dysfunction in approximately one fifth of hypertensive patients for whom concomitant LVH was found through resting electrocardiography. These normal limits can now be evaluated prospectively for their potential clinical value.

Key Words: normal limits; gated SPECT; left ventricular volume; ejection fraction

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Stress–rest myocardial perfusion SPECT is commonly used for diagnostic and prognostic assessment among patients with suspected or known coronary artery disease (CAD). These applications depend on the identification of reversible and fixed myocardial perfusion defects, which measure the magnitude of stress-inducible myocardial ischemia and underlying fibrosis. With the relatively high concentration of radioactivity available from ^{99m}Tc-based myocardial perfusion scintigraphy agents, myocardial SPECT images can be R wave gated according to the electrocardiogram. The resultant end-diastolic and end-systolic images can then be used to assess left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) and left ventricular ejection fraction (LVEF). Validation studies indicate that measurements of left ventricular volumes (LVVs) and LVEF by this approach are highly reproducible (*1,2*). Furthermore, the accuracy of gated SPECT LVV and LVEF measurements has been established from comparisons with measurements obtained with other imaging techniques, including multiple-gated equilibrium (*1–3*) and first-pass radionuclide ventriculography (*3*), 2-dimensional echocardiography (*4*), and x-ray contrast ventriculography (*5*). Studies have suggested that gated SPECT LVEF measurements add incremental information to myocardial perfusion data in the clinical evaluation of CAD patients (*6*). Gated SPECT can be used to assess resting LVVs and

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For correspondence or reprints contact: Alan Rozanski, MD, Division of Cardiology, St. Luke's-Roosevelt Hospital Center, 114th St. and Amsterdam Ave., New York, NY 10025.

LVEF. Hence, in this study, we assessed the results of gated SPECT in patients with a low likelihood of CAD to determine normal measurements for both gated SPECT LVV and gated SPECT LVEF. We then applied these normal limits to assessment of the frequency of LVV and LVEF abnormalities in patients with and without underlying systemic arterial hypertension.

MATERIALS AND METHODS

Patient Population

The population consisted of 214 patients who had a low (<10%) likelihood of CAD before the results of stress–rest myocardial perfusion SPECT were assessed. The likelihood of CAD was based on a Bayesian analysis of age, sex, anginal symptoms, risk factors, and (if treadmill stress was used) the results of exercise electrocardiography (*7*). Patients with documented CAD, a history of myocardial infarction, or a history of coronary revascularization were excluded. The population included 95 men and 119 women, with a mean age of 52 ± 13 y. The patients were neither purposefully included nor purposely excluded on the basis of visual or quantitative reported myocardial perfusion abnormalities.

Stress Testing

Myocardial perfusion SPECT was performed on each patient in conjunction with either exercise or pharmacologic stress. Maximal exercise treadmill testing was performed using the standard Bruce protocol. Blood pressure was recorded using a cuff sphygmomanometer at rest, during each stage of exercise, at peak exercise, and at 2-min intervals after exercise. The patients exercised to exhaustion, with premature termination for severe angina, high-grade ventricular arrhythmia, or exertional hypotension. For the 10% of patients who were imaged after a dipyridamole infusion, intravenous dipyridamole was injected with an infusion pump at 0.14 mg/kg/min for 4 min. ^{99m}Tc-sestamibi was injected 3 min after the end of the infusion. Intravenous aminophylline was given for severe chest pain or hypotension. Continuous electrocardiography (ECG) monitoring in 3 leads (aVF, V_1, and V_5) was performed during exercise and pharmacologic stress; 12-lead ECG was performed during each 3-min interval of exercise, at the time of peak exercise, and each minute after exercise for 5 min. Similarly, 12-lead ECG was performed before, during, and for 4 min after the dipyridamole infusion. The ECG response during stress was measured 0.08 s after the J point and was compared with baseline values. The response was considered ischemic if horizontal or downsloping ST-segment depression of ≥1 mm or upsloping ST-segment depression of ≥1.5 mm occurred. ECG evidence of left ventricular hypertrophy (LVH) in patients more than 35 y old was defined as a total exceeding 35 mm in men and 25 mm in women for the R wave in lead aVL and the S wave in lead V_3 on ECG tracings (*8*).

