Time Course of Left Ventricular Remodeling After Myocardial Infarction

— A Two-Dimensional Echocardiographic Study —

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In order to forecast the clinical course of acute myocardial infarction (MI), the time course of the functional changes of the left ventricular myocardium that result in remodeling was evaluated with two-dimensional echocardiography (2DE). The study group comprised 45 patients with anterior MI treated with successful percutaneous transluminal coronary angioplasty. 2DE studies were performed on days 1, 3, 7 and 14; months 1 and 3 and 1 year after MI, and the following parameters were recorded: (1) infarcted wall thickness, (2) traced length of the endocardium and of the epicardium on end-diastolic apical long axis images, and (3) wall motion score (total of asynergy scores of 16 segments of left ventricle (LV); normal: 0, hypokinesis: 1, akinesis: 2, dyskinesis: 3). According to the peak creatine kinase (CK) level, patients were classified into L group (CK $\geq$ 8000 U/L, n=16), M group (8000 $>$ CK $\geq$ 4000, n=13) and S group (CK $<$ 4000, n=16). The following results were obtained. (1) There was progressive thinning of the infarcted myocardium up to 1 month after (1 day: 9.3 ± 1.7 , 14 days: 6.3 ± 1.7 vs 1 month: 5.9 ± 1.8 mm, $p<0.05$; vs 1 year: 5.9 ± 1.9 mm, NS). (2) Dilatation of the LV cavity occurred shortly after MI and continued up to 14 days (endocardium at 14 days: 176.8 ± 13.6 vs 1 day: 164.1 ± 11.4 mm, $p<0.01$; vs 1 year: 176.3 ± 12.7 mm, NS). (3) The wall motion score improved rapidly by 14 days, and continued to improve gradually to 1 year (1 day: 12.2 ± 3.4 , 14 days: 6.8 ± 4.0 , 1 year: 4.6 ± 3.1). (4) The expansion ratio (endocardial length at 14 days/1 day) was significantly greater in the L group than in the S group ($p<0.05$). Comparing the groups, the LV cavity of the L group remained dilated up to 14 days, whereas that of the S and M groups was dilated up to 7 days (L group 14 days: 179.3 ± 11.9 vs 1 day: 156.9 ± 9.2 mm, $p<0.01$; vs 1 year: 180.0 ± 14.1 mm, NS) (S group 7 days: 171.7 ± 13.6 vs 1 day: 161.5 ± 7.2 mm, $p<0.01$; vs 1 year: 172.7 ± 14.4 mm, NS) (M group 7 days: 170.5 ± 10.5 vs 1 day: 157.7 ± 14.5 mm, $p<0.05$; vs 1 year: 177.08 ± 9.6 mm, NS). Serial 2DE on days 1 and 14 after MI were useful for evaluating the course of LV remodeling and to forecast cardiac function in the chronic phase of MI. Determining the length of hospital stay on the basis of infarction size is justified. (*Jpn Circ J* 2000; 64: 421–429)

Key Words: Acute myocardial infarction; Echocardiography; Hospitalization; Ventricular remodeling

It has been proven that early reperfusion after acute myocardial infarction (AMI) due to coronary artery occlusion can reduce the infarct size and preserve left ventricular (LV) function.^{1–7} Left ventricular remodeling is known to be associated with cardiac function problems and with poor prognosis in terms of survival.^{8,9} However, the functional changes of the LV myocardium that result in remodeling after AMI have not been extensively studied thus far. The present study used two-dimensional echocardiography (2DE) to evaluate the time course of LV remodeling following myocardial infarction.

