

# Incremental prognostic value of left ventricular function by myocardial ECG-gated FDG PET imaging in patients with ischemic cardiomyopathy

Cesar A. Santana, MD, PhD,<sup>a</sup> Leslee J. Shaw, PhD,<sup>c</sup> Ernest V. Garcia, PhD,<sup>a</sup> Marina Soler-Peter, MD,<sup>d</sup> J. Candell-Riera, MD, PhD,<sup>d</sup> Gabriel B. Grossman, MD,<sup>a</sup> Elizabeth G. Krawczynska, MD, PhD,<sup>a</sup> Tracy L. Faber, PhD,<sup>a</sup> Aida Ribera,<sup>d</sup> Viola Vaccarino, MD, PhD,<sup>b</sup> Raghuvver Halkar, MD,<sup>a</sup> and Marcelo F. Di Carli, MD<sup>e</sup>

**Background.** The purpose of this study was to determine the independent value of left ventricular (LV) functional parameters derived from gated fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) to predict prognosis in patients with ischemic cardiomyopathy undergoing myocardial viability assessment.

**Methods and Results.** We studied 90 consecutive patients with coronary artery disease and low LV ejection fraction ( $26\% \pm 7\%$ ) undergoing gated FDG PET to assess myocardial viability for potential revascularization. The primary endpoint for this analysis was the occurrence of cardiac death, myocardial infarction, or worsening heart failure (HF) to New York Heart Association class IV. During follow-up ( $22 \pm 14$  months), 21 patients had an event (17 died, 4 had myocardial infarctions, and 4 had worsening HF). On Cox regression analysis, the event-free survival rate at 2 years was lower for patients with an end-diastolic volume (EDV) of 260 mL or greater (relative risk, 2.7;  $P = .014$ ), end-systolic volume (ESV) of 200 mL or greater (relative risk, 2.5;  $P = .021$ ), and LV mass of 143 g or greater (relative risk, 1.6;  $P = .009$ ). In a risk-adjusted model, EDV ( $\chi^2 = 68$ ,  $P < .0001$ ) and ESV ( $\chi^2 = 75$ ,  $P = .035$ ) added a significant amount in the estimation of events over the perfusion-FDG mismatch pattern ( $\chi^2 = 40$ ,  $P < .001$ ). In a stratified Cox model, patients with PET mismatch, LV ejection fraction lower than 25%, and EDV of 260 mL or greater had the lowest survival rate ( $P = .006$ ). These patients showed an apparent survival benefit with revascularization but without an improvement in HF symptoms.

**Conclusion.** LV functional parameters determined by gated FDG PET have incremental prognostic value over viability information in patients with ischemic cardiomyopathy. Our data suggest that patients with residual viability and advanced cardiac remodeling are at high clinical risk. In these patients the apparent survival benefit of revascularization may not be associated with a measurable improvement in HF symptoms. (J Nucl Cardiol 2004;11:542-50.)

**Key Words:** Prognosis • viability • positron emission tomography • ventricular function

---

## See related article, p. 524

---

The development of electrocardiography (ECG)-gated positron emission tomography (PET) imaging by

use of a metabolic agent such as fluorine 18 fluorodeoxyglucose (FDG) has allowed the simultaneous assessment of ventricular function and metabolism in a single procedure.<sup>1</sup> The combined assessment of myocardial perfusion and metabolism and left ventricular (LV)

From Departments of Radiology<sup>a</sup> and Medicine,<sup>b</sup> Emory University School of Medicine, Atlanta Cardiovascular Research Institute, Atlanta, Ga,<sup>c</sup> Vall d'Hebron University Hospital, Barcelona, Spain,<sup>d</sup> and Brigham and Women's Hospital, Harvard Medical School, Boston, Mass.<sup>e</sup>

Funded in part by the National Institutes of Health; National Heart, Lung, and Blood Institute grant Nos. K01 HL70422 and R01 HL68904; and the 2001 American Society of Nuclear Cardiology/Fujisawa Award for Basic or Applied Scientific Research in Nuclear Cardiology.

Received for publication Feb 17, 2004; final revision accepted July 12, 2004.

Reprint requests: Cesar A. Santana, MD, PhD, Department of Radiology, Emory University, 1364 Clifton Road NE, Atlanta, GA 30322; [csantan@emory.edu](mailto:csantan@emory.edu).

1071-3581/\$30.00

Copyright © 2004 by the American Society of Nuclear Cardiology. doi:10.1016/j.nuclcard.2004.07.005

function, determined by gated PET, provides important predictors of prognosis in patients with coronary artery disease (CAD) and LV dysfunction.<sup>2-4</sup> Normal or increased FDG uptake in dysfunctional segments with reduced blood flow at rest (PET mismatch) indicates the presence of viable (hibernating) myocardium, whereas a concordant reduction in blood flow and FDG uptake (PET match) indicates predominantly nonviable myocardium. This combined approach (ie, perfusion and metabolism) has proven useful for identifying patients with LV dysfunction and CAD in whom function, survival rate, and symptoms are likely to improve after revascularization. These observations suggest that noninvasive investigation of the amount of viable myocardium should be an important component of the prognostic evaluation of patients with LV dysfunction.<sup>5-13</sup>

The prognostic value of LV ejection fraction (EF) in detecting the risk of cardiac events has been well documented with different methods such as contrast ventriculography, echocardiography, radionuclide ventriculography, or perfusion gated single photon emission computed tomography (SPECT).<sup>14-18</sup> Rest or exercise LVEF is one of the major determinants of long-term survival in patients with CAD.<sup>19,20</sup> In addition, end-systolic volume (ESV) is an independent predictor of cardiac death in patients after myocardial infarction and coronary artery bypass surgery.<sup>21-23</sup> The purpose of this study was to determine whether parameters of LV function including EF, end-diastolic volume (EDV), and ESV determined by gated FDG PET provide independent prognostic value over the perfusion-metabolism PET pattern of mismatch in patients with CAD and severe LV dysfunction.

