Timing of Peak Troponin T and Creatine Kinase-MB Elevations After Percutaneous Coronary Intervention*

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Study objective: The prognostic significance of elevations in creatine kinase-MB and troponin T (cTnT), which have been conventionally measured 6 to 8 h after percutaneous coronary intervention (PCI), has been established. However, the time to peak biomarker appearance in the circulation has not been defined and is the purpose of this pilot study.

Design: Nonrandomized, nonconsecutive patient cohort.

Setting: Clinical practice, Mayo Clinic, Rochester, MN.

Patients: Cohort (n = 57) undergoing elective PCI.

Interventions: cTnT and creatine kinase (CK)-MB measured at baseline, 2 h, 4 h, 8 h, and ≥ 12 h (mean ± SEM, 18 ± 5 h) after PCI.

Measurements and results: Postprocedure cTnT elevations were detected in 30 of 57 patients (53%). Of these, 4 of 30 patients (13%) had peak cTnT at 4 h (0.80 ± 0.40 ng/mL), 5 of 30 patients (17%) had peak cTnT at 8 h (1.07 ± 0.48 ng/mL), and 21 of 30 patients (70%) had peak cTnT at ≥ 12 h (0.21 ± 0.06 ng/mL); 22 of 30 patients received abciximab. Elevations in CK-MB occurred in 14 of 57 patients (25%). Of these, 3 of 14 patients (21%) demonstrated peak CK-MB at 2 h (18.5 ± 7.9 ng/mL) and the remainder (11 of 14 patients, 79%) during the 12- to 20-h interval (20.2 ± 4.4 ng/mL); 12 of 14 patients received abciximab.

Conclusion: More cTnT than CK-MB elevations occur after PCI; however, both biomarkers demonstrate a longer time to peak value than anticipated in clinical practice. Early surveillance monitoring (< 12 h) does not detect peak biomarker levels, especially in patients with normal baseline values. If peak levels are to be used to determine prognosis, then longer time intervals should be used for post-PCI surveillance. The timing of peak elevations appears to be influenced by baselines values as well. Early elevations may reflect the conjoint effects of injury associated with the disease process and the intervention itself. These data suggest that a re-evaluation of surveillance monitoring to account for the variability reported and the influence of baseline elevations of biomarkers may improve the prognostic power of the measurements.

Key words: biomarkers; coronary artery disease; creatine kinase-MB; peak values; percutaneous coronary intervention; troponin T

Abbreviations: CK = creatine kinase; cTnT = creatine kinase-MB and troponin T; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty

The prognostic importance of elevations in biomarkers such as total creatine kinase (CK), CK-MB, and troponin T and I after percutaneous coronary intervention (PCI) is well accepted.1–9 The measurement of CK-MB has for years been the mainstay for determining prognosis after PCI. CK-MB and troponin T (cTnT) or CK-MB and troponin I are more sensitive and specific markers of myocardial injury and are now preferred.2,10,11 It has been conventional to monitor serum biomarker levels 6 to 8 h following the completion of coronary interventions, and these values have usually been used to attempt to define prognosis. The implicit assumption has been that by these times peak or near-peak values have been attained. However, the relationship between revascularization procedures...
and the time to biomarker release and appearance in the blood and the time to peak levels has never been rigorously defined. CK-MB or troponin T values generally peak approximately 18 to 24 h after the onset of a myocardial infarction. However, acute reperfusion shortens the time to peak protein concentration in the blood, and increases the absolute peak and the rate of decline in the circulation. Conversely, reduced blood flow may delay the appearance of markers in the blood. Therefore, the timing of surveillance monitoring to detect peak biomarker levels may be critical following procedures where occlusion, reperfusion and, at times, reduced blood flow can occur. The purpose of this pilot study was to measure levels of troponin T and CK-MB at predetermined time intervals following PCI to establish the timing of peak biomarker concentration. By design, the study attempted to include an equal number of patients undergoing complex procedures who received IIb/IIIa inhibitor therapy and uncomplicated procedures where patients did not receive such therapy to capture the broadest range of patients possible.

