The Distinction Between Coronary and Myocardial Reperfusion After Thrombolytic Therapy by Clinical Markers of Reperfusion

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Objectives. We sought to examine the hypothesis that rapid resolution of ST-segment elevation in acute myocardial infarction (AMI) patients with early peak creatine kinase (CK) after thrombolytic therapy differentiates among patients with early recanalization between those with and those without adequate tissue (myocardial) reperfusion.

Background. Early recanalization of the epicardial infarct-related artery (IRA) during AMI does not ensure adequate reperfusion on the myocardial level. While early peak CK after thrombolysis results from early and abrupt restoration of the coronary flow to the infarcted area, rapid ST-segment resolution, which is another clinical marker of successful reperfusion, reflects changes of the myocardial tissue itself.

Methods. We compared the clinical and the angiographic results of 162 AMI patients with early peak CK (<212 h) after thrombolytic therapy with (group A) and without (group B) concomitant rapid resolution of ST-segment elevation.

Results. Patients in groups A and B had similar patency rates of the IRA on angiography (anterior infarction: 93% vs. 93%; inferior infarction: 89% vs. 77%). Nevertheless, group A versus B patients had lower peak CK (anterior infarction: 1,083 ± 585 IU/ml vs. 1,950 ± 1,216, p < 0.01; and inferior infarction: 940 ± 750 IU/ml vs. 1,350 ± 820, p = 0.18) and better left ventricular ejection fraction (anterior infarction: 49 ± 8, vs. 44 ± 8, p < 0.01; inferior infarction: 56 ± 12 vs. 51 ± 10, p = 0.1). In a 2-year follow-up, group A as compared with group B patients had a lower rate of congestive heart failure (1% vs. 13%, p < 0.01) and mortality (2% vs. 13%, p < 0.01).

Conclusions. Among patients in whom reperfusion appears to have taken place using an early peak CK as a marker, the coexistence of rapid resolution of ST-segment elevation further differentiates among patients with an opened culprit artery between the ones with and without adequate myocardial reperfusion.

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Early peak CK (within the first 12 h) was found in 168 patients. Fifty-one patients had late peak CK; and in one patient the peak CK could not be determined due to a technical problem. From the original cohort of 168 patients with early peak CK, 6 patients were excluded: 4 underwent rescue percutaneous transluminal coronary angiography (PTCA) within the first hours; in 1 patient complete left bundle branch block developed after inclusion; and in another patient, the ECG recording was not adequate for analysis of ST-segment changes. The aggregate ST-segment elevations (Σ ST↑) in the three contiguous leads showing the highest initial ST-segment elevation were calculated in two ECGs: one immediately before the administration of thrombolytic therapy and the other 2 h later. Postthrombolysis early resolution of ST-segment elevation was defined as a decrease of at least 50% in the Σ ST↑ between the two ECGs. The changes in Σ ST↑ were evaluated independently and blindly by two investigators. The patients with early CK were divided into two groups based on the presence or the absence of early resolution of ST-segment elevation.

**Radionuclide assessment of left ventricular function.** Left ventricular ejection fraction (LVEF) was evaluated with rest multigated equilibrium blood pool scan performed in the 45° left anterior oblique projection. Global left ventricular function was assessed at discharge and 2, 6 and 12 months later.

**Coronary angiography.** Of the 162 patients, 125 consecutive patients underwent coronary angiography within 96 h. The perfusion status of the IRA was assessed using the Thrombolysis In Myocardial Infarction (TIMI) criteria for reperfusion, and the artery was considered patent when TIMI perfusion flow 2 or 3 was established. Thereafter, the number of coronary arteries with significant (≥50%) stenosis was determined.

**Clinical follow-up.** The patients were followed up during their hospitalization for any cardiac adverse event and for 2 years after their discharge through repeated visits to our outpatient clinic at intervals of 2, 6, 12 and 24 months. For the comparison of the clinical outcome, we specified in the present study a combined clinical end point of congestive heart failure and/or mortality which have a good clinical correlation with the extent of myocardial damage.

**Statistical analysis.** In the comparison of patients with ST-segment elevation resolution with those without, continuous variables are presented as mean ± SD and the differences are assessed by standard t test. Discrete variables are presented as numbers of patients or percentage, and differences are assessed by chi square or Fisher’s exact test.

