Effect of Glycoprotein IIb/IIIa Receptor Blockade on Recovery of Coronary Flow and Left Ventricular Function After the Placement of Coronary-Artery Stents in Acute Myocardial Infarction

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Background—Apart from its established effects on vessel patency after percutaneous coronary revascularization, glycoprotein IIb/IIIa receptor blockade by abciximab may improve myocardial perfusion by inhibition of the interaction of platelets and platelet aggregates with the microvasculature. We investigated the effect of abciximab with stent placement in acute myocardial infarction.

Methods and Results—In a prospective randomized trial, patients undergoing stenting in acute myocardial infarction within 48 hours after onset of symptoms were randomly assigned to receive either standard-dose heparin or abciximab plus low-dose heparin. Immediately after the procedure and at 14-day angiographic follow-up, we assessed flow velocity in the recanalized vessel with the Doppler wire and regional wall motion by the centerline method. End points were changes in papaverine-induced peak flow velocities and in wall motion indices. We assigned 98 patients to standard heparin and 102 to abciximab. We obtained 152 paired flow measurements and 151 paired left ventricular function studies. Residual stenoses of the treated lesions did not differ between the 2 groups. Improvement of peak flow velocity (mean [95% CI]: 18.1 cm/s [13.6 to 22.6 cm/s], n=80, versus 10.4 cm/s [5.4 to 15.4 cm/s], n=72, P=0.024) and wall motion index (0.44 SD/chord [0.29 to 0.59 SD/chord], n=79 versus 0.15 SD/chord [0.00 to 0.30 SD/chord], n=72, P=0.007) was significantly greater in patients assigned to abciximab than in those on heparin alone. At follow-up, the abciximab group had a higher global left ventricular ejection fraction than the heparin group (62% [59% to 65%] versus 56% [53% to 59%], P=0.003).

Conclusions—Abciximab had important effects beyond the maintenance of large-vessel patency. It improved the recovery of microvascular perfusion and concomitantly enhanced the recovery of contractile function in the area at risk.

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Key Words: myocardial infarction ■ stents ■ glycoproteins ■ blood flow ■ ventricles

In acute myocardial infarction (AMI), myocardial salvage after timely recanalization of the infarct-related artery is critically dependent on coronary blood flow to the area at risk.1 With regard to patency of the infarct-related artery, randomized trials have shown that direct PTCA is superior to established protocols of thrombolysis,2,3 and additional benefit may be derived from stent placement.4 The adequacy of reperfusion in AMI, however, depends not only on persistent patency of the infarct-related artery but also on the integrity of the distal circulation. At the microcirculatory level, distal embolization of platelet aggregates formed at the treated plaque,5 release of vasoconstrictive platelet mediators,6 and/or vascular reperfusion injury due to cardiac inflammatory responses may compromise the recovery of perfusion.7 To this end, it has been shown that the pattern of reperfusion after recanalization of the infarct-related artery with stent placement varies considerably between patients.8 In most patients, coronary flow reserve improves within the next 2 weeks, whereas in others, maximal coronary flow falls below the level achieved initially.8 Perfusion patterns are closely linked to the recovery of contraction in the infarct region and may thus be a target for pharmacological modification.8,9 Glycoprotein IIb/IIIa receptor blockade may not only maintain patency of the recanalized vessel but also prevent embolization of platelet aggregates into the distal circulation.10,11 In this prospective randomized trial on patients with AMI, we investigated microvascular and contractile recovery of the infarct region after revascularization with stent placement and compared the effect of peri-
interventional glycoprotein IIb/IIIa blockade by abciximab with that of standard heparin therapy. Specifically, we tested the hypothesis that compared with conventional treatment, abciximab improves the recovery of papaverine-induced coronary peak flow velocity and of wall motion in the infarct area within 14 days after successful stent placement in the infarct-related artery.

