Myocardial Viability Testing and the Effect of Early Intervention in Patients With Advanced Left Ventricular Systolic Dysfunction

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Background—The clinical value of revascularization and other procedures in patients with severe systolic heart failure is unclear. It has been suggested that assessing ischemia and viability by positron emission tomography (PET) with fluorodeoxyglucose (FDG) imaging may identify patients for whom revascularization may lead to improved survival. We performed a propensity analysis to determine whether there might be a survival advantage from revascularization.

Methods and Results—We analyzed the survival of 765 consecutive patients (age 64±11 years, 80% men) with advanced left ventricular systolic dysfunction (ejection fraction ≤35%) and without significant valvular heart disease who underwent PET/FDG study at the Cleveland Clinic between 1997 and 2002. Early intervention was defined as any cardiac intervention (surgical or percutaneous) within the first 6 months of the PET/FDG study. In the entire cohort, 230 patients (30%) underwent early intervention (188 [25%) had open heart surgery, most commonly coronary artery bypass grafting, and 42 [5%] had percutaneous revascularization); 535 (70%) were treated medically. Using 39 demographic, clinical and PET/FDG variables, we were able to propensity-match 153 of the 230 patients with 153 patients who did not undergo early intervention. Among the propensity-matched group, there were 84 deaths during a median of 3 years follow-up. Early intervention was associated with a markedly lower risk of death (3-year mortality rate of 15% versus 35%, propensity adjusted hazard ratio 0.52, 95% CI 0.33 to 0.81, P=0.0004).

Conclusions—Among systolic heart failure patients referred for PET/FDG, early intervention may be associated with improved survival irrespective of the degree of viability. (Circulation. 2006;113:230-237.)

Key Words: heart failure ■ revascularization ■ ischemia ■ nuclear medicine ■ mortality
had been obtained for clinical purposes; the requirement for written informed consent was waived.

The methods by which clinical data are obtained prospectively and electronically in our laboratory have been described in detail. Before stress testing (whether exercise or, as in this case, pharmacological), all patients undergo a structured interview and chart review. Data are prospectively collected regarding symptoms, risk factors, diagnoses, medicines taken, and prior cardiac procedures. Glomerular filtration rate was calculated with the modification of diet in renal disease equation. Data regarding surgical procedures were obtained from the Cleveland Clinic Foundation Cardiovascular Information Registry (CVIR). Established quality control mechanisms are in place for both stress laboratory and CVIR electronic data; these include random reviews of raw data and periodic quality control meetings of key personnel.

PET/FDG Technique
PET was performed on a Posicam positron emission tomograph by previously reported techniques. After an overnight fast, an intravenous catheter was placed, and its patency was maintained with normal saline. Monitoring of the patient’s blood pressure and cardiac rhythm was performed throughout the procedure.

To ascertain correct patient position, 20 mCi of rubidium-82 was infused intravenously, and a 3-minute PET scan was performed starting 65 seconds later to determine location of the heart. After correct patient positioning, a set of transmission images was obtained over 15 to 25 minutes (to achieve 60 to 70 million counts). Subsequently, PET images of rest myocardial perfusion were obtained beginning 65 seconds after intravenous infusion of 60 mCi of rubidium-82. For pharmacological stress, dipyridamole 0.57 mg/kg IV was infused continuously over 4 minutes. Four minutes later, 60 mCi of rubidium-82 was infused intravenously for stress perfusion imaging.

Metabolic imaging with FDG was performed in the glucose-loaded state after perfusion imaging. An oral glucose load (50 g of dextrose-containing solution) was given 1 hour before IV administration of 5 to 8 mCi of FDG. In diabetics, blood glucose level was measured and adjusted to 55 to 100 mg/dL with 2 to 8 U IV of regular insulin according to a sliding scale. The patient was then repositioned on the scanner with skin markers placed at the time of the perfusion study. Metabolic imaging was performed for 20 minutes, starting a minimum of 45 minutes after FDG injection.

After correction for attenuation and reconstruction, the perfusion and metabolic images were examined with 5% and 10% color scales on a computer monitor. Each of 24 myocardial segments was considered normal, ischemic, hibernating, or scar according to previously published criteria. In brief, myocardial ischemia was considered present if relative perfusion worsened by 15% or more from rest to stress. Hibernation was deemed present if relative FDG activity exceeded rest perfusion by 15% or greater. Myocardial scar were identified by matching perfusion and metabolic defects, with each defect exhibiting a relative tracer concentration <70% of maximal myocardial activity.

