Extensive Left Ventricular Remodeling Does Not Allow Viable Myocardium to Improve in Left Ventricular Ejection Fraction After Revascularization and Is Associated With Worse Long-Term Prognosis

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Background—Extensive left ventricular (LV) remodeling may not allow functional recovery after revascularization, despite the presence of viable myocardium.

Methods and Results—Seventy-nine consecutive patients with ischemic cardiomyopathy (left ventricle ejection fraction [LVEF] 29±7%) underwent surgical revascularization. Before revascularization, viability was assessed by metabolic imaging with F18-fluorodeoxyglucose and SPECT. LV volumes and LVEF were assessed by resting echocardiography. LVEF was re-assessed by echocardiography 8 to 12 months after revascularization. Three-year clinical follow-up (events: cardiac death, infarction, and hospitalization for heart failure) was also obtained. Forty-nine patients had substantial viability; 5 died before re-assessment of LVEF. Of the remaining 44 patients, 24 improved ≥5% in LVEF after revascularization, whereas 20 did not improve in LVEF. LV end-systolic volume was the only parameter that was significantly different between the groups (109±46 mL for the improvers versus 141±31 mL for the nonimprovers; P<0.05). The change in LVEF after revascularization was linearly related to the baseline LV end-systolic volume, with a higher LV end-systolic volume associated with a low likelihood of improvement in LVEF after revascularization. During the 3-year follow-up, the highest event-rate (67%) was observed in patients without viable myocardium with a large LV size, whereas the lowest event rate (5%) was observed in patients with viable myocardium and a small LV size. Intermediate event rates were observed in patients with viable myocardium and a large LV size (38%), and in patients without viable myocardium and a small LV size (24%).

Conclusion—Extensive LV remodeling prohibits improvement in LVEF after revascularization and affects long-term prognosis negatively, despite the presence of viability. (Circulation. 2004;110[suppl II]:II-18–II-22.)

Key Words: myocardial viability ■ hibernating myocardium ■ heart failure ■ left ventricle remodeling ■ surgical revascularization

Patients with chronic ischemic left ventricular (LV) dysfunction and substantial viability (extending to ≥25% of the LV) are likely to improve in function after revascularization.1–3 Still, a subset of patients with substantial viability does not improve in function after revascularization. Meta-analysis of 20 studies with 598 patients focusing on assessment of viability with metabolic imaging (with F18-fluorodeoxyglucose [FDG]) before revascularization demonstrated that the specificity of viability testing was lower than the sensitivity (93% versus 58%). A lower specificity is partially related to the fact that patients with viable myocardium do not improve in function after revascularization. It has been suggested that a severely dilated LV (extensive remodeling) may not allow functional recovery after revascularization.5,6 Currently, not much information is available on this issue. In particular, the relation between LV size and viability, in some cases, and improvement of function after revascularization, in other cases, is not known. Moreover, the prognostic value of viability in combination with LV size is unknown.

Accordingly, we have studied 79 consecutive patients who were referred for surgical revascularization; in these patients, LV dimensions, LV ejection fraction, and viability were assessed preoperatively and outcome (improvement in LV ejection fraction, long-term prognosis) were assessed.

Methods

Patients and Study Protocol

The study population consisted of 79 patients with ischemic cardiomyopathy who were already scheduled for surgical revasculariza-
tion. The patients presented with heart failure and 34% had accompanying angina pectoris. The decision for revascularization was based on clinical grounds (symptoms, presence of ischemia, and angiographic findings). None of the patients experienced acute infarction or decompensated heart failure in the period between imaging and surgery. All patients were stable during the study. Patients with severe (grade 3 to 4+) mitral regurgitation were excluded. The study protocol was as follows. Within 1 week before surgery, resting perfusion was assessed by technetium-99m tetrofosmin SPECT, glucose use was assessed by FDG SPECT, and regional contractile (dy)function was assessed by 2-dimensional echocardiography. In addition, the LV ejection fraction and LV volumes (end-systolic, end-diastolic) were assessed from 2-dimensional echocardiography. Eight to 12 months after surgery, 2-dimensional echocardiography was repeated to assess LV ejection fraction. Follow-up was performed up to 3 years after revascularization. Each patient gave informed consent to the study protocol that was approved by the local Ethics Committee.

