Elevated Troponin I Level on Admission Is Associated With Adverse Outcome of Primary Angioplasty in Acute Myocardial Infarction

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Background—In patients with acute myocardial infarction (AMI) undergoing thrombolytic therapy, an elevated troponin level on admission is associated with a lower reperfusion rate and a complicated clinical course. Whether an elevated troponin level on admission similarly predicts an adverse outcome in patients undergoing primary angioplasty is currently unknown and was investigated in the present study.

Methods and Results—Cardiac troponin I (cTnI) was determined on admission in 110 consecutive patients with AMI associated with ST-segment elevation or left bundle branch block who underwent primary angioplasty. Fifty-four patients (49%) had an elevated cTnI (>0.4 ng/mL) on admission. In patients with elevated cTnI, primary angioplasty was less likely to achieve TIMI 3 flow (as classified by the Thrombolysis in Myocardial Infarction trial) in univariate (76% versus 96%, P=0.03) or in multivariate (odds ratio 0.1, 95% CI 0.02 to 0.54) analysis. Patients with elevated cTnI were more likely to develop congestive heart failure (23% versus 9%, P<0.05) and death, heart failure, or shock (30% versus 9%, P=0.006). Elevated cTnI remained a significant predictor of the composite end point after controlling for other clinical data that were available early in the course, including time to presentation and angiographic results (relative risk 5.2, 95% CI 1.03 to 26.3). During a follow-up of 426±50 days, elevated admission cTnI was a predictor of cardiac mortality (11% versus 0%, P=0.012), adverse cardiac events (cardiac mortality or nonfatal reinfarction; 19% versus 5.4%, P=0.04), and adverse cardiac events plus target vessel revascularization (32% versus 14%, P=0.054).

Conclusions—In patients with ST-segment elevation AMI, an elevated cTnI on admission is associated with an increased risk of primary angioplasty failure and a more complicated clinical course. (Circulation. 2000;102:1611-1616.)

Key Words: angioplasty n myocardial infarction n reperfusion n proteins

Plasma levels of cardiac troponin (cTn) provide important prognostic information that is useful for the risk stratification of patients with acute coronary syndromes.1−15 In patients with acute myocardial infarction (AMI), elevated levels of cTnI on admission predict a higher incidence of congestive heart failure (CHF), shock, and death.3,5,10,15 Although primary angioplasty has been suggested to be the preferred reperfusion strategy in AMI patients with elevated cTnI,5,15 the prognostic value of early cTn assessment in these patients has not been reported. In the present study, we examined the prognostic value of an elevated cTnI on admission in patients with ST-elevation AMI undergoing primary angioplasty.

Methods

Study Population

The study population consisted of 110 consecutive patients with AMI associated with ST-segment elevation or left bundle branch block (LBBB) who were treated with primary angioplasty at Cedars-Sinai Medical Center from June 1, 1997, to December 31, 1998. Blood was sampled for cTnI routinely on admission in each patient who presented with clinical manifestations consistent with acute coronary syndrome. The diagnosis of AMI was based on the presence of ischemic chest pain of >30-minute duration and ST-segment elevation of at least 1 mm in ≥2 contiguous ECG leads or LBBB. Patients were referred for primary angioplasty if they had been admitted within 12 hours of the onset of symptoms with evidence of ongoing ischemia (persistent pain with ST-segment elevation or LBBB). Myocardial necrosis was confirmed by an increase in cTnI.

cTnI Determination

Venous blood for cTnI levels was collected in EDTA-coated tubes immediately after the patient arrived at the emergency department (admission cTnI). Two-sided immunoassay with 2 monoclonal antibodies specific for the cardiac isotype of cTnI was used (Dade Behring). The minimal detection concentration of this assay is <0.35 ng/mL, which is higher than the 97th percentile of the distribution of cTnI levels in the healthy population. As per hospital protocol, the second cTnI level was determined 12 hours later.
Coronary Angiography and Angioplasty

