Value of Vasodilator Left Ventricular Ejection Fraction Reserve in Evaluating the Magnitude of Myocardium at Risk and the Extent of Angiographic Coronary Artery Disease: A ^{82}Rb PET/CT Study

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Our aim was to determine the value of vasodilator left ventricular ejection fraction (LVEF) reserve (stress ejection fraction – rest ejection fraction) in evaluating the magnitude of myocardium at risk and the anatomic extent of underlying severe coronary artery disease (CAD). **Methods:** We studied 510 consecutive patients with suspected CAD undergoing gated rest and vasodilator stress ^{82}Rb PET/CT. Patients were categorized as having no perfusion abnormalities, mild, moderate, or severe reversible perfusion defects. In a subgroup of 68 patients with coronary angiography, patients were categorized as having 0-vessel, 1-vessel, 2-vessel, or left main/3-vessel disease. **Results:** Patients without coronary risk factors who comprised our control group as well as patients with coronary risk factors and normal perfusion demonstrated a high LVEF reserve (7% ± 7% and 5% ± 6%, respectively). The mean LVEF reserve was negative (–0.2% ± 8%) in patients with severe reversible defects and in patients with 3-vessel (–6% ± 8%) and left main (–8% ± 5%) disease. Among the clinical and scintigraphic variables studied, male sex, rest ejection fraction, and increasing magnitude of myocardium at risk predicted a lower LVEF reserve, whereas LVEF reserve was the only independent predictor of left main/3-vessel disease (P = 0.008). An LVEF reserve of more than +5% had a positive predictive value of only 41% but a negative predictive value of 97% for excluding severe left main/3-vessel CAD. **Conclusion:** During ^{82}Rb PET/CT, LVEF increases with vasodilator stress in patients without significant stress-induced perfusion defects or severe left main/3-vessel CAD. A high LVEF reserve appears to be an excellent tool to exclude left main/3-vessel CAD noninvasively.

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Excluding severe left main or 3-vessel coronary artery disease (CAD) as the basis for symptoms and reversible perfusion defects may be as important as diagnosing it, because it has important implications for further testing and prognosis (*1*). Relative assessment of myocardial perfusion with SPECT or PET remains an accurate means to diagnose CAD (*2*). Nonetheless, this approach often uncovers only the territory supplied by the most severe coronary artery stenosis, leading to frequent underestimation of the anatomic extent of CAD. Despite severe reduction in myocardial vasodilator perfusion reserve, overt perfusion defects diagnostic of multivessel CAD may be apparent in only a small proportion of patients (29%–35%) with severe 3-vessel disease (*3–5*). Clinical and exercise parameters are important in identifying left main or 3-vessel disease, but these parameters are of limited value in the setting of vasodilator stress (*3*). Likewise, high-risk scintigraphic markers (transient cavity dilation, poststress stunning, lung uptake) are useful but also insensitive (sensitivity, 19%–29%) (*3,6–8*) to definitively exclude severe 3-vessel or left main CAD. Quantitative myocardial perfusion imaging with PET is yet another tool for noninvasive detection of severe 3-vessel or balanced ischemia (*9*) that is technically demanding and not widely available for clinical use.

^{82}Rb PET/CT with vasodilator stress is increasingly being used clinically for the evaluation of CAD and provides excellent quality perfusion and gated images at rest and during peak stress. Typically, vasodilator stressors induce

heterogeneity in regional myocardial blood flow in regions with and without coronary stenosis without precipitating actual myocardial ischemia. Several experimental studies in animals demonstrated a relationship between myocardial blood flow and contractility. Early studies by Gregg in dogs (*10*) demonstrated that increases in myocardial blood flow are potent stimuli for changes in myocardial contractility. Later studies not only confirmed this finding but also suggested that an increase in flow in excess of that required to supply metabolic demands augments myocardial contractility (*11*). Furthermore, more recently, using a canine model of chronic coronary artery occlusions, Bin et al. demonstrated that reduced subendocardial flow reserve was related to regional dipyridamole-induced myocardial dysfunction (*12*). On the basis of these experimental data, we hypothesized that left ventricular ejection fraction (LVEF) reserve (stress ejection fraction – rest ejection fraction) would be inversely related to the magnitude of jeopardized myocardium in humans and that patients with extensive areas of jeopardized myocardium would not be able to demonstrate a high LVEF reserve. Thus, a high LVEF reserve would indicate a smaller magnitude of jeopardized myocardium and thereby aid in excluding the presence of underlying severe 3-vessel and left main CAD. Our objective was to determine the value of LVEF reserve assessed by rest-stress ^{82}Rb PET in evaluating the magnitude of myocardium at risk and the extent of angiographic CAD.

MATERIALS AND METHODS

This was a prospective cohort study of 510 consecutive patients undergoing gated rest and vasodilator stress ^{82}Rb PET myocardial perfusion imaging for evaluation of suspected CAD. Patients with prior revascularization (coronary artery bypass surgery or percutaneous coronary intervention) or Q waves on electrocardiogram (ECG) were excluded. Patients with inadequate gating, arrhythmias (atrial fibrillation/flutter, frequent ectopy), or known valvular heart disease were excluded. The human research committee of Brigham and Women's hospital approved this study.

^{82}Rb PET Myocardial Perfusion Imaging Protocol

All patients were studied using a whole-body PET/CT scanner (Discovery ST; GE Healthcare) after an overnight fast. Patients refrained from caffeine-containing beverages or theophylline-containing medications for 24 h before the study. Antianginal medications (β-blockers, calcium blockers, and nitrates) were withheld on the morning of the test.

