Functional Recovery of Subepicardial Myocardial Tissue in Transmural Myocardial Infarction After Successful Reperfusion

An Important Contribution to the Improvement of Regional and Global Left Ventricular Function

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Background—The transmural extent of myocardial necrosis after an acute coronary artery occlusion can vary considerably. The contribution of residual subepicardial viable myocardium to global left ventricular function is largely unknown.

Methods and Results—We studied 12 patients with single-vessel disease 1 week after successful reperfusion of a first transmural anterior myocardial infarction (MI). With PET, myocardial blood flow (MBF) and glucose metabolism were measured regionally, and the viability was graded as normal, mismatch, or match with severely (<50% of normal) or intermediately (50% to 80% of normal) impaired MBF. Magnetic resonance tagging was used to regionally quantify fiber strains, wall thickening, and ejection fraction in patients 1 week and 3 months after the MI and in age-matched healthy volunteers. From 1 week to 3 months, subepicardial fiber shortening improved significantly in the match region (MBF <50%, 5.1±7.0% to −9.9±8.7%; MBF of 50% to 80%, −7.1±7.6% to −14.9±7.9%). This was associated with an improvement in regional ejection fraction in the infarcted myocardium (29.6±21.8% to 43.5±15.5%, P<0.0001) and in normal regions (54.3±15.1% to 56.5±13.1%, P=0.013), contributing to an increase in global ejection fraction from 44.2±22.2% to 49.3±17.9% (P<0.0001).

Conclusions—Functional recovery of viable subepicardial regions is a mechanism of late improvement in regional and global ejection fraction after a so-called transmural MI. (Circulation. 1999;99:36-43.)

Key Words: myocardial infarction ■ magnetic resonance imaging ■ tomography ■ reperfusion

Several studies have demonstrated the presence of viable but ischemically compromised tissue in infarcted myocardium.1 In canine studies, the subendocardial lateral boundaries of a myocardial infarction (MI) are established within the first 40 minutes, whereas the MI enlarges in a transmural wave front over a period of 3 to 6 hours.2 In patients, the final lateral boundaries of the infarcted area closely correspond to the myocardium at risk, whereas a variable degree of transmural progression determines the final extent of necrosis.3 Islands of viable tissue, especially in the subepicardial layers, remain intermixed with necrotic cells, and if antegrade flow in the infarct-related artery is restored, a late improvement in myocardial perfusion and metabolism in this nonviable myocardium has been observed in humans.4 However, a possible concomitant functional improvement in these subepicardial layers of a transmural MI has not been studied in humans.

The purpose of the present study was to investigate transmural differences in functional recovery in relation to the degree of viability in patients with a first transmural MI.

Methods

Patient Selection

Twelve patients with a first anterior MI were selected for the study; in all patients, the left anterior descending coronary artery could be successfully reperfused by either thrombolytic therapy or rescue angioplasty, and no significant lesions were present in other coronary arteries.

For comparison, we also studied a control group of 31 age-matched volunteers (age, 59.5±7.1 years) without evidence of cardiac disease.

Study Protocol

Both PET and magnetic resonance (MR) tagging studies were performed at 5±2 days (range, 2 to 10 days) after the acute event
A repeated MR tagging study was performed after 3 months (range, 82 to 96 days; 3-month study).

**Measurement of Regional Myocardial Viability With PET**

All patients were studied by use of the hyperinsulinemic euglycemic clamp technique. Five serial images were acquired during infusion of 20 mCi of $[^{13}N]$NH$_3$ in a whole-body tomograph. Fifty minutes later, 10 mCi of $[^{18}F]$deoxyglucose ($[^{18}F]$FDG) was injected, and serial images were recorded for 70 minutes.

A 3-dimensional (3D) delineation of the left ventricular (LV) wall was used to construct a polar map (33 regions: 1 apical region and 4 rings of 8 regions each) for every frame of the dynamic study. A flow index was calculated as the ratio of $[^{13}N]$NH$_3$ uptake in each region over the $[^{13}N]$NH$_3$ uptake in the region with the highest uptake (reference region). A metabolic index was defined as the ratio of the glucose use in each region over that in the reference zone. Regions with a flow index of $>80\%$ were considered normal. In the remaining regions, a flow-metabolism mismatch pattern was as-

<table>
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<tr>
<th>Patient</th>
<th>Age/Sex</th>
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<th>TIMI Flow</th>
<th>Residual Grade Stenosis, %</th>
<th>TIMI Flow</th>
<th>Residual Grade Stenosis, %</th>
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<td>ACEI, BB, ASA</td>
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</table>

**TABLE 1. Characteristics of the 16 Patients With Acute Transmural MI**

CK indicates creatine kinase; TIMI flow grade, the patency of the left anterior descending coronary artery according to the Thrombolysis in Myocardial Infarction (TIMI) trial’s system for grading recanalization after MI; ASA, aspirin; BB, β-blockers; ACEI, ACE inhibitors; and N, nitrates.

