Clinical Significance of Early Postoperative Elevated Cardiac Troponin-I Concentration in Non-cardiac Surgical Patients

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Purpose: Even in postoperative patients, cardiac troponin-I (cTnI) concentration can increase for a number of reasons. Identifying whether an increase is caused by clinically important postoperative complication such as acute myocardial infarction or by some other factor is thus of paramount importance. This study examined the cause of elevated concentration of cTnI during the early postoperative period, and compared the clinical features between patients with elevated cTnI concentration brought on by coronary artery disease (CAD) compared with those having a non-CAD cause.

Methods: Postoperative cTnI concentration was measured in 3,878 patients during 30 months. We selected those patients, 155 in all, whose cTnI concentration exceeded normal value (0.78 ng/ml) more than once within seven days after surgery. The study was conducted with data collected retrospectively. We categorized patients into CAD and non-CAD group.

Results: Of the 155 study subjects, 31 patients were in the CAD group and 124 were in the non-CAD group. The mean age of patients in CAD group (69.6±9.3) was older than that of non-CAD (63.6±13.9). The median value of peak cTnI concentration was higher in the CAD group. In the non-CAD group, 22 patients (17.7%) expired. Death occurred due to sepsis (21.6%), hypovolemic shock (38.1%) and arrhythmia (50%) in study subjects with elevated cTnI. There was one death in the CAD group.

Conclusion: The patients with elevated postoperative cTnI concentration showed higher 28 day-mortality than those without elevation, especially in those without CAD. (*J Acute Care Surg* 2014;4:58-66)

Key Words: Troponin I, Postoperative period, Coronary artery disease

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Introduction

Cardiac troponin-I (cTnI) is a sensitive and specific biochemical marker of myocardial injury. The concentration of cTnI has been shown to increase in coronary artery disease (CAD), such as acute myocardial infarction [1,2]. It is a more accurate marker of the diagnosis and prognosis of myocardial

infarction than the level of creatine kinase in muscles/brain (CK-MB) [3-5]. In addition, the concentration of cTnI allows for the early identification of the presence of acute coronary disease [6]. However, several causes other than acute coronary syndrome can increase the concentration of cTnI; such as cardiac procedures, noncardiac major operations, arrhythmia, heart failure, and renal failure. Studies have demonstrated that

elevation of cTnI concentration is responsible for the overproduction of inflammatory and endothelial factors associated with abnormal myocardial microcirculation and with endothelial dysfunction, as well as with circulating factors (e.g., nitrous oxide, tumor necrosis factor- α [TNF- α], interleukin [IL]-1 beta, and IL-6) induced in surgery or by infection [7-9].

Postoperative cardiac complications include hypertension, arrhythmia, myocardial ischemia, myocardial infarction, and heart failure. Among these, myocardial ischemia and infarction were clinically very important, with mortality reaching almost 30%. Because characteristic symptoms of infarction are usually absent in postoperative patients, it is very important to identify whether an increase in the concentration of cTnI in surgical patients is caused by acute myocardial infarction or some other factor [10-12].

This study examined the cause of an elevated concentration of cTnI in noncardiac surgical patients during the early postoperative period and compared clinical features between patients with elevated cTnI concentration due to CAD and those whose cTnI concentration had increased due to a non-CAD cause.

Methods

Study Population

A total of 31,052 patients underwent surgery at the Department of Surgery of Sungkyunkwan University, Samsung Medical Center over a 30-month period from January 2010 to June 2012. Of these, the postoperative cTnI concentration was measured in 3,878 patients. The concentration of cTnI was determined mainly in patients with a high risk of cardiac complications or comorbidity, patients who had undergone emergency surgery, patients with sepsis, and patients with signs of acute coronary syndrome or symptoms. Among this group, 155 patients whose cTnI concentration was determined within seven days after the surgery and where the concentration exceeded the normal value more than once were included in the study. The patients younger than 20 years old, patients whose cTnI concentration had increased before the surgery and patients who had undergone cardiac surgery, orthopedic surgery, thoracic surgery, or neurosurgery were excluded (Fig. 1).

