Predictive value of perioperative cardiac Troponin I for adverse outcome in coronary artery bypass surgery

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Abstract

Objectives: Cardiac Troponin I (cTnI) is a well-known marker for myocardial damage in patients undergoing aorto-coronary bypass grafting (CABG) peaking 6–8 h after aortic declamping. The aim of this study was to evaluate cTnI release in the course of CABG procedures early, i.e. after the cessation of cardiopulmonary bypass (CPB) in order to recognize unstable cardiac function leading to hemodynamic deterioration and resulting in an adverse outcome (AO). AO is defined as the onset of myocardial infarction and/or death peri/postoperatively.

Methods: Five-hundred and forty consecutive patients who underwent CABG were evaluated for cTnI release immediately prior to and at the end of the operation. The aim of this study was to evaluate cTnI release in the course of CABG procedures early, i.e. after the cessation of cardiopulmonary bypass (CPB) in order to recognize unstable cardiac function leading to hemodynamic deterioration and resulting in an adverse outcome (AO). AO is defined as the onset of myocardial infarction and/or death peri/postoperatively.

Results: There were six deaths (1.1%) in the entire series, Q-wave myocardial infarction occurred in 19 patients (3.5%), AO was experienced by 21 patients (3.9%). The mean preoperative cTnI level was 0.04 ng/l; for all other patients, this was 0.37 ng/l (mean 0.3 ng/l (mean ± standard deviation) for the entire group. The END cTnI level for the AO-group was 0.91 ± 0.5 ng/l; for all other patients, this was 0.37 ± 0.3 ng/l (P < 0.001). Changes in intraoperative cTnI levels relative to time course showed a marked increase for the AO-group (0.0038 ± 0.0035 ng/l*min) as compared with non-AO patients (0.0019 ± 0.0015 ng/l*min; P = 0.028). The receiver operating characteristic curve indicates a cTnI level at CPB-end of higher than 0.495 ng/l with an area under the curve of 0.83 as the optimal cut-off point for predicting AO with a sensitivity and specificity of 76.2%.

Conclusions: The cTnI release as determined at the end of CABG procedures represents a strong predictor of an AO after surgery. Analyzing blood samples for cTnI with an automated device on site in the OR provides for immediate results, so specific diagnostic and therapeutic interventions can be performed before hemodynamics deteriorate.

Keywords: Troponin I; Coronary surgery; Predictor for outcome

1. Introduction

Numerous models assessing both preoperative variables and perioperative cardiac events in coronary artery bypass grafting (CABG) were developed to predict the outcome after surgery [1–3]. These models can be used for preoperative individual risk-stratification and the comparison of results between hospitals using equality-of-risk groups. However, when intraoperative parameters or postoperative complications are added to the input data, most of the preoperative variables lost their significance in multivariate analysis [4]. This emphasizes the need for perioperative data in predicting outcome. Cardiac Troponin I (cTnI) is suggested to be highly specific for myocardial cell damage. Previous studies on the evaluation of cTnI in coronary artery bypass surgery have confirmed a significant release of this marker, peaking 6–8 h after aortic declamping [5,6]. However, there is a lack of studies concerning cTnI release in CABG procedures at the end of the operation. The aim of
our study was to assess the value of Troponin I as a predictor of an adverse outcome (AO) after surgery when evaluated after cessation of cardiopulmonary bypass (CPB) and before sternal closure. At this point, cTnI release when measured on site in the operation room (OR) may represent an early diagnostic tool for unstable cardiac function leading to hemodynamic deterioration. An elevated cTnI level may indicate the need for immediate therapeutic measures, i.e. insertion of the intra-aortic balloon pump, reexamination of graft patency, application of afterload reducing drugs. Without such an early diagnostic tool for an imminent catastrophe, hemodynamic deterioration often occurs like a bolt from the blue when the chest is already closed, so emergency re-exploration must be performed. These situations are well-known prerequisites for an AO after surgery.

2. Patients and methods

From December 1998 to January 2000, 540 consecutive patients who underwent CABG at the Passau General Hospital were prospectively evaluated for Troponin I release as a marker for an AO after coronary artery bypass surgery. AO is defined as myocardial Q-wave infarction and/or death in the course of the peri/postoperative hospital stay. Patients with any of the following criteria were excluded from the study: (1), operation within 7 days of an acute myocardial infarction; (2), emergency operation for both unstable angina and acute coronary occlusion at angioplasty; (3), CABG operations associated with any other cardiac surgical procedures; (4), preoperative renal dysfunction requiring hemodialysis; (5), reoperative surgery.

