CLINICAL STUDIES

Time From Onset of Symptoms to Thrombolytic Therapy: A Major Determinant of Myocardial Salvage in Patients With Acute Transmural Infarction

DETLF G. MATHEY, MD, FACC,* FLORENCE H. SHEEHAN, MD,† JOACHIM SCHOFER, MD,* HAROLD T. DODGE, MD, FACC†

Hamburg, West Germany and Seattle, Washington

To determine whether myocardial salvage after successful intracoronary or intravenous thrombolysis is time dependent, the relation between left ventricular wall motion and the time to treatment was studied in 69 patients admitted less than 3 hours after onset of acute transmural myocardial infarction (42 patients with reperfusion by intracoronary streptokinase, 27 by intravenous urokinase). A similar significant relation between the time to treatment and the severity of regional hypokinesia at follow-up was found in the intracoronary and intravenous groups. To better define this relation, particularly during the early phase of infarction, the groups were combined.

In patients in whom thrombolytic treatment was initiated within 2 hours after symptom onset, wall motion at follow-up was within 2 standard deviations of the normal mean in 82% (14 of 17 patients). If treatment was started 2 to 5 hours after symptom onset, the probability of improved wall motion decreased to 46% (24 of 52 patients, \( p < 0.025 \)). The time/wall motion relation appeared to be independent of infarct location, angiographically visible collateral vessels and the presence of subtotal coronary artery occlusion. The severity of hypokinesia at follow-up study correlated with the magnitude of peak serum creatine kinase (\( r = -0.71 \)), indicating that thrombolytic therapy initiated within 2 hours after the onset of symptoms improves regional left ventricular function and reduces infarct size more than later therapy does.

(J Am Coll Cardiol 1985;6:518–25)

Several studies (1–5) in patients with acute myocardial infarction have shown that left ventricular function significantly improves after lysis of the coronary thrombus. These studies compared mean values of treated patients with those of untreated or unsuccessfully treated patients. In our experience, however, wall motion at the site of the infarction improves in only 40% of reperfused patients (6,7).

Animal studies (8–15) have shown a significantly close relation between the size of the infarct and the duration of coronary artery occlusion. To determine whether the degree of myocardial salvage in patients is time dependent, we studied the relation between regional wall motion measured from acute and follow-up contrast cineangiograms and the time from the onset of symptoms until the initiation of thrombolytic therapy. If a close relation between these two variables exists, then an early time period may be defined during which there is a high probability that the patients will benefit from successful thrombolysis, and a later time period during which the probability of benefit is less. In the present study we determined the relation between the time from symptom onset until initiation of thrombolytic therapy and recovery of wall motion at the infarct site for both intracoronary and intravenous thrombolysis.

Methods

Patient selection. Sixty-nine patients (60 men, 9 women, age range 17 to 68 years) who met the following criteria were included in the study: 1) Severe ischemic chest pain lasting for more than 30 minutes and hospital admission within 3 hours after the onset of symptoms; 2) more than 2 mm ST elevation in two or more electrocardiographic leads; 3) age 70 years or younger; 4) no contraindications...
against thrombolysis; and 5) availability of acute and follow-up coronary and left ventricular contrast cineangiograms adequate for evaluation.

These criteria were met by 42 patients admitted between October 1979 and August 1982, who underwent intracoronary thrombolysis and 27 patients admitted subsequently who underwent intravenous thrombolysis. The risks and benefits of thrombolytic therapy were explained to the patient or his relatives, or both, and written informed consent was obtained.

For comparison, the data of 19 (10 streptokinase- and 9 urokinase-treated) patients who never manifested reperfusion or who had rethrombosis are also included. These patients were all enrolled in the study at the same time as the patients who had reperfusion under the same entry criteria and received the same treatment.

**Methods of thrombolysis.** *Intracoronary thrombolysis.* Cardiac catheterization and intracoronary administration of streptokinase were performed as previously described (16). An intravenous bolus of 10,000 U of heparin was injected. First, the unaffected, and then the infarct artery was visualized. Streptokinase was infused into the ostium of the coronary artery at 4,000 U/min until the artery began to open, and then at 2,000 U/min for at least 45 minutes after reperfusion or until a total dose of 250,000 U was given. At the end of the study, left ventricular angiography was performed at 50 frames/s in the 30° right anterior oblique projection. Angiography was repeated at follow-up, usually before hospital discharge 2 to 3 weeks later.

