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# The Relationship between Cardiotrophin-1 and Troponin-I in Coronary Arterial Bypass Grafting on the Beating Heart: A Prospective Study

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## ABSTRACT

**Objective:** Cardiotrophin-1 (CT-1) is closely associated with many cardiovascular diseases, such as hypertension, myocardial infarction (MI), and heart failure, and exhibits a cardioprotective effect in ischemia-reperfusion injury. The aim of this study was to evaluate the relationship between CT-1 and Troponin-I (Tn-I) in off-pump coronary artery bypass (OPCAB) grafting on the beating heart.

**Methods:** Seventy-eight patients (mean age 60.8 ± 9.7 years, 79.5% male) undergoing elective OPCAB surgery were included in this study undertaken between July 1, 2012 and July 1, 2013 in the Department of Cardiology and Cardiac Surgery, University School of Medicine Hospital. Venous blood samples were collected 5 minutes before OPCAB surgery and 6 hours after surgery. Plasma CT-1 levels were measured using the ELISA method.

**Results:** Compared to the preoperative period, Tn-I and CT-1 values were higher in the postoperative period [0.255 ng/mL (0.030-0.430) versus 0.045 ng/mL (0.005-0.090), $P < .001$; and 33.7 pg/mL (15.8-98.5) versus 8.7 pg/mL (0.68-25.4), $P < .001$]. There was also an elevation in white blood cells, aspartate aminotransferase, creatine kinase (CK), and creatine kinase MB (CK-MB) values, as well as a decrease in hemoglobin values ($P < .001$). When a correlation analysis for postoperative CT-1 was performed, there was a significant positive correlation between postoperative CK, CK-MB, and Tn-I levels ($r = 0.250$, $P < .027$; $r = 0.270$, $P = .017$; and $r = 0.241$, $P < .034$).

**Conclusion:** CT-1 was found to be associated with Tn-I, which is used to detect myocardial damage after OPCAB surgery. CT-1 may also be used to detect myocardial damage.

## INTRODUCTION

Coronary artery disease (CAD) is the leading cause of death worldwide [Onat 2001]. Coronary artery bypass (CAB) graft surgery is a surgical technique to treat CAD. Off-pump coronary artery bypass grafting on the beating heart (OPCAB) has several advantages over conventional CAB, such as shorter surgery time, lower rates of cardiac ischemia, shorter intensive care duration, lower blood transfusion requirements, higher graft patency in the early period, and lower mortality rates. For these reasons, OPCAB has become increasingly preferred over conventional CAB [Cleveland 2001]. Even with new technologies, mortality and morbidity associated with perioperative myocardial ischemia/reperfusion damage are still major problems. Postoperative clinical examinations and electrocardiography (ECG) can be insufficient in detecting myocardial damage. Therefore, many biochemical indicators are used to evaluate myocardial damage. The most common among these are creatine kinase MB (CK-MB) and troponin (Tn-I) [Roberts 1974; Katus 1991].

Cardiotrophin-1 (CT-1) is a member of the interleucin-6 cytokine superfamily. CT-1 mRNA is produced in the adult human heart, skeletal muscles, ovaries, colon, prostate, and lungs. CT-1 plays a major role in ischemic heart disease pathogenesis. CT-1 expression is elevated in hypoxic situations to protect myocytes from ischemic and reperfusion injuries and apoptosis. It is shown that pro-oxidants and physiologic hypoxia increase CT-1 release [Adams 1993; Wen 2005; Sauer 2004; Hishinuma 1999].

In this study, we aimed to evaluate the relationship between CT-1 and Tn-I in myocardial damage in patients undergoing elective OPCAB and the relationship with other cardiac biomarkers.

## MATERIALS AND METHODS

Seventy-eight patients who were admitted for CAB surgery to the Department of Cardiology and Cardiac Surgery, University School of Medicine Hospital between July 1, 2012 and July 1, 2013 were included in this study. Patients with recent myocardial infarction (MI) (<1 month) prior to CAB surgery, acute or chronic kidney failure, left ventricular systolic dysfunction, chronic inflammatory disease, malignancy, acute infection, liver failure (>2X ALT up limit), and unknown preoperative or postoperative CT-1 levels were excluded from the study.