The anesthetic technique was standardized for all patients. Etomidate (0.2–0.3 mg/kg) and sufentanil (3–5 mg/kg) were used for induction. Neuromuscular blockade was achieved with Pancuronium bromide (0.2 mg/kg). Anesthesia was maintained using either a continuous infusion of sufentanil (30–60 mg/h or boluses of 3–4 mg/kg). According to clinical requirements, additional isoflurane was given. Initial anticoagulation was accomplished with 3 mg/kg body weight of heparin and was supplemented as required in order to maintain an activated clotting time of 400 s or above.

2.1. Surgical technique

All patients were operated on through median sternotomy and with standard CPB techniques using a disposable hollow fiber oxygenator. In all patients, aprotinin was administered according to the Hammersmith scheme. A loading dose of 2 million kallikrein inactivation units (KIU) was given before sternotomy, followed by an infusion of 0.5 × 10^8 KIU/h until the end of the operation. Additionally, 2 million KIU was added to the priming volume. Myocardial protection consisted of systemic hypothermia (32°C), topical cooling with iced saline or slush, and intermittent cold antegrade blood cardioplegia with or without retrograde cardioplegia delivered into the aortic root or coronary sinus, as appropriate. Proximal anastomoses were completed either during a single period of myocardial ischemia or on a beating heart using an aortic partial occlusion clamp, according to the surgeon’s preference. In all but 21 patients, at least one internal mammary artery graft was used.

Blood samples for Troponin I assays were drawn immediately before the induction of anesthesia and after the termination of CPB. With no need for centrifugation, whole blood samples were measured with the novel automated Stratus CS™ fluorometric enzyme immunoassay analyzer (Dade–Behring) running on site in the OR. Results could be obtained within 15 min.

After surgery, analgesia was continued by intravenous boluses of piritramid (0.1–0.2 mg/kg), and sedation was maintained with a propofol infusion adapted according to clinical needs until the patients were ready to be extubated. Both a 12-lead electrocardiogram, recorded 6, 12, 24 and 48 h postoperatively, and serial arterial blood samples for creatine kinase (CK) and CK-MB, collected at the same intervals, and daily thereafter until the 7th postoperative day, served for diagnosis of a recent myocardial infarction.

2.2. Statistical analysis

Quantitative data were expressed as means ± standard deviation. For group comparisons, the non-parametric Mann–Whitney U-test for two independent samples was applied. Relative frequencies are given in percentages and compared with the χ^2 test or Fisher’s Exact test for expected cell counts of less than five. The relationship between cardiopulmonary bypass time (CPB time) in minutes and change in troponin level was assessed by means of linear regression analysis. The respective P value indicates the significance of the effect of covariate CPB time. A receiver operating characteristic (ROC) curve was used to evaluate the optimal cut-off value of the troponin level at the end of CPB in order to predict AO. The Youden-index was applied as an optimality criterion.

Multiple logistic regression analysis was performed to evaluate the relevant risk factors and troponin levels for predicting AO. The following factors were included: age over 70 years, sex, diabetes, severe left ventricular dysfunction (EF, ejection fraction < 40%), Cleveland Clinic preoperative severity score, aortic cross-clamp time, CPB time, troponin level at CPB termination, high preoperative serum creatinine level (>1.9 mg%) and the number of grafts performed. Both variable selection procedures (stepwise forward and stepwise backward regressions) yielded the same final model. The variables excluded are as follows: age over 70 years, aortic cross-clamp time, diabetes, Cleveland Clinic score; LV dysfunction; high creatinine level, number of grafts. For the remaining parameters, the logistic regression was performed again. Ninety-five percent confi-
dence intervals for odds ratios were calculated in order to indicate precision of the estimates.
All \( P \) values are two-sided and subject to a 5% significance level.

3. Results

Two patients were withdrawn from the study. One experienced deep sternal infection with mediastinitis and died from sepsis, the second patient suffered from postoperative bowel ischemia and died rapidly from multi-organ failure. Definitively, no signs of primarily cardiac failure could be noticed in either of the patients.

Table 1 shows the preoperative Troponin I level and the AO rate resulting from myocardial infarctions and death. The preoperative Troponin I level was 0.04 ± 0.17 ng/l. There were 19 (3.5%) myocardial infarctions and six deaths (1.1%), resulting in 21 patients with an AO (3.9%), classed as group 2. Group 1 contains all other patients.

Patient characteristics according to outcome groups are depicted in Table 2.

