The beneficial effect of revascularization on jeopardized myocardium: reverse remodeling and improved long-term prognosis

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Abstract

Objectives: To evaluate the impact of viability/ischemia before revascularization on improvement in systolic performance, reverse remodeling, symptoms and long-term prognosis post-revascularization. Methods: Fifty patients underwent thallium-201 imaging before revascularization to assess stress-induced ischemia and viability (‘jeopardized myocardium’). Left ventricular (LV) ejection fraction (EF), LV end-systolic volume index (LVESVI) and LV end-diastolic volume index (LVEDVI) were determined before and 3 months post-revascularization. Graft/vessel patency was controlled by repeat angiography. Long-term follow-up data (New York Heart Association (NYHA) class, hard events) were acquired up to 3 years. Results: Patients with \( \geq 5 \) jeopardized segments on thallium-201 imaging demonstrated improvement of LVEF at 3 months (from 35 \( \pm \) 6 to 43 \( \pm \) 6\%, \( P \leq 0.001 \)), with reverse remodeling (LVESVI decreased from 68 \( \pm \) 16 to 52 \( \pm \) 14 ml/m\(^2\), \( P < 0.001 \); LVEDVI decreased from 103 \( \pm \) 21 to 91 \( \pm \) 18 ml/m\(^2\), \( P < 0.001 \)), and improved in NYHA class with excellent long-term prognosis (0\% event rate). Conversely, patients with \(< 5 \) jeopardized segments failed to improve in LVEF (34 \( \pm \) 4 vs. 33 \( \pm \) 7\%, NS), and exhibited ongoing remodeling (LVESVI increased from 70 \( \pm \) 14 to 78 \( \pm \) 23 ml/m\(^2\), \( P < 0.001 \); LVEDVI increased from 106 \( \pm \) 19 to 116 \( \pm \) 25 ml/m\(^2\), \( P < 0.001 \)), without improvement in NYHA class, and worse long-term prognosis (29\% event rate). Conclusion: Patients with jeopardized myocardium benefit from revascularization with improvement in LVEF, reverse remodeling, improvement in NYHA class and favorable long-term prognosis. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Viable myocardium; Heart failure; Nuclear imaging; Remodeling

1. Introduction

Thallium-201 imaging has been used successfully for the noninvasive assessment of myocardial viability in patients with chronic ischemic left ventricular (LV) dysfunction and allows prediction of improvement of LV function post-revascularization [1–4]. However, it has been stressed recently that improvement of LV function after revascularization may not be the ideal end-point against which preoperative viability should be tested [1–4]. Preferably, viability testing should be used to predict reverse remodeling and long-term prognosis [1–4]. In the current study we have addressed these issues. In a cohort of consecutive patients undergoing revascularization, we have used thallium-201 imaging and related the presence/absence of viable tissue to: (1) the post-operative change in LV ejection fraction (EF); (2) the change in LV end-systolic (LVESV) and end-diastolic (LVEDV) volume indexes; (3) the change in heart failure symptoms; and (4) long-term prognosis. Moreover, the success of revascularization was determined by repeat angiography 3 months post-revascularization.

2. Materials and methods

2.1. Patients, study protocol

Patients who were already scheduled for revascularization were included if they fulfilled the following inclusion criteria: (1) stable, chronic coronary artery disease; (2) depressed LV function (LVEF <40\%); (3) no concomitant

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valvular disease (patients with 3–4 + mitral regurgitation were excluded); (4) no previous surgical revascularization; (5) no recent myocardial infarction (<4 weeks before the study). The results of the thallium-201 study did not influence the decision to revascularize. For the decision to revascularize the following data were used: symptoms and other clinical data, exercise testing, resting echocardiography and angiographical results. Indications for revascularization were heart failure in all patients. Within 1 month of revascularization, coronary angiography, resting 2D echocardiography and thallium-201 imaging were performed. Three months after revascularization a resting 2D echo and cardiac catheterization (to assess graft/vessel patency) were performed.