Methods

Subjects

Forty five patients who underwent reperfusion therapy during percutaneous transluminal coronary angioplasty

(PTCA) at Chiba Emergency Medical Center during the period from November 1993 to August 1995 were entered into the study according to the following criteria: (1) transmural anterior wall AMI with single-vessel coronary artery disease ($>50\%$ reduction in luminal diameter), (2) no evidence of previous myocardial infarction, and (3) successful PTCA achieving satisfactory reperfusion of the coronary artery. The patients were all male and the mean age was 56.4 ± 9.4 (SD) years (Table 1). Collateral flow was graded using the scale devised by Rentrop et al: grade 0: no

Table 1 Patient Characteristics

Total no.	45 (all male)
Age (years)	56.4 ± 9.4
Affected segment	
6	33
7	12
Recanalization time	$5\text{ h }39\text{ min}\pm 4\text{ h }26\text{ min}$
Peak CK/CK-MB (U/L)	$6617\pm 3924/312\pm 190$
Collateral circulation	
Grade 0	24
Grade 1	16
Grade 2	5
Grade 3	0

(Received November 17, 1999; accepted March 3, 2000)

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Fig 1. Apical long-axis images of the left ventricle at end-diastole on the first day of myocardial infarction (A) and at 1 month (B).

Fig 2. Schematic illustration of endocardial and epicardial outlines traced on the apical long-axis images of the left ventricle.

angiographically visible filling of any collateral channels; grade 1: collateral filling of the distal branches of the recipient artery, but not the epicardial portion of the artery; grade 2: partial collateral filling of the recipient epicardial artery; and grade 3: complete collateral filling of the recipient epicardial artery.¹⁰ Restenosis was noted in 24.4% of patients; 3 patients who had no evidence of myocardial ischemia on ^{99m}Tc-methoxy-isobutyl isonitrile (MIBI) scanning 1 month after successful PTCA, but developed total obstruction 3 months later were included in the study; 10 patients underwent staged PTCA for the restenosed lesions and the patency of the vessels was maintained except in 1 patient.

There were not any patients with clinical symptoms of congestive heart failure. All patients were discharged

Fig 3. Sixteen segments of the left ventricle according to the guidelines of the American Society of Echocardiography. The outer one-third of the circle represents the cardiac base, the middle third the mid-portion and the inner third represents the apical region. A, Anterior; AS, anteroseptal; PS, posteroseptal; I, inferior; P, posterior; L, lateral.

following 11 to 29 days (mean $\pm$ SD: 15.9 $\pm$ 4.3 days) of hospitalization. They were all treated with aspirin, nitrate and a calcium antagonist from the second day of admission, and angiotensin-converting enzyme inhibitors were used in 16 patients.

Procedures

The 2DE studies were performed with a 3.5-MHz mechanical sector scanner (Model SSZ-203, Aloka), and adequate images of the cardiac chambers and LV wall motion were obtained for detailed analyses of topographic variables and LV asynergy. Patients underwent an initial

Fig4. Time course of change in the thickness of the infarcted wall.

Fig5. Representative endocardial and epicardial tracings in a 46-year-old male patient with total occlusion of the left anterior descending artery (#6) with the peak CK level of 7023 U/L. (A) Serial endocardial and epicardial outlines drawn each day on the same screen to demonstrate the configuration changes of the left ventricle. (B) The endocardial and epicardial outlines at day 1, day 14 and 1 year are depicted. Bulging of the left ventricular wall was evident up to day 14 following infarction, but there were no apparent changes noted thereafter.

echocardiographic study on the first day after AMI and the studies were repeated on days 3, 7 and 14, 1 and 3 months and 1 year after infarction. LV morphology and function were assessed on the apical long-axis images, including the antero-apical region.

The following parameters were analyzed serially to assess LV remodeling.

(1) The wall thickness of the infarcted area on the apical long-axis image frozen at end-diastole (Fig 1A,B).

(2) The lengths of the LV endocardial and epicardial outlines traced on the apical long-axis images at end-diastole from the posterior mitral leaflet attachment to the aortic valve ring (Fig 2).

(3) Wall motion scores. The left ventricle was divided

Fig6. Time course of changes in LV expansion.