A CT-based transmission scan (~10 s, ~30 mA) was obtained before the rest and after the stress perfusion study. The CT portion of PET/CT in this analysis was used solely for correction of photon attenuation by the soft tissues and was not used for a calcium score or coronary angiography. Regional myocardial perfusion was assessed at rest after the intravenous administration of 1,480–2,220 MBq (40–60 mCi) of ^{82}Rb. Gated image acquisition was started 90–120 s after completion of the radionuclide infusion and continued for 5 min. Vasodilator stress was performed using standard infusions of adenosine (140 μg/kg/min for 6 min) or dipyridamole (142 μg/kg/min for 4 min). Eighty-six percent of the patients had rest followed by dipyridamole (81%) or adenosine (5%) stress testing. Adenosine stress followed by rest ^{82}Rb imaging was used in 14% of the patients (predominantly, those scheduled for concurrent CT coronary angiography). Three minutes into the adenosine infusion or 3 min after the completion of the dipyridamole infusion, a second dose of ^{82}Rb (equal to rest dose) was administered and gated images were acquired in the same manner. The heart rate, systemic blood pressure, and 12-lead ECG were recorded at baseline and at every minute during and for 10 min after the stress test.

Images were reconstructed using iterative reconstruction protocols (30 iterations and 2 subsets). A reconstruction 3-dimensional PET filter was used (Butterworth filter cutoff frequency, 10; order, 5). Left ventricular end-diastolic volumes, end-systolic volumes, and ejection fraction were calculated using commercially available software (Emory Cardiac Tool Box; Emory University Hospital). Endocardial border detection was automatic with manual adjustment whenever deemed necessary. LVEF reserve was calculated as in stress LVEF – rest LVEF and reported as the absolute difference in ejection fraction percentage (not as the difference expressed as a percentage). We used receiver-operating-characteristic curve analysis and also studied 2 commonly accepted threshold values for abnormality of LVEF reserve (+5% and –5%) from radionuclide angiography studies. Five observers performed the ejection fraction determinations prospectively for the 510 patients (each measurement was reviewed and modified when needed by the 2 independent readers). Two of the 5 observers independently measured LVEF in 36 studies with an interobserver variability in measurement of LVEF of 5.4, measured as the coefficient of variability (1.98 times SD).

Analysis of Myocardial Perfusion Images

Two experienced observers assessed myocardial perfusion images using a standard 17-segment model (*13*) and a 5-point scoring system (0 = normal, 1 = mild reduction in tracer uptake, 2 = moderate reduction, 3 = severe reduction, and 4 = absent tracer uptake). Global summed scores were computed for the stress images (summed stress score, reflecting the combined extent and severity of ischemia plus scar) and rest images (summed rest score, reflecting the extent and severity of myocardial scar). The difference between summed stress score and summed rest score was computed (summed difference score, reflecting the combined extent and magnitude of reversible myocardial perfusion defects/ischemia). Interobserver variability between the 2 readers was determined in a separate subgroup of 20 patients (10 normal and 10 abnormal). Both readers concordantly grouped 19 of 20 scans as normal or abnormal. Interobserver agreement for scan interpretation was found to be excellent ($\kappa = 0.95$) with regard to the overall diagnosis of CAD.

Myocardial perfusion defects involving the anterior wall, septum (except basal inferior septum), and apex were assigned to the left anterior descending distribution; the inferior wall and basal inferior septum were assigned to the right coronary artery distribution. Lateral wall defects were assigned to the left circumflex coronary distribution. Myocardial perfusion image interpretation and assignment of coronary distribution of defects were performed blinded to the results of coronary angiography.

Coronary Angiography

Sixty-eight patients underwent coronary angiography using standard technique within 6 mo of the index PET/CT study at the clinical discretion of the patient's cardiologist. All of these patients were clinically stable (not hospitalized) between the 2

tests. Cineangiograms of the coronary arteries were obtained in multiple projections using a Philips Integris BH3000 angiographic system (9 in. [22/17/13 cm] triple-mode high-contrast image intensifier) (Philips Netherlands BV). The angiographic criterion used to define the presence of severe CAD was a visually determined diameter stenosis of ≥70% for the left anterior descending, left circumflex, and right coronary arteries or their major branches, and ≥50% for the left main coronary segment as described in the patients' clinical coronary angiogram reports.

Study Groups

We used a summed stress score of <2 to define normal (summed stress score < 2, $n = 309$) and abnormal (summed stress score ≥ 2, $n = 157$) myocardial perfusion groups. Unlike SPECT (where a summed stress score < 4 is used to define normal), attenuation correction with ^{82}Rb PET is accurate and we do not anticipate any perfusion defects in patients with normal perfusion (other than apical thinning); hence, we used a lower threshold summed stress score to distinguish normal versus abnormal scans. A control group of patients with <10% pretest likelihood of CAD on the basis of the Diamond and Forrester classification was also included ($n = 44$) (*14,15*). The control group was composed of patients who were referred for reasons such as preoperative evaluation, arrhythmia, nonspecific ECG abnormalities, palpitations, before renal donor surgery and the rest who were referred for various other nonclassic reasons without chest pain or dyspnea. Patients were considered to have angiographic multivessel disease when the left main or all 3 major coronary arteries were obstructed according to the criteria described.

Statistical Analysis

Continuous variables are described as mean ± SD and compared using the Student t test or a paired t test as appropriate. Differences between discrete variables were assessed using a χ^2 test. Multiple group comparisons for LVEF reserve across categories of ischemia and categories of angiographic CAD were performed using an ANOVA test with post hoc comparisons (Tukey B test). Predictors of LVEF reserve were assessed using multiple linear regression analysis. Next, to select the strongest predictors of left main/3-vessel disease, we entered known clinical and biologically plausible predictors into a multivariable logistic regression model using a stepwise selection process, with an entry and stay criteria of $P = 0.2$. The likelihood ratios for diagnosis of left main/3-vessel CAD were determined by receiver-operating-characteristic curve analysis using MedCalc for windows, version 8.1.0.0 (MedCalc Software). Sensitivity, specificity, and positive and negative predictive values for diagnosis of severe left main/3-vessel CAD were calculated. For all analyses, a 2-sided α of 0.05 was used to define statistical significance. All other analyses were performed using SPSS version 11.5. (SPSS Inc.).