According to the diagnostic criteria of the World Health Organization for myocardial infarction, the cut off value of TnI concentration as determined by an ADVIA Centaur TnI-Ultra assay (Siemens, Tarrytown, NY, USA) is 0.78 ng/ml.

Fig. 1. Study design. cTnI: cardiac troponin-I, STEMI: ST segment elevated myocardial infarction, NSTEMI: non-ST segment elevated myocardial infarction, SICMP: stress induced cardiomyopathy, CAG: coronary angiogram.

Thus, an elevation of cTnI concentration in the present study was defined as the concentration exceeding 0.78 ng/ml. In all cases, the cTnI concentration was determined with an ADVIA2120 (Siemens).

The cause of the increase in the cTnI concentration was determined by a cardiology specialist based on a coronary angiogram (CAG), echocardiography, and clinical features. The patients whose cTnI concentration was increased because of CAD were classified as the CAD group, whereas those whose cTnI concentration was increased because of non-CAD-related factors were classified as the non-CAD group. CAD was classified as stenosis of more than 50% on more than 2 mm of the main coronary artery on the CAG [13]. Non-CAD was classified as a stenosis of less than 50% or normal on the CAG. The patients in the non-CAD group had not undergone an angiogram because there was a clear cause of the increased cTnI concentration other than CAD, or the increase was attributed to non-CAD-related factors based on the clinical opinion of the cardiology specialist and the results of echocardiography. The cause of the non-CAD was judged on clinical factors. The increase in the concentration of cTnI was attributed to the surgery itself, provided that there had not been any particular cause for the rise in the concentration.

Data Collection and Statistical Analysis

The clinical data on the patients were collected retrospectively from the electronic medical record. The information was obtained on the cTnI concentration 28 days before the surgery and within seven days after the surgery. With respect to comorbidity, the study examined whether the patients had diabetes mellitus (DM), hypertension, hyperlipidemia, ischemic heart disease, cardiomyopathy, heart failure, arrhythmia, renal failure, cerebrovascular disease, and other vascular diseases. It also examined whether a preoperative percutaneous coronary intervention (PCI) or a coronary artery bypass graft (CABG) had been conducted and whether the patients had been prescribed heart-related drugs, such as aspirin, clopidogrel, warfarin, beta-blockers, or calcium channel blockers. Furthermore, the study collected information on the ejection fraction (EF) at the preoperative echocardiogram. Data

were also obtained on the surgical procedure types, planned or unplanned operation, and the American Society of Anesthesiologists Physical Status (ASA) score. With regards to clinical outcomes, information was collected on the number of hospital days, 28-day mortality, and 90-day mortality.

A student's t-test and Mann-Whitney test was conducted to compare the continuous variables. For the categorical variables, a chi-square test and Fisher's exact test were used. The results were expressed as the mean±standard deviation or the median and interquartile range. In the multivariate analysis of the increase in the cTnI concentration in CAD, bipartite logistic regression analysis was conducted by adjusting beta-blocker, hyperlipidemia, comorbidity of ischemic heart disease and high cTnI peak concentration (>3.7 ng/ml) among the preoperative medications, in addition to the patient's basic information that included age, sex, and operation type. The clinical sensitivity (83.9%) and the specificity (61.3%) of a cTnI peak concentration cut-off value of 3.7 ng/ml were assessed by receiver operation characteristic curve analysis. Any case where the p-value was less than 0.05 was considered statistically significant. The data were analyzed using IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA).

Results

Clinical Characteristics

Among the 3,878 patients whose cTnI concentration had been tested, the concentration had increased within seven days after the surgery in 155 (4%) patients. The clinical characteristics of all the patients are shown in Table 1. Sixty of the patients (38.7%) had ischemic heart disease, and 30 patients (19.4%) had undergone a coronary procedure, such as CABG or PCI. Seventy-seven patients (49.7%) had undergone an unplanned operation. The number of hospital days was 18.8 days. The 28-day mortality and the 90-day mortality was 14.8% (n=23) and 18.7% (n=29), respectively. In contrast, in the 3,723 patients whose cTnI concentration had not increased, the 28-day mortality and the 90-day mortality was 2.6% (n=96) and 4.0% (n=150), respectively.

