Factors that determine recovery of left ventricular function after thrombolysis in patients with acute myocardial infarction

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With the technical assistance of Suzanne Mitten and Jane Wygant

ABSTRACT The coronary and ventricular angiograms of 47 patients with acute myocardial infarction in whom reperfusion was achieved by intracoronary streptokinase were quantitatively analyzed to determine the factors that affect recovery of regional left ventricular function after reperfusion. Hypokinesis in the infarct region was measured by the centerline method and expressed in terms of standard deviations (SDs) from normal. Severity of coronary artery stenosis was measured quantitatively. Hypokinesis showed more significant improvement after thrombolysis in patients with minimum stenosis diameter of greater than 0.4 mm than in those with severe residual stenosis, i.e., stenosis producing a minimum diameter of 0.4 mm or less (1.0 ± 1.3 SD/chord, n = 31, vs 0.0 ± 0.9 SD/chord, n = 7; p < .05). Improvement in hypokinesis was greater in patients who received thrombolytic therapy within 2 hr than in those treated later (2.1 ± 1.1, n = 8, vs 0.7 ± 1.0 SD/chord, n = 28; p < .001). These results indicate that angiographic reperfusion alone may not be sufficient: reperfusion must provide adequate flow and be achieved early to salvage myocardial function.


There have been many studies of the efficacy of thrombolytic therapy in achieving reperfusion, salvaging myocardial function, and reducing mortality. However, the reported efficacy of streptokinase, the most frequently used agent, in reducing mortality has varied widely in several randomized trials.1-3 Randomized studies measuring change in the ejection fraction, a powerful predictor of survival,4 have also had conflicting results.3, 5-7 One reason is that the ejection fraction may not sensitively reflect changes in regional function at the infarct site because of the influence of compensatory hyperkinesis of the noninfarcted region.8, 9

However, even when regional function was measured, significantly improved function was observed in only 40% of patients with angiographically proven sustained reperfusion,8 indicating that factors other than achievement of reperfusion affect the recovery of left ventricular function.

The present study was performed to determine the effect of the following factors on recovery of regional left ventricular wall motion in patients undergoing reperfusion: (1) the time delay from onset of chest pain to reperfusion, (2) the severity of residual stenosis at the conclusion of thrombolytic therapy, (3) the severity of acute left ventricular dysfunction, (4) the location and severity of the acute occlusion, and (5) the time from infarction to follow-up study.

Materials and methods

Patient populations. The effect of acute severity of functional abnormality, location of thrombosis, and residual stenosis was studied in previously reported patients8 in whom reperfusion was achieved with intracoronary streptokinase therapy. All patients were admitted to the Eppendorf Hospital less than 3 hr after onset of chest pain that was unresponsive to sublingual nitroglycerin and all had 2 mm or greater ST segment elevation without significant Q waves in the leads of ST elevation on the admission electrocardiogram. This group represents 30% of all patients admitted with acute myocardial infarction during the study period and 70% of all patients treated with thrombolytic therapy. The other 30% were excluded because they were ad-
mitted more than 3 hr after onset of symptoms, they refused to undergo follow-up angiography, or they had angiograms unsuitable for quantitative analysis or because reperfusion was not successful.

All patients underwent immediate contrast angiographic examination of the arteries supplying the noninfarcted and infarcted areas. Each then received an intracoronary streptokinase infusion at 4000 U/min until reperfusion, then at 2000 U/min for at least 45 min longer, followed by a ventriculographic examination in the 30 degree right anterior oblique projection. Postreperfusion anticoagulation during hospitalization was achieved with either aspirin and dipyridamole or intravenous heparin. All patients underwent repeat coronary and ventricular angiography 45 ± 47 days later. The effect of the timing of follow-up angiography was determined in 13 patients who consented to undergo a third cardiac catheterization late (8 months to 2 years) after thrombolytic therapy.

The time to treatment was defined as the time elapsed from onset of chest pain until thrombolytic therapy was initiated.

The cine films of the ventriculograms and coronary angiograms were analyzed at the University of Washington.

