PATHOPHYSIOLOGY AND NATURAL HISTORY
CORONARY ARTERY DISEASE

Arteriographic predictors of spontaneous improvement in left ventricular function after myocardial infarction

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ABSTRACT To better characterize the changes in left ventricular ejection fraction after myocardial infarction, we compared radionuclide ventriculograms obtained acutely and 2 weeks after acute myocardial infarction in 40 patients. These patients underwent angiography within a mean of 4 h and 20 min after the onset of symptoms of infarction and either received no therapy (32 patients who were control subjects in a thrombolysis trial) or did not experience reperfusion (eight patients) despite receiving streptokinase infusions. In all 40 patients, the change in left ventricular ejection fraction over 2 weeks was small (+2.6%). Patients were then grouped according to the presence or absence of residual flow on their angiograms. Residual flow was considered to be present in 21 patients, in 12 by virtue of subtotal occlusion of the artery supplying the area of infarct and in nine because of well-developed coronary collaterals to the distal infarct artery. Mean change in ejection fraction for patients with residual flow was +6.9 ± 2.3% vs −2.2 ± 1.7% for patients without residual flow (p < .01). Fourteen of 21 (67%) patients with residual flow had a spontaneous rise in ejection fraction of greater than 5%, as compared with two of 19 (11%) patients without residual flow (p < .01). Time to peak level of creatine kinase (CK) was significantly shorter in the residual flow group (15 vs 23 h, p < .01), while the peak level of CK was lower (1550 vs 2220 IU) in these patients. This latter difference did not reach statistical significance (p = .10). Of patients with residual flow, those with subtotal occlusion had greater improvement in ejection fraction (9.6 ± 3.0%) than those with collateral vessels (3.2 ± 3.2%). We conclude that spontaneous improvement in left ventricular ejection fraction is frequently observed in patients after acute myocardial infarction and that the presence of residual flow on angiograms obtained shortly after appearance of symptoms is predictive of subsequent improvement. These findings must be considered when evaluating the results of nonrandomized acute myocardial infarction trials.


IN RECENT YEARS a variety of interventions designed to limit myocardial necrosis by early reperfusion of coronary arteries have been proposed.1–4 To evaluate the impact of these interventions on left ventricular function, most investigators have used serial radionuclide ventriculography. Improvements observed between the short-term and 2 week follow-up study have been ascribed to myocardial salvage secondary to successful intervention.

The variability of sequential radionuclide ventriculograms has been shown to be small in patients with ventricular dysfunction due to chronic ischemic heart disease.5, 6 However, considerably greater variability has been reported when serial studies are performed during the peri-infarction period,7–9 even in the absence of any immediate intervention. As a result, a significant number of postinfarction patients may be expected to demonstrate spontaneous improvement in left ventricular function.

To further characterize these spontaneous changes after infarction, and to determine whether these changes can be predicted on the basis of coronary anatomy at the time of angiographic examination shortly after appearance of symptoms of myocardial infarction, we undertook the following study.

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Methods

Patients. Forty patients studied as part of a randomized acute myocardial infarction reperfusion trial form the study population for this report. This patient group was derived from a series of 61 patients who presented within 4 hr of the onset of symptoms of myocardial infarction. Inclusion criteria consisted of chest pain of greater than \( \frac{1}{2} \) hr duration that was unresponsive to nitroglycerin and associated with at least 2 mm of ST elevation in two or more contiguous electrocardiographic leads. Patients underwent angiography at a mean of 4 hr and 20 min after the onset of symptoms of acute myocardial infarction.

Since this study was designed to examine spontaneous changes in left ventricular ejection fraction, those patients in whom reperfusion was accomplished during angiography are not discussed further, but have been reported previously.\(^\text{10}\) Twenty-one patients were excluded on this basis. Of the remaining 40 patients, there were 12 with subtotal occlusions of the artery supplying the area of infarct in whom no thrombolysis was attempted (according to our particular reperfusion protocol design) and 28 patients with persistent total occlusions of this artery (eight randomly assigned to streptokinase therapy and 20 assigned to a control group; figure 1). These 40 patients form the basis of this report.