* indicates patients who had elective/rescue angioplasty.
Functional Recovery of Subepicardial Tissue

TABLE 2. Regional Myocardial Viability With PET

<table>
<thead>
<tr>
<th>Patient</th>
<th>Normal</th>
<th>Mismatch</th>
<th>50% to 80%</th>
<th>&lt;50%</th>
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<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>1</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
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<tr>
<td>12</td>
<td>16</td>
<td>2</td>
<td>9</td>
<td>5</td>
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</tbody>
</table>

Mean: 18.4 2.5 6.8 4.3
SD: 4.7 2.1 2.6 4.5

Quantitative assessment of regional viability with PET in 32 regions of LV, graded as normal, mismatch, or match. PET results for LV apex were omitted because MR tagging did not involve this region.

TABLE 3. Recovery of Regional Myocardial Function Between 1-Week and 3-Month Studies

<table>
<thead>
<tr>
<th></th>
<th>Match Pattern (BF&lt;50%)</th>
<th>Match Pattern (BF 50% to 80%)</th>
<th>Mismatch Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 Week 3 Months</td>
<td>1 Week 3 Months</td>
<td>1 Week 3 Months</td>
</tr>
<tr>
<td>End-diastolic wall thickness</td>
<td>1.15±0.18 (P&lt;0.0001)</td>
<td>1.16±0.18 (P&lt;0.0001)</td>
<td>1.27±0.17 (P&lt;0.0001)</td>
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<tr>
<td>Wall thickening</td>
<td>18.2±21.0 (P=0.54)</td>
<td>21.4±20.8 (P=0.76)</td>
<td>29.2±22.1 (P=0.18)</td>
</tr>
<tr>
<td></td>
<td>19.8±22.0</td>
<td>22.2±19.6</td>
<td>23.1±17.5</td>
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<tr>
<td>Fiber strain</td>
<td></td>
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<tr>
<td>Subepicardial</td>
<td>-5.1±7.0 (P=0.035)</td>
<td>-7.1±7.6 (P&lt;0.0001)</td>
<td>-14.8±8.3 (P=0.69)</td>
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<tr>
<td>Subendocardial</td>
<td>-5.5±9.7 (P=0.46)</td>
<td>-8.2±10.4 (P=0.0036)</td>
<td>-16.3±10.3 (P=0.62)</td>
</tr>
<tr>
<td>Cross-fiber strain</td>
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<td></td>
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<tr>
<td>Subepicardial</td>
<td>3.2±6.0 (P=0.016)</td>
<td>0.9±8.0 (P&lt;0.0001)</td>
<td>-6.9±7.3 (P=0.39)</td>
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<tr>
<td>Subendocardial</td>
<td>-11.1±7.8 (P=0.033)</td>
<td>-17.0±11.2 (P&lt;0.0001)</td>
<td>-26.4±10.1 (P=0.97)</td>
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<tr>
<td>Ejection fraction</td>
<td>20.9±18.9 (P=0.188)</td>
<td>26.0±18.1 (P&lt;0.0001)</td>
<td>54.8±17.4 (P=0.94)</td>
</tr>
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</table>

BF indicates blood flow.

acquisition of 3 k-lines per heart beat (repetition time, 14 ms; echo time, 8 ms; flip angle, variable; field of view, 400 mm; matrix, 180×256; slice thickness, 8 mm). End-diastolic and end-systolic time points were acquired.

MRI with tagging has been used to mark sites in the myocardium noninvasively, to subsequently image the LV at different times during the cardiac cycle, and to calculate the normal and shear strains of the myocardium. A 3D deformation analysis of the myocardium can be performed with the use of perpendicular short- and long-axis images. The LV myocardium was thus divided into 32 small cuboids encompassing the entire LV except for the apex (Figure 1).

