Late Reperfusion for Acute Myocardial Infarction Limits the Dilatation of Left Ventricle Without the Reduction of Infarct Size

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Background. While previous clinical studies have shown a possible beneficial effect of the reperfusion performed at a relatively late phase of acute myocardial infarction ("late reperfusion") in preventing left ventricular enlargement, the mechanism has not been clarified.

Methods and Results. Of 89 patients with an initial anterior myocardial infarction, reperfusion was successful in 69. These 69 were divided into three groups according to the time required to achieve reperfusion after the onset of symptoms: early-reperfused (<3 hours from the onset to reperfusion; n=22), intermediate-reperfused (3 to 6 hours from the onset to reperfusion; n=28), and late-reperfused (>6 hours from the onset to reperfusion; n=19). The 20 patients whose infarct-related artery were occluded in the acute phase as well as 1 month later was classified as nonreperfused. Infarct size, evaluated as defect volume by 30Ti single-photon emission computed tomography 1 month after the onset, was 1593±652 units (mean±SD) in the late-reperfused group, significantly larger than that of the intermediate-reperfused (1066±546 U) or the early-reperfused groups (372±453 U) but not different from that of the nonreperfused group (1176±562 U). Wall motion abnormality index as well as global ejection fraction evaluated by left ventriculography 1 month after the onset showed that late reperfusion did not preserve the left ventricular wall motion and function. These results indicate that the earlier reperfusion decreased the size of the infarction and preserved left ventricular function, whereas late reperfusion (>6 hours after onset) did not limit infarct size or preserve left ventricular function. In contrast, the end-diastolic volume index did not differ significantly among the early-reperfused (50±15 mL/m2), intermediate-reperfused (54±14 mL/m2), and late-reperfused (53±19 mL/m2) groups; those were significantly smaller than that of the nonreperfused group (68±12 mL/m2; P<.05). Left ventriculographic data obtained in both the acute and chronic phase in 39 patients showed that left ventricular volumes increased significantly during the course of myocardial infarction only in the nonreperfused group.

Conclusions. Late reperfusion appeared to prevent ventricular dilatation following acute myocardial infarction independent of the limitation of infarct size. (Circulation. 1993;88:2565-2574.)

KEY WORDS • myocardial infarction • reperfusion • left ventricle • infarction

Reperfusion of the occluded coronary arteries during the early phase of acute myocardial infarction has been shown to reduce infarct size, preserve the left ventricular function, and improve the short- and long-term prognoses.1-7  Reperfusion achieved after the completion of myocardial necrosis, in most cases within 3 to 4 hours after the coronary occlusion (6 hours maximum), probably has little effect on limiting the size of infarction.8-12  However, it cannot be ruled out that the reperfusion salvages a small epicardial rim of myocytes and thereby prevents the expansion of myocardial infarction.13  Several clinical trials,14-16 including large-scale studies of thrombolytic therapy, have shown the beneficial effects of the reperfusion performed at the relatively late phase of acute myocardial infarction ("late reperfusion") on reducing the mortality of predischarge as well as postdischarge, although late reperfusion did not improve left ventricular function. Nevertheless, several animal studies focused on the discordance of mortality reduction and left ventricular function revealed that late reperfusion prevented both the enlargement of the left ventricle and aneurysm formation without reducing infarct size.13,17  Previous clinical studies also18-22 indicated a preventive effect of late reperfusion on left ventricular dilatation. However, it remains controversial whether such beneficial effects are relating to the reduction of infarct size; Villari et al18 showed that infarct size determined by peak creatine kinase activities was smaller in patients treated with late reperfusion than that in patients treated with conventional therapy. In contrast, two other studies19,20 indicated the opposite results. It
should be noted that all of these studies failed to show that early reperfusion salvaged the myocardium.

In this study, we investigated the relation between infarct size and the size of the left ventricular cavity in patients with an anterior infarction and whose infarct-related artery could be examined angiographically in both the acute and chronic phase. We also clarified the beneficial effect of late reperfusion.