**Materials and Methods**

Troponin T and CK-MB were measured in a nonrandomized, nonconsecutive cohort of patients (n = 57) during the period of September to November 2000. Patients were referred for elective coronary angiography and PCI with the diagnosis of progressive symptomatic coronary artery disease. Thrombolysis in Myocardial Infarction (TIMI) grade 3 coronary artery blood flow was established in all patients. Troponin T and CK-MB were measured at 2 h, 4 h, 8 h, and 12 to 20 h (mean ± SEM, 17.9 ± 0.46 h) postprocedure.

Abciximab was used in conjunction with the intervention when deemed clinically indicated. The dose was 0.25 mg/kg IV followed by 0.125 μg/kg/min for 12 h after PCI. All patients received aspirin (325 mg) before the intervention, and patients receiving stent implantation received clopidogrel (375 mg) prior to stent placement. Subsequently, peak biomarker levels were determined at each time interval. Any increase in cTnT ≥ 0.03 ng/mL (the value at which the coefficient of variability of the assay is ≤ 10%) and CK-MB ≥ 6.2 ng/mL was defined as a clinically significant elevation. Troponin T assays were performed using highly sensitive and precise third-generation assay (Elecsys; Roche Diagnostics; Indianapolis, IN). The cTnT assay has a coefficient of variability of 10% at a value of 0.035 ng/mL and 20% at 0.015 ng/mL. The limit of detection is ≤ 0.01 ng/mL.

Table 1—Clinical Profile of Patients Undergoing PCI

<table>
<thead>
<tr>
<th>Variables</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>66 ± 10</td>
</tr>
<tr>
<td>Male/female gender, No.</td>
<td>44/13</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13 (23)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>37 (65)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>43 (75)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>22 (38)</td>
</tr>
<tr>
<td>Prior coronary artery bypass graft surgery</td>
<td>17 (30)</td>
</tr>
<tr>
<td>Coronary artery disease severity One-vessel</td>
<td>22 (38)</td>
</tr>
<tr>
<td>Two-vessel</td>
<td>20 (35)</td>
</tr>
<tr>
<td>Three-vessel</td>
<td>15 (26)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>56 ± 12</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SE or No. (%) unless otherwise indicated.

CK-MB was also measured on the Elecsys analyzer. Values are expressed as mean ± SEM, and p values ≤ 0.05 were considered statistically significant. Comparisons between groups were performed using χ² sample t tests. This investigation was approved by the Mayo Foundation Institutional Review Board and included only patients who gave informed consent for research analysis as required by Minnesota Statute 144.335.

Table 2—Clinical Treatment Profile of Patients Undergoing PCI (n = 57)

<table>
<thead>
<tr>
<th>Patients, No.</th>
</tr>
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<tbody>
<tr>
<td>Had troponin elevations at baseline (two of five)</td>
</tr>
<tr>
<td>patients also had CK-MB elevations at baseline</td>
</tr>
<tr>
<td>Stented and received abciximab</td>
</tr>
<tr>
<td>Stent only (no abciximab)</td>
</tr>
<tr>
<td>PTCA only, no stent (one fourth with abciximab)</td>
</tr>
<tr>
<td>Total who received abciximab</td>
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</tbody>
</table>

**Results**

The baseline clinical characteristics of the 57 patients included in the study are shown in Table 1. The procedural treatment profile of patients undergoing PCI is shown in Table 2. Fifty-six percent of these patients received IIb/IIIa inhibitor therapy (abciximab) in association with the procedure, and 39% were stented without IIb/IIIa inhibitor. Four of the 57 patients (7%) were treated with percutaneous transluminal coronary angioplasty (PTCA)-only therapy; of these, 1 patient received abciximab.

Table 3 shows the PCI treatment profile for those patients who demonstrated elevations in cTnT and CK-MB. Twenty-four of 57 patients demonstrated cTnT elevations, with the majority receiving stent placement (92%) and abciximab (75%). Fourteen of...
57 patients demonstrated elevations in CK-MB, with all patients receiving stents and 86% treated with abciximab.