In our analysis, we considered the percent of left ventricular myocardium showing viability but with compromised perfusion (or “total ischemia”) as the sum of percent left ventricular ischemia and percent left ventricular hibernation.

Early Intervention and Definition of Time Zero
Early intervention was defined as any cardiac (surgical or percutaneous) procedure performed within the first 6 months of the PET/FDG study date. If no intervention was performed by then, patients were considered to be only medically treated. These patients are henceforth referred to as the “medically treated” group.

Because this was a high-risk group of patients, some patients possibly died while awaiting a planned intervention. This could erroneously attribute mortality to medical management when the true intention-to-treat was otherwise. To minimize this error, we calculated median time between the PET/FDG test and intervention among patients who had an early intervention (median time 8 days). For patients who underwent early intervention, we defined time zero as the time of the intervention. For patients who were managed medically, we defined time zero as PET/FDG date plus 8 days.

Patients who died within the first 8 days of the PET/FDG test were excluded from the analysis (n=8). Investigators comparing surgical and medical treatment of patients with angina and coronary artery disease previously used this technique.

End Point
The primary end point was death due to all causes, which is objective, clinically relevant, and unbiased, which is not the case with cardiac-specific causes of death, as we and others have discussed elsewhere. This end point was determined with the Social Security Death Index, The high degree of specificity of the Social Security Death Index has been documented. A previous investigation from our stress laboratory yielded a sensitivity of 97%; this can be considered the proportion of successful follow-up. We chose to use the Social Security Death Index instead of the National Death Index to allow for longer follow-up. The censoring date was February 1, 2003. Median follow-up among survivors was 3 years (range 0.8 to 6.1 years).

Statistical Analysis
The cohort was divided into 2 groups: (1) Patients who had early intervention (surgical or percutaneous; early intervention group), and (2) those who did not (medically treated group). Differences between the groups were tested by χ2 tests and Wilcoxon rank-sum tests as appropriate. The association of early intervention with time to death was tested by the construction of Kaplan-Meier curves and by Cox proportional hazards modeling, with confirmation by nonproportional hazards analysis by a multiphase wholly parametric method. We tested for nonproportional hazards by means of Schoenfeld residuals. Assumptions of linearity were relaxed by means of restricted cubic splines. Good model calibration was confirmed by comparing observed versus predicted survival curves among multiple bootstrap-generated strata of risk.

Although multivariable regression modeling is often used to account for baseline differences, it may lead to invalid conclusions when those differences are marked or numerous. Therefore, we constructed a nonparsimonious logistic-regression model in which early intervention was the dependent variable and variables listed in Table 1 were independent ones. With this model, a propensity score quantifying the likelihood of early intervention was calculated for all patients. Early intervention patients and medically treated patients were then matched on the basis of their propensity score. Specifically, we used a greedy matching technique in which we first attempted to match to 5 decimal points of propensity score (ie, to the nearest 0.00001) and gave up on matching if we were unable to match by at least 1 decimal point. We have used the propensity analysis techniques to accommodate for selection biases in previous investigations of smoking, coronary revascularization in multivessel coronary artery disease, and ventricular ectopy associated with stress testing.

This effectively created a cohort of patients in which half had early intervention and half had medical treatment; characteristics of these 2 groups were nearly identical (Table 2). In part because some patients who had early interventions were very different from those who did not, we could only match a subset of early intervention patients. Although this may seem problematic, it actually helps solve the problem of reaching erroneous conclusions about the impact of treatment by comparisons of unlike groups, the “apples and oranges” problem.