Fig7. Time course of the improvement in the wall motion score.

into 16 segments according to the guidelines of the American Society of Echocardiography¹¹ and the wall motion of each segment was assessed visually (Fig3). The ventricular wall abnormality was graded as follows: normal, 0; hypokinesis, 1; akinesis, 2; and dyskinesis, 3. Wall motion scores were obtained by summing the scores

of each segment.

(4) Infarct size and ventricular dilatation. The serum creatine kinase (CK) level was measured on admission and every 6 h until the peak level was reached. Infarct size was estimated from the peak serum CK level, and the patients were divided into 3 groups on this basis: L group (peak CK

level ≥ 8000 U/L, $n=16$), S group (peak CK level <4000 U/L, $n=16$) and M group peak CK level $4000-8000$ U/L, $n=13$). The time course of the changes in endocardial length of these groups was measured.

Data Analysis

All measurements were made by a single observer. Intraobserver variability was 0.4 ± 0.5 mm for the thickness of the infarcted wall, 0.37 ± 0.3 cm for the endocardial length and 0.5 ± 0.5 for the wall motion score.

Results are given as mean $\pm$ SD. Differences were evaluated by the paired or unpaired t test and assumed significant for $p < 0.05$.

Results

Time Course of Changes in the Thickness of the Infarcted Wall

The thickness of the infarcted wall at day 3 was noted to be significantly less than that at day 1 (8.2 ± 1.7 vs 9.3 ± 2.0 mm; $p < 0.01$), and progressive thinning of the infarcted wall was noted 1 month after the infarction (5.9 ± 1.8 mm), with the lower limit of thickness at 1 month being 4.0 mm. It was evident that thinning of the infarcted wall starts almost immediately after the infarction and continues for 14–28 days (Fig 4).

Time Course of Changes of the Endocardial and Epicardial Lengths

Serial endocardial and epicardial outlines were drawn each day on the same screen to demonstrate the configuration changes of the left ventricle (Fig 5). Bulging of the LV wall was evident up to day 14 following infarction, but there were no apparent changes noted thereafter.

Measurement of the endocardial and epicardial outlines showed that at day 14 these were significantly greater than at day 1 (endocardial: 176.8 ± 13.6 , 164.1 ± 11.4 mm, $p < 0.01$; epicardial: 196.1 ± 9.9 , 189.3 ± 11.6 mm, $p < 0.01$), but at 1 year were found to be not significantly different from day 14 (176.3 ± 12.7 and 196.1 ± 9.9 mm, respectively). These observations revealed that dilation of the LV cavity took place within the first 14 days after infarction and that it remained dilated to a similar extent thereafter (Fig 6).

Time Course of the Wall Motion Score

Averaged wall motion scores at each observation demonstrated a remarkable decrease by day 14 following infarction, indicating improvement in the wall motion. Slow, but steady improvement of the wall motion was noted up to 1 year after infarction (Fig 7).

Infarct Size and Ventricular Dilation

The ratio of the endocardial length at day 14 to that at day 1 in the L group was significantly greater than in the S

group (1.16 ± 0.11 , 1.08 ± 0.07 , respectively; $p < 0.05$) (Fig 8). There was no difference in age of the patient or wall thickness of the infarcted segment on admission between the L and S groups (Table 2).

Comparison of the endocardial lengths of each group at each time point demonstrated a significant and progressive increase in L group from day 1 to day 14 (179.3 ± 11.9 , 156.9 ± 9.2 mm, respectively; $p < 0.01$), and there was no significant change in the length up to 1 year after infarction (180.0 ± 14.1 mm). On the other hand, in the S and M groups a significant increase of the endocardial length was noted from day 1 to day 7 (S group: 171.7 ± 13.6 , 161.5 ± 7.2 mm, respectively; $p < 0.01$; M group: 170.5 ± 10.5 , 157.7 ± 14.5 mm, respectively; $p < 0.05$), but at 1 year the length was not significantly different from that at day 7 (S group: 172.7 ± 14.4 mm; M group: 177.08 ± 9.6 mm) (Fig 9). These results suggested that the ventricular remodeling process continues for the first 2 weeks following a large myocardial infarction, but subsides within 1 week in cases of smaller infarctions.