## METHODS

### Patient Population

The population studied was selected from a cohort of 137 consecutively tested patients between January 1995 and April 1999 undergoing rest myocardial perfusion and ECG-gated FDG metabolism PET studies in the assessment of myocardial viability for potential myocardial revascularization. Of the original 137 patients, 47 were excluded: 27 because of imaging issues (technical problems in 16 and no images available in 11) and 20 with LVEF greater than 40%. Finally, 90 patients with documented CAD and severe LV dysfunction (LVEF <40%; mean, 26% ± 7%) were enrolled in this study.

Importantly, all of these 90 patients had previous myocardial infarction: 85 (94%) with a transmural myocardial infarction and 5 (6%) with a nontransmural myocardial infarction. In 29 (32%) of these patients the diagnosis was made during the admission to the hospital for myocardial infarction. In the remaining 61 (68%), the

diagnosis of myocardial infarction was made by use of the patients' clinical history (enzyme-documented or electrocardiogram). In addition, all patients had at least one rest myocardial perfusion defect when quantitatively compared with a normal rubidium 82 database. Our institutional review board approved the study protocol including follow-up procedures.

### PET Imaging

Resting regional myocardial perfusion and glucose uptake were assessed with PET by use of Rb-82 as the flow tracer and FDG as a metabolic tracer. PET imaging was performed with a whole-body Siemens ECAT EXACT 921 tomograph (Siemens Medical Solutions, Hoffman Estates, Ill). Studies were acquired in the glucose-loaded state, after the oral administration of 50 g of glucose. A 5-minute transmission scan was recorded for correction of photon attenuation. Myocardial perfusion images were then obtained for 7 minutes after the intravenous administration of 1300 and 1850 MBq (35-50 mCi) Rb-82. Then, 370 MBq (10 mCi) FDG was injected intravenously, and after 30 to 45 minutes (to allow for metabolic trapping of FDG in the myocardium), gated FDG images were acquired for 25 minutes at 8 frames per cardiac cycle.<sup>24,25</sup>

All images were reconstructed with segmented attenuation correction derived from the 5-minute transmission scan. Images were reconstructed with filtered back-projection by use of a Hahn smoothing filter cutoff at 1 cycle per centimeter. The recommended scatter correction supplied by the scanner manufacturer (Siemens Medical Solutions software, version 7.1b) was used. The 8 frames of ECG-gated images were added to form a single-frame static image for assessment of glucose metabolism. A temporal 1-2-1 filter was applied to the gated images. Three sets of images were generated: rest Rb-82, rest summed FDG, and gated FDG. After reconstruction, all images were reoriented into short-axis views and then loaded into the Emory Cardiac Toolbox (ECTb, Syntermed, Atlanta, Ga).

### LV Function by Gated FDG PET

LV function was determined by use of the ECTb software. The method for calculating LV function and LV mass has been validated extensively against other imaging modalities.<sup>26-29</sup> In brief, ECTb analyzed all gated short-axis tomographic slices to locate points corresponding to left ventricle-shaped objects imbedded within time-varying 3-dimensional count distributions. Endocardial offsets from end-diastolic midmyocardial points were defined to be half the myocardial thickness, assumed to be 1 cm thick uniformly at end diastole, based on magnetic resonance imaging studies.<sup>26</sup> To estimate end systole and endocardial

boundaries, wall thickening was computed from Fourier fits of regional myocardial count change in the 8 R-R intervals, assuming systolic count increases to be linearly related to myocardial wall thickening. Output from the ECTb program included wall thickening polar maps, wall motion display, LVEF, EDV, ESV, stroke volume, and LV mass.<sup>26</sup>

### Image Interpretation

The ECTb program was used to display all images. Two readers independently scored rest Rb-82 and rest FDG images using tomographic slices of the heart and 20-segment-model polar-map representations. The readers then classified the patient's perfusion-metabolism pattern as normal, match, or mismatch. When the readers disagreed, the interpretation was established by consensus. The scoring classification (normal, match, or mismatch) was based on whether a patient with mismatch would be expected to receive benefits from cardiac surgery. The criterion for mismatch was as follows: greater than 15% of the myocardium (3/20 segments) with moderately reduced uptake of Rb-82 and FDG uptake greater than Rb-82 within the same area. This criterion was selected based on the notion that patients with large perfusion-metabolism mismatches (>18% of the myocardium) determined by cardiac PET exhibit the greatest clinical benefit with revascularization.<sup>6</sup>

### Follow-up

Patients were followed up for a mean of  $22 \pm 14$  months (range, 0.23-54 months). Follow-up was performed by an experienced physician without knowledge of the patient's clinical history and PET scan results. Follow-up consisted of reviewing each patient's medical records and conducting scripted telephone interviews with the patient or primary relative. During the interview and review of the patient's medical record, cardiac events were documented, including angina class (Canadian Cardiovascular Society class), New York Heart Association (NYHA) heart failure class, enzyme-documented myocardial infarction, cardiac intervention (including percutaneous coronary intervention, coronary artery bypass surgery, cardiac transplant, and angiogenesis), and death (all-cause and cardiovascular disease).