Strain Computations

The images were processed by a dedicated contouring system. After identification of the intersections between the tags and the epicardial and endocardial contours, the long- and short-axis coordinates were merged to obtain 1 unique set of xyz coordinates for each time point. Next, translation of xyz data was performed to a local fiber coordinate system. The new axes were radial (R) using the perpendicular direction to the wall; fiber (F), tangent to the surface and parallel to the local fiber orientation at either the epicardium or endocardium; or cross fiber (X), tangent to the surface and perpendicular to F. Fiber directions were obtained from histological fiber angle data in cadaver studies. Normal and shear strains were computed from the displacements from end diastole to end systole. Positive radial strains represented wall thickening; negative strains, wall thinning; and negative fiber strains, quantified shortening of the myocardium along the local direction of the actively contracting fibers. Positive strains represented fiber lengthening (usually not present in normal myocardium); cross-fiber strains were representative of the deformation of the myocardium perpendicular to the fiber orientation and were related to interaction with fibers at a distance.

Regional and Global Ejection Fraction

The regional ejection fraction quantified the amount of intracavitary blood ejected by each cuboid during systole by use of the intracavitary volume delimited by the converging tag lines and each cuboid. Furthermore, a global LV ejection fraction was obtained by a summation of the regional ejection fraction in each of the 32 cuboids (thereby excluding the apex) and from the 4-chamber long-axis...
images by use of the area-length method as is done in echocardiography.

**Myocardial Wall Thickness**
The true myocardial wall thickness was obtained in a 3D fashion by adjusting the tag length for wall curvature in the longitudinal direction.

**Matching the Data From PET and MR Tagging**
Regional analysis of myocardial viability, strain, and function was performed similarly. The lateral walls were divided into 4 levels, each consisting of 8 segments. Matching of the MR tagging and PET results was accomplished by use of anatomic landmarks. PET results for the LV apex were omitted because MR tagging did not cover this region.

**Reproducibility of Repeated MR Tagging Studies**
To assess the degree of reproducibility between repeated MR tagging studies, 2 MR tagging studies were performed on consecutive days in 5 healthy volunteers. The percentage of variability, calculated as the absolute value of the difference between 2 measurements divided by the mean value, and SD were used to study the interstudy variability.

**Statistical Analysis**
All data are expressed as mean±SD. All data were normally distributed except regional ejection fraction, which showed a slight skew. Comparisons were performed with Student’s t test for paired or unpaired comparisons, a Wilcoxon signed rank, or a multiple ANOVA with Scheffe’s test when appropriate.

**Results**

**Patient Characteristics and Angiographic Findings**
Twelve patients, 10 men and 2 women (age, 62±8 years [mean±SD]) were studied (Table 1). Between the 1-week and 3-month studies, there were no significant differences in heart rate or blood pressure (72±13 bpm and 146±13/84±8 mm Hg at the 1-week study versus 70±11 bpm and 147±13/83±7 mm Hg at the 3-month study; P=NS).

All patients received thrombolysis within 6 hours after the onset of symptoms. In 3 patients, a rescue angioplasty was performed because of failed thrombolysis. Evolution of ECG and enzymatic parameters were indicative of successful reperfusion in all patients. Nevertheless, all patients developed new Q waves in the anterior leads and had significant positive cardiac enzymes (Table 1).

In 6 patients, an elective angioplasty of the residual stenosis was performed at 1 to 5 days after initial reperfusion but before the MR tagging and PET studies (Table 1).

**Regional Viability on PET**
For a total of 32 regions, a normal flow pattern was found in 18.4±4.7 regions, a mismatch pattern was found in 2.5±2.1 regions, and a match pattern with an MBF between 50% and 80% was seen in 6.8±2.6 regions and with an MBF <50% in 4.3±4.5 regions (Table 2).

**Regional LV Function at 1 Week**
At 1 week, all strain parameters were significantly more impaired in areas with a match pattern than in areas with a mismatch pattern or in the normal, remote myocardium (P<0.0001 for all) (Table 3). In the matched myocardium, the functional damage of the myocardium was similar for all layers. Subepicardial cross-fiber strain was the most impaired, with mean positive values indicating substantial systolic bulging; negative values of thickening correspond to regional wall thinning during systole. The result was a significant decrease in ejection fraction most pronounced for the matched myocardium (MBF <50%, 20.9±18.9%; MBF of 50% to 80%, 29.6±21.8%), gradually improving over the mismatch to the normal flow regions. Compared with control subjects, however, even these remote normal regions showed a diminished function (54.3±15.1% in the “normal” myocardium versus 65.5±10.0% in control subjects; P<0.0001).

Compared with healthy control subjects, a significant increase in LV end-diastolic and end-systolic volumes was found (103±30 and 62±27 mL in patients with acute MI [Table 4] versus 84±16 and 30±10 mL in control subjects; P=0.0077 and P<0.0001, respectively). In the first week after the acute event, the LV end-diastolic wall thickness was significantly larger in all regions compared with healthy volunteers (P<0.0001 for all), possibly because of a preexisting hypertrophy or an early hypertrophic remodeling.

