Lack of Myocardial Perfusion Immediately After Successful Thrombolysis
A Predictor of Poor Recovery of Left Ventricular Function in Anterior Myocardial Infarction

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Background. We investigated myocardial perfusion dynamics after thrombolysis and its clinical implications.

Methods and Results. We studied 39 patients with acute anterior myocardial infarction (AMI). Myocardial contrast echocardiography (MCE) was performed before and immediately after successful reflow with intracoronary injection of sonicated Ioxaglate. The average segmental score by two-dimensional echocardiography (graded 0, normal, to 3, akinetic/dyskinetic) and global ejection fraction (left ventricular ejection fraction, LVEF%) by left ventriculography were measured at 1 day and at 4 weeks after reflow. Hypokinesis in the infarct region was assessed by the centerline method and expressed in terms of standard deviations (regional wall motion [RWM]: SD/chord) of normal. Immediately after reflow, 39 of 39 patients (group A) showed significant contrast enhancement within the risk area. The other nine patients (23%, group B), however, showed the residual contrast defect in the risk area (myocardial no reflow). There were no significant differences in the elapsed time, angiographic collateral grade, and degree of residual stenosis between group A and group B. Before reflow, both groups exhibited similar levels of global and regional left ventricular function. Improvement in global (LVEF, average segmental score) and regional left ventricular function was greater in group A than in group B (average segmental score, 0.44±0.41 versus 0.97±0.36, p<0.01; LVEF, 56.4±13.4 versus 42.7±8.9, p<0.05; RWM, −1.87±0.85 versus −3.18±0.52, p<0.005).

Conclusions. MCE demonstrates that angiographically successful reflow cannot be used as an indicator of successful myocardial reperfusion in AMI patients. The residual contrast defect in the risk area demonstrated immediately after reflow is a predictor of poor functional recovery of the postsischemic myocardium. (Circulation 1992;85:1699–1705)

Key words • no reflow phenomenon • echocardiography, contrast • myocardial reperfusion • cardiac function

In recent years, an interest in preserving acutely ischemic myocardium has led to the development of interventional techniques for restoring coronary perfusion to the jeopardized myocardium.1-3 Coronary arteriography was used to evaluate the success of these techniques; however, it does not provide an assessment of myocardial perfusion. Myocardial contrast echocardiography (MCE) is a relatively new method of visualizing the territory of a coronary artery through the intracoronary injection of microbubbles.4-8 Thus, contrast defects on echocardiography obtained before coronary reflow denote the size of the risk area, and those obtained after successful coronary reflow denote regions of no reflow.

In this study, MCE was used to examine the patterns of myocardial perfusion after successful reflow in patients with acute myocardial infarction (AMI) and to assess the clinical significance of these patterns.

Methods

Study Population

Fifty-two consecutive patients with anterior AMI underwent MCE during emergent catheterization. These patients were admitted to our hospital between December 1988 and March 1990 and were treated with either intracoronary thrombolysis or coronary angioplasty within 6 hours of the onset of chest pain. The diagnosis of AMI was made on the basis of chest pain duration ≥30 minutes occurring within 6 hours of presentation, ST segment elevation ≥2mm in two contiguous electrocardiographic leads, and a greater than threefold increase in serum creatine kinase levels. Thirteen patients were excluded from analysis because of inadequate image quality (4), inability to identify the culprit vessel (1), previous AMI (1), and high-grade
residual stenosis (>90%) (7). This report is, therefore, based on the remaining 39 patients (mean age, 60 years; 29 men, 10 women) in whom coronary reflow was achieved by intracoronary thrombolysis in 10 and by angioplasty in 29. Informed consent was obtained from each patient. The majority of these patients (36) had Q wave AMI.