Coronary angiography followed by primary angioplasty was performed with standard techniques. Adjunctive therapy, intra-aortic balloon counterpulsation, and temporary pacing were used as indicated. After the procedure, all patients were treated with aspirin (325 mg/d). Patients that received an intracoronary stent were also treated with ticlopidine (250 mg BID) or clopidogrel (75 mg/d) for 4 weeks. The angiograms were reviewed by 2 expert observers who did not perform the angioplasty and were blinded to clinical and laboratory data. The initial and final flow in the infarct-related artery (IRA) was assessed according to the classification of the Thrombolysis in Myocardial Infarction (TIMI) trial.16 Collateral flow to the IRA was assessed as previously reported.17 Significant stenosis of the coronary artery was defined as narrowing in excess of 50% compared with the uninvolved segment of the artery. The angioplasty was defined as successful with the establishment of TIMI 3 flow and residual stenosis of <30%.

Clinical Follow-Up

In-Hospital Follow-Up

The patients were followed up during the hospital stay for a prespecified combined end point composed of 3 adverse events related to the extent of myocardial damage: CHF, shock, and/or death after the initial angiography. A standard 2D echo-Doppler study was performed before hospital discharge, and the left ventricular ejection fraction (LVEF) was determined by using Simpson’s biplane method.

Long-Term Follow-Up

Patients were followed for 426 ± 50 days. Information was obtained by telephone questionnaire, review of hospital and primary physician records, and death certificates. Complete follow-up data were obtained in all patients. The data were analyzed for the following end points: cardiac mortality, cardiac events (cardiac mortality and nonfatal reinfarction), cardiac event, and target-vessel revascularization.

Statistical Analysis

Comparisons between groups were performed by using t tests for continuous variables and χ² tests or Fisher exact tests for categorical variables. Stepwise multivariate logistic regression was applied to identify independent predictors of primary angioplasty success and the occurrence of the prespecified end point of death, CHF, and shock during hospital stay. Stepwise multivariate hazard Cox regression was used to identify the independent predictors of the occurrence of cardiac events during the follow-up period. Kaplan-Meier curves for event-free survival according to admission cTnI were compared with log-rank statistics.

Results

Of the 110 consecutive patients included in the present study, admission cTnI level was elevated (≥0.4 ng/mL) in 54 patients (49%), with a value of 17 ± 54 (range 0.4 to 313) ng/mL. In the other 56 patients (51%), the cTnI level on admission was within the normal range (<0.4 ng/mL), with a value of 0.13 ± 0.07 ng/mL. All patients underwent angioplasty, except for 1 patient with elevated cTnI who underwent emergency CABG for severe 3-vessel coronary artery disease (CAD).

As shown in Table 1, there were no significant differences in the baseline characteristics and clinical features at presentation before the primary angioplasty between patients with elevated cTnI and those with normal cTnI on admission.

Time to Presentation and cTnI Levels

There was no correlation between the time from the onset of symptoms to presentation and the admission cTnI level. The mean time to presentation was 212 ± 186 minutes for patients with elevated cTnI and 179 ± 171 minutes for patients with normal cTnI on admission (P = 0.38). The proportion of patients with elevated cTnI among patients who were admitted within 2, 4, 6 or >6 hours after the onset of symptoms was 39%, 41%, 64%, and 59%, respectively (P for trend 0.4).

In linear regression analysis, there was no correlation between the time from the onset of symptoms and the admission cTnI levels, either in the entire study population or among the patients with elevated cTnI on admission ($r^2=0.005, P=1$).

Coronary Angiography and Angioplasty Results

The distribution of IRA and the proportion of patients with 3-vessel CAD were similar in both groups. The proportion of
TABLE 2. Angiographic Findings

