Time Course of Functional Improvement in Stunned Myocardium in Risk Area in Patients With Reperfused Anterior Myocardial Infarction

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Background. The beneficial effect of coronary reflow on myocardial salvage may be assessed more accurately than in previous studies if the size of risk area is taken into account, particularly because the size of risk area varies significantly among patients. In this study, the risk area was determined with myocardial contrast echocardiography to investigate the time course of functional recovery of posts ischemic myocardium within the risk area in patients with reperfused anterior myocardial infarction.

Methods and Results. The study population consisted of 21 patients with anterior myocardial infarction who achieved coronary reflow within 6 hours of onset by means of thrombolysis or coronary angioplasty. Myocardial contrast echocardiography was performed with the injection of hand-agitated Haemacel (5 ml) into the right and left coronary arteries before coronary reflow, and the risk area was defined as the area of contrast perfusion defect in the apical long-axis view. The ratio of the endocardial length of abnormal contraction (dyskinesis/akinesia) segment to that of contrast defect segment (AS/CD) was determined at days 1, 2, 3, 7, 14, and 28 of reflow. Before reflow, the length of contrast defect correlated well with the segment length of dyskinesis/akinesia. The values for AS/CD in patients with successful reperfusion significantly and progressively decreased until day 14; 1.00±0.02 at day 1, 0.93±0.11 at day 2 (p<0.05 versus day 1), 0.84±0.16 at day 3 (p<0.05 versus day 2), 0.80±0.13 at day 7 (p<0.01 versus day 2), 0.73±0.10 at day 14, and 0.72±0.10 at day 28. Greater improvement in function was obtained in patients reperfused within 4 hours than in those reperfused at ≥4 hours (AS/CD at day 28, 0.64±0.12 versus 0.75±0.09, p<0.05).

Conclusions. Thus, a significant amount of myocardium, an average of 28% in segment length of the risk area, is salvaged in patients with reperfused anterior myocardial infarction. Major functional improvement seems to be achieved within 14 days of reflow. (*Circulation* 1993;87:355–362)

Key Words • echocardiography • contrast media • stunned myocardium • reperfusion • risk area

Intracoronary thrombolysis and coronary angioplasty are widely performed for restoring coronary flow to the jeopardized myocardium in patients with acute myocardial infarction. Coronary reflow, if achieved in the early stage of infarction, may limit the progression of myocardial necrosis and should enhance the functional recovery of posts ischemic myocardium. The extent to which coronary reperfusion salvages the function of severely ischemic myocardium is of clinical importance but remains controversial because the identification and quantification of the risk area in the acute phase of infarction has been difficult in patients with conventional methods. The risk area obviously varies among patients even with the same occlusion site in the same coronary artery; therefore, analysis of changes in infarct size and regional function after reperfusion is meaningful only if examined in relation to the initial risk area.

The purpose of this study was to investigate the beneficial effect of early coronary reperfusion on myocardial salvage and to elucidate the process of functional recovery of posts ischemic myocardium within the risk area in patients with reperfused anterior infarction. In this study, myocardial contrast echocardiography (MCE) was used to determine the risk area as an area of contrast perfusion defect in the acute stage of infarction. Then, regional contraction in the risk area was serially assessed with echocardiographically determined endocardial length of abnormal contractile segment within the risk area. The results were also compared between reperfused patients and nonreperfused patients to clarify the beneficial effect of coronary reperfusion in itself.

Methods

Study Population

MCE was performed in the acute stage in 28 consecutive patients who were admitted to the coronary care...
unit of Sakurabashi Watanabe Hospital for an acute transmural myocardial infarction of the anterior wall from 1987 to 1988. The diagnosis of an anterior infarction was made on the basis of chest pain of at least 30 minutes' duration occurring within 6 hours of presentation, ST segment elevation of at least 2 mm in two continuous ECG leads, and a greater than threefold increase in serum creatine kinase levels. Seven of these patients were excluded from analysis: four because of inadequate image quality, two because of inadequate coronary reperfusion (Thrombolysis in Myocardial Infarction Trial [TIMI] grades 0, 1, and 2), and one because of inability to identify the culprit vessel. Therefore, this report is based on the remaining 21 patients (19 men, two women; age range, 42–74 years) in whom coronary reperfusion was achieved by intracoronary thrombolysis (urokinase, 480,000–960,000 units) in seven patients and by angioplasty in 14 patients. All patients had Q-wave myocardial infarction. The study protocol was approved by the hospital's ethics committee. Informed consent was obtained from each patient by one of the investigators.