Protocol

Each patient was rested in the supine position. On the completion of the diagnostic coronary arteriography and left ventriculography, sonicated Ioxaglate (2 ml, intracoronary) (Hexabrix-320, Tanabe, Tokyo) containing microbubbles of a mean size of 12 μm was injected into the left coronary artery for MCE. A commercially available mechanical sector scanner (model SAL-38B, Toshiba, Tokyo; carrier frequency of 3.5 MHz) was used. Imaging was initiated 10 seconds (mean) before contrast injection and was continued for 70 seconds (mean) with constant gain settings. Images were recorded on 1.27-cm videotape using a VHS recorder (model BR-6000, Victor, Yokohama). MCE was performed in three views: the parasternal long-axis view and short-axis view at the level of papillary muscle and the apical long-axis view. After completion of contrast injection into the left coronary artery, the injection was performed into the right coronary artery. Only parasternal short-axis and apical long-axis views were recorded. MCE was repeated about 15 minutes (7–18 minutes) after successful reflow. The lead II electrocardiogram was continuously monitored during and after MCE. A 12-lead electrocardiogram was recorded before and immediately after the completion of MCE.

All patients underwent echocardiographic examination for left ventricular regional wall motion before reflow and at a mean of 28 days (range, 26–30 days) later. The echocardiographic examination included short-axis views at the mitral valve and midpapillary muscle levels and the apical long-axis view. Coronary arteriography and left ventriculography were repeated 24–33 days (mean, 29 days) after reflow. No patients showed significant progression of stenosis in the infarct-related artery or in the other coronary arteries.

Analysis of Myocardial Contrast

Echocardiographic Data

Images recorded on videotape were analyzed using a commercially available off-line computer system (model LA-500, PIAS, Osaka). For the assessment of the risk area and residual contrast defect, we used the apical long-axis view of the left ventricle. Because no contrast enhancement was observed in the apical long-axis view after contrast injection into the right coronary artery in this study population, only contrast images obtained from left coronary artery injection were used. To define the risk area region showing no contrast effect before reflow, the end-diastolic frame of the postinjection cycle showing the best delineation between contrast-enhanced and nonenhanced myocardium was selected for analysis.

The patients were divided into two groups based on the pattern of contrast enhancement in the risk area by MCE performed after reflow. The presence or absence of residual contrast defect was the only criterion for patient classification. The measurement used to assess reperfusion was a risk area–length ratio: ratio = (endocardial length of residual contrast defect after reflow)/(endocardial length of defect before reflow). When this length ratio exceeded 0.25, it was considered indicative of incomplete myocardial reperfusion. Other echo planes were used for confirmation of the residual contrast defect.

Reproducibility of Results

The reproducibility of measuring the endocardial length of the contrast defect was assessed in five patients by repeating the injection of sonicated Ioxaglate. Intraobserver variability was defined by one observer making duplicate measurements in 10 randomly selected images. Interobserver variability was defined by another observer making a single set of measurements. These observers were blinded to patient data and the result of the other observer.

Analysis of Echo Wall Motion

Images recorded on the day after infarction and 4 weeks later were used for the analysis of left ventricular wall motion. The left ventricle was divided into 17 segments (eight segments on each short-axis slice at the levels of the mitral valve, midpapillary muscle, and apical segment on apical long-axis view). Wall motion in each segment was evaluated as follows: 3, akinetic/dyskinetic; 2, severely hypokinetic; 1, hypokinetic; 0, normal. Average segmental score was determined by two independent observers. In cases of disagreement, consensus was established with a third observer.

Analysis of Catheterization Data

The right anterior oblique views of left ventriculograms obtained immediately after infarction and 4 weeks later were used for the assessment of global and regional left ventricular function. End-diastolic and end-systolic endocardial contours were traced in the frames with maximal and minimum volume, respectively. Left ventricular volume was calculated by the area–length method. Global ejection fraction (left ventricular ejection fraction, LVEF%) was calculated from end-diastolic and end-systolic left ventricular volumes (LVEDV and LVESV) as (LVEDV–LVESV)×100/LVEDV.