**Methods**

**Patient Selection**

Subjects were selected from 142 consecutive patients who were admitted to the coronary care unit of the Osaka Police Hospital with an acute anterior myocardial infarction during the 96-month period of January 1984 through December 1991 within 24 hours from onset. Inclusion criteria were the presence of persistent ST segment elevation of ≥0.2 mV in two or more leads on the standard 12-lead ECG and severe chest pain lasting >30 minutes; less than 80 years of age; no prior history of myocardial infarction; and absence of cardiomyopathy, severe valvular disease, ventricular septal defect, or cardiogenic shock (systolic pressure <80 mm Hg). Patients with the following conditions were excluded: severe untreated hypertension, perfusion state of the infarct-related artery exceeded Thrombolysis in Myocardial Infarction (TIMI) grade 2 at initial angiography, extension of infarction observed during the study, reocclusion of the infarct-related vessel demonstrated by angiography performed during the chronic phase, and, finally, reperfusion of the totally occluded infarct-related artery during the acute phase demonstrated angiographically in the chronic phase. Ultimately, 89 patients were admitted to the study. The details for the exclusion are shown in Table 1.

After having their informed consent obtained, patients were catheterized and received urokinase or tissue-type plasminogen activator (see details below). On the initial coronary angiography, 80 of the 89 patients showed a perfusion of TIMI grade 0 at the proximal portion of the left anterior descending artery, while 9 other patients showed a perfusion of TIMI grade 1 at the similar lesion.

Successful thrombolysis (TIMI criteria grade 2 or 3) was obtained in 49 of the 89 patients. When thrombolysis achieved a grade below TIMI grade 2, acute coronary angioplasty was performed (in 23 patients). Reperfusion was achieved in 20 patients (87%) and failed in 3 patients. Finally, 69 patients depicted antegrade coronary flow confirmed angiographically after reperfusion therapy that was maintained until the angiographic reexamination in the chronic phase; this group was defined as having successful reperfusion. In 22 such patients, reperfusion was obtained within 3 hours of the onset of the initial severe chest pain (early-reperfused group). In 28 cases, it was achieved between 3 to 6 hours (intermediate-reperfused group), and it took more than 6 hours in 19 patients (late-reperfused group). The mean time to reperfusion in each group appears in Table 2. In 20 other patients, coronary reperfusion was not achieved at the completion of reperfusion therapy, and total occlusion was confirmed during the chronic phase. This group is defined as the nonreperfused group.

The treatment was almost identical among these groups, including emergency coronary angioplasty and the medications administered after thrombolytic therapy, except for the use of intravenous heparin and aspirin. The latter were administered to the patients with successful reperfusion, but not to the nonreperfused patients. Nitrates and calcium antagonists were administered orally followed by the infusion of nitroglycerin. No patients received β-blockers or angiotensin converting enzyme inhibitors during the study. The protocol for this clinical investigation was approved by the Ethical Committee for Clinical Research of Osaka Police Hospital.

**Protocol for Catheterization and Reperfusion Therapy**

After 5000 U heparin had been given by IV bolus infusion, coronary angiography was performed with Judkins technique. When the total occlusion of the
TABLE 2. Clinical and Angiographic Characteristics of 89 Patients According to Time of Reperfusion

<table>
<thead>
<tr>
<th></th>
<th>Early (≤3 h)</th>
<th>Intermediate (3 to 6 h)</th>
<th>Late (&gt;6 h)</th>
<th>Nonreperfused</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>22</td>
<td>28</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Age, y (range)</td>
<td>56±9 (37-74)</td>
<td>58±10 (30-74)</td>
<td>57±11 (29-77)</td>
<td>54±11 (34-75)</td>
</tr>
<tr>
<td>Gender, % male</td>
<td>95</td>
<td>79</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Time to admission, h* (t)</td>
<td>1.8±1.0 (0.5-2.6)</td>
<td>3.7±0.7 (2.5-5.3)</td>
<td>7.8±5.3 (4.1-23)</td>
<td>7.2±6.5 (4-18)</td>
</tr>
<tr>
<td>Time to reperfusion, h* (t)</td>
<td>2.4±0.4 (1.5-3.0)</td>
<td>4.2±0.7 (3.1-6.0)</td>
<td>10.0±4.9 (6.1-24.0)</td>
<td>. . .</td>
</tr>
</tbody>
</table>