<table>
<thead>
<tr>
<th>IRA, n (%)</th>
<th>Elevated cTnI (n=54)</th>
<th>Normal cTnI (n=56)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>23 (42)</td>
<td>20 (36)</td>
<td></td>
</tr>
<tr>
<td>LCX</td>
<td>7 (13)</td>
<td>9 (16)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>22 (41)</td>
<td>26 (46)</td>
<td>0.7</td>
</tr>
<tr>
<td>SVG</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>3-Vessel CAD, n (%)</td>
<td>20 (38)</td>
<td>16 (29)</td>
<td>0.34</td>
</tr>
<tr>
<td>IRA TIMI flow 2–3 (on initial angiogram), n (%)</td>
<td>20 (38)</td>
<td>17 (31)</td>
<td>0.41</td>
</tr>
<tr>
<td>Collateral flow</td>
<td>0.6±1.1</td>
<td>0.22±0.6</td>
<td>0.04</td>
</tr>
<tr>
<td>Stenting, n (%)</td>
<td>29 (55)</td>
<td>37 (66)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; and SVG, saphenous vein graft.

patients with TIMI 2 or TIMI 3 flow in the IRA on the initial angiogram was also similar (Table 2).

Of the 56 patients with normal cTnI on admission, primary angioplasty was successful in 54 (96%). Two patients had TIMI 2 flow despite successful dilatation of the culprit lesion. In contrast, in patients with an elevated cTnI on admission, angioplasty was successful in only 40 patients (76%) (P=0.003 compared with patients with normal cTnI, Figure 1). The failure of angioplasty was due to the inability to cross the culprit lesion in 5 patients (9%), and in 8 patients (15%), the postangioplasty TIMI flow was ≤2 despite the successful dilatation of the culprit lesion. There were no significant differences between the 2 study groups in the use of platelet glycoprotein IIb/IIIa inhibitors (79% versus 89%, P=0.19).

By multivariate analysis, the cTnI level on admission was an independent predictor of the success of the primary angioplasty after controlling for age, sex, risk factors for CAD, and clinical features on admission, including time to presentation, initial angiographic findings, and use of adjunctive therapy during the procedure. The final model for prediction of angioplasty success included elevated cTnI on admission (relative risk [RR] 0.10, 95% CI 0.02 to 0.54), the LAD as the IRA (RR 0.18, 95% CI 0.04 to 0.73), and TIMI flow before angioplasty (RR 2.5, 95% CI 1.1 to 5.7). This model had a global $\chi^2$ value of 14, with $P=0.0009$.

Indices of Myocardial Damage

Despite the similar extent of ST-segment elevation on admission ECG in the 2 groups of patients (number of leads with ST elevation 2.5±2.7 versus 3.2±2.3, P=0.11), Q-wave MI pattern on predischarge ECG tended to be more common in patients with elevated cTnI compared with patients with normal cTnI (47% versus 30%, $P=0.09$). The predischarge LVEF was significantly lower in patients with elevated admission cTnI (46±10% versus 51±11%, $P=0.04$).

In-Hospital Clinical Course

Patients with elevated cTnI on admission had a significantly higher incidence of CHF (22% versus 9%, $P<0.05$) and a significantly higher incidence of the combined end point of CHF, shock, and/or death (30% versus 9%, $P=0.006$). All 3 patients who died during the initial hospital stay had elevated admission cTnI (Table 3).

Elevated cTnI on admission was an independent predictor of the combined end point (RR 5.2, 95% CI 1.03 to 26.26) even after adjustments for demographic and clinical characteristics (Table 1), angiographic findings (Table 2), and success of angioplasty. The other independent predictors of the composite end point were Killip class (RR 12.6, 95% CI 3.4 to 46.6) and angiographic success of angioplasty (RR 0.12, 95% CI 0.02 to 0.62). When only the 94 patients with successful angioplasty were analyzed, elevated cTnI on admission was still associated with a greater incidence of CHF, shock, and/or death during the hospital stay (22% versus 6%, $P=0.026$). Failed angioplasty was associated with worse overall prognosis, with 53% incidence of CHF, shock, and/or death. Six of the 13 patients with failed angioplasty and elevated cTnI had an adverse event, and 2 died. The 2 patients with failed angioplasty and normal admission cTnI had adverse events, but none of them died.