Ten patients (eight men, two women; age, 58±6 years) with Q-wave myocardial infarction of the anterior wall who did not achieve successful coronary reperfusion were used as a control group. We performed coronary arteriography in the acute stage and recognized complete occlusion in the proximal portion of the left anterior descending coronary artery. Intracoronary thrombolysis was performed in eight patients, but we could not obtain successful reperfusion. Two patients did not receive reperfusion therapy because they were admitted to our coronary care units 10 and 14 hours after the onset of symptoms. MCE was not performed in all patients, but routine two-dimensional echocardiographic examination was performed in the same manner as in the patients who achieved successful reperfusion. Repeat coronary arteriography in the chronic stage revealed the complete occlusion of the same coronary site as in the acute stage in all patients.

Study Protocol

Each patient rested in the supine position. On completion of diagnostic coronary angiography and contrast ventriculography, we performed MCE with the intracoronary injection of 5 ml of hand-agitated 3.5% polygelin colloid solution (Haemaccel, Hoechst Japan, Osaka) into the left coronary artery. The commercially available mechanical sector scanner (model SAL-38B, Toshiba, Tokyo; carrier frequency of 3.5 MHz) was used. An apical long-axis view of the left ventricle was recorded continuously before, during, and for about 1 minute after contrast injection without adjustment of initially determined gain setting. Echo images were recorded on 1.27-cm videotape with a VHS recorder (BR-6400, Victor, Yokohama). Then, contrast injection (5 ml) was repeated into the right coronary artery, and the same echo image was recorded. ECG lead II was continuously monitored during and after MCE. A 12-lead ECG was recorded before and immediately after the completion of MCE.

An apical long-axis view of the left ventricle was recorded before reflow (day 1) and at days 2, 3, 7, 14, and 28 of reflow by an electrical sector scanner (model SSH-65A, Toshiba; carrier frequency of 3.75 MHz). These echo images were recorded on the same video-cassettes. We referred to the initial echo images before each echo examination in order to depict the same echo view insofar as possible.

Coronary angiography was repeated 28 days (range, 24–31 days) after the onset of myocardial infarction. All patients who achieved coronary reflow exhibited no significant progression of stenosis in the infarct-related artery as well as in the other coronary arteries.

Data Analysis

Apical long-axis views were analyzed for assessment of risk area and for analysis of regional wall motion. Since no contrast enhancement was observed in this image after contrast injection into the right coronary artery, only contrast images obtained after contrast injection into the left coronary artery were used for analysis. The risk area was determined in the end-diastolic frame of the postinjection cycle showing the best delineation between contrast-enhanced and non-contrast-enhanced myocardium. The risk area was defined as an area not showing contrast enhancement (Figure 1). A commercially available image analyzer (model LA-500, PIAS, Osaka) was used to measure the endocardial length of the contrast defect segment for the quantification of the size of the risk area.

Abnormal contraction was defined as akinesis or dyskinesis, showing no inward endocardial motion during systole (Figure 2). The endocardial length of the end-diastolic segment showing dyskinesis/akinesis was measured in each follow-up echo study. Recovery of wall motion within the risk area was assessed with the ratio of the endocardial length of the abnormal contractile segment to that of the contrast defect segment (AS/CD) at each study. The AS/CD at 28 days of reperfusion was used to assess the extent of myocardial necrosis in the risk area.

Analysis of Catheterization Data

The right anterior oblique view of left ventriculograms obtained shortly after infarction and 4 weeks later were used for the determination of end-diastolic volume and ejection fraction. End-diastolic and endsystolic endocardial contours were traced in the frames with maximum and minimum volumes, respectively. Left ventricular end-diastolic volume (LVEDV) was calculated by the area–length method and was divided by the body surface area to determine LVEDV index (LVEDVI, in milliliters per square meter). Left ventricular ejection fraction (LVEF, in percent) was calculated using LVEDV and left ventricular end-systolic volume (LVESV) as (LVEDV – LVESV)×100/LVEDV.

Collateral channels were graded in the initial arteriograms as follows: none, no collaterals; poor, incomplete slow opacification of the distal vessel; intermediate, slow but complete opacification of the distal vessel; good, distal vessel opacified as well as the normal vessel. Cinefilms were analyzed in a random sequence by an angiographer blinded to patient data.

Reproducibility of Data

The reproducibility of measuring the endocardial length of the contrast defect was assessed in five patients by repeating injection of the contrast medium. Percent absolute difference of two trials was 3.7±2.0%.
other observer. Intraobserver variability of the length of the contrast defect was 2.0±2.3% (absolute difference). Interobserver variability of the length of the contrast defect was 5.2±3.0% (absolute difference). An observer measured the length of abnormal contractile segment in 20 randomly selected echo images at two times. The difference was 4.1±4.0% (absolute difference). The interobserver variability of the length of abnormal contractile segment in 20 randomly selected echo images was 5.9±4.3% (absolute difference).