**Functional Recovery at 3 Months**
Fiber strains in the matched myocardium showed more recovery than those in the mismatched and normal regions. This was most pronounced for the subepicardial region in which both fiber and cross-fiber strains improved significantly; the increase was most striking in the region with an MBF between 50% and 80%. In the subendocardial layers, improvement was also present for the matched myocardium but only in the region with an MBF between 50% and 80%. In the normally perfused, remote areas, subendocardial fiber shortening and cross-fiber shortening increased significantly (Figure 2). Wall thickening did not change significantly between 1 week and 3 months in either region, but the increased fiber contractions at the subepicardium resulted in more epicardial inward motion and a very significant increase in regional ejection fraction from 29.6±21.8% to...
43.5 ± 15.5% (P < 0.0001) (Figure 3). The other regions manifested no or only a small increase.

Wall thickness at end diastole decreased significantly in all regions from 1 week to 3 months but remained higher than in the control population.

Global LV ejection fraction (summation of all the cuboids) was 44.2 ± 22.2% at 1 week (compared with 46 ± 8% from LV angiography), increased to 49.3 ± 17.9% at 3 months (P < 0.0001), but remained significantly lower than in healthy control subjects (65.5 ± 10.0%; P < 0.0001 for both). The values obtained with the area-length method showed similar trends (41 ± 11% to 49 ± 7%; P < 0.05). The LV end-diastolic volume increased from 103 ± 30 to 114 ± 27 mL (P = 0.0085), whereas no significant changes were found for LV end-systolic volume (62 ± 27 versus 59 ± 18 mL; P = 0.34).

Reproducibility of Repeated MR Tagging Studies
No statistically significant differences were found between the 2 measurements. The interstudy variability for the ejec-

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**Figure 2.** Fiber and cross-fiber shortening at epicardium (EPI) and endocardium (ENDO) at 1 week and 3 months for different regions: normal, mismatch, match with MBF 50% to 80% of normal, and match with MBF < 50% of normal (mean percent ± SD at end systole).
tion fraction was $4.7 \pm 1.9\%$ and varied between $3.7 \pm 1.8\%$ and $10.7 \pm 2.6\%$ for the fiber strains.

**Discussion**

**Combined PET-MR Tagging Approach**

Several approaches have been proposed to detect the degree of myocardial viability and functional recovery after MI.\textsuperscript{4,16–19} We investigated patients with a first anterior transmural MI, combining PET and MR tagging, to compare regional function with the level of flow and metabolism.

**Early Findings**

Our findings at 1 week show that contractile function of the infarcted region was significantly impaired. In addition, in the mismatch and normal areas, a depressed function compared with control subjects was present. These findings confirm previous research showing a functional impairment of non-infarcted myocardium,\textsuperscript{20} which is very likely related to increased wall stress,\textsuperscript{21} although a vasomotor dysfunction may also contribute.\textsuperscript{22}

**Late Recovery**

Recovery at 3 months is present mainly in the match region with an MBF of 50% to 80% and can be related to improved fiber contraction in the subepicardial layers of this part of the infarct territory. All infarctions in this study could be defined as transmural infarctions. Nevertheless, a functional recovery was clearly demonstrated even in the matched myocardium with severely reduced MBF. Because we looked at deformation of the myocardium in the direction of the actively contracting fibers, this study strongly suggests the presence of viable myocardial tissue in the subepicardial layers of a transmural MI, not detectable by PET, which gradually recovers after the acute event. In the matched myocardium with a severe reduction in MBF, functional recovery in the subepicardial layers, however, is insufficient to improve regional ejection fraction; this can also be inferred from the limited increase in subendocardial cross-fiber shortening. These regions very likely correspond to the myocardium showing the largest infarct “transmurality,” whereas matched regions with intermediate MBF are representative of less severe transmural infarct extensions. Although the results of this study could not be compared with patients in whom reperfusion failed, restoration of blood flow with salvage of the subepicardial fibers is the most likely mechanism underlying this functional recovery, and even when regional ejection fraction is not increased, improvement in subepicardial contraction could limit infarct expansion and development of an aneurysm.

Detection of the most marked cross-fiber recovery in the subendocardium of the matched region with an MBF of 50% to 80% indirectly supports the finding of a larger improvement in active fiber contraction in the subepicardium of the same region caused by myocardial tethering.\textsuperscript{12,23} The smaller but significant recovery of the subendocardial fiber shortening in the matched myocardium with an MBF between 50% and 80% suggests the presence of subendocardial islands of viable myocardial tissue.