All 40 patients were subsequently shown to have had acute myocardial infarctions by serial enzyme analysis and electrocardiography. No attempt was made to standardize postmyocardial infarction management in these patients with the exception that patients with incomplete occlusion of the artery supplying the area of infarct received full heparinization. Only one patient underwent coronary bypass graft surgery on day 7 for recurrence of angina.

Radionuclide studies. Resting radionuclide ventriculograms were obtained from all patients within 2 hr of completion of the angiographic examination and at a mean of 13.2 days after myocardial infarction. Global left ventricular ejection fractions were determined from the left anterior oblique view by standard radionuclide techniques. A change in ejection fraction in a given patient of greater than 5% was considered to be beyond the intrinsic variability of the technique and thus was considered to be significant.

Enzymatic studies. Total creatine kinase (CK) levels were determined at the time of admission, every 4 hr for the first 24 hr, and every 6 hr for the next 24 hr. Of the 40 patients studied, complete CK data were available for 33. Peak level of CK and time to peak (after onset of symptoms) were calculated for these patients.

Angiographic subgroups. Each patient's coronary angiogram was examined by two angiographers for the presence or absence of residual flow (figure 2). Residual flow was considered to be present if the artery supplying the area of infarct was subtotally or totally occluded and there were well-developed coronary collaterals to the infarct zone. Coronary collaterals were graded by two independent angiographers, as previously described.\(^\text{11}\) Well-developed coronary collaterals were considered to be present when most or all of the distal segments of the occluded coronary artery were well opacified in a retrograde fashion. Patients with total occlusions and with no or poorly developed coronary collaterals were considered to have no residual flow. Disagreements as to collateral status were adjudicated by a third angiographer.

Statistical analysis. Continuous variables are presented as mean ± SEM. Times to peak level of CK were not distributed normally and are presented with the use of the median and the interquartile range. Statistical analysis was performed by paired and unpaired t tests, with \( p < .05 \) considered to indicate significance.

Results

For all 40 patients the mean ejection fraction shortly after infarction was 42.7 ± 2.3% and it increased to 45 ± 2.3 at 2 weeks follow-up (figure 3). The mean change in ejection fraction of +2.5% was not statistically significant. Sixteen patients had a greater than 5% improvement in their ejection fractions at follow-up as compared with the initial value.

Residual flow was present in 21 patients and absent in 19. The two groups were not significantly different with respect to sex, age, vessel supplying infarct, extent of coronary artery disease, or acute ejection fraction (table 1). Of those 21 patients with residual flow, 67% (14 of 21) demonstrated spontaneous improvement in ejection fraction of greater than 5%; only 11% (two of 19) of the patients without residual flow had

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FIGURE 1. Selection of the study population. Patients with subtotal occlusion of the infarct-related artery on their initial angiograms were not treated with streptokinase and are included. Those patients whose infarct-related arteries were initially totally occluded but in whom reperfusion was achieved are excluded.
such an improvement (figure 4). This difference was significant at p < .01. The mean interval change in ejection fraction was +6.9 ± 2.3% for the residual flow group vs −2.2 ± 1.7% for the group without residual flow (p < .01; see figure 5). Time to peak level of CK was also significantly shorter (p < .05) in the patients with residual flow (median 15 [interquartile range 13 to 21.5] vs 23 [interquartile range 21.5 to 26]). A trend toward lower peak CK values for the residual flow group vs the group without residual flow was observed (1550 ± 227 vs 2220 ± 344), but the difference did not reach statistical significance (p = .10).

Of the 21 patients with residual flow, 12 had subtotal occlusions while nine had total occlusions with well-developed coronary collaterals. No significant differences in demographic parameters were observed between the two groups (table 2). Spontaneous improvement in left ventricular ejection fraction was relatively common in both subgroups; 75% (nine of 12) of those with subtotal occlusions and 57% (five of nine) of those with total occlusions and coronary collaterals experienced spontaneous improvement. The change in ejection fraction in the coronary collateral group was intermediate between that in the group without residual flow and the group of patients with subtotal occlusion of the artery supplying the area of infarct (figure 6). While patients without residual flow had a decrease in ejection fraction of 2.2 ± 1.7%, in patients with coro-

Prior myocardial infarction and history of angina were infrequent clinical observations that were equally represented in the groups and did not correlate with subsequent changes in ejection fraction. Specifically, coronary collaterals were not more prevalent in patients with as compared with patients without previous history of angina.