**Analysis of left ventriculograms.** The cine films were projected and the end-diastolic and end-systolic endocardial contours were traced from the frames with maximum and minimum volume, respectively, from a normal nonpostpremature sinus beat. No attempt was made to correct for the translational motion of the heart within the chest because (1) the methods of doing so described thus far are arbitrary and empirical,10 and (2) the apex is an unreliable landmark for realigning the end-diastolic and end-systolic contours.11,12 Left ventricular volume was calculated by the area-length method.13 Wall motion was measured by the centerline method along 100 chords constructed perpendicular to a centerline drawn midway between the end-diastolic and end-systolic contours (figure 1), normalized for heart size, and expressed in units of standard deviations (SDs) from the mean motion in 64 normal subjects. Regional wall motion abnormality was calculated as the mean motion of chords lying in the most hypokinetic 50% of the territory of the infarct artery, and expressed in SDs per chord. The derivation of this method has been previously described.8,14,15

**Analysis of coronary cineangiograms.** The coronary cineangiogram obtained at the conclusion of thrombolytic therapy was projected and the contours of the lumen of the infarct artery at the site of thrombosis were traced two or three times by each of two observers and digitized. The diameter of the lumen was measured along chords constructed perpendicular to a centerline drawn in midlumen and corrected for image magnification and pin-cushion distortion as previously described16 (figure 2). The minimum diameter of the stenosis was determined from the optimal view, or calculated as the mean diameter measured from orthogonal views, and the percent stenosis was calculated.

**Statistical analysis.** Statistical analysis was performed with Student’s t test (to compare two groups of patients and to assess change in arterial dimension between the four to six measurements made before with those made after thrombolytic therapy), linear regression (to correlate two continuous variables), one-way analysis of variance (to compare the function in more than two patient groups), and discriminant analysis (to determine which factors best distinguished patients with improved ventricular function from those without improvement17). Values are expressed as the mean ± SD.

**Results**

**Patient characteristics.** There were 41 men and six women ranging in age from 28 to 82 years (mean 52 ± 13 years). Thrombosis was in the left anterior descend-ing coronary artery in 19, the right coronary artery in 21, and the circumflex artery in seven patients.

**Effect of site of thrombosis.** None of the patients had a thrombosis located distally in the infarct artery. However, patients with thrombosis of the circumflex had significantly less hypokinesis early after infarction in the infarct region, as viewed in the 30 degree right anterior oblique projection, than patients with thrombosis of the left anterior descending or right coronary arteries, and they exhibited no functional recovery after reperfusion (table 1). Circumflex lesions were

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**FIGURE 1.** Centerline method of regional wall motion analysis. A, End-diastolic and end-systolic left ventricular endocardial contours and centerline constructed by the computer midway between the two contours. B, Motion is measured along 100 chords constructed perpendicular to the centerline. C, Motion at each chord is normalized by the end-diastolic perimeter to yield a shortening fraction. Motion along each chord is plotted for each patient (solid line). The mean motion in the normal ventriculogram group (dashed line) and one SD above and below the mean (dotted lines) are shown for comparison. D, Standardized motion. The wall motion of the patient is now plotted in units of SDs from the normal mean (dotted line). The normal ventriculogram group mean is represented by the horizontal zero line. Vertical lines delimit the most hyperkinetic and most hypokinetic parts of the anterior and inferior regions.
therefore excluded from the subsequent analyses. Lesions of the left anterior descending and right coronary arteries were analyzed together since the severity of hypokinesis measured early after infarction and the magnitude of improvement after reperfusion were similar in their territories (table 1).

Effect of the severity of residual stenosis. The severity of residual stenosis in the infarct artery could be quantitatively assessed in 38 patients. As seen in figure 3 there was virtually no improvement in regional wall motion in patients in whom the absolute minimum diameter of the stenosis was less than 0.4 mm after thrombolysis (mean change = 0.0 ± 0.9 SD/chord, n = 7). This lack of recovery of function could be explained by rethrombosis in only two of the seven cases, and contrasts significantly (p < .05) with the improvement of 1.0 ± 1.3 SD/chord in patients with stenosis diameter greater than 0.4 mm (from −2.2 ± 1.0 to −1.7 ± 1.2 SD/chord, n = 31, p < .001). The relationship was the same for the left anterior descending and right coronary arteries. There was a similar but less significant relationship between change in regional function and the severity of residual stenosis if expressed in terms of percentage of diameter stenosis. Function did not change in patients with permanent occlusions unresponsive to streptokinase.