Rest–Exercise ^{99m}Tc-Sestamibi Myocardial Perfusion SPECT

The patients were studied according to a 1- or 2-day protocol. For the 1-d protocol, the patients first received injections of 8–10 mCi ^{99m}Tc-sestamibi at rest, and tomographic images were obtained 60 min later. The patients then received injections of 25–30 mCi ^{99m}Tc-sestamibi at peak exercise or in conjunction with a dipyridamole infusion. Patients exercising on a treadmill continued exercising for 90 s after the injection. The patients were imaged 30 min after completion of exercise or pharmacologic stress. If a 2-day protocol was used, the patients were injected with 20–30 mCi ^{99m}Tc-sestamibi for both the rest and the stress studies.

For SPECT data acquisition, 64 projections were obtained over a circular 180° orbit. The time per projection was 25 s for the rest study and 20 s for the stress study. The scintillation camera was set on a 140-keV energy peak with a 20% window, and a high-resolution collimator was used. The projection images were corrected for radioactive decay occurring during acquisition and were prefiltered using a 2-dimensional Butterworth filter with a cutoff frequency of 0.52 cycles/cm, power 5, for stress studies and 0.4 cycles/cm, power 10, for rest studies. Transaxial tomograms were reconstructed at 1-pixel thickness (6.4 mm) using backprojection with a ramp filter. Short-axis tomograms of the entire left ventricle were extracted from the reconstructed transaxial tomograms through coordinate reorientation with interpolation.

Gated SPECT

Summed tomograms were reconstructed into transaxial slices. On the transaxial slice that exhibited the largest left ventricular cavity (greatest midventricular diameter), a line was drawn to bisect the left ventricle and form the midventricular vertical long-axis (VLA) slice. On this image, a line was again drawn to bisect the left ventricle and form the midventricular horizontal long-axis (HLA) slice. At these locations in the heart, the complete gated tomographic dataset was used to construct 8 frames per cardiac cycle of dynamic HLA and VLA tomograms. The 8 HLA and VLA midventricular images were then centered, end-diastolic and end-systolic frames were determined, and endocardial borders were generated, all automatically (*2*). An observer verified each automatic choice and made changes if necessary. The automation success rate for these algorithms has been reported to be 85% (*2*). End-diastolic and end-systolic ventricular volumes were computed from the VLA and HLA endocardial borders as corrected for the measured tomographic line spread function of the gamma camera (*1*). LVEF was then computed by dividing stroke volume (i.e., LVEDV minus LVESV) by LVEDV.

Statistical Analysis

LVV and LVEF indices were first analyzed among patient groups by single-factor ANOVA. A probability value less than 0.05 was used to indicate a statistically significant difference between patient groups. When ANOVA found significance, Dunn (Bonferroni) adjustment was applied to multiple-group comparisons to determine the pair of patient groups that was significantly different. This approach involved adjusting the critical F probability level by dividing α by the number of contrasts or comparisons. Homogeneity of variances was assumed for the groups being compared. Simple linear regression was used to determine the relationship between 2 independent variables.

The mathematic forms of distributions for each parameter were analyzed to determine whether curves were normally distributed for normotensive patients. Our motivation was to determine whether associating 2 SDs from the mean with 95% confidence limits was meaningful. The Wilks-Shapiro test for normality was used, for which an associated probability value less than 0.05 indicates that the distribution is not gaussian. We determined whether distributions were gaussian to see if a 2-SD threshold could be interpreted in a straightforward way as representing the 95% confidence limit of normality. Linear regression analysis was used to assess whether significant correlations existed between volumes or volume indices and ejection fractions, and between these parameters and age or resting heart rate, to help interpret

findings. For this analysis, the probability of no association between the 2 variables being tested was determined. All analyses were performed using commercially available statistical software (GB-STAT V6.0; Dynamic Microsystems, Inc., Silver Springs, MD).

RESULTS

LVEF and LVV

Table 1 shows mean measurements for LVV and LVEF for the 3 groups of patients with a low likelihood of CAD: those without hypertension, those with hypertension and no LVH, and those with hypertension and LVH. Because LVV and LVEF measurements were similar in low-likelihood patients without hypertension and low-likelihood patients with hypertension and no LVH, these patients were combined into 1 group for subsequent analyses (group 1, n = 178), whereas the 36 patients with a history of both hypertension and LVH on the resting electrocardiogram formed group 2. Compared with the other 2 groups, the LVH group had larger values for LVESV and LVEDV and significantly lower mean resting LVEF values. LVV and LVEF measurements did not significantly differ among patients exercising on a treadmill or stressed pharmacologically, nor were differences seen between 1-day and 2-day protocol studies.