Discussion

Consistent with prior studies of ejection fraction, after myocardial infarction the mean ejection fraction of the 40 patients in this study did not change significantly. However, 25 of 40 patients had a change in ejection fraction (rise or fall) of greater than 5%, a change greater than the intrinsic variability of the ra-
dionuclide ventricular measurement of ejection fraction.5  Recently Wackers et al.9 demonstrated that as many as 56% of patients with documented acute myocardial infarction may have significant spontaneous changes in left ventricular ejection fraction during the early hours of infarction. Although it is tempting to ascribe these changes in ejection fraction to fluctuating autonomic tone, changing loading conditions, or pharmacologic interventions, we believed that the changes might also have been due to more fundamental ana-

![FIGURE 4. Comparison of the spontaneous changes in ejection fraction over the course of the hospitalization in patients with and without residual flow to the infarct zone. Data from patients with greater than 5% increase in the ejection fraction are indicated by the dashed lines.](image)

![FIGURE 5. The mean change in ejection fraction, time to peak CK activity, and peak CK activity in patients with and without residual flow to the infarct zone at the time of the angiographic examination.](image)

### TABLE 1
Characteristics of study population

<table>
<thead>
<tr>
<th>Residual flow</th>
<th>Absent</th>
<th>Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57 ± 0.0</td>
<td>54 ± 1.8</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>17 (89%)</td>
</tr>
<tr>
<td>Female</td>
<td>2 (11%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Infarct-related vessel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>10 (53%)</td>
<td>14 (67%)</td>
</tr>
<tr>
<td>Cx</td>
<td>2 (10%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>RCA</td>
<td>7 (37%)</td>
<td>5 (24%)</td>
</tr>
<tr>
<td>CAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>9 (47%)</td>
<td>13 (62%)</td>
</tr>
<tr>
<td>Double</td>
<td>5 (26%)</td>
<td>5 (24%)</td>
</tr>
<tr>
<td>Triple</td>
<td>5 (26%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Acute EF (%)</td>
<td>42.4 ± 3.8</td>
<td>42.9 ± 2.7</td>
</tr>
</tbody>
</table>

LAD = left anterior descending coronary artery; Cx = circumflex artery; RCA = right coronary artery; CAD = coronary artery disease; EF = ejection fraction.

![TABLE 2](image)

### TABLE 2
Characteristics of patients with residual flow due to well-developed collaterals or a subtotally occluded vessel

<table>
<thead>
<tr>
<th>Well-developed coronary collaterals</th>
<th>Subtotal occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>9</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53 ± 3.6</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>Female</td>
<td>0</td>
</tr>
<tr>
<td>Infarct-related vessel</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>Cx</td>
<td>0</td>
</tr>
<tr>
<td>RCA</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>CAD</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>6 (67%)</td>
</tr>
<tr>
<td>Double</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Triple</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>Acute EF (%)</td>
<td>45.6 ± 5.1</td>
</tr>
</tbody>
</table>

Abbreviations are as in table 1.
supplying the area of infarct, or those with total occlusion and well-developed collaterals, had significant improvement of global left ventricular ejection fraction (change in ejection fraction + 6.9%) relative to patients with no residual flow (change in ejection fraction - 2.2%).

Since there were no differences between the two groups with regard to age, sex, location of infarct, extent of coronary artery disease, or ejection fraction during the early hours of infarction, these factors could not have significantly influenced the results.

**Subtotal occlusion.** The most dramatic improvements in global ejection fractions were seen in the subgroup of patients with residual flow who had antegrade filling of the artery supplying the infarct at the time of the initial angiographic examination. It is presumed, although not proven, that these patients had spontaneous reperfusion of the infarct-related artery. Several recent studies have suggested that spontaneous reperfusion that occurs early after the onset of acute myocardial infarction may alter the degree of irreversible myocardial damage and hence influence the change in ejection fraction seen in the postinfarction period. De Feyter et al. performed coronary angiographic examinations in patients 6 to 8 weeks after acute infarction and found that those with anterior myocardial infarction and spontaneous recanalization of the infarct-related artery had significantly less myocardial damage and a higher ejection fraction than patients with inferior infarction and persistent occlusion. Similar trends were noted in patients with anterior myocardial infarction. It was hypothesized that spontaneous recanalization may have increased flow to the border zones and thus limited extension of infarct.