In supplementary analyses, we examined the association of early intervention with mortality in the entire cohort. We performed 2 sets of Cox analyses. In the first, we adjusted for the propensity score and other covariates. In the second, we adjusted for the covariates listed in Table 1 without including the propensity score in the model. All analyses were performed with SAS (version 9.1; SAS, Inc) and S-plus (version 6.2; Insightful, Inc). Greedy propensity matching was performed with an SAS macro written by Lori Parsons (available and accessed on September 8, 2004, at http://www2.sas.com/proceedings/sugi26/p214–26.pdf). Cox regression modeling was...
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<th>Variable</th>
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<td>63±11</td>
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ACE indicates angiotensin-converting enzyme. Other abbreviations as in text.
*Plus-minus values are mean±SD.
†P values are for the comparison among all groups.
‡Glomerular filtration rate using the abbreviated modification of Diet in Renal Disease (MDRD) study equation (in mL · min⁻¹ · 1.73 m⁻²) = 186 × (serum creatinine in mg/dL)⁻¹.154 × (age in years)⁻¹.203 × 0.742 in female subjects, ×1.210 in black subjects.
§Values for ischemia and hibernation do not appear to add up because of highly skewed distributions of these variables.
<table>
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<td>Scar</td>
<td>30 (17, 46)</td>
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<td>Hibernation</td>
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<td>18 (4, 29)</td>
<td>17 (4, 31)</td>
<td>0.83</td>
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*Plus-minus values are mean±SD.
†Glomerular filtration rate using the abbreviated modification of Diet in Renal Disease (MDRD) study equation (in mL·min⁻¹·1.73 m⁻²)=186×(serum creatinine in mg/dL)⁻¹.154×(age in years)⁻0.203×0.742 in female subjects, ×1.210 in black subjects.
‡Values for ischemia and hibernation do not appear to add up because of highly skewed distributions of these variables.
performed with the use of the Design and Hmisc libraries of Harrell.42

Results

Baseline Characteristics

There were 765 patients eligible for analyses (age 64±11 years, 80% men). There were 230 patients (30%) who underwent early intervention (188 [25%] had open heart surgery and 42 [5%] had percutaneous revascularization), whereas 535 (70%) were treated medically. Among the 188 patients who underwent surgery, 175 (93%) had coronary artery bypass grafting (CABG) with or without valvular surgery (33 patients had combined CABG and valve surgery, and 142 had isolated CABG without valve surgery), 3 patients had isolated valve surgery, 2 patients had the Batista procedure, 2 patients had the Dor procedure, and 6 patients had heart transplantation.

The clinical and PET/FDG-related characteristics of all patients are summarized in Table 1. Compared with the patients who underwent early intervention, patients who were treated medically had more insulin-treated diabetes mellitus, chronic obstructive pulmonary disease, and atrial fibrillation or flutter and worse renal function. Angiotensin-converting enzyme inhibitors, loop diuretics, and nitrates were more commonly used in patients treated medically. There were no marked differences in age, gender, race, ejection fraction, or the use of aspirin, β-blockers, calcium channel blockers, digoxin, and statins. Regarding PET/FDG findings, patients who were treated medically had more scar but less combined ischemia and hibernation.

Mortality

During a median follow-up of 3 years, there were 230 deaths of all causes. Among patients treated medically, there were 184 deaths (34%), and among early intervention patients, there were 46 deaths (20%).

Propensity Matching

Propensity matching was performed to match patients who underwent early intervention to those who were treated medically. The C statistic of the logistic-regression model used to generate the propensity score was 0.82, which indicates good discrimination between those undergoing and not undergoing early intervention. The baseline characteristics of the propensity-matched cohort are shown in Table 2. The 2 groups were well matched.

In this propensity-matched cohort (153 patients in each group), there were 84 deaths. Among the 153 patients in the propensity-matched group who underwent early intervention, there were 123 (80%) who had open-heart surgery and 30 (20%) who had percutaneous revascularization. Among the 123 patients who underwent surgery, 113 (92%) had CABG with or without valvular surgery (23 patients had combined CABG and valve surgery, and 90 had CABG without valve surgery), 2 patients had isolated valve surgery, 2 patients had the Dor procedure, and 6 patients underwent heart transplantation. As shown in Figure 1, early intervention was associated with a marked reduction in mortality. After being matched on propensity score and adjusted for total combined ischemia and hibernation, scar, and ejection fraction, early intervention was predictive of improved survival (adjusted hazard ratio 0.52, 95% CI 0.33 to 0.81, \( P=0.004 \)). The amount of total combined ischemia and hibernation tended to predict mortality (\( P=0.06 \)). Of note, early intervention was associated with lower risk of death across the range of ischemia and hibernation (Figure 2).