The subjects' demographic information and medical histories were recorded, including age, sex, smoking history, alcohol

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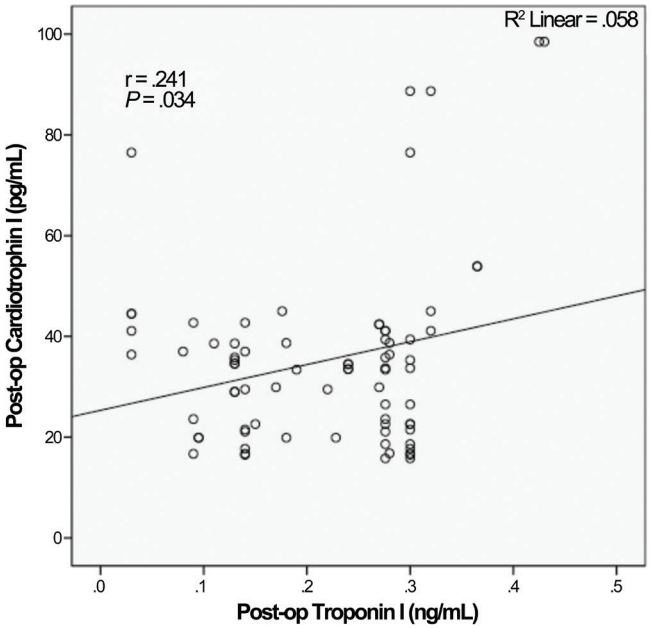
Table 1. Patient Demographics and Basic Clinical Features

| | |
|---|---|
| M/F sex, n (%) | 62 (79.5)/16 (20.5) |
| Age, y | 60.8 ± 9.6 |
| Diabetes mellitus, n (%) | 32 (41) |
| Hypertension, n (%) | 68 (87.2) |
| Hyperlipidemia, n (%) | 30 (38.5) |
| Family history, n (%) | 52 (66.7) |
| Obesity, n (%) | 8 (10.3) |
| Smoking, n (%) | 44 (56.4) |
| Alcohol consumption, n (%) | 30 (38.5) |
| Statin, n (%) | 16 (20.5) |
| Beta-blocker, n (%) | 34 (43.6) |
| ACE inh/ARB, n (%) | 38 (48.7) |
| ICU stay, d | 1.1 ± 0.8 |
| Hospital stay, d | 5.03 ± 0.8 |

Data are presented as the mean ± SD where indicated. ACE inh indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICU, intensive care unit.




Correlation between postoperative CT levels and postoperative Tn-1 levels in patients.

consumption history, family history, presence of diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL), obesity, and other diseases. Medications were also recorded.

### *Anesthesia, Surgical, Pharmacologic, and Postoperative Protocol*

All patients were premedicated with morphine. Standardized anesthetic techniques were used along with sufentanil, midazolam, and vecuronium, and standard OPCAB surgery was undertaken via median sternotomy. Esmolol was given when necessary to reduce the heart rate. Coronary grafting was performed on a beating, normothermic heart using internal thoracic artery (ITA), and/or radial artery, and/or peripheral vein grafts from the lower extremities. A U-shaped stabilizer (Octopus, Medtronic, Minneapolis, MN, USA) was used to dampen the movement of the beating heart and consequently to isolate the region for anastomosis. Proximal anastomosis of the aorta was performed using tangential clamping. An initial dose of 1.5 mg/kg body weight of heparin was administered after harvesting the internal mammary artery to achieve systemic anticoagulation during surgery. Activated clotting time (ACT) was adjusted to a target of over 300 s. ACT was measured using a kaolin-activated system. After the end of the grafting procedure, the effect of the heparin was reversed by protamine administration (1:1 ratio) to achieve an ACT of approximately 150 s. Intraoperative shed blood was collected and retransfused before the end of surgery. Postoperative treatment in the intensive care unit (ICU) was standardized. No postoperative shed mediastinal blood was retransfused. Whole blood transfusion was administered when hemoglobin decreased to less than 10 mg/dL. Oral aspirin (100 mg once per day) and subcutaneous injection of low molecular weight heparin (0.6 mL twice per day) was started on the first postoperative day. The use of inotropes was decided by the doctors in charge in the ICU based on postoperative status.

