Influence of treatment delay on long-term left ventricular function in patients with acute myocardial infarction successfully treated with primary angioplasty

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Background Myocardial salvage has been shown to be dependent on the time elapsed from the onset of acute myocardial infarction (AMI) to reperfusion. The aim of this study was to evaluate the importance of time to reperfusion for left ventricular function recovery after primary angioplasty (percutaneous transluminal coronary angioplasty [PTCA]) for AMI.

Methods Ninety-five patients undergoing long-term successful PTCA for AMI were studied. Echocardiography was performed before and 3, 7, 30, 90, and 180 days after PTCA. End-diastolic volume index (EDVI) and end-systolic volume index (ESVI), ejection fraction, and left ventricular wall motion score index (WMSI) were evaluated.

Results Patients were divided into group A, 23 patients reperfused within 2 hours; group B, 32 patients reperfused between 2 and 4 hours; group C, 22 patients reperfused between 4 and 6 hours; and group D, 18 patients reperfused between 6 and 12 hours. Both EDVI and ESVI were reduced in groups A and B at 90 days. Groups C and D did not show any changes of EDVI and ESVI at any stage throughout the study. Ejection fraction improved only in groups A and B at 30, 90, and 180 days. At study entry, WMSI was similar in all groups. After 7 days, in group A and in group B, WMSI was improved; no changes were observed in group C, and mild deterioration was observed in group D at 3 and 7 days. Subsequent evaluations showed progressive improvement of WMSI in all groups.

Conclusions Myocardial salvage is achieved only in patients revascularized within 4 hours from AMI onset. However, revascularization after 6 hours may be worthwhile by preventing ventricular remodeling. (Am Heart J 2001;141:603-9.)
neous transluminal coronary angioplasty (PTCA) was considered successful when the final angiographic control, performed 15 minutes after the last balloon inflation, showed patency of the infarct-related vessel, without major dissections and with TIMI flow grade 3. Patients were then transferred to the coronary care unit, where they received intravenous treatment with heparin and nitrates and oral treatment with β-blockers, angiotensin-converting enzyme inhibitors, and acetylsalicylic acid.

Study design

Acute MI was diagnosed if a patient had persistent chest pain lasting for >30 minutes and had ST-segment elevation of ≥1 mm in at least 2 contiguous leads. Soon after the diagnosis of MI was made, patients were transferred from the casualty department or the coronary care unit to the catheterization laboratory, where they underwent immediate left ventriculography, coronary angiography, and PTCA. Patients underwent primary PTCA because of the policy adopted in our institutions. All patients underwent a control coronary angiogram and left ventriculogram 24 hours and 6 months after PTCA. Four-hourly monitoring of cardiac enzymes (creatine kinase [CK] and CK/MB) continued until normalization. Echocardiography was performed before PTCA and 3, 7, 30, 90, and 180 days after the procedure. Patients with acute, subacute, or late reocclusion of the infarct-related vessel were excluded from the study.

Left ventricular function

Echocardiography was performed with a phased-array electronic ultrasound system (SONOS 2500, Hewlett Packard, Andover, Mass). Images were recorded on VHS, and end-diastolic and end-systolic frames were selected from the 3 standard apical views. End-diastolic (EDV) and end-systolic (ESV) volumes were calculated by the biplane area-length method. Measurements were obtained in duplicate from each view and averaged and corrected for body surface area, to be expressed as volume indexes (left ventricular EDV-ESV indexes minus EDVI/ESVI). Left ventricular systolic frames were obtained from the parasternal short-axis view at the level of the papillary muscles and from the apical 4-chamber, 2-chamber, and long-axis views and were digitized. Image acquisition was triggered by the R wave. The computer (PRE-VUE III, Nova Microsonics-ATL, Bothell, Wash) was programmed to capture 8 sequential frames at 50-ms intervals throughout the entire systolic phase. Data were acquired from all image planes in a digital cineloop format, stored on a floppy disk, and reviewed on a dedicated review station (REVUE TM, Nova Microsonics-ATL). For each single view, the 4 echocardiographic examinations obtained in the individual patients were played back on a quad display. The slow motion or frame-by-frame review mode was used as required.

