Early Versus Delayed Revascularization in Patients With Ischemic Cardiomyopathy and Substantial Viability: Impact on Outcome

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Background—Patients with ischemic cardiomyopathy and viable myocardium may improve in function and prognosis following revascularization. Delayed revascularization may result in less favorable outcome, and therefore the impact of timing of revascularization on long-term outcome was evaluated.

Methods and Results—Patients (n=85) with ischemic cardiomyopathy and substantial viability (≥25% of the left ventricle) on dobutamine stress echocardiography underwent surgical revascularization. Based on the waiting time for revascularization, patients were divided into 2 groups: early (≤1 month) and late (>1 month) revascularization. Left ventricular ejection fraction (LVEF) was assessed before and 9 to 12 months after revascularization; follow-up data were acquired up to 2 years after revascularization. Hence, 40 patients underwent early (20±12 days) and 45 late (85±47 days) revascularization. Baseline characteristics of the two groups were comparable. Preoperative deaths were 0 in the early and 2 in the late group. Patients with early revascularization remained shorter time in the intensive care unit (2.4±1.5 days versus 5.9±2.1 days for the late group, P<0.05). Low output syndrome was observed more frequently in the late group (8% versus 22%, P=0.06). On long-term follow-up, mortality (5% versus 20%, P<0.05) and re-hospitalization for heart failure (10% versus 24%, NS) were higher in the late group. LVEF improved from 28±9% to 47±12% (P<0.05) in the early group and remained unchanged in the late group (27±10% versus 25±7%, NS).

Conclusion—Patients with ischemic cardiomyopathy and viable myocardium benefit from early revascularization (with improvement in LVEF and favorable prognosis), whereas delayed revascularization of these patients is associated with worse outcome. (Circulation. 2003;108[suppl II]:II-39-II-42.)

Key Words: myocardial viability • hibernating myocardium • heart failure • surgical revascularization

Patients with ischemic cardiomyopathy and a substantial amount of dysfunctional but viable (hibernating) myocardium have a high likelihood to improve in function after revascularization.1–6 Moreover, in these patients, an improvement in symptoms was observed, with a superior long-term survival.1–6 Accordingly, assessment of viability (hibernation) is used to guide therapy in patients with ischemic cardiomyopathy, and patients with viable myocardium should be considered for revascularization. It has also been demonstrated that patients with viable myocardium who are treated medically are at high risk for future cardiac events.7 In daily practice, revascularization can frequently not be performed immediately and waiting times exist. Retrospective studies have indicated that patients with viable myocardium who are treated medically had a high event (and death) rate. A meta-analysis performed by Allman and colleagues,7 including 24 studies with 3088 patients, demonstrated that the cardiac death rate was 16% in patients with viable myocardium who were treated medically as compared with 3% in patients with viable myocardium who underwent revascularization. Based on these observations, it has been suggested that dysfunctional but viable myocardium is an unstable substrate which may progress to cell death unless adequate restoration of blood flow is obtained.

Accordingly, prolonged time before revascularization may unfavourably influence outcome in patients with ischemic cardiomyopathy and viable myocardium.5,9

In the current study, the influence of waiting time for revascularization in patients with ischemic cardiomyopathy and viable myocardium on outcome was evaluated in a large group of patients.

Patients and Methods

Patients and Study Protocol

The study population consisted of 85 patients with ischemic cardiomyopathy and substantial viable myocardium who were already...
scheduled for surgical revascularization. The patients presented with heart failure and 24% had accompanying angina pectoris. The decision for revascularization was based on clinical grounds (symptoms/presence/absence of ischemia/viability, and angiographic findings). All patients were stable during the study. Patients with severe mitral regurgitation were excluded. The patients were divided into two groups according to the waiting time for revascularization; the waiting time was dictated by the discretion of the referring physician and the availability of resources. The waiting time was considered the time interval between assessment of viability by dobutamine stress echocardiography (DSE) and the date of surgical revascularization. Group I (early revascularization group) consisted of 40 patients who underwent revascularization within 30 days (1 month) from DSE and group II (late revascularization group) consisted of 45 patients with a waiting time >30 days.