### Results

Of the 162 patients with early peak CK who comprise the subject of the present study, 71 had anterior infarct and 91 had inferior infarct. While among the patients with anterior infarct, 35 (49%) had early resolution of ST-segment elevation; 73 (80%) with inferior infarct had early resolution. Thus, while among the patients with early ST-segment resolution, 32% had anterior AMI and 68% inferior AMI; among those without early ST-segment resolution, 67% had anterior AMI and 33% inferior AMI. Therefore, the results are being presented according to infarct site.

The baseline characteristics of the patients are shown in Table 1. Patients with and without rapid resolution of ST-segment elevation had similar baseline characteristics regardless of infarct site except for a trend toward earlier administration of thrombolytic therapy in patients without early resolution of ST-segment elevation, which reached statistical significance in patients with anterior infarction.

**Indices of infarct size and left ventricular function.** Early resolution of ST-segment elevation was associated with lower peak CK of 1,083 ± 888 versus 1,950 ± 1,216 (p < 0.01) for anterior and 940 ± 750 versus 1,350 ± 820 (p = 0.18) for inferior infarction. Patients with early ST-segment elevation resolution also had significantly better left ventricular function at discharge and throughout the follow-up period (Table 2).

**Angiographic results.** Fifty-seven of the 71 patients with anterior infarction were subsequently catheterized. The late patency rate was identical in patients with (28 of 30; 93%) and without (25 of 27; 93%) early resolution of the ST-segment elevation.

Among the 91 patients with inferior infarction, 68 were catheterized, and again the late patency rate of the IRA did not differ significantly between patients with (89%) and without (77%) early resolution of ST-segment elevations (p = 0.34). Multivessel coronary artery disease was demonstrated in 57% versus 37% (p = 0.14) of anterior infarct patients with

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### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Anterior MI</th>
<th>Inferior MI</th>
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<tbody>
<tr>
<td></td>
<td>Present (n = 35)</td>
<td>Absent (n = 36)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>57 ± 10</td>
<td>58 ± 9</td>
</tr>
<tr>
<td>Female/male</td>
<td>7/28</td>
<td>6/30</td>
</tr>
<tr>
<td>Previous myocardial infarction (% patients)</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Time from symptoms to therapy (min)</td>
<td>133 ± 56</td>
<td>108 ± 38*</td>
</tr>
<tr>
<td>Time to peak creatine kinase (h)</td>
<td>7.0</td>
<td>7.0</td>
</tr>
</tbody>
</table>

*p = 0.03.
and without early resolution of ST-segment elevation, respectively, and in 53% versus 64% in patients with inferior infarction with and without early ST-segment resolution.

Clinical course. There were no significant differences in the in-hospital clinical course between patients with and without rapid ST-segment resolution regardless of infarct site, except for a higher rate of reinfarction in patients with anterior infarct with as compared with those without rapid ST-segment resolution (17% vs. 0%, p = 0.01) (Table 3). However, at the end of the 2-year follow-up period, patients with early resolution of ST-segment elevation had lower incidence of chronic heart failure and mortality (Table 4) and significantly lower prevalence of the combined end point of heart failure and/or mortality whether they had anterior or inferior infarction: 3% versus 19% (p = 0.05) in patients with anterior and 3% versus 22% (p < 0.05) in patients with inferior infarct. The long-term incidence of adverse events did not differ significantly between patients with anterior and inferior infarct in patients with and those without early ST-segment elevation resolution. Thus, we present in Figure 1 the results of the comparison of patients with and without rapid ST-segment resolution in the whole study population (regardless of infarct site). Patients with rapid ST-segment resolution had significantly lower incidence of chronic heart failure (1% vs. 13%, p < 0.01) and mortality (2% vs. 13%, p < 0.01), although they had higher incidence of reinfarction (27% vs. 9%, p = 0.02).