### *Laboratory*

Venous blood samples were collected immediately before CAB and 6 hours after CAB; venous blood samples of the patients were studied for serum Tn-I and CT-1 and for routine biochemical analysis. Tn-I and CT-1 were studied in separated sera. The blood samples were stored at -20°C until analysis of the CT-1, which was measured using a CT-1 enzyme-linked immunosorbent assay kit maintained at 4°C. Results were measured as pg/mL.

All patients were examined using ECG to determine their basal rhythm (sinus rhythm, atrial fibrillation [AF], etc) preoperatively and postoperatively. Patients were followed for 30-day mortality and stroke development after discharge. Postoperative cardiovascular events were described as cardiac death, non-fatal MI, new AF development, cerebrovascular events, and acute renal failure. CAB-related MI was defined as Tn values 10 × 99th percentile upper reference limit (URL) during the first 48 hours following CABG, occurring from a normal baseline Tn value (≤ 99th percentile URL) and/or either (i) new pathological Q waves or new LBBB, or (ii) angiographically documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality [Thygesen 2012]. Cerebrovascular events were defined as transient ischemic attack (TIA) (detected with clinical examination and imaging modalities), hemorrhagic stroke, and ischemic stroke.

Table 2. Changes in Laboratory Values between Preoperative and Postoperative Period in Patients

| | Preoperative | Postoperative | *P** |
|---|---|---|---|
| WBC (K/μL) | 7.9 ± 1.6 | 10.5 ± 2.1 | <.001 |
| Hb (g/dL) | 13.6 ± 1.3 | 10.4 ± 1.3 | <.001 |
| Urea (mg/dL) | 33.3 ± 7.8 | 35.3 ± 12.3 | .157 |
| CRE (mg/dL) | 0.9 ± 0.1 | 0.9 ± 0.37 | .079 |
| AST (IU/L) | 25.1 ± 9.7 | 37.8 ± 17.8 | <.001 |
| ALT (IU/L) | 25.0 ±13 | 23.8 ±14.7 | .442 |
| CK (IU/L) | 79 (22-311) | 615 (118-936) | <.001 |
| CK-MB (IU/L) | 18 (9-40) | 26 (20-83) | <.001 |
| Tn-I (ng/mL) | 0.045 (0.005-0.090) | 0.255 (0.030-0.430) | <.001 |
| CT-1 (pg/mL) | 8.7 (0.68-25.4) | 33.7 (15.8-98.5) | <.001 |

*Values in bold are statistically significant. WBC indicates white blood cell; Hb, hemoglobin; CRE, creatinine; AST, aspartate amino transferase; ALT, alanine amino transferase; CK, creatine kinase; CK-MB, creatine kinase MB; Tn-I, troponin-I; CT-1, cardiotrophin-1.

***Statistical Analysis***

Statistical analysis was performed using the Statistical Package for Social Sciences for Windows (SPSS version 16). Continuous variables are expressed as mean ± standard deviation (SD) and median, minimum, and maximum (min, max). Categorical variables are given as number and percentage (%). The groups were compared according to the distribution of continuous variables using Student t, Mann–Whitney U, and Kruskal–Wallis tests. Categorical variables were compared using a Chi-square test. Correlation analyses were performed using Pearson and Spearman tests. Statistical significance was determined as $P < .05$.

## RESULTS

Seventy-eight patients were included in the study. The demographic and clinical characteristics of the subjects are shown in Table 1; the mean age was 60.8 ± 9.7 years, 79.5% were male. Of the subjects, 41% had DM, 87.2% had HT, 38.5% had HL, 66.7% had a family history of heart disease, 10.3% were obese, 56.4% had a history of smoking, and 38.5% had a history of alcohol consumption (Table 1).