RESULTS

Baseline Clinical and Hemodynamic Characteristics

The study cohort consisted of 510 consecutive patients (mean age, 61 y; 59% female) referred for evaluation of suspected CAD based on the presence of chest pain or nonclassic symptoms with multiple risk factors (Table 1). More men than women had abnormal myocardial perfusion imaging results. ST segment depression during stress was seen in 3% of the patients (15/510).

The baseline ECG was entirely normal in only 17% of patients. The rest of the patients demonstrated various baseline abnormalities, such as left ventricular hypertrophy (5%); left bundle branch block (5%); nonspecific ST, T, or ST/T changes (30%); and various other nonspecific changes (sinus tachycardia or bradycardia, atrial abnormalities, or intraventricular conduction delays).

Systemic Hemodynamics in Control, Normal, and Abnormal Groups

Rest hemodynamics was similar across all patient groups. The heart rate and rate·pressure product (systolic

TABLE 1
Baseline Characteristics of Study Cohort

Characteristics	Control patients ($n = 44$)	Normal MPI ($n = 309$)	Abnormal MPI ($n = 157$)	All patients ($n = 510$)
Age (y [mean ± SD])	53 ± 13	61 ± 13	66 ± 12*	61 ± 13
Female (%)	50	70	40*	59
Body mass index (kg/m^2 [mean ± SD])	28 ± 6	32 ± 8	32 ± 9	32 ± 8
Hypertension (%)	0	83	81	75
Diabetes (%)	0	31	36	30
Dyslipidemia (%)	39	56	60	55
Smoking (%)	14	13	16	14
β-Blockers (%)	14	52	61	52
Calcium channel blockers (%)	7	20	19	19
ACEI inhibitors (%)	2	40	39	36
Nitrates (%)	0	8	11	8
Any chest pain (%)	0	49	30*	39
Typical angina (%)	0	10	6	8
Dyspnea (%)	0	28	28	26
ST segment depression (%)	0	1.3	6.4†	2.8

*$P \leq 0.01$ compared with normal MPI.
†$P \leq 0.05$ compared with normal MPI.
MPI = myocardial perfusion imaging; ACEI = angiotensin-converting enzyme inhibitors.

blood pressure × heart rate) at peak stress were lower in the abnormal group (Table 2). The rate·pressure product increased from rest to peak stress in all study groups.

Left Ventricular Volumes and Ejection Fraction Reserve in Control, Normal, and Abnormal Groups

Mean end-diastolic volume increased from rest to stress in all 3 study groups, suggesting increased preload during peak hyperemia (Fig. 1A; Table 3). However mean end-systolic volume decreased from rest to stress only in the controls and in the group with normal myocardial perfusion (Fig. 1B; Table 3). Thus, although mean LVEF increased from rest to peak stress in all 3 groups, the magnitude of change in LVEF from rest to stress (LVEF reserve) showed a stepwise decline from control to the abnormal groups (Fig. 1C; Table 3). Mean LVEF and ejection fraction reserve were similar in patients undergoing adenosine or dipyridamole stress (Table 4).

Relation Between LVEF Reserve and Magnitude of Stress-Induced Perfusion Abnormalities

Overall, the magnitude (i.e., extent and severity) of reversible stress defects (summed difference score) was inversely related to the measured LVEF reserve ($r = -0.3$, $P < 0.001$) (Fig. 2). Furthermore, the mean LVEF reserve was negative ($-0.2\% \pm 7\%$) only in patients with severe reversible perfusion defects (summed difference score ≥ 8) and lower compared with patients with normal myocardial perfusion imaging or mild-to-moderate reversible perfusion defects ($P \leq 0.05$ for each comparison) (Fig. 3). Independent predictors of LVEF reserve were determined using multivariable linear regression analysis including variables listed in Table 5. Only male sex, rest ejection fraction, and increasing magnitude of myocardium at risk predicted a lower LVEF reserve.

Relation Between LVEF Reserve and Anatomic Extent of CAD

Sixty-eight patients underwent coronary angiography within 6 mo of the ^{82}Rb PET study. Of these 68 patients, 15 (22%) showed nonobstructive CAD, 23 (34%) single-vessel CAD, 13 (19%) 2-vessel CAD, 9 (13%) 3-vessel CAD, and 8 (12%) left main disease. Angiographic coronary collaterals were seen in 5% of the patients.

Mean LVEF reserve decreased with increasing extent of anatomic CAD (Fig. 4). The mean LVEF reserve was negative in patients with 3-vessel ($-6\% \pm 8\%$) and left main ($-8\% \pm 5\%$) disease, which was significantly lower than that of patients with nonobstructive or single-vessel disease ($P < 0.005$ for each comparison).

We used multiple logistic regression analysis to determine independent predictors of severe left main/3-vessel CAD. In this model, we included age, female sex, history of diabetes, history of hypertension, magnitude of reversible defects (summed difference score), magnitude of scar (summed rest score), number of diseased vessels on perfusion imaging, rest LVEF, stress LVEF, LVEF reserve, and LVEF reserve normalized to rest LVEF (model χ^2, 25; $P = 0.003$). The only significant independent predictor of left main/3-vessel CAD was the LVEF reserve (odds ratio, 0.8; 95% confidence intervals [CI], 0.7–0.9; $P = 0.0005$)—that is, for each unit increase in LVEF reserve, the odds of left main/3-vessel CAD decreased by 20%. Similarly, for each unit decrease in LVEF reserve, the odds of left main/3-vessel CAD increased by 30% (odds ratio, 1.3; 95% CI, 1.1–1.5; $P = 0.0005$).