Table 4 shows the timing of peak cTnT and CK-MB elevations after intervention. Postprocedure cTnT elevations were detected in 42% of patients. Of these, no patients demonstrated peak cTnT levels by 2 h after PCI. One of the 24 patients (4%) had peak cTnT elevation at 4 h after PCI (3.14 ng/mL), 3 of 24 patients (12.5%) had peak cTnT at 8 h after PCI (1.73 ± 0.48 ng/mL), and 20 of 24 patients (83%) had peak cTnT at 12 to 20 h (mean, 18 ± 0.5 h) after PCI (0.22 ± 0.06 ng/mL). The differences in cTnT levels late (12 to 20 h) were often substantial (range, 0.02 to 1.14 ng/mL; mean difference, >0.1 ng/mL). The majority (18 of 24 patients) with cTnT elevations were receiving abciximab. Of the 33 patients who underwent PCI without a postprocedure cTnT elevation, only 10 patients received abciximab.

Elevations in CK-MB mass after PCI occurred in only 14 of 57 patients (25%). Of these, 3 of 14 patients (21%) demonstrated peak CK-MB at 2 h after PCI (18.5 ± 7.9 ng/mL), and the remainder during the 12- to 20-h intervals (11 of 14 patients, 79%; 20.2 ± 4.4 ng/mL). No peak CK-MB levels were detected at 4 h or 8 h after PCI. Thirteen of 14 patients with CK-MB elevations also had elevations of cTnT, with 12 of 14 occurring during the 12- to 20-h interval. Similar to the patients with cTnT elevations, the majority (12 of 14 patients) with CK-MB elevations received abciximab. Only 2 of 14 patients underwent stent therapy without adjunctive IIb/IIIa therapy. Of the 43 patients without elevations in CK-MB after PCI, 20 patients (46%) were receiving abciximab.

Five of the 57 patients undergoing PCI had elevations in baseline cTnT levels. In retrospect, it is likely from the cardiac enzyme findings that these patients experienced some degree of cardiac injury in the 72 to 96 h before the procedure. When these baseline elevations are excluded from the study (Table 5), 100% of the cTnT elevations are recorded in the 12- to 20-h interval. Seventy-nine percent of these patients received abciximab. Similarly, 92% of the CK-MB elevations were observed in the 12- to 20-h time interval after PCI, with only one patient demonstrating a peak level at the 2-h interval.

Data were also analyzed for other cut-points for cTnT (≥0.01 ng/mL and ≥0.10 ng/mL) and similar findings were demonstrated when baseline elevations were excluded. Eighty percent and 92% of peak levels for cTnT and CK-MB, respectively, were recorded in the 12- to 20-h interval when cTnT cut-point was ≤0.01 ng/mL, and 100% and 92%, respectively, when the cut-point was ≤0.10 ng/mL.

**Discussion**

The results of our pilot study indicate that the clinical practice convention of surveillance monitoring for elevations in cTnT and CK-MB at 6 to 8 h following elective catheter-based coronary artery interventions will not detect peak elevations in the majority of patients. This may be a reason for the variability in results reported across studies.

As in previous reports, 13–18 myocardial injury was diagnosed in more patients based on cTnT elevations (42% of postprocedural patients) than CK-MB elevations (25% of patients). The majority of elevations of both biomarkers (83% for cTnT; 79% for CK-MB)
were detected late (12 to 20 h following PCI). The absolute magnitude of late cTnT elevations was lower than when peak values were present at 4 h and 8 h (0.80 ng/mL and 1.07 ng/mL, respectively, vs 0.21 ng/mL; p < 0.05). If prognosis is predicted only on peak levels, then the findings of elevations at 4-h and 8-h peaks would suggest a poorer prognosis for those groups than those with later elevations which was the majority of patients. In our study, these earlier elevations occurred in patients with baseline elevations of cTnT. When patients with these baseline elevations are removed from the analysis, all post-PCI cTnT elevations occurred in the 12- to 20-h interval. Since most (79%) of the patients with cTnT elevations in the 12- to 20-h interval, and these occurred at 2 h after the procedure. The majority (12 of 14 patients; 86%) with CK-MB elevations also received abciximab. In the group of patients without evidence of CK-MB elevations (a less complex group), only 46% (20 of 43 patients) were treated with abciximab.

