Admission troponin T, advanced age and male gender identify patients with improved myocardial tissue perfusion after abciximab administration for ST-segment elevation myocardial infarction

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Summary
The aim was to investigate the effect of abciximab on microvascular perfusion in different subgroups of patients undergoing direct PCI for acute STEMI. We enrolled 145 consecutive patients with TIMI grade 3 flow after direct PCI for acute STEMI. The GPIIb/IIIa inhibitor abciximab was administered in 57 patients (39.3%). Myocardial perfusion was the primary outcome measure and was assessed by analysis of cardiac troponin T wash-out. Treatment effects on myocardial perfusion and clinical outcome were tested for predefined subgroups including patients with an admission cTnT ≥ 0.1 µg/L, diabetes mellitus, male gender, age > 70 years, and time from symptom onset to reperfusion > 6 hours. A significant improvement of cTnT washout was seen in patients with an admission cTnT ≥ 0.1 µg/L in males and in older patients. Improved tissue level reperfusion did not translate into a significant reduction of cardiac mortality or the incidence of the combined endpoint consisting of cardiac death, nonfatal reinfarction and need for target vessel revascularisation during 30 day- and long-term follow-up (mean 274 days). In conclusion, adjunctive administration of abciximab improves myocardial perfusion in patients with normal epicardial flow after direct PCI, particularly in patients with an cTnT ≥ 0.1 µg/L on admission, age over 70 years and male gender.

Keywords
Troponin T, microcirculation, GP IIb/IIIa inhibitors

Introduction
In acute ST-segment myocardial infarction (STEMI), early and complete epicardial reperfusion is of major prognostic significance and remains the main therapeutic goal. With the use of primary balloon angioplasty in combination with coronary stenting a normal epicardial reperfusion can successfully be established in more than 90% of patients with acute STEMI (1, 2).

Some 25% of patients believed to have successful reperfusion retain microvascular obstruction which is associated with an adverse prognosis (3, 4). While peri-interventional administration of the GPIIb/IIIa inhibitor abciximab has been shown to improve both epicardial and microvascular flow after direct PCI or fibrinolytic therapy (5-7), the effects on clinical outcomes of GPIIb/IIIa inhibitors after direct PCI are less consistent and may depend on patient selection, use of different coronary stents and time of abciximab administration. (1, 8, 9) It is reasonable to speculate that patients who are at risk of developing microvascular obstruction will benefit most from abciximab therapy. A higher propensity to retain or develop impaired microvascular perfusion despite restoration of normal epicardial blood flow has been reported for diabetics, older patients, males, for those presenting late after onset of symptoms and for those with cardiac troponin levels already elevated on admission (10-15).
A variety of methods to assess microvascular perfusion has been described, however, most of these techniques are retrospective and difficult to apply. We performed the present study to evaluate the effects of abciximab on myocardial tissue level perfusion and clinical outcomes in patients with an elevated cTnT on admission and in several other subsets of patients. To test the effects of abciximab on myocardial perfusion, patients were monitored for early release kinetics of cardiac troponin T (cTnT) after successful epicardial reperfusion.

Methods

From January 1999 to October 2001, 145 consecutive patients who underwent successful epicardial reperfusion by direct PCI for acute STEMI were enrolled. Diagnosis of STEMI was based on new ST-elevation (>0.1 mV) in at least two contiguous leads and was confirmed retrospectively by an increase of CK or CK-MB activity to twice the upper limit of normal and a characteristic ascending limb of CK-MB. Patients had to present within 12 hours after symptom onset.

Patients underwent coronary angiography and primary PCI within 30 minutes after admission. Procedural success was defined as a residual diameter stenosis < 30% and restoration of normal epicardial flow. Epicardial flow was graded according to the grade scale of the TIMI study group (16). Presence of post-interventional thrombus and/or coronary dissections were exclusion criteria for the study (see below). Further lesion characteristics were not analysed as patients almost exclusively presented with an occluded infarct related artery and the recanalization by angioplasty/stenting prevents a reliable characterization of the target lesion.

The glycoprotein IIb/IIIa receptor inhibitor abciximab was administered at the discretion of the interventional cardiologist immediately after the procedure (bolus of 0.25 mg/kg followed by an infusion of 0.125 µg/kg/min for 12 hours). Patients requiring abciximab for compromised coronary flow or large coronary dissections (NHLBI grade D-F) after recanalization of the infarct related artery were excluded.

