Time Course of Functional Recovery of Stunned and Hibernating Segments After Surgical Revascularization

Jeroen J. Bax, MD; Frans C. Visser, MD; Don Poldermans, MD; Abdou Elhendy, MD; Jan H. Cornel, MD; Eric Boersma, MSc; Arthur van Lingen, PhD; Paolo M. Fioretti, MD; Cees A. Visser, MD

Background—Recovery of function is possible in patients with ischemic cardiomyopathy when left ventricular dysfunction is caused by stunning or hibernation. It is plausible that recovery of function after revascularization may take a longer time in hibernating myocardium compared with stunned myocardium. Accordingly, the time courses of functional recovery in hibernating and stunned myocardium were compared.

Methods and Results—Patients (n = 26) with ischemic cardiomyopathy undergoing surgical revascularization were studied; regional perfusion (resting ²⁰¹Tl single-photon emission CT), glucose utilization (¹⁸F-2-deoxyglucose single-photon emission CT), and contractile function (2D echocardiography) were assessed before revascularization. Dysfunctional segments with normal perfusion/glucose utilization were considered to be stunned, and dysfunctional segments with reduced perfusion/preserved glucose utilization were considered to be hibernating. Contractile function was reevaluated 3 months (early) and 14 months (late) after revascularization. Of the 266 dysfunctional segments, 57 (22%) were stunned, 62 (23%) were hibernating, and 147 (55%) were scar tissue. In stunned myocardium, contractile function improved significantly at 3 months, without further improvement at 14 months; 61% of the stunned segments improved at 3 months, and 9% improved at 14 months. In hibernating myocardium, contractile function improved at 3 months, with a further improvement at 14 months; 31% of the hibernating segments improved at 3 months, and 61% showed (additional) recovery at 14 months.

Conclusions—Stunned myocardium is likely to demonstrate early recovery of function, whereas hibernating myocardium may take a longer time to (fully) recover in function after revascularization. (Circulation. 2001;104[suppl I]:I-314-I-318.)

Key Words: hibernation • revascularization • heart failure • stunning, myocardial

Patients with ischemic cardiomyopathy and viable jeopardized myocardium have been demonstrated to benefit from revascularization, in terms of recovery of contractile function, improvement of heart failure symptoms, and long-term prognosis.1,2 From the many viability studies focusing on recovery of contractile function after revascularization, it has become clear that there is a large variation in the percentage of viable segments with improvement after revascularization.3 Initial data suggest that some segments recover early in contractile function after revascularization, whereas other segments may take a longer time to (fully) recover.4,5 However, not many data are available on the time course of recovery of function after revascularization.4,5 It has been suggested that the duration of recovery may be related to the severity of damage on the myocyte level.6 Although segments with preserved perfusion and glucose utilization (stunned myocardium) may represent tissue with less ultrastructural damage, segments with reduced perfusion but preserved glucose utilization (hibernating myocardium) may represent more severely damaged myocardium.7 Therefore, stunned myocardium may recover early after revascularization, whereas hibernating myocardium may take a longer time to improve in contractile function after revascularization. This issue has been addressed in the present study, in which patients with ischemic cardiomyopathy were evaluated early (3 months) and late (14 months) after revascularization. Dysfunctional myocardium was divided into stunning, hibernation, and scar tissue (on the basis of scintigraphic assessment of perfusion and glucose utilization), and early and late functional follow-up were compared in these groups.

Methods

Study Population and Study Protocol
Twenty-six patients with coronary artery disease and ischemic cardiomyopathy who were scheduled for surgical revascularization were included. All patients presented with heart failure symptoms,
and 54% were in New York Heart Association (NYHA) class III or IV: 10 patients had accompanying angina pectoris. Indications for surgery were heart failure in all patients and heart failure with angina in 10 patients. The decision for revascularization was based on clinical grounds (symptoms, presence/absence of ischemia, and angiographic results) and taken independently from the scintigraphic data. Further characteristics are shown in Table 1. All patients were stable during the study. Patients with severe mitral regurgitation were excluded. The patients were not included in our previous studies. Each patient gave informed consent to the study protocol, which was approved by the ethics committees of the participating hospitals.