Physiologic Influences on LVEF and LVVs

Five factors that may potentially relate to LVV and LVEF measurements were analyzed: age, sex, body surface area, resting heart rate, and left ventricular volume.

LVEF correlated only weakly with age ($r = -0.23$; $P = 0.002$), and volume indices did not correlate with age ($r = -0.10$; $P = 0.21$).

As shown in Table 2, the comparative values for LVV and LVEF differed significantly in group 1 according to sex. Mean resting LVV measurements were significantly higher, and LVEF was significantly lower, in men than in women. To assess the potential causes of this sex difference, the normotensive men and women were compared for differences in loading conditions. The mean resting heart rate in men was 68 ± 13 bpm, whereas in women it was 72 ± 13 bpm (P = NS). The mean systolic blood pressure in men, 132 ± 17 mm Hg, was virtually indistinguishable from the 132 ± 20 mm Hg found in women (P = NS).

TABLE 1
LVEF and LVV Measurements Among Patient Subgroups with Low Likelihood of CAD

Parameter	Normotensive subgroup (n = 98)	HBP subgroup (n = 80)	LVH subgroup (n = 36)
LVEF (%)	63 ± 10	64 ± 10	57 ± 13*
LVEDV (mL)	73 ± 29	80 ± 33	93 ± 55
LVESV (mL)	28 ± 17	31 ± 19	47 ± 42†
LVEDV index (mL/m²)	41 ± 14	41 ± 14	50 ± 32
LVESV index (mL/m²)	15 ± 9	16 ± 9	26 ± 25*

*$P < 0.05$ vs. normotensive and HBP subgroup.
†$P < 0.05$ vs. normotensive subgroup.
HBP = high blood pressure.

TABLE 2
Mean Sex Values for LVEF and LVV Measurements in Group 1 Patients

Parameter (%)	Men (n = 78)	Women (n = 100)
LVEF	59 ± 9	67 ± 9*
LVEDV	95 ± 31	62 ± 22*
LVESV	40 ± 19	21 ± 13*
LVEDV index	48 ± 14	35 ± 11*
LVESV index	20 ± 9	12 ± 7*
Body surface area	1.97 ± 0.21	1.75 ± 0.20*

*$P < 0.000001$.

A significant relationship was seen between body surface area and LVESV ($r = 0.22$; $P = 0.001$) and between body surface area and LVEDV ($r = 0.31$; $P \leq 0.0001$).

No significant relationship was seen between resting heart rate and LVEF in group 1 ($r = 0.13$; $P = 0.08$). However, higher resting heart rates were weakly associated with lower resting LVEDV indices ($r = -0.26$; $P < 0.0001$) (Fig. 1).

A significant relationship was seen between resting LVEF and resting LVEDV index in group 1, with higher resting LVEF values among patients with smaller LVEDV index values ($r = -0.60$; $P < 0.0001$) (Fig. 2). This relationship was similar for men ($r = -0.47$; $P < 0.0001$) and women ($r = -0.55$; $P < 0.0001$).

Criteria for Abnormal LVEF and Volume Findings

The criteria for abnormality were based on analyses of only group 1 because of the higher LVV and lower LVEF measurements in group 2. LVV and LVEF indices in group 1 were normally distributed, so values exceeding 2 SDs of mean values were used to define abnormality at the 95% confidence limit. Men and women were separated for these

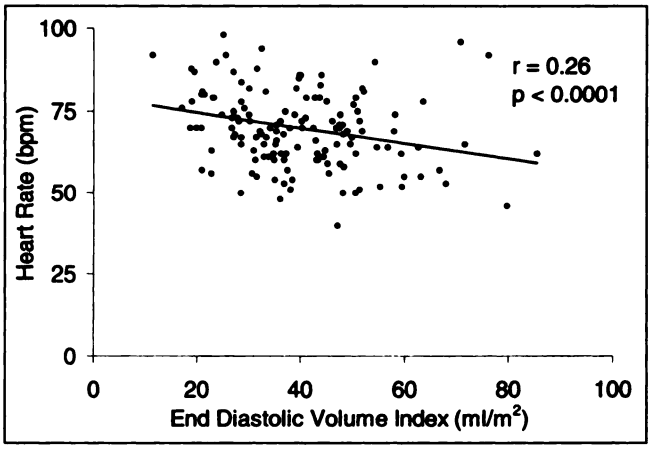

FIGURE 1. Relationship between heart rate (vertical axis) and LVEDV index (horizontal axis) for normotensive patients was weak but significant.