On admission, all patients received 500 mg acetylsalicylic acid followed by 100 mg daily and a heparin bolus of 5000 IU followed by an aPTT adjusted infusion rate. Patients who received a coronary stent received 300 mg clopidogrel followed by 75 mg daily for 4 weeks.

Patients were followed for a mean of 274 days using hospital records, questionnaires and telephone contact. Endpoints were cardiac death as well as a combined endpoint consisting of cardiac death, nonfatal reinfarction and target-vessel reintervention (percutaneous coronary interventions, coronary-artery bypass surgery).

The study was approved by the local ethics committee of the University of Luebeck. All patients gave written informed consent.

Serum marker analyses

For early risk stratification, cardiac troponin T (cTnT) levels were measured using a qualitative or quantitative rapid bedside assay (Trop T or Cardiac Reader, Roche Diagnostics, Mannheim, Germany). Patients were divided into troponin positive and negative using a cut-off value of 0.1 µg/L.

For assessment of myocardial perfusion cTnT was measured quantitatively using a one-step EIA based on electrochemiluminescence technology (Elecsys 2010, Roche, Mannheim, Germany). The lower detection limit of this assay is 0.01 µg/L with a recommended diagnostic threshold of 0.03 µg/L. The inter-assay coefficients of variation (between day imprecision data set of at least 11 runs) at different concentrations were 20% for 0.015 µg/L, 10% for 0.03 µg/L and 5% for 0.08 µg/L.

For evaluation of release kinetics, cTnT concentrations were measured just prior to recanalization of the infarct related artery (T0) and 60-minutes after reperfusion (T60).

Derivates of the release curves were calculated as follows: T-60: concentration obtained 60 minutes after reperfusion; 60-min ratio: concentration at 60 minutes (T60) divided by concentration just prior to reperfusion (T0).

Since ratios were not normally distributed, 60-minute cTnT ratios were divided into quartiles. Those patients in the lowest cTnT ratio quartile were classified as having the most impaired microcirculation.

Patient subgroups

We tested the effects of abciximab in different prespecified subgroups including cTnT ≥ 0.1 µg/L on admission, age >70 years, male gender, presence of diabetes and time from symptom onset to reperfusion > 6 hours. All analyses regarding clinical outcome and myocardial tissue perfusion were conducted for the entire study cohort and for each of the predefined subgroups.

Statistical analysis

All data analyses were performed using the Statistical Package for Social Sciences (SPSS for Windows 8.0, SPSS Inc, Chicago, Illinois, USA) software. Continuous variables were compared by t-test when normally distributed. Otherwise comparisons were made by Mann-Whitney –U test. Categorical variables were tested by use of Fisher’s exact test. Kaplan Meier curves were generated for assessment of event-free survival. A two-tailed p of ≤0.05 was considered to be statistically significant for all analyses.

Results

Of the 145 patients who were enrolled in this trial, 57 patients received abciximab (39.3%). Both groups matched well with regard to baseline clinical characteristics and key angiographic features. Furthermore, the treatment rates among the predefined subgroups did not differ (Table 1).
Release kinetics of cardiac troponin T

Complete analysis of cTnT release could be obtained for all patients studied. Median cTnT ratios in the quartiles were 2.04, 6.87, 24.62 and 134.65 (Fig. 1).

There were no significant differences between the treatment groups regarding the T0 and T60 cTnT values (0.41 µg/l vs. 0.4 µg/l and 4.6 µg/l vs. 3.7 µg/l).

In the overall study population, the percentage of patients with T60/T0 ratios in the lowest quartile was significantly lower among patients receiving abciximab (12.3% vs. 30.7%, p = 0.015), indicating an improved tissue level perfusion by abciximab (Fig. 2). Subgroup analysis revealed that not all patients derived the same degree of benefit. A significant improvement of myocardial microcirculation by abciximab treatment was noted only among patients with an admission troponin T ≥ 0.1 µg/L, patients > 70 years of age and males (Table 2).

Clinical outcome

Cardiac mortality was 3.4% (5 of 145 patients) at 30 days. Cardiac death was limited to the first 30 days with no additional deaths occurring during follow-up. Treatment with abciximab did not reduce mortality rates to a significant degree (1.8% vs. 4.5%, p = n.s.) in the overall study population.