Diagnostic Accuracy of LVEF Reserve to Diagnose Left Main/3-Vessel CAD

On receiver-operating-characteristic curve analysis, the positive likelihood ratio and, consequently, the posttest odds of severe left main/3-vessel CAD increased exponentially with a decrease in LVEF reserve below +5%. This threshold was sensitive and showed an excellent negative predictive value to exclude severe left main/3-vessel CAD (sensitivity, 94%; negative predictive value, 97%). However, it had a limited specificity and positive predictive value (55% and 41%, respectively). An abnormal LVEF reserve (less than +5%) was seen in 30%, 62%, and 94% in patients with single-vessel, 2-vessel, and left main/3-vessel CAD, respectively. Conversely, a threshold of less than −5% had sensitivity, specificity, and positive and negative

TABLE 2
Hemodynamics in Study Groups

Characteristic	Control patients ($n = 44$)	Normal MPI ($n = 309$)	Abnormal MPI ($n = 157$)	All patients ($n = 510$)
Rest HR (bpm)	70 ± 15	69 ± 13	70 ± 13	70 ± 13
Peak stress HR (bpm)	87 ± 17	83 ± 16	79 ± 15*	82 ± 16
Rest SBP (mm Hg)	141 ± 23	150 ± 24	147 ± 27	148 ± 25
Peak stress SBP (mm Hg)	135 ± 25	143 ± 27	136 ± 29*	140 ± 28
RPP (rest)	10,014 ± 2,852	10,397 ± 2,491	10,242 ± 2,750	10,316 ± 2,599
RPP (peak stress)	11,798 ± 3,209†	11,812 ± 3,131†	10,758 ± 3,155*†	10,316 ± 2,599†

*ANOVA, $P < 0.05$ across groups.
†$P < 0.01$ compared with rest.
MPI = myocardial perfusion imaging; HR = heart rate; SBP = systolic blood pressure; RPP = rate·pressure product.
Data are presented as mean ± SD.

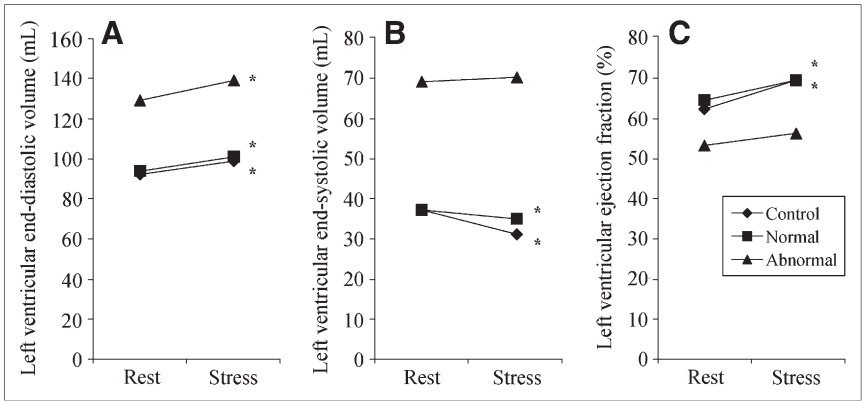

FIGURE 1. Mean left ventricular end-diastolic volumes (A), end-systolic volumes (B) and ejection fraction (C) at rest and peak vasodilator stress in control patients and patients with normal and abnormal myocardial perfusion studies. *$P < 0.001$ compared with rest values.

predictive values of 59%, 94%, 77%, and 87%, respectively. Furthermore, an LVEF reserve of more than + 8% excluded left main/3-vessel CAD (negative predictive value, 100%), whereas an LVEF reserve of equal to or more than −14%—although insensitive (present in only 25% of patients)—was diagnostic of left main/3-vessel CAD (positive predictive value, 100%).

Value of LVEF Reserve and Myocardial Perfusion for Delineating Anatomic Extent of CAD

The addition of an abnormal LVEF reserve did not increase significantly, the overall sensitivity of perfusion imaging (92% vs. 94%). However, as shown in Figures 5A and 5B, 79% of patients were correctly identified as having multivessel disease using the combination of perfusion and abnormal LVEF reserve, compared with only 50% of patients identified by myocardial perfusion alone. Figures 6 and 7, respectively, demonstrate case examples when an abnormal LVEF reserve helped identify left main/3-vessel CAD that was not evident on perfusion images (balanced ischemia) and when an abnormal LVEF reserve helped uncover more extensive disease than identified by perfusion imaging alone. However, PET perfusion information was more sensitive than LVEF reserve alone in identifying the presence of CAD, in the overall group (92% vs. 59%) and in patients with 1-vessel and 2-vessel CAD (87% vs. 30%, and 100% vs. 62%, respectively).

TABLE 3
Left Ventricular Volumes and Ejection Fraction in Study Groups

Variable	Gated rest	Gated peak stress	Stress–Rest
Control (n = 44)			
LVEDV (mL)	92 ± 28	99 ± 32*	7 ± 13
LVESV (mL)	37 ± 17	31 ± 14*	−5 ± 8†
LVEF (%)	62 ± 9	69 ± 8*	7 ± 7†
Normal MPI (n = 309)			
LVEDV (mL)	94 ± 42	101 ± 43*	6 ± 13†
LVESV (mL)	37 ± 29	35 ± 29*	−3 ± 7†
LVEF (%)	64 ± 10	69 ± 10*	5 ± 6†
Abnormal MPI (n = 157)			
LVEDV (mL)	129 ± 63	139 ± 65*	10 ± 18
LVESV (mL)	69 ± 58	70 ± 61	0.5 ± 14
LVEF (%)	53 ± 17	56 ± 17*	3 ± 7

*$P \leq 0.0001$ compared with rest values.
†$P \leq 0.01$ compared with abnormal MPI group.
EDV = end-diastolic volume; ESV = end-systolic volume; MPI = myocardial perfusion images.
Data are presented as mean ± SD.