Angiographic findings before reperfusion

| No. of vessels ($) | 86/9/5 | 78/22/0 | 89/11/0 | 88/12/0 |
| Perfusion grade    |        |         |         |         |
| 0                  | 19      | 26      | 17      | 18      |
| 1                  | 3       | 2       | 2       | 2       |
| Grade of collaterals |       |         |         |         |
| 0                  | 17      | 21      | 13      | 8       |
| 1                  | 1       | 5       | 3       | 7       |
| 2                  | 4       | 2       | 3       | 5       |
| 3                  | 0       | 0       | 0       | 0       |
| Acute angioplasty, % | 32      | 25      | 28      | 20      |

*Mean±SD.

1Interval from onset of chest pain to admission.

2Interval from onset of chest pain to reperfusion.

3Number of vessels showing significant stenosis. The early- and intermediate-reperfusion groups included hospitalized patients or patients diagnosed during transport to the hospital, resulting in rapid achievement of reperfusion after admission.

proximal portion of left anterior descending coronary artery was confirmed after the intracoronary administration of 0.1 mg nitroglycerin, 960 000 U urokinase over 45 minutes or recombinant tissue-type plasminogen activator (0.75 mg/kg) over 1 hour was administered into the coronary artery or intravenously. Recanalization was confirmed by injecting a minimal amount of contrast medium into infarct-related artery every 5 to 10 minutes. Corresponding perfusion status after recanalization was identified by coronary angiography using an adequate amount of contrast material. Successful thrombolysis was defined as TIMI grade 2 or 3. Patients with a perfusion status of less than TIMI grade 2 at the completion of thrombolytic therapy received coronary angioplasty. Reperfusion was achieved in 49 patients only by thrombolytic therapy; combined treatment with angioplasty was administered to 20 patients. There was no difference in the number of patients who received acute successful angioplasty among three successful reperfusion groups (Table 2). All patients were reexamined angiographically during the chronic phase (35±28 days after onset; range, 21 to 73 days; median, 32 days).

Estimation of Infarct Size by 201TI Single-Photon Emission Computed Tomography

Myocardial tomograms were obtained about 4 weeks (29±18 days) after the onset of myocardial infarction. Single-photon emission computed tomography (SPECT) was performed with a large field of view rotating single-crystal gamma camera (ZLC 7500, Shimadzu, Kyoto, Japan) equipped with a low-energy, high-resolution collimator and interfaced to the computer (Schintipack 70A, Shimadzu, Kyoto, Japan). Image acquisition commenced in the 30° right anterior oblique projection approximately 3 hours after the injection of 5 mCi 201TI. Thirty-two sequential images separated by 5.6° intervals were acquired over 180°. Data were stored on a 64×64 matrix for subsequent analysis.

To assess the size of myocardial infarct, the image of left ventricle was sliced into six layers at equidistant intervals perpendicular to its long axis (Fig 1A). The distribution of myocardial radioactivity for each slice was determined with a circumferential profile technique whereby each individual short-axis slice was normalized by the maximal count activity within the slice (Reference 25; Fig 1). The center of the left ventricle, maximal search radius, right ventricular junction, and boundaries of the left ventricular cavity were determined from the midcavity short-axis slice by a single investigator blindly. The maximal search radius was constructed around the outer border of the left ventricle; thus, right ventricular activity was effectively excluded. The circumferential curve at each slice of a patient was compared with the corresponding slice from that of normal data obtained previously from 60 normal subjects. Mean defect severity at each slice was determined by the area under the circumferential curve smaller than 2 SD below of normal. Defect volume was defined as the summation of the mean severity of the defect of each slice and expressed by arbitrary unit, representing the extent of damaged myocardium in the total left ventricle.