To determine whether the lack of functional improvement in some adequately reperfused patients was the result of restenosis, its severity at follow-up was measured in five randomly selected patients. In all five luminal diameter had increased further by 0.20 to 0.65 mm (mean 0.3 ± 0.2 mm). Nevertheless, function deteriorated in two of these. However, when the time delay from onset of symptoms to treatment was examined in the 31 adequately reperfused patients, we found that regional function improved more in patients treated within 2 hr than in those in whom streptokinase was administered later than 2 hr after the onset of pain (2.6 ± 0.6, n = 6, vs 0.7 ± 1.0 SD/chord, n = 25, respectively; p < .002).

Effect of time to treatment and reperfusion. Figure 4 illustrates the relationship between the magnitude of change in regional function at the infarct site and the time from onset of chest pain to treatment in the 36 patients in whom reperfusion was achieved and who

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tbody>
<tr>
<td>Effect of site of thrombosis on left ventricular function in patients with acute myocardial infarction after intracoronary streptokinase therapy</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Infarct artery</th>
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<th>RCA</th>
<th>CFX</th>
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<td>Acute hypokinesis</td>
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<tr>
<td>(SD/chord)</td>
<td>−2.8 ± 0.6</td>
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<td>n</td>
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<td>.05</td>
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<tr>
<td>Reperfused patients</td>
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<tr>
<td>without rethrombosis</td>
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<tr>
<td>Acute hypokinesis</td>
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<tr>
<td>(SD/chord)</td>
<td>−2.8 ± 0.7</td>
<td>−2.7 ± 1.0</td>
<td>−1.4 ± 1.0</td>
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<td>Follow-up hypokinesis</td>
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</tr>
<tr>
<td>(SD/chord)</td>
<td>−1.8 ± 1.2</td>
<td>−1.8 ± 1.0</td>
<td>−1.5 ± 0.9</td>
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<tr>
<td>n</td>
<td>17</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>p value</td>
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<td>.01</td>
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<tr>
<td>Change in hypokinesis</td>
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<tr>
<td>(SD/chord)</td>
<td>1.0 ± 1.0</td>
<td>0.9 ± 1.3</td>
<td>−0.1 ± 0.5</td>
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<tr>
<td>p value vs CFX</td>
<td>.04</td>
<td>.05</td>
<td></td>
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</table>

LAD = left anterior descending coronary artery; RCA = right coronary artery; CFX = circumflex coronary artery.

aBy one-way analysis.

bBy paired t test, early vs follow-up.
did not suffer rethrombosis. Patients treated with streptokinase within 2 hr after onset of symptoms experienced significantly greater improvement than patients treated later \((2.1 \pm 1.1, n = 8, \text{vs} 0.7 \pm 1.0 \text{SD/chord}, n = 28; \ p < .001)\). Similar results were obtained for time to artery opening: patients in whom reperfusion was achieved within 2.5 hr after onset of symptoms improved by \(2.2 \pm 1.1 \text{SD/chord (n = 7)}\), which was significantly more than patients reperfused later \((0.7 \pm 1.0 \text{SD/chord, n = 29, p < .001})\). In three patients regional function improved by more than 1 SD/chord to within 1 SD/chord of normal at follow-up even though reperfusion was achieved 3 hr or more after onset of symptoms. All three had total thrombosis of the left anterior descending coronary artery without collaterals.

**Other factors**

*Acute abnormality in left ventricular function.* The change in hypokinesis in the infarct region after thrombolysis correlated with the severity of hypokinesis early after infarction \((r = - .52, \ p < .001, n = 42\) patients not experiencing rethrombosis) such that the magnitude of improvement was greatest in patients with the most depressed regional function at the time of infarction (figure 5).

*Time from acute infarction to follow-up angiography.* Elev-

**FIGURE 4.** Effect of time to thrombolytic therapy on functional recovery after reperfusion. Change in hypokinesis at the infarct site is plotted against time to onset of treatment. Functional recovery is significantly greater if treatment is instituted less than 2 hr after onset of symptoms. Filled circles indicate patients in whom reperfusion was achieved in less than 2.5 hr after onset of symptoms.
en late ventriculograms, obtained 502 ± 258 days after infarction, could be analyzed. All of the patients were clinically stable between the second and third studies. In the patients in whom reperfusion was successful there was a small but significant late increment in regional wall motion (from −2.8 ± 1.1 early after infarction to −1.9 ± 1.3 at the second study 25 ± 8 days after infarction [p < .05] to −1.5 ± 1.0 SD/chord at the third study [p < .01 vs early, p < .05 vs second study]). There was no significant change in hyperkinesis or in ejection fraction from the early study to the second or third study.

