Cardiac troponin I as an early marker of myocardial damage after coronary bypass surgery

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Abstract

Study objective: To evaluate the performance of cardiac specific markers, cardiac troponin I (cTnI) and CK-MB by mass assay (CK-MB mass), for the early diagnosis of myocardial ischemia and/or infarction after coronary bypass surgery. Methods: Prospective clinical, electrocardiographic and biologic follow-up of 117 patients undergoing isolated coronary surgery with the use of intermittent anterograde normothermic blood cardioplegia. Blood samples for biochemical analysis were drawn before surgery (T0) and at 2 (T1), 6 (T2), 10 (T3) and 20 h (T4) after aortic cross-clamp release. Without knowledge of the biochemical data, patients were classified according to the electrocardiographic evolution into two groups: group 1, uneventful recovery and group 2, evidence of ischemia/infarction based on continuous ST-T segment monitoring and 12-lead ECG. Results: No patients had abnormal markers at T0. At T1, although both markers were elevated, no difference was noted between the two groups. At T2, 6 h after surgery, cTnI and CK-MB mass levels were significantly higher in group 2 than in group 1 (median = 17 μg/l, Interquartile Range (IR): 14.7–27.3 vs. 3.1 μg/l, IR: 1.9–5.3 for cTnI and median 42.5 μg/l, IR: 27.1–95.7 vs. 13.6 μg/l, IR: 9.5–18.5 for CK-MB mass). A receiver operating characteristic (ROC) curve analysis shows that a cTnI value of 13.1 μg/ml has 100% specificity and 90% sensitivity to separate both groups, whereas a value of 33.2 μg/ml for CK-MB mass has a specificity of 100% and a sensitivity of 73%. At T3 and T4, the same difference was noted between the groups. cTnI values in all six patients with a Q-wave infarction were ≥ 20 ng/ml, whereas only one of five patients with prolonged ischemia had cTnI level > 20 ng/ml. Conclusion: As soon as 6 h postoperatively, cTnI and CK-MB by mass assay were able to separate those patients with an uneventful recovery from those with significant ischemia. This is particularly useful in frequent cases when the ECG is difficult to interpret. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Troponin I; CK-MB; Myocardial ischemia; Infarction; Coronary surgery

1. Introduction

The diagnosis of myocardial infarction after coronary revascularization surgery remains challenging. It is usually based upon the development of a new Q-wave on the postoperative ECG and the elevation of cardiac enzymes. However, this definition misclassifies patients with non-Q-wave infarction and does not classify those with conduction disturbances or ventricular pacing. Moreover, the interpretation of enzymatic release, is complicated by skeletal muscle damage occurring during surgery and by some degree of myocardial damage expected after cardioplegic arrest.

Cardiac troponin I (cTnI) is reported to be very specific for myocardial cell damage without cross-reactivity with the skeletal muscle isoform [1]. The specificity of cTnI has been confirmed in various situations and
patients’ groups, i.e. myocardial infarction, contusion, myocarditis and renal failure patients [2–8].

Previous studies on the evaluation of cTnI after cardiac surgery have confirmed a significant release of this marker, peaking 6–8 h after aortic unclamping, even in uncomplicated cases [9,10], and have suggested that cTnI is able to confirm the diagnosis of postoperative myocardial infarction.

Our aim was to evaluate the usefulness of cTnI as an early marker of excessive postoperative myocardial damage, when a specific therapeutic intervention can still be efficient. We also compared the performance of cTnI with the CK-MB mass assay, which is more sensitive and specific than the previous routinely used immunoinhibition assay [11,12].

2. Patients and methods

With institutional approval and informed consent, 117 patients scheduled for coronary surgery were investigated. Reoperations as well as combined coronary and valvular operations were excluded from the study.