Analysis of Coronary and Ventricular Angiograms

Coronary angiograms obtained both during the acute phase and 1 month after onset were assessed visually by two independent observers in blind fashion. Reperfusion was defined as the complete opacification of the
infarct-related artery after the completion of reperfusion therapy. Collaterals to the infarct-related artery were evaluated from the pretreatment angiogram and graded on a four-point scale according to the definition of Rentrop et al.\(^2\): grade 0, no collateral vessel; grade 1, side branches of the artery to be perfused via collateral vessels are filled without visualization of the epicardial segment; grade 2, the epicardial segment via collateral vessels partially filled; and grade 3, the epicardial segment via collateral vessels is filled completely. The extent of disease in the noninfarcted arteries was also assessed. Any stenosis >75% in the noninfarcted vessels was defined as "significant" for the purpose of determining the presence or absence of multivessel disease.

Left ventriculography was performed with the patient in the 30° right anterior oblique position using a power injection. The endocardial contours of the left ventricle at end diastole and end systole in left ventriculograms obtained about 1 month (35±28 days) after symptom onset were traced independently by three different observers. In 39 patients, left ventriculography was also performed after the completion of reperfusion therapy and analyzed by the procedure used during the chronic phase. In the other 50 patients, left ventriculography was not performed during the acute phase due to unstable hemodynamics or to the limitation of the total amount of contrast medium used. Left ventricular volume was calculated by the area-length method\(^2\) and used to determine the ejection fraction.\(^2\) Regional wall motion was calculated by the centerline method.\(^3\) A computer generated the centerline between the systolic and diastolic contours, and 100 equally spaced chords were drawn perpendicular to the centerline (Fig 2). Chord 1 was drawn at the intersection of the aortic contour and the anterobasal left ventricular wall, and chord 100 was drawn at the junction of the left ventricular contour and the posterior aortic contour. The measured motion of each chord was normalized for heart size by dividing it by the length of the end-diastolic perimeter and then expressed in terms of standard deviation units (SD) above or below normal mean motion of chords. Normal chord motion in our laboratory was derived from ventriculograms of 100 patients with normal left ventricular function without coronary artery or valvular disease (Fig 2).

Abnormality in wall motion was calculated by two approaches (Fig 2). First, the severity of hypokinesia in the infarct site was calculated as the mean of the chord lying in the hypokinetic area and expressed as SD/chord. Second, the circumferential extent of hypokinesia

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**Fig 1.** Calculation of mean severity of the defect by \(^99m\)Tc single-photon emission computed tomography. A, Image of left ventricle is sliced into six layers at equidistant intervals perpendicular to its long axis. B, Each slice is divided into 32 segments at 11.25° intervals. C, The circumferential curve of the patient is obtained by plotting the radioactivity of segments. Mean severity of the defect is determined as the area under the circumferential curve depressed more than 2 SD from the normal data (shown by arrows). Data are expressed in arbitrary units.

**Fig 2.** Centerline method of regional wall motion analysis. A, Centerline is obtained as the point midway between the end-diastolic and end-systolic endocardial contours. Motion is measured along 100 chords constructed perpendicular to the centerline. B, The patient’s wall motion (solid line) is plotted in units of SD of the normal data. Wall motion abnormality in the central infarct region (hatched area) is calculated by averaging the motion of chords lying within the regions. The region indicated by the open column is the territory of left anterior descending artery, and the region shown by the dotted column is the hypokinetic region at which chord motion was depressed more than 2 SD below the normal mean.
was also calculated as the set of contiguous chords whose motion was depressed more than 2 SD below the normal mean and expressed as a percentage of the endocardial contour length.

**Measurement of Peak Creatine Kinase Activity**

Blood samples for the measurement of creatine kinase activity were drawn every 3 hours for the first 24 hours and every 6 hours for the next 24 hours. Serum creatine kinase activity was determined spectrophotometrically by the method of Rosalki.31

**Statistical Analysis**

Data are expressed as mean±SD. Multiple comparisons among groups were performed by one-way ANOVA combined with Scheffé's test. The χ² test or Fisher's exact test was used for analyzing categoric variables among the four groups. Paired data were compared by paired t test. Results were considered statistically significant at P<.05.

**Results**

**Patient Characteristics**

There were no significant differences between groups in age, gender, extent of coronary artery disease, the degree of collateral at the initial angiographic examination, or perfusion state of the infarct-related artery during the acute phase before reperfusion therapy (Table 2). Hemodynamic variables on admission were comparable among the four groups (data not shown).