DISCUSSION

Although myocardial perfusion imaging is an accurate means to detect obstructive CAD, its ability to delineate the extent of anatomic disease remains limited. Further, with vasodilator stress testing there are no simple clinical markers to indicate degree of hyperemia achieved, leading to concern of underestimation of disease burden from submaximal hyperemia when the scan demonstrates only small or no perfusion defects in patients with a high clinical suspicion of severe CAD. Thus, exclusion of severe left main or 3-vessel CAD as the basis for clinical symptoms is also an important goal of noninvasive imaging for suspected CAD. In a large number of patients with suspected CAD, the current study results demonstrate that measures of LVEF reserve assessed during vasodilator stress ^{82}Rb PET can be used as an aid to perfusion imaging to better delineate the magnitude of jeopardized myocardium and more precisely define the extent of underlying anatomic CAD compared with perfusion data alone. Our findings show an inverse relationship between the extent and severity of stress perfusion abnormalities and the magnitude of change in LVEF from rest to peak stress. More important, the rise in LVEF during peak stress was inversely related to the extent of obstructive CAD on coronary angiography. A positive LVEF reserve of more than +5%, had an excellent negative predictive value (97%) for excluding the presence of severe left main or 3-vessel CAD.

Unlike vasodilator SPECT with technetium agents in which stress gated images are obtained approximately 45 min after stress (*16*), ^{82}Rb PET enables measurement of left ventricular function during peak hyperemia. By combining the assessment of myocardial perfusion with LVEF reserve,

TABLE 4
Left Ventricular Volumes and Ejection Fraction in Study Groups by Type of Stress Agent Used

Variable	Dipyridamole vs. adenosine		
	Gated rest	Gated peak stress	Stress–rest
Control (n = 44)			
LVEDV (mL)	98 ± 20 vs. 90 ± 30	102 ± 21 vs. 98 ± 35	8 ± 12 vs. 4 ± 14
LVESV (mL)	42 ± 13 vs. 35 ± 18	34 ± 13 vs. 31 ± 15	−4 ± 7 vs. −8 ± 10
LVEF (%)	63 ± 9 vs. 58 ± 6	68 ± 9 vs. 69 ± 8	6 ± 7 vs. 10 ± 7
Normal MPI (n = 309)			
LVEDV (mL)	95 ± 45 vs. 92 ± 31	101 ± 45 vs. 97 ± 34	6 ± 13 vs. 6 ± 14
LVESV (mL)	38 ± 31 vs. 34 ± 20	35 ± 31 vs. 32 ± 21	−3 ± 7 vs. −2 ± 9
LVEF (%)	63 ± 11 vs. 64 ± 9	69 ± 11 vs. 68 ± 9	5 ± 6 vs. 4 ± 7
Abnormal MPI (n = 157)			
LVEDV (mL)	127 ± 63 vs. 139 ± 69	137 ± 63 vs. 147 ± 75	11 ± 17 vs. 7 ± 19
LVESV (mL)	68 ± 57 vs. 80 ± 63	67 ± 59 vs. 81 ± 66	1 ± 14 vs. −2 ± 15
LVEF (%)	54 ± 17 vs. 49 ± 16	57 ± 17 vs. 51 ± 17	3 ± 7 vs. 2 ± 8

EDV = end-diastolic volume; ESV = end-systolic volume; MPI = myocardial perfusion images.
None of the comparisons between adenosine and dipyridamole are statistically significant. Data are presented as mean ± SD.

the overall high sensitivity of PET was maintained even in patients with single-vessel and 2-vessel CAD, providing an additional tool to effectively exclude the presence of left main/3-vessel CAD due to balanced ischemia. Thus, our results confirm the value of peak stress (^{201}Tl) (*17*) or poststress (^{99m}Tc SPECT) (*16*) LVEF as highly specific for predicting severe CAD and further the clinical implications by showing the value of a positive LVEF reserve to exclude severe angiographic CAD with a high degree of certainty.

Our study confirms prior evidence from exercise radionuclide angiography studies that changes in ejection fraction from rest to peak stress are influenced by other factors in addition to the extent of CAD, such as sex and resting ejection fraction (*18*). Contrary to an earlier report with exercise radionuclide angiography (*18*), male sex, not female sex, was an independent predictor of lower ejection fraction reserve in our study. The precise explanation for this difference is unclear but, if confirmed in other studies, raises the possibility that the underlying mechanism for changes

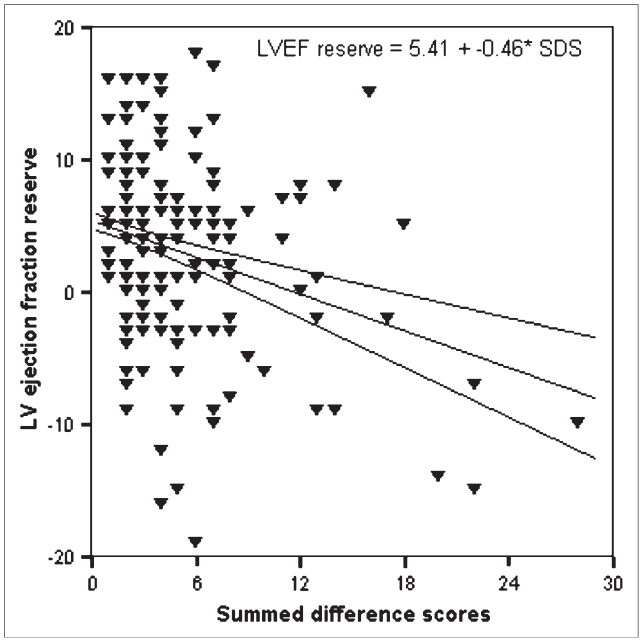

FIGURE 2. Scatter plot shows relation between magnitudes of stress-induced perfusion defects and LVEF reserve. SDS = summed difference score.