Methods

Study Cohort and Procedural Outcome

The study included patients with AMI undergoing revascularization by stent placement within 48 hours after onset of pain. Inclusion criteria were (1) typical anginal pain lasting >30 minutes, (2) a coronary artery lesion that was deemed suitable for stent placement, (3) ST-segment elevation of ≥1 mm in ≥2 contiguous leads, (4) elevation in creatine kinase ≥3 times the upper limit of normal with a concomitant rise in MB isoenzyme, and (5) coronary artery occlusion with angiographic appearance of fresh thrombus. We recruited patients who met criteria 1 and 2 plus at least 1 of criteria 3 through 5. Exclusion criteria were inability to give informed consent, history of vasculitis or chronic steroid treatment, and contraindications to 1 of the study drugs. All eligible patients who gave written informed consent were randomized by means of sealed envelopes. Patients, but not physicians, were blinded to the assignment of treatment. The study was carried out according to the Declaration of Helsinki and was approved by our institutional ethics committee.

Study Protocol

Before catheterization, all patients received heparin 5000 U and aspirin 500 mg IV. Once the decision was made for stent placement, patients were randomized to 1 of 2 treatment regimens. Patients assigned to treatment with glycoprotein IIb/IIIa receptor blockade received a bolus of abciximab 0.25 mg/kg body wt, followed by continuous infusion of 10 μg/min for 12 hours, plus an additional dose of heparin 25 000 U intra-arterially. In patients assigned to usual care, we administered heparin 10 000 U intra-arterially, followed by intravenous heparin infusion 1000 U/h for the first 12 hours after sheath removal. Immediately after reestablishing antegrade flow, we gave an intracoronary bolus dose of 0.2 mg nitroglycerin in both groups. Stent placement was performed as described previously.12 We used 5 different types of slotted-tube stents, which were evenly distributed between the study groups (Palmaz-Schatz, Multilink, Nir, Pura A, and InflowDynamics). If, after stent placement, residual thrombus remained and caused impairment of flow (TIMI grade ≤2) or lumen narrowing of >50%, operators were allowed to administer abciximab in the usual-care group. In both groups, postinterventional antithrombotic therapy consisted of ticlopidine 250 mg BID for 4 weeks and aspirin 100 mg BID throughout the study.

Immediately after completion of the intervention, coronary flow velocities in the stented segment were measured with the Doppler FloWire and analyzed by the FloMap system (Cardiometrics) as described previously.8 We positioned the tip of the Doppler wire at the proximal end of the stented segment to ensure a reproducible sampling site that is not subject to vasomotor changes. Doppler flow velocity spectra were analyzed on-line to determine time-averaged peak velocity. We determined basal and peak coronary flow velocities after intracoronary bolus doses of papaverine (10 mg for the right and 12 mg for the left coronary artery). Thereafter, we performed single-plane left ventriculography in the 30° right anterior oblique view. At 14±1 days after the initial intervention, coronary and left ventricular (LV) angiography and flow velocity measurements were repeated. When indicated, repeat PTCA was performed before the second flow velocity measurement.

Quantitative Angiography

We used nonionic contrast medium (ioversol) in all patients. Images of coronary and LV angiograms (Hicor, Siemens) were stored on compact disks and analyzed off-line (MEDIS Medical Imaging Systems) by operators unaware of the study groups to which the patients were assigned.8,12 Global LV ejection fraction was determined by the area-length method. To quantify regional LV wall motion, we used the centerline method.8,13 Within the region of interest, the mean wall motion of the abnormally contracting (≤−1 SD from normal) contiguous chords was determined to yield the wall motion index of that region.8,13 This result was expressed in SD (from normal) per chord (SD/chord). In addition, we determined the number of chords within the region of interest showing hypokinesis (≤−1 SD).

Study End Points and Measures of Clinical Outcome

The differences in papaverine-induced coronary flow velocity and in wall motion index between the initial study and 14-day follow-up were primary end points. In addition, we analyzed basal flow velocities, coronary flow reserve (ratio of peak flow velocity and basal flow velocity), number of chords with hypokinesis, and global LV ejection fraction. Secondary end point was the clinical outcome during 30-day follow-up.