Angiotensin-converting enzyme inhibitors tended to be used in patients who were older (60.4 ± 10.0 , 53.5 ± 8.2 years, respectively, $p < 0.05$) and whose infarct size was larger (CK $7,802.4 \pm 3,121.3$, $6,083.7 \pm 4,237.8$, respectively, NS, MB 411.2 ± 223.6 , 269.0 ± 150.2 , respectively, $p < 0.05$). However, there was no significant difference in the ratio of the endocardial length at 1 month to that at day 1 between the 2 groups (1.11 ± 0.08 , 1.14 ± 0.11 , respectively, NS) (Fig 10).

Fig 8. Infarct size and expansion. L, CK ≥ 8000 ; S, CK < 4000 U/L.

Table 2 Characteristics of the L, M and S Group Patients

	L group (n=16) CK ≥ 8000 U/L	M group (n=13) 8000 > CK ≥ 4000 U/L	S group (n=16) CK < 4000 U/L
Expansion ratio (endocardial length 14 day/1 day)	1.16 ± 0.11	1.14 ± 0.1	1.08 ± 0.07
Peak CK (U/L)	10660 ± 3132	6236 ± 1049	2971 ± 1006
Age (years)	57 ± 10.5	57.7 ± 9.6	55.3 ± 9.9
Thickness of infarcted wall on admission (mm)	9.6 ± 1.9	9.0 ± 1.8	9.1 ± 1.4
Recanalization time	4 h 21 min $\pm$ 2 h 2 min	6 h 13 min $\pm$ 1 h 46 min	7 h 41 min $\pm$ 6 h 37 min
Hospitalization (days)	19.1 ± 4.6	14.7 ± 3.6	13.2 ± 2.5

Fig 9. Infarct size and expansion. L, CK ≥ 8000 ; M, $8000 > \text{CK} \geq 4000$; S, CK < 4000 U/L.

Fig 10. Angiotensin-converting enzyme (ACE) inhibitor and remodeling. ACE-inhibitor(+), n=16; ACE-inhibitor(-), n=29.

Discussion

As a consequence of myocardial infarction, changes in the LV size, shape and myocardial thickness, involving both the infarcted and noninfarcted segments, are seen. An increase in the size of the infarcted segment, known as

infarct expansion, is defined as 'acute dilatation and thinning of the area of infarction'^{1-6,8,12,13} After AMI, the noninfarcted myocardium compensates with hyperkinesis to maintain the total ventricular function, and in the chronic phase, hypertrophy of the noninfarcted segments of the myocardium takes place. With an extensive infarction, not

only the infarcted segment but all the remaining myocardium becomes dilated, resulting in an increase in LV volume. These changes in LV architecture, including the initial expansion of the infarcted myocardial segment and the subsequent dilatation and local hypertrophic changes during the months after the infarction, are referred to as 'ventricular remodeling'⁸

With the wide application of PTCA in recent years, early reperfusion therapy has reduced the incidence of mechanical complications, including ventricular rupture and post-infarction angina pectoris, following AMI, and because of that, cardiac rehabilitation can be done much more safely and uneventfully than previously. The aim of cardiac rehabilitation is not only improvement of the remaining myocardial function, but also correction of deconditioning by improving the respiratory and muscular functions, resumption of social activities and improvement of the quality of life.^{23,24} Early mobilization apparently reduces the deleterious effect of prolonged bed rest and promotes clinical recovery. However, the histopathological changes in AMI consist of necrosis of the infarcted myocardium followed by a scarring process that supposedly takes 6–8 weeks.¹⁴ Based on that time course, prolonged bed rest used to be recommended, but now patients who have been treated for an AMI, especially those treated with PTCA, are being discharged from hospital much earlier, as long as they do not develop significant functional problems such as congestive heart failure. To justify such a practice, noninvasive evaluation of the LV myocardial changes following AMI is essential.