Echocardiographic examinations were performed by 4 different physicians, of whom 2 are coauthors of this article. Both analog and digital images were interpreted by 2 independent investigators who had no knowledge of the patient’s status. The left ventricle was divided into 16 segments as previously described.¹⁸ For each segment, systolic wall motion and thickening were visually graded with the following semiquantitative scoring system: normal or hyperkinesia, 1; hypokinesia, 2; akinesia, 3; and dyskinesia, 4. A left ventricular wall motion score index (WMSI) was derived for the entire left ventricle by using the sum of individual scores divided by the total number of analyzed segments. Inadequately visualized segments were not scored. The interobserver and intraobserver agreement in interpretation of regional function, with the use of the above scoring and analysis system, were 88% and 93%.

Statistical analysis

The Wilcoxon signed rank test was used to compare means of continuous variables and the chi-square test or the Fisher exact test for discrete variables. Bonferroni’s correction for multiple testing was performed where appropriate. A value of P < .05 was considered significant.

Results

Depending on the time elapsed from the occurrence of the first symptoms and the achievement of reperfusion, patients were divided into 4 groups: group A, 23 patients reperfused within 2 hours; group B, 32 patients reperfused between 2 and 4 hours; group C, 22 patients reperfused between 4 and 6 hours; and group D, 18 patients reperfused between 6 and 12 hours. Maximal CK and CK/MB release were not significantly different in the 4 groups. No differences between the groups were observed for the prevalence of the culprit vessel, for the location of infarction, for the prevalence of multivessel disease, and for the preintervention TIMI flow of the infarct-related artery. The prevalence of significant collateral flow to the infarct area before PTCA was similarly low in all groups (χ² = 1.16, P = .76). None of the patients showed grade 3 collateral flow. Tables I and II show clinical and angiographic data of study patients.

Left ventricular volumes and ejection fraction

Figures 1 through 3 and Table III show trends and figures of end-diastolic volume index (EDVI), end-systolic volume index (ESVI), and ejection fraction (EF) in the 4 groups of patients. Compared with basal values, both EDVI and ESVI were similar in the 4 groups at days 3 and 7 after PTCA. On day 30, these parameters were significantly reduced in group A and were further decreased at 90 days in groups A and B, with no additional changes at 6 months. Conversely, patients of groups C and D did not show any significant changes in EDVI and ESVI at any stage after PTCA. EDVI and ESVI remained stable and higher than in groups A and B from day 30. EF was significantly and similarly impaired at baseline in all groups. Also, this parameter showed a trend toward improvement in groups A and B, which became significant at 30 days for group A and at 90 days for both, with further improvement at 180 days. As for EDVI and ESVI, no significant changes in EF were observed in groups C and D at any stage after PTCA.
Segmental left ventricular function

Figure 4 and Table III show the behavior of WMSI in the 3 groups during follow-up. At study entry, WMSI was similar in all groups. However, significant differences between patients were already evident after 7 days from the infarction, when, in group A and group B, WMSI started to improve, whereas no changes were observed in group C. In group D, a marked deterioration was noted from the third day after infarction: At the 7-day control, this trend was confirmed. Subsequent evaluations showed improvement of WMSI in all groups. However, compared with the prerevascularization control, improvement at 6 months was significant only in group A and, to a lesser extent, in group B. In group C, there was no further deterioration, whereas in group D, ventricular function was worse than at study entry. WMSI was also significantly better in group C compared with group D from 90 days after infarction.
Discussion

Reperfusion therapy for acute MI has dramatically reduced mortality rates, especially when achieved early enough to salvage substantial amount of myocardium. Accordingly, although the gain in left ventricular function and survival by reperfusion therapy is strongly dependent on the time elapsed from symptom onset until treatment, some studies have shown that time to treatment is not crucial for survival after primary PTCA. This has been partly confirmed by a recent report showing that time to reperfusion is important up to 2 hours only. After 2 hours, recovery of left ventricular function is modest and survival relatively independent from the time of reperfusion. These data suggest that factors other than myocardial salvage may be responsible for improved survival observed in patients undergoing primary PTCA after 2 hours.

Major findings of the study

To our knowledge, this is the first study addressing the relation between the time elapsed from the beginning of MI to reperfusion and the extent of myocardial salvage in patients with sustained coronary artery patency after mechanical recanalization. The study does not specifically evaluate myocardial salvage, although this can be surmised by the improvement of left ventricular function. The results of our investigation show that in the setting of acute MI, reperfusion by primary PTCA yields beneficial effects on myocardial salvage only when patients are reperfused within the first 4 hours from the onset of symptoms. In fact, both EF and segmental wall motion improved only in these patients and remained practically unchanged in those reperfused between 4 and 6 hours. In keeping with older reports, improvement in left ventricular function could be observed up to 3 months after infarction, and no further improvement could be observed at a later stage. In patients reperfused after 6 hours, segmental wall motion progressively deteriorated in the first postinfarction period, and it stabilized in the subsequent follow-up.