Regarding medications, 20.5% of the subjects were using statins, 43.6% were using beta blockers, and 48.7% were using an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) (Table 1). The length of time spent in the ICU was 1.1 ± 0.8 days. The average length of hospital stay was 5.03 ± 0.8 days.

There were no significant differences in urea, creatinine, or ALT levels between the preoperative period and the postoperative period. However, white blood cell (10.5 ± 2.1 versus 7.9 ± 1.6, $P < .001$), AST (37.8 ± 17.8 versus 25.1 ± 9.7, $P < .001$), CK [615 (118-936) versus 79 (22-311), $P < .001$], and CK-MB [26 (20-83) versus 18 (9-40), $P < .001$] levels were higher in the postoperative period compared to the preoperative period (Table 2). Tn-I [0.255 ng/mL (0.030-0.430) versus 0.045 ng/mL (0.005-0.090), $P < .001$] and CT-1 pg/mL [33.7 (15.8-98.5) versus 8.7 pg/mL (0.68-25.4), $P < .001$] values were higher in the postoperative period compared to the preoperative period (Table 2).

Table 3. Correlation of Parameters with Postoperative CT-1

| CT-1 | Post-op Tn-I | Post-op CK | Post-op CK-MB |
|---|---|---|---|
| r value | 0.241 | 0.250 | 0.270 |
| *P* value | .034 | .027 | .017 |

CK indicates creatine kinase; CK-MB, creatine kinase MB; Tn-I, Troponin-I; CT-1, cardiotrophin-1; Post-op, postoperative; Pre-op, preoperative.

The correlation analysis revealed that postoperative CT-1 was positively correlated with postoperative Tn-I levels ($r = 0.241$, $P < .034$) (Figure) and CK and CK-MB ($r = 0.250$, $P < .027$; $r = 0.270$, $P = 0.017$) levels (Table 3).

There were 22 cardiovascular events in 20 patients (2 nonfatal MIs, 16 new onset AF developments, and 4 cerebrovascular events) and no deaths. When patients with and without cardiovascular events were compared, there was no significant difference in postoperative CK, CK-MB, or Tn-I levels; however, there were significant postoperative differences in CT-1 values [38.2 (16.7-98.5) versus 33.4 (15.8-88.7); $P = .037$] and DM prevalence (70% versus 31%; $P = .002$) in patients with cardiovascular events compared to those without cardiovascular events.

## DISCUSSION

We showed that in the postoperative period, CT-1 was increased and was well correlated with Tn-I and other cardiac biomarkers (CK and CK-MB) used to detect myocardial damage after CAB surgery.

OPCAB has become increasingly preferred over conventional CAB in recent years. Postoperative myocardial damage is still a major problem associated with CAB grafting surgery. Even with all the intraoperative myocardial protection measures and advancements in surgery, there can be different kinds of myocardial damage. Ischemia occurs in 5-15% of patients and can progress to myocardial necrosis [Greaves 1996]. Force et al [Force 1990] and Chaitman et al [Chaitman 1983] showed that patients with perioperative MI have a poorer three-year survival rate. To detect myocardial damage, CK, CK-MB, AST, and other more sensitive and specific biomarkers like Tn-I are used [Roberts 1974; Katus 1991]. Perioperative ischemia is associated with postoperative complications, increased hospital mortality, and longer hospitalization. Thus, there is an interest in this field in order to make diagnosis of perioperative myocardial ischemia with higher sensitivity and specificity. CT-1, which release hypoxic situations to protect myocytes from ischemic and reperfusion

injuries and apoptosis, was thought to be useful in detection of myocardial ischemia related to CAB.