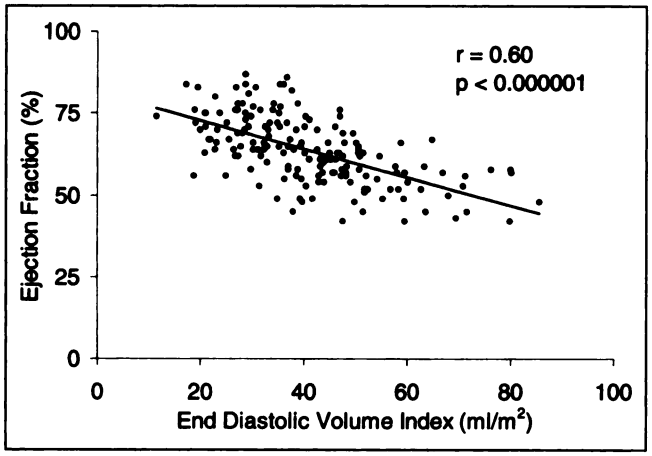

FIGURE 2. Relationship between resting LVEF (vertical axis) and LVEDV index (horizontal axis) for normotensive patients was significant: the smaller the LVEDV, the higher the LVEF.

analyses, given the marked sex differences in mean LVV and LVEF measurements (Table 3).

Frequency of LVV and LVEF Abnormalities

Using the criteria for test abnormality based on group 1, we assessed the frequency of abnormal LVV and LVEF measurements in low-likelihood patients, including those with and without concomitant ECG evidence of LVH. Occult LVV abnormalities occurred in only 6% of low-likelihood patients without LVH but 19% of hypertensive patients with LVH ($P < 0.05$). LVEF abnormalities occurred in only 1% of low-likelihood patients without LVH but 22% of hypertensive patients with LVH ($P < 0.0001$).

DISCUSSION

Gated SPECT has emerged as an accurate method for measuring LVV and LVEF (*1–5,9–13*). However, functional cardiac tests require identification of normal limits for use in diagnosis. Three groups conventionally have been used for generating normal limits for cardiac measurements: patients with normal coronary arteriography findings, healthy volunteers, and patients with a low Bayesian pretest probability of CAD (*14*). Posttest referral bias can preferentially concentrate patients with abnormal test responses among patients with normal coronary arteriography findings (*15*), and healthy volunteers offer no practical advantage over patients with a low likelihood of CAD (*14*). Thus, to generate normal limits for SPECT LVV and LVEF measurements, we assessed a large cohort of patients with a low likelihood of CAD.

TABLE 3
Abnormal-Finding Criteria Based on Group 1 Patients

Parameter (%)	Men (n = 78)	Women (n = 100)
LVEF	<41	<49
LVEDV (mL)	>157	>106
LVESV (mL)	>78	>47
LVEDV index (mL/m²)	>76	>57
LVESV index (mL/m²)	>38	>26

Because hypertension may independently influence LVV and LVEF measurements in low-likelihood patients, the patients were subdivided into 3 clinical subgroups: normotensive patients, hypertensive patients without LVH, and hypertensive patients with ECG evidence of LVH. Compared with the other 2 groups, hypertensive patients with electrocardiographic evidence of LVH manifested significantly higher LVV and lower LVEF measurements. Thus, we excluded this subgroup when calculating LVV and LVEF normal limits from gated SPECT studies.

Age and Sex Differences

In concordance with prior observations from resting radionuclide ventriculography, age correlated only weakly with LVEF and did not correlate with LVV (*16*). By contrast, significant sex differences were noted. In women, resting LVV measurements were significantly smaller and LVEF was significantly higher, even after adjusting LVVs for body surface area. Similar sex-specific differences were also noted in another recent study using gated SPECT (*17*).