**Statistical Analysis**

Data are expressed as mean±SD. Statistical analysis of changes in AS/CD was computed by ANOVA and Scheffe's F test for repeated measures. When comparing two different groups for certain variables, a one-way ANOVA for factor analysis was applied. Differences were considered significant at p<0.05.

**Results**

**Safety**

Duration of contrast effect was 32±8 seconds. No patients showed hemodynamic derangement, intractable arrhythmias (ventricular fibrillation or ventricular tachycardia), or the augmentation of chest pain during and immediately after MCE. Intracoronary injection of the contrast medium did not produce further changes in QRS wave or ST-T segment in a 12-lead ECG recorded immediately after MCE. Ventricular ectopy was not observed, but atrial ectopy (one beat) was observed in one patient.

**Risk Area and Wall Motion Abnormalities Before Reflow**

In the initial coronary arteriography, collateral filling to the distal vessel of the infarct-related artery was graded as none in four patients and poor in 17 patients. No contrast enhancement was observed in the apical long-axis view after contrast injection into the right coronary artery. Figure 1 shows apical long-axis images at end diastole and end systole after the injection of contrast medium into the left coronary artery before reflow. Although the basal region of the interventricular septum and posterior wall shows significant contrast enhancement, the area of contrast defect extends from the distal region of the septum to the cardiac apex. Although the positive contrast segment exhibits inward motion during systole, the contrast defect segment did exhibit akinesis. The value for AS/CD before coronary reflow was 1.00±0.02, suggesting that lengths of segments showing abnormal contraction coincide with those of the contrast defect segment.

**Improvement of Regional Wall Motion After Reflow**

Figure 3 illustrates changes in AS/CD until day 28 of reflow in patients who achieved successful coronary reflow. After day 3 of reflow, the AS/CD was <1.0, and no patient exhibited infarct expansion during follow-up period. The AS/CD of 1.00±0.02 before reflow decreased significantly at day 2 (0.93±0.11, p<0.01 versus before reflow). Statistically significant decreases in AS/CD were observed until day 14 (day 3, 0.84±0.16, p<0.05 versus day 2; day 7, 0.80±0.13, p<0.01 versus day 2; and day 14, 0.73±0.10, p<0.01 versus day 3). No
Further statistically significant reduction in AS/CD was observed after day 14 (0.72±0.10 at day 28).

In eight patients reperfused within 4 hours of onset, the reduction in AS/CD appeared to be more rapid and greater than in those reperfused later than 4 hours. The relation between elapsed time and infarct size within the risk area, expressed by AS/CD at day 28, is shown in Figure 4. The value for AS/CD at day 28 in patients reperfused within 4 hours of onset was significantly lower than in those reperfused later than 4 hours (0.64±0.12 versus 0.75±0.09; p<0.05).

In 17 of 21 patients studied, adequate left ventriculograms were obtained in both acute and chronic stages. Figure 5 illustrates the changes in LVEDVI and LVEF.
in reperfused patients. There were no differences in LVEDVI at baseline study. At delayed study, LVEDVI in those patients reperfused within 4 hours of onset was apparently lower than those reperfused later than 4 hours (85±18 versus 111±38 ml/m²), but the difference was not significant. There was also no difference in LVEF at baseline study between the two groups. The patients reperfused within 4 hours showed significant improvement in this parameter from the base to the delayed studies (50±8% versus 59±10%, p<0.05) and showed significantly better global function in the delayed study compared with those reperfused later than 4 hours (p<0.05).

Patency of Infarct-Related Artery and Infarct Size

To assess the beneficial effect of coronary reflow on infarct size, we compared the ratio of the infarct size to the size of the risk area between 21 reperfused patients and 10 nonreperfused patients with persistent occlusion of the infarct-related artery. Since MCE was not performed in 10 nonreperfused patients, we measured the lengths of segments showing abnormal contraction at days 1 and 28 of infarction to determine the segment length ratio (AS-28/AS-1). As shown in our results, the endocardial length of the contrast defect was almost compatible with that of the abnormal contraction segment before reflow. Values for AS-28/AS-1 in reperfused patients were significantly lower than those in the nonreperfused patients (0.73±0.11 versus 0.93±0.08; p<0.01) (Figure 6). Although the value of AS-28/AS-1 was <0.9 in each reperfused patient, three of 10 nonreperfused patients showed AS-28/AS-1 >1.0, indicating the progression of the infarct expansion.