Statistical Analysis

All data were analyzed on an intention-to-treat basis. Discrete variables, expressed as counts, were tested by Fisher’s exact test. Results of continuous variables, reported as mean±SD or as mean (95% CI), were tested by the t test for paired and unpaired samples, as appropriate. The effect of treatment and of other covariables on changes in coronary flow velocity or wall motion index was also assessed by stepwise multiple linear regression analysis. We used the SPSS 7.5 software package for all statistical analyses. A value of P<0.05 in the 2-tailed test was regarded as significant.

Results

Study Cohort, Procedural Outcome, and Angiographic Follow-Up

The study enrolled 200 consecutive patients; 98 were assigned to usual care and 102 to abciximab treatment. Except for 2 patients with ST-segment elevation and early intervention, all developed significant creatine kinase elevation. The study groups were homogeneous with respect to baseline demographic, clinical, and angiographic characteristics (Table I).

In 4 patients, the intervention was unsuccessful for technical reasons. These were failure to recanalize the infarct-related occlusion and inability to cover a large residual dissection in 1 patient of each group. After stent placement in the usual-care group, large residual thrombi remained in 10 patients and were associated with TIMI grade 2 flow in 4 patients. In all patients with large residual thrombi, we administered abciximab secondarily, which dissolved the clots in 8 patients. Substantial residual thrombi or TIMI grade 2 flow was not encountered in any of the patients with successful stent placement assigned to abciximab. In the 4 patients with unsuccessful procedures and in 13 patients with hemodynamic instability, we did not perform flow velocity measurements and LV angiography.

Twelve patients with successful stent placement did not undergo repeat angiography at 14 days. This was because of death in 6 patients (see below), coronary artery bypass
graft surgery for left main stenosis after successful recana-

lization of an occluded right coronary artery in 1 patient assigned to abciximab, severe peripheral vascular disease in 1 patient, and patient refusal after an uneventful clinical course in 4 patients.

We obtained paired coronary flow velocity measure-

ments in 152 patients and paired LV angiographies in 151 patients. The causes for missing studies are summarized in Table 2. Between the 2 groups, there were no significant differences in the rate of paired flow velocity measurements or LV angiograms ($P<0.5$), nor was the distribution of causes for missing studies different between the 2 groups ($P>0.6$).

**Coronary Flow Velocities in the Infarct-Related Artery**

At the initial study, both treatment groups had similar basal and peak flow velocities in the recanualized coronary artery (Table 3). Within 14 days, peak flow velocities increased significantly in both treatment groups and basal flow velocity increased significantly in the abciximab group (Figure 1). The increase in peak flow velocity in patients assigned to abciximab was significantly larger than that in patients assigned to usual care (Figure 1). Thus, at follow-up, peak flow velocities in the abciximab group were significantly higher than those in the usual-care group, and basal flow velocities were higher by trend (Table 3). In both treatment groups, we found significant increases in coronary flow reserve in the infarct-related artery (Table 3). These were not affected by the treatment regimen, however, and there were no significant differences in coronary flow reserve between the abciximab group and the usual-care group either at the initial study or at follow-up.

With regard to potential determinants of coronary flow velocity, the 2 treatment groups were homogeneous with respect to vessel size, minimal luminal diameter, and residual stenosis of the treated segment both in the initial study and at follow-up (Table 3). The same held true for arterial blood pressure and pulse rate during the flow velocity measurements as well as LV end-diastolic pressures (Table 3). Multiple linear regression analysis revealed assignment to treatment with abciximab as the single independent predictor ($P=0.026$) for the increase in peak flow velocity. Apart from the assigned treatment, the model included baseline demographic, clinical, and angiographic characteristics (Table 1) as well as hemodynamic and quantitative angiographic data (Table 3).

**Regional and Global LV Function**

Improvement of regional LV function within the first 2 weeks, assessed by wall motion index or number of chords with hypokinesis, was significantly greater in patients assigned to abciximab than in those assigned to usual care (Figure 2). By multiple linear regression analysis with the same independent variables as in the model for peak flow velocity (see above), the assigned treatment was a significant ($P=0.017$) independent predictor for the increase in wall motion index. The only other independent predictor was TIMI flow grade before the intervention ($P=0.007$).