Regional wall motion of the ventriculogram was assessed with the centerline method, using 100 chords. Each shortening fraction was normalized to the end-diastolic perimeters of the left ventricle. This normalized motion in the left anterior descending artery bed (chords 10–66) was expressed as standard deviation from the mean value previously determined in 38 age-matched normal subjects (regional wall motion×SD/chord). The extent of severely hypokinetic segment was assessed as the number of contiguous chords showing motion ≤–2 SD.

Collateral channels were graded as follows from the initial angiography: 0, no collaterals; 1, incomplete slow opacification of the distal vessel; 2, slow but complete opacification of the distal vessel; 3, distal vessel well opacified as well as the normal vessel. Cine films were...
analyzed in a random sequence by an angiographer blinded to patient data.

Statistical Analysis
All data are expressed as mean±SD. Comparisons between two groups were made with the unpaired t test. Comparisons between results of the initial and delayed studies were made using the paired t test. Differences were considered significant at a value of p<0.05 (two-sided).

Results

Safety
No patients exhibited hemodynamic derangements, malignant ventricular arrhythmias, or augmentation of chest pain during or after intracoronary injection of sonicated Ioxaglate. There was no change in mean arterial pressure between before and immediately after MCE (105±19 mm Hg versus 103±18 mm Hg). Although ventricular ectopy was not observed, single atrial ectopy was observed in two patients immediately after contrast injection. There were no changes in heart rate during or immediately after the completion of MCE (87±12 beats per minute versus 86±12 beats per minute). No additional electrocardiographic changes were observed immediately after the completion of MCE.

Reproducibility of Results
The mean length of the risk area measured in two sequential injections was 97±22 mm and 99±21 mm, respectively; mean difference between the two was 4.0±3.4 mm. The area of the residual contrast defect was always clearly defined. Mean length of the residual contrast defect in the two sequential injections was 56±16 mm and 57±17 mm, respectively (absolute difference, 4.4±3.9 mm). Absolute difference in the length of the risk area measured by the same observer at two different times was 2.4±2.2 mm, and that measured by two observers was 4.0±2.4 mm. Absolute difference in the length of the residual contrast defect measured by the same observer at two different times was 2.2±1.9 mm, and that measured by two different observers was 3.0±2.8 mm.

Myocardial Perfusion
The risk area in the anterior interventricular septum, anterior free wall, and cardiac apex was clearly defined as a negative contrast area in all study patients before reflow by the injection of sonicated Ioxaglate into the left coronary artery.

Significant contrast enhancement was observed within the predetermined risk area immediately after coronary reflow in 30 (77%) of 39 patients. These patients were classified as group A (Figure 1). In comparison, a sizable contrast defect was noted in nine patients after successful reflow. These patients were classified as group B. Figure 2 represents an example showing a large residual contrast defect within the risk area. Most of the risk area, including interventricular and cardiac apex, failed to show contrast enhancement even after successful reflow. The residual contrast defects usually presented in the cardiac apex and extended toward the base. The risk area–length ratio was 0.02±0.04 in group A and 0.61±0.12 in group B patients.

Table 1 summarizes characteristics of group A and group B patients. There were no differences in the time between symptoms and reflow, angiographic collateral grade, and selection of reperfusion treatment (thrombolysis or angioplasty) between group A and group B patients.

Recovery in Left Ventricular Function
Changes in the average segmental score between initial and delayed echo studies are summarized in Figure 3. There was no difference in the average segmental score between group A and group B patients (0.89±0.37 versus 1.07±0.32, NS) in the baseline pre-reflow study. The group A patients showed a significantly greater improvement in average segmental score compared with group B patients in the delayed study (0.44±0.41 versus 0.97±0.36, p<0.01).