**Intravenous thrombolysis.** An intravenous bolus of 2 million U of urokinase was administered in the emergency room (17). Patients then underwent immediate coronary and left ventricular angiography an average of 1.1 ± 0.6 hours after the urokinase injection. No heparin was administered. The patients were restudied 2 to 3 weeks later before hospital discharge.

**Analysis of coronary angiograms and left ventricular function.** All angiograms were analyzed at the University of Washington. Identification of the infarct artery was based on the location of 1) ST elevation on the electrocardiogram, 2) hypokinetic wall motion on the ventriculogram, and 3) residual stenosis or thrombotic material, or both, in the coronary artery. Coronary artery patency was defined as prompt and complete filling of the suspected infarct artery with good runoff of the contrast medium. Coronary angiograms were assessed by two independent observers. To measure left ventricular function, the cine films were projected, and the end-diastolic and end-systolic endocardial contours were traced from the frames with maximal and minimal volume, respectively, from a normal sinus beat that was not preceded by a premature beat. Measurement of the ejection fraction and of regional wall motion abnormality was performed as previously described (7). Briefly, left ventricular chamber volume was calculated using the area-length method.

Wall motion was measured along 100 chords constructed perpendicular to a center line drawn midway between the end-diastolic and end-systolic contours (Fig. 1), and normalized by the end-diastolic perimeter. Abnormality in chordal motion at the infarct site was expressed in units of standard deviations (SD) from the mean wall motion of 64 normal patients. The selection criteria and description of this normal reference group has been previously described (7,18). Hypokinesia is indicated by negative values, hy-

**Figure 1.** Centerline method of regional wall motion analysis. A, End-diastolic and end-systolic left ventricular endocardial contours and centerline (dotted) 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 the patient (solid line). The mean motion in the normal ventriculographic group (second dashed line) and 1 standard deviation above and below the mean (first and third dashed lines) are shown for comparison. D, Standardized motion. The wall motion of the patient is now plotted in units of standard deviations from the normal mean (vertical dotted line). The normal ventriculographic group mean is represented by the horizontal dotted line. Vertical solid lines delimit the most hyperkinetic and most hypokinetic parts of the anterior and inferior regions.
perkinesia by positive values. Regional wall motion was calculated as the mean motion of chords lying in the most hypokinetic 50% of the infarct artery territory, and expressed in SD/chord. The derivation of this method has been previously described (7,18). A normal, non-postpremature sinus beat was analyzable in both acute and follow-up ventriculograms in 21 patients treated with urokinase and in the follow-up study alone in 6 patients.

The duration of ischemia in patients receiving intracoronary streptokinase was the time elapsed from symptom onset until angiographically documented reperfusion was achieved. The time to treatment was measured from symptom onset until thrombolytic therapy was initiated by either the intracoronary or the intravenous route.

Results

Intracoronary thrombolysis. Of the 52 patients, 42 achieved sustained reperfusion after streptokinase infusion. The influence of time to thrombolytic therapy was analyzed in these 42 patients. The data of the other 10 (5 without reperfusion and 5 with rethrombosis) are included for comparison in Table I. Before thrombolysis, 7 (17%) of the 42 patients had a subtotal coronary occlusion. Collateral vessels were visualized in only three of the patients.

Global ejection fraction in patients with successful intracoronary thrombolysis was 56 ± 15% in the acute study and not significantly different at follow-up study (55 ± 14%). Regional wall motion at the site of the infarct, however, improved significantly from an abnormally depressed acute value (-2.3 ± 1.0 SD/chord) to -1.7 ± 1.2 SD/chord at follow-up (p < 0.001). The time to initiation of intracoronary streptokinase infusion was 3.0 ± 1.0 hours (range 1.2 to 5.5); reperfusion was achieved 35 ± 15 minutes later.

