Short- and Long-term Prognostic Value of Postoperative Cardiac Troponin I Concentration in Patients Undergoing Coronary Artery Bypass Grafting

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Background: The value of postoperative cardiac troponin I (cTnI) has been shown to indicate a higher risk of in-hospital death after cardiac surgery. The authors therefore assessed the long-term prognostic value of cTnI in patients undergoing elective coronary artery bypass grafting.

Methods: Consecutive patients (n = 202) were included and divided into two groups according to the postoperative value of cTnI ($<$ or $\geq$ 13 ng/ml). In-hospital mortality and nonfatal cardiac events (delayed extubation $>$ 24 h; postoperative requirement of inotropic agent; ventricular and supraventricular arrhythmia; postoperative myocardial infarction) were recorded. Survivors were then followed up over a 2-yr period. Data are median and odds ratio (95% confidence interval).

Results: Of all patients, 174 (86%) had a low cTnI (4.1 ng/ml; range, 1.1–12.6) and 28 (14%) had a high cTnI (23.8 ng/ml; range, 13.4–174.6). In-hospital mortality was not significantly different (4 *vs.* 2%), whereas long-term mortality (18 *vs.* 3%, *P* = 0.006) and mortality from cardiac cause (18 *vs.* 1%, *P* < 0.001) was greater in patients with a high cTnI. A high cTnI was a significant factor predicting death (odds ratio, 7.3 [2.0–27.1]) or death from cardiac causes (odds ratio, 37.4 [4.2–334.4]). Nonfatal cardiac events were also more frequent in the hospital (64 *vs.* 41%, *P* = 0.02) and within the 2-yr follow-up period (39% *vs.* 16%, *P* = 0.03) in patients with high cTnI.

Conclusion: A high postoperative peak of cTnI is associated with increased risk of death, death from cardiac causes, and nonfatal cardiac events within 2 yr after coronary artery bypass grafting.

POSTOPERATIVE serum cardiac troponin I concentration (cTnI) is increased in all patients undergoing cardiac surgery, an observation that highlights the essential sensitivity of this biochemical marker and a constant level of perioperative myocardial injury. Numerous factors can explain such an increase in cTnI after cardiac surgery,

even in the absence of postoperative myocardial infarction (MI).[1] The type of surgery,[2] the choice of cardioplegic solution, its mode of delivery,[3] and the use of intraoperative aprotinin[4] all influence postoperative cTnI release in patients scheduled for cardiac surgery. Several studies have described the kinetics of cTnI elevation after cardiac operations in adults,[5–7] but the cutoff values for MI diagnosis and the prediction of poor clinical outcome remain unclear.

The prognostic value of isolated cTnI elevation is well established in patients with unstable angina pectoris[8,9] and in critically ill intensive care unit (ICU) patients.[10] The independent prognostic value of cTnT has been also reported in patients with pulmonary embolism.[11] In cardiac surgery, Immer *et al.*[12] showed an accurate prediction of early postoperative complications from the peak value of cTnI in infants and children. In adult patients undergoing cardiac surgery, including coronary artery bypass grafting (CABG) and conventional valve replacement, Lasocki *et al.*[13] recently reported that an increased cTnI was associated with major postoperative complications and that a high peak postoperative cTnI ($>$13 ng/ml) was a strong and independent predictor of in-hospital mortality after cardiac surgery. However, the long-term prognostic value of elevated cTnI remains unknown after cardiac surgery.

Therefore, the aim of the present study was to evaluate the short- and long-term prognostic value of an elevated peak cTnI in adult patients undergoing elective CABG.

Materials and Methods

Patient Population

Consecutive patients undergoing elective CABG with extracorporeal circulation for symptomatic coronary disease were enrolled prospectively in the study from January 1999 to January 2000 at the Saint-Martin Hospital. Institutional approval was obtained (Comité Consultatif pour la Protection des Personnes se Prêtant à la Recherche Biomédicale (CCPPRB) Pitié-Salpêtrière, Paris). Waived written informed consent was authorized because the study was solely observational and pre- and postoperative cTnI measurements were systematically performed in routine practice. Exclusion criteria included emergency surgery, reoperative procedures, concomitant valve repair or replacement, concomitant vascular surgery, a recent history ($<$ 4 weeks) of acute MI, or a preoperative value of cTnI greater than 0.6 ng/ml,

and preoperative chronic renal failure (estimated creatinine clearance < 60 ml/min using the Cockcroft formulae).[14]

