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Original Article

Perioperative Factors Associated With Changes in Troponin T During Coronary Artery Bypass Grafting

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Objective: Investigate important clinical and operative variables associated with increases in cardiac troponin T (cTnT) as indicators of myocardial injury after coronary artery bypass grafting (CABG).
Design: Prospective cohort study.
Setting: Single university hospital.
Participants: The study comprised 626 patients undergoing isolated CABG from April 2008 through April 2010 with a validation cohort (n = 686) from 2015-2017.
Interventions: None.
Measurements and Main Results: Perioperative variables were registered prospectively. The extent of diffuse coronary atherosclerosis and significant stenoses were assessed with preoperative coronary angiography. Mixed model analysis was used to construct a statistical model explaining the course of cTnT concentrations. The model was adjusted for preoperative and intraoperative/postoperative myocardial infarction (MI) for independent assessment of additional variables. Clinical factors associated with increased cTnT concentrations during and after CABG were longer duration of cardiopulmonary bypass ($p < 0.001$), higher preoperative creatinine ($p < 0.001$), New York Heart Association functional classification IV ($p = 0.006$), reduced LVEF ($p = 0.034$), higher preoperative C-reactive protein ($p = 0.049$), and intraoperative/postoperative MI ($p < 0.001$). Factors associated with decreasing cTnT concentrations during CABG were higher BSA ($p < 0.001$) and a recent preoperative MI ($p < 0.001$). The extent of diffuse coronary atherosclerosis and significant stenoses were not associated with changes in cTnT ($p = 0.35$). Results were similar in the validation cohort.
Conclusions: Left ventricular ejection fraction, New York Heart Association classification, kidney function, inflammation status, duration of cardiopulmonary bypass, body surface area, and preoperative MI were associated with the cTnT rise-and-fall pattern related to myocardial injury after CABG. Information regarding these variables may be valuable when using cTnT in the diagnostic workup of postoperative MI.

Key Words: coronary artery bypass grafting; troponin T; myocardial infarction

CARDIAC TROPONIN T (cTnT) is a plasma marker demonstrating myocardial injury that may be caused by a multitude of pathophysiologic conditions including myocardial infarction (MI).

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According to the fourth universal definition of myocardial infarction, 2 measurements of cTnT, whereby 1 is greater than the 99th percentile of the reference value, are necessary as is the fulfillment of at least 1 of 5 specified additional criteria.[1] During cardiac surgery, surgical trauma and ischemia-reperfusion injury resulting in myocardial injury contribute to cTnT release.[2] Therefore, higher thresholds for cTnT concentrations are set for an MI diagnosis in this setting.[1,3]

In clinical practice, however, large variations in cTnT concentrations are observed among patients without other indications of an MI after cardiac surgery, and many patients have higher concentrations than those included in the MI definition. There is a knowledge gap to explain these interindividual differences, which renders cTnT concentrations more difficult to use as part of the diagnostic workup for a suspected MI. Better understanding of factors related to increased cTnT concentrations, therefore, may contribute to more accurate diagnostics of MI after cardiac surgery.

The authors hypothesized that preoperative factors such as inflammatory status, age, sex, and the degree of diffuse coronary atherosclerosis could influence the perioperative cTnT concentration course. The aim of the present study was to investigate associations between perioperative cTnT concentrations and important clinical and operative variables, including the extent and distribution of preoperative diffuse coronary atherosclerosis, in patients undergoing coronary artery bypass grafting (CABG). This study used multivariate mixed models to evaluate variables associated with the perioperative dynamic pattern of troponin T, which distinguishes the present study from most previous studies that often included few variables or focused on peak troponin T concentrations.

Patients and Methods

This study is a part of a larger research program, in which clinical data are registered prospectively in a local database for heart surgery at a tertiary hospital. Data were verified perioperatively and later controlled by a senior anesthesiologist (RS). The study was approved by the Norwegian Data Inspectorate and the Regional Research Ethics Committee. All included patients gave informed consent.