2.2. Thallium-201 imaging

2.2.1. Data acquisition
All patients performed a symptom-limited multistage bicycle exercise test. Thallium-201 chloride (111 MBq) was injected intravenously at peak exercise and the initial stress images were obtained. Redistribution images were obtained 3–4 h after exercise. Twenty-four hours thereafter, the delayed resting images were obtained, while medication was restarted. Single photon emission computed tomography (SPECT) images were obtained using a wide-field-of-view rotating gamma camera equipped with a low-energy all-purpose, parallel-hole collimator (Starcam, GE, USA) centered on the 72 keV (20% window) and 167 keV (20% window) photon peaks. The camera was rotated over an angle of 180° (from −40° right anterior oblique to 140° left posterior oblique, obtaining 32 projections). Data were stored in a 64×64, 16-bit matrix. From the raw scintigraphic data, 6 mm thick (1 pixel) transaxial slices were obtained by filtered back-projection. The slices were not corrected for attenuation. Further reconstruction yielded long- and short-axis slices perpendicular to the heart axis.

2.2.2. Quantitative data analysis
The short-axis slices from the stress, 3–4 h redistribution and 24 h delayed images were analyzed using automatic quantitative circumferential profile analysis [5]; from these data, polar maps were reconstructed. The polar maps were divided into 20 segments: six basal segments, six midventricular segments and six apical segments, while the apex was represented by two segments.

2.2.3. Assessment of jeopardized myocardium
Both ischemia and viability were evaluated. Segments (on the stress, 3–4 h redistribution, 24 h delayed polar maps) were classified as having normal thallium-201 uptake (>75% of maximum uptake), moderately reduced thallium-201 uptake (50–75% of maximum uptake) or severely reduced uptake (<50% of maximum uptake). Segments were classified as ischemic when a perfusion defect was present on the stress images and significant redistribution occurred on the 3–4 h redistribution images (>10% increase in activity). Segments were classified as viable when the activity on the late images was normal (>75% tracer uptake), moderately reduced (>50% tracer uptake) or when significant redistribution was present (>10% increase in activity from the 3–4 h redistribution images to the 24 h delayed images). For the outcome after revascularization both ischemia and viability are important. Therefore, segments were classified as ischemic and/or viable (jeopardized). Segments with a fixed perfusion defect and activity <50% were classified as scar tissue. A patient was classified as ‘jeopardized but viable’ when five or more (representing >20% of the left ventricle) segments were classified as jeopardized. The remaining patients were classified as ‘non-jeopardized’.

2.3. Assessment of LVEF and LV volumes before and after revascularization
Contractile function was evaluated by resting 2D echocardiography before revascularization. Four standard views of the left ventricle were recorded on videotape: parasternal long- and short-axis views and apical two- and four-chamber views. The images were analyzed off-line by two observers unaware of the SPECT images. LV volumes (LVESV, LVEDV) were derived from the cine-loop images (apical two- and four-chamber views, biplane Simpson’s rule) that were obtained before and after revascularization. The LVEF was derived from the LV volumes. Each measurement was derived from the average of three cycles (avoiding postectopic beats). All volumes were normalized to the body surface area (m²) calculated from the patient’s height and weight. Variability of assessment of LVEF and LV volume indexes was assessed in ten randomly chosen patients; both intra- and inter-observer variability was excellent (r = 0.96, P < 0.01 and r = 0.94, P < 0.01, respectively).

2.4. Assessment of graft/vessel patency
Cardiac catheterization was performed before revascularization, using the modified Seldinger approach (right femoral artery). Lesions with a >50% reduction in luminal cross-sectional diameter in one or more of the major coronary arteries were considered significant. Three months post-revascularization, coronary angiography was repeated and graft/vessel patency was confirmed.

2.5. Symptoms, long-term follow-up
Functional status (heart failure symptoms) was assessed according to the New York Heart Association (NYHA) criteria. In each patient, the functional status before, 3 months post-revascularization and at late follow-up (up to 3 years) was determined by interviews and physical examinations conducted by an investigator blinded to the thallium-201 data.