We also performed a supplementary analysis that involved all 765 patients. Again, after adjustment for propensity score, total combined ischemia and hibernation, scar, and ejection fraction, early intervention was associated with a lower risk of death (adjusted hazard ratio 0.49, 95% CI 0.33 to 0.72, \( P=0.0003 \)). Among all patients, the amount of total combined ischemia and hibernation was predictive of death (adjusted hazard ratio 2.87 for increase from 0% to 25%, 95% CI 1.87 to 4.40, \( P<0.0001 \)). As with the model that involved propensity-matched patients, we found that mortality was lower with early intervention across the range of ischemia and hibernation (Figure 3).

In supplementary analyses that included all 765 patients, early intervention was predictive of reduced mortality by

Figure 1. Propensity-matched patients. Mortality curves of patients treated medically (no intervention) and patients undergoing early intervention.

Figure 2. Association between predicted 3-year mortality and the amount of compromised viable myocardium (ischemic and hibernating) determined by PET/FDG study according to performance of early intervention among propensity-matched patients. Curves were derived from multivariable Cox regression models with all continuous variables set to medians and categorical variables set to mode.
segments that demonstrate perfusion metabolism mismatch.\textsuperscript{46} The intention of revascularizing patients who demonstrate significant left ventricular dysfunction who may benefit from revascularization have focused mainly on markers of viability, with the clinical relevance of revascularizing patients who had severe heart failure due to markedly depressed left ventricular systolic function.

Despite the improved medical therapies for patients with heart failure, morbidity and mortality remain high.\textsuperscript{44} In the Coronary Artery Surgery Study (CASS), revascularization decreased mortality in middle-aged patients with reduced left ventricular function compared with medical therapy\textsuperscript{45}; however, there were few patients who had severe heart failure due to markedly depressed left ventricular systolic function.

Figure 3. Association between predicted 3-year mortality and the amount of compromised viable myocardium (ischemic and hibernating) determined by PET/FDG study according to performance of early intervention among all patients. Curves were derived from multivariable Cox regression models with all continuous variables set to medians and categorical variables set to mode.

Attempts to identify the subset of patients with left ventricular dysfunction who may benefit from revascularization have focused mainly on markers of viability, with the clinical relevance of revascularizing patients who demonstrate significant viability. PET/FDG identifies this viable tissue in segments that demonstrate perfusion metabolism mismatch.\textsuperscript{46} Revascularization of segments that show a mismatch pattern predicts recovery of regional and possibly global ventricular dysfunction.\textsuperscript{47,48} Prognostic implications of viability studies and whether revascularization improves survival among these patients remain unsettled issues. A number of retrospective studies have addressed the prognostic importance of viability testing and the outcome of revascularization\textsuperscript{7–17}; however, these studies were limited by small numbers of patients enrolled, different viability methodologies used, different end points, and soft end points. This has led to different and sometimes contradicting results.\textsuperscript{7–17}

To the best of our knowledge, the present study represents one of the largest cohorts of patients with advanced heart failure undergoing PET/FDG that has been systematically studied. We found that early cardiac intervention (surgical or percutaneous) within the first 6 months of the PET/FDG study was associated with markedly improved survival during a median of 3 years’ follow-up. There was no apparent interaction between survival benefit associated with early cardiac intervention and the amount of viable tissue (ischemic and hibernating tissue) identified by PET/FDG.

In designing the present study, we were concerned about including all types of mechanical intervention, as opposed to just revascularization. However, had we focused on comparing revascularization versus medical therapy, we would have had to exclude subjects undergoing other types of mechanical treatments. This would have created a serious selection bias that, by removing nonrevascularization patients thought to be too ill or too healthy to undergo some other type of procedure, would have made medical therapy appear more or less hazardous than it might actually be. By instead analyzing all types of mechanical intervention versus only medical therapy, we were able to study the entire consecutive cohort of heart failure patients referred for PET/FDG imaging and thereby minimize selection biases.

The mechanisms by which early mechanical interventions improve outcome are not clear and require further study. Possibilities include less ischemia, improved myocardial function, regression of hypertrophy, and stabilization of arrhythmic substrate. It is noteworthy that survival differences were not noted until 5 to 6 months of follow-up (Figure 1). This might be because of an excessive early mortality associated with periprocedural complications among those who underwent mechanical interventions.