With the exception of sex, both groups evidenced a well comparable profile. The mean age in group 1 was 64.8 years as compared with 65.9 years in group 2. Thirty-six percent of patients in group 1 were older than 70 years and 33% in group 2. Seventy-one percent of patients were male in group 1 and 38% in group 2 (\( P = 0.002 \)). Poor left ventricular ejection fraction (EF of \( <40\% \)) occurred in 14% of group 1 as compared with 19% in the AO group 2. The preoperative Cleveland Clinic severity score was 2.05 for group 1 patients and 2.29 for group 2 patients. In group 1, 31% of patients suffered from diabetes, whereas this figure was 19% in group 2. Of the patients in group 1, 4.4% had elevated preoperative serum creatinin levels as compared with none in group 2. The intraoperative variables are shown in Table 3. The aortic cross-clamp and CPB time were significantly longer in group 2 compared with group 1. Group 1 patients had a mean of 3.4 grafts and group 2 patients had a mean of 3.7 grafts. The preoperative Troponin I levels were comparably low for both groups. In contrast, at the end of CPB, the Troponin I levels were significantly different: in group 1, the level was 0.37 ng/l, and 0.91 ng/l in the AO group, respectively. The change of troponin relative to time course evidenced a faster increase for group 2 than for group 1. Fig. 1 shows the linear regression line for change in Troponin I level by operation time for group 2. There was no significant increase (\( P = 0.426 \)) within this group.

The ROC curve (Fig. 2) indicates a cTnI level of 0.495 ng/l calculated by the Youden-index, with the area under the curve of 0.83 as the optimal cut-off value for predicting an AO with a sensitivity and specificity of 76%.

Multiple logistic regression analysis revealed CPB time (odds ratio, 1.03) and Troponin I level at CPB-end (odds ratio, 17) as independent predictors for an AO following routine coronary artery bypass surgery (Table 4). Moreover, male sex has a significantly negative, and in this way, reducing effect on AOs (odds ratio, 0.26). Thus, female sex is a further independent predictor for an AO following routine coronary artery bypass surgery according to our analysis.

4. Discussion

cTnI has been shown to predict the risk of mortality and of cardiac events in patients with unstable angina [6,7], to estimate infarct size after reperfusion [8], and to be a specific marker of cardiac damage during coronary artery bypass surgery [5,9,10]. Moreover, there is no cross-reactivity with the skeletal muscle isoforms and it was demonstrated that it does not increase in healthy people, even under excessive muscular activity or as the result of non-cardiac operations.
Elevated preoperative Troponin T levels in patients undergoing elective CABG appear to identify a subgroup of patients with unrecognized myocardial necrosis or reversible myocardial cell injury, who are at a greater risk of cardiac events after the operation and who could benefit from improved methods of anesthesia, myocardial protection, surgical revascularization, and preoperative stabilization with both medical treatment and IABP [12]. The preoperative cTnI level in our patients averaged at 0.04 ng/l for the entire group and 0.15 ng/l for the AO group, respectively. This was not statistically significant in univariate analysis nor was preoperative Troponin I an independent predictor for an AO in multivariate analysis.

Postoperatively, moderate elevation of Troponin I indicates reversible minor myocardial damage occurring in most patients undergoing CABG [6,13]. However, the identification of patients who are at risk of developing postoperative complications based on intraoperative myocardial infarction and heart failure as early as possible is desirable, as it allows for prompt adequate therapeutic interventions (i.e. insertion of the balloon pump, re-exploration of grafts, administration of afterloading drugs) before hemodynamic deterioration occurs. ECG changes are difficult to interpret at this point (bundle branch block, pacing, pericardial inflammation, ventricular hypertrophy) [13]; however, cTnI above a well-defined cut-off value would allow for identification of patients at risk. Serum Troponin T levels higher than 3.4 ng/l 48 h after CABG and serum Troponin I levels higher than 3.9 ng/l 24 h postoperatively were found by Carrier and coworkers to be the most reliable indicators for perioperative myocardial infarction [6]. Recently, by measuring cardiac Troponin T with monoclonal antibodies, they found, 36–48 h after CABG, a blood level of Troponin T lower than 0.65 ng/l to indicate the absence of major perioperative myocardial damage, and a level higher than 1 ng/l to correlate with perioperative myocardial infarction. In our patients, early postoperative Troponin I levels averaged at 0.37 ng/l in the non-AO group (no death, no myocardial infarction) as compared with 0.91 ng/l in the AO group. The ROC curve indicates 0.495 ng/l, calculated by the Youden-index, as the optimal cut-off value with a sensitivity and specificity of 76% and an area under the curve of 0.83.