**Hemodynamics and Angiographic Findings at Chronic Phase**

Hemodynamic variables (heart rate, blood pressure, end-diastolic pulmonary artery pressure, and cardiac index) in the chronic phase did not differ significantly among the four groups (data not shown). The perfusion state of the infarct-related vessel was TIMI grade 3 in three reperfused groups; however, that in the nonreperfused group was less than TIMI grade 1. Stenosis of infarct-related artery during the chronic phase was 62±7% in the early-reperfused group, 69±5% in the intermediate-reperfused group, and 68±7% in the late-reperfused group, respectively, and not significantly different.

**Infarct Size**

As shown in Fig 3A, the defect volume of the late-reperfused group (1593±652 U) was significantly greater (P<.05) than that of both the early-reperfused group (372±453 U) and the intermediate-reperfused group (1066±546 U). However, it was similar to that of nonreperfused group (1736±562 U), which was also significantly greater than that of both the early-reperfused and the intermediate-reperfused groups (P<.05).

The peak serum creatine kinase value (Fig 3B) was 2151±1757 U/L in the early-reperfused group, significantly lower than the values in the other three groups. There were no significant differences in peak serum creatine kinase values among the intermediate-reperfused (3730±2070 U/L), late-reperfused (387±1710 U/L), and nonreperfused groups (3144±1193 U/L).

![Fig 3. Bar graphs of effect of reperfusion on infarct size.](http://circ.ahajournals.org/content/97/15/2569)

**Global and Regional Left Ventricular Functions**

The global ejection fraction (EF; Fig 4A) was in this order: early-reperfused (55±12%), intermediate-reper-

![Fig 4. Bar graphs of effect of reperfusion on global and regional left ventricular function.](http://circ.ahajournals.org/content/97/15/2569)

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was also observed in the end-systolic volume index (ESVI) (Fig 5B); the ESVI of late-reperfused group (30±13 mL/m²) was larger (but not significantly) than that of the early-reperfused group (23±10 mL/m²) as well as the intermediate-reperfused group (28±11 mL/m²) but significantly smaller than that of the nonreperfused group (41±11 mL/m²). However, the stroke volume index did not differ significantly (data not shown).

**Changes in Left Ventricular Function in Patients With Paired Left Ventriculographic Data**

Left ventriculography was performed in 39 patients soon after the completion of the reperfusion therapy and again in 1 month after symptom onset. There were no significant differences in the clinical and angiographic characteristics between the patients with versus those without paired ventriculographic data (Table 3). The left ventricular functions observed during the chronic phase in patients with paired left ventriculograms resembled those obtained from all patients in each group. There were no significant differences in left ventricular function during the acute phase among the four groups (Table 4). The EDVI, ESVI, and hypokinetic areas of the early-, intermediate-, and late-reperfused groups did not increase significantly during the course of myocardial infarction. In contrast, the EDVI in the nonreperfused group increased significantly, and the hypokinetic area did not change. These data indicate that the EDVI in the nonreperfused group during the chronic phase significantly exceeded that of the other groups.

**Discussion**

Our results indicate that late reperfusion provides a possible beneficial effect in preventing the enlargement of left ventricular cavity induced by myocardial infarction, although it did not limit the size of infarction. In contrast, our study clearly indicates that early reperfusion salvages myocardium. Previous clinical studies demonstrated the prevention of enlargement by late reperfusion but failed to show evidence that it was not related to the reduction in infarct size. The differences between our study and others indicated below could clarify the contribution of late reperfusion on infarct size. First, the interval between symptom onset and reperfusion was not confirmed in previous studies due to a lack of performance of coronary angiograms in the acute phase. In this study, the perfusion states of infarct-related artery were evaluated during the acute phase to clarify the time at which reperfusion can be obtained. The patients whose infarct-related artery was reperfused successfully but reocluded during the chronic phase were excluded. Recanalization of the infarct-related artery during the chronic phase was observed in some patients in whom reperfusion failed during the acute phase. These patients were also excluded from this study because of an uncertain time of reperfusion. Collateral flow was also evaluated on coronary angiograms performed during the acute phase because their presence during the acute phase prevents aneurysm formation as well as limits the infarct size.