Among the 155 patients whose cTnI concentration had

Table 1. Baseline characteristics

Variable	Value (n=155)
Median age, y (range)	68 (56~73)
Sex (male)	118 (76.1)
ASA score	3 (2~3)
Pre-operative medication	
Aspirin	48 (31.0)
Clopidogrel	36 (23.2)
Warfarin	14 (9.0)
Beta-blocker	46 (29.7)
Calcium channel blocker	53 (34.2)
Comorbidity	
Diabetes mellitus	57 (36.8)
Hypertension	90 (58.1)
Hyperlipidemia	36 (23.2)
Ischemic heart disease	60 (38.7)
Cardiomyopathy	15 (9.7)
Heart failure	18 (11.6)
Arrhythmia	34 (21.9)
Chronic renal failure	33 (21.3)
Cerebrovascular disease	37 (23.9)
Vascular disease	46 (29.7)
Previous coronary procedure	30 (19.4)
Ejection fraction (range)	62 (50~67)
Peak cTnI concentration during ICU admission (ng/ml)	3.55 (1.48~9.13)
Time of cTnI concentration elevation (day)	1 (0~2)
Type of operation	
Major abdominal surgery	77 (49.7)
Major vascular surgery	38 (24.5)
Minor surgery	25 (16.1)
Transplantation	15 (9.7)
Unplanned operation	77 (49.7)
Length of hospital stay (day)	18.8 (10.9~38.8)
28-days mortality	23 (14.8)
90-days mortality	29 (18.7)

Values are presented as median (interquartile range) or number (%). ASA score: American Society of Anesthesiologists Physical Status score, cTnI: cardiac troponin-I, ICU: intensive care unit. Major abdominal surgery: upper/ lower gastrointestinal disease, hepatobiliary, pancreas, splenectomy, adrenalectomy and exploration including bleeding control; major vascular surgery: abdominal aortic aneurysm, aorta and other named vascular operation; minor surgery: arteriovenous fistula, cholecystectomy, appendectomy; transplantation: liver and kidney transplantation.

increased, the rise was due to CAD in 31 (20%) patients among this group, seven patients had ST segment elevated myocardial infarction (STEMI), and 24 patients had non-STEMI. In the 124 (80%) patients whose cTnI concentration had increased

Table 2. Cause of cardiac troponin-I concentration elevation in coronary artery disease (CAD) and non-CAD

Variable	Value
CAD (n=31)	
STEMI	7 (22.6)
NSTEMI	24 (77.4)
Non-CAD (n=124)	
Surgery	41 (33.1)
Sepsis	37 (29.8)
Hypovolemic shock	21 (16.9)
Arrhythmia	10 (8.0)
Acute heart failure	7 (5.6)
Post cardiopulmonary resuscitation	5 (4.0)
Pulmonary embolism	1 (0.8)
Hypertensive cardiomyopathy	1 (0.8)
Cardiac tamponade	1 (0.8)

Values are presented as number (%).

STEMI: ST segment elevated myocardial infarction, NSTEMI: non-STEMI.

due to non-CAD causes, the non-CAD causes included surgery, sepsis, hypovolemic shock, arrhythmia, acute heart failure, post cardiopulmonary resuscitation, pulmonary embolism, hypertensive cardiomyopathy, and cardiac tamponade (Table 2).

Comparison between CAD Group and Non-CAD Group

The comparison between the two groups is presented in Table 3. The CAD group was statistically significantly older than the non-CAD group, with the average age in the former 70 years (62~78 years) and 66 years (55~73 years) in the latter. The median value of the peak cTnI concentration during intensive care unit (ICU) admission was statistically significantly higher in the CAD group ($p<0.05$). There was no difference between the two groups in terms of the sex ratio of men and women, ASA score, coronary procedure, CABG, PCI, medication taken before the surgery, EF, echocardiogram results, and type of surgery conducted. Among the comorbidities, the incidence of DM, hypertension, hyperlipidemia, and ischemic heart disease was significantly higher in the CAD group. However, there was no difference between the two groups in terms of cardiomyopathy, heart failure, arrhythmia, renal failure, cerebrovascular disease, and other vascular diseases.