Anesthesia was induced with midazolam (0.05 mg/kg) and sufentanyl (3 μg/kg) and muscle paralysis was obtained using vecuronium (0.1 mg/kg). Anesthesia was maintained using a continuous infusion of sufentanyl (0.5 μg/kg per h) and propofol (0.1–0.25 mg/kg per h). According to clinical requirement, propofol infusion rate was increased or additional isoflurane was given. Cardio-pulmonary bypass was instituted with a heparin-bonded circuit. Heparin was given for an activated clotting time > 450 s (300 U/kg). Cardiac arrest was obtained by intermittent infusion in the aortic root of hyperkaliemic normothermic blood. The interval between two successive infusions, that defined a period of ischemic arrest, never exceeded 15 min.

In all but one patient, at least one internal mammary artery graft was used; in 42 patients (38%), both mammary arteries were used and in 25 patients (23%), the right gastro-epiploic artery was implanted on the right coronary artery. A median of four distal anastomoses were performed per patient (range 1–5). The mean bypass duration was 99 ± 33 min and mean total aortic crossclamp time was 66 ± 22 min. A median of four (range 2–6) ischemic arrest periods occurred per patient with a total duration of 54 ± 18 min.

After surgery, ST segment in two leads was continuously monitored in the operating room and in the intensive care unit (HP665®, Hewlett-Packard or AS/3R®, Datex). Analgesia was obtained by a continuous infusion of sufentanyl (0.3 μg/kg per h) during 6 h and intravenous boluses of piritramide (2–4 mg) thereafter. Sedation was maintained with a propofol infusion adapted according to clinical needs (0.1–0.2 mg/Kg per h) until the patients were ready to be extubated.

Blood samples for enzymes and troponin I assays were drawn immediately before induction, 2 h (T1), 6 h (T3), 10 h (T4) and 20 h (T5) after aortic cross-clamp release. Blood samples for troponin I and CK-MB mass assay were centrifuged and the plasma frozen and stored at −20°C for later determination. Troponin I was measured using a specific enzyme-linked immunosorbent assay and CK-MB mass using a fluorometric enzyme assay (StratusR, Dade).

<table>
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<th>Table 1</th>
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<td>Comparison of cTnI values</td>
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<td>cTROPONIN-I (μg/ml)</td>
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<tr>
<td>Group 1 (n = 99)</td>
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<td>Group 2 (n = 11)</td>
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<td>Infarction (n = 6)</td>
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<td>Ischemia (n = 5)</td>
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Median (interquartile range).
* Group 2 statistically different from group 1 (P<0.001).

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Table 2

Comparison of CK-MB values

<table>
<thead>
<tr>
<th>CK-MB (μg/l)</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
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<tbody>
<tr>
<td>Group 1 (n = 99)</td>
<td>10.1 (1.3–18.4)</td>
<td>13.6 (9.5–18.5)</td>
<td>11.8 (8.4–16.2)</td>
<td>11.3 (6.3–16.6)</td>
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<tr>
<td>Group 2 (n = 11)</td>
<td>11.2 (2.7–25.0)</td>
<td>42.5 (27.1–95.7)*</td>
<td>42.6 (31.2–65.2)*</td>
<td>29.7 (21.2–64.4)*</td>
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<tr>
<td>Infarction (n = 6)</td>
<td>3.95 (1.2–11.4)</td>
<td>58 (18.6–136)</td>
<td>52.5 (37.5–68.8)</td>
<td>35.5 (21.9–62.6)</td>
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<tr>
<td>Ischemia (n = 5)</td>
<td>21.7 (10.0–29.6)</td>
<td>35 (31.9–58.6)</td>
<td>30.5 (18.2–58.5)</td>
<td>29.7 (21.7–59.9)</td>
</tr>
</tbody>
</table>

Median (interquartile range).
* Group 2 statistically different from group 1 (P<0.001).
A 12-lead electrocardiogram was systematically recorded at the same time intervals. Additional recordings were obtained if ST segment changes of at least 1 mm from baseline occurred and lasted >15 min or whenever deemed clinically necessary.