2-Dimensional Echocardiography
All echocardiograms were acquired with a HP Sonos-5500 imaging system with a 1.8-MHz transducer using secondary harmonic imaging to optimize endocardial border visualization. Four standard views (apical 2-chamber and 4-chamber views, parasternal short-axis and long-axis views) were digitized on optical disks and also stored on videotape. Two experienced reviewers scored the regional contractile function. The left ventricle was divided according to the standard 16-segment model suggested by the American Society of Echocardiography.7 Regional wall motion and systolic wall thickening were scored using a 5-point grading scale: 1, normal; 2, mild hypokinetic; 3, severe hypokinetic; 4, akinetic; and 5, dyskinetic. Segments with severe hypokinesia, akinesia, or dyskinesia were considered dysfunctional and evaluated for myocardial viability.

The LV volumes (end-systolic, end-diastolic) and LV ejection fraction were calculated from the conventional apical 2-chamber and 4-chamber images using the biplane Simpson technique. The first echocardiogram was performed within 1 week before surgery and the follow-up echocardiogram was performed 8 to 12 months after revascularization. An improvement LV ejection fraction ≤5% after revascularization was considered clinically significant, as described previously.8

Assessment of Viability by SPECT
Patients received, after a light breakfast, an intravenous injection of technetium-99m tetrofosmin (600 MBq) to evaluate resting perfusion. FDG imaging, to evaluate myocardial glucose use, was performed after Acipimox administration (500 mg, oral dose) in all patients. Acipimox (a nicotinic acid derivative) enhances myocardial FDG uptake by reducing the plasma level of free fatty acids.9,10 In addition, a light meal was provided to stimulate endogenous insulin release to further enhance cardiac FDG uptake.10 Sixty minutes after the meal, FDG (185 MBq) was injected, and after an additional 45 minutes to allow cardiac FDG uptake,10 dual-isotope simultaneous acquisition SPECT was performed. A triple-head gamma camera system (Picker Prism 3000XP) was used, equipped with commercially available high-energy 511-keV collimators. The energies were centered on the 140-keV photon peak of technetium-99m tetrofosmin with a 15% window (on each side of the peak) and on the 511-keV photon peak of FDG with a 15% window. Data acquisition was performed over 360° (120 sectors of 3°), with a total imaging time of 32 minutes. Data were stored in a 64×64, 16-bit matrix.

Data Reconstruction and Analysis
From the raw scintigraphic data, 6-mm-thick (1-pixel) transaxial slices were reconstructed by filtered back-projection using a Butterworth filter (cutoff frequency at 0.17 cycle/pixel of order 3.5). No attenuation correction was used. Further reconstruction yielded standard short-axis and long-axis projections perpendicular to the heart axis. The technetium-99m tetrofosmin and FDG data were reconstructed simultaneously to obtain exact alignment of the perfusion and metabolic images.10 The perfusion and FDG short-axis slices were displayed in polar maps, which were normalized to maximum activity (set at 100%); the polar maps were divided into 16 segments matching the echocardiographic segments. Segments with normal tracer uptake (activity >75%), and segments with a perfusion defect (activity ≤75%) with a relatively increased FDG uptake (>10% as compared with perfusion activity, perfusion–metabolism mismatch) were considered viable. Segments with concordantly reduced perfusion and FDG uptake (perfusion–metabolism match) were considered nonviable. A patient was considered to have substantial viability in the presence of 4 or more dysfunctional but viable segments (≥25% of the LV).8

Assessment of Functional Status and Long-Term Follow-Up
Functional status was assessed before revascularization according to the New York Heart Association (NYHA) criteria (for symptoms of heart failure) and the Canadian Cardiovascular Society (CCS) classification (for angina pectoris). The long-term follow-up was performed by chart review and telephone contact. Follow-up data (events) were acquired up to 3 years. Events included cardiac death, myocardial infarction, and hospitalization for heart failure.

Statistical Analysis
Continuous data were expressed as mean±SD and compared using the Student t test for paired and unpaired data when appropriate. Comparison of proportions was performed using χ² analysis. Differences in cardiac event rates (cardiac death, myocardial infarction, and hospitalization for heart failure) over time were analyzed by the method of Kaplan–Meier and log-rank test. For all tests, P<0.05 was considered significant.