The time of first elevation of cTnI concentration in the two

Table 3. Baseline characteristics of coronary artery disease (CAD) and non-CAD groups

Variable	CAD (n=31)	non-CAD (n=124)	p-value
Median age, y (range)	70 (62~78)	66 (55~73)	0.030
Sex (male)	27 (87.1)	91 (73.4)	0.109
ASA score	3 (2~3)	3 (2~3)	0.367
Pre-operative medication			
Aspirin	12 (38.7)	36 (29.0)	0.297
Clopidogrel	8 (25.8)	28 (22.6)	0.704
Warfarin	0 (0.0)	14 (11.3)	0.074
Beta-blocker	6 (19.4)	40 (32.3)	0.160
Calcium channel blocker	9 (29.0)	44 (35.5)	0.498
Comorbidity			
Diabetes mellitus	18 (58.1)	39 (31.5)	0.006
Hypertension	26 (83.9)	64 (51.6)	<0.001
Hyperlipidemia	14 (45.2)	22 (17.7)	<0.001
Ischemic heart disease	27 (87.1)	33 (26.6)	<0.001
Cardiomyopathy	2 (6.5)	13 (10.5)	0.737
Heart failure	6 (19.4)	12 (9.7)	0.205
Arrhythmia	7 (22.6)	27 (21.8)	0.923
Chronic renal failure	7 (22.6)	26 (21.0)	0.844
Cerebrovascular disease	10 (32.3)	27 (21.8)	0.221
Vascular disease	11 (35.5)	35 (28.2)	0.429
Previous coronary procedure	7 (22.6)	23 (18.5)	0.611
Ejection fraction (range)	61.5 (47.8~67.0)	62 (55.5~66.5)	0.538
Peak cTnI concentration during ICU admission (ng/ml)	10.56 (4.59~19.65)	2.98 (1.25~6.44)	<0.001
Time of cTnI concentration elevation (day)	1 (0~3)	1 (1~2)	0.050
Type of operation			0.047
Major abdominal surgery	14 (45.2)	63 (50.8)	
Major vascular surgery	8 (25.8)	30 (24.2)	
Minor surgery	9 (29.0)	16 (12.9)	
Transplantation	0 (0.0)	15 (12.1)	
Unplanned operation	13 (41.9)	64 (51.6)	0.335
Length of hospital stay (day)	19.9 (11.7~29.6)	18.7 (10.8~40.8)	0.971
28 days mortality	1 (3.2)	22 (17.7)	0.048
90 days mortality	2 (6.5)	27 (21.8)	0.050

Values are presented as median (interquartile range) or number (%).

ASA score: American Society of Anesthesiologists Physical Status score, cTnI: cardiac troponin-I, ICU: intensive care unit. Major abdominal surgery: upper/lower gastrointestinal disease, hepatobiliary, pancreas, splenectomy, adrenalectomy and exploration including bleeding control; major vascular surgery: abdominal aortic aneurysm, aorta and other named vascular operation; minor surgery: arteriovenous fistula, cholecystectomy, appendectomy; transplantation: liver and kidney transplantation.

groups is shown in Fig. 2. The rise in the cTnI concentration over time, it increased for the first time within three days after the surgery in more than 80% of the patients in both groups (Fig. 2A). The median of the dates during which the cTnI concentration increased was 1.5 days for the CAD group, whereas it was 1.7 days for the non-CAD group. There was a tendency for the cTnI to increase a little faster after the surgery in the CAD group, but this was not statistically significant.

When the transition in the cTnI concentration over time was compared in the two groups using a linear mixed model, the cTnI concentration was higher in the CAD group, and it took longer to fall in this group. However, there was not a statistically significant difference ($p=0.527$, Fig. 2B).