The rates of the combined endpoint at 30 days and at the end of follow-up were 8.8% and 26.3% with abciximab and 11.4% and 21.6% without abciximab (Fig 3). These differences did not reach statistical significance (Table 3). The effect of abciximab on clinical outcome was not different whether patients received coronary stents or balloon angioplasty alone (data not shown).

Discussion

The salutary effects of abciximab and other glycoprotein IIb/IIIa inhibitors in conjunction with percutaneous coronary interventions have been unequivocally established for elective revascularization (17) as well as for interventions in acute cor-
Table 3: Relative risk for clinical endpoints according to abciximab treatment.

<table>
<thead>
<tr>
<th></th>
<th>with abciximab</th>
<th>without abciximab</th>
<th>RR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>all patients</td>
<td>n=57</td>
<td>n=88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM pos</td>
<td>6/42 (14.3)</td>
<td>21/70 (30)</td>
<td>0.8 (0.7-1.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>DM neg</td>
<td>1/15 (6.7)</td>
<td>6/18 (33.3)</td>
<td>0.7 (0.5-1.02)</td>
<td>0.1</td>
</tr>
<tr>
<td>Age&lt;70 yrs</td>
<td>7/44 (15.9)</td>
<td>18/66 (27.3)</td>
<td>0.87 (0.7-1.1)</td>
<td>0.25</td>
</tr>
<tr>
<td>Age&gt;70 yrs</td>
<td>0/13</td>
<td>9/22 (40.9)</td>
<td>0.6 (0.4-0.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Males</td>
<td>7/44 (15.9)</td>
<td>20/64 (31.3)</td>
<td>0.78 (0.64-0.96)</td>
<td>0.02</td>
</tr>
<tr>
<td>Females</td>
<td>2/13 (15.4)</td>
<td>7/24 (29.2)</td>
<td>0.84 (0.6-1.2)</td>
<td>0.45</td>
</tr>
<tr>
<td>Time to reperfusion&lt;6h</td>
<td>6/46 (13)</td>
<td>20/72 (27.8)</td>
<td>0.83 (0.7-1.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>Time to reperfusion≥6h</td>
<td>1/11 (9.1)</td>
<td>7/16 (43.8)</td>
<td>0.62 (0.4-1.0)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

DM: diabetes mellitus

Table 2: Odds for worst microvascular reperfusion (lowest quartile of cTnT T60/T0 ratio) according to prespecified subgroups.

<table>
<thead>
<tr>
<th></th>
<th>with abciximab</th>
<th>without abciximab</th>
<th>RR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 day outcome, n (%)</td>
<td>n=57</td>
<td>n=88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>death</td>
<td>2 (3.5)</td>
<td>5 (5.7)</td>
<td>0.98 (0.9-1.05)</td>
<td>0.7</td>
</tr>
<tr>
<td>cardiac death</td>
<td>1 (1.8)</td>
<td>4 (4.5)</td>
<td>0.97 (0.92-1.03)</td>
<td>0.65</td>
</tr>
<tr>
<td>AMI</td>
<td>1 (1.8)</td>
<td>1 (1.1)</td>
<td>1.01 (0.97-1.05)</td>
<td>1.0</td>
</tr>
<tr>
<td>TVR (PCI)</td>
<td>0</td>
<td>4 (4.5)</td>
<td>0.96 (0.9-1)</td>
<td>0.15</td>
</tr>
<tr>
<td>TVR (CABG)</td>
<td>3 (5.3)</td>
<td>2 (2.3)</td>
<td>1.03 (0.96-1.1)</td>
<td>0.38</td>
</tr>
<tr>
<td>Combined endpoint</td>
<td>5 (8.8)</td>
<td>10 (11.4)</td>
<td>0.97 (0.87-1.1)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Table 2: Odds for worst microvascular reperfusion (lowest quartile of cTnT T60/T0 ratio) according to prespecified subgroups.