**Study Design**

At baseline, the following parameters were obtained: (1) left ventricular (LV) ejection fraction (LVEF), assessed by radionuclide ventriculography (RNV); (2) segmental contractile function, assessed by 2D echocardiography; (3) regional perfusion, assessed by early resting 201TI single-photon emission CT (SPECT); and (4) regional glucose utilization, assessed by 18F-2-deoxyglucose (FDG) SPECT. Early (3 months after revascularization) and late (14 months after revascularization) segmental contractile function (2D echo) was reevaluated.

**Assessment by RNV**

LVEF was assessed by equilibrium RNV before revascularization. RNV was performed at rest with the patient in the supine position after the administration of 740 MBq of 99mTc. Images were acquired with a γ camera (Orbiter, Siemens Corp) with a small field of view, oriented in the 45° left anterior oblique position with a 5° to 10° caudal tilt. The LVEF was calculated from the 45° left anterior oblique view by an automated technique.

**SPECT Studies**

**Regional Perfusion**

The SPECT studies were performed with a dual-head rotating γ camera system (ADAC Laboratories). Myocardial perfusion was assessed by early resting 201TI SPECT (injection of 111 MBq 201TI chloride, with imaging performed within 10 to 15 minutes after tracer injection). Data acquisition was performed over 360°, with a total imaging time of 16 minutes. Data were stored in a 16-bit matrix (64×64). From the raw scintigraphic data, 6-mm-thick (1-pixel) transaxial slices were reconstructed by filtered back projection (Hanning filter, 0.63 cycle/cm). Slices were not corrected for attenuation. Further reconstruction yielded long- and short-axis projections perpendicular to the heart axis.

**Regional Glucose Utilization**

Myocardial glucose utilization was evaluated by FDG SPECT during hyperinsulinemic euglycemic clamping to optimize and standardize the metabolic conditions. The technical details of the FDG SPECT studies have been described previously. For the data acquisition, the same dual-head γ camera system (as for the perfusion data), equipped with 511-keV collimators (van Mullekom, Nuclear Fields), was used. Reconstruction of data was identical to that of the perfusion studies. The perfusion and FDG study were performed on the same day. Cardiac medication was continued during the SPECT studies.

**SPECT Image Analysis**

The perfusion and FDG SPECT data were analyzed quantitatively as described previously. Briefly, circumferential profiles (60 radii, highest pixel activity per radius) from the available short-axis slices were generated and displayed in polar map format. The polar maps were divided into 16 segments (use of similar segments as for 2D echo; see below). Segmental activities were compared with normal databases, and perfusion defects were identified (when segmental activities were <2 SD below normal).

**SPECT Tissue Characterization**

The dysfunctional segments (identified by 2D echo; see below) were classified as follows: Dysfunctional segments with normal perfusion were characterized as stunned myocardium. Dysfunctional segments with a perfusion defect and a (relatively) increased FDG uptake were classified as hibernating myocardium. Dysfunctional segments with concordantly reduced perfusion and FDG uptake were classified as scar tissue. These segments were subdivided into nontransmural scars (tracer activities of ≥60%) and transmural scars (tracer activities <60%).