Etievent and coworkers found no positive correlation between aortic cross-clamping time and cTnI level at 6 h after CABG [5], and we did not, even for our patients with

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Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-clamp (min)</td>
<td>60.0 (±17.6)</td>
<td>73.7 (±22.8)</td>
<td>0.008</td>
</tr>
<tr>
<td>CPB time</td>
<td>81.8 (±24.7)</td>
<td>107.5 (±32.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Grafts/patient</td>
<td>3.4 (±1)</td>
<td>3.7 (±1)</td>
<td>0.18</td>
</tr>
<tr>
<td>Troponin IND (ng/l)</td>
<td>0.04 (±0.15)</td>
<td>0.15 (±0.47)</td>
<td>0.26</td>
</tr>
<tr>
<td>Troponin END (ng/l)</td>
<td>0.37 (±0.26)</td>
<td>0.91 (±0.55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Troponin/time (ng/l*min)</td>
<td>0.0019 (±0.0015)</td>
<td>0.0038 (±0.0035)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

a Values are expressed as means (±SD).
b X-clamp, aortic cross-clamp time; Troponin IND, troponin before induction of anesthesia; Troponin END, troponin at CPB-end; Troponin/time, change of troponin relative to time course.

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Fig. 1. Change in troponin level related to CPB time (ng/l).

Fig. 2. ROC curve for troponin level at CPB-end.
AO at the end of CPB. Ante/retrograde cold blood cardioplegia and complete revascularization seems to minimize the extent of myocardial damage caused by aortic clamping, but cannot prevent myocardial infarction and heart failure because of remaining ischemic areas that could not be grafted.

4.1. Limitations of the study

The endpoint of the study is defined as predicting AO including myocardial infarction and death peri/postoperatively by analyzing cTnI release intraoperatively. Postoperative myocardial infarctions and death due to both surgical failures and ICU problems contribute to that, however, by nature. Thus, these events cannot be predicted by intraoperative cTnI levels.

The results presented in this study are calculated on a powerful number of patients with positive outcomes, however, on a limited number with AOs, as severe ischemia and myocardial infarction are rare events after CABG. Notwithstanding, we end up with a sensitivity and specificity of 76% for cTnI levels at the end of CPB in predicting AOs.

In conclusion, cTnI release, as determined at the end of CPB, represents a predictor of an AO after surgery. Analyzing blood samples for cTnI with an automated device on site in the OR provides for immediate results, so that specific therapeutic interventions can be performed before a catastrophe occurs.

References


Appendix A. Conference discussion

Dr C. Baufreton (Angers, France): In 1998, it has been published that the level of oxygenation during cardiopulmonary bypass (CPB) may be detrimental for the patient in terms of enzymatic release from myocardium. Then, I would like to know in your study, since CPB time has something to do with postoperative AO, if you measured or analyzed the impact of oxygenation during CPB. Did you perform your operation using a high level of oxygenation during CPB time? Because the event is there already.

Dr van Ingen: No, we did not take the oxygenation of the patient into account, in our study, and we operated with a moderate level of oxygenation during CPB.

Dr P. Sergeant (Leuven, Belgium): I enjoyed your presentation very much and also the way you approached the problem. In an earlier analysis, when we used the word predictor, we meant in fact preceding the procedure. Are you certain about the word predictor when you said about your results? Because the event is there already.

Dr van Ingen: Perhaps one could describe it as an indicator that something has happened, not so much a predictor. So I could change the word to ‘indication’. To ‘indicate’ that something can happen.
Dr O. Alfieri (Milan, Italy): If you have a patient who is well but has changes in troponin, what do you do? Do you change your policy? Do you insert, for instance, an intra-aortic balloon?

Dr van Ingen: Yes. First of all, you have to consider: was I able to revascularize this patient completely? So, for instance, if you used arterial grafts and you are not sure of it and you have this raise in troponin, you can put a venous graft, let’s say, for instance, to the LAD. On another level, and we did that, as a matter of fact, you can decide to put in, even though the patient is doing clinically well, an intra-aortic balloon pump.

Dr S. Takamoto (Tokyo, Japan): I would like to ask about the cause of the elevation of troponin. Is that relating to myocardial protection or the procedure itself?

Dr van Ingen: It is an indicator of myocardial damage. It is not related to the aortic clamp time. It is certainly related to the bypass time, as I showed. I can’t remember from the literature whether the protection had any influence. In most papers that I read on the subject, they did use retrograde blood cardioplegia, and as I said, it is certainly an indication of ischemia of the myocardium whether related to the protection or not.