There was a significant relation between time to treat-ment and the severity of regional hypokinesia at the infarct site (Fig. 2). Compared with those treated later, patients treated less than 2 hours after symptom onset had significantly greater improvement in regional and global left ventricular function, and less severe hypokinesia at follow-up study (Table 1). Eighteen (53%) of 34 patients treated 2 or more hours after symptom onset had severe residual hypokinesia at follow-up study (as defined by hypokinesia more severe than 2 SD below normal), whereas only 1 (12%) of 8 patients treated earlier than 2 hours had residual abnormalities of wall motion at the infarct site.

When patients whose pretreatment angiograms revealed only subtotal occlusions were eliminated from analysis, there still remained a significantly greater improvement in regional wall motion in patients with total occlusion treated within 2 hours than in those treated later (2.1 ± 1.2 [n = 6] versus 0.5 ± 1.0 [n = 30] SD/chord, p < 0.002).

Intravenous thrombolysis. In patients with patent coronary arteries after urokinase therapy, global ejection fraction did not change from acute (54 ± 10%) to follow-up (52 ± 11%) study. Acute and follow-up values were also not significantly different from those of the intracoronary streptokinase-treated group.

Wall motion at the infarct site improved significantly from an abnormally depressed acute value (-2.3 ± 1.1 SD/chord) to follow-up value (-1.7 ± 1.3 SD/chord, p < 0.02). There was no significant difference in either acute or follow-up wall motion values between the intracoronary streptokinase- and intravenous urokinase-treated groups. Intravenous thrombolytic therapy was begun 2.0 ± 0.8 hours after symptom onset, significantly earlier than intracoronary streptokinase was given (p < 0.001).

A significant relation between the time from onset of symptoms to initiation of intravenous urokinase and regional wall motion was seen. Only in patients treated within 2 hours was residual hypokinesia at follow-up significantly

Table 1. Effect of Intracoronary Streptokinase on Recovery of Left Ventricular Function (42 patients)

<table>
<thead>
<tr>
<th>Time to Treatment</th>
<th>Reperfused Patient Group</th>
<th>Nonreperfused or Rethrombosed Patient Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;2 h (n = 8)</td>
<td>&gt;2 h (n = 34)</td>
</tr>
<tr>
<td></td>
<td>p Value†</td>
<td></td>
</tr>
<tr>
<td>Regional hypokinesia (SD/chord)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>-2.9 ± 1.3</td>
<td>-2.4 ± 0.9</td>
</tr>
<tr>
<td>Follow-up</td>
<td>-1.1 ± 1.0</td>
<td>-1.9 ± 1.2</td>
</tr>
<tr>
<td>Delta</td>
<td>1.8 ± 1.3</td>
<td>0.5 ± 1.0</td>
</tr>
<tr>
<td>p Value†</td>
<td>0.006</td>
<td>0.011</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>51 ± 16</td>
<td>57 ± 15</td>
</tr>
<tr>
<td>Follow-up</td>
<td>58 ± 15</td>
<td>54 ± 14</td>
</tr>
<tr>
<td>Delta</td>
<td>7 ± 10</td>
<td>-3 ± 9</td>
</tr>
<tr>
<td>p Value†</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Unpaired t test, patients treated <2 vs. >2 hours after onset of symptoms; †paired t test, acute vs. follow-up study; §one way analysis of variance, reperfused <2 hours vs. nonreperfused or rethrombosed patient. Delta = difference between acute and follow-up values; SD = units of standard deviations.
less severe than in patients without reperfusion (Table 2). Serial determinations of serum creatine kinase revealed that maximal creatine kinase was lower in patients who were treated within 2 hours and who had achieved reperfusion than in those treated later or who had not achieved reperfusion (Table 2).