**2D Echocardiography**

Regional contractile function was evaluated by resting 2D echo before and after revascularization (early, 3 months; late, 14 months). Four standard views of the left ventricle were recorded (videotape and digitized in cine-loop format): parasternal long- and short-axis views and apical 2- and 4-chamber views. The images before and after revascularization and the images early and late after revascularization were reviewed (random order) offline, and consensus was achieved by 2 observers unaware of the SPECT data and the timing of the echocardiographic data (before versus after revascularization). For alignment of the echo data and SPECT data, the left ventricle was divided into 16 comparable segments: 4 apical segments, 6 distal segments (anterior, anterolateral, inferolateral, inferior, inferoseptal, and anteroseptal), and 6 basal segments (comparable to the distal segments) were identified. Both inward wall motion and wall thickening were analyzed. Each segment was assigned a wall motion score (WMS) of 1 to 4: 1, normal or mildly hypokinetic; 2, severely hypokinetic (decreased endocardial excursion and systolic wall thickening); 3, akinetic (absence of endocardial excursion and systolic wall thickening); and 4, dyskinetic (paradoxical outward movement in systole). Improvement of segmental WMS by ≥1 grade was considered significant. Improvement from dyskinesia to akinesia was not considered improvement of function.

**Statistical Analysis**

Descriptive results are expressed as mean±SD. Patient data were compared by using the Student t test for paired and unpaired data when appropriate. Comparison of proportions was performed by χ² analysis. Simultaneous comparison of >2 mean values was per-
formed by using 1-way ANOVA. A value of $P<0.05$ was considered significant.

**Results**

**Contractile Function: Baseline Versus Early/Late Follow-Up**

Two patients died (1 in-hospital death and 1 death during the 14-month follow-up; thus, perioperative mortality of 8.3%); the majority of the remaining 24 patients improved significantly in heart failure symptoms (only 5 remained in NYHA class III/IV) and angina pectoris (3 still complained of chest pain).

Resting 2D echocardiography identified abnormal contractile function in 266 (69%) segments. Of these 266 dysfunctional segments, 124 segments were severely hypokinetic, 127 were akinetic, and 15 were dyskinetic. Early recovery was observed in 67 (25%) segments (27 akinetic and 40 hypokinetic), whereas late or additional recovery was observed in 48 (18%) segments (1 dyskinetic; late recovery, only 37, and additional recovery, 11); 151 (57%) segments exhibited no recovery at all. Mean WMS was 2.4±0.5 in segments with early recovery, 2.5±0.5 in segments with late recovery, and 2.7±0.5 in segments without recovery.

**Tissue Characterization by SPECT**

Of the 266 dysfunctional segments, 57 (22%) demonstrated normal perfusion and glucose utilization and were classified as stunned. Sixty-two (23%) exhibited reduced perfusion and preserved glucose utilization and were classified as hibernating. The remaining 147 (55%) segments had concordantly reduced perfusion and glucose utilization and were considered as scar tissue. On the basis of the aforementioned definitions, 36 (24%) were classified as nontransmural scars, and 111 (76%) were classified as transmural scars.

The highest mean segmental WMS at baseline was observed in transmural scars (3.0±0.5, $P<0.05$ versus other groups), followed by that in hibernating myocardium (2.6±0.5, $P<0.05$ versus other groups), whereas the lowest mean segmental WMS was observed in nontransmural scars and stunned myocardium (2.0±0.2 and 2.1±0.3, respectively).

**Tissue Characterization Versus Functional Outcome**

In stunned myocardium, the mean segmental WMS decreased significantly at 3 months and remained unchanged at late follow-up (Figure 1). The distribution of segments within each WMS at the different time points is shown in Table 2.

In hibernating myocardium, the mean segmental WMS improved significantly at 3 months, with a further improvement at 14 months (Figure 1). Importantly, the mean segmental WMS at 14 months was comparable between the stunned and hibernating segments. The distribution of segments within each wall motion score at the different time points is shown in Table 2.

In the nontransmural and transmural scars, the mean segmental WMS remained unchanged at early and late follow-up (Figure 1). The distribution of segments within each WMS at the different time points is shown in Table 2.