### Statistical Analysis

The primary endpoint for this analysis was the occurrence of ischemic heart disease-related death, myocardial infarction, or worsening NYHA heart failure to class IV. All continuous data were presented as mean  $\pm$  SD and percentages for discrete variables. Comparisons between groups were assessed by a *t* test for continuous

variables and by a Fisher exact or  $\chi^2$  test for discrete variables. Survival curves were constructed by use of a risk-adjusted (controlling for sex, diabetes, coronary disease history, and NYHA class at baseline) multivariable Cox proportional hazards model. Univariable and multivariable analyses were performed by use of Cox proportional hazards modeling techniques. Candidate variables based on the multivariable models included those with a *P* value < .20. For the final multivariable model, *P* < .10 was considered for retention of variables in the model. Because of the exploratory nature of this analysis, model-overfitting procedures were considered but with the use of more liberal guidelines of 1 variable for approximately every 5 outcomes. The incremental value of adding a variable to a multivariable model was assessed by use of a change in  $\chi^2$ . In addition, independent predictive information was assessed by a stepwise Cox regression analysis.

To examine the proportional risk reduction with revascularization, a multivariable model was evaluated that included the PET perfusion and function variables, historical data, and coronary revascularization. From this model, the predicted probabilities of an event were calculated. By use of a general linear model, the predicted probabilities were compared for patients undergoing coronary revascularization in varying subsets.

The purpose of this study was to detail an exploratory analysis of the prognostic value of measures of LV function and volumes in addition to previously reported PET mismatch data. As such, we collected available patient information, but because of a lack of prior evidence, statistical power was considered on a post hoc basis. A post hoc computation of available statistical power (ie, threshold  $\beta > 80$ ) revealed that the enrollment of 90 patients would yield an expected  $\beta$  in the range of .26 to .99 for the evaluation of outcome differences for LVEF ( $\beta = .36$ ), LV mass ( $\beta = .36$ ), EDV ( $\beta = .92$ ), and ESV ( $\beta = .99$ ). On the basis of our post hoc calculations, this effect was selected as the smallest effect that would be important to detect, in the sense that any smaller effect would not be of clinical or substantive significance. It is also assumed that this effect size is reasonable, in the sense that an effect of this magnitude could be anticipated in viability testing. The criterion for significance ( $\alpha$ ) has been set at .05. The test is 2-tailed, which means that an effect in either direction will be interpreted.

## RESULTS

### Baseline Characteristics of Patients

Patients enrolled in this study had advanced coronary heart disease. All patients had significant coronary artery stenosis and previous myocardial infarction (Table

**Table 1.** Clinical characteristics of the 90 CAD patients undergoing rubidium/gated FDG imaging for myocardial viability testing

Study population	Data
Age (y)	62 ± 10
Female	17 (19%)
Diabetes mellitus	16 (18%)
Hypertension	32 (36%)
Prior heart failure symptoms	25 (28%)
Prior coronary bypass surgery	12 (13%)
Prior percutaneous coronary intervention	13 (14%)
Prior myocardial infarction	90 (100%)
Transmural myocardial infarction	85 (94%)
Nontransmural myocardial infarction	5 (6%)
NYHA class	
1	69 (76%)
2	4 (4%)
3	10 (11%)
4	7 (8%)
Catheterization results	
1=Vessel disease	10 (11%)
2=Vessel disease	31 (34%)
3=Vessel disease	49 (54%)
LVEF by FDG gated PET (%)	26 ± 7
EDV by FDG gated PET (mL)	184 ± 78
ESV by FDG gated PET (mL)	138 ± 68
LV mass by FDG gated PET (g)	181 ± 48
PET interpretation	
Mismatch	38 (42%)
Match	52 (58%)

1). In addition, more than 25% of the population had cardiac surgery, hypertension, or heart failure. The mean LVEF by gated FDG PET was 26% ± 7%. A total of 38 patients exhibited a perfusion-metabolic mismatch pattern, whereas 52 patients had a match pattern between perfusion and metabolism.

### Clinical Outcomes

During the follow-up period (mean, 22 ± 14 months), 19 patients died; 17 of these deaths were categorized as cardiac death (Table 2). A total of 21 patients (23%) experienced a combined endpoint of cardiac death, nonfatal myocardial infarction, or worsening heart failure as determined by a change to NYHA class IV heart failure. Thirty-one patients underwent cardiac surgery after the PET study. The mean period between the gated FDG study and surgery was 6 ± 8 days. Decisions related to patient treatment were made by the attending cardiologist based on clinical criteria

**Table 2.** Rates of clinical outcome during follow-up (mean, 22 ± 14 months)

Death from all causes	19 (21%)
Cardiac death	17 (19%)
Myocardial infarction	4 (4%)
Heart failure admission	22 (24%)
Unstable angina admission	31 (34%)
Percutaneous coronary intervention	10 (11%)
Coronary bypass surgery	21 (23%)
Heart transplantation	3 (3%)
Angiogenesis	4 (4%)
Combined endpoint*	21 (23%)

\*Defined as cardiac death, nonfatal myocardial infarction, or NYHA class IV heart failure.

and supported by information such as patient clinical status, results of the PET study, and other data.

