Chronic pre-treatment of statins is associated with the reduction of the no-reflow phenomenon in the patients with reperfused acute myocardial infarction

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Aims Early statin treatment has beneficial effects on prognosis after acute coronary syndrome. The no-reflow phenomenon determines the prognosis after acute myocardial infarction. We investigated the effects of statin treatment before admission on the development of the no-reflow after infarction.

Methods and results We performed intracoronary myocardial contrast echocardiography in 293 consecutive patients with acute myocardial infarction undergoing successful primary percutaneous coronary intervention. There were no significant differences in the incidence of the no-reflow between the patients with and without hypercholesterolaemia. The 33 patients receiving chronic statin treatment before admission had lower incidence of the no-reflow than those without it (9.1 and 34.6%, \( P = 0.003 \)). They also showed better wall motion, smaller left ventricular dimensions, and better ejection fraction at 4.9 ± 2.2 months later. Multivariable logistic regression analysis revealed that statin pre-treatment was a significant predictor of the no-reflow along with anterior wall infarction, ejection fraction on admission, and additional ST-elevation after reperfusion, whereas total cholesterol was not.

Conclusion Chronic pre-treatment with statins could preserve the microvascular integrity after acute myocardial infarction independent of lipid lowering, leading to better functional recovery.

Introduction

The no-reflow phenomenon after primary percutaneous coronary intervention is associated with greater infarct size, worse functional recovery, and higher incidence of complications after acute myocardial infarction.1–3 Early treatment with 3-hydroxy-3-methylglutaryl coenzyme-A inhibitors (statins) has the beneficial effects on clinical prognosis after acute coronary syndrome.4–8 Statin treatment is also associated with a marked reduction in event rate and mortality after coronary intervention independent of the lipid lowering.8–11 Beyond their lipid-lowering effects, statins have favourable effects on platelet adhesion,12 thrombosis,13–16 endothelial function,17–21 plaque stability,16,22 and inflammation.10,23–25 These pleiotropic effects could contribute to the preservation of microvascular function during ischaemia and reperfusion.26 In the present study, we investigated whether the chronic statin treatment before the onset of acute myocardial infarction could reduce the no-reflow after primary coronary intervention.

Methods

Study population

Between April 1999 and October 2004, consecutive 323 patients with first acute myocardial infarction underwent primary coronary intervention to totally or subtotally occluded coronary artery, followed by intracoronary myocardial contrast echocardiography, within 24 h after symptom onset. The diagnosis of infarction was based on the chest pain, prolonged \( \geq \) 30 min, ST-segment elevation of \( \geq 2 \) mm in at least two contiguous electrocardiography leads, and greater than three-fold increase in serum creatine kinase levels. Cardiac symptoms lasting \( < 30 \) min that occurred within 48 h before onset of infarction was defined as pre-infarction angina.27 Thirty patients were excluded because of poor echocardiographic images (20 patients), cardiogenic shock (four patients), allergy to Ioxaglate (three patients), and unsuccessful coronary intervention (three patients). Therefore, the final study population consisted of 293 patients. The study protocol was approved by the hospital’s Ethics Committee. One of the investigators obtained informed consent from each patient before cardiac catheterization.

Study protocol

Just after admission, we performed echocardiographic study with SONOS 5500 (Philips Medical Systems) following 12-leads electrocardiogram, because it provided the essential information for the risk stratification, despite of some delay to reperfusion time.
All patients received aspirin (243 mg) orally at least 30 min before coronary angiography and intravenous infusion of nifedipine at 6 mg/h for 24 h after admission. Glycoprotein IIb/IIIa inhibitors were not available in Japan. After intravenous heparin (100 U/kg) administration, we performed coronary angiography using the right femoral approach to determine culprit lesion and collateral channels. After intracoronary injection of nitroglycerin, we performed coronary intervention with angioplasty and/or stenting to make the residual diameter stenosis reduced to <50%. We gave intracoronary injection of verapamil in 17 patients (5.8%) showing slow flow after intervention. We repeatedly recorded 12-leads electrocardiogram during coronary intervention to observe additional ST-segment elevation after reperfusion.27 A mean of 15 min after intervention, we performed myocardial contrast echocardiography as previously reported.1,27,28 We injected 2 mL of sonicated loxaglate (Hexabrix-320, Tanabe) into the culprit artery and recorded echocardiogram from the parasternal short-axis, the apical two- and four-chamber views using SONOS 100 (Philips Medical Systems) (Figure 1). Then, we performed left ventriculography and measured left ventricular end-diastolic and end-systolic volume indices and ejection fraction by the biapical Simpson’s rule.