It is difficult to exclude the effect of collaterals on infarct size as well as left ventricular function; however, there were no differences among the four groups in the grade of collateral flow during the acute phase. These
TABLE 3. Clinical and Angiographic Characteristics of Patients With or Without Acute Ventriculograms According to Time of Reperfusion

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Early (≤3 h)</th>
<th>Intermediate (3 to 6 h)</th>
<th>Late (&gt;6 h)</th>
<th>Nonreperfused</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>+ 10, - 12</td>
<td>+ 12, - 16</td>
<td>+ 8, - 11</td>
<td>+ 9, - 11</td>
</tr>
<tr>
<td>Age, y* (range)</td>
<td>58±7, 57±11, 57±9</td>
<td>58±11, 57±14, 57±9</td>
<td>55±12, 56±12</td>
<td></td>
</tr>
<tr>
<td>Gender, % male</td>
<td>100, 92, 67</td>
<td>94, 100, 100</td>
<td>100, 100</td>
<td></td>
</tr>
<tr>
<td>Duration to reperfusion, h (†)</td>
<td>2.4±0.4, 2.3±0.4, 4.3±0.9</td>
<td>4.2±0.5, 11.7±6.2, 8.8±3.6</td>
<td>10/1, 9/2/0, 11/1/0</td>
<td></td>
</tr>
<tr>
<td>No. of vessels: 1/2/3 (‡)</td>
<td>9/1/0, 11/0/1, 11/1/0</td>
<td>11/5/0, 8/0/0, 9/2/0</td>
<td>8/1/0, 9/2/0</td>
<td></td>
</tr>
<tr>
<td>Perfusion grade: 0/1 (§)</td>
<td>8/2/0/0, 11/1/0/0</td>
<td>11/1/0/0, 15/1</td>
<td>7/1, 10/1, 8/1</td>
<td></td>
</tr>
<tr>
<td>Collaterals grade: 0/1/2/3 ($)</td>
<td>7/0/3/0, 10/1/1/0</td>
<td>9/2/1/0, 12/2/1/0</td>
<td>6/0/2/0, 7/3/1/0</td>
<td>2/4/3/0, 6/3/2/0</td>
</tr>
<tr>
<td>Acute angioplasty, %</td>
<td>10, 42, 8</td>
<td>31, 13</td>
<td>36, 11</td>
<td></td>
</tr>
<tr>
<td>Defect volume</td>
<td>371±515, 372±418, 1079±490, 1057±601</td>
<td>1314±518, 1796±684</td>
<td>1525±132, 1908±191</td>
<td></td>
</tr>
<tr>
<td>Peak CK, IU/L</td>
<td>1989±1750, 2287±1829, 3704±2053, 3749±2150</td>
<td>3481±2384, 4160±1035, 3026±1315</td>
<td>3513±1097</td>
<td></td>
</tr>
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</table>

*Mean±SD.
†Time from symptom onset to reperfusion (mean±SD).
‡Number of vessels showing significant stenosis.
§TIMI grade.
| Classification according to Rentrop et al.27 |

Mean conditions made it possible for us to clarify the exact time of reperfusion during the acute phase and to minimize the bias based on collaterals between groups. Second, the method used to evaluate infarct size is crucial, and only indirect measures of infarct size are available in clinical study. We used two independent indexes of infarct size: peak creatine kinase activity and defect volume as determined by 201Ti SPECT. The peak creatine kinase activity may be influenced by the state of the perfusion of the infarct-related artery as shown in animal experiments34 and clinical studies.35 However, the defect volume, which is correlated closely with pathological measurements of infarct size,25 is likely to be independent of the perfusion of infarct-related artery.36 Although defect volume is influenced by the location of the infarct, we studied only anterior infarction. The third difference is the heterogeneity of the location of the infarct among the study population.18-22 Subsequent dilatation of the left ventricular cavity after the myocardial infarction is followed by expansion of the infarct, which occurred soon after the onset of infarction and continued for 1 week.37-40 This expansion was influenced by size and location of the infarct.41 Previous studies on infarct expansion noted that these changes occurred more frequently and were severe in the case of anterior infarction.38-40 In the normal left ventricle, the anterior wall contracts more than the posterior or the inferior wall; thus, a similar degree of depression of function after anterior infarction would be expected to produce more severe derangements.42 We studied only patients with their first anterior infarction to clarify the relation between infarct size and cavity size 1 month after symptom onset.