Long-Term Follow-Up

During a mean follow-up of 426±50 days, patients with elevated admission cTnI had a significantly higher incidence

![Figure 1. Comparison of primary angioplasty success rate, defined as achievement of TIMI grade 3 flow with residual stenosis <30%, according to admission cTnI level.](http://circ.ahajournals.org/doi/10.1161/CIRCULATIONAHA.117.032701)
of cardiac mortality and of cardiac events (Table 3, Figure 2). The Kaplan-Meier curves for event-free survival in the 2 groups were statistically different (Figure 3, $P < 0.04$ by log-rank statistics). The 2 curves diverged early and were separated further over the first few months. Admission cTnI elevation remained a significant predictor of the occurrence of cardiac events after adjustment for differences in age, sex, risk factors for CAD, angiographic extent of CAD, success of primary angioplasty, and time to presentation in stepwise Cox regression analysis. Only the cTnI level on admission (OR 3.57, 95% CI 0.99 to 13.0) and age (OR 1.05 95% CI 1.0 to 1.09) were independent predictors of the occurrence of cardiac events.

cTnI Threshold

To determine the best discriminant level in predicting primary angioplasty success and in-hospital course, we examined the OR and $\chi^2$ values of different admission cTnI discriminant levels (0.2, 0.4, 0.6, 1.0, 1.5, and 3.0 $\mu$g/mL). Any elevation of cTnI on admission was associated with a lower success rate for primary angioplasty and a more complicated in-hospital course. However, a cutoff point of 0.4 $\mu$g/mL gained the highest $\chi^2$ value (9.87) and OR (9.45) for primary angioplasty success as well as for the occurrence of CHF, shock, and/or death ($\chi^2$ 7.9, OR 4.3).

Discussion

The present study demonstrated that in patients with AMI who present with ST-segment elevation or LBBB, an elevated cTnI level at admission is associated with a lower success rate for primary angioplasty, a higher risk for in-hospital death, CHF, or shock, and higher long-term cardiac mortality and nonfatal reinfarction.

Admission cTn and Duration of Symptoms

In the present study, no correlation was found between the duration of the pain and the cTnI levels on admission. In multivariate analysis, the time to presentation did not provide incremental prognostic information over admission cTnI. These findings are in agreement with the results of the troponin substudy of the Global Utilization of Streptokinase and TPA for Occluded Arteries (GUSTO) IIa trial, in which 58% of the patients presented with ST elevation. On the other hand, in a larger study of patients with ST elevation, Ohman et al found a significant correlation between symptom duration and the likelihood of a positive qualitative cTnT test on admission. This difference may be due to the larger patient population that was enrolled within 6 hours of symptoms in the later study as well as the use of a different assay for troponin. Furthermore, 30% of the patients in that study who had a positive troponin test were admitted within the first 2 hours of symptoms, and the relation between 30-day mortality and pain duration was much stronger in those with negative cTnT on admission. Hamm et al reported a shorter duration of pain (3.1 hours, on average, compared with 5.4 hours after the beginning of chest pain) in patients with negative compared with positive cTn tests. However, in their study, only half of the patients with elevated cTn levels had elevated levels at admission; the other half had elevated levels at ≥4 hours after arrival. These findings suggest that admission cTn levels correlate poorly with the duration of symptoms. Symptoms are only a crude marker of the onset of ischemia, and elevated cTn levels may reflect more accurately the extent and duration of the myocardial ischemia.

Success of Reperfusion Therapy

In a study by Stubbs et al, noninvasive signs of reperfusion were noted after thrombolytic therapy in 50% of patients with elevated admission cTnT compared with 72% of patients with normal admission cTnT. In the TIMI 10B study, admission cTnI levels were significantly lower in the patients that achieved TIMI 3 flow in the 60-minute angiogram after thrombolytic therapy, and in a study by Stewart et al, these levels were lower in patients that achieved TIMI 3 flow in the 90-minute angiogram.