Table 2. Left Ventricular Function

<table>
<thead>
<tr>
<th>LVEF</th>
<th>Anterior MI</th>
<th>Inferior MI</th>
<th>p Value</th>
<th>Anterior MI</th>
<th>Inferior MI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
<td></td>
<td>Present</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>Discharge</td>
<td>49 ± 9</td>
<td>44 ± 8</td>
<td>0.01</td>
<td>56 ± 12</td>
<td>51 ± 10</td>
<td>0.1</td>
</tr>
<tr>
<td>2 Months</td>
<td>50 ± 11</td>
<td>45 ± 9</td>
<td>0.04</td>
<td>60 ± 11</td>
<td>54 ± 9</td>
<td>0.04</td>
</tr>
<tr>
<td>6 Months</td>
<td>52 ± 10</td>
<td>49 ± 9</td>
<td>0.19</td>
<td>56 ± 11</td>
<td>52 ± 9</td>
<td>0.08</td>
</tr>
<tr>
<td>12 Months</td>
<td>53 ± 9</td>
<td>47 ± 10</td>
<td>0.01</td>
<td>59 ± 10</td>
<td>53 ± 11</td>
<td>0.03</td>
</tr>
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</table>

MI = myocardial infarction.

Discussion

In the present study we found in a cohort of 162 patients with AMI and early peak CK after thrombolytic therapy concomitant rapid ST-segment elevation resolution only in 67% of the patients. Despite similar late (96 h) patency rate of the IRA on angiography, the patients with rapid resolution of ST-segment elevation as compared with those with early peak CK but without rapid ST-segment elevation resolution benefitted more from thrombolysis judged from smaller enzymatic infarct size, more preserved LVEF, and eventually better long-term clinical outcome. These results suggest that in patients with early peak CK, ST-segment resolution may reflect myocardial reperfusion and salvage better than early peak CK alone.

Comparison with previous studies of nonangiographic signs of reperfusion. Although much has been written about the reliability of early ST-segment resolution and early peak CK to detect early reperfusion after thrombolytic therapy (5–14), little is known about the relationship between these two signs. Silber et al. (9) showed an improved LVEF and survival in patients with early resolution of ST-segment elevation and early peak CK after thrombolysis as compared with those with either one or none of these signs. It was also shown that each, that is, early ST-segment resolution and early peak CK, are independent predictors of infarct artery patency (8).

Our results are in strong agreement with those of van’t Hof et al. (18), who recently showed that rapid ST-segment elevation resolution after successful primary PTCA reflected myocardial reperfusion rather than the restoration of flow in the

Table 3. In-Hospital Clinical Outcome

<table>
<thead>
<tr>
<th></th>
<th>Anterior MI</th>
<th>Inferior MI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>Chronic CHF</td>
<td>1 (3%)</td>
<td>5 (14%)</td>
<td></td>
</tr>
<tr>
<td>Reinfarction</td>
<td>6 (17%)</td>
<td>0 (0%)*</td>
<td></td>
</tr>
<tr>
<td>CAGB</td>
<td>2 (6%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>PTCA</td>
<td>18 (50%)</td>
<td>14 (39%)</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>0 (0%)</td>
<td>2 (6%)</td>
<td></td>
</tr>
</tbody>
</table>

All results are presented as number of patients. *p = 0.01. CAGB = coronary artery bypass graft surgery; CHF = congestive heart failure; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

Table 4. Long-Term (2-Year) Clinical Outcome

<table>
<thead>
<tr>
<th></th>
<th>Anterior MI</th>
<th>Inferior MI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic CHF</td>
<td>1 (3%)</td>
<td>5 (14%)</td>
<td></td>
</tr>
<tr>
<td>Reinfarction</td>
<td>10 (28%)</td>
<td>1 (3%)†</td>
<td></td>
</tr>
<tr>
<td>Revascularization</td>
<td>24 (69%)</td>
<td>19 (53%)†</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>0 (0%)</td>
<td>4 (11%)</td>
<td></td>
</tr>
<tr>
<td>CHF and/or mortality</td>
<td>1 (3%)</td>
<td>7 (19%)*</td>
<td></td>
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</table>

*p = 0.05; †p < 0.05; ‡p < 0.01. Abbreviations as in Table 3.
IRA and was a predictor of the extent of myocardial damage and of clinical outcome.

