Admission Troponin T Level Predicts Clinical Outcomes, TIMI Flow, and Myocardial Tissue Perfusion After Primary Percutaneous Intervention for Acute ST-Segment Elevation Myocardial Infarction

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Background—In ST-segment elevation myocardial infarction, a troponin T $\geq 0.1 \mu g/L$ on admission indicates poorer prognosis despite early reperfusion. To evaluate the underlying reason, we studied the value of cardiac troponin T (cTnT) for prediction of outcomes, epicardial blood flow, and myocardial reperfusion after primary percutaneous intervention.

Methods and Results—Patients (n=140) admitted within 12 hours after onset of symptoms were stratified by admission cTnT. Epicardial and myocardial reperfusion were graded by the TIMI score and by measurement of relative increases of myoglobin, cTnT, and creatine kinase (CK)-MB 60 minutes after recanalization, respectively. cTnT was positive in 64 patients (45.7%) and was associated with longer median time intervals to admission (5.5 versus 3.5 hours, $P<0.001$) and higher mortality rates after 30 days (12.5% versus 3.9%, $P=0.06$) and 9 months (14% versus 3.9%, $P=0.005$). cTnT independently predicted a 3.2-fold risk for incomplete epicardial reperfusion ($P=0.03$). In addition, cTnT $\geq 0.1 \mu g/L$ was associated with more severely impaired myocardial perfusion despite normal epicardial flow, as indicated by lower 60-minute ratios of myoglobin (2.6 versus 7.6, $P=0.007$), cTnT (6.6 versus 29.2, $P=0.001$), and CK-MB (3.5 versus 21.4, $P=0.002$) and a tendency for less resolution of ST-segment elevations (54% versus 60%, $P=0.08$).

Conclusions—cTnT predicts poorer clinical outcomes, lower rates of postprocedural TIMI 3 flow, and more severely compromised myocardial perfusion despite normal epicardial flow. Thus, a cTnT-positive patient may require more aggressive adjunctive therapy when treated by percutaneous coronary intervention. The impact of preexisting or evolving microvascular dysfunction and the effect of therapies that target myocardial perfusion require further prospective evaluation. (Circulation. 2001;104:630-635.)

Key Words: microcirculation ■ reperfusion ■ myocardial infarction ■ angioplasty ■ prognosis

After thrombolytic therapy or direct percutaneous coronary interventions (PCI) in ST-segment elevation myocardial infarction, nearly one fourth of all patients retain an impaired microvascular perfusion despite restoration of normal flow in the epicardial infarct-related artery.1 Several studies have clearly demonstrated that microvascular dysfunction is associated with more severely impaired regional and global left ventricular (LV) function and higher mortality rates.2–4 Therefore, the goal of reperfusion therapy should be not only restoration of epicardial flow but also myocardial perfusion. Diagnostic tests for identification of microvascular dysfunction, such as coronary Doppler flow wire, myocardial contrast echocardiography, MRI, and $^{99m}$Tc sestamibi single photon emission CT, however, are still investigational and not widely available.5

Recently, several clinical studies found that elevated troponins on admission predicted worse short- and long-term prognosis and higher rates of failed thrombolytic therapy or primary PCI in patients with ST-segment elevation myocardial infarction.6–10 The exact reason why a positive troponin on admission may be linked to a worse outcome is unsettled but may involve more extensive tissue damage due to longer periods of preinterventional myocardial ischemia, a lower success rate of reperfusion, and microvascular dysfunction. Among other things, the latter may be a result of preexisting microembolization from unstable plaque11 due to microvascular obstruction from downstream embolization of fragmented thrombus during pharmacological or mechanical thrombus resolution or from endothelial cell swelling.12

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Therefore, the present study sought to evaluate epicardial coronary flow and myocardial perfusion after direct PCI in patients stratified by admission coronary troponin T (cTnT). Epicardial flow was graded by TIMI score, and myocardial perfusion was estimated by measurement of myoglobin, cTnT, and creatine kinase (CK)-MB concentrations before and 60 minutes after PCI, providing a diagnostic tool that previously proved effective for noninvasive estimation of tissue level reperfusion after thrombolytic therapy.14–16

Methods

Study Population

From January 1998 to January 2000, 140 consecutive patients were enrolled. On admission, patients were stratified into cTnT-positive and cTnT-negative on the basis of a rapid qualitative or quantitative bedside assay.17 Inclusion criteria were new significant ST-segment elevations in ≥2 consecutive leads and admission within 12 hours after onset of symptoms. Diagnosis of acute myocardial infarction was confirmed retrospectively by an increase of CK or CK-MB activity twice above normal. To exclude subacute myocardial infarction within the previous 10 to 14 days, we enrolled only patients with ascending limbs of CK-MB mass and cTnT in serial measurements.