There are a number of important limitations to consider. Although all patients had an ejection fraction ≤35%, the symptoms of heart failure associated with this systolic dysfunction may be highly variable. We did not have data on functional status such as New York Heart Association classification or on presence or absence of mild dementia. The medical therapy over the period between 1997 and 2002 was not standardized and could be highly variable between different physicians and referral centers. Many patients in the early intervention group received medical therapy, which also was not standardized. The survival benefit of early intervention may actually be an evidence of worsened survival with uncontrolled and variable medical therapy, more advanced comorbidities, or medication side effects. Although we used propensity scoring and propensity matching to reduce bias and confounding related to multiple baseline differences, propensity methods can only account for variables that are measured. Despite propensity matching, it is possible that patients who were not referred for early intervention were inherently sicker in ways that we could not measure. Only a large-scale, properly performed randomized trial can account for both measured and unmeasured confounders. Although we cannot know for sure why certain patients underwent intervention and others did not, it is noteworthy that the most important of measured predictors associated with treatment were those obtained from PET/FDG imaging (Table 1).

There were few patients (n = 34) who had early intervention without any viability on PET/FDG imaging, which makes it difficult to comment on the value of intervention in the absence of documented viability. Furthermore, perhaps because the degree of viability was such a strong predictor for referral for intervention, our ability in assessing the interac-
tion between PET viability and early intervention is therefore further limited. Performing a trial to show that intervention is substantially more effective with extensive ischemia or viability would require a very high sample size, because interaction terms require larger samples than standard comparative investigations. For example, if one were to postulate event rates of 10% and 30% with and without intervention among patients without viability (meaning an absolute risk reduction of 20%) and corresponding event rates of 20% and 50% among patients with viability (meaning an absolute risk reduction of 30%), the ratio of risk ratios is only 1.2. Were one to assume that 25% of patients have substantial ischemia, such a trial would require approximately 10,000 patients.

We considered all interventions (surgical revascularization, percutaneous revascularization, and other operations) as one for reasons just explained; because of small numbers, we could not analyze each procedure separately. We did not systematically measure viability by other means, including dobutamine echocardiography and MRI. The patients included were highly selected, coming from a tertiary care center with a special interest in heart failure and heart failure surgery.

Large, prospective, randomized controlled clinical trials are needed to better understand the role of revascularization and other mechanical interventions among patients with systolic heart failure and the significance of viability testing in guiding the decision-making process. Some trials are already ongoing, but it will be years before the results of these studies will become available. In the interim, our findings are consistent with the hypothesis that among patients with evidence of myocardial viability, early mechanical intervention may improve survival.

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Disclosures
None.

References
CLINICAL PERSPECTIVE

Established therapies for patients with severe systolic heart failure, irrespective of cause, include β-blockers and angiotensin-converting enzyme inhibitors. An area of great uncertainty, however, is whether to consider revascularization for those who also have substantial coronary artery disease. One approach that has intuitive appeal is to target revascularization to those patients who appear to have a large burden of ischemia and/or myocardial viability by noninvasive testing, such as by PET imaging. However, this has never been formally tested in a large-scale, randomized trial. The current investigation used a sophisticated statistical method called propensity matching to identify 2 groups of patients who look very much alike except for the fact that 1 group received mechanical interventions for severe systolic heart failure, whereas the other did not. The fact that a substantial improvement in survival was seen suggests that a strategy of aggressive intervention may well be appropriate. What was a bit surprising is that this strategy appeared to be operative across the entire range of ischemic burden as assessed by PET scanning. This suggests that revascularization in the setting of left ventricular dysfunction confers its benefit by means other than relieving ischemia; perhaps it “works” by stabilizing the arrhythmic substrate. For now, clinicians should probably seriously consider mechanical revascularization for patients who have angina, some degree of ischemic burden, and an inadequate response to standard medical therapy. Whether or not mechanical intervention should be recommended on a more routine basis will require performance of a large-scale, prospective, randomized trial.
Myocardial Viability Testing and the Effect of Early Intervention in Patients With Advanced Left Ventricular Systolic Dysfunction
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