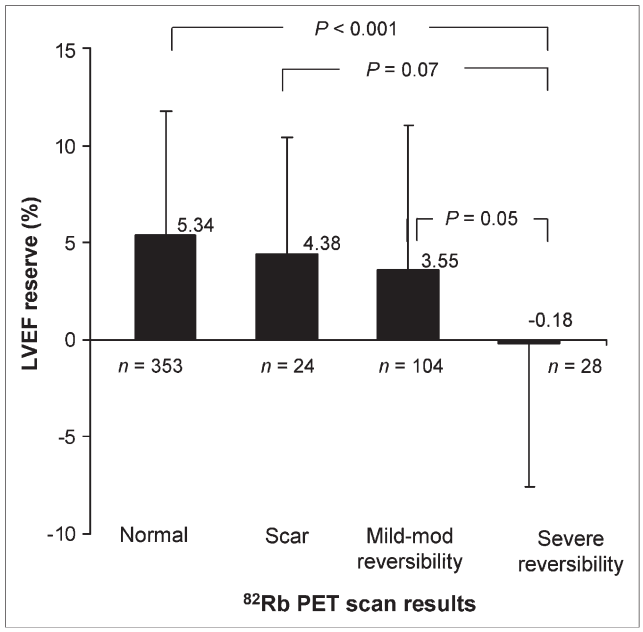

FIGURE 3. Relation between magnitudes of stress-induced perfusion defects and LVEF reserve. Values represent mean ± SD. mod = moderate.

TABLE 5
Independent Predictors of LVEF Reserve

Variable	B	95% confidence intervals		*P* value
Female sex	1.5	0.3	2.8	0.02
Age	0.03	−0.2	0.1	NS
Hypertension	−1.3	−2.7	0.2	NS
Diabetes	−0.9	−2.2	0.4	NS
ACEI use	−0.4	−1.7	0.8	NS
Calcium channel blockers' use	−0.5	−1.9	1.0	NS
Nitrate use	0.4	−1.7	2.5	NS
Mode of stress (ado vs. dipy)	1.2	−0.2	2.7	NS
Summed stress score	−0.4	−0.5	−0.2	<0.001
Summed difference score	−0.1	−0.4	0.1	NS
Rest LVEF	−0.2	−0.3	−0.2	<0.001

B = unstandardized coefficient; NS = not significant; ACEI = angiotensin-converting enzyme inhibitors; ado = adenosine; dipy = dipyridamole.
Model summary: $R = 0.4$; $R^2 = 0.14$; F = 8.4; $P = 0.001$.

in ejection fraction with exercise stress may be different compared with those with vasodilator stress.

Relation Between LVEF Reserve and Myocardial Perfusion

The exact pathophysiologic relation between myocardial blood flow and function cannot be determined from this study. Adenosine (directly) and dipyridamole (indirectly) cause coronary and peripheral vasodilation via activation of adenosine A_{2A} receptors and peripheral adenosine A_{2A} and perhaps A_{2B} receptors, respectively (*19*). This leads to a modest reduction in after load with a reflex increase in heart rate (*20*) and a concomitant increase in preload to the left ventricle (*21*) and ejection fraction (*20,22*). Increased preload is a well-known stimulus for increased myocardial contractility via the Frank−Starling mechanism. In addition, increased coronary blood flow appears to be a potent stimulus for increased myocardial contractility (Gregg phenomenon) (*10,23*). Despite increased preload in all patient groups, only the patients with increased coronary blood flow during peak hyperemia (control and normal groups) demonstrated an increase in LVEF during peak stress. Conversely, patients with severe reversible defects (i.e., groups with attenuated increase in coronary flow during peak hyperemia) demonstrated an attenuated LVEF response, thereby supporting the Gregg hypothesis. The difference between our findings and those of a prior angiographic study is likely due to the selection of patients with more severe CAD and the ability to analyze tomographic LV volumes (rather than by contrast ventriculography (*24*)).

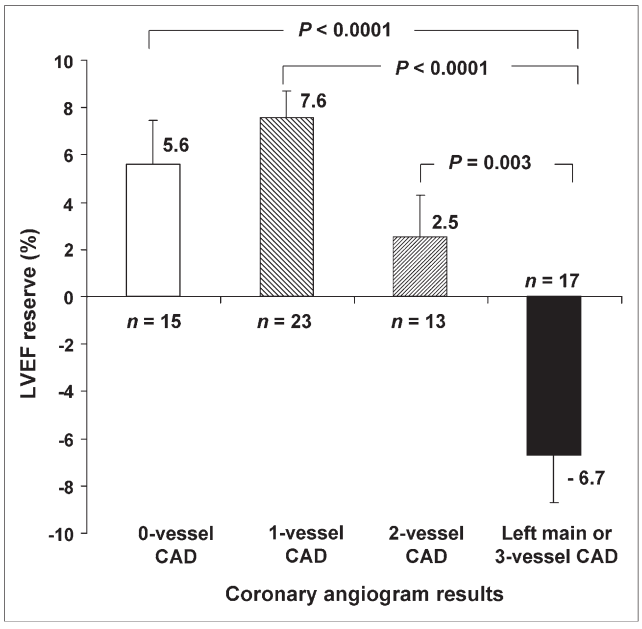

FIGURE 4. Relation between angiographic extent of CAD and LVEF reserve. Values represent mean ± SD.