<table>
<thead>
<tr>
<th>30 day outcome, n (%)</th>
<th>with abciximab</th>
<th>without abciximab</th>
<th>RR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>death</td>
<td>2 (3.5)</td>
<td>5 (5.7)</td>
<td>0.98 (0.9-1.04)</td>
<td>0.48</td>
</tr>
<tr>
<td>cardiac death</td>
<td>1 (1.8)</td>
<td>4 (4.5)</td>
<td>0.97 (0.92-1.03)</td>
<td>0.65</td>
</tr>
<tr>
<td>AMI</td>
<td>2 (3.5)</td>
<td>4 (4.5)</td>
<td>0.99 (0.93-1.06)</td>
<td>1.0</td>
</tr>
<tr>
<td>TVR (PCI)</td>
<td>4 (7)</td>
<td>8 (9.1)</td>
<td>0.98 (0.89-1.1)</td>
<td>0.77</td>
</tr>
<tr>
<td>TVR (CABG)</td>
<td>8 (14)</td>
<td>5 (5.7)</td>
<td>1.1 (0.98-1.23)</td>
<td>0.13</td>
</tr>
<tr>
<td>Combined endpoint</td>
<td>15(26.3)</td>
<td>19 (21.6)</td>
<td>1.1 (0.9-1.3)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

AMI: acute myocardial infarction; TVR: target vessel revascularization; PCI: percutaneous coronary intervention.

Figure 2: Distribution of patients among cTnT T60/T0 quartiles according to abciximab treatment. The first quartile depicts the lowest T60/T0 ratio as surrogate for the poorest microvascular perfusion. Striped bars: patients treated with abciximab; black bars: patients without abciximab treatment. *p = 0.015.
onary syndromes without ST-segment elevation. (18-20) There have however been inconsistent reports regarding its beneficial effects on mortality and the incidence of other major adverse cardiac events in the clinical setting of acute STEMI (1, 5, 8).

Microvascular perfusion
Despite the importance of restoring flow to the epicardial infarct related artery, the issue of microvascular perfusion has gained increasing attention over the past few years. About one fourth of patients show signs of impaired tissue level perfusion despite an open infarct related artery (3). Persistence of microvascular obstruction is associated with higher cardiac mortality and morbidity following acute infarction (3, 4). Microvascular obstruction occurs at the centre of the infarcted zone due to occlusion of capillaries with blood cell aggregates and necrotic debris (21), leading to “no-reflow” despite epicardial reperfusion. Further mechanisms believed to contribute to impairment of tissue-level perfusion include pre-existing microembolization from unstable plaques (22), downstream embolization of fragmented thrombus during pharmacological or mechanical thrombus resolution (23), as well as release of vasoconstrictive platelet mediators (24) or cardiac inflammatory responses (25). The presence of microvascular obstruction is associated with greater infarct size (4) leading to poorer global left ventricular function in the early postinfarction phase (3, 26). During the chronic phase, microvascular obstruction adversely affects left ventricular remodelling contributing to the adverse long-term prognosis (3, 4, 27).

Several methods for detection of microvascular obstruction have been described, including ST-segment resolution (6), myocardial contrast echocardiography (3), radionuclide studies (28), doppler flow wire velocities (5), myocardial perfusion grade (29) and cardiac magnetic resonance imaging (4). More recently, early release kinetics of cardiac markers were found to allow estimation of tissue level reperfusion following successful direct PCI (11).

Abciximab therapy has been shown to improve myocardial perfusion with either thrombolytic therapy or primary PCI. In combination with tPA, abciximab lead to higher rates of complete ST-segment resolution (6); in conjunction with primary PCI it increased peak coronary flow velocity as assessed by flow doppler wire and improved left ventricular function (5).

In the present study, administration of abciximab lead to an accelerated release of cardiac troponin T as shown by higher 60-minute ratios in the overall study population. Consistently, a recent study reported that abciximab improves tissue level perfusion as measured by corrected TIMI Frame Count and Myocardial Blush Grade (7). The beneficial effects of abciximab on myocardial perfusion have been related to its ability to block platelet aggregation as well as platelet-leukocyte interaction (30).

The role of ST segment resolution as a diagnostic tool for evaluation of microvascular perfusion remains unclear since our data do not demonstrate any detectable effect of abciximab on ST segment resolution (data not shown). Late presentation may be a potential reason for this finding, as there is strong evidence from the TIMI-14 and In TIME-II trials that the probability to achieve complete ST segment resolution decreases by 6% per hour from the onset of symptoms to reperfusion therapy (31).

Not all patients derive the same degree of benefit from abciximab in terms of improved microvascular perfusion. There is speculation that the beneficial effect is more pronounced in subgroups of patients with a higher propensity to retain or to develop microvascular obstruction.