Of 1,028 patients (>18 y old) undergoing cardiac surgery from April 1, 2008, to April 19, 2010, 642 patients underwent primary isolated CABG surgery. Coronary angiography was performed preoperatively. Eight patients were excluded owing to missing or poor quality of the coronary angiogram, and 8 patients were excluded owing to missing preoperative variables, resulting in 626 patients eligible for the study. Of these, 19 patients were diagnosed with a definite postoperative MI according to the second universal definition of myocardial infarction, which was the definition applicable at the time the patients underwent surgery.[4] The statistical models were fitted both including (n = 626) and (as a sensitivity analysis) excluding (n = 607) these patients. When including them, they were indicated by a "yes/no postoperative MI" variable, permitting simultaneous independent evaluation of the effect size of a diagnosed MI and the other variables of interest. Power calculations showed that given alpha = 0.05 and including 600 patients, the power was 84% to identify a variable explaining 12% of the variation in cTnT concentrations, which was considered a reasonable strength of association for the relevant variables for inclusion in the analysis.

Two scores that considered the degree of diffuse coronary atherosclerosis and number of significant stenoses, respectively, were calculated for each patient based on the preoperative angiogram using quantitative coronary angiography (Xcelera R4, 4.1.1; Philips Medical Systems Eindhoven, Netherlands). The 3 epicardial coronary arteries were divided into 16 segments as proposed by the American Heart Association (Fig 1, A).[5,6] Criteria for diffuse atherosclerosis were change of caliber, pebbled arteries, and/or other signs of angiographically insignificant plaques. A significant stenosis was defined as >50% narrowing of the artery. One point was given for diffuse atherosclerosis and 1 point for significant stenosis present in each segment. Segments that had 1 significant stenosis but otherwise were clean were scored 0 for diffuse atherosclerosis and 1 for significant stenosis. The segment scores thereafter were multiplied with a published segment multiplication factor (Fig 1, B) to form a Modified Gensini score,[7] where diffuse coronary atherosclerosis was weighted as 1 and significant stenosis was weighted as 4. The maximum possible score was 92. One coauthor (EK) performed the scoring, and 9 angiograms also were assessed by another coauthor (EM). The mean difference in the Modified Gensini score was 1 point (standard deviation 9.3) between the 2 scorers. cTnT was measured 3 times in each patient (ie, in blood samples drawn preoperatively [the day before surgery] and the first and second postoperative mornings) (Modular E170; Roche Diagnostics, Basel, Switzerland). Concentrations of <10 ng/L were reported as 10 ng/L. From June 22, 2009, cTnT was measured using a high-sensitivity assay. Thorough method validation showed that small differences were found for concentrations <100 ng/L. This did not interfere with the essential results of the present study. C-reactive protein (CRP) and creatinine were measured routinely preoperatively (Modular P; Roche Diagnostics). Body surface area (BSA) was calculated using DuBois' formula.[8,9] Information on diagnosis of preoperative and postoperative MI was found in the database; diagnosis was made clinically at the time of occurrence using contemporary criteria.[4]

Left ventricular ejection fraction (LVEF) was assessed using the modified Simpson method by area tracing of the endocardial border in the ventricular cavity in end diastole and end systole in the apical 4- and 2-chamber views. For 135 patients, LVEF was only recorded as "normal". Therefore LVEF was used as a binary variable. Due to few patients with very low LVEF, the categories "pathological" (≤30%) and "reduced" (>30%-50%) were grouped together, and "normal" (>50% or recorded as "normal") was the other LVEF category.

All patients underwent an on-pump procedure. Patients treated with acetylsalicylic acid were administered 75 mg or 160 mg. A standard anesthetic technique with fentanyl (Alpharma, Bridgewater Township, NJ); sodium thiopental (Pentothal; Hospira, Lake Forest, IL); and pancuronium