We measured triglyceride, total- and high-density lipoprotein cholesterol within 24 h after admission using a standard method. Hypercholesterolaemia was considered present if it was previously diagnosed or total cholesterol on admission was greater than 220 mg/dL. Whether statins had been administered before admission was determined from the detailed interview or medical records. We performed echocardiography, coronary angiography, and left ventriculography at 4.9 ± 2.2 months later, except in five patients who could not be followed.

**Table 1** Lipid profile of the study patients

<table>
<thead>
<tr>
<th></th>
<th>Normocholesterolaemia</th>
<th>Hypercholesterolaemia</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>136</td>
<td>35</td>
<td>122</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>173 ± 31</td>
<td>204 ± 51*</td>
<td>219 ± 40*</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol (mg/dL)</td>
<td>45 ± 12</td>
<td>46 ± 11</td>
<td>45 ± 12</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>94 ± 68</td>
<td>114 ± 86</td>
<td>136 ± 100**</td>
</tr>
</tbody>
</table>

P-values for the differences among the three subsets by ANOVA analysis. *P < 0.0001 vs. normocholesterolaemia. **P < 0.001.

Analysis of echocardiographic data

Two independent observers blinded to patients’ data independently evaluated wall motion in each of the 16 myocardial segments as endorsed by the American Society of Echocardiography, and scored it as follows: 4 = dyskinesia, 3 = akinesia, 2 = severely hypokinesia, 1 = hypokinesia, and 0 = normokinesia or hyperkinesia. We defined the risk area as myocardial segments showing dyskinesia, akinesia, or severe hypokinesia on admission. Wall motion score was calculated as the sum of the scores within the risk area.

An experienced echocardiographer analysed contrast echo images. We defined the no-reflow zone as a contrast perfusion defect after intervention in end-diastolic images. When it exceeded a quarter of the risk area, myocardial reperfusion was considered incomplete (no-reflow) (Figure 1).1,27,28

Statistics

All data are expressed as mean ± standard deviation except the elapsed time to reperfusion and creatine kinase, which are expressed as median plus interquartile range (25–75th percentile) because of non-normal distribution and wide standard deviation. We made comparisons by one-way ANOVA for continuous variables, and significance of difference was calculated with Tukey’s HSD test for factor analysis. However, homogeneity of variance assessed by Levene’s test was violated in the time to reperfusion, creatine kinase, wall-motion score, and end-diastolic volume index at follow-up for comparison between statin subgroups, and they were compared with Kruskal-Wallace test. Categorical variables were compared with the Fisher’s exact test. The relation between statin pre-treatment and the incidence of the no-reflow was also examined with the bootstrap resampling analysis to calculate the 95% confidence interval of the differences in the incidence. Univariable and multivariable logistic regression analyses were used to identify independent predictors for the no-reflow. The factors predicting the no-reflow with P < 0.1 in the univariable analysis were used for the multivariable analysis. The linearity of the logit among the continuous variables used in the multivariable analysis was confirmed with Box-Tidwell test. Differences were considered significant at P < 0.05 (two-sided). JMP version 5.0.1 (SAS Institute) was used for statistical analysis except bootstrap analysis, which was performed with R (R Foundation for Statistical Computing).

Results

Patients characteristics

Among the 293 study patients (mean age, 60 ± 11; range 25–91), 233 patients (79.5%) were male. The culprit artery was the left anterior descending artery in 173 patients, the left circumflex artery in 29 patients and the right coronary artery in 91 patients. The median of the time from the...
symptomatic onset to coronary reperfusion was 4.0 (2.9–7.9) h, and it was 3 h or less in 85 patients (29.0%). Stents were implanted in 211 patients (72.0%). Thrombus-aspirating devices were used in 158 patients (53.9%). Thrombolysis In Myocardial Infarction flow grade 3 was finally achieved in 244 patients (83.3%). The median of peak creatine kinase and creatine kinase-MB level was 3286 (1861–5660) and 172 (85–292) IU/L, respectively. Hypercholesterolaemia was diagnosed in 156 patients (53.2%). Eighty-nine patients (30.4%) had diabetes mellitus, 150 patients (51.2%) had hypertension, and 207 patients (70.6%) were current smokers. The 268 patients (91.5%) received angiotensin-converting enzyme inhibitor or angiotensin receptor blocker after admission, and 150 patients (51.2%) received β-blocker.