The study protocol included DSE, and assessment of left ventricular (LV) ejection fraction (EF) using radionuclide ventriculography (before and 9 to 12 months after revascularization). Follow-up was performed up to 2 years after revascularization. Each patient gave informed consent to the study protocol that was approved by the local Ethics Committee.

Assessment of Viability
Beta-adrenergic blocking agents were withdrawn 36 hours before DSE; other cardiac medications were continued. Low-high dose DSE (up to 40 μg/kg/min with addition of 2 mg atropine if necessary) was performed as described previously. Interpretation of the DSE studies was performed by two experienced observers blinded to the clinical data. Inter- and intra-observer agreement for analysis of DSE studies were reported previously (92% and 94%, respectively). The echocardiograms were analyzed according to the 16-segment model. Segmental wall motion and thickening were scored according to a 5-point scale: 1=normal, 2=mildly hypokinetic, 3=severely hypokinetic, 4=akineti, and 5=dyskinetic. Severely dysfunctional segments (score 3 or more) were evaluated for viability. The four patterns that were observed in dysfunctional segments during DSE included: (1) biphasic response (improvement of wall motion during low dose (5 and 10 μg/kg/min), followed by worsening of wall motion during high dose dobutamine); (2) sustained improvement (improvement during low and/or high dose dobutamine without subsequent deterioration of wall motion); (3) worsening (immediate deterioration of wall motion during dobutamine infusion); and (4) no change (no change in wall motion during DSE).

Dysfunctional segments were classified viable when they exhibited any of the patterns except for the “no change” pattern. A patient was considered to have substantial viability in the presence of 4 or more dysfunctional but viable segments (≥25% of the LV).

Assessment of Left Ventricular Ejection Fraction Before and After Revascularization
LVEF was assessed before and 9 to 12 months after surgical revascularization, using radionuclide ventriculography. Radionuclide ventriculography was performed at rest with the patient in the supine position after the administration of 740 MBq of 99mTc-technetium. Images were acquired with a small-field-of-view gamma camera (Orbiter, Siemens Corp, Iselin, NJ), oriented in the 45-degree left anterior oblique position with a 5 to 10° caudal tilt. The LVEF was calculated from the 45-degree left anterior oblique view by an automated technique.

Assessment of Functional Status and Long-term Follow-up
Functional status was assessed according to the New York Heart Association (NYHA) criteria (for symptoms of heart failure) and the Canadian Cardiovascular Society (CCS) classification (for angina pectoris). Symptoms were evaluated before revascularization and at 2-year follow-up. The long-term follow-up was performed by chart review and telephone contact. Follow-up data (events) were acquired up to 2 years. Events included cardiac death, myocardial infarction, and hospitalization for heart failure. Moreover, the number of days the patient stayed in the intensive care unit were noted, and the number of patients experiencing low-output syndrome (defined as the need for high dosages of inotropic medication, and/or intra-aortic balloon pumping to sustain adequate hemodynamic status).

Statistical Analysis
Continuous data were expressed as mean ± SD and compared using the Student’s t test for paired and unpaired data when appropriate. Comparison of proportions was performed using chi-square analysis. Survival of the two groups (early versus late revascularization) was compared using Kaplan-Meier curves. Differences between survival curves were tested with the log-rank chi-square statistic. For all tests, a probability value <0.05 was considered significant.

Results
According to the waiting time, the patients were divided into two groups. Group I, the early revascularization group, consisted of 40 patients; the mean waiting time was 20±12 days, and group II, the late revascularization group, consisted of 45 patients with a mean waiting time of 85±47 days. Complete revascularization was attempted in all patients; arterial grafts were used in 92% of patients.