An echocardiographic examination was performed 24 h after surgery in all patients with new Q-waves and in those who sustained prolonged ST segment modification.

Two patients were taken back to the operating room for bleeding and were withdrawn from the study. Five other patients were also excluded because their ECG could not be interpreted (left bundle branch block in three and ventricular pacing in two patients). According to their clinical evolution, the 110 remaining patients were divided into two groups:

Group 1 (n = 99): patients with an uneventful post-operative course.

Group 2 (n = 11): patients with evidence of an ischemic event. This group includes patients with a myocardial infarction (n = 5, new Q-wave on ECG and new segmental wall motion abnormality on echocardiography) and patients with a prolonged ischemia (n = 6, ST-T change lasting >15 min but no new Q-wave on ECG or new echocardiographic abnormality).

Non-parametric Wilcoxon rank sum tests was used for between groups comparison. As the groups were compared at four time points to keep an α-level for the multiple comparisons < 0.05, the P-value of each individual comparison was considered significant at a level of 0.05/4 = 0.012.

Receiver operating characteristic (ROC) curves were constructed and compared to assess the specificity and sensitivity of the biological markers at each time point. ROC curves were compared using the method proposed by Hanley and Mc Neil [13]. A P-value < 0.05 was considered to indicate statistical significance.

3. Results

Troponin I and CK-MB levels before surgery were all below the upper limit of the reference interval (< 0.4 ng/ml for cTnI and < 20 μg/l for CK-MB).

Median and interquartile values of cTnI and CK-MB are presented in Tables 1 and 2 for the two groups at each time interval.

At T1, 2 h after aortic unclamping, no significant difference was noted between the groups.

At T2 (Fig. 1), cTnI and CK-MB levels were significantly different in group 1 and 2 (P < 0.0001). The ROC curve analysis for cTnI shows that a value of 8.4 μg/l has a sensitivity of 100% with a specificity of 89% to diagnose an ischemic event, whereas 13.1 μg/l has a specificity of 100% with a sensitivity of 90%. For CK-MB, the ROC curve reveals that 18.5 μg/l has a sensitivity of 91% combined with a specificity of 76% and the value of 33.2 μg/l has a specificity of 100% with a sensitivity of 73%. The area under the ROC curve is 0.99 for cTnI (95% confidence interval (CI) = 0.94–0.998) and 0.88 for CK-MB (95% CI = 0.803–0.935) which were not statistically different (P = 0.086).

At T3 (Fig. 2), group 1 is significantly different from group 2, both for cTnI and CK-MB (P < 0.0001). On the ROC curve, a cTnI value of 14.9 μg/l has a specificity of 100% with a sensitivity of 90% to separate groups 1 and 2. The area under the ROC curve is 0.959 (95% CI = 0.903–0.987). The ROC curve analysis of CK-MB shows that 29.9 μg/l has a specificity of 99% and a sensitivity of 82%. The areas under both curves were not statistically different (P = 0.902).

At T4 (Fig. 3), the values of cTnI and CK-MB are still significantly different between groups 1 and 2 (P < 0.0001). The ROC curve of cTnI discloses that a value >13.4 μg/l has a specificity of 100% for the diagnosis of an ischemic event with a sensitivity of 63%. For CK-MB, 18.4 μg/l has a specificity of 84% and a sensitivity of 89%. The area under the ROC curve of cTnI (0.941, 95% CI = 0.875–0.978) was not statistically different from the area under the curve of CK-MB (0.898, 95% CI = 0.822–0.949). (P = 0.457).

4. Discussion

After coronary surgery, a highly specific marker of myocardial cell damage could be highly valuable because the concomitant skeletal muscle lesions induce the release of unspecific markers such as lactic dehydrogenase, aspartate aminotransferase, CK and even CK-MB.

Also, some degree of intraoperative myocardial damage is expected during the aortic cross-clamping time, leading to elevated levels of specific markers even in patients with an uneventful recovery, as found by Mair et al. [10].