### Outcome Assessment by Clinical History

As this group was relatively homogeneous with regard to CAD history and LVEF, there were no significant differences between patients with and without events (cardiac death, myocardial infarction, or NYHA heart failure class IV) based on historical factors (Table 3).

### Outcome Assessment by Gated FDG PET

Table 4 details a comparison of mean LV functional parameters in patients with and without cardiac events. Because of the inclusion of patients with systolic dysfunction, mean LVEF measurements did not vary by outcome status ( $P = .27$ ). However, estimates of LV volumes and mass were predictive of subsequent clinical outcomes. Mean measurements of EDV (216 mL vs 164 mL,  $P = .002$ ), ESV (164 mL vs 123 mL,  $P = .005$ ), stroke volume (52 mL vs 42 mL,  $P = .009$ ), and LV mass (199 g vs 169 g,  $P = .004$ ) were consistently higher in patients with cardiac events as compared with patients without cardiac events.

Although LVEF revealed a trend toward significance ( $P = .14$ ), on unadjusted Cox analysis, optimal risk stratification was noted for patients with an EDV of 260 or greater mL or an EDV lower than 260 mL, yielding annualized event rates of 25.1% versus 15.4% ( $P = .013$ ). Similarly, patients with an ESV of 200 mL or greater or an ESV lower than 200 mL had event rates of 26.3% and 16.3%, respectively, annually ( $P = .003$ ). Patients who had an LV mass measurement of 143 g or greater had an event rate of 20.6% per year as compared with an 8% yearly event rate in patients with an LV mass of less than 143 g ( $P = .022$ ).

**Table 3.** Comparison between patients without events\* and those with events by use of patients' baseline characteristics on univariable Cox proportional hazard analysis

	No events (n = 69)	Events (n = 21)	P value
Age	62 ± 10 y	63 ± 10 y	.65
Male	55 (80%)	18 (86%)	.09
Previous MI	21 (30%)	8 (38%)	.96
Previous CABG	7 (10%)	5 (24%)	.21
Previous PCI	10 (14%)	3 (14%)	.92
Hypertension	25 (36%)	7 (33%)	.80
Diabetes	13 (19%)	3 (14%)	.53
Heart failure	17 (25%)	8 (38%)	.18

MI, Myocardial-infarction, CABG, coronary artery bypass graft surgery, PCI, Percutaneous coronary intervention.

\*Combined endpoint defined as cardiac death, nonfatal myocardial infarction, or NYHA class IV heart failure.

**Risk-Adjusted Cox Proportional Hazards Survival Analysis**

Multivariable risk-adjusted (controlling for sex, diabetes, CAD history, and NYHA class) Cox regression model analysis similarly defined an EDV of 260 mL or greater, ESV of 200 mL or greater, and LV mass of 143 g or greater as independent estimators of major adverse cardiac events (Figure 1). On the basis of this analysis, there was a directly proportional relationship to LV functional parameters and cardiac events such that patients with higher LV volumes or mass had a higher rate of death, myocardial infarction, or NYHA class IV. Specifically, event-free survival rates at 2 years were 52% and 80% for patients with an EDV of 260 mL or greater and those with an EDV lower than 260 mL, respectively (relative risk, 2.7 [95% confidence interval (CI), 1.2-5.8];  $P = .014$ ); 54% and 82% for patients with an ESV of 200 mL or greater and those with an ESV

**Table 4.** Comparison of Mean ECG-gated FDG PET ventricular function measures in patients with and without events

	No events (n = 69)	Events (n = 21)	P value
EF	27% ± 8%	25% ± 7%	.27
EDV	164 ± 70 mL	216 ± 81 mL	.002
ESV	123 ± 60 mL	164 ± 73 mL	.005
Stroke volume	42 ± 17 mL	52 ± 17 mL	.009
LV mass	169 ± 46 g	199 ± 45 g	.004

lower than 200 mL, respectively (relative risk, 2.5 [95% CI, 1.2-5.5];  $P = .021$ ); and 67% and 94% for patients with an LV mass of 143 g or greater and those with an LV mass of less than 143 g, respectively (relative risk, 1.6 [95% CI, 1.5-17.0];  $P = .009$ ).