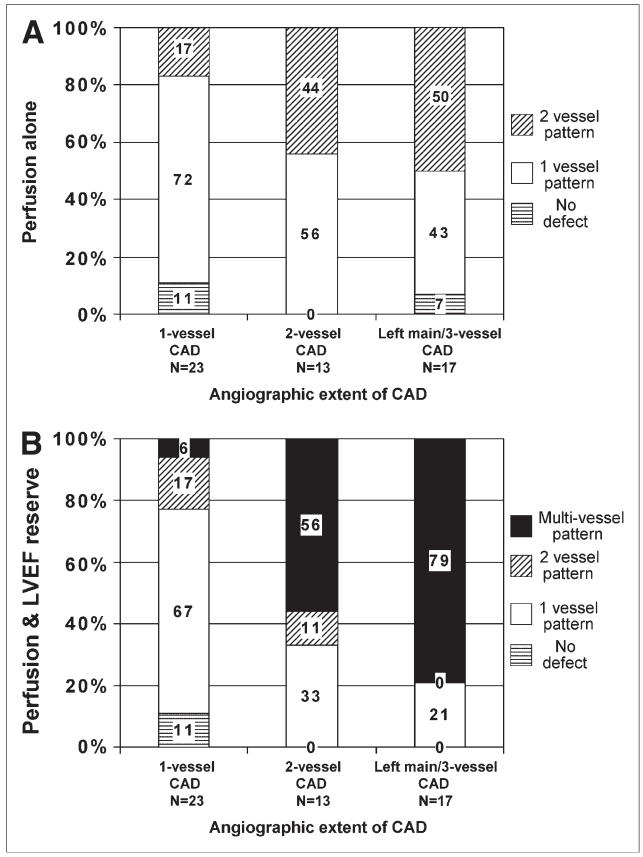

FIGURE 5. (A and B) Agreement between extent of CAD determined by coronary angiography (*x*-axis) and myocardial perfusion defects alone (A) and by combined myocardial perfusion defects and abnormal LVEF reserve (B). No patients demonstrated defects in 3-vessel distribution. Disease extent was underestimated in half of patients with severe left main/3-vessel disease (no defects in 7% and defect in 1-vessel distribution in 43%). By combining perfusion and LVEF reserve, no patients were missed and most patients were correctly classified as having left main/3-vessel disease (86%).

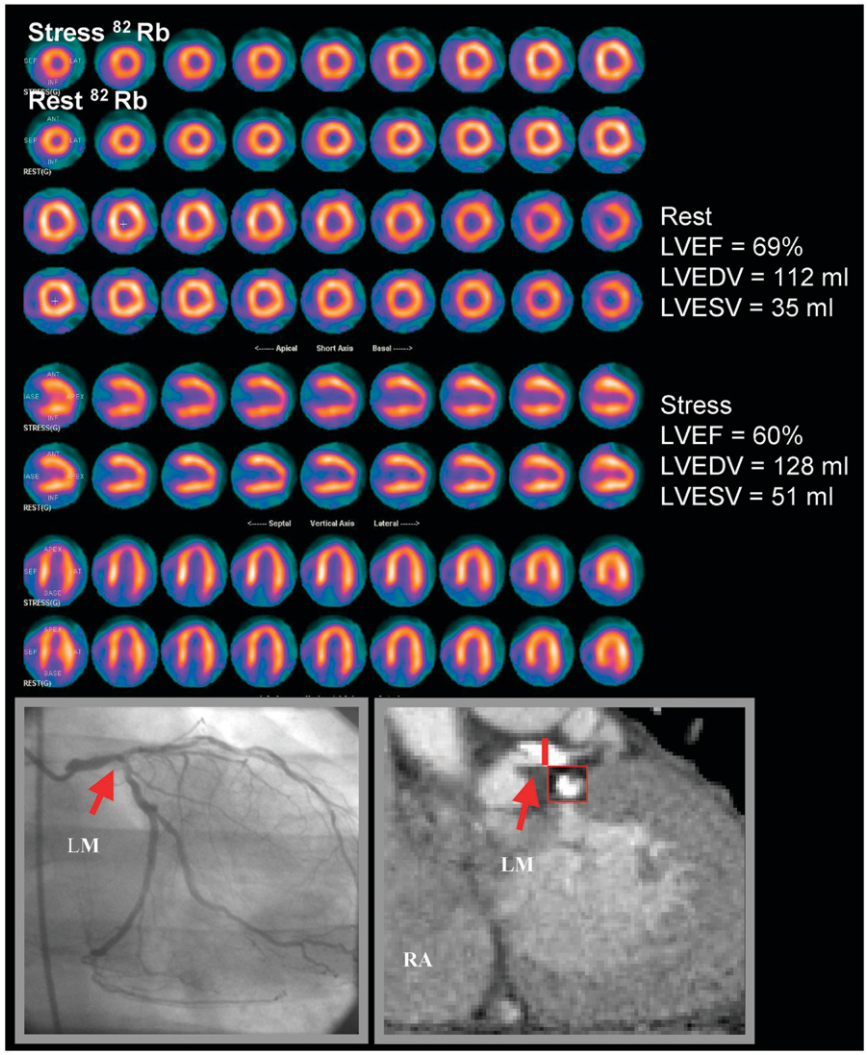

FIGURE 6. Relatively unremarkable rest-stress myocardial perfusion images with a significant decrease in LVEF during peak stress. Patient also had CT coronary angiogram immediately after PET study that demonstrated left dominant anatomy and severe calcified left main disease (bottom right; inset is cross section through left main artery) that was subsequently confirmed by catheter coronary angiography (bottom left). He underwent coronary artery bypass surgery. LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LM = left main coronary artery; RA = right atrium.

Coronary steal (intra- or intercoronary steal) is another potential mechanism for LV dysfunction in patients with severe multivessel CAD (*25*). Coronary collaterals, a marker of intercoronary steal, were infrequent in our cohort, making this a less plausible explanation for our findings. However, patients with severe multivessel CAD demonstrate global subendocardial ischemia from intracoronary steal (redirection of flow from the subendocardium to subepicardium) with vasodilator stress (*26*). Because the subendocardium plays a major role in myocardial thickening, this transmural gradient of myocardial blood flow in favor of the subepicardium seems to be a more plausible explanation for decreased LVEF during peak stress in patients with severe reversible defects or left main/3-vessel CAD.