Our own results allow the identification of subgroups of patients in whom the beneficial effect on microvascular perfusion was especially pronounced such as patients with an admission cTnT ≥0.1 µg/l, and males older than 70 years.
Several investigators have unequivocally confirmed that elevation of cTnT on admission is a predictor for less efficient epicardial perfusion after direct PCI or fibrinolytic therapy and is independently associated with an adverse prognosis in STEMI (11, 12, 29, 32, 33). Furthermore, an elevation of admission cTnT was found to identify patients who retain microvascular obstruction despite successful epicardial perfusion (10). This finding serves as a possible explanation for the observation that even among patients with TIMI grade 3 flow, a positive cTnT is associated with an adverse clinical outcome. (13) Recent results confirmed the association between cTnT status and microvascular obstruction in patients with non-ST-elevation acute coronary syndromes (10).

Our data suggest that men are at a higher risk of retaining or developing microvascular obstruction since abciximab improved myocardial flow better in men than in women. The reasons for this finding remain speculative but may involve hemorheological differences, including increased red blood cell aggregation and decreased red blood cell deformability in men (37).

Our finding that patients over 70 years benefit from abciximab correlates well with data from a previous trial demonstrating that increasing age is an independent predictor of non-reflow in STEMI (34).

Although previous studies were able to demonstrate an impaired microvascular perfusion after fibrinolytic therapy among diabetic patients (15), we were not able to detect a beneficial effect of abciximab on myocardial perfusion in this patient subgroup. Diabetics are known to show platelet abnormalities, including larger platelet size (35) and enhanced fibrinogen binding (36). The larger platelet size correlates with enhanced platelet aggregation (37) as well as increased numbers of GPIIb/IIIa receptors (38). These underlying platelet abnormalities, however, do not appear to translate into a difference in the degree of platelet inhibition achieved with abciximab during and early after PCI (39), which underlines our results.

Clinical outcome
Bearing in mind that the present study was not conducted for hard end points given the low clinical event rate in patients with TIMI 3 flow, we found that although cardiac mortality and morbidity tended to be lower in abciximab treated patients, these findings did not reach statistical significance and need to be further clarified in larger study cohorts. Only diabetic patients had lower rates of the combined endpoint which was largely driven by fewer target vessel reinterventions. Although this may be a chance finding due to the small patient numbers, it is in line with previous observations about the reduction of restenosis rates by abciximab treatment in diabetic patients (40), an effect which has been attributed to the pleiotropic effects of abciximab on platelet and leucocyte-endothelial interaction via GP IIb/IIIa, MAC-1 and vitronectin inhibition.

Limitations
The major limitation of this study is the fact that patients were not randomized to receive abciximab. However, we believe that a selection bias is less likely since restoration of TIMI 3 grade flow was a prerequisite for inclusion and presence of large or flow-limiting dissections and postinterventional thrombus were strict exclusion criteria. Moreover, patients matched well with regard to baseline clinical characteristics.

Our study was not designed to evaluate potential clinical benefits of abciximab and is definitely underpowered to exclude potential clinical benefits of abciximab treatment neither for the entire cohort, nor in subgroups. However, the study is very much in line with recent literature that has shown how abciximab apparently fails to amply improve clinical outcomes in patients treated invasively for STEMI, emphasizing the importance of individualizing therapy (6, 8, 41).

Assessment of cardiac microcirculation and reperfusion success using surrogate markers such as troponin T wash out does not represent a well validated technique. Troponin washout was previously employed to assess the success of thrombolytic therapy noninvasively. Our data indicate that troponin wash-out might be accurate enough not only to detect TIMI 3 flow but also to assess tissue level reperfusion. However, further studies are mandatory to validate this application of troponin testing.

Conclusions
In patients with TIMI grade 3 flow after primary PCI for STEMI adjunctive abciximab therapy leads to an improvement of myocardial microcirculation. This beneficial effect on tissue-level perfusion is more pronounced in certain subgroups that seem to have a propensity for microvascular obstruction. Thus, the study results emphasize the importance of individualizing therapy in STEMI. Identification of these patients can easily be accomplished by clinical characteristics and measurement of baseline troponin levels. Our study was not undertaken to observe a clinical benefit in this generally low-risk cohort of patients with normal epicardial flow to the infarct related artery after direct PCI. However, we believe that the subset of patients with microvascular obstruction despite an open epicardial artery may benefit from adjunctive abciximab treatment. Given the overall small number of clinical events, a considerably larger patient cohort is necessary to prove this hypothesis.
References