The median length of hospital days was 19.9 (11.7~29.6) in the CAD group and 18.7 (10.8~40.8) in the non-CAD group and there was not a significant difference. However, mortality

Fig. 2. (A) Time of first elevation of cardiac troponin-I (cTnI) concentration over than 0.78 ng/ml. (B) Log transformation of level of cTnI concentration along the pod. OP day: operative day, Pod: post-operative day, CAD: coronary artery disease.

was statistically significantly higher in the non-CAD group; the 28-day mortality was 3.2% in the CAD group vs. 17.7% in the non-CAD group, and the 90-day mortality was 6.5% vs. 21.8%.

According to the results of the univariate analysis, the increase in the cTnI concentration in the CAD group was closely related to age, diabetes DM, hypertension, hyperlipidemia, and ischemic heart disease. In the multivariate analysis, preoperative beta-blocker medication (odds ratio [OR], 0.22; 95% confidence interval [CI], 0.06~0.83; $p=0.025$), comorbidity associated with ischemic heart disease (OR, 14.36; 95% CI, 3.92~52.57; $p<0.001$) and a high peak concentration of cTnI (OR, 8.39; 95% CI, 2.20~31.95; $p=0.002$) were statistically significantly independent factors related to CAD. There was no statistical correlation between CAD and age, sex, hyperlipidemia-related comorbidity, and surgery type (Table 4).

Discussion

In only 20% of cases in the present study, CADs, such as STEMI and non-STEMI, were responsible for the elevation of cTnI concentration after surgery. Non-CAD causes were responsible for the increase in 80% of cases. In these cases, the rise was attributed to a variety of causes, including surgery, sepsis, hypovolemic shock, arrhythmia, acute heart failure, pulmonary embolism, and cardiac tamponade. The results indicate that factors other than coronary diseases are frequently

Table 4. Multivariate predictors of post-operative coronary artery disease

Variable	OR (95% CI)	p-value
Age (per year)	1.02 (0.97~1.07)	0.554
Sex (male)	0.74 (0.15~3.77)	0.717
Pre-operative medication		
Beta-blocker	0.22 (0.06~0.83)	0.025
Comorbidity		
Hyperlipidemia	3.49 (0.96~12.63)	0.057
Ischemic heart disease	14.36 (3.92~52.57)	<0.001
Cardiac troponin-I concentration	8.39 (2.20~31.95)	0.002
Type of operation		
Major abdominal surgery	1	0.234
Major vascular surgery	0.42 (0.11~1.63)	0.210
Minor surgery	2.47 (0.55~11.04)	0.235
Transplantation	0 (0~∞)	0.998

OR: odds ratio, CI: confidence intervals. Major abdominal surgery: upper/lower gastrointestinal disease, hepatobiliary, pancreas, splenectomy, adrenalectomy and exploration including bleeding control; major vascular surgery: abdominal aortic aneurysm, aorta and other named vascular operation; minor surgery: arteriovenous fistula, cholecystectomy, appendectomy; transplantation: liver and kidney transplantation.

the source of the increase in the cTnI concentration after surgery. Jeremias and Gibson [14] reported that a variety of diseases, such as sepsis, hypovolemia, atrial fibrillation, congestive heart failure, pulmonary embolism, myocarditis, myocardial contusion, and renal failure, could lead to a rise in the level of cTnI and that such a rise would not necessarily result from

thrombotic coronary artery occlusion. Kellum et al. [15] reported that 55% of critically ill patients with no acute CAD showed an increase in the concentration of cTnI and troponin-T (TnT) and that the concentration of cTnI increased in critically ill patients with no cardiovascular disease. Moreover, they argued that the blood TNF- α and IL-6 might be related to the rise in the concentration of cTnI, because these were increased in the patients in whom troponin was detected. As shown in other studies, the rise in the concentration of cTnI might be due to secondary to myocardial ischemia, which occurs cause of the mismatch between the oxygen quantity supplied and the oxygen quantity consumed in cardiac muscle during surgery [16,17].

The comparison of the CAD group and the non-CAD group revealed several clinical differences. First, the CAD group had more patients with underlying diseases, such as DM, hypertension, hyperlipidemia, and ischemic heart disease. In addition, the median of the cTnI concentration peak level was 10.56 ng/ml in the CAD group and it was significantly higher than in the non-CAD group (2.98 ng/ml). The period during which the cTnI concentration increased did not have any statistical significance (1 vs. 1; $p=0.05$).