Perioperative Management

All patients were premedicated orally with lorazepam (2.5 mg the day before surgery and on the morning of surgery). Beta-blocker agents were given until the day of surgery in chronically treated patients. Standardized total intravenous anesthesia (target control propofol infusion, remifentanil, and pancuronium bromide) and monitoring techniques (5-lead electrocardiogram with computerized analysis of ST segment and invasive arterial blood pressure) were used in all patients. Cardiopulmonary bypass was performed under normothermia and the left internal mammary artery was used in all patients. Myocardial protection was achieved by intermittent antegrade warm blood cardioplegia and the heart was defibrillated after aortic unclamping if sinus rhythm did not resume spontaneously. No patient received intravenous aprotinin, which is reserved for high-risk bleeding operations in our institution. After termination of cardiopulmonary bypass, catecholamines and antiischemic drugs were used when necessary at the discretion of the attending anesthesiologist. All patients were admitted postoperatively into the cardiac ICU for at least 48 h. Patients received aspirin (300 mg, oral or intravenous) and a low molecular weight heparin (nadroparin 2,850 U Anti-Xa, subcutaneous; Fraxiparine®, Sanofi-Synthelabo, Paris, France) in the postoperative period, beginning 6 h after surgery in the absence of significant mediastinal bleeding (> 50 ml/h). Beta-blocker agents were continued postoperatively in chronically treated patients. Diagnostic criteria for perioperative MI were the appearance of new Q waves of more than 0.04 s and 1 mm deep or a reduction in R waves of more than 25% in at least two continuous leads of the same vascular territory. Daily 12-lead electrocardiogram recordings were assessed by an experienced clinician blinded to the clinical and biochemical information.

Measurements of cTnI Concentration

Blood samples were collected preoperatively and 24 h after the end of surgery. A technician who was blinded to the clinical and electrocardiogram data performed assays. cTnI concentrations were measured by a sensitive and highly specific immunoenzymometric assay (AxSYM Troponin-I MEIA assay, Abbott Laboratories, Rungis, France) that detects both free and complexed cTnI and allows the detection of cTnI within the range of 0.3–50 ng/ml, requiring appropriate dilutions when necessary. Values greater than 0.6 ng/ml were considered abnormal. The within-run coefficient of variation was 6% and the between-run coefficient of variation was 11%.

Clinical Outcome and Follow-up

Patients were divided into two groups according to the postoperative peak cTnI: group 1, cTnI less than 13 ng/ml (low cTnI) and group 2, cTnI greater than or equal to 13 ng/ml (high cTnI). This cutoff value was chosen in accordance with the recent study of Lasoki et al.,[13] who showed that a postoperative peak value of cTnI greater than or equal to 13 ng/ml after conventional adult heart surgery was a strong and independent predictor of in-hospital death. Moreover, Jacquet et al.[15] reported a cutoff value of 13.4 ng/ml after CABG, which showed a significant difference between patients with an uneventful recovery and those with myocardial ischemia and infarction. The cutoff value of cTnI was verified a posteriori using the receiver operating curve method.

To analyze the in-hospital outcome, the following postoperative variables were recorded: time to discharge from hospital, prolonged length of stay in ICU (> 5 days), Simplified Acute Physiologic Score,[16] nonfatal cardiac events, and in-hospital death. Causes of death were recorded and classified as cardiac (heart failure, MI, ventricular arrhythmia) or noncardiac (hemorrhage, respiratory failure, sepsis, or other causes). Nonfatal cardiac events included delayed extubation (> 24 h), postoperative requirement of an inotropic agent, use of an intraaortic balloon pump in the ICU, postoperative MI, postoperative ventricular arrhythmia (any sustained ventricular arrhythmia requiring treatment), and postoperative atrial fibrillation or flutter.

To analyze the long-term outcome, the survivors after hospital discharge were followed over 24 months after surgery (6, 12, and 24 months) to record death and nonfatal cardiac events. During these visits, patients underwent physical examination, electrocardiogram, and transthoracic echocardiography to determine left ventricular ejection fraction. Moreover, all cardiac events noted by the general practitioner, the cardiologist, or during any admission to a hospital were recorded. In patients who did not fulfill this complete cardiac assessment, the patients or their relatives as well as their general practitioner and/or cardiologist were subsequently contacted by telephone for a 2-yr follow-up interview to at least obtain information concerning survival. In case of death, all information available (hospital chart, death certificate) was used to classify death as from a cardiac cause or not. Sudden death was considered as death from a cardiac cause.