Discussion

The beneficial effect of coronary reflow on myocardial salvage should be more accurately determined than in the previous studies if the size of the risk area is measured, regardless of the occlusion site of the coronary artery. In this study, the risk area was defined before reflow with MCE to assess the time course of
functional recovery of postischemic myocardium within the risk area by quantitative two-dimensional echocardiography in patients with reperfused anterior infarction. Our results demonstrated that coronary reflow was followed by an improvement in up to 28% of the segment length of the risk area. Greater improvement was observed in patients reperfused within 4 hours than in those reperfused after 4 hours. There was no improvement in wall motion abnormalities in nonreperfused patients. This functional improvement in postischemic myocardium was usually achieved within 14 days of reflow.

Functional Improvement of Postischemic Myocardium

Reperfusion of the ischemic myocardium salvages a substantial amount of the myocardium within the risk area, but there has been limited clinical information on the time course of its functional recovery. Several experimental studies demonstrated that functional recovery of the salvaged but stunned myocardium requires several days or even weeks after prolonged coronary occlusion.10-12 Charuzi et al13 analyzed wall motion abnormalities with two-dimensional echocardiography in patients with reperfused myocardial infarction to suggest that recovery of both regional and global left ventricular function may require at least 10 days after reflow. In this study, we extended their method and serially assessed the improvement in regional function within the risk area during the acute to chronic stage of reperfused anterior infarction. The AS/CD was determined at days 1, 2, 3, 7, 14, and 28 of reflow. In patients who achieved coronary reflow, significant reduction of the value for AS/CD was found in 3 days of reflow. The maximal reduction of the values for AS/CD was found in 7 days of reflow, and no further statistically significant reduction was observed on and after day 14. Thus, the early coronary reflow may be effective in the protection of infarct expansion as well as improvement in regional function. The majority of this improvement seems to be achieved within 14 days of reflow.

Coronary Reflow and Salvage of Ischemic Myocardium

Although it is well known that early coronary reflow is promising in salvage of the jeopardized myocardium,2-4 the extent to which the ischemic myocardium can be salvaged within the risk area remains to be solved. The size of the risk area should vary among individuals even with coronary occlusion at the apparently comparable level of the same vessel. Therefore, analysis of changes in the infarct size and regional function is meaningful only if examined in relation to the initial risk area. In this study, we assessed the infarct size as a ratio to the size of the risk area. In patients who achieved reflow, AS/CD at day 28 was significantly reduced, by an average of 28%, compared with the value at day 1. Moreover, the extent of abnormal contraction was significantly lower than in those with persistent coronary occlusion. Therefore, if the size of the risk area is taken into consideration, timely coronary reperfusion (<6 hours) has a beneficial effect on the salvage of a significant amount of the postischemic myocardium, i.e., an average of 28% of the risk area.

In a canine experiment, Ellis et al12 demonstrated that the ratio of necrotic myocardium to myocardium at risk was reduced from 89.1% to 23.9% in the reperfused group when reperfusion was carried out 2 hours after coronary occlusion. In their study, a greater amount of the myocardium (>70%) can be salvaged by coronary reflow compared with the results of this study (average, 28%). In addition to species difference, several other factors may explain these differences. In clinical settings, at least 2-4 hours has usually passed by the time of restoration of coronary reflow by intracoronal thrombolysis and/or coronary angioplasty. Whereas they determined the size of myocardial necrosis using a histological approach, we assessed the size of infarction with the extent of wall motion abnormalities relative to that of the risk area.

The earlier coronary reflow is considered to be preferable in limiting the infarct size. In the present study, AS/CD at day 28 and LVEF were significantly lower in patients reperfused within 4 hours of onset than in those reperfused later than 4 hours. These results are in accordance with those of previous studies.14,15 Moreover, changes in AS/CD demonstrated that major improvement in regional function is accomplished within 3 days in more than half of the patients reperfused within 4 hours. Thus, the earlier the coronary reflow is achieved, the larger the amount of jeopardized myocardium that can be salvaged and the more rapidly improvement in regional function may be obtained.

Collaterals play an important role in the attenuation of the infarct size. Sabia et al16 assessed the functional significance of collaterals by MCE in patients with recent acute myocardial infarction (12±7 days after onset). They indicated that collateral perfusion territory was visualized by extensive “positive” contrast area and that these collateral flows were effective in the preservation of the perfusion territory. In this study, however, no patients studied showed collateral perfusion in the apical long-axis view during contrast injection into the right coronary artery before reflow. Several factors may explain these differences: 1) MCE was performed in the very early stage of infarction (within 6 hours of the onset), and 2) the patients we studied exhibited angiographically none or poor collaterals. This poor development of collateral channels is likely to account for the small variability in AS/CD on the day of infarction. In patients with well-developed collateral channels that come from the right coronary artery, the risk area, defined as an area of contrast defect, may be overestimated with the use of contrast injection only into the left coronary artery, and the discrepancy between the size of the contrast defect segment and that of the abnormal contractile segment should become evident.