Patients underwent coronary angiography 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.13 Coronary stents were implanted in patients with residual diameter stenoses >30% and TIMI flow ≤2 and for large coronary dissections (NHLBI grade D to F). The glycoprotein (GP) IIb/IIIa–receptor antagonist abciximab was given for persistently impaired coronary flow (TIMI flow) 1) despite stenting or in patients with TIMI 3 flow in the presence of large intracoronary thrombi.

On admission, all patients received 500 mg acetylsalicylic acid followed by 100 mg/d and a parenteral heparin bolus of 5000 IU followed by an activated partial thromboplastin time–adjusted infusion rate of 1200 IU/h. After removal of the arterial sheath, low-molecular-weight heparin (120 IU dalteparin twice daily) was started for 48 hours and switched to 70 IU/d for ≥5 days. Patients who required a coronary stent received 300 mg clopidogrel followed by 75 mg/d for 4 weeks.

Patients were followed up prospectively for a mean of 274 days by use of hospital records, questionnaire, and telephone contact. The end points were cardiac death and a combined end point comprising cardiac death, nonfatal reinfarction, or target vessel reintervention (PCI, CABG).

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

Serum Marker Analyses

For early risk stratification, cTnT levels were measured with a qualitative or quantitative rapid bedside assay (Trop T, Roche Diagnostics). For assessment of myocardial perfusion, cTnT was measured quantitatively with a 1-step electroimmunoassay based on electrochemiluminescence technology (Elecsys 2010, Roche). The lower detection limit of this assay is 0.01 μg/L, with a recommended diagnostic threshold of 0.1 μg/L. CK-MB mass (CK-MB STAT, Roche) and myoglobin (Myoglobin STAT, Roche) concentrations were analyzed with the Elecsys 2010 system. The lower detection limit is 0.1 μg/L for CK-MB and 15 μg/L for myoglobin.

C-reactive protein concentrations were measured on admission and serially every 24 hours to determine peak concentrations.

For evaluation of release kinetics, cTnT, CK-MB mass, and myoglobin concentrations were measured after placement of the sheath into the femoral artery and 60 minutes after recanalization of the infarct-related artery.

Derivatives of the release curve of cardiac markers were calculated as follows: T0, concentration obtained 60 minutes after recanalization; 60-minute ratio, concentration at 60 minutes (T60) divided by concentration (T0) just before recanalization (T0/T60); 60-minute ratio, subtraction of the concentrations before and 60 minutes after recanalization subdivided by 60, (T0−T60)/60, and expressed as μg · L−1 · min−1.

ST-Segment Resolution

For assessment of ST-segment resolution, serial 12-lead ECG recordings just before PCI and immediately on return to the intensive care unit were analyzed by an observer blinded to the clinical data. Patients with bundle-branch block, pacemaker rhythm, or incomplete or poorly interpretable ECG recordings were excluded. The ST segment in the lead showing maximal deviation was measured 60 ms after the J point. The reduction of the ST segment was expressed in absolute values (millimeters) or as relative reductions from baseline expressed as percent resolution.

Statistical Analysis

All data analyses were performed with the Statistical Package for Social Sciences (SPSS for Windows 8.0, SPSS Inc) 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 χ2 or Fisher’s exact test. Among related variables, those with the greatest univariate risk were selected for multivariate modeling. Statistical assessment was performed by use of the log-rank test with P<0.05.