**Incremental Prognostic Value of LV Functional Parameters**

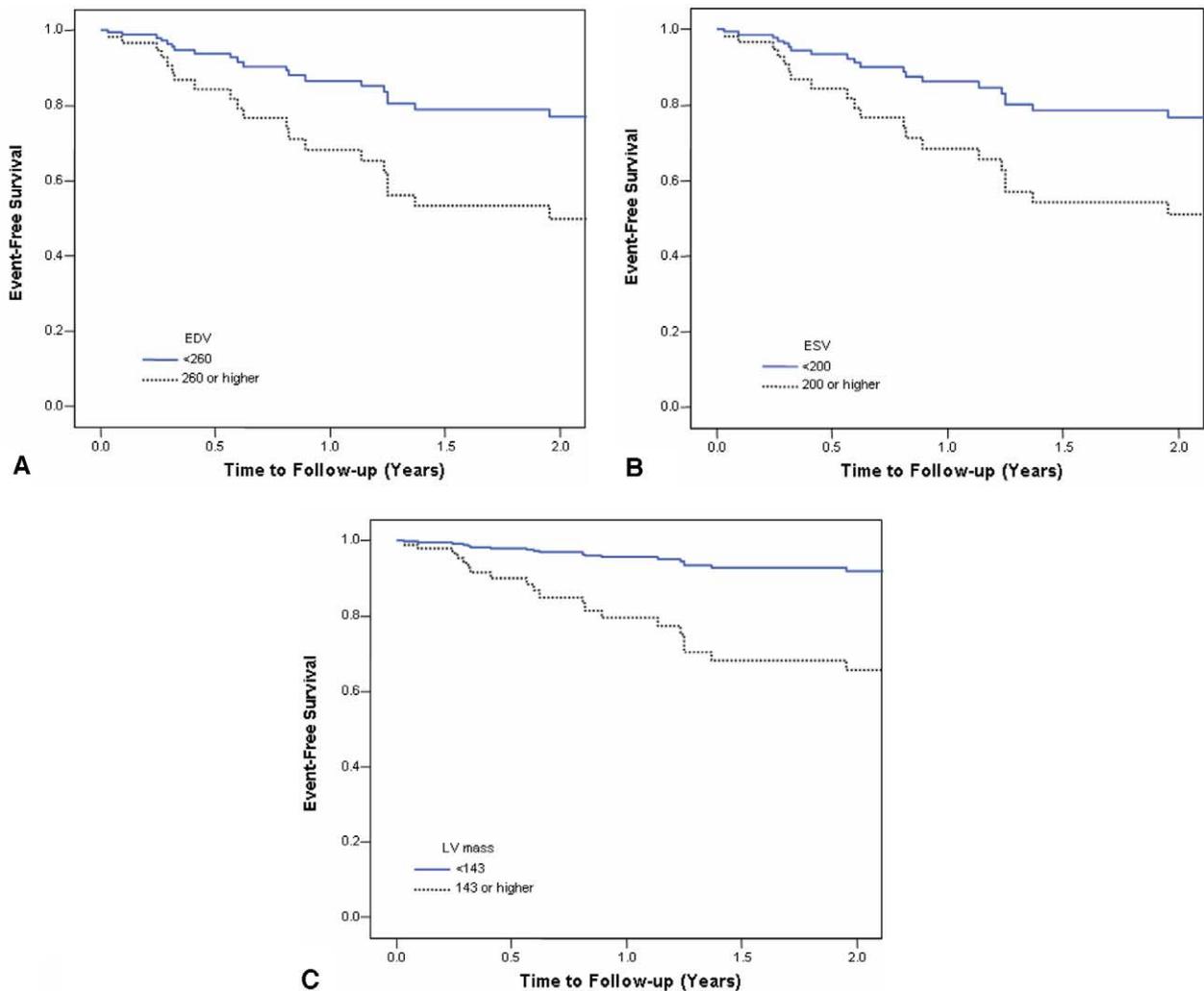
Figure 2 shows the results of the  $\Delta \chi^2$  method to assess the incremental value of measures of LV size and function over and above the PET mismatch pattern. In a risk-adjusted model (clinical history model  $\chi^2 = 22$ ,  $P < .0001$ ), the mismatch pattern was a significant predictor of events ( $\chi^2 = 40$ ,  $P < .001$ ), but as shown in this figure, the addition of EDV to the model added a substantial amount in the estimation of cardiac events ( $\chi^2 = 68$ ,  $P < .0001$ ) whereas ESV added marginally more predictive information above EDV ( $\chi^2 = 75$ ,  $P = .035$ ). In a forward stepwise Cox regression model, EDV was the single greatest estimator of cardiac events ( $P < .0001$ ) when compared with historical data (sex, diabetes, coronary disease history, and NYHA class at baseline) and the PET mismatch data.

**Interaction Between LV Function, LV Size, and Viability Pattern**

We then explored the possible interactions between LVEF, LV size (EDV), and PET mismatch for predicting clinical events. In a stratified Cox model, patients with PET mismatch, LVEF lower than 25%, and EDV of 260 mL or greater had the lowest 2-year event-free survival rate (43%) compared with those with LVEF lower than 25% and EDV lower than 260 mL (84%) and those with LVEF greater than 25% and EDV lower than 260 mL (92%) ( $P = .003$ ). In this exploratory analysis, there was a significant interaction between the presence of a PET mismatch, LVEF lower than 25%, and EDV of 260 mL or greater ( $P = .006$ ).

**Effects of Revascularization on Clinical Outcomes**

During follow-up, 31 patients underwent coronary revascularization. In a nonrandomized analysis, coronary revascularization was associated with improved survival rate (model  $\chi^2 = 18$ ,  $P < .0001$ ; revascularization,  $P = .036$ ). Follow-up coronary revascularization (n = 31) occurred more often in patients with evidence of viability (57% vs 25%,  $P = .043$ ). In this observational comparison, the overall absolute reduction in events with coronary revascularization was 28%. Coronary revascularization resulted in an absolute improvement in event-free survival rate of 22% for patients with an LVEF of 25%



**Figure 1.** A, Risk-adjusted (controlling for sex, diabetes, coronary disease history, and NYHA class at baseline) Cox proportional hazards survival rates free of cardiac death, nonfatal myocardial infarction, or NYHA class IV in patients with EDV of less than 260 mL or 260 mL or greater (A), in patients with ESV of less than 200 mL or 200 mL or greater (B), and in patients with LV mass of less than 143 g or 143 g or greater (C).

or lower and EDV of 260 mL or greater ( $P = .035$ ). By comparison, patients with viability (PET mismatch) but EDV of 260 mL or greater had the highest event-free survival rate (approximately 86%, with an absolute improvement of 11% with revascularization).