In a previous study, CT-1 was collected from transmyocardial coronary sinus blood, radial artery blood, and peripheral vein samples before CAB. Peripheral CT-1 levels were not different than CT-1 levels in coronary sinus blood samples and radial artery blood samples before CPB [Tian 2011]. Furthermore, CT-1 levels increased significantly 5 and 20 minutes into surgery compared to baseline levels. However, peripheral CT-1 levels did not change significantly in the postoperative period compared to baseline levels [Tian 2011]. In another study, CT-1 levels did not change significantly after surgery compared to baseline levels [Wei 2008]. In our study, patient selection was elective; there was no recent MI history, and the off-pump CAB technique was used. There was a significant elevation in CK and CK-MB levels in the postoperative period. There was also a significant increase in Tn-I and CT-1 levels in the postoperative period. The correlation analysis revealed that postoperative CT-1 levels were correlated with postoperative CK, CK-MB, and Tn-I levels. These findings have suggested that CT-1 levels are elevated as a result of hypoxia and cellular-level injury in myocytes caused by perioperative ischemic, mechanic, or inflammatory mechanisms. Therefore, CT-1 may be used to determine perioperative hypoxia and cellular injury, like Tn-I etc.

CT-1 is an important molecule in the neurohormonal response to cardiac injury [Richards 2000]. Due to its different effects on the heart, CT-1 is considered not only as a marker of disease, but it can also be involved in pathological changes of cardiovascular diseases, such as hypertension, valve diseases, congestive heart failure, and coronary artery diseases. Elevated serum levels of CT-1 have been observed in patients with unstable angina, acute myocardial infarction, and heart failure, and they are obviously correlated with the degree of left ventricular systolic dysfunction [Tsutamoto 2007; Talwar 2000a; Talwar 2002; Talwar 2000b]. Available evidence supports the beneficial effects of CT-1 in promoting myocardial cell survival, inducing hypertrophy of remaining myocytes, and proliferation and migration of fibroblasts from adjacent viable myocardium. In this way, CT-1 reduces myocyte loss with the repopulation of the infarct scar and improves the ventricular performance [Freed 2003a; Freed 2003b]. Myocardial ischemic injury occurs during bypass surgery. CT-1 released in the reperfusion period can be cardioprotective in patients undergoing CABG. Ghosh et al demonstrated that CT-1 has a protective effect against ischemia in human adult myocardium, which can significantly decrease CK leakage [Ghosh 2000]. They found that the protection is afforded when tissue is exposed to CT-1 for 24 hours [Ghosh 2000]. When our study results are considered, CT-1 may be used as a marker for showing ischemic damage caused by bypass surgery. Furthermore, CT-1 may be used for predicting cardiac events within 1 month following bypass surgery.

Diabetes is a well-established risk factor for CAB and is associated with an increased rate of early and late adverse events after myocardial revascularization by CAB [Luciani 2003]. In our study, we found an association between cardiovascular events and DM prevalence. In addition, we observed a relationship between cardiovascular events and CT-1 values. A previous study showed that plasma CT-1 measurements can provide additional prognostic information that can predict mortality in patients with cardiovascular disease [Tsutamoto 2007; Khan 2006]. Our findings suggest that CT-1 may be useful in predicting postoperative complications in OCAB.

In previous studies, the incidence of AF development in post-CAB surgery patients was 10-50% [Ad 1999]. In our study, the incidence of new AF was 20.5%. In addition, there was a significant decrease in Hb levels after surgery. Anemia is a well-known risk factor for perioperative mortality and morbidity. Anand et al report that every 1 g/dL decrease in hemoglobin levels is associated with a 16% increase in mortality [Anand 2004]. However, in our study, anemia did not affect 30-day cardiovascular events.

Major postoperative neurologic complications account for a large percentage of morbidity. In an eight-week postoperative period, there are cognitive changes in 25-30% of patients, but these typically partially resolve in a year [Smith 1988; Gillinov 1991]. However, some studies show lower cognitive dysfunction, lower cerebral edema, and lower stroke incidence in OPCAB patients compared to conventional bypass patients [Stroobant 2005; Marui 2012]. In our study, only four patients (5.1%) had a cerebrovascular event, which may be due to a preference in OPCAB technique.

### *Limitations*

Our study was conducted with a limited patient group and in a limited timeframe. Therefore, the evaluation of CT-1 may need a larger population and randomized prospective studies to better understand the role of myocardial damage in OPCAB patients.

### *Conclusion*

CT-1 may be used as a predictor of perioperative myocardial ischemia. CT-1 measurement, along with CK, CK-MB, and Tn-I measurements, may show the presence and severity of ischemia.

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