Initial severity of stenosis. Patients with subtotal occlusions had significantly less severe acute wall motion abnormality than patients with total occlusions (table 2). Regional function improved as much in seven patients with subtotal occlusions, in whom minimum diameters of stenosis increased significantly after thrombolytic therapy, as in patients with total occlusions in whom reperfusion was achieved.

Comparison of the factors that influence functional recovery. The power of the preceding factors in determining whether function improved in patients undergoing reperfusion was evaluated by discriminant analysis. The severity of residual stenosis was more powerful than time to reperfusion (absolute standardized coefficient .79 and .69, respectively) in distinguishing patients with from those without 1 SD or more improvement in regional wall motion at the infarct site. The time to reperfusion was slightly more powerful than initial severity of hypokinesis in distinguishing patients with from those without severe residual hypokinesis (below −2 SD/chord) at follow-up (absolute standardized coefficient = .88 and .78, respectively). Since time to angiographic reperfusion is known in

![FIGURE 5. Effect of acute abnormality in left ventricular function on recovery after reperfusion. Change in the severity of hypokinesis at the infarct site is plotted against acute severity of hypokinesis in patients with sustained reperfusion. The dashed vertical and horizontal lines demarcate function thresholds showing that improvement exceeding 1, 2, or 3 SD/chord was seen only in patients with acute function more depressed than 1, 2, or 3 SD/chord below normal, respectively.]

### TABLE 2
**Effect of reperfusion on function in patients with subtotal and total occlusions**

<table>
<thead>
<tr>
<th></th>
<th>Total occlusion (n = 35)</th>
<th>Subtotal occlusion (n = 7)</th>
<th>p value*</th>
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</thead>
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<tr>
<td>Hypokinesis in infarct region (SD/chord)</td>
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<td></td>
</tr>
<tr>
<td>Early study</td>
<td>−2.6 ± 1.0</td>
<td>−2.0 ± 0.5</td>
<td>.023</td>
</tr>
<tr>
<td>Follow-up study</td>
<td>−1.9 ± 1.1</td>
<td>−1.1 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Change</td>
<td>0.7 ± 1.2</td>
<td>0.9 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>p value b</td>
<td>.001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early study</td>
<td>56 ± 15</td>
<td>53 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up study</td>
<td>55 ± 14</td>
<td>55 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>Change</td>
<td>−1 ± 10</td>
<td>2 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>p value b</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

*By unpaired t test, total vs subtotal occlusion.

bBy paired t test, early vs follow-up.
patients treated with intracoronary streptokinase, this parameter was used in the discriminant analysis. However, time to initiation of treatment was a covariate and behaved similarly, although slightly less powerfully. Mean time from onset of treatment to reperfusion was 0.55 ± 0.27 hr (range 0.20 to 1.25 hr). The remaining factors tested lacked sufficient discriminant power for selection.

Discussion

Major factors that influence functional recovery after reperfusion. The results of the present study indicate that the efficacy of reperfusion in salvaging myocardium in patients with myocardial infarction is significantly influenced by the severity of residual stenosis and the time delay from onset of symptoms to initiation of thrombolytic therapy.

Our data confirm an early observation by Merx et al.\textsuperscript{18} that the ejection fraction may fall if coronary flow is slow after thrombolysis and represent the first quantitative analysis of the relationship between recovery of ventricular function and severity of residual stenosis. There are two mechanisms that may explain why functional recovery is precluded by severe residual stenosis. First, reperfusion may be inadequate to salvage myocardium or to support contraction, since experimental studies have shown that ischemia continues when reflow is restricted\textsuperscript{19} and ventricular function deteriorates when coronary blood flow falls below a critical threshold.\textsuperscript{20} Second, as previously reported by Harrison et al.,\textsuperscript{21} rethrombosis and reinfarction are more likely to occur in the presence of a severe residual stenosis. Others have reported a lack of correlation between functional outcome and their estimate of residual percent stenosis.\textsuperscript{22} However qualitative assessment is not sufficiently accurate to detect the small but critical differences in severity noted here,\textsuperscript{23} and coronary flow and flow resistance relate to the absolute dimension of a stenosis,\textsuperscript{24, 25} not to the percentage of stenosis. In the present study, the absolute minimum diameter of the lumen was measured in the view affording optimal visualization of the artery. Little increase in accuracy was derived from biplane analysis because the difference between diameters measured from two orthogonal views averaged less than 0.17 mm in this study (n = 5), which is similar to the published accuracy of ±0.15 mm for this method.\textsuperscript{26} Some patients had improved ventricular function despite residual stenosis that was more severe than previously reported to cause myocardial infarction.\textsuperscript{26} However, measurement of the stenosis at the conclusion of angiographic examination overestimates its severity since this systemic fibrinolytic state continues for some hours after cessation of streptokinase infusion\textsuperscript{27} and severity of stenosis is generally less at follow-up.\textsuperscript{21}