Endpoints

The primary endpoint for the comparison between the two groups was death within 2 yr after surgery. Secondary endpoints included nonfatal cardiac events (atrial fibrillation or flutter, ventricular arrhythmia, congestive heart failure, myocardial infarction) during the period of hospitalization and within 2 yr after surgery, mortality in

the hospital, and mortality from cardiac causes within 2 yr after surgery.

Statistical Analysis

According to a preliminary study in our institution, we made the hypothesis that mortality in patients with a low cTnI ($<$ 13 ng/ml) is lower than 3% and that mortality in patients with a high cTnI is greater than 20%, and we estimated that 15% of patients undergoing CABG surgery had a high postoperative cTnI. Assuming an α risk of 0.05 and a β risk of 0.20, we determined that at least 175 patients should be analyzed in our study (NQuery Advisor 3.0, Statistical Solutions Ltd, Cork, Ireland). We therefore decided to include 200 consecutive patients, taking into account patients lost at follow-up over a 2-yr period.

Data are expressed as mean $\pm$ SD or median [extremes], as appropriate. Continuous variables were analyzed with unpaired Student t and Mann–Whitney U tests. Categorical variables were compared by Fisher's exact tests. The association between a high postoperative cTnI and 2-yr mortality was evaluated by the odds ratio and its 95% confidence interval. Event-free survival curves were computed according to the Kaplan-Meier method. Comparison of survival between the two groups was performed using the log-rank test. The receiver operating characteristic curve was used to verify *a posteriori* the best threshold for cTnI to predict death over a 2-yr period after surgery. The best threshold was the one that minimized the distance to the ideal point (sensitivity = specificity = 1) on the receiver operating characteristic curve. All P values were two-tailed and a P value of less than 0.05 was considered significant. Statistical analysis was performed using NCSS 6.0 software (Statistical Solutions Ltd, Cork, Ireland).

Results

Patients Characteristics

During the study period, 202 consecutive patients were included prospectively. Of these, 174 (86%) patients had a low ($<$ 13 ng/ml) postoperative peak cTnI and were allocated to group 1 and 28 (14%) patients had a high ($\leq$ 13 ng/ml) postoperative peak cTnI and were allocated to group 2. Table 1 shows the characteristics of these two groups. There were no significant differences for all preoperative and intraoperative data between the groups.

Short-term Prognosis

In-hospital postoperative data in the two groups of patients are shown in table 2. The median cTnI was 4.1 [range, 1.1–12.6] ng/ml in group 1 and 23.8 [range, 13.4–174.6] ng/ml in group 2. Four (2%) patients died before discharge from hospital; three were in group 1 and one was in group 2. No significant difference was

Table 1. Characteristics of Patients according to Postoperative Value of cTnI (group 1 $<$ 13 ng/ml^{-1} and group 2 $\geq$ 13 ng/ml^{-1})

	Group 1 (n = 174)	Group 2 (n = 28)	P Value
Age, yr	64 ± 9	64 ± 10	NS
Male	155 (89)	28 (100)	NS
Female	19 (11)	0 (0)	
BSA, m²	1.90 ± 0.16	1.86 ± 0.13	NS
Preoperative LVEF (%)	63 ± 12	66 ± 12	NS
Basal cTnI, ng/ml^{-1}	0 [0–0.6]	0 [0–0.4]	NS
Diabetes mellitus	48 (28)	9 (32)	NS
Preoperative medications			
Nitrates	102 (59)	20 (71)	NS
Calcium blockers	87 (50)	13 (46)	NS
Beta blockers	109 (63)	18 (64)	NS
RAS inhibitors	59 (34)	8 (29)	NS
Diuretics	22 (13)	4 (14)	NS
No. of grafts	3 [1–4]	3 [2–4]	NS
CPB time, min	90 ± 22	95 ± 26	NS
ACC time, min	48 ± 13	51 ± 16	NS

Values are mean ± SD, median [range], or number (%).

ACC = aortic cross-clamping; BSA = body surface area; CPB = cardiopulmonary bypass; cTnI = cardiac troponin I; LVEF = left ventricular ejection fraction; NS = no significant difference between groups; RAS = renin angiotensin system.

found between the two groups. All deaths were from noncardiac causes (3 sepsis, 1 acute respiratory failure). Postoperative MI only occurred in patients with a high cTnI, and delayed extubation ($>$ 24 h) and prolonged length of stay in ICU ($>$ 5 days) occurred more frequently in these patients (table 2). In contrast, no significant difference in time to hospital discharge was observed between the two groups (table 2). No patient required an intraaortic balloon pump during the ICU stay.