Immediately after recanalization of the infarct-related artery, global and regional LV function of the infarct zone were similar in both treatment groups (Table 4). At follow-up, the
Infarct-related wall motion abnormalities were significantly less in the abciximab group than in the usual-care group (Table 4). Concordant changes were found in global LV ejection fraction (Table 4).

We found a significant correlation between changes in peak flow velocity and changes in wall motion index ($r = 0.20, P = 0.022$). A similar trend was observed for the relation of changes in peak flow velocity to changes in LV ejection fraction ($r = 0.15, P = 0.09$).

### Clinical Outcome

Although angiography at 14 days did not detect any stent vessel occlusions, target lesion reintervention with additional stent placement had to be performed in 4 patients of the control group. During 30-day follow-up, 2 patients of the abciximab group and 9 patients of the control group had adverse cardiac events (OR [95% CI]: OR, 0.20 [0.04 to 0.94], $P = 0.031$), including death (2 versus 4; OR, 0.47 [0.08 to 2.93], $P = 0.44$), nonlethal...
TABLE 4. Indices of Wall Motion in the Infarct Region and Global LV Ejection Fraction

<table>
<thead>
<tr>
<th></th>
<th>Abciximab (n=79)</th>
<th>Usual Care (n=72)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediately after stent placement</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Wall motion index, SD/chord</td>
<td>−2.08±0.64</td>
<td>−2.04±0.57</td>
<td>0.71</td>
</tr>
<tr>
<td>Chords with hypokinesis, n</td>
<td>32±20</td>
<td>32±20</td>
<td>0.77</td>
</tr>
<tr>
<td>Global ejection fraction, %</td>
<td>55.7±12.4</td>
<td>53.5±13.5</td>
<td>0.30</td>
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<tr>
<td>At 14-day follow-up</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Wall motion index, SD/chord</td>
<td>−1.64±0.69</td>
<td>−1.89±0.59</td>
<td>0.017</td>
</tr>
<tr>
<td>Chords with hypokinesis, n</td>
<td>17±18</td>
<td>25±19</td>
<td>0.016</td>
</tr>
<tr>
<td>Global ejection fraction, %</td>
<td>62.2±13.2</td>
<td>55.9±12.6</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Data are expressed as mean value±SD.

Discussion

Various studies have shown that abciximab effectively prevents abrupt reocclusion after percutaneous coronary revascularization procedures, particularly when performed in high-risk settings such as AMI or unstable angina. Our present prospective randomized study presents evidence that in AMI, abciximab has important effects beyond the maintenance of large-vessel patency after stent placement. As our major finding, we showed that peri-interventional administration of abciximab improves the recovery of coronary vascular function and of regional wall motion compared with conventional heparin treatment.

Recovery of Coronary Flow to the Area at Risk

In patients assigned to abciximab, the increase in peak flow velocity at the site of recanalization during the first 2 weeks after the intervention was almost twice that in patients assigned to usual care. This differential effect of the 2 treatment regimens could not be attributed to differences in patency of the infarct-related vessel. The 2 groups were homogeneous with respect to vessel diameter and residual stenosis of the treated lesion. Similarly, there were no inequalities in hemodynamic conditions. These findings strongly suggest a microvascular mechanism for the larger increase in peak flow velocity after administration of abciximab compared with usual care. We did not directly measure myocardial blood flow in the infarct region. However, the stent ensured exact positioning and constant vessel diameters at the sample volume of the Doppler wire in both flow velocity studies. The changes in peak flow velocity thus may be taken as a reliable indicator of changes in maximal myocardial blood flow in the infarct region.

In the abciximab group, we also found a significant increase in basal flow velocity at the site of revascularization that was not observed in the usual-care group. Accordingly, coronary flow reserves at follow-up were not significantly different between the 2 treatment groups. Previous studies have shown that an increase in the number of functional vascular segments contributes substantially to the recovery of myocardial blood flow during reperfusion in AMI. The differential effect of our 2 treatment regimens may thus be explained by an increased number of functional vascular segments after abciximab treatment compared with usual care, rather than by an increase in flow reserve of the individual segments.