**Combined intracoronary and intravenous patient group.** To define the correlation between the time from onset of symptoms to the initiation of thrombolytic therapy and wall motion in the infarct area, particularly during the early phase, intravenous urokinase- and intracoronary streptokinase-treated patients were considered as one group. In view of the similar relation between time to treatment and wall motion, it appears to be justifiable to combine the two treatment groups for this purpose. A treatment initiated within 2 hours after the onset of symptoms was associated with a regional wall motion at follow-up within 2 standard deviations of normal in 14 (82%) of 17 patients. If treatment was administered 2 to 5 hours after symptom onset, the probability of improved wall motion decreased to 46% (24 of 52 patients) ($p < 0.025$) (Fig. 3). To exclude the possibility that those patients who were treated early had an initially normal or less depressed wall motion, the change in regional wall motion from acute to follow-up study was plotted against the time to treatment, revealing a similar relation in patients who were treated early and late (Fig. 4). In addition, there was no correlation between the degree of acute wall motion abnormality and time to treatment (Fig. 5). To study the effects of infarct location on the time/wall motion relation, patients with an anterior and those with an inferior wall infarct were compared. There was no significant difference between these two groups (Fig. 3).

![Figure 2. Relation between time to treatment, plotted on the x axis, and severity of residual hypokinesia at follow-up, plotted on the y axis in 42 patients with reperfusion by intracoronary streptokinase. Time is expressed in hours from onset of chest pain to initiation of thrombolytic therapy. Hypokinesia in the infarct region is expressed in standard deviations (SD) from normal.](image)

### Table 2. Effect of Timing of Intravenous Urokinase Therapy on Recovery of Left Ventricular Function (27 patients)

<table>
<thead>
<tr>
<th>Time to Treatment</th>
<th>Reperfused Patient Group</th>
<th>Nonreperfused or Rethrombosed Patient Group</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;2 h</td>
<td>&gt;2 h</td>
<td></td>
</tr>
<tr>
<td>Regional hypokinesia (SD/chord)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>$-2.0 \pm 0.9(8)$†</td>
<td>$-2.4 \pm 1.1(13)$</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up</td>
<td>$-1.2 \pm 1.4(9)$</td>
<td>$-2.1 \pm 1.0(18)$</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Delta</td>
<td>$0.8 \pm 1.2(8)$</td>
<td>$0.4 \pm 0.9(13)$</td>
<td>NS</td>
</tr>
<tr>
<td>p Value†</td>
<td>0.080</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>$57 \pm 7(8)$</td>
<td>$53 \pm 11(13)$</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up</td>
<td>$54 \pm 14(9)$</td>
<td>$48 \pm 9(18)$</td>
<td>NS</td>
</tr>
<tr>
<td>Delta</td>
<td>$-2 \pm 12(8)$</td>
<td>$-3 \pm 10(13)$</td>
<td>NS</td>
</tr>
<tr>
<td>p Value†</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Maximal creatine kinase</td>
<td>$714 \pm 854(12)$</td>
<td>$1,471 \pm 1,288(18)$</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Unpaired $t$ test, treatment time <2 hours vs. nonreperfused or rethrombosed patient group; †paired $t$ test, acute vs. follow-up study; ‡numbers in parentheses indicate the number of patients. Delta = difference between acute and follow-up values; NS = not significant.
Figure 3. Relation between time to thrombolytic treatment and severity of residual hypokinesia at follow-up in all 69 treated patients. See Figure 2 for more detail.

Serum creatine kinase and regional left ventricular function. Figure 6 shows the relation between the severity of hypokinesia in the infarct region measured at follow-up and the peak creatine kinase value from serial studies in patients treated with urokinase. There is a significant non-linear correlation \( r = -0.71 \).

Discussion

Comparison with previous studies. Our study shows that myocardial salvage after intracoronary and intravenous thrombolysis is time dependent in patients with acute anterior or inferior wall myocardial infarction. This is in accordance with previous studies, which demonstrate a greater improvement in global left ventricular ejection fraction or a smaller infarcted area in patients who achieved reperfusion early. Schwarz et al. (2) found that in patients with a peak creatine kinase of less than 1,000 U/liter, improved global ejection fraction and a smaller thallium defect, the duration of symptoms was shorter than in patients without such improvement (3.9 versus 4.8 hours). Rentrop et al. (1) defined the critical time interval for myocardial salvage to be 4 hours, during which the majority of patients will have improved left ventricular function if thrombolysis is successful. Schroeder et al. (19) reported a significant relation between the time to treatment and the "infarct area." In all

Figure 4. Relation between time to thrombolytic treatment and change in hypokinesia at the infarct site in all 69 treated patients. See Figure 2 for more detail.
of these studies, however, very few patients were treated within 2 hours of onset of chest pain, which makes it difficult to define a time/salvage relation.