In 29 of the 39 patients, left ventriculography was performed in both acute and chronic stages. There was no significant difference in LVEF at baseline study. The group A patients showed significant improvement in this parameter from the baseline to the delayed studies (42.3±11.0% versus 56.4±13.4%, p<0.001), with group B patients showing no statistically significant improvement (34.7±8.9% versus 42.7±8.9%, NS).

As for the changes in the circumferential extent of segments showing severe hypokinesis between baseline and delayed studies, a significant reduction in this parameter was found in group A patients (47.7±7.1 versus 23.1±18.2, p<0.001), but no reduction was noted in group B patients (53.2±4.6 versus 49.8±8.4, NS). There were no differences in the degree of regional wall motion abnormality in the territory of the left anterior descending coronary artery between group A and group B (−3.26±0.43 SD/chord versus −3.36±0.15 SD/chord, NS) in the baseline study. The group A patients, however, showed less wall motion abnormality than group B patients in the delayed study (−1.87±0.85 SD/chord versus −3.18±0.52 SD/chord, p<0.005).

Discussion
In this study, a residual perfusion defect immediately after thrombolysis was observed in the previously occluded myocardial bed in nine of the 39 patients. In these patients, the recovery in global and regional contractile function was less than in patients without a residual perfusion defect. These observations indicate that angiographically successful reflow does not necessarily indicate adequate myocardial perfusion. Additionally, the demonstration of the presence or absence of residual perfusion defects is useful for predicting functional recovery of the postischemic myocardium.

No Reflow Phenomenon
Our data demonstrate that residual perfusion defects were observed even after successful thrombolysis in one fourth of anterior AMI patients receiving aggressive recanalization in the acute phase of their AMI. This inadequate perfusion of the postischemic myocardium indicates the no reflow phenomenon. Since the first experimental reports of Kloner et al., it is well recognized that the no reflow phenomenon is observed during thrombolysis after prolonged coronary occlusion. Although the mechanism of this phenomenon is not
clear, it has been associated with extensive myocardial necrosis and microcirculatory damage. Our data extended these observations into the clinical setting and indicate that the presence of this phenomenon is indeed a parameter of poor functional recovery and may, therefore, be associated with more severe necrosis.

Kemper et al compared the extent of perfusion defect on MCE after reflow with the morphological distribution of infarction after reflow in a canine experiment. They demonstrated that perfusion defect was limited to the infarcted myocardium. Villanueva et al also studied patterns of myocardial reperfusion in a canine model by MCE. They demonstrated that MCE-defined perfusion defect after reflow relates closely to TTC-derived infarct size. Our clinical observations indirectly confirm these findings. Other experimental studies also suggested that the no reflow phenomenon should be related to paucity of microcirculation that has been destroyed by the infarction process. According to these studies, it has been predicted that, in patients with AMI, the recovery of contractile function in the risk area may be worse in those with residual perfusion defects than in those without. In the current study, little or no improvement in global and regional left ventricular function was observed in the patients with residual perfusion defects. Thus, in the patients with AMI, the lack of myocardial perfusion after reflow may be related to lack of microvascular integrity, which may simply mean worse muscle necrosis.

We compared the elapsed time and angiographic collateral grade between patients with and without residual perfusion defects. A previous experimental study suggested that the no reflow phenomenon becomes worse over time and that elapsed time was one of the determinants of no reflow. However, in the current study, there were no differences in the elapsed time or in the grade of angiographic collaterals between patients with and without residual perfusion defect. The study population, however, was limited to patients who achieved thrombolysis within 6 hours of symptom onset, and no patient in this study had well developed collaterals in the initial coronary arteriograms.

It is interesting to note whether patterns of myocardial reperfusion are different between thrombolysis and coronary angioplasty. Residual coronary stenosis, which limits myocardial flow, may be more severe in thrombolysis compared with angioplasty. On the other hand, abrupt restoration of myocardial blood flow by angioplasty might promote damage of the posts ischemic coronary microvascular bed. Although this study was
concerned with only patients with residual coronary stenosis <90%, the results of this study imply that there is no difference in the selection of reperfusion treatment (thrombolysis or angioplasty) between patients with and without residual perfusion defect.