In the multivariate analysis, comorbidity related to ischemic heart disease and a high peak concentration of cTnI showed a positive correlation with CAD, and preoperative beta-blocker medication displayed a negatively correlated with CAD. The elevation of cTnI might be due to CAD if the patients had underlying ischemic heart disease or peak cTnI was more than 3.7ng/ml. Another possibility is that the incidence of CAD was lower among the patients who had taken preoperative beta-blocker medication. The incidence of CAD among the patients who had ischemic heart disease would be expected to increase due to the presence of coronary artery damage. Another study demonstrated that the peak concentration of cTnI was of no assistance as a marker of CAD [3]. In this study, in the CAD group, the increase of cTnI concentration was likely due to cardiac injury rather than to surgery, sepsis, or shock. Several studies have reported that a preoperative beta-blocker helps to prevent postoperative cardiac problems [18]. However, this protective effect is generally seen only in patients whose revised

cardiac risk index (RCRI) score is more than 2. In the present study, the patients who had taken a preoperative beta-blocker already had comorbidity. Such patients would be expected to have an RCRI score of 0 or 1. Thus, the increase in the concentration of cTnI among the patients who had taken a beta-blocker was likely due to CAD in only a few cases. However, there is no way of verifying this, as there were no data on the RCRI score.

Other studies conducted at this medical center have compared CAD and non-CAD patients, confirmed by coronary angiography in the medical ICU with suspected myocardial infarction [19]. This study found that male sex and focal hyperkinesia on echocardiography were independently associated with CAD. Generally, there is high possibility of CAD if focal hyperkinesia present on echocardiography. In current study, because of the absence of data about echocardiography on focal hyperkinesia after an increase in cTnI, it was not possible to determine whether there was an association with CAD.

With regard to th clinical outcomes, 28 days mortality was 17.7% among the non-CAD group compared to 3.2% in the CAD group. Thus, it can be deduced that factors other than CADs affected death after surgery [20]. The prognosis of the patients who underwent treatments, such as PCI, following a CAG for CAD was good. Although we were unable to compare the severity score between the patients in the present study, the high mortality in the non-CAD group was likely due to these underlying diseases because the mortality was higher than in the patients with other diseases (e.g., sepsis: 21.6%; hypovolemic shock: 38.1%; arrhythmia: 50%). An increase in cTnI has been shown to be an independent predictive factor of long-term mortality. In a systemic review, Levy et al. [21] reported that an increase in the concentration of troponin among noncardiac surgery patients was a predictive factor of mortality for the first year after surgery independently. Babuin et al. [22] also reported that the troponin concentration of patients in the ICU of an internal medicine unit was a predictive factor of long- and short-term mortality. Another study concluded that information on the troponin concentration could be useful in treating surgical patients or critically ill patients and establishing a follow-up strategy [23].

This study has several limitations. First, this study is a retrospective study conducted at a single center. Thus, there is likely an inherent bias in the study. Second, not all the patients received a diagnosis of CAD and non-CAD through a CAG. As a result, there is the possibility that an unconfirmed CAD patient was included in the non-CAD group. Third, non-CAD causes were based solely on clinical parameters. Therefore, the actual cause that non-CAD increases the concentration of cTnI is not known (was not confirmed). Fourth, as a severity score was not used to predict the mortality, the reported difference in mortality outcomes may not be accurate. However, this study is significant in that includes a large number of patients (3,878) who underwent surgery in the past four years. It is also the first report in South Korea to confirm the clinical significance of an increase in the concentration of cTnI in non-cardiac surgical patients.

In conclusion, an increase in the cTnI concentration during the early postoperative period occurred due to a variety of factors, with the increase in a substantial number of cases caused by factors other than CAD. In addition, comorbidities associated with ischemic heart disease, preoperative beta-blocker medication, and a high cTnI concentration were significantly correlated with CAD. A large-scale prospective study is needed to determine the causes of the increase in postoperative cTnI concentrations.

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