Various formats for serial blood sampling to detect elevations in cardiac biomarkers have been reported in conjunction with clinical trials of periprocedure therapies.\textsuperscript{1,3,5,23–25} These have ranged from immediate through 48 to 72 h, but generally entail serial sampling ranging over the intervals of < 1 h to 4 h, 6 h, 8 h, 12 h, 18 h, and 24 h after the onset of symptoms or postprocedure. No systematic analysis has provided guidelines for optimal monitoring time intervals to capture peak cTnT or CK-MB levels. By convention and also by European Society of Cardiology/American College of Cardiology consensus document recommendation,\textsuperscript{20} the intervals of 6 to 9 h and 24 h after PCI have generally been selected for blood sampling. Recommendations have also been made to obtain routine measurements at baseline and 8 h and 16 h after PCI.\textsuperscript{3} Bertinchant et al\textsuperscript{27} reported a time to median peak cTnT of 21 h following uncomplicated PTCA. The findings of our study and the data from Bertinchant et al\textsuperscript{27} suggest that a longer time interval than the more conventional 6- to 8-h interval for surveillance biomarker monitoring after PCI should be adopted, and a standardized approach to surveillance monitoring employed in clinical research if peak values are being used to define prognosis.

However, the range of timing of peak elevations for both cTnT and CK-MB among the time interval groups following uncomplicated procedures suggests that perhaps the pattern may be as important as the peak values. Patients receiving abciximab who had more complex procedures elaborated biomarkers later and had lower peak values. If this is universally the case, then peak values that occur early may be due to better reperfusion and may be of less prog-

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**Table 5—Timing of Peak Elevations After PCI (n = 52)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>No Biomarker Elevations</th>
<th>Time After PCI, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>cTnT, ng/mL</td>
<td>&lt;0.03</td>
<td>2</td>
</tr>
<tr>
<td>Patients, No. (%)</td>
<td>33 (63)</td>
<td>0/19</td>
</tr>
<tr>
<td>Received abciximab, No./total</td>
<td>10/33</td>
<td></td>
</tr>
<tr>
<td>CK-MB mass, ng/mL</td>
<td>&lt;6.2</td>
<td>6.85</td>
</tr>
<tr>
<td>Patients, No. (%)</td>
<td>44 (77)</td>
<td>1/12 (8)</td>
</tr>
<tr>
<td>Received abciximab, No./total</td>
<td>20/40</td>
<td></td>
</tr>
</tbody>
</table>

*No baseline elevations; threshold cTnT ≥ 0.03 ng/mL. Data are presented as mean ± SEM unless otherwise indicated.†Mean, 18 ± 0.5 h.

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nostic significance despite a greater magnitude. The timing of peak elevations appears also to be influenced by baseline values. Therefore, early elevations (2 to 10 h) may reflect the combined effects of the intrinsic disease presentation with cardiac injury and the intervention itself.

Since the release rate (the amount of marker depleted from the myocardium that appears in the plasma) is flow dependent, especially for CK-MB, early marker elevations may be of less significance than later, perhaps even lower, marker elevations. Myocardial release rates of biomarkers may also vary under different clinical conditions. Release rates associated with minimal myocardial injury after PCI (late peak) may be quite different from the release rates under conditions of the more profound injury of acute myocardial infarction and reperfusion therapy (early peak). Even analyses such as the area under the time-concentration curve may not be correct for such differences. It may be that the type of analysis done in the Troponin in Planned PTCA/Stent Implantation With or Without Administration of the Glycoprotein IIb/IIIa Receptor Antagonist Tirofiban trial is necessary to understand and fully utilize the prognostic significance of this biomarker release in this setting; in that study, peak levels were often not observed until 48 h after procedure.

In conclusion, although cTnT elevations are more likely to occur after PCI than CK-MB elevations, both markers demonstrate a longer time to peak value than generally anticipated in clinical practice. Thus, longer time intervals should be used for surveillance monitoring postprocedure if peak values are to be accurately determined for prognosis. Only then will accurate analyses based on peak values be achievable. Studies then should be able to clarify the magnitude of these effects and whether peak elevations alone provide the best prognostic information and/or the best way to assess the effects of adjunctive therapies.

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