The apparent contradiction of recovery of regional ejection fraction without an improvement in wall thickening in the infarct region suggests that the mechanism for ejection relies on both wall thickening and epicardial inward motion. If epicardial function recovers with increased deformation and inward motion, the epicardium can push the more endocardially located layers toward the cavity without a significant increase in wall thickening but nevertheless with an improved regional ejection fraction.

Absence of a significant functional recovery between 1 week and 3 months in myocardial regions showing a mismatch pattern at 1 week is unexpected. These regions are the
least represented in these patients with an aggressive reperfusion strategy and at the 1-week study already show a function comparable to the normal, remote areas, which leaves little room for further improvement. They could contain both normal and ischemic or necrotic tissue in various proportions. Also, increases in wall stress in these mismatch areas at the edge of the infarction could explain the lack of recovery of these load-dependent functional parameters. Further study in patients with larger areas of mismatch myocardium is needed.

In the normal myocardium, a small but significant recovery in regional ejection fraction was demonstrated as a consequence of an improved subendocardial fiber and cross-fiber shortening. Because this region has normal myocardial flow, the most likely mechanism is an improved stress-strain relation as a consequence of the functional recovery in the infarct region. Lowering the wall stress in noninfarcted myocardium represents a favorable remodeling after thrombolytic therapy. Compensatory hyperkinesis in the noninfarcted region seems less likely because this region has significantly lower myocardial strains compared with a control group.

**Study Limitations**

**Number of Patients**

The number of patients included in this study is small, mainly because of the elaborate study protocol. By analyzing the changes in strains in every segment from 1 week to 3 months, we obtained statistically significant results for those regions that contain a sufficient number of segments and are equally distributed among patients. This is clearly the case for the normal and match regions with MBF of 50% to 80%, less so for the match regions with MBF <50%, and not so for the mismatch regions (Table 2). The results obtained in the mismatch regions, therefore, have to be interpreted with caution. When segments are unevenly spread among patients, the magnitude of the results could also be influenced.

**Reliability of MR Myocardial Tagging**

The accuracy of MR myocardial tagging to study myocardial deformation has been validated by means of solid and deformable phantom models.24,25 The technique allows precise quantification of complex 3D motion and deformation patterns, and the results correspond very well with those obtained by invasive methods that use metallic markers sewn in the myocardium.12,26-27 Variability percentages were small and comparable with previous reports that used MR imaging to quantify LV parameters.28 So although there is ample evidence to support the intrinsic accuracy of the technique, the limitations of the present study are introduced by the need to match MRI and PET data and the imprecision of matching serial MRI studies. Although matching was optimized using the same distribution of regional segments and aligning anatomic landmarks, some degree of malalignment cannot be discarded, affecting primarily the border zones.

Matching serial MRI studies with different LV volumes is another problem. Because dilatation of the ventricle usually is not homogeneous and the tag distribution is, we could not completely be certain that we had matched regions between the first and second MRI examinations. The mismatch error is in principle limited to regions in which changes in volume or shape are very localized, but we saw no large aneurysms on control MRI or echo studies.

**Quantification of LV Ejection Fraction**

Global ejection fraction was rather high for patients with a transmural anteroapical infarction. This is very likely due to exclusion of the LV apex. When the volumetric or angiographic data were used for ejection fraction calculation, consistently smaller LV ejection fractions were obtained.

**Use of Fiber Strains**

Although the calculation of fiber and cross-fiber shortening could suffer from the use of cadaver measurements rather than actually measured pathological fiber angles, use of fiber strains was preferred over principal or local cardiac strains because this greatly enhances the understanding of underlying mechanical phenomena.15 Changes in principal and local cardiac strains showed completely consistent results with changes primarily in the subepicardium.

**Conclusions**

This study for the first time relates regional functional impairment of a first transmural anterior MI to the degree of viability and shows that recovery of subepicardial fibers of a transmural infarct region significantly contributes to the late improvement in regional and global LV function. Whereas early reperfusion is undoubtedly extremely important for limiting overall infarct size, restoration of flow in the infarct-related vessel can also preserve fibers in the subepicardial and lateral border zone of a transmural infarction. Although similar studies in patients in whom reperfusion failed are needed, we can speculate that the absence of reperfusion and subsequent recovery of the subepicardial region of a transmural infarct region will lead to infarct expansion, ventricular remodeling, and possibly aneurysm formation.

**Acknowledgments**

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