Mechanism of Beneficial Effect for Late Reperfusion

The defect volume in patients of the late-reperfused group was significantly exceeded by that of the early- and intermediate-reperfused groups and was slightly

TABLE 4. Changes in Left Ventricular Function in Patients With Paired Left Ventriculographic Data

<table>
<thead>
<tr>
<th>Group</th>
<th>Early (n=10)</th>
<th>Intermediate (n=12)</th>
<th>Late (n=8)</th>
<th>Nonreperfused (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute</td>
<td>Chronic</td>
<td>Acute</td>
<td>Chronic</td>
</tr>
<tr>
<td>EF, %</td>
<td>45±11</td>
<td>57±9*</td>
<td>43±7</td>
<td>50±14</td>
</tr>
<tr>
<td>EDVI, mL/m²</td>
<td>50±10</td>
<td>47±11</td>
<td>50±11</td>
<td>53±18</td>
</tr>
<tr>
<td>ESVI, mL/m²</td>
<td>27±6</td>
<td>20±6*</td>
<td>28±9</td>
<td>28±14</td>
</tr>
<tr>
<td>Wall motion abnormality index, SD/chords</td>
<td>3.6±1.0</td>
<td>2.0±1.18*</td>
<td>4.47±0.98</td>
<td>3.21±1.19</td>
</tr>
<tr>
<td>Extent of hypokinesis</td>
<td>43±15</td>
<td>18±17*</td>
<td>52±4</td>
<td>43±13*</td>
</tr>
</tbody>
</table>

*P<.05 vs acute phase.
smaller than that of the nonreperfused group, although differences were not significant. Thus, late reperfusion reportedly had no effect on the limitation of infarct size, whereas early reperfusion did, as suggested by previous studies. The comparison of peak creatine kinase activity among the four groups also suggested a similar conclusion, although the discordance with defect volume may be explained by a washout of creatine kinase activity by the reperfusion. Thus, our results indicate that late reperfusion has little benefit on limiting infarct size. However, it cannot be excluded that the reperfusion did salvage a small epicardial rim of myocardium at risk, which could not be detected by our methods.

The EDVI and ESVI during the chronic phase in the early-, intermediate-, and late-reperfused groups were similar; however, those of the nonreperfused group significantly exceeded those of other groups. In contrast, left ventricular volume during the acute phase did not differ among groups in patients with paired left ventriculographic data. The prevention of subsequent dilatation of left ventricle in early- and intermediate-reperfused groups was due to the limitation of infarct size as indicated by defect volume. In the early-reperfused group, the limitation of infarct size also preserves the regional as well as the global function and limits the extent of the hypokinetic lesion. The limitation of infarct size in the intermediate-reperfused group was not sufficient to preserve left ventricular function, but it was still effective in limiting the extent of the hypokinetic lesion and preserving the global ejection fraction. However, late reperfusion had no effect on either the preservation of regional and global left ventricular function or the limitation of extent of hypokinetic lesion, in agreement with the previous studies. This is caused by the lack of effects of late reperfusion on limitation of infarct size, as discussed. Nevertheless, the size of the left ventricular cavity, including both the EDVI and ESVI in patients in the late-reperfused group, was significantly smaller than that of the nonreperfused group as shown by data on patients with paired left ventriculographic data. These findings suggest that the prevention of the dilatation of the left ventricular cavity by late reperfusion was produced but that its mechanism was independent of limiting infarct size.