Baseline characteristics of the two groups were comparable (Table I). In particular, the extent (and distribution) of viable tissue and the extent of scar tissue were comparable between the two groups. Moreover, baseline LVEF was also comparable (28±9%, range 14% to 33%, in group I and 27±10%, range 12% to 35%, in group II, NS). The time from first infarction to the study was 4.8±1.4 years in group I and 5.9±2.1 years in group II (P<0.05), and the time from diagnosis of heart failure to the study was 1.4±0.7 years in group I as compared with 1.9±1.2 years in group II (P<0.05).

There were no preoperative deaths in group I and there were two preoperative deaths (4%) in group II (1 sudden cardiac death, 1 ongoing heart failure). One patient in group I and two patients in group II experienced an intraoperative myocardial infarction. Group I patients stayed significantly shorter in the intensive care unit (2.4±1.5 days versus 5.9±2.1 days, P<0.05). Also, more group II patients exhibited low-output syndrome in the intensive care unit, although the difference was not significant (22% versus 8%, P=0.06).
Long-term follow-up was obtained up to 2 years after revascularization (median follow-up 720 days, range 12 to 720 days; ie, the follow-up was completed until first hard event or otherwise until 2 years).

On long-term follow-up (up to 2 years after revascularization), two patients died (cause: heart failure) in group I as compared with 9 in group II (1 sudden cardiac death, 8 heart failure).

Accordingly, mortality after revascularization was significantly higher in group II (5% versus 20%, \( P<0.05 \), 1). Early mortality (<30 days of surgery) occurred in two patients of group II (persistent heart failure) and in one patient of group I (heart failure following infarction). Four patients who died post-operatively had a previous CABG, as compared with one patient in group I. Two patients had a left ventricular aneurysm, I died post-operatively (heart failure).

Hospitalization for heart failure occurred in 4 (10%) patients in group I, as compared with 11 (24%) patients in group II (NS).

LVEF had improved significantly in group I (from 28±9% to 40±12%, \( P<0.05 \) ) and remained unchanged in group II (27±10% versus 25±7%, NS).

Finally, NYHA class had improved in both groups: from 3.3±0.6 to 2.0±0.8 (\( P<0.05 \)) in group I and from 3.4±0.3 to 2.3±0.7 (\( P<0.05 \)) in group II. CCS score had improved from 3.8±0.5 to 1.3±0.2 (\( P<0.05 \)) in group II.

## Discussion

Assessment of myocardial viability is important to guide management of patients with ischemic cardiomyopathy.\(^1\)–\(^6\)

Patients with substantial viable myocardium have a high likelihood to improve in LV function, symptoms, and long-term prognosis.\(^1\)–\(^7\)

The findings in the current study indicate that early revascularization in patients with viable myocardium is warranted and that delayed revascularization has an adverse effect on improvement of function and long-term outcome.

### Beneficial Effect of Revascularization of Viable Myocardium and the Influence of Delayed Revascularization

Various studies have demonstrated the beneficial effect of viable myocardium on outcome after revascularization, in terms of improvement of regional and global LV function.\(^1\)–\(^3\),\(^6\)–\(^7\) In the current study, an improvement in global LV function was confirmed, but only in the patients with short waiting time. Besides improvement of function, the presence of viable myocardium is also linked to a favorable prognosis in patients undergoing revascularization.\(^7\) In contrast, a high event-rate was demonstrated in patients with viable myocardium who were treated medically.\(^7\) Based on these observations, it has been proposed that dysfunctional but viable myocardium provides an unstable substrate placing patients at high risk for future cardiac events.\(^7\) In line with this hypothesis is the current observation that two patients (with extensive viable myocardium) died during the waiting time for revascularization.