According to the ACC/AHA guidelines in 1996 for the management of patients with AMI, the majority of patients who remain asymptomatic after an uncomplicated myocardial infarction can very safely resume their prior activities within 2 weeks, although there are few data to support this recommendation.²⁴ Recently it was proven that not only myocardial performance and hemodynamic changes determine the functional capacity of post-myocardial infarction patients, but that skeletal muscle function and oxygen delivery are also very significant factors.

Nonetheless, it is critically important to follow the serial morphological and functional changes of the left ventricle after an AMI, so that one can determine when patients can safely resume physical activity and the intensity of it. In several previous studies, resumption of physical activities was determined on the basis of the incidence of major adverse events. In the present study, we used 2DE to evaluate the time course of LV remodeling in patients with an AMI, to determine the appropriate time to resume normal activities.

It is known that a ventricle with extensive infarct expansion undergoes remodeling that leads to congestive heart failure, particularly with antero-apical infarctions because the antero-apical myocardium is most vulnerable to expansion because of its thin wall and curvature. From a hemodynamic standpoint also, such a change in the antero-apical region would result in a significant decrease in cardiac output. Based on these facts, we evaluated the LV remodeling primarily on the apical long-axis images that visualize the antero-apical region well, whereas many other studies have only dealt with the short-axis view of the left ventricle. Because it was rather difficult to clearly differentiate the infarcted segment from the noninfarcted area, we analyzed the degree of ventricular enlargement, which includes infarct expansion and also the stretching of the infarcted

myocardium, to be exact. However, the magnitude of the stretching of the noninfarcted myocardium should be minimal, therefore in present study we assumed that the ventricular enlargement was primarily due to the expansion of the infarcted myocardium.

According to the classical experiment by Tennant and Wiggers in 1935, the LV wall of a dog showed systolic bulging immediately after ligation of the coronary artery. In humans, Matsuzaki et al reported that acute myocardial ischemia due to vasospastic angina resulted in prompt impairment of contraction as well as wall thinning with systolic expansion of the left ventricle.¹⁶ They concluded that this was primarily due to the incapability of the myocardium to resist the intraventricular pressure rise during systole. From those observations, it appears to be reasonable to assume that LV dilatation takes place immediately after AMI, as was demonstrated on the echocardiographic observations on admission of the present patients. Therefore, our main interest was the subsequent irreversible changes in LV morphology. Although the pathological process of scarring of the infarcted area takes approximately 2 months, the echocardiographic observations in present study demonstrated that the dilation process of the left ventricle following an AMI was completed within 2 weeks, which indicates that ventricular expansion occurs while the collagen fibers are not yet tight.^{15,18} Weisman et al suggested that the thinning of the infarcted wall could be attributed to (1) cell rupture, (2) a reduction in the intercellular space, (3) stretching of myocytes, and (4) slippage of myocytes with a decreased number of cells in the infarcted wall.¹⁷ The reason why the extent of endocardial dilatation was greater than that of the epicardium appears to be because the ischemic changes progress from the subendocardial to the epicardial tissue.¹³ The time course and degree of LV dilatation following myocardial infarction appear to be related to the size of infarction, and to the amount of surviving myocardium, which determines the degree of remodeling.

The present study showed that the process of thinning of the infarcted area appears to be slower than that of ventricular dilatation, which is assumed to be because of extensive fibroblast proliferation and collagen deposition that makes the ventricular wall resistant to dilation in the face of intraventricular pressure from a relatively early phase following infarction, and possibly because a decrease in the infarcted area. This study did not include patients in whom early perfusion was not achieved, so whether the time course and degree of myocardial thinning and dilatation would be different in such patients remains to be seen, but it is conceivable that there would have more extensive changes without reperfusion therapy. There was also no case in which the thickness of the infarcted wall became less than 4 mm. The thickness of the infarcted wall is less than 4 mm in most patients with ventricular aneurysm, so the lower limit of wall thickness for the development of a ventricular aneurysm is approximately 4 mm.