**Figure 1.** Segmental WMS in 4 categories at baseline and at 3 months and 14 months after revascularization. In segments with transmural (Transm) and nontransmural (Nontransm) scars, WMS did not change throughout the entire study. In stunned segments, WMS improved significantly at 3 months and remained unchanged at 14 months ($P<0.05$ vs baseline). In hibernating segments, WMS improved significantly at 3 months ($P<0.05$ vs baseline) and showed further improvement at 14 months ($^*P<0.05$ vs baseline and 3 months).

When the individual segments were considered, the majority of the segments with improvement at early follow-up were stunned ($P<0.05$ versus others, Figure 2), whereas the majority of the segments that revealed (additional) recovery at late follow-up were hibernating ($P<0.05$ versus others, Figure 2). Nontransmural and transmural scars revealed a low incidence of recovery of contractile function, both at early and late follow-up ($P<0.05$ versus stunned/hibernating myocardium) (Figure 2).

**TABLE 2. Distribution of Segments According to SPECT Classification at Baseline and at 3 and 14 Mo After Revascularization**

<table>
<thead>
<tr>
<th>WMS Score</th>
<th>Baseline</th>
<th>3 mo</th>
<th>14 mo</th>
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</thead>
<tbody>
<tr>
<td>Stunned segments, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMS 4</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>WMS 3</td>
<td>8</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>WMS 2</td>
<td>49</td>
<td>27</td>
<td>22</td>
</tr>
<tr>
<td>WMS 1</td>
<td>...</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>Hibernating segments, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMS 4</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>WMS 3</td>
<td>34</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>WMS 2</td>
<td>27</td>
<td>36</td>
<td>20</td>
</tr>
<tr>
<td>WMS 1</td>
<td>...</td>
<td>13</td>
<td>36</td>
</tr>
<tr>
<td>Nontransmural scars, n</td>
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<tr>
<td>WMS 4</td>
<td>...</td>
<td>...</td>
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<tr>
<td>WMS 3</td>
<td>9</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>WMS 2</td>
<td>27</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>WMS 1</td>
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<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Transmural scars, n</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>WMS 4</td>
<td>14</td>
<td>27</td>
<td>34</td>
</tr>
<tr>
<td>WMS 3</td>
<td>87</td>
<td>68</td>
<td>64</td>
</tr>
<tr>
<td>WMS 2</td>
<td>10</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>WMS 1</td>
<td>...</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

n indicates number of segments or scars.
Moreover, 61% of the stunned segments compared with 31% of the hibernating segments revealed recovery at the 3-month follow-up ($P<0.05$), and 61% of the hibernating segments compared with 9% of the stunned segments exhibited (additional) recovery at late follow-up ($P<0.01$). Interestingly, 30% of the stunned segments and 8% of the hibernating segments failed to improve in function at late follow-up.

**Discussion**

Assessment of viable myocardium has become an important component of the diagnostic evaluation of patients with chronic ischemic LV dysfunction.\textsuperscript{1,2} If viable tissue is present, improvement of LV function, heart failure symptoms, and long-term prognosis may be anticipated after coronary revascularization.\textsuperscript{1,2} In contrast, patients without viable tissue did not improve in LV function, heart failure symptoms, or long-term prognosis.\textsuperscript{1,2} When the increased risk of surgical revascularization in patients with severely depressed LV function (as also observed in the present study, with perioperative mortality 8.3%) is considered, the presence/absence of viable myocardium may help to justify the decision to revascularize or not. From the studies that have focused on the prediction of functional recovery after revascularization, it has become clear that viable myocardium may have normal perfusion and glucose utilization (stunned myocardium) or may show reduced perfusion with preserved glucose utilization (hibernating myocardium).\textsuperscript{7} Scar tissue, on the other hand, exhibited reduced perfusion and reduced glucose utilization, with a mild reduction in perfusion/glucose utilization in nontransmural scars and a severe reduction in transmural scars.\textsuperscript{7} Histopathologic studies have suggested that there may be a gradual increase of ultrastructural damage and percentage of fibrosis in these 4 subgroups (stunning, hibernation, nontransmural scar, and transmural scar).\textsuperscript{11–14}

From the large number of studies evaluating perfusion and glucose utilization in patients undergoing revascularization, it has become clear that segments with severely reduced perfusion and glucose utilization virtually never improve in function after revascularization.\textsuperscript{3} Moreover, histopathologic studies have demonstrated that in these segments, fibrosis is mainly present.\textsuperscript{11–14} In the present study, these segments demonstrated the highest mean segmental WMS, indicating severely depressed systolic function. Furthermore, the mean segmental WMS remained unchanged over time, indicating no delayed recovery of function.