Long-term follow-up was derived from patient inter-
views, chart reviews or telephone contact. Follow-up data were acquired up to 3 years. Only hard events were considered during follow-up. Early events were in-hospital mortality/infarction, while late events were cardiac death (defined by the hospital chart documenting arrhythmic death or death attributable to congestive heart failure, myocardial infarction or cardiac arrest) and nonfatal myocardial infarction.

2.6. Statistical analysis

Continuous data were expressed as mean ± SD and compared using the Student’s t-test for paired and unpaired data when appropriate. Univariate analysis for categorical variables was performed using the χ²-test with Yates’ correction. The event-free (for definition of events see above) survival of these two groups of patients was compared using Kaplan–Meier curves. Differences between event-free survival curves were tested with the log-rank χ² statistic. For all tests, a P value of < 0.05 (two-sided) was considered significant.

3. Results

3.1. Study population

A total of 54 patients were initially included in the study; four patients did not complete the study protocol (one fatal infarction before the study, one irreversible congestive heart failure, and two refusals to undergo surgery), leaving 50 patients (for characteristics see Table 1). Thirty-seven underwent surgical revascularization, and 13 percutaneous transluminal coronary angioplasty (PTCA). All stenosed vessels were revascularized. At 3 months, all grafts/dilated vessels were patent.

Table 1

<table>
<thead>
<tr>
<th>Group A (n = 26)</th>
<th>Group B (n = 24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66 ± 7</td>
<td>63 ± 9</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>20/6</td>
<td>20/4</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>1.3 ± 0.5</td>
<td>1.0 ± 0.3</td>
</tr>
<tr>
<td>Vessel disease</td>
<td>2.6 ± 1</td>
<td>2.2 ± 1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>15</td>
<td>10</td>
</tr>
</tbody>
</table>

Medications before/after revascularization

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 26)</th>
<th>Group B (n = 24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digitalis</td>
<td>16/6**</td>
<td>14/14</td>
<td>NS/&lt;0.05</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>24/16**</td>
<td>22/24</td>
<td>NS/&lt;0.01</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>6/6</td>
<td>5/8</td>
<td>NS/NS</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>25/24</td>
<td>22/22</td>
<td>NS/NS</td>
</tr>
<tr>
<td>Angiotensin antagonists</td>
<td>5/5</td>
<td>4/7</td>
<td>NS/NS</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>14/15</td>
<td>16/17</td>
<td>NS/NS</td>
</tr>
<tr>
<td>CCB</td>
<td>5/5</td>
<td>5/3</td>
<td>NS/NS</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>4/2</td>
<td>3/5</td>
<td>NS/NS</td>
</tr>
<tr>
<td>Lipid lowering</td>
<td>10/15*</td>
<td>6/10*</td>
<td>NS/NS</td>
</tr>
</tbody>
</table>

* MI, myocardial infarction; ACE, angiotensin-converting enzyme; CCB, calcium channel blockers. *P < 0.05, pre- vs. post-revascularization values; **P < 0.01, pre- vs. post-revascularization values.

3.2. Thallium-201 imaging

In the 50 patients a total of 1000 segments were analyzed on thallium-201 imaging and classified as follows: 317 segments were normal (>75% tracer uptake at stress); 130 segments were ischemic; 230 segments were viable; 323 segments were scar tissue. Based on the thallium-201 data, the patients were divided into two groups. Group A consisted of 26 patients with ≥5 jeopardized segments, and group B consisted of 24 patients with <5 jeopardized segments. One of the patients in group B died peri-operatively, and is not included in the functional follow-up analysis (LVEF/LV volumes) but is included in the survival analysis.

3.3. Functional outcome vs. thallium-201 imaging

The baseline characteristics were not different between the patients in groups A and B except for diabetes (Table 1). The LVEF and volumes in groups A and B before and after revascularization are shown in Table 2. Baseline LVEF was similar in groups A and B. In group A, LVEF increased significantly from 35 ± 6 to 43 ± 6% (P < 0.001), whereas the LVEF in group B remained unchanged (34 ± 4 vs. 33 ± 7%, NS). Baseline LVEDVI was comparable between both groups. In group A, LVEDVI decreased significantly from 103 ± 21 to 91 ± 18 ml/m² (P < 0.001). Of interest, LVEDVI increased in group B, from 106 ± 19 to 116 ± 25 ml/m² (P < 0.001). Baseline LVESVI was similar between the two groups. In group A, LVESVI decreased significantly from 68 ± 16 to 52 ± 14 ml/m² (P < 0.001), whereas...
LVESVI increased significantly in group B from 70 ± 14 to 78 ± 23 ml/m² (P < 0.001). The changes in all of these parameters were significantly different between the two groups (Table 3) and pointed in opposite directions: reverse remodeling in group A and ongoing remodeling in group B.