Long-term Prognosis

Among the 202 patients, four (2%) died in the hospital and 198 (98%) patients were discharged. Twenty-nine (14%, 28 in group 1 and one in group 2) patients were

Table 2. In-hospital Postoperative Data According to Postoperative Value of cTnI (group 1 $<$ 13 ng/ml^{-1} and Group 2 $\geq$ 13 ng/ml^{-1})

	Group 1 (n = 174)	Group 2 (n = 28)	P Value
Delayed extubation $>$ 24 h	5 (3%)	4 (14%)	0.023
Postoperative			
Myocardial infarction	0 (0%)	6 (21%)	$<$0.001
Use of inotropic agents	23 (13%)	7 (25%)	NS
Ventricular arrhythmia	19 (11%)	7 (25%)	NS
Atrial fibrillation	50 (29%)	9 (32%)	NS
All cardiac events	71 (41%)	18 (64%)	0.02
SAPS II score	23 [12–38]	25 [11–40]	NS
ICU stay $>$ 5 d	29 (17%)	13 (43%)	0.003
In-hospital stay, d	8 (5–46)	8 (5–29)	NS
In-hospital mortality	3 (2%)	1 (4%)	NS

Values are mean ± SD, median [range], or number (%).

cTnI = cardiac troponin I; ICU = intensive care unit; NS = non significant; SAPS = Simplified Acute Physiologic Score.[16]

Table 3. Cardiac Events over 24 Months in Patients Discharged Alive from Hospital according to Postoperative Value of cTnI (group 1 < 13 ng/ml^{-1} and group 2 ≥ 13 ng/ml^{-1})

|	Group 1 (n = 143)	Group 2 (n = 26)	P value
LVEF, %	60 ± 11	64 ± 10	NS
Atrial fibrillation	6 (5)	5 (28)	0.004
Congestive heart failure	8 (6)	0 (0)	NS
Ventricular arrhythmia	9 (7)	4 (22)	0.057
All nonfatal cardiac events	21 (16)	7 (39)	0.03

Values are mean ± SD or number (%). Patients underwent complete cardiac follow-up.

cTnI = cardiac troponin I; LVEF = left ventricular ejection fraction (last measurement); NS = non significant.

lost to complete follow-up, so that 169 (84%, 143 in group 1 and 26 in group 2) patients were completely followed up over a 2-yr period after surgery. Nonfatal cardiac events were significantly more frequent in group 2 (table 3). In contrast, left ventricular ejection fraction was unchanged in both groups when compared with preoperative values (table 3).

Information concerning survival was missing in only one patient (from group 1). Six (4%) patients died from cardiac causes (4 myocardial infarction, 1 congestive heart failure, 1 sudden death) over the 2-yr study period; one was in group 1 and five were in group 2. Among these six patients, only one had experienced postoperative MI. Mortality rate (18 vs. 3%, P = 0.006) (fig. 1) and mortality rate from cardiac causes (18 vs. 1%, P < 0.001) were significantly greater in patients with a high postoperative cTnI. A high postoperative cTnI was a significant variable predicting death over a 2-yr period after surgery (odds ratio: 7.3 [2.0–27.1], P = 0.003) and death from cardiac causes (odds ratio: 37.4 [4.2–334.4], P < 0.001).

The receiver operating characteristic curve showed that the best cutoff value of cTnI to predict death over a 2-yr period after surgery was between 12.1 and 13.4 μg/ml.
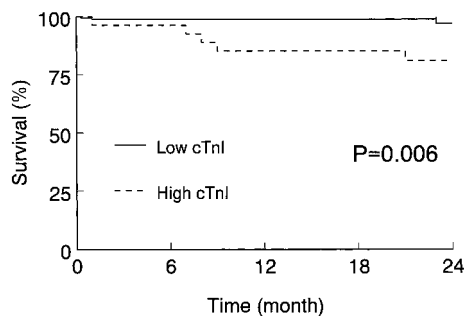
Fig. 1. Cumulative percent of surviving patients according to elevation of cardiac troponin I (cTnI). Group 1 (n = 174; cTnI < 13 ng/ml) and group 2 (n = 28; cTnI ≥ 13 ng/ml). Only one patient (in group 1) was lost on follow-up after 1 yr. *P* value refers to between-group comparison (log-rank test).