**Early peaking CK levels.** Ong et al. noted that patients with acute myocardial infarction and spontaneously occurring rapid release of CK-MB (mean time to peak CK activity = 11.6 ± 2.7 hr) had significant improvement in their global and regional left ventricular ejection fractions as assessed with radionuclide ventriculography performed within 24 hr of infarction and at hospital discharge. Based on the fact that rapid release of CK appeared to be a marker of reperfusion in thrombolysis trials, Ong et al. suggested that spontaneous reperfusion during acute infarction resulted in improvement of global and regional left ventricular function.

The present study both confirms and extends the findings of Ong et al. Peak CK activity in the subgroup of patients in this study with antegrade flow through the infarct-related artery at the time of angiographic examination occurred at 15 hr (interquartile range 12.3 to 15.5) as compared with 23 hr (interquartile range 21.1 to 26.0) in patients with total occlusion (regardless of coronary collateral status) of the infarct-related artery (p < .01). The mean 9.6% increase in ejection fraction during the course of the hospitalization is nearly identical to the 10% increase noted by Ong et al. in patients with early-peak CK. Thus, the present study angiographically confirms that early patency of the infarct-related vessel is responsible for the accelerated washout of CK-MB and is associated with spontaneous improvement in left ventricular function.

**Coronary collaterals.** Patients in the study with well-developed collaterals to the distal infarct vessel also exhibited a tendency toward improved left ventricular function at 2 weeks follow-up (change in ejection fraction +3.2%) relative to patients with total occlusion and poorly developed or no collaterals (change in ejection fraction - 2.2%). In the past, studies assessing the ability of coronary collaterals to limit infarct size in man have yielded conflicting results. To a large extent this controversy resulted from studies in which a patient's collateral status was determined at some time remote from the myocardial infarction. We have recently reported that development of coronary collaterals in man after myocardial infarction occurs rapidly over a period of days. Therefore, the fact that colla-
terials are present more than a few days after infarction does not accurately reflect the situation that existed during the critical hours immediately after coronary occlusion. In this study, in which collateral status was evaluated within a few hours of infarction, those patients with well-developed collaterals tended to have a slight improvement in left ventricular function that was not seen in patients without well-developed collaterals. The fact that the improvement in ejection fraction was rather modest suggests that the myocardial recovery was limited to a relatively narrow zone.

Recently, analysis of regional wall motion has been reported to be a more sensitive measure of myocardial salvage than changes in global ejection fraction in patients with reperfused acute infarction. While this increased sensitivity has been useful in demonstrating benefit in some reperfusion trials, the magnitude of spontaneous improvement observed in our patients with residual flow was sufficiently large to be detected by global changes in ejection fraction. It is possible that additional patients in our series may have had slight improvement in left ventricular function that would have been uncovered by regional wall motion analysis; however, the clinical and prognostic significance of such changes remain to be determined.

In reporting their experience with interventions aimed at producing early reperfusion in patients with acute myocardial infarction, several investigators have suggested that the patients most likely to demonstrate functional improvement after successful interventions include those with subtotally occluded infarct vessels and those with readily visualized collaterals to the distal infarct-related artery. The present study suggests that improvement in left ventricular function may be expected to occur spontaneously in a majority of these patients even without use of immediate interventions. These findings further reinforce the need for randomized studies to determine whether the benefits observed in some patients after reperfusion result from successful medical intervention or merely reflect the natural history of a subgroup of patients with acute myocardial infarction.

In summary, we found that spontaneous changes in left ventricular ejection fraction are frequently observed in patients after acute myocardial infarction. Furthermore, the presence of residual flow documented at the time of angiographic examination shortly after appearance of symptoms correlates well with subsequent spontaneous improvement in left ventricular function. This spontaneous improvement must be considered when evaluating the results of nonrandomized acute myocardial infarction intervention trials.

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