**Influence of factors other than time.** In addition to the duration of symptoms, other factors such as the presence of subtotal occlusion (20) or of collateral vessels could be important determinants of myocardial salvage (21,22). In the group of 42 patients undergoing intracoronary thrombolysis who had a pretreatment coronary angiogram with visualization of the nonaffected coronary artery, both factors could be evaluated. In this series, the incidence of subtotal coronary occlusion was 12% (Fig. 2). These patients were distributed throughout the whole range of wall motion values with no relation to the duration of symptoms. Angiographically visible collateral vessels were demonstrated in only three patients. Although the number of patients is limited, the data suggest that these factors cannot explain the good recovery in wall motion in patients treated within 2 hours after symptom onset.

*Intracoronary thrombolysis.* In the intracoronary streptokinase-treated group, reperfusion is well defined. The time from the onset of intracoronary streptokinase infusion to reperfusion is variable and ranges from 12 to 75 minutes. To determine whether this variability influences the time dependency of myocardial salvage, the effect of time to treatment versus time to reperfusion on recovery of regional

---

**Figure 5.** Relation between time to thrombolytic treatment and severity of hypokinesia in the acute study in all 69 treated patients. IC = intracoronary; IV = intravenous. See Figure 2 for more detail.

**Figure 6.** Relation between severity of hypokinesia in the follow-up study and peak creatine kinase in 21 patients.
left ventricular function was compared. With the exception of an expected parallel shift to the right, the relation was not significantly different. Thus, variability in the time from onset of treatment to reperfusion appears to have no significant influence on this relation in this study.

**Intravenous thrombolysis.** We then evaluated the relation between time to treatment and recovery of regional wall motion after thrombolytic therapy was administered intravenously in the emergency room and before angiography. Coronary angiography was performed immediately after thrombolytic therapy, 1.1 ± 0.6 hours after urokinase injection. We observed the same correlation between time to treatment and regional wall motion in the groups with intravenous and intracoronary drug administration. Thus, because both groups were comparable with regard to the time dependency of myocardial salvage, they were analyzed together. The correlation between time to treatment and residual left ventricular wall motion became even more evident with a higher p value of less than 0.025.

**Role of degree of initial wall motion abnormality.** To exclude the possibility that patients with good wall motion at follow-up had better wall motion initially than patients whose regional wall motion at follow-up was decreased more than 2 standard deviations below normal, the correlation between time to treatment and change in regional wall motion between the acute and follow-up angiograms was also analyzed (Fig. 4) and a similar relation was found. Moreover, the degree of initial wall motion abnormality was independent of the time from the onset of symptoms to the onset of treatment. Thus, residual left ventricular wall motion at the site of the infarct indirectly reflects the amount of myocardium salvaged, and the recovery of ventricular function after thrombolytic therapy can be evaluated from a follow-up ventriculogram alone. As we have previously observed (7), the ejection fraction was too insensitive and failed to reflect the improvement in regional wall motion in the infarct site because of the concomitant decrease in the amount of acute compensatory hyperkinesia in the noninfarct region.

**Clinical implications.** These data permit prediction of the results of thrombolysis in terms of myocardial salvage. However, reperfusion after intravenous thrombolysis should be verified promptly after treatment. Whether patients who subsequently have reperfusion will benefit from thrombolysis cannot be concluded from our results. To achieve a residual abnormality in regional function that is less than 2 standard deviations below normal in more than 80% of the patients, thrombolytic therapy should be started within 2 hours. This appears to be independent of the presence of a subtotal occlusion or angiographically visible collateral vessels. Between 2 and 5 hours after the onset of symptoms, the probability of myocardial salvage decreases to less than 50%.

The results of our study imply that thrombolysis should be administered within 2 hours after the onset of symptoms to obtain maximal recovery of ventricular function. The time delay between the onset of symptoms and hospital admission is mainly caused by the patient’s delay in seeking medical attention. Every measure that shortens this delay will help to increase the number of patients undergoing thrombolysis within 2 hours, thus increasing the benefit of thrombolysis in acute myocardial infarction.

**References**