3.4. NYHA functional class

NYHA functional class at baseline was comparable between groups A and B (2.9 ± 0.7 vs. 2.7 ± 0.5, respectively). In group A, NYHA class improved significantly from 2.9 ± 0.7 at baseline to 2.1 ± 0.6 at 3 months post-revascularization (P < 0.001), and improved further to 1.6 ± 0.6 (P < 0.001) at late follow-up. In contrast, in group B, NYHA class did not change at 3 months post-revascularization or at long-term follow-up (2.7 ± 0.6 vs. 2.7 ± 0.7, NS).

3.5. Follow-up vs. thallium-201 imaging

The follow-up duration was 26 ± 9 months (range 1–38 months). During this period, a total of seven events occurred in the 50 patients. The early events (<1 month) included one peri-operative death due to acute myocardial infarction and subsequent irreversible heart failure. The late events included seven late cardiac deaths (two sudden death, four due to refractory heart failure and one due to acute myocardial infarction). All events occurred in the 24 non-jeopardized patients (29% event rate). The number of events was significantly higher in group B, as evidenced by Kaplan–Meier analysis (P < 0.01 by log-rank test, see Fig. 1).

4. Discussion

LVEF improved significantly in the patients with jeopardized myocardium. However, it has recently been stressed that improvement of function may not be the ideal end-point to determine the success of revascularization [1–4]. Revascularization of jeopardized myocardium may also have a beneficial effect by attenuating LV dilatation and remodeling, reducing ventricular arrhythmias and the risk of fatal ischemic events [1–4].

In view of these hypotheses, the data presented in the current study are important. In patients with jeopardized myocardium, significant reductions in ESVI and EDVI in patients with jeopardized myocardium were observed, thereby confirming the expected attenuation of dilatation/remodeling and even indicating reverse remodeling. In contrast, in the patients without jeopardized myocardium, LV volume indexes increased after revascularization, demonstrating ongoing remodeling. Previous studies have demonstrated that improvement in heart failure symptoms post-revascularization mainly occurred in patients with viable myocardium [6,7]. It is likely that the improvement in heart failure symptoms, observed in the patients with jeopardized myocardium, can (in part) be attributed to the reverse remodeling.

In addition, in patients with jeopardized myocardium, long-term prognosis was excellent, whereas patients without jeopardized myocardium exhibited a high event rate, in line with previous studies. It seems plausible that the superior survival in the patients with jeopardized myocardium can (in part) be related the improvement of LVEF (directly improving pump function), the reversed remodeling (reducing heart failure) and (possibly) the prevention of fatal

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![Fig. 1. Kaplan–Meier analysis of event-free survival of the patients in the two groups. The event rate was significantly higher in group B. Group A: patients with jeopardized myocardium; group B: patients without jeopardized myocardium.](image-url)
ischemic events (by revascularization of jeopardized myocardium).

The major limitation of the current study is the fact that functional follow-up was obtained at 3 months, whereas additional recovery of function may occur up to 1 year [8]; this may also be true for the effects on LV volumes.

4.1. Conclusions

Patients with jeopardized myocardium exhibited an improvement of LVEF, in combination with a decrease in LVEDVI and LVESVI, indicating reverse remodeling in these patients; also, heart failure symptoms improved and long-term prognosis was favorable in these patients. Patients without jeopardized myocardium did not improve in LVEF, and the remodeling process continued, associated with no improvement in symptoms and a lower event-free survival. Thus, the beneficial effect of revascularization of jeopardized myocardium appears to extend beyond improvement of LV function.

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