It is then mandatory to define the expected normal range of this marker after coronary surgery and to correlate its blood levels with an independent sign of myocardial cell ischemia and/or necrosis.

New Q-wave on the ECG is highly specific of myocardial infarction but not very sensitive, especially for the diagnosis of non-transmural infarction. We tried to detect all the ECG modifications suggestive of prolonged ischemia, whether or not evolving towards a transmural necrosis. Routine continuous ST segment monitoring allows detection of ST modifications into two leads. Of course, a 12-leads monitoring would be more accurate to detect localized ischemia but unfortunately is not yet routinely available. Patients were included in the group if ST changes lasted >15 min. This
threshold was chosen for practical reasons (time delay necessary for the detection of the changes and the confirmation by a 12-lead recording) as well as for theoretical reasons (no cell necrosis is usually detected for ischemia lasting <15–20 min in experimental conditions) [14,15].

If the occurrence of a prolonged ischemic episode is considered as criterion of an abnormal post-operative evolution, the dosage of cTnI dosage allows the classification of the patients with a high degree of certitude as soon as at the sixth postoperative hour ($T_2$).

An early identification of the patients seems interesting for several reasons. First, in situations where one cannot interpret the ECG (left bundle branch block, ventricular pacing), cTnI dosage would inform us of the presence of myocardial suffering that could otherwise be neglected. Secondly, when ECG changes are difficult to interpret (pericardial inflammation, ventricular hypertrophy), the concomitant dosage of cTnI would allow a better assessment of the ECG and prompt adequate therapeutic interventions.

At the sixth hour, we anticipate that an adequate therapeutic intervention can still salvage myocardium at risk: studies on thrombolysis after myocardial infarction suggest, indeed, that reperfusion within 6 h after the onset of coronary occlusion can limit cell necrosis. It seems thus reasonable, in peculiar cases based upon the ECG and cTnI level, to consider the possibility of a diagnostic angiography or even a resternotomy to limit myocardial cell necrosis.

When we compared cTnI to CK-MB, that is widely used for the diagnosis of myocardial infarction, no statistically significant difference was noticed. As expected, CK-MB by mass assay also had a high sensitivity and specificity for the diagnosis of prolonged ischemia. However, the ROC curve analysis disclosed a better performance of cTnI but did not reach the level of statistical significance.
Fig. 2. Upper panels: individual data plot and box-and-whisker plot of cTnI and CK-MB at 10 h postoperatively ($T_3$) in groups 1 and 2. In small, box-and-whisker plot of cTnI and CK-MB for the subgroups 'infarction' and 'prolonged ischemia'. Lower panels: ROC curve for cTnI and CK-MB at $T_3$. 

$p<0.0001$
For both markers, the measurements at 10 h after aortic unclamping confirmed the diagnosis of ischemia/infarction with high accuracy. In all patients with a Q-wave infarction, cTnI levels were $\geq 20$ mg/ml, whereas only one of five patients with ischemia had a level $\geq 20$ mg/ml.

Later determinations (24 h after surgery) performed identically for both markers, probably because all the episodes of prolonged ischemia in this series occurred during the first 4 postoperative hours.

The values presented in this study are calculated on a limited number of true positive patients because, fortunately, ischemia and infarction are rare events after coronary surgery. However, sensitivity and specificity are very high and would probably remain significant in a larger cohort of patients.

In conclusion, as soon as 6 h postoperatively, at a time that transmural necrosis is potentially still preventable by means of a therapeutic intervention, cTnI dosage allows differentiation of patients with an un-

.eventful course (cTnI < 8.3 $\mu$g/l) from those presenting with a prolonged ischemia and/or infarction (cTnI > 13 $\mu$g/l). If the levels are between 8.3 and 13 $\mu$g/l, some degree of uncertainty persists and patient’s management depends on whether sensitivity or specificity is favoured in an individual situation.

References