Thirty-three patients had chronically received statins before admission: 23 patients had received pravastatin (5–40 mg/day), six patients simvastatin (5–10 mg/day), and four patients atorvastatin (10–30 mg/day). Among the 138 patients with hypercholesterolaemia, no significant difference was observed in total cholesterol between those with and without statin pre-treatment, whereas both had lower total cholesterol than those with normcholesterolaemia (Table 1). The patients with normcholesterolaemia also had lower triglyceride value than those without pre-treatment, but not than those with statin pre-treatment. There were no significant differences in high-density lipoprotein cholesterol among the three subsets. The incidence of anterior wall infarction tended to be lower in the patients with statins (42.4 vs. 60.0%) though not significant (P = 0.06).

### No-reflow phenomenon and pre-treatment of statins

The 93 patients (31.7%) showed the no-reflow, and they had higher peak creatine kinase [median: 5478 (3147–8358) vs. 2644 (1328–4459) IU/L, P < 0.0001] and creatine kinase-MB [254 (173–377) vs.135 (76–239) IU/L, P < 0.0001] than the reflow group (n = 200, 68.3%). The no-reflow group had higher wall motion score on admission and at the follow-up study than the reflow group (Table 2). Magnitude of improvement in wall motion score was significantly lower in the no-reflow group (3.4 ± 5.3 vs. 5.7 ± 5.7, P = 0.003). Although no significant differences were observed on admission, the no-reflow group showed larger end-diastolic volume index (67 ± 16 vs. 60 ± 13 mL/m², P = 0.0004) at the follow-up study. The no-reflow group also had larger end-systolic volume index and lower ejection fraction on admission and at the follow-up study (Table 2).

There were no significant differences in the incidence of the no-reflow between the patients with and without hypercholesterolaemia (30.8 vs. 32.9%, respectively; P = 0.70). Among the 33 patients receiving statin pre-treatment, the no-reflow was observed only in three patients (9.1%), whereas it was observed in 90 out of 260 patients without statin pre-treatment (34.6%, P = 0.003). The incidence was almost similar between the 122 patients with hypercholesterolaemia but without statin pre-treatment (36.1%) and in those with normcholesterolaemia (33.8%). Therefore, we treated these two subsets as one category (those without statin pre-treatment) for the later analysis. Because the number of the patients with statin

### Table 1

<table>
<thead>
<tr>
<th>Enzymatic and functional parameters in the study patients</th>
<th>All patients</th>
<th>Reflow</th>
<th>No-reflow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak creatine kinase, IU/L</td>
<td>3286 (1861–5660)</td>
<td>2644 (1328–4459)</td>
<td>3391 (1854–5887)</td>
</tr>
<tr>
<td>Peak creatine kinase-MB, IU/L</td>
<td>172 (85–292)</td>
<td>135 (76–239)</td>
<td>254 (173–377)</td>
</tr>
<tr>
<td>Wall motion score on admission</td>
<td>14.3 ± 6.0</td>
<td>13.3 ± 6.1</td>
<td>16.2 ± 6.5</td>
</tr>
<tr>
<td>Wall motion score at the follow-up</td>
<td>9.0 ± 6.7</td>
<td>6.7 ± 6.5</td>
<td>6.5 ± 6.5</td>
</tr>
<tr>
<td>Left ventricular end-diastolic volume index, mL/m²</td>
<td>63 ± 14</td>
<td>62 ± 14</td>
<td>66 ± 17</td>
</tr>
<tr>
<td>Left ventricular end-systolic volume index, mL/m²</td>
<td>32 ± 10</td>
<td>30 ± 9</td>
<td>38 ± 15</td>
</tr>
<tr>
<td>Ejection fraction on admission</td>
<td>50 ± 8</td>
<td>48 ± 9</td>
<td>52 ± 9</td>
</tr>
<tr>
<td>Ejection fraction at the follow-up</td>
<td>50 ± 11</td>
<td>46 ± 11</td>
<td>53 ± 9</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Enzymatic and functional parameters in the study patients</th>
<th>All patients</th>
<th>With statin</th>
<th>Without statin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>293</td>
<td>200</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Peak creatine kinase, IU/L</td>
<td>3286 (1861–5660)</td>
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<td>3391 (1854–5887)</td>
<td>0.14</td>
</tr>
<tr>
<td>Peak creatine kinase-MB, IU/L</td>
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<td>135 (76–239)</td>
<td>254 (173–377)</td>
<td>&lt;0.0001</td>
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<td>Wall motion score on admission</td>
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</table>
Statins pre-treatment was an independent predictor for the no-reflow. Although a non-randomized observational study, the present study suggested that statin pre-treatment might reduce the no-reflow after infarction independent of its lipid lowering effects, resulting in the better functional outcomes.