Two possible mechanisms may explain the improvement in regional function in patients who did not exhibit perfusion defects after successful reflow. In these patients, ischemic damage to the myocardium and to the coronary microcirculation is less severe compared with the patients with residual contrast defect; therefore,

**FIGURE 3.** Plots of average segmental score in the acute and chronic stages of myocardial infarction. Data of patients without residual contrast defect: group A, open circles; data of patients with residual contrast defect: group B, closed circles. These comparisons reveal that the greater improvement in this parameter is observed in group A compared with group B.

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<th>Table 1. Clinical Characteristics</th>
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<td><strong>Group</strong></td>
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<td>Male (%)</td>
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Collateral graded as good, 3; intermediate, 2; poor, 1; none, 0. Groups A and B denote the patients without and with residual contrast defect in the risk area immediately after reperfusion, respectively.

Values are expressed as mean±SD.
restoration of myocardial blood flow through a relatively preserved coronary microcirculation would promote the salvage of the posts ischemic myocardium.

Comparison With Previous Studies

Schofer et al 18 injected radioactive microalbumin aggregates after intracoronary thrombolysis and demonstrated 99m Tc perfusion defects in all patients. Their prevalence of no reflow was much higher than noted in our study (23%). In contrast to Schofer’s study, the majority of our patients (74%) underwent coronary angioplasty. The difference in the severity of residual coronary stenosis may explain the difference in our results. In addition to microvascular damage, perfusion could be limited to a myocardial bed because of severe epicardial stenosis. This phenomenon, however, does not represent the classic no reflow phenomenon.

Limitations

Regional contrast intensity can be influenced by several factors, including 1) the size and number of microbubbles injected, 2) the injection volume of the contrast medium, and 3) factors affecting ultrasonic reflection such as gain setting, depth of penetration, axial and lateral resolution, gray scale compression, and the nonlinearity of echo amplitude. In the current study, the same echo plane and the same intracoronary injection volume of the sonicated microbubbles were used for the determination of presence or absence of contrast perfusion defect. Thus, the effects of the aforementioned factors might have been minimized.

The diameter of the microbubbles produced by sonication in this study was 12±3 μm, which is larger than red blood cells. Their intravascular rheology, therefore, may be different from that of red cells. New contrast media, such as sonicated albumin, are smaller in size than these microbubbles and are being applied to humans as red cell tracers. 19 These new contrast media should promote better understanding of the flow dynamics of red blood cells in the posts ischemic microcirculation.

The apical long-axis view during contrast injection into left coronary artery was chosen for risk area assessment in this study, because no contrast enhancement was observed in this echo view after contrast injection into the right coronary artery. In cases with well developed collateral channels that come from the right coronary artery, the risk area may be overestimated with the present method. We should make contrast injection into both right and left coronary arteries in the same echo view for the quantification of the risk area as an area of contrast defect.

Clinical Applications

Because the absence of adequate myocardial perfusion after successful reflow predicts poor recovery in regional function, patients showing this phenomenon are likely to show infarct expansion and heart failure. Such patients may need aggressive forms of unloading therapy. 20

Several experimental studies indicated that the no reflow phenomenon was significantly attenuated by administration of several drugs (superoxide dismutase and catalase 13 or adenosine 21). Although these drugs have not been used in clinical settings, MCE might be a promising method in the evaluation of the effect of these interventions on the no reflow phenomenon in experimental as well as in clinical studies.

Using MCE, we can simultaneously assess regional wall motion and myocardial perfusion in patients with AMI. The mechanism of abnormalities in regional motion may be evaluated in relation to the abnormalities in regional perfusion.

The use of MCE in conjunction with coronary arteriography can provide information on regional myocardial blood flow and epicardial coronary anatomy, which might be useful in determining therapeutic strategies.

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