Results
Baseline Characteristics
A total of 79 patients were prospectively studied, including 72 men with a mean age of 70±8 years. Seventy-four (94%) patients had a previous infarction ≥3 months before inclusion in the study. The average time of infarction to the study was 2.4±3.7 years.

Seventeen (22%) patients had hypertension, 14 (18%) had diabetes, 9 (11%) had severe pulmonary disease, 9 (11%) had impaired renal function, and 12 (15%) had peripheral vascular disease. Nine (11%) patients had a history of a previous CABG. They had, on average, 2.4±0.8 stenosed coronary arteries. Complete revascularization of all stenosed lesions was obtained.

The mean LV ejection fraction was 29±7% (range 10% to 35%). The mean NYHA class score was 3.2±0.8 and the CCS score was 2.8±0.6.

Viability, LV Size, and Improvement in LV Ejection Fraction
Based on the SPECT findings, the patients were divided into viable (n=49) and nonviable (n=30) patients. There were no differences between the viable and the nonviable patients, except for the number of viable segments (by definition): 6.9±2.8 versus 2.2±1.7 dysfunctional but viable segments. In the viable patients, 5 patients died before reassessment of LV ejection fraction had occurred (3 heart failure deaths, 1 fatal infarction, and 1 sudden cardiac death). In the nonviable patients, 3 patients died before reassessment of LV ejection fraction (2 heart failure deaths, 1 multi-organ failure 3 days after surgery).
In the remaining 44 viable patients, the LV ejection fraction improved modestly from 27 ± 5% to 32 ± 5% (P<0.05), whereas the LV ejection fraction remained unchanged in the remaining 27 nonviable patients (28 ± 9% versus 27 ± 11%; NS). On an individual basis, only 11% of the nonviable patients demonstrated an improvement ≥5% in LV ejection fraction, as compared with 55% of the viable patients (P<0.05).

When the viable patients were divided according to the presence or absence of improvement in LV ejection fraction after revascularization, no significant differences were noted, except that the viable patients without improvement in LV ejection had a higher LV end-systolic volume, a larger end-diastolic LV diameter, and a trend toward a higher LV end-diastolic volume; resting LVEF in particular was not different (Table). In the improvers, the mean improvement in LVEF was 10 ± 4%.

Mild mitral regurgitation was present in 2 (10%) patients without improvement in LVEF as compared with 3 (12.5%) patients with improvement in LVEF.

The number of grafts was comparable between patients with and without improvement in LVEF and medication (beta-blockers, ACE inhibitors, diuretics, and anticoagulants) was also not different between the 2 groups.

Figure 1 demonstrates the relation between the LV end-systolic volume at baseline and the change in LV ejection fraction after revascularization. When the LV end-systolic volume increased, the likelihood of improvement in LV ejection fraction decreased.

Viability, LV Size, and Prognosis
A total of 23 (29%) events occurred in the 79 patients during 3 years of follow-up. There were 12 (15%) cardiac deaths, including 5 early (within 30 days of surgery) and 7 late deaths; there were 4 nonfatal infarctions (1 early and 3 late after revascularization) and 7 rehospitalizations for heart failure (all late after revascularization). There were 12 events in 49 patients with an improved LV ejection fraction, as compared with 11 events in 30 nonimprovers (NS).

Based on the median LV end-systolic volume (130 mL), the patients were divided into 4 groups: with substantial viability (≥4 dysfunctional but viable segments), without substantial viability (<4 dysfunctional but viable segments), with a relatively large LV size (LV end-systolic volume ≥130 mL), and with a relatively small LV size (LV end-systolic volume <130 mL). The highest event rate (67%) was observed in the patients without viable myocardium with a large LV size (6 of 9 patients); the lowest event-rate (5%) was observed in the patients with viable myocardium with a small LV size (1 of 20 patients). Intermediate event rates were observed in the patients with viable myocardium and a large LV size (38%, 11 of 29 patients) and in the patients without viable myocardium and a small LV size (24%, 5 of 21 patients).

Despite the presence of viability, the event rate increased in parallel to the LV end-systolic volume: in viable patients with an LV end-systolic volume ≥130 mL, the event rate was 37%, as compared with 53% in patients with an LV end-systolic volume ≥160 mL and 63% in patients with a volume ≥180 mL.

The cardiac event curves according to viability and LV size are shown in Figure 2.