Factors related to the no-reflow phenomenon

We performed univariable logistic regression analysis for prediction of the no-reflow using the factors listed in Table 3. Age, smoking, absence of statin pre-treatment, anterior wall infarction, additional ST-elevation, wall motion score, and ejection fraction on admission were the significant predictors in the univariable analysis, whereas total cholesterol was not. Then, we performed multivariable logistic regression analysis using these parameters. Statin pre-treatment was an independent predictor of the no-reflow along with anterior wall infarction, ejection fraction on admission, and additional ST-elevation (Table 4). We did not include the creatine kinase and creatine kinase-MB in the model because their differences were consequence of the no-reflow and could not be its predictors.

Discussion

We investigated the effects of statin pre-treatment on the no-reflow in 293 patients with acute myocardial infarction undergoing primary coronary intervention. The 33 patients receiving chronic statin pre-treatment had lower incidence of the no-reflow and better functional recovery than those without statin. Multivariable logistic analysis revealed that statin pre-treatment was an independent predictor for the no-reflow. Although a non-randomized observational study, the present study suggested that statin pre-treatment might reduce the no-reflow after infarction independent of its lipid lowering effects, resulting in the better functional outcomes.
Statins and the no-reflow after acute myocardial infarction

Several studies demonstrated that embolization with micro-thrombi and atheromatous plaque debris from lipid-rich lesion could be a major cause of the no-reflow after infarction. The alteration in plaque components and reducing lipid-burden by statin pre-treatment could reduce embolic particles during coronary intervention. Statin pre-treatment protects against myocardial damage during coronary intervention and reduces the infarction after it through anti-inflammatory effects as well as plaque-stabilizing effects. These effects might be related with the reduction of microvascular injury in the present study.

Statins reduce the expression of monocyte adhesion molecules and reduce serum P-selectin levels in the patients with acute coronary syndrome. These effects might prevent capillary obstruction caused by plugging of platelets/leukocytes. Statin treatment preserves the coronary microvascular permeability, which might lead to the reduction of intracoronary occlusion after reperfusion. The restoring of endothelial dysfunction with statin might also be associated with the prevention of the no-reflow.

The onset-reperfusion time was relatively long in the present study, and microvascular dysfunction might have already developed before reperfusion. Statin might have protective effects during ischaemia in these cases, and better wall motion and ejection fraction on admission in the statin group might be the early reflections of these effects.

The benefit of microvascular protection by statin pre-treatment is limited only to the selected patients. The present results suggested that statins should be administered more comprehensively to patients at high risk for coronary heart disease before they develop infarction. Also, further study is required, whether statin administered just before primary intervention could protect microvasculature and reduce infarct size, as shown in the experimental models.

Predictor of the no-reflow phenomenon

In our previous study on anterior wall infarction, wall motion score on admission, number of Q-waves on initial electrocardiogram, spontaneous recanalization of culprit lesion, and the absence of pre-conditioning angina are independent predictors related to the no-reflow. We did not include the number of Q-waves in the present model including inferior or posterior wall infarction. Pre-infarction angina does not have a protective effect on the inferior wall infarction as shown in the present study. Although thrombus aspiration devices along with standard coronary intervention might improve myocardial perfusion after infarction, it did not reduce the no-reflow in the present study (Table 3).

Limitation of the study

As a single-centre observational study, some biases might be inevitable in the present study. It is possible, for example, that the patients on statin were selected patients receiving overall better clinical care that might affect the clinical outcomes. To reduce the small sample bias, we used the bootstrap technique, a data-based simulation method for statistical inference. Random samples of size n are produced from the original data by sampling with replacement. Each of these ‘bootstrap’ samples provides estimate of the parameter of interest. Repeating the sampling a large number of times provides information on the variability of the estimator. Still, confounding might be present and the association between the statin pre-treatment and the no-reflow is not necessarily causal. The small sample size, along with the short follow-up period, is also the probable reason why statin pre-treatment did not reduce the major adverse cardiac events.

We could not analyse the effects of differences in the pre-treatment period and in type and dose of the statins. Peak creatine kinase and creatine kinase-MB values might underestimate the infarct size in the presence of microvascular dysfunction because washout of the enzyme might be delayed. Area under the curve of creatine kinase release could reflect infarct size more correctly. We did not measure the low-density lipoprotein cholesterol level, and could not calculate it based on the Friedewald formula because some had triglyceride more than 400 mg/dL. We also did not measure high-sensitive C-reactive protein, the change of which by statin treatment might affect the prognosis after infarction.

Conflict of interest: none declared.

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