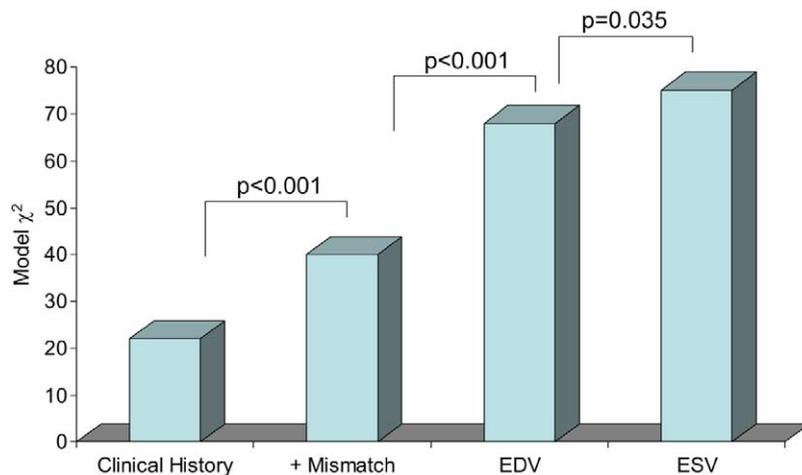
### Change in Quality of Life During Follow-up

Quality-of-life data, defined as NYHA class, were available for all 90 patients. At follow-up, 76%, 4%, 4%, and 11% of patients had NYHA class I, II, III, and IV, respectively. Approximately 60% of patients with NYHA class III or IV at baseline exhibited improvement at 2 years of follow-up ( $P = .001$ ). Figure 3 details the change in NYHA class by PET mismatch and EDV

measures of less than 260 mL and of 260 mL or greater. Worsening quality of life occurred more often in patients with an EDV of 260 mL or greater (17% within the match pattern and 44% within the mismatch pattern,  $P = .03$ ).

### DISCUSSION

This study revealed that, in a population with severely reduced LVEF due to CAD referred for myocardial viability testing, measures of LV remodeling (ie, LV volumes and mass) have incremental prognostic value over the perfusion-metabolism PET mismatch pattern in predicting cardiac events. In a risk-adjusted Cox model, the 2-year event-free survival rate was consistently



**Figure 2.** Incremental value (defined as  $\Delta \chi^2$  statistic) of LV volumes over and above clinical history and PET mismatch data.

higher for patients with relatively preserved LVEF as well as heart size and mass compared with those with severely reduced LVEF and advanced cardiac remodeling. Furthermore, our results also suggest that there is an interaction between the pattern of viability and LV functional parameters—that is, patients with evidence of residual viability (PET mismatch) in a heart with severely reduced LVEF (<25%) and advanced remodeling (EDV >260 mL) showed the poorest survival rate compared with those with relatively preserved LVEF and LV size.

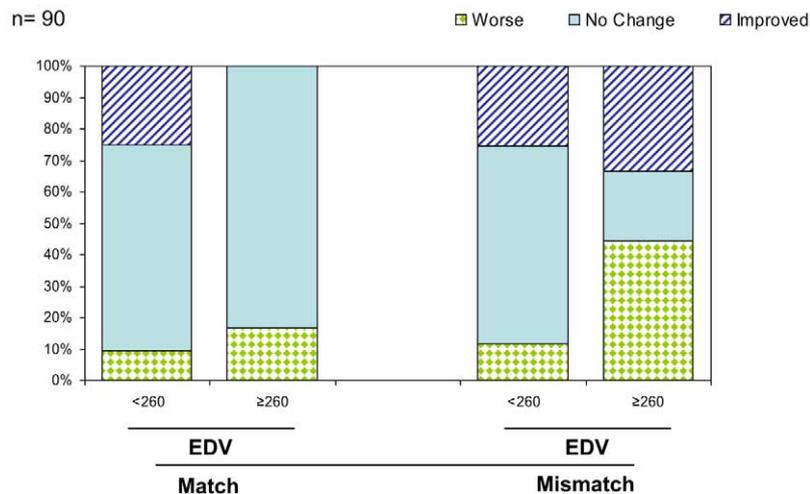
Our data suggest that coronary revascularization in patients with residual viability but advanced cardiac remodeling may result in improvement in survival rates. The event-free survival rate in this latter cohort was 86%, decidedly higher than the rate for those not undergoing coronary revascularization (approximate survival benefit of 11% for revascularization). However, this apparent survival benefit was not associated with a consistent improvement in heart failure symptoms, as nearly 70% of those patients showed either no change or worsening of symptoms during follow-up (Figure 3).

These results of this study extend the observations of previous studies in several important ways. Our results demonstrate the added prognostic value of measures of LV function and degree of remodeling over and above mismatch measures for stratifying risk in patients with impaired cardiac function due to CAD. Thus these data support the notion that physicians should integrate more than evidence of mismatch in their management decisions but also indicate that evidence of LV remodeling is a key factor in risk assessment. In this series of 90 patients, measures of LV function may be suboptimal for risk assessment when all patients have severely depressed systolic function. In addition, our data illustrated

the importance of LV volumes as necessary ingredients in effective risk stratification.