Results

Baseline Characteristics

The clinical characteristics of the entire study group stratified by cTnT are displayed in Table 1. Groups compared favorably with respect to most demographic variables except for prevalence of male sex (P=0.01) and diabetes mellitus (P=0.04). Median time intervals from onset of symptoms to reperfusion therapy were significantly longer (5.5 versus 3.5 hours, P<0.001) in cTnT-positive than in cTnT-negative patients. The distribution of patients with a positive or negative cTnT result on admission according to time intervals from onset of symptoms to admission is displayed in the Figure. Peak levels of C-reactive protein were significantly higher (P=0.002). Peak CK-MB tended to be higher (P=0.08), whereas LV ejection fractions tended to be lower, in cTnT-positive patients (P=0.09).

Clinical Outcome

The outcomes stratified by admission cTnT at 30 days and after a mean of 274 days are presented in Table 2.

At 30 days, rates of all-cause mortality were significantly higher (15.6% versus 3.9%, P=0.02) and rates of cardiac mortality tended to be higher (12.5% versus 3.9%, P=0.06) in cTnT-positive than in cTnT-negative patients. Rates of the combined end point and of either component were not significantly different.

At 9 months, all-cause and cardiac mortality rates were significantly higher in cTnT-positive versus cTnT-negative patients (18.8% versus 3.9%, P=0.05, and 14% versus 3.9%, P=0.03, respectively). Rates of total vascular resistance with CABG were significantly higher (14% versus 3.9%, P=0.03), whereas rates of target vessel revascularization with PCI tended to be lower (5% versus 13.2%, P=0.09), in cTnT-positive than in cTnT-negative patients. Rates of the combined end point and rates of nonfatal reinfarction were statistically not different between the 2 groups.
Epicardial Coronary Flow

In 118 patients (84.3%), primary PCI successfully restored epicardial TIMI 3 flow in combination with a residual diameter stenosis of <30%. In 22 patients, restoration of normal epicardial flow failed. A total of 108 patients (77%) received coronary stents and 49 patients (35%) the GP IIb/IIIa antagonist abciximab.

Epicardial flow remained more frequently compromised (TIMI flow <3) in cTnT-positive than in cTnT-negative patients (25% versus 7.9%; OR [95% CI] 3.89 [1.42 to 10.6], P=0.009).

Failed reperfusion was associated with higher rates of evolving cardiogenic shock (35.3% versus 7.6%, OR [95% CI] 6.7 [1.98 to 22.2], P=0.004), all-cause mortality (35.3% versus 6.8%, 7.5 [2.2 to 25.64], P<0.001), and cardiac mortality (35.3% versus 4.2%, 12.3 [3.2 to 47.6], P<0.001).

In multivariate analysis, cTnT was the most powerful predictor of reperfusion success and was superior to time intervals from onset of symptoms to reperfusion therapy (Table 3).

Given the poorer angiographic success, the proportion of patients treated with GP IIb/IIIa antagonists tended to be higher (44% versus 28%, P=0.052) in cTnT-positive than cTnT-negative patients, whereas rates of coronary stenting were comparable (75% versus 79%).

Myocardial Perfusion

Tissue perfusion was analyzed in 118 patients with normal epicardial flow and residual diameter stenosis of <30%. Of these, 48 patients (40.7%) were cTnT-positive and 70 (59.3%) cTnT-negative patients.

Ratios and slopes of all cardiac markers were significantly lower in cTnT-positive patients, suggesting impaired myocardial reperfusion (Table 4).

Interpretable ECGs for ST-segment analysis were available in 104 patients. Twelve-lead ECGs were obtained immediately before coronary angiography and on return of the patient to the intensive care unit, a median of 144 minutes (interquartile range 117 to 173 minutes) after the initial ECG.
Absolute reduction of ST segments and number of patients with >50% or 70% resolution of ST segments was comparable in cTnT groups. Only the relative ST-segment resolution tended to be higher (P<0.08) in cTnT-negative patients, suggesting less impaired myocardial perfusion (Table 4).

**Discussion**

We investigated the value of cTnT for prediction of outcomes and epicardial and myocardial reperfusion after direct PCI. Measurement of cardiac markers is an established method for noninvasive estimation of reperfusion success after thrombolytic therapy.14 Because a rapid release of soluble cardiac markers indicates myocardial reperfusion at the tissue level, we used this technique, which has not been tested previously in patients undergoing direct PCI.