The beneficial effect of abciximab on recovery of vascular function in the infarct area can be explained by blockade of the glycoprotein IIb/IIIa receptor, which prevents embolization of platelet aggregates as well as platelet adhesion to the injured endothelium. In addition, blockade of the vitronectin receptor, another β3-integrin, and of β3-integrins, such as Mac-1 on leukocytes, may contribute by inhibition of the interaction of leukocytes with the reperfused microvasculature. Such interaction induces procoagulant and cytotoxic inflammatory responses. 

Recovery of Contraction in the Area at Risk

Previous clinical studies revealed a close relation between recovery of perfusion and recovery of contraction in the infarct region. Supporting a functional impact of our findings on coronary flow velocity, we obtained a significant correlation between the recovery of peak flow velocity and the improvement of wall motion index. Most importantly, both the wall motion index and the number of chords with hypokinesis indicated improved recovery of LV function in the infarct area in patients assigned to abciximab compared with usual care. Notably, these changes translate into a higher global LV ejection fraction at follow-up in the abciximab group. These findings underscore the important impact that peri-interventional treatment with abciximab has on the recovery of wall motion in the infarct region.

Clinical Relevance

We investigated the effect of abciximab in a cohort that comprised the entire spectrum of patients with AMI referred to a tertiary-care hospital within 48 hours after
onset of pain. Thus, apart from patients with Q-wave AMI within the first 12 hours, our study included patients with non-Q-wave AMI, those with persistent angina for >12 hours, and those with failed thrombolysis. Multiple regression analysis demonstrated that the beneficial effect of abciximab was independent of these clinical covariables. abciximab thus improved the recovery of coronary flow and regional LV function in a very broad spectrum of patients with AMI.

Although our study was not sufficiently powered to address the differential effect of the treatment regimens on clinical outcome, adverse cardiac events were significantly fewer in the abciximab group than in the usual-care group. This beneficial effect of abciximab is consistent with the results of the recently published EPISTENT study.19 In addition, our studies of contractile function strongly support the administration of abciximab in patients undergoing stent placement in AMI.

Methodological Considerations and Limitations of the Study

In accordance with our preceding study on recovery of coronary flow in AMI, we used papaverine to assess coronary vasodilator capacity.8 Papaverine has been extensively validated in the analysis of coronary flow dynamics.20,21 Adenosine exerts a comparable vasodilator effect,22 but it is preferred by some investigators because of a lower risk of torsade de pointes tachycardia. Nevertheless, we did not experience any adverse event due to side effects of papaverine.

The fact that physicians were not blinded to the assignment of treatment represents a limitation of our study. Consequently, bias on the part of the investigators cannot be fully excluded as a factor influencing clinical treatment. However, flow velocities were ascertained by automated computerized evaluation, and the angiographic evaluations were performed by blinded operators. Bias in the assessment of the primary end points can thus be excluded. In 10 patients of the usual-care group, operators administered abciximab to deter a detrimental outcome of the intervention. These crossovers do not confound the principal trial results, because the functional and clinical outcome of the usual-care group most probably would have been even less favorable without them. In some patients, we could not obtain paired LV angiograms or flow wire measurements. This problem was similar in previous studies and affected both study groups to the same extent.13 Moreover, the distribution of the causes for missing studies was similar in both groups. Therefore, we cannot assume a relevant distortion of the trial results by missing studies.

Implications

Our study shows that in patients undergoing coronary stent placement in AMI, peri-interventional administration of abciximab has important beneficial effects beyond the maintenance of large-vessel patency. Abciximab improves the recovery of coronary perfusion at the level of the distal vascular bed and concomitantly enhances the restoration of LV function in the infarct area. Our findings support the concept that not only large-vessel patency but also improvement of microvascular perfusion is an achievable and rewarding goal in the treatment of patients with AMI.

Glycoprotein IIb/IIIa receptor blockade offers a novel strategy toward this goal.

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References


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