Previous studies have shown that, among patients with severe LV dysfunction, those with evidence of viability by PET (perfusion-metabolism mismatch) have a consistently lower event-free survival rate than those without viability when treated with medical therapy alone.<sup>5,7,12,13</sup> The published data also suggest that this poor survival rate can be improved significantly by early referral to revascularization.<sup>5</sup> These initial findings with FDG PET have been confirmed by subsequent studies using noninvasive imaging with either nuclear testing or echocardiography. Allman et al<sup>11</sup> recently reported a metaanalysis of 24 studies that documented long-term patient outcomes after viability imaging by SPECT, PET, or dobutamine echocardiography in 3088 patients (2228 men and 860 women) with a mean EF of  $32\% \pm 8\%$  and follow-up for  $25 \pm 10$  months. The results demonstrated that in patients with evidence of viable myocardium, a strong association was present between revascularization and improved outcomes, particularly in those with severe LV dysfunction.

Although our findings are consistent with the results of this metaanalysis, our results show that the mismatch pattern is one of an array of predictors of outcome when compared with measures of LV function and remodeling. Indeed, our results demonstrated a directly proportional relationship between LV functional parameters and cardiac events such that patients with higher LV volumes or mass had a higher rate of death, myocardial infarction, or worsening symptoms to NYHA class IV over a 2-year follow-up period. In a risk-adjusted model, measures of LV volumes added a substantial amount in the estimation of cardiac events over that provided by historical variables as well as the PET mismatch. These findings are in



**Figure 3.** Change in NYHA class at 2 years' follow-up for all patients.

keeping with the notion that patients with a low LVEF (<35%) represent a high-risk group with a significantly greater annual mortality rate than those with preserved LV function and that survival rates decline in proportion to the severity of LV dysfunction and the degree of LV remodeling.<sup>19,23,30-34</sup>

### Limitations

Although prior reports in the area of viability testing have limited sample sizes, our series is constrained by the availability of 90 CAD patients with an LVEF lower than 40%.<sup>11</sup> A post hoc sample size calculation revealed that the current sample was sufficiently powered to detect differences between some quantitative measures of LV volumes and function but not in the categoric assessment of mismatch subsets. The inclusion of a greater number of patients could help to elucidate the influence of the possible confounding factors such as risk factors, prior medical conditions, or type of medical treatment. The evaluation of changes in event-free survival rate with revascularization is a nonrandomized comparison and is confounded by selection bias. Another limitation is that the estimation of LV mass by the ECTb program assumes a uniform 1-cm thickness at end diastole not accounting for thinned-out scar tissue. This may explain why LV mass data did not provide incremental prognostic power over EDV and ESV measurements.

### Conclusions

LV functional parameters determined by gated FDG PET have incremental prognostic value over viability information, as assessed by the perfusion-metabolism PET mismatch, in patients with CAD and severe LV

dysfunction. Our data suggest that patients with residual viability and advanced cardiac remodeling have the highest clinical risk. In these patients the apparent survival benefit of revascularization may not be associated with a measurable improvement in heart failure symptoms.

### Acknowledgment

Some of the authors (E.V.G. and T.L.F.) receive royalties from the sale of the Emory Cardiac Toolbox related to the research described in this article. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict-of-interest practice. The other authors have indicated they have no financial conflicts of interest.

### REFERENCES

- Garcia EV, Vansant JP. Assessment of mechanical function as an adjunct to myocardial perfusion/metabolism emission tomography studies. *J Nucl Med* 1994;35:1005-6.
- Marshall RC, Tillisch JH, Phelps ME, et al. Identification and differentiation of resting myocardial ischemia and infarction in man with positron computed tomography 18F-labeled fluorodeoxyglucose and N-13 ammonia. *Circulation* 1981;64:766-78.
- Tillisch J, Brunken R, Marshall R, et al. Reversibility of cardiac wall-motion abnormalities predicted by positron tomography. *N Engl J Med* 1986;314:884-8.
- Udelson JE. Steps forward in the assessment of myocardial viability in left ventricular dysfunction. *Circulation* 1998;97:833-8.
- Di Carli MF, Davidson M, Little R, et al. Value of metabolic imaging with positron emission tomography for evaluating prognosis in patients with coronary artery disease and left ventricular dysfunction. *Am J Cardiol* 1994;73:527-33.
- Di Carli M, Asgarzadie F, Schelbert HR, et al. Quantitative relation between myocardial viability and improvement in heart failure symptoms after revascularization in patients with ischemic cardiomyopathy. *Circulation* 1995;92:3436-44.
- Di Carli MF, Maddahi J, Rokhsar S, et al. Long-term survival of patients with coronary artery disease and left ventricular dysfunction.