**Implications of Admission cTnT for Prognosis and Restoration of Normal Epicardial Flow**

Previous studies have unequivocally demonstrated that a positive cTnT on admission carries an increased risk for major cardiac events and death.6–10 For unknown reasons, thrombolytic therapy and direct PCI were less effective in cTnT-positive patients.7,9,10,18 It was speculated that the hazard associated with cTnT was due to more severe ischemic damage, less myocardial salvage, impaired microvascular perfusion, refractory thrombi, or a more thrombophilic milieu. In fact, benefits of thrombolytic therapy have not been observed beyond 12 hours after onset of infarction.19,20 The propensity for incomplete reperfusion or angiographic no-reflow after direct PCI is inversely related to the duration of ischemia.21 Our data consistently confirm that longer durations of ischemia, as also indirectly indicated by elevated blood levels of cTnT on admission, are associated with higher failure rates of mechanical reperfusion and higher rates of microvascular malperfusion. As a consequence, cTnT-positive patients may sustain larger infarcts, as suggested by higher peak levels of C-reactive protein and a tendency for higher peak CK-MB levels and lower LV ejection fractions. It is intriguing to speculate that cTnT may represent a more reliable marker of duration of ischemia than the subjective report of duration of pain. The accuracy of the latter is limited by different thresholds of pain perception, episodes of spontaneous reflow and occlusion, the alleviation of ischemia by collateral blood flow, and ischemic preconditioning. Because

### TABLE 2.  Patient Outcomes

<table>
<thead>
<tr>
<th></th>
<th>cTnT-Positive (n=64)</th>
<th>cTnT-Negative (n=76)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>30 Days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>10 (15.6)</td>
<td>3 (3.9)</td>
<td>4.5 (1.1–17.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>8 (12.5)</td>
<td>3 (3.9)</td>
<td>3.5 (0.9–13.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Nonfatal reinfarction</td>
<td>...</td>
<td>1 (1.3)</td>
<td>...</td>
<td>0.4</td>
</tr>
<tr>
<td>Total vascular resistance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>5 (7.8)</td>
<td>2 (2.6)</td>
<td>3.1 (0.6–16.7)</td>
<td>0.2</td>
</tr>
<tr>
<td>PCI</td>
<td>1 (1.6)</td>
<td>4 (5.2)</td>
<td>0.3 (0.03–2.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>Combined end point</td>
<td>13 (20.3)</td>
<td>9 (11.8)</td>
<td>1.9 (0.7–4.8)</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Long-term</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>12 (18.8)</td>
<td>3 (3.9)</td>
<td>5.6 (1.5–20.9)</td>
<td>0.005</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>9 (14)</td>
<td>3 (3.9)</td>
<td>3.9 (1.03–15.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Nonfatal reinfarction</td>
<td>1 (1.6)</td>
<td>5 (6.5)</td>
<td>0.2 (0.03–1.9)</td>
<td>0.2</td>
</tr>
<tr>
<td>Target vessel revascularization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>9 (14)</td>
<td>3 (3.9)</td>
<td>3.9 (1.03–15.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>PCI</td>
<td>3 (5)</td>
<td>10 (13.2)</td>
<td>0.3 (0.09–1.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Combined end point</td>
<td>22 (34)</td>
<td>18 (23.7)</td>
<td>1.7 (0.8–3.5)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Values given as absolute counts with relative frequencies in parentheses.

### TABLE 3.  Multivariate Analysis on Clinical Predictors for Postprocedural TIMI Flow <3

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SEM</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&gt;70 vs &lt;70 y)</td>
<td>0.51</td>
<td>0.56</td>
<td>1.67</td>
<td>0.56–4.97</td>
<td>0.36</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>0.48</td>
<td>0.54</td>
<td>1.61</td>
<td>0.56–4.62</td>
<td>0.37</td>
</tr>
<tr>
<td>Cardiogenic shock on admission (yes/no)</td>
<td>0.069</td>
<td>1.25</td>
<td>1.07</td>
<td>0.09–12.33</td>
<td>0.96</td>
</tr>
<tr>
<td>Anterior vs nonanterior infarct</td>
<td>0.67</td>
<td>0.53</td>
<td>1.95</td>
<td>0.69–5.5</td>
<td>0.2</td>
</tr>
<tr>
<td>cTnT (&gt;0.1 vs ≤0.1 μg/L)</td>
<td>1.17</td>
<td>0.57</td>
<td>3.2</td>
<td>1.05–9.83</td>
<td>0.04</td>
</tr>
<tr>
<td>Time to admission (ROC cutoff 5.0 h)</td>
<td>0.36</td>
<td>0.53</td>
<td>1.43</td>
<td>0.5–4.0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

ROC indicates receiver operating characteristic curve.
pain perception and pain thresholds are altered in diabetes mellitus, it is not surprising that in our study, diabetic patients presented later and already had elevated cTnT.