A load-dependent measure of systolic function such as LVEF is expected to increase during peak hyperemia due to lower peripheral vascular resistance from nonselective vasodilator agents. Vascular resistance after ischemia or hyperemic stress is known to be higher in both the peripheral and the coronary beds in patients with atherosclerosis, coronary risk factors, and microvascular angina (*27,28*). Indeed, the degree of impairment in peripheral vasodilator reserve relates closely to impairment in coronary vasodilator reserve (*28*). Impaired peripheral vasodilator reserve may be the underlying reason for the limited positive predictive value of a low LVEF reserve. Abnormal vasodilator LVEF reserve may not only indicate impaired coronary vasodilator reserve but may also be an important surrogate marker for overall vascular health.

Clinical Implications

LVEF reserve is a simple parameter that can be obtained routinely during rest-vasodilator stress ^{82}Rb imaging. Demonstration of a normal LVEF reserve can exclude severe left main/3-vessel disease with a high degree of certainty and facilitate management decisions. Also, a normal LVEF reserve with mildly abnormal PET is predictive of less extensive CAD and may not warrant coronary angiography. The presence of abnormal myocardial perfusion and abnormal LVEF reserve suggests extensive and severe CAD and may warrant coronary angiography. In selected patients, such as those with a high clinical probability of

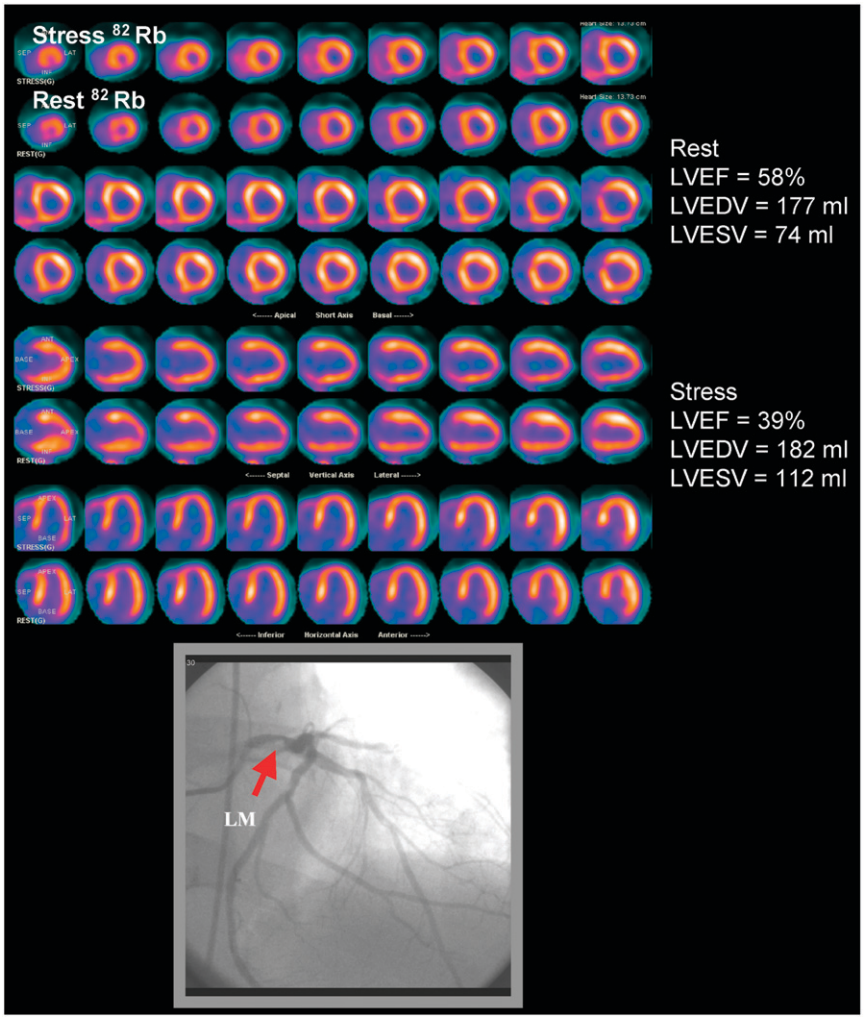

FIGURE 7. Rest-stress myocardial perfusion PET/CT images in patient with severe angina demonstrate small region of moderate reversibility in middle and basal inferolateral walls. Gated study demonstrated significant decrease in LVEF during peak stress. Catheter coronary angiography demonstrated left dominant anatomy and severe left main CAD (bottom panel). Patient underwent coronary artery bypass surgery. LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LM = left main coronary artery.

severe CAD (left main/3-vessel disease) (*29*), no significant perfusion abnormalities may conceivably be a false- negative result (*30*). In those instances, a low LVEF reserve may warrant further evaluation (e.g., CT coronary angiography) to exclude severe CAD.

Limitations

This is a single-center study with several limitations. Patients were referred for coronary angiography on the basis of clinical and imaging results. Thus, the results may have been influenced by posttest referral bias and warrant further confirmation. The use of adenosine stress followed by rest imaging may have attenuated the LVEF reserve in patients with severe ischemia. However, this seems unlikely because no significant differences were found on univariable or multivariable analyses. Also, the prognostic value of peak stress gating merits further study.

CONCLUSION

LVEF reserve during vasodilator ^{82}Rb PET is inversely related to the magnitude of myocardium at risk. A normal LVEF reserve appears to be an excellent diagnostic tool to exclude severe left main/3-vessel CAD, whereas a severely reduced LVEF reserve may be diagnostic of severe left main/3-vessel CAD.

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