- tion: implications for the role of myocardial viability assessment in management decisions. *J Thorac Cardiovasc Surg* 1998;116:997-1004.
8. Di Carli MF. Predicting improved function after myocardial revascularization. *Curr Opin Cardiol* 1998;13:415-24.
  9. Maddahi J, Blitz A, Phelps M, Laks H. The use of positron emission tomography imaging in the management of patients with ischemic cardiomyopathy. *Adv Card Surg* 1996;7:163-88.
  10. Di Carli MF. Assessment of myocardial viability post-myocardial infarction. *J Nucl Cardiol* 2002;9:229-35.
  11. Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. *J Am Coll Cardiol* 2002;39:1151-8.
  12. Eitzman D, Al-Aouar Z, Kanter HL, et al. Clinical outcome of patients with advanced coronary artery disease after viability studies with positron emission tomography. *J Am Coll Cardiol* 1992;20:559-65.
  13. Lee KS, Marwick TH, Cook SA, et al. Prognosis of patients with left ventricular dysfunction, with and without viable myocardium after myocardial infarction: relative efficacy of medical therapy and revascularization. *Circulation* 1994;90:2687-94.
  14. Candell-Riera J, Llevadot J, Santana C, et al. Prognostic assessment of uncomplicated first myocardial infarction by exercise echocardiography and Tc-99m tetrofosmin gated SPECT. *J Nucl Cardiol* 2001;8:122-8.
  15. Shaw LJ, Hachamovitch R, Berman D, et al. The economic consequences of available diagnostic and prognostic strategies for the evaluation of stable angina patients: an observational assessment of the value of precatheterization ischemia. Economics of Noninvasive Diagnosis (END) Multicenter Study Group. *J Am Coll Cardiol* 1999;33:661-9.
  16. Hachamovitch R, Berman D, Shaw LJ, et al. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death. *Circulation* 1998;97:535-43.
  17. Shaw LJ, Peterson ED, Kesler K, et al. A meta-analysis of pre-discharge risk stratification after acute myocardial infarction with stress electrocardiographic, myocardial perfusion, and ventricular function imaging. *Am J Cardiol* 1996;78:1327-37.
  18. Iskandrian AS, Chae SC, Heo J, et al. Independent and incremental prognostic value of exercise single-photon emission computed tomographic thallium imaging in coronary artery disease. *J Am Coll Cardiol* 1993;22:665-70.
  19. Shaw LJ, Heinle SK, Borges-Neto S, et al. Prognosis by measurements of left ventricular function during exercise. Duke Noninvasive Research Working Group. *J Nucl Med* 1998;39:140-6.
  20. Marie PY, Danchin N, Durand JF, et al. Long-term prediction of major ischemic events by exercise thallium-201 single-photon emission computed tomography: incremental prognostic value compared with clinical exercise testing, catheterization, and radionuclide angiographic data. *J Am Coll Cardiol* 1995;26:879-86.
  21. White HD, Norris RM, Brown MA, et al. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation* 1987;76:44-51.
  22. Hamer AW, Takayama M, Abraham KA, et al. End-systolic volume and long-term survival after coronary artery bypass graft surgery in patients with impaired left ventricular function. *Circulation* 1994;90:2899-904.
  23. Sharir T, Germano G, Kavanagh PB, et al. Incremental prognostic value of post-stress left ventricular ejection fraction and volume by gated myocardial perfusion single photon emission computed tomography. *Circulation* 1999;100:1035-42.
  24. Bom HS, Vansant JP, Pettigrew RI, et al. Determination of myocardial viability with ECG-gated fluorodeoxyglucose F-18 positron emission tomography. *Clin Positron Imaging* 1999;2:183-90.
  25. Votaw JR, White M. Comparison of 2-dimensional and 3-dimensional cardiac 82Rb PET studies. *J Nucl Med* 2001;42:701-6.
  26. Faber TL, Cooke CD, Peifer JW, et al. Three-dimensional displays of left ventricular epicardial surface from standard cardiac SPECT perfusion quantification techniques. *J Nucl Med* 1995;36:697-703.
  27. Cooke CD, Folks RD, Oshinski JN, et al. Determination of ejection fraction and myocardial volumes from gated FDG PET studies: a preliminary validation with gated MR [abstract]. *J Nucl Med* 1997;38:55P.
  28. Nichols K, Lefkowitz D, Faber T, et al. Echocardiographic validation of gated SPECT ventricular function measurements. *J Nucl Med* 2000;41:1308-14.
  29. Santana CA, Soler M, Cooke CD, et al. Determination of left ventricular ejection fraction from ECG-gated FDG PET studies: validation with contrast ventriculography [abstract]. *J Nucl Med* 2000;41:163P.
  30. Bonow RO. Myocardial viability and prognosis in patients with ischemic left ventricular dysfunction. *J Am Coll Cardiol* 2002;39:1159-62.
  31. Muhlbaier LH, Pryor DB, Rankin JS, et al. Observational comparison of event-free survival with medical and surgical therapy in patients with coronary artery disease: 20 years of follow-up. *Circulation* 1992;86:II198-204.
  32. Emond M, Mock MB, Davis KB, et al. Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. *Circulation* 1994;90:2645-57.
  33. Louie HW, Laks H, Milgater E, et al. Ischemic cardiomyopathy. Criteria for coronary revascularization and cardiac transplantation. *Circulation* 1991;84:II290-5.
  34. Yamaguchi A, Ino T, Adachi H, et al. Left ventricular volume predicts postoperative course in patients with ischemic cardiomyopathy. *Ann Thorac Surg* 1998;65:434-8.

#### AVAILABILITY OF BACK ISSUES

As a service to our subscribers, copies of back issues of the *Journal of Nuclear Cardiology* for the preceding 5 years are maintained and are available for purchase from Elsevier Inc. until inventory is depleted. Please write to Elsevier Inc., Subscription Customer Service, 6277 Sea Harbor Dr, Orlando, FL 32887, or call 800-654-2452 or 407-345-4000, for information on availability of particular issues and prices.