More recent studies have emphasized the existence of nontransmural scars.\textsuperscript{15} Shivalkar et al\textsuperscript{12} have shown that percentage fibrosis was significantly less in myocardium with mildly reduced perfusion/glucose utilization than in segments with severely reduced perfusion/glucose utilization. The present results showed that the mean segmental WMS was significantly less in segments with nontransmural infarction compared with segments with transmural infarction, indicating relatively preserved systolic function in these segments. Still, virtually no recovery of function was observed in these segments. However, long-term prognosis may be better in patients with nontransmural infarction compared with those with transmural infarction, because the “viable” epicardium in nontransmural infarction may prohibit remodeling.\textsuperscript{16}

In contrast to the (non)transmural scars, many studies have demonstrated that improvement of function after revascularization occurs in viable segments. However, the incidence of recovery varies significantly among these different studies.\textsuperscript{3} It is worth mentioning that >90% of these studies have evaluated recovery of function within 3 months after revascularization.\textsuperscript{3} However, the few available studies with longer follow-up have shown that a delayed recovery of function may occur.\textsuperscript{4,5,17,18} Thus, the variance in recovery of function in the studies may (in part) be related to the time course of recovery after revascularization. The differences in time course of recovery may be related to the severity of ultrastructural damage before revascularization. Stunned myocardium may have less damage than hibernating myocardium and may, therefore, exhibit early recovery of function after revascularization. In the present study, stunned myocardium had relatively preserved systolic function (as evidenced by the relatively low WMS), and 61% of the segments exhibited early recovery of function after revascularization. In contrast, hibernating myocardium had a higher WMS (indicating more severely depressed systolic function) and showed a delayed recovery of function (61% of the segments showed additional recovery at late follow-up). Moreover, the WMS at early and late follow-up were not different in the stunned segments, but the WMS in the hibernating segments showed a gradual improvement over time (Figure 1). Importantly, the stunned and hibernating segments showed a comparable WMS at late follow-up, indicating a similar degree of recovery of systolic function after revascularization.

In 30% of the stunned segments, no recovery of function was observed. This finding could possibly be related to the limited resolution of SPECT imaging. Some segments, classified as stunned, may have contained relatively small subendocardial scars, with a slight reduction in tracer uptake in the endocardial layers. SPECT equipment is not able to identify these small local reductions in tracer uptake; therefore, these segments were classified as normal. However, these segments are not capable of improving function after revascularization. With the enhanced resolution of MRI, better delineation of subendocardial perfusion may become possible.\textsuperscript{15}
Limitations of the Study
Several limitations of the present study should be acknowledged: (1) Perfusion and glucose utilization were measured by SPECT. Although absolute quantification of perfusion and glucose metabolism is possible with PET, it is not possible with SPECT. (2) Functional follow-up was assessed at 3 and 14 months. Therefore, precise timing when recovery of function took place is not possible (an intermediate time point would have been helpful for more precise timing). (3) Angiography was not performed after revascularization; thus, graft patency was not evaluated. (4) Alignment between scintigraphic data and echocardiographic data remains difficult; some misalignment may have influenced the results. (5) Finally, no biopsies were taken during revascularization; therefore, the results could not be related to histology.

Study Conclusions
Stunned myocardium is likely to demonstrate early recovery of function, whereas hibernating myocardium may take a longer time to (fully) recover in function after revascularization.

References
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