The present study extends this observation to patients treated with primary angioplasty. Elevated cTnI levels were an independent predictor of the lower success rate of primary angioplasty. These results are particularly striking in light of the high utilization of platelet glycoprotein IIb/IIIa inhibitors.
and stents in patients with and without elevated cTnI. The lower rate of successful reperfusion in patients with elevated admission cTnI was primarily due to slow blood flow (TIMI flow <3) in the IRA in spite of successful dilatation of the culprit lesion. This angiographic finding is the hallmark of the “no-reflow” phenomenon and is associated with extensive microvascular damage within the jeopardized myocardium. As previously suggested, elevated cTnI on admission appears to be an independent marker of an early and extensive myocardial damage that is associated with extensive microvascular damage.

**Admission cTn Levels and Prognosis**

Recent reports suggest that in patients with acute coronary syndrome, the cTn level on admission is an independent predictor of death or AMI. In a prospective analysis of 855 patients with unstable angina or AMI who presented within 12 hours of the onset of symptoms enrolled in the GUSTO IIa study, elevated cTnT on admission was associated with a 3-fold higher 30-day mortality. The predictive value of elevated cTnT remained strong even after adjustment for ECG changes and creatine kinase MB levels. Similar were the findings from retrospective analysis of 2 large trials, TIMI IIIB and the Fragmin During Instability in Coronary Artery Disease (FRISC) study.

Fewer data regarding the prognostic value of admission troponin levels in patients with ST-elevation AMI exist, and there are no data regarding the prognostic significance in patients treated with primary angioplasty. In the study by Stubbs et al., the differences in early mortality (11% versus 4%) were not statistically significant ($P=0.11$) in patients with elevated compared with normal admission cTnT levels, respectively. The differences, however, were significant at the 1- and 3-year follow-ups. In the GUSTO IIa trial, patients with ST-elevation AMI and elevated levels of cTnT on admission compared with patients with normal levels had higher rates of death in a 30-day follow-up (13% versus 4.7%). Recently, in the 1266 patients treated with thrombolytic therapy in the GUSTO III trial, elevated cTnT on admission was shown to be an independent predictor of a higher 30-day mortality.

In the present study, the more extensive damage in patients with elevated cTnT at admission was reflected in the higher incidence of CHF, shock, in-hospital death, and a decreased predischARGE LVEF. In the analysis of the GUSTO IIa study, the findings were similar; the incidence of shock was 7%, and CHF was 13% in patients with elevated cTnT on admission, but these values were only 1% and 6%, respectively, in patients with normal admission cTnT. Similarly, the GUSTO III patients with elevated cTnT had a higher incidence of CHF and of cardiogenic shock despite the administration of thrombolytic therapy.

The follow-up in the present study demonstrated that elevated cTnI was also a strong independent predictor of higher long-term cardiac death and nonfatal reinfarction. The higher failure rate of the primary angioplasty in patients with elevated cTnI contributed to the worse early and late outcomes. However, cTnI elevation remained a significant predictor of the clinical outcomes even after controlling for the differences in the angioplasty results.

**Discriminant cTnI Level**

The predictive value of admission cTnI was strongest with the discriminant level of cTnI, 0.4 ng/mL. In a previous study, a discriminant level of $\geq 0.2$ ng/mL cTnT was found to have higher $\chi^2$ values compared with a borderline elevated cTnT level of 0.1 ng/mL. However, further increase of the threshold beyond this level compromises the negative prognostic value of the test for predicting reperfusion therapy success and clinical outcome in patients with evolving AMI. These data suggest that most of the information derived from early cTnI levels can be obtained by the use of bedside kits in patients with AMI, as recently demonstrated with a kit for cTnT.

**Study Limitations**

We recognized several limitations of the present study. The relatively small number of patients included in the study mandates caution in the interpretation of the results, especially because this is the first study that addressed the prognostic value of troponin levels in patients undergoing primary angioplasty. The present study reports the experience of a single center in which primary angioplasty is the principal reperfusion strategy. Therefore, the results may not be reproduced in other settings. In the present study, we used cTnI as determined by quantitative method. Our conclusions should not be extended to cTnT or other methods of troponin determination without further validation.

**Conclusions**

An elevated cTnI level ($>0.4$ ng/mL) in patients admitted with chest pain and ST-segment elevation identifies a subgroup of patients with lower success of primary angioplasty and worse short- and long-term prognosis.

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