The limitation of infarct expansion by late reperfusion independent of the limitation of infarct size was first shown in the animal model by Hochman and Choo, who considered that altered tissue properties following reperfusion might explain reduction of infarct expansion by reperfusion, even though reperfusion was performed relatively late without myocardial salvage. Previous histopathological studies showed increased hemorrhage, cell swelling, edema, and contraction band necrosis in the reperfused infarct. These changes made the infarcted myocardium stiffer and it is likely to resist the intraventricular pressure, leading to a reduction in infarct expansion. Another explanation is an acceleration in healing followed by reperfusion, as suggested in pigs or rats. Infarct expansion occurred early (1 day), before the inflammatory reaction, and progressed passively during the first 5 to 7 days with resorption of the dead myocardial tissue. This second process may be inhibited by the acceleration of healing after reperfusion, resulting in a lesser expansion. The islands of residual subepicardial viable cells in the reperfused heart that could not be detected significantly by conventional methods are considered to be a third mechanism. The number of residual viable cells may not be large but may be sufficient to keep the subepicardial rims in myocardial infarcts stiff against pressure.

**Effect of Treatment**

Expansion of the infarct is influenced by variables that affect ventricular loading conditions and ventricular wall stress. For example, high blood pressure increases afterload and systolic wall stress and hastens expansion of the infarct. In contrast, reduction of ventricular preload and afterload by vasodilators prevents such expansion. In our studies, hemodynamics, including systolic blood pressure, pulmonary artery end-diastolic pressure, and cardiac index in the acute as well as in the chronic phase, were similar among the four groups (data not shown). Each patient in our study routinely received afterload reduction therapy by nitroglycerin infusion followed by the oral administration of nitrate as well as by a calcium antagonist. The concomitant use of other medications, especially β-blockers and angiotensin converting enzyme inhibitors, also prevented infarct expansion via a reduction in afterload. An initial study suggested that the sulfhydryl group in captopril may act as a free radical oxygen scavenger to limit reperfusion injury. The inhibition of angiotensin II and bradykinin breakdown by captopril also enhances coronary vasodilation. However, we did not administer these agents during the study. In the reperfusion group, heparin was started immediately and continued until the fourth or fifth day after reperfusion. Aspirin was also administered. In contrast, the nonreperfused group did not receive such medications after an attempt at thrombolysis. Aspirin and heparin are reported to accelerate the patency rate but not to affect infarct size. Aspirin may have had a beneficial effect on the reduction in mortality through late patency of infarct artery; however, its administration would not alter the outcome in this study.

**Mortality and Late Reperfusion**

In the late-reperfusion group, the time between symptom onset to reperfusion ranged from 6.1 to 24 hours. The results suggest that reperfusion within 24 hours of symptom onset would prevent left ventricular dilatation. No study has investigated the effect of reperfusion beyond 24 hours. In the ISIS-2 study, a significant reduction in mortality was observed in patients treated with streptokinase between 6 and 12 hours compared with patients not given such treatment. A reduction of mortality was still observed in patients treated with streptokinase 12 to 24 hours after symptom onset. The mechanism for this reduction is not known. Although the size of the ventricular cavity was not measured in that study, the prevention of the enlargement of left ventricular cavity size may have contributed to the reduction in mortality, as White et al showed that ESVI and EDVI are major predictors of mortality following a myocardial infarction. The prevention of these effects on the enlargement of cavity size by late reperfusion may explain the discrepancy between mor-
tality versus left ventricular function that has been observed in large-scale trials.\textsuperscript{14-16}

In conclusion, we found that the performance of reperfusion beyond the limit considered for the salvage of ischemic myocardium could prevent left ventricular dilatation. This preventive effect may be beneficial because it can explain the reduction in mortality induced by late reperfusion even though the size of infarct was not reduced in previous clinical trials.\textsuperscript{14-16} All the patients who participated in the present study had an initial anterior infarction and were treated similarly after admission. Nevertheless, the study population was small, and the time during which reperfusion was attempted was limited. Additional prospective and randomized studies on late reperfusion with a careful examination of left ventricular size and function are required to clarify the latest time at which the clinical benefits of reperfusion could be obtained following a myocardial infarction.

References


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Circulation. 1993;88:2565-2574
doi: 10.1161/01.CIR.88.6.2565

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