Identification of the Risk Area

Previous studies demonstrated the usefulness and accuracy of MCE in the determination of perfusion territory of the coronary artery as well as the risk area.5,6,15,17-21 In this study, we successfully delineated the risk area as an area of contrast defect in the apical long-axis view by injecting the contrast medium into the right and left coronary arteries before reflow in the majority of initial study patients. No significant deleterious effect was observed during MCE examination.

Several groups have attempted to elucidate the relation between the risk area and the extent of wall motion
abnormalities. In a canine experiment, Buda et al. demonstrated that regional wall thickening abnormalities correspond well to the actual risk area and pointed out the possibility that the extent of regional endocardial motion abnormalities might overestimate the extent of regional dysfunction. In contrast, Pandian et al. found little difference in the detection of infarction by means of endocardial motion abnormalities versus wall thickening in a canine study examining different infarct sizes. The extent of endocardial segment not showing inward motion during systole correlated well with that of the risk area determined with MCE in this study, although our method depends on visual inspection. Our results are in accordance with the observations of Pandian et al and suggest that the segment length of abnormal contraction before reflow can be regarded as a rough estimate of the size of risk area in clinical settings.

Although abnormal contractile segment was well coincident with contrast defect segment in our study, this does not necessarily indicate the absence of functional border zone in patients. No inward motion during systole was a criterion of abnormal wall motion in this study. If the segment of functional border zone that may exist in the periphery of the contrast-enhanced segment before reflow showed hypokinetic motion, the size of the functional border zone could not be assessed by our method. Scatter in AS/CD before reflow, although small, may be explained by the interindividual difference in the size of the functional border zone.

Limitations

Measurement of endocardial segmental length can be influenced by the setting of the echo plane. In our series of echo examinations, we tried to depict the same echo plane as in the initial recording insofar as possible by referring to initial echo images. The infarct expansion shown in the clinical course might also influence the length of the abnormal contractile segment. However, no patients with patent infarct-related artery showed infarct expansion or aneurysm within 4 weeks of infarction.

In patients with critical residual coronary stenosis, the myocardial contraction within the risk area may be depressed even after reperfusion, and this functionally depressed myocardium is called “hibernating myocardium.” This abnormal contractile segment should not simply be regarded as an area of myocardial infarction. In this study, however, patients with TIMI grades 0, 1, and 2 residual stenosis were excluded, and no patients showed recollusion of the infarct-related artery in the convalescent stage.

In patients with occlusions in other than the left anterior descending coronary artery, we cannot define the risk area as an area of contrast defect. Thus, we excluded patients with multivessel disease from the study population.

It is well known that necrosis progresses from the endocardium to epicardium (wave-front phenomenon) and coronary reflow stops this progression of necrosis. For this reason, looking only at the endocardial motion does not seem to be sufficient for the quantification of myocardial salvage (especially extent of epicardial salvage). However, the transmural extent of necrosis may be different within the risk area. In the region of less transmural damage, endocardial motion should improve in the convalescent stage because of relatively preserved contractile function of epicardium. Therefore, the assessment of recovery of endocardial motion may well provide estimates of the amount of myocardial salvage.

Shrinkage of the infarct scar may possibly contribute to the decrease in abnormal contractile segment relative to contrast defect segment. However, we could not quantify the amount of shrinkage in our patients.

Clinical Implications

Coronary blood flow may be augmented by intraaortic balloon pumping or administration of vasodilators or free radical scavengers, and the augmentation may be associated with the increased contractile function of the stunned myocardium. However, whether these interventions enhance the rate of functional improvement of the postischemic myocardium and augment the extent of myocardial salvage remains to be seen. Little information has been available on serial changes in regional myocardial function after myocardial reperfusion in humans. This study provides important baseline data for future studies to evaluate the interventions of maximizing the rate and magnitude of improvement in the stunned myocardium after reperfusion.

Several drugs aimed at reduction of infarct size have been investigated in experimental as well as clinical studies. In clinical settings, regional and/or global left ventricular wall motion has been analyzed for evaluation of the effects of such drugs. However, it would be meaningful only if these data were analyzed in relation to the initial infarct size, particularly because the initial risk area varies greatly among patients. The current method should be useful for the evaluation of the effect of drug interventions on the extent of myocardial salvage in the risk area.

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