Resting heart rate was significantly higher among women. However, because the relationship between resting heart rate and LVV or LVEF is only modest, this factor was not likely to have accounted for the large differences in LVV and LVEF between the 2 sexes. More notably, the association between resting LVV and resting LVEF was significant: the smaller the resting LVEDV, the higher the resting LVEF. Other investigators have noted a similar relationship (*18*). Because women in general have smaller hearts, as seen in this study, a proportionately greater mean resting LVEF could be explained simply on this basis. Indeed, a significant linear relationship exists between LVESV or LVEDV and body surface area. Relative to this issue, the ability of gated SPECT methods to accurately compute LVV and LVEF in small hearts has recently been called into question (*5,19,20*). Increased counts of scintigraphic images at end-systole complicated the identification of left ventricular endocardial borders. The root of this problem may be that counts from close myocardial walls spill into opposite walls, thereby distorting count profiles and causing their local maxima to be misregistered toward the center of the left ventricular cavity. This locational error could result in artifactually high mean LVEF calculations, because the effect would be most pronounced at end-systole. Because more women than men have relatively small hearts, this effect could result in skewing of normal limit calculations based on the gated SPECT technique. This problematic finding warrants further investigation.

Comparison with LVEF and LVV Measurements by Other Modalities

No significant differences were noticeable between the mean gated SPECT LVEF in this study (63% ± 10%) and that obtained previously by echocardiography (60% ± 5%) (*21*), MRI (65% ± 5%) (*22*), angiography (67% ± 8%) (*23*),

or cine CT (63% ± 5%) (*24*). The larger SD of gated SPECT LVEF values, compared with those of the other imaging modalities, is most likely caused by overestimation of the highest LVEFs by gated SPECT. The mean normal LVEDV measurements of this study correspond closely to those reported for echocardiography (*21*) and MRI (*22*) but are less than those reported for angiography (*23*) and cine CT (*24*). These findings are consistent with previous studies showing that although gated SPECT LVVs agree closely with echocardiographic LVVs (*2,4*), gated SPECT LVVs are significantly lower than LVVs obtained from contrast angiography (*5*). This trend is attributed mainly to the fact that modeling the left ventricle according to the method for gated SPECT LVEF analyses (*1–3*) parallels standard echocardiographic left ventricular modeling (*21*), whereas angiographic drawings on right anterior oblique 30° projections often include larger amounts of outflow tract than are revealed by ^{99m}Tc-sestamibi SPECT images (*5*).

This investigation has several limitations. The use of only 8 gates to span R-R intervals is an important limitation of gated SPECT, likely underestimating LVEF by several percentage points, on average, compared with other modalities (*10,11*). Also, the normal limits of LVVs found by this study are specific to the particular gated SPECT method used (*2*). However, the mean normal LVV and LVEF values found with the echocardiographic analog gated SPECT method used here (*2*) are virtually indistinguishable from those found by the most widely used gated SPECT method, which is based on gaussian curve fitting (*6,11,17*).

Application of Abnormal Test Criteria

When the derived normal limit criteria for LVV and LVEF were applied to the 2 hypertensive subgroups in this study, abnormal LVEF values were not found among the 80 hypertensive patients without ECG evidence of LVH. However, abnormally low LVEF values were present in more than one fifth of hypertensive patients with ECG evidence of LVH. This finding results in the larger SD of LVV and LVEF measurements in this subgroup of patients. Similar differences between the 2 groups were noted for LVEDV index. Thus, occult left ventricular dysfunction was identified commonly in the hypertensive patients with ECG evidence of LVH, despite a low Bayesian likelihood of CAD.

CONCLUSION

The results of this investigation advance the potential clinical application of gated SPECT LVV and LVEF measurements by providing their normal limits. The use of separate sex-specific normal limits for LVV and LVEF parallels the use of separate sex-specific normal limits that is routine in interpretation of stress–rest myocardial perfusion SPECT data. However, whereas use of sex-specific normal limits for LVVs may be based on physiologic differences between the sexes, differences in LVEF between the sexes may relate, in part, to technical factors such as difficulty in tracing end-systolic endocardial borders in patients with small hearts. Advances in this technology would now be aided by 2 steps: first, the evaluation of normal limits in other laboratories to determine the robustness of our normal limits and, second, the application of these normal limits to subgroups of patients with CAD to determine the practical clinical value of the measurements, especially for assessing prognosis.

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