The need for very early reperfusion agrees with earlier studies in experimental animals showing that macroscopic infarction develops 40 min after coronary occlusion.\textsuperscript{28} In clinical studies, Mathey et al.\textsuperscript{29} found that both residual regional wall motion abnormality at follow-up and peak levels of creatine were significantly lower in patients reperfused by intravenous urokinase administered within 2 hr after onset of symptoms than in patients in whom reperfusion was not successful but not significantly lower than in patients treated later than 2 hr after onset of pain. Schroder et al.\textsuperscript{30} found that the extent of severe regional hypokinesis measured 4 weeks after infarction in reperfused patients correlated significantly with increasing duration of ischemia. Rentrop\textsuperscript{31} observed that changes in ejection fraction correlated with duration of symptoms in patients without collaterals, although in those with collaterals functional recovery was unrelated to the time to reperfusion. Schwarz et al.\textsuperscript{32} reported that regional and global function was higher and infarct size estimated by creatine kinase release was lower in patients undergoing reperfusion less than 4 hr after onset of symptoms than in patients undergoing reperfusion later or not at all. Although the time threshold differs in these studies, the results agree with early experimental work showing that the amount of myocardium salvaged by reperfusion decreases with progressively longer occlusions. The report of Smalling et al.\textsuperscript{22} stating that ventricular function improves as much in patients undergoing reperfusion 12 to 18 hr after onset of symptoms as in those treated earlier has not been confirmed.

Other factors affecting the evaluation of functional recovery after reperfusion. Our results show that functional recovery after reperfusion is inversely proportional to the severity of regional hypofunction present at the time of acute infarction. These data agree with previous reports that patients with low ejection fractions early after infarction experience greater improvement after reperfusion than patients with higher initial ejection fractions.\textsuperscript{22, 34} This finding is not unexpected, since reperfusion does not result in greater than normal ventricular function. Indeed, because follow-up function in patients undergoing reperfusion does tend toward a common end point, normality, the residual abnormality in ventricular function at follow-up can also be used as a comparative measure of myocardial salvage after thrombolytic therapy if the initial abnormality is similar in the groups being compared.
In our study, the patients with subtotal occlusions before streptokinase therapy had significantly less severe hypokinesis early after infarction than patients with total occlusions. Nevertheless, they manifested as great an improvement in regional function as patients with total occlusions. This is in agreement with previous reports.\(^{30, 34}\) However, one must be cautious in attributing the improvement to thrombolytic therapy since Leiboff et al.\(^5\) found that untreated patients with subtotal occlusions also experienced significant improvement in ejection fraction.

Our finding of a further increase in regional function late after reperfusion agrees with a preliminary report by Terrosu et al.,\(^35\) although others have observed no late improvement in function.\(^{22}\) The magnitude of the increase was small compared with that seen in the first few weeks after infarction.

Our results agree with previous reports that reperfusion of either artery results in improved regional function.\(^{31, 36}\) Another factor reported to enhance functional recovery after reperfusion is the presence of collaterals to the infarct artery.\(^{31, 37}\) This could not be confirmed in the present study because only three of our patients (6%) had collaterals.

We conclude that thrombolytic therapy in patients with acute myocardial infarction has the potential for salvaging left ventricular function. However, simple achievement of angiographic reperfusion may not be adequate. The results of the present study indicate that reperfusion should be achieved very early in the course of infarction, and may need to be supplemented by additional, definitive revascularization procedures to maximize functional recovery.

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