Possible mechanisms for the absence of ST-segment resolution in patients with early peak CK. Few mechanisms might be suggested for the absence of rapid resolution of ST-segment elevation despite early peak CK and for the diminished myocardial salvage in those patients:

(1) Previous studies showed that after thrombolytic therapy (1–4) or direct PTCA (18–23), coronary reflow in the ischemic myocardium might not have occurred despite early and adequate reopening of the IRA. The “no-reflow” phenomenon is due to microvascular dysfunction, which is caused by swelling of the endothelial cells, perivascular edema, intramural hemorrhage, capillary plugging by erythrocytes and leukocytes, and small vessels spasm (19,21,24–28). As a result of the inadequacy of the myocardial reperfusion, the no-reflow phenomenon is associated with poor myocardial functional recovery (3,4,29). The myocardium supplied by the reperfused IRA is not uniformly affected by the no-reflow phenomenon (3,4,25), and this phenomenon occurs to a variable extent in different patients (1,3,4). Thus, while the areas of the jeopardized myocardium with preserved microvasculature might account for the early peak CK after restoration of flow in the IRA, the extent of the jeopardized myocardium without effective reflow due to microvasculature damage would determine the eventual amount of myocardial salvage and whether concomitant rapid resolution of ST-segment elevation occurs and to what extent.

This theoretical explanation agrees with previous studies (19,21), which showed that the no-reflow phenomenon after direct PTCA for AMI is associated with persistent ST-segment elevation and myocardial damage despite the demonstration of patent IRA, and that reversal of the no-reflow is associated with resolution of the ST-segment elevation (21).

Kenner et al. (4) showed that the anterior, as opposed to the inferior, myocardial infarcts were more prone to the no-reflow phenomenon, supposedly due to the larger amount of ischemic muscle and therefore higher wall stress and regional oxygen demand and less collateral flow in the former infarcts. Thus, this may explain our finding of higher prevalence of early resolution of ST-segment elevation among patients with inferior as compared with those with anterior myocardial infarcts.

(2) During acute ischemia the ST-segment elevation on the surface ECG reflects the loss of resting membrane potential and shortening of the plateau phase of the action potential in the ischemic myocardium. Both changes are accounted for by an increase in the extracellular potassium concentration, and therefore, the washout of tissue potassium as a consequence of successful reperfusion results in rapid resolution of ST-segment elevation. Since the potassium ion is a smaller molecule than CK, in patients with CK washout, as evidenced by early peak CK, elevated extracellular potassium in areas that were washed out may not account for persistent ST-segment elevation. Previous experimental studies showed that peroxidation of myocytes membrane lipids by oxidative stress might lead to loss of resting membrane potential (30–32) and to abbreviation of the action potential duration (30,32,33), which are similar to the ones occurring as a result of ischemia.

Reperfusion of ischemic myocardium might be accompanied by accelerated generation of oxygen-derived free radicals and membrane lipids per oxidation (34,35). These radicals, which play a major role in the pathogenesis of “reperfusion injury,” might also account for persistent ST-segment elevation despite rapid washout of the extracellular potassium along with the CK accounting for the continued myocardial tissue injury.

Study limitation. The patients in the present study were not catheterized immediately after the administration of thrombolytic therapy, and differentiation between TIMI grade II and III in the IRA was not made. Thus, one might claim that the differences between the patients with and without early resolution of ST-segment elevation lie in an earlier and/or higher grade of vascular reperfusion. However, previous studies that did differentiate between TIMI grade II and III showed that patients with TIMI grade II in early angiography did not have an abrupt increase in plasma CK and had an enzyme curve similar to the patients with TIMI 0 and I (36). Because all the patients in the present study had early peak CK differences in the epicardial coronary arteries, flow grade in the IRA itself could not explain the findings of the present study. Moreover, Kenner et al. (4) did not find any correlation between the TIMI grade flow in the epicardial artery and the occurrence of no-reflow as defined by contrast echocardiography. It should be remembered that in patients with prior infarct in the same site, persistent ST-segment elevation from the previous infarct might interfere with the interpretation of ST-segment changes.

Clinical implication. Although the immediate role of thrombolytic therapy for AMI is early recanalization and restoration of flow in the IRA, the eventual aim of all reperfusion strategies is the achievement of adequate reperfusion at the tissue level and thus myocardial salvage. However, that might not occur with early restoration of TIMI grade III in the IRA (1–4). Therefore, early evaluation of the quality of myocardial reperfusion might have important prognostic value. In the present study among patients with an early peak CK, which is considered as a marker of reperfusion, we
observed that the presence or absence of rapid resolution of ST-segment elevation differentiates between patients with patent artery and improved myocardial perfusion (and better clinical outcome) and patients with patent artery but without successful myocardial reperfusion and worse prognosis and outcome.

References