Use of Cardiac Troponin I to Diagnose Perioperative Myocardial Infarction in Coronary Artery Bypass Grafting

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Cardiac troponin I (cTnI) is a regulatory protein unique to myocardium. We used a cardiospecific 30-min ELISA to measure cTnI in EDTA-plasma samples serially drawn from 28 patients before and after coronary artery bypass grafting (CABG)—26 elective and 2 salvage cases. The cTnI increase in 22 of the elective CABG patients, who did not have perioperative myocardial infarction (not-PMI), reflected the inevitable myocardial damage caused by cannulation and cardioplectic arrest, with peak values of 1.7 ± 1.0 μg/L (mean ±2 SD = 3.7 μg/L), the peaks occurring on average 8 h (range 4–24) after aortic unclamping. Two of the 22 not-PMI, elective CABG patients showed cTnI peaks >3.0 μg/L (3.9 and 3.4 μg/L), indicating more extensive perioperative myocardial damage than the other 20, as confirmed by clinical and electrocardiographic or echocardiographic signs, although creatine kinase isoenzyme MB (CKMB) activity was below our PMI decision limit of 20 U/L (25°C). As classified by electrocardiography, echocardiography, and increased CKMB activity, four of the 26 elective CABG patients did have a PMI. One patient with Q-wave PMI had peak cTnI ~30 μg/L, and three with non-Q-wave PMI had lower peak values (~5 μg/L). The two salvage CABG cases had increased cTnI before surgery. One developed a Q-wave acute myocardial infarction with a 3-h cTnI peak of ~35 μg/L. We conclude that, after elective CABG, cTnI peaks >3.7 μg/L and concentrations >3.1 μg/L at 12 h or >2.5 μg/L at 24 h indicate PMI with high probability.

Indexing Terms: creatine kinase/enzyme mass concentration vs activity/isoenzymes

Cardiac troponin I (cTnI, molecular mass 22 500 Da), one of the three isoforms of TnI, is a regulatory protein unique to heart muscle (1).5 TnI is the inhibitor of the troponin–tropomyosin regulatory complex that confers calcium sensitivity to actomyosin ATPase activity in striated muscle, thereby regulating the interaction of actin and myosin in striated muscles (2). cTnI has an extra 30 residues on the NH2 terminus. Its unique amino acid sequence shows ~40% dissimilarity (1) from the two skeletal muscle isoforms (slow-twitch and fast twitch), making this analyte a promising candidate as cardiospecific laboratory marker for myocardial damage. cTnI is the only TnI isotype located in the myocardium (1, 3). Skeletal muscle does not express cTnI in any developmental stage or in response to any pathologic stimuli (3). Recently, an enzymoimmunometric assay highly specific for cTnI has been developed (4) at its efficiency for diagnosing myocardial damage or myocardial infarction, particularly in the presence of concomitant skeletal muscle damage, demonstrated (5). Here we report our evaluation of cTnI in the diagnosis of perioperative myocardial infarction (PMI) in patients undergoing coronary artery bypass grafting (CABG).

Materials and Methods

Subjects

The procedures followed were in accordance with the Helsinki Declaration of 1975, as revised 1983. After obtaining patients' informed consent, we investigated 28 consecutive CABG patients (25 men, 3 women; age 45–73, mean 61 years), 26 elective and 2 salvage case.

Fifteen elective CABG patients underwent surgery for unstable angina, the other 11 for stable angina per se. Indications for surgical revascularization were left main coronary artery stenosis in 9 patients and three-vessel disease in 17. Eighteen patients had a history of a previous myocardial infarction. The preoperative left ventricular ejection fraction was 51% ± 15% (<40% in seven patients).

Four of the elective CABG patients had a PMI: one patient a Q-wave, and three a non-Q-wave form. Q-wave PMI was diagnosed when the following criteria were fulfilled: (a) Creatine kinase (CK) MB activity >50 U/L on the first postoperative day (6, 7); (b) appearance of new persistent Q-waves >0.04 s or equivalents (1 wave increment leading to an R/S ratio >1 in leads V1 and V2) in electrocardiography (ECG); and (c) the development of new persisting regional wall motion abnormalities in echocardiography. Non-Q-wave PMI was diagnosed when the following criteria were fulfilled: (a) Development of new ST-T alterations (ST segment depression or elevation >0.1 mV at 0.08 s after the J point T wave inversion) lasting at least 24 h in at least contiguous leads of the same vascular territory of Q standard 12-lead ECG, and (b) CKMB activity >20 U/L on the first postoperative day (7–9).

In all patients ECG recordings were obtained preoperatively, immediately postoperatively, 24 h later, and before discharge from hospital. Patients who develop
symptoms suggestive of myocardial ischemia had additional ECG recordings according to clinical requirements. ECGs were assessed by an experienced cardiologist without knowledge of the subjects or diagnoses. Most of the patients were monitored intraoperatively by ransesophageal echocardiography. Serial venous blood samples were obtained in a differential order before induction of anesthesia; before surgery; before cardiopulmonary bypass; after aortic unclamping (AU); 1, 2, 3, 4, 8, 12, 16, 20, 24, and 48 h later; and daily from days 2 to 7.

Anesthesia and operative techniques. Anesthesia was induced with midazolam, 0.3–0.4 mg/kg of body weight and fentanyl, 5–10 μg/kg in all patients. Endotracheal intubation was facilitated with vecuronium, 0.1 mg/kg; anesthesia was maintained by using a continuous infusion of fentanyl (20 μg/kg per hour) and midazolam (0.15 mg/kg per hour). Additional bolus doses of fentanyl and isoflurane (<1.5%) were given according to clinical requirements. Standard cardiopulmonary bypass technique with moderate systemic hypothermia and aortic crossclamping was used in all patients. Myocardial protection was achieved by infusion of cold hyperkalemic cardioplegic solution (modified St. Thomas solution) into the aortic root and by additional topical cooling. The mean bypass time was 117 min (71–216 min) and the mean aortic crossclamping time was 59 min (37–106 min). On average, 4 (range 2–5) grafts per patient were implanted. Internal mammary artery (IMA) was used as the bypass vessel in 18 patients.

Laboratory Analysis

Blood collection. Venous blood was collected in EDTA-containing tubes (Sarstedt, Nümbrecht, Germany) and immediately centrifuged. CKMB activities were measured without delay. Plasma for cTnI and CKMB mass measurements was frozen in aliquots and stored at −20°C until analysis.

CKMB activities. CKMB catalytic concentrations were measured after immunoinhibition at 25°C by means of an N-acetylcysteine-activated, optimized ultraviolet test from Merck (Darmstadt, Germany). The normal range of CKMB activity measured by this method is <10 U/L.

CKMB mass concentrations. CKMB mass concentrations were determined by a sensitive two-site enzyme immunoassay (Abbott, N. Chicago, IL) that are highly specific for CKMB (10). The normal range for noncardiac surgical patients is <7.0 μg/L (11).

cTnI. cTnI concentrations were measured by a one-step, rapid immunoenzymometric assay (ERIA; Diagnostics Pasteur, Marnes-la-Coquette, France). This assay shows no cross-reactivity with skeletal muscle TnI or other cardiac proteins (4); the assay time is ~30 min. By this assay, cTnI was not detectable (<0.1 μg/L) in healthy blood donors (4).

Data Analysis

Data are given as mean ± SD unless otherwise stated. Linear correlation coefficients (Pearson) were calculated. Repeated-measures analysis of variance (ANOVA) and Student’s t-tests were used. P <0.05 was considered significant.

Results

Time Course of cTnI Concentration in Plasma of Elective CABG Patients Without PMI (not-PMI)

Figure 1 shows cTnI concentration time courses during the first 24 h after AU in 22 not-PMI patients. cTnI increased significantly (P = 0.0001) over baseline values after AU (0 ± 0.1 vs 1.7 ± 1.0 μg/L), but peak values did not exceed 4 μg/L (mean ± 2 SD = 3.7 μg/L; see Fig. 1). Peak values occurred ~8 h after AU (range 4–24 h). We often observed a prolonged increase in cTnI rather than a distinct peak; this resulted in a prolonged, fluctuating mean increase in cTnI within 8–16 h after AU (Figs. 1 and 2). We used a cutoff value for cTnI (mean + 2 SD) concentrations in not-PMI of 3.1 μg/L at 12 h and of 2.5 μg/L at 24 h after AU (Fig. 1). Although the increase and peak for cTnI paralleled that for CKMB (see Figs. 1–3), cTnI on average stayed increased for 3 days longer than CKMB. In not-PMI patients the relative increase in cTnI over baseline after CABG was significantly (P <0.016) higher than the increase in CKMB catalytic and mass concentrations (17.0 ± 9.8 vs 2.1 ± 0.9 times and 5.8 ± 2.6 times the upper limit of the reference interval in noncardiac surgical patients, respectively). cTnI peak concentrations correlated closely with CKMB catalytic and mass concentration peak values (r = 0.92 and 0.93, respectively; P = 0.0001). There was no correlation of CKMB activity or mass, or of cTnI peak values, with aortic crossclamping time (0.2 ≤ r ≤ 0.43; 0.08 ≤ P ≤ 0.45); and the peak values for these three measures showed no significant difference between patients in whom the IMA was used as a bypass vessel and patients who received only saphenous vein grafts for myocardial revascularization.

Only 2 of the 22 not-PMI patients had cTnI peaks >3 μg/L (3.9 and 3.4 μg/L, respectively; see Figs. 1 and 2), indicating more extensive myocardial damage than the others. Both patients had unequivocal clinical, ECG, or echocardiographic evidence for perioperative myocardial ischemia; however, their CKMB activity was below our PMI limit of 20 U/L (25°C). One patient developed a transient left bundle branch block in ECG and a new transient regional wall motion abnormality by echocardiography immediately after weaning from bypass. This patient had intraoperative graft revision (thrombectomy) for graft thrombosis of the left circumflex artery graft. In the other patient extracorporeal circulation was reestablished because of intraoperative cardiac pump failure. This patient showed intraoperative, transient ST-segment elevations in ECG, and new positive T-waves, which persisted until discharge, developed in the region of a preoperative myocardial infarction scar with previous negative T-waves. In contrast to catalytic and mass concentrations of CKMB, the cTnI peak values and cTnI time courses of both patients differed markedly from the average for the not-PMI patients (see Figs. 1 and 2). cTnI release in these two patients was similar to that in patients with non-Q-wave PMI (Fig. 3).
cTnI in Elective CABG Patients with PMI

cTnI concentrations of PMI patients (one Q-wave, three non-Q-wave PMI) differed significantly from those of not-PMI patients (repeated measures ANOVA, $P = 0.0001$) and were significantly ($P < 0.021$) higher from 8 h after AU until postoperative day 7 (Fig. 3, left). Peak values were significantly ($P = 0.0016$) higher and exceeded 4.5 µg/L in all patients. One patient with Q-wave PMI had a cTnI peak of ~30 µg/L, and three non-Q-wave PMIs patients had peaks of ~5 µg/L (Fig. 3). Moreover, these patients had peaks occurring later ($P = 0.0263$) than in not-PMI patients (on average 8 vs 24 h after AU). In all four PMI patients, cTnI exceeded 3.1 µg/L at 12 h and 2.5 µg/L at 24 h after AU. cTnI time courses paralleled CKMB mass and activity (Figs. 1–3); however, cTnI stayed increased for several days longer than CKMB mass and catalytic concentrations.

The relative peak increases in cTnI of PMI patients (mean 3.3 times, range 1.4–8.9) compared with cutoff value obtained in not-PMI CABG patients (3.7 µg/L) were higher (but not significantly so; $P = 0.068$) than the relative peak increases in CKMB mass of these patients (mean 2.2 times, range 0.66–5.76). From the CKMB mass peak values measured in our not-PMI patients, we calculated a cutoff value (mean + 2 SD) for CKMB mass peak concentrations of 77.8 µg/L (Fig. 1B). In one non-Q-wave PMI patient the CKMB mass peak did not exceed 77.8 µg/L (curve B in Fig. 3, bottom).

cTnI Time Courses in Salvage CABG

Both of the salvage CABG patients showed ST elevations in ECG preoperatively, and one developed new persisting Q-waves after CABG. In both patients the preoperative onset of myocardial infarction was indicated by increased cTnI concentrations already before induction of anesthesia (4.0 and 8.2 µg/L, respectively). In the patient with Q-wave acute myocardial infarction cTnI peaked (36.2 µg/L) 3 h after AU; in the other patient (non-Q-wave acute myocardial infarction), the cTnI peak (11.8 µg/L) was at 10 h after AU.

**Discussion**

PMI in CABG patients is an important clinical even with negative prognostic implications (12). Although extensive Q-wave PMI are reliably detected by ECG and conventional CKMB activity measurements, smaller PMIs may be easily missed (12). CKMB activity measurements also do not meet the current needs for a highly sensitive marker of minor myocardial tissue damage, which is necessary to compare different means of cardioprotection (13).

To the best of our knowledge this is the first report of cTnI release after CABG. A major finding of this study was that cTnI is a sensitive marker of perioperative myocardial tissue damage. PMI in elective CABG patients could be reliably identified by its characteristic cTnI release. Both peak concentration and time of peak

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**Fig. 1.** Cardiac troponin I (A) and CKMB mass concentrations (B) in 22 elective coronary artery bypass graft patients without perioperative myocardial infarction (not-PMI).

- cTnI concentrations of two borderline patients (elective CABG) with clinical, ECG, or echocardiographic signs of more extensive perioperative myocardial damage than in others. Mean values at given time points; error bars indicate 2 SD.

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were diagnostic criteria. All PMI had cTnI peak concentrations >4.5 μg/L, and the peaks occurred ~24 h after IOU. Like all other myocardial markers, cTnI increases significantly after CABG in not-PMI patients, which leads to potential difficulties in interpreting test results. However, in contrast to its behavior in PMI, cTnI release in not-PMI patients was characterized by a slight and protracted increase, starting from 1 h after AU on; peak values were <4 μg/L and occurred most frequently 1–16 h after AU. On average, cTnI could be detected until postoperative day 4 in not-PMI patients. Cannulation of the right atrium, cardiopulmonary arrest, prolonged surgery, inadequate cardioplegia, and the like may cause small amounts of myocardial damage and lead to TnI release in not-PMI patients.

In elective not-PMI patients, the relative increase in TnI over preoperative baseline values was significantly more than that of CKMB catalytic and mass concentrations, and postoperative cTnI concentrations differed markedly in these patients. A wide range of myocardial lamination not always indicated by CKMB mass or activity s obviously common even in not-PMI patients. cTnI measurements can detect these small differences in myocardial tissue damage and are, therefore, potentially useful in evaluating surgical procedures and different techniques of cardioprotection. Such larger differences in the extent of perioperative myocardial damage are plausible, given the heterogeneity of our 22 not-PMI patients, e.g., with respect to aortic crossclamping time, the number of implanted grafts per patient, and the severity of their underlying coronary artery disease. In not-PMI patients, neither cTnI nor CKMB mass or activity peaks correlated with aortic crossclamping time. This suggests that in uncomplicated routine CABG the cardiopulmonary technique used is sufficiently protective to make aortic crossclamping time a minor determinant of perioperative myocardial tissue damage. cTnI peaks
were also not significantly higher in patients in whom the IMA was used as a bypass graft. The additional skeletal muscle injury attendant to taking down IMA pedicles apparently did not affect cTnl or CKMB mass and activity release.

Two of the 22 non-PMI patients showed cTnl peaks >3.0 μg/L (3.9 and 3.4 μg/L), an indication of more extensive perioperative myocardial damage than the others. This was confirmed by clinical and ECG or echocardiographic signs, although their CKMB activity was below our PMI cutoff of 20 U/L (25°C). In contrast to CKMB mass and activity, cTnl concentrations of both borderline patients differed markedly from the other non-PMI patients and were similar to that of the patients with non-Q-wave PMI. Thus, these two borderline cases were detected by cTnl and missed by CKMB mass and activity. In addition, the relative cTnl increases in PMI patients were higher than that of CKMB mass. One patient with non-Q-wave PMI showed only a small CKMB mass increase and the peak concentration did not exceed the cutoff value calculated from CKMB mass peaks measured in our non-PMI patients. Therefore, cTnl may be superior to CKMB mass and activity, particularly in detecting small perioperative myocardial necrosis.

However, we recognize several limitations of this study. Our CABG patients were classified on the basis of current PMI criteria, which include CKMB catalytic concentrations. These CKMB activity limits, established and evaluated in large cohorts of CABG patients (6–9, 14), may have to be replaced, given the more sensitive and specific enzyme immunoassays now available for measuring CKMB mass concentrations. These mass-based assays may increase the diagnostic sensitivity of CKMB for small myocardial damage (11, 14–16). Although we measured CKMB mass concentrations in all patients reported here, we classified the patients according to their CKMB activities, because thus far, cutoff values for CKMB mass concentration in PMI have not yet been set, awaiting the investigation of comparably large CABG cohorts as those used in CKMB activity studies. In addition, there is no accepted criterion for the diagnosis of small, non-Q-wave PMIs and smaller myocardial damage not fulfilling standard PMI criteria (9, 12, 17).

The reliability of all diagnostic criteria used (e.g., ECG, myocardial scintigraphy, echocardiography, and CKMB changes) has been repeatedly criticized (18). Indeed, no true gold standard was utilized in this study. We might have used positron emission tomography but this imaging technique is difficult to perform during the early postoperative period and also is currently not available at our institution. Therefore, we could not evaluate cTnl and CKMB mass or activity independently and could not unequivocally demonstrate that cTnl is superior to CKMB in diagnosis of PMI—although, in contrast to CKMB mass and activity, cTnl allows late diagnosis of PMI several days after surgery as well. However, measurement of cTnl seems to be superior to that of CKMB mass and activity in the diagnosis of small perioperative myocardial necrosis and is not necessarily fulfilling routine criteria for PMI.

In summary, we conclude that cTnl is a sensitive and specific marker of perioperative myocardial damage and reliably identifies PMI during CABG. Frequent blood sampling indicated that cTnl peak concentrations >3.0 μg/L and that cTnl >3.1 μg/L at 12 h or >2.5 μg/L at 2 h after AU indicate PMI with high probability.

We dedicate this paper to Helmut Wachter of Innsbruck, Austria, on the occasion of his 65th birthday.

References