Discussion
Assessment of viability has become important in the management of patients with ischemic cardiomyopathy. Different techniques are available and FDG imaging is considered the most sensitive technique for the detection of
dysfunctional but viable myocardium.15 Meta-analysis of 20 studies with 598 patients has shown a sensitivity of 93%.4 The problem, however, is the lower specificity. Data from the meta-analysis demonstrated a specificity of 58%. The lower specificity has been of concern and has also been encountered in clinical practice when some patients with viable myocardium do not improve in function after revascularization. This lower specificity is observed not only with FDG imaging but also with other forms of radionuclide imaging. The failure of viable myocardium to recover in function after revascularization may be related to various issues. One important issue, suggested recently by Yamaguchi et al, is the presence of extensive LV remodeling. The authors evaluated 41 patients undergoing surgical revascularization and demonstrated that 10 of 16 (63%) patients with extensive remodeling had heart failure after surgery and that in these patients, the LV ejection fraction did not improve after revascularization (24% ± 6% versus 25% ± 6%, NS). In this study, preoperative viability testing was not performed. In the current study, we have evaluated the relation between viability and LV size and improvement in LV ejection fraction after revascularization. In line with the literature, we observed that patients without viable myocardium had a low likelihood of recovery of function. In addition, we observed that a substantial number of patients (55%) with viable myocardium improved in LV ejection fraction after revascularization, but at the same time, the 45% of patients with viable myocardium did not improve after revascularization. Careful analysis of these patients revealed that only the LV volumes were different between the 2 groups, with only the LV end-systolic volume being significantly larger in the patients with viable myocardium without improvement in LV ejection fraction after revascularization. This finding is not surprising, because LV end-systolic volume has been identified several years ago as a strong prognostic marker in patients after myocardial infarction.16 To further explore the relation interaction between LV remodeling and the likelihood of recovery of viable patients, we evaluated the change in LV ejection fraction as a function of the baseline LV end-systolic volume (Figure 1). The patients with a lower LV end-systolic volume had a higher likelihood of improvement in LV ejection fraction after revascularization. These observations extend the results from Yamaguchi et al3 and suggest that extensive remodeling of the LV may indeed prevent improvement in LV ejection fraction after revascularization, despite the presence of substantial (≥25% of the LV) viable myocardium.

The next important issue is the prognostic value of the presence/absence of viability in relation to LV size. In particular, do the patients with viable myocardium, with a larger LV size, without improvement in LV ejection fraction benefit from surgical revascularization? Louie et al6 have shown that patients with an LV end-diastolic dimension ≥70 mm had a poor survival after surgical revascularization, but a specific analysis on the relation between viability, LV size, change in LV ejection fraction, and long-term survival was not performed. In the current study, we have used the median LV end-systolic volume (130 mL) to divide the patients into patients with a (relatively) large LV and a smaller LV. Combination of the LV size and presence/absence of viability allowed separation of high-risk and low-risk patients, as demonstrated in Figure 2. Patients without viable myocardium and a large LV had the highest event rate (67%) as compared with the lowest event rate (5%) observed in patients with viable myocardium and a small LV. These findings indicate that combination of these 2 parameters may allow superior risk stratification before surgical revascularization as compared with viability assessment alone.

**Limitations**

Echocardiography was used to assess recovery of function after revascularization. This technique may not be the most accurate technique to assess LVEF, although it has been used in most studies.4 Improvement in LVEF ≥ 5% was considered significant. This is the value used most frequently in studies as a measure of improvement in LVEF, although it can be debated whether it is clinically meaningful. However, the mean change in LVEF was 10±4% in the viable patients who exhibited improvement in LVEF, and this value is probably clinically important.

Graft occlusion may prevent recovery of function after revascularization, and this was not systematically evaluated in our patients. However, none of the patients experienced new symptoms of angina during the follow-up period.

**Conclusion**

LV end-systolic volume substantially influences outcome after revascularization. Despite the presence of viable myocardium, patients with a large LV may not improve in LV ejection fraction after revascularization. In addition, patients with a large LV end-systolic volume have a worse long-term prognosis as compared with patients with a smaller LV end-systolic volume. The combination of viability testing and assessment of LV end-systolic volume may allow superior risk stratification of patients with ischemic cardiomyopathy undergoing surgical revascularization.
References
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