Various studies have provided insight in the morphology of dysfunctional but viable myocardium.\(^8\)–\(^10\) In these studies, biopsies of viable myocardium were obtained during surgery. The structural findings included a loss of contractile material (sarcomeres, but also proteins including myosin, titin, and α-actinin), accumulation of glycogen, collagen, and formation of fibrosis.\(^8\) Studies have indicated that ultrastructural damage may vary extensively, and that the severity of damage was related to the time needed for (complete) recovery of function.\(^1\)–\(^6\),\(^8\)

Additional studies have indicated that the longer the duration of hibernation (viability), the more severe the ultrastructural damage will be.\(^8\) In particular, Schwarz and colleagues\(^8\) have demonstrated that hibernation exhibited a time-dependent deterioration because of progressive structural degeneration with enhanced fibrosis. Elsässer et al\(^10\) have illustrated the presence of apoptosis in patients with hibernating myocardium. Based on these observations, Schelbert\(^11\) has suggested recently that ongoing hibernation may eventually result in cell death and early revascularization should be attempted to allow maximal recovery of function after revascularization.

In the current study, patients with ischemic cardiomyopathy and substantial dysfunctional but viable myocardium who underwent delayed revascularization had a less favorable postoperative course as evidenced by longer stay in the intensive care unit, more often low-output syndrome with the need for high dosages of inotropes and/or intraaortic balloon pumps, in line with previous observations.\(^8\) Moreover, recovery of function was less in patients with delayed revascularization, and these patients showed more events during 2-year follow-up, comparable with previous data.\(^8\) In addition, these patients had a longer history of disease before revascularization.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Group I (early revasc, ( n=40 ) pts)</th>
<th>Group II (late revasc, ( n=45 ) pts)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>59±11</td>
<td>61±7</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>36/4</td>
<td>42/3</td>
<td>NS</td>
</tr>
<tr>
<td>DM (15%)</td>
<td>6</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>HT (20%)</td>
<td>8</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Severe COPD</td>
<td>3 (8%)</td>
<td>5 (11%)</td>
<td>NS</td>
</tr>
<tr>
<td>Renal failure</td>
<td>4 (10%)</td>
<td>3 (7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous CVA</td>
<td>1 (3%)</td>
<td>3 (7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous MI</td>
<td>40 (100%)</td>
<td>43 (90%)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>5 (13%)</td>
<td>7 (16%)</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA</td>
<td>3.3±0.6</td>
<td>3.4±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>CCS</td>
<td>2.6±0.8</td>
<td>2.4±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>VD</td>
<td>2.5±0.7</td>
<td>2.7±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>28±9</td>
<td>27±10</td>
<td>NS</td>
</tr>
<tr>
<td>Nr viable segs</td>
<td>5.1±3.8</td>
<td>4.9±3.5</td>
<td>NS</td>
</tr>
<tr>
<td>Nr scar segs</td>
<td>3.9±3.4</td>
<td>3.7±2.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass grafting; CCS, Canadian Cardiovascular Score; DM, diabetes mellitus; HT, hypertension; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; revasc, revascularization; segs, segments; VD, vessel disease.
tion, as evidenced by the longer time interval from first infarction and diagnosis of heart failure to revascularization.

Altogether, the available evidence from the two previous studies on the topic of delayed versus early revascularization and the findings in the current study suggest that longer duration of hibernation results in more severe structural damage on the myocyte level, clinically translating in absence of recovery of function with a less favorable long-term prognosis.

Limitations
The number of patients in the 2 groups is relatively small. Moreover, biopsies were not obtained in the current study, and, therefore, the relation between the severity of ultrastructural damage and the waiting time for revascularization cannot be explored.

In addition, the time interval between assessment of viability by DSE and the time of surgery was used to separate patients with early and late revascularization; information on duration of hibernation before entrance in the study is not available, although the time interval from first infarction and diagnosis of heart failure was longer in group II, indicating longer duration of disease.

Finally, graft patency was not assessed, and graft occlusion may have affected the results.

Conclusion
The waiting time for revascularization significantly affects outcome after revascularization of patients with ischemic cardiomyopathy and viable myocardium. Early revascularization resulted in improvement of LV function associated with a favorable long-term survival; in contrast, late revascularization did not result in improvement of LV function and was associated with a significantly higher mortality during 2-year follow-up.

References
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