The regional wall motion in the jeopardized ischemic zone improved rapidly for the first 14 days after infarction, and then continued to improve gradually. The contractility of stunned but viable myocardium is apparently restored shortly after infarction and the slow, continuous improvement of wall motion in the chronic phase is considered to be due primarily to hypertrophy of salvaged myocytes.¹⁹ A previous study that assessed the viability of the myocardium using ¹²³I-betamethyl-p-indophenyl-pentadecanoic

acid (BMIPP) demonstrated that the recovery of fatty acid metabolism in the ischemic area was slower than that of regional wall motion.²² Thus, the restoration process of both mechanical contractile function and cellular metabolism of salvaged myocardium may well go on beyond day 14 after infarction. It is also known that after AMI intact myocardium shows a compensatory hypercontractile response up to the 3rd day after infarction.²⁰ Although this was not apparent in the present study, it is possible that the hemodynamic parameters appeared to be better than they actually were for the first 3 days or so.

The extent of infarction apparently made a difference in the degree of ventricular expansion and the time of its completion, and cases with less extensive infarction were associated with less remodeling. In the group with a maximum CK of less than 4000 U/L, the expansion process was completed within 7 days, whereas in the group with a maximum CK greater than 8000 U/L, it was completed in 14 days. From these observations, at least from the stand point of remodeling, patients with a relatively small infarct and no complications, such as significant arrhythmias, pericardial effusion or mural thrombosis, can be discharged after 7 days of hospitalization and those with a large infarct after 14 days' admission, as long as their clinical course is not complicated by cardiac failure. However, Litwin et al reported that after a large myocardial infarction in rats, noninfarcted myocardial tissue developed contractile dysfunction with an increase in the stiffness and amount of collagen and hypertrophy of myocytes in 6 weeks, and that only minimal functional changes were evident in the animals with a smaller infarctions.²¹ In the present patients, some of them with extensive infarction, particularly those with a maximum CK of more than 10000 U/L, showed impairment of wall motion of the noninfarcted region in the chronic phase. In those cases, no significant difference was noted in terms of the time course of LV dilatation from the other cases and no dilatation was obvious at day 14 after infarction. In addition, the ventricular wall thickness in the noninfarcted region was less than that during the acute phase, which suggests that the degree of ventricular dilatation exceeded that of compensatory hypertrophy.^{8,21} Thus, although the ventricular remodeling in cases of extensive infarction is completed by day 14 after infarction, the changes in the noninfarcted myocardium, which were not apparent in the present study, will be present. Although most patients actually tolerate the current exercise therapy, clinicians need to be very careful in terms of the duration and method of rehabilitation following AMI.

Although there was no significant difference between the L and S groups in terms of age, body surface area and the initial wall thickness of the infarcted segment, the assessment of the extent of infarction by the maximum CK method may not be accurate in elderly patients, who not infrequently show ventricular functional impairment that is much more than what is anticipated from the maximum CK level. Therefore, the therapeutic plan should be assessed carefully on an individual basis.

Conclusions

Serial evaluation of the ventricular morphology by repeated echocardiograms in cases of AMI was clinically useful, particularly the evaluation on day 14, which was valuable in terms of anticipating the subsequent LV remodeling and function in the chronic phase. In Chiba

Emergency Medical Center where the present study was undertaken, the duration of hospital admission was shortened from 21 to 7–14 days, according to the extent of infarction. Currently, patients with a maximum CK of less than 5000 U/L are kept in hospital for 7 days, those with a maximum of 5000–10000 for 10 days, and 14 days for patients with a maximum CK of more than 10000 U/L. The present results justified this policy. However, extensive infarction can manifest as functional impairment of the noninfarcted myocardium, so in view of the fact that the remodeling process goes on for longer than 14 days in such cases, the length of hospital stay should always be determined carefully in each case.

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