Microvascular Perfusion

Different methods for assessment of microvascular perfusion are currently being investigated. In our study, microvascular perfusion was assessed by means of ST-segment resolution on serial ECG and by measurement of early marker increases. Analysis of ST segments is established for noninvasive estimation of reperfusion success after thrombolytic therapy but is less well documented after PCI. Recent evidence suggests that the degree of ST-segment resolution after thrombolytic therapy correlates not only with epicardial vessel patency but also with microvascular perfusion as assessed by myocardial contrast echocardiography. In our study, behavior of ST segments after angiographically successful PCI was heterogeneous, ranging from complete normalization of ST segments to further increase of ST segments (data not shown).

Reperfusion of the infarct-related artery with thrombolytic agents caused a rapid, marked washout into the blood, and several variables, including relative increases of marker concentrations, are used for prediction of vascular patency. The usefulness of 60-minute ratios and slopes of myoglobin, CK-MB, and cTnT has been documented in previous studies confirming epicardial patency angiographically.

Clinical Implications

Our study shows that an elevated cTnT identifies patients at risk for subsequent death. This may be a result of incomplete restoration of epicardial flow despite early primary PCI. Second, even when normal epicardial flow was obtained, these patients disclosed microcirculatory malperfusion. Previous studies suggest that microvascular dysfunction affects outcomes even after successful reperfusion of the epicardial arteries. In clinical practice, however, assessment of microvascular dysfunction is frequently retrospective, and available techniques are difficult to apply. Thus, the cTnT status on admission may aid in the selection of patients in whom adjunctive therapies that are targeted to improve epicardial and microvascular flow, such as coronary stenting or GP IIb/IIIa antagonists, are warranted.

| TABLE 4. Cardiac Markers and ST-Segment Resolution in Patients With Postprocedural TIMI 3 Flow |
|---------------------------------------------------------------|-------------------------------|-------------------|-----------------|-----------------
|                  | cTnT-Positive (n=48) | cTnT-Negative (n=70) | OR (95% CI) | P     |
| CK-MB on admission, IU/L | 15 (8; 32) | 7 (6; 11) | ... | <0.001 |
| CK-MB peak, IU/L | 132.5 (63; 240) | 99.5 (56; 162.5) | ... | 0.03  |
| cTnT before reperfusion, µg/L | 0.4 (0.14; 1.35) | 0.03 (0.01; 0.1) | ... | <0.001 |
| CK-MB before reperfusion, µg/L | 30.8 (10.5; 111.8) | 4.3 (2.6; 11.2) | ... | <0.001 |
| Myoglobin before reperfusion, µg/L | 470 (178; 988) | 139 (60; 449) | ... | <0.001 |

Values given as medians with interquartile range in parentheses unless indicated otherwise.
Limitations

Our study is underpowered to fully exclude sample size error or unforeseen bias. Our observations on the prognostic role of cTnT and its value to predict success of reperfusion therapies, however, are supported by several large-scale clinical trials. 7.9, 10, 18

Enrollment of an unselected cohort of patients with acute myocardial infarction may explain the lower patency rates observed in this study compared with randomized clinical trials. Moreover, patients were not randomized to receive adjunctive therapies, such as coronary stents or GP IIb/IIIa receptor antagonists. A confounding effect of coronary stenting is unlikely, however, because the vast majority received coronary stents. In ST-segment elevation myocardial infarction, GP IIb/IIIa receptor antagonists are known to improve epicardial and microvascular flow 29 and to reduce rates of major cardiac events. 30, 31 In our study, however, a confounding effect seems unlikely, because GP IIb/IIIa antagonists were given only to patients with suboptimal angiographic results and compromised epicardial flow. Analysis of myocardial perfusion by relative increases of cardiac markers, however, was restricted to patients with successful restoration of normal epicardial flow.

References


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