These findings indicate that significant myocardial salvage can only be achieved with early reperfusion (within 4 hours). Yet in patients reperfused between 4 and 6 hours, and, to a lesser extent, in those reperfused after 6 hours, left ventricular remodeling and dilation can be prevented.

Previous studies had shown that in patients with acute infarction, myocardial salvage is greatest if reperfusion by primary PTCA is achieved within the first 2 hours from symptom onset and very modest after 2 hours. We surmise that the reasons for the difference between findings reported in previous research and those of the current study might be dependent on the fact that we included only patients with sustained patency of the infarct-related coronary artery, eliminating the problem of contaminating the data with patients with unsuccessful reperfusion or reocclusion of the infarct artery. Additionally, studies with isonitrile perfusion agents as markers of myocardial salvage before primary PTCA and at the time of hospital discharge can be difficult to compare with our study, in which myocardial salvage was rather gathered from long-term left ventricular function monitoring. Indeed, in both acute and chronic ischemic heart disease, myocardial perfusion and contraction do not always match. After myocardial infarction, the recovery of perfusion and wall motion may continue well after the subacute phase. Several patients exhibit relative hypoperfusion in viable tissue as late as 5 weeks after infarction, and progressive improvement of perfusion in the infarcted area is commonly observed between 5 weeks and 7 months.
MI and left ventricular dilation

A progressive increase in left ventricular dimensions is common after MI and predicts a poor prognosis, particularly when associated with reduced EF. The magnitude of the necrotic area plays a significant role in determining this process, but the size of the infarct is not the only factor influencing ventricular expansion, which is in fact more often associated with total occlusion of the infarct-related vessel. Indeed, late restoration of flow has been suggested to prevent ventricular dilation in both experimental and clinical studies with both thrombolytic agents and elective PTCA performed as late as 21 days after the acute event. The effect is thought to be mainly related to prevention of left ventricular dilation, even though the presence of residual viability appears to be inversely related to the time elapsed from the occurrence of the acute event.

Beneficial effect of late recanalization: Potential mechanisms

The “open artery hypothesis” is based on the observation that despite equivalent degrees of severity and extension of myocardial injury, those hearts in which experimental coronary ligation is released develop less ventricular dilation than those whose occlusion is maintained. Indeed, because left ventricular dilation after MI can be caused by lengthening of viable adjacent segments, a patent infarct-related artery may limit remodeling by enabling earlier formation of a firmer myocardial scar. Avoidance of unfavorable left ventricular geometry results in many secondary later benefits, such as reduction of wall stress, prevention of volume overload, hypertrophy, and improvement of EF. In our study, even though patients revascularized after 6 hours did not show any significant myocardial salvage, they also did not exhibit a trend toward progressive deterioration of left ventricular function, as it is usually observed after infarction in patients in whom the infarct-related artery remains occluded. In groups A and B, ESVI and EDVI progressively improved up to 90 days after the infarction, whereas in groups C and D, they remained stable throughout the study. Our results are in keeping with those of a recent study that addressed the influence of an additional treatment delay inherent to the


<table>
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<th>Study groups</th>
<th>A</th>
<th>B</th>
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<tr>
<td><strong>EDVI (mL/m²)</strong></td>
<td></td>
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<tr>
<td>Basal</td>
<td>86 ± 16</td>
<td>85 ± 15</td>
<td>87 ± 18</td>
<td>84 ± 17</td>
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<td>3 d</td>
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<td>79 ± 16</td>
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<td>7 d</td>
<td>79 ± 16</td>
<td>80 ± 14</td>
<td>87 ± 21</td>
<td>86 ± 29</td>
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<tr>
<td>30 d</td>
<td>75 ± 16 †‡</td>
<td>77 ± 14 †‡</td>
<td>85 ± 20</td>
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<tr>
<td>90 d</td>
<td>70 ± 15 †‡</td>
<td>72 ± 11 †‡</td>
<td>82 ± 23</td>
<td>82 ± 27</td>
</tr>
<tr>
<td>180 d</td>
<td>70 ± 11 †‡</td>
<td>69 ± 14 †‡</td>
<td>81 ± 17</td>
<td>83 ± 22</td>
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<td>52 ± 11</td>
<td>48 ± 9</td>
<td>52 ± 10</td>
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<tr>
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<td>46 ± 12</td>
<td>43 ± 7</td>
<td>51 ± 8</td>
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<td>7 d</td>
<td>44 ± 11</td>
<td>42 ± 8</td>
<td>50 ± 11</td>
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<tr>
<td>30 d</td>
<td>39 ± 10 †</td>
<td>41 ± 11</td>
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<tr>
<td>90 d</td>
<td>34 ± 8 †‡</td>
<td>35 ± 10 †‡</td>
<td>46 ± 7</td>
<td>50 ± 8</td>
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<tr>
<td>180 d</td>
<td>34 ± 9 †‡</td>
<td>35 ± 9 †‡</td>
<td>46 ± 12</td>
<td>50 ± 10</td>
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<td><strong>EF</strong></td>
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<tr>
<td>90 d</td>
<td>51 ± 6 †‡</td>
<td>52 ± 7 †‡</td>
<td>44 ± 4</td>
<td>39 ± 5</td>
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<tr>
<td>180 d</td>
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<td>50 ± 5 †‡</td>
<td>43 ± 4</td>
<td>40 ± 5</td>
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<td><strong>WMSI</strong></td>
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<tr>
<td>Basal</td>
<td>2.43 ± 0.62</td>
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<td>2.38 ± 0.70</td>
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<tr>
<td>3 d</td>
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<td>3.08 ± 0.87*</td>
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<tr>
<td>7 d</td>
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<td>2.61 ± 0.66</td>
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<td>30 d</td>
<td>1.88 ± 0.48 †§</td>
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<tr>
<td>90 d</td>
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<td>2.31 ± 0.65 †*</td>
<td>2.82 ± 0.71</td>
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<tr>
<td>180 d</td>
<td>1.63 ± 0.40 †§</td>
<td>1.82 ± 0.39 †§</td>
<td>2.30 ± 0.77 †*</td>
<td>2.79 ± 0.78</td>
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Significance levels: EDVI, *P < .05 within group vs basal; †P < .01 within group vs basal; ‡P < .05 between groups vs group C and D. ESVI, *P < .05 within group vs basal and 3 days; †P < .01 within group vs basal and 3 days; ‡P < .05 between groups vs group C and D. EF, *P < .05 within group vs basal; †P < .01 within group vs basal; ‡P < .05 between groups vs group D; §P < .05 between groups vs group C; ¶P < .01 between groups vs group D. WMSI, *P < .05 within group vs basal; †P < .01 between groups vs group D; ‡P < .05 within group vs basal; †P < .01 within group vs basal; ‡P < .05 between groups vs group D; §P < .05 between groups vs group C; ¶P < .01 between groups vs group D. WMSI, *P < .05 between groups vs group D; †P < .01 between groups vs group C; ¶P < .01 between groups vs group D. WMSI, **P < .05 between groups vs group D.
transfer to a tertiary referral center for primary angioplasty of patients with acute MI who were first admitted to hospitals without invasive facilities. In that study, the additional delay (yet all patients were reperfused within 6 hours) had a deleterious effect on myocardial salvage reflected by a larger infarct size and a lower EF, but the 6-month clinical outcome was not affected.

Study limitations

One limitation of this study is that there was no control group of patients without a patent infarct-related artery. However, this selection was made on purpose because it eliminated the problem of contaminating the data with patients with unsuccessful reperfusion or reocclusion of the infarct artery.

At the time of data collection, IIb-IIIa receptor antagonists were not yet available. It is possible that their use could improve myocardial reperfusion during primary PTCA. In our study, their effect would have been mainly on cardiac microcirculation because long-term patency of the infarct-related artery was a prerequisite to enter the study. Despite these considerations, we believe that even in the IIb-IIIa receptor antagonist era, the time interval between infarct onset and reperfusion is likely to remain the most important predictor of myocardial salvage.

Conclusions

Our study shows that in the setting of acute infarction, significant myocardial salvage can be achieved only in patients in whom reperfusion is achieved within 4 hours from symptom onset. However, revascularization after the 6th hour might be worthwhile because it prevents ventricular dilation and remodeling. Previous studies have shown that mechanical revascularization improves left ventricular function even when performed up to 21 days after the acute event. Future investigations should address whether revascularization after the first 6 hours from infarction onset should be performed as soon as possible or planned on an elective basis.

We thank Diana Mauro for secretarial assistance.

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