Discussion

The main result of the present study is that a high (≥13 ng/ml) value of postoperative cTnI, whatever the cause, is associated with a significant increase in risk of death and death from cardiac causes within 2 yr after CABG in adult patients. A high cTnI was associated with a 37-fold increase in the risk of cardiac death at 2 yr. Moreover, nonfatal cardiac events (especially atrial fibrillation) were also more frequent in the hospital and within a 2-yr period after CABG in patients with a high postoperative cTnI. To our knowledge, this is the first study evaluating the long-term prognostic value of a high cTnI after adult cardiac surgery. Thus, whatever might be the mechanism of myocardial tissue insult, the overall amount of cardiac cells injured during cardiac surgery, reflected by postoperative cTnI release, is correlated with the short- and long-term cardiac clinical outcomes.

We also found in the present study that in-hospital cardiac morbidity was increased when postoperative cTnI levels were increased. The results showed that both delayed extubation and prolonged length of stay in the ICU occurred more frequently in patients with a high cTnI. In contrast, we did not find any significant difference in mortality in the hospital. A likely explanation is the low in-hospital mortality in our study (2%), because we only included patients with a low perioperative risk. An overall mortality of 4.8% in cardiac surgery was reported for a multinational European study that included 19,030 patients.[17] Recently, Lasocki et al.[13] found a mortality rate of 5.6% in a population including more high-risk patients. In that study, the postoperative peak cTnI was a strong and independent predictor of in-hospital death and major postoperative complications after CABG or conventional valve surgery.[13] Our results are consistent with these findings, because we observed delayed extubation and prolonged length of stay in the ICU in patients with a high postoperative cTnI.

Our results could have significant implications for clinical practice. First, an elevated cTnI may indicate an inappropriate cardiac protection and/or inappropriate grafting procedure. Second, an elevated cTnI may also indicate a more severe coronary artery disease that could evolve unfavorably on a long-term basis. These two hypotheses are not exclusive. The definition of a global strategy for the protection of myocardial cells to reduce the consequences of the perioperative tissue loss is one of the main postoperative therapeutic goals in cardiac surgery. In addition, more aggressive decisions could be taken at the bedside early on to restore or improve the energetic myocardial balance in the subgroup of high-risk patients with a high postoperative cTnI, regardless of their clinical condition at the time. As coronary artery grafting *per se* does not lead to an important release of cTnI,[18] in contrast with more complex surgical procedures,[19] it is likely that our patients with a high cTnI

experienced greater postoperative ischemic myocardial damage. The stringent electrocardiogram criteria used to diagnose MI were expected to screen out nontransmural MI, so that the true incidence of perioperative MI was probably underestimated in our study. Non–Q-wave MI occurred more frequently than Q-wave MI in the perioperative period.[20] Unfortunately, MI after cardiac surgery represents the greatest diagnostic difficulty because we do not have a highly sensitive and specific method of diagnosis. The late mortality attributable to non–Q-wave MI is, however, high.[21] Thus, a high postoperative cTnI could predict an increased risk of long-term mortality, probably because it allows non–Q-wave MI or minor myocardial cell injury that one might otherwise have overlooked. A high cTnI after elective CABG could then suggest early subclinical postoperative ischemic myocardial damage and lead the physicians to further investigate the patients and rapidly proceed to invasive revascularization techniques if necessary. The preservation of myocardial energetic balance at any step of the postoperative care seems to be fundamental. Continuous administration of beta-blocker agents during the perioperative period has been shown to reduce postoperative MI and the risk for death at 2 yr in coronary artery disease patients undergoing noncardiac surgery[22] and might also be of some benefit in patients undergoing CABG. However, further studies are needed to understand the precise mechanisms involved in an abnormal elevation of cTnI after CABG surgery; then, appropriate strategies to improve survival in these high-risk patients must be tested. According to the mechanisms involved, these strategies may be directed to the perioperative period and/or to the long-term supervision of the coronary artery disease.

Some remarks must be included to assess the limitations of our study. First, our study was performed in low-risk patients and thus further studies are required to determine the long-term prognostic value of elevated postoperative cTnI in high-risk patients. Second, various assays for cTnI are available and no standardization has yet been obtained.[1] The cutoff value may thus differ from one assay to another. Moreover, the cutoff value chosen in our and previous studies,[13,15] should be considered as only indicative because of the small size of the populations tested.

In conclusion, our prospective study provides evidence that a high postoperative cTnI is an indicator of short- and long-term adverse outcome in patients undergoing CABG. A single postoperative cTnI permits the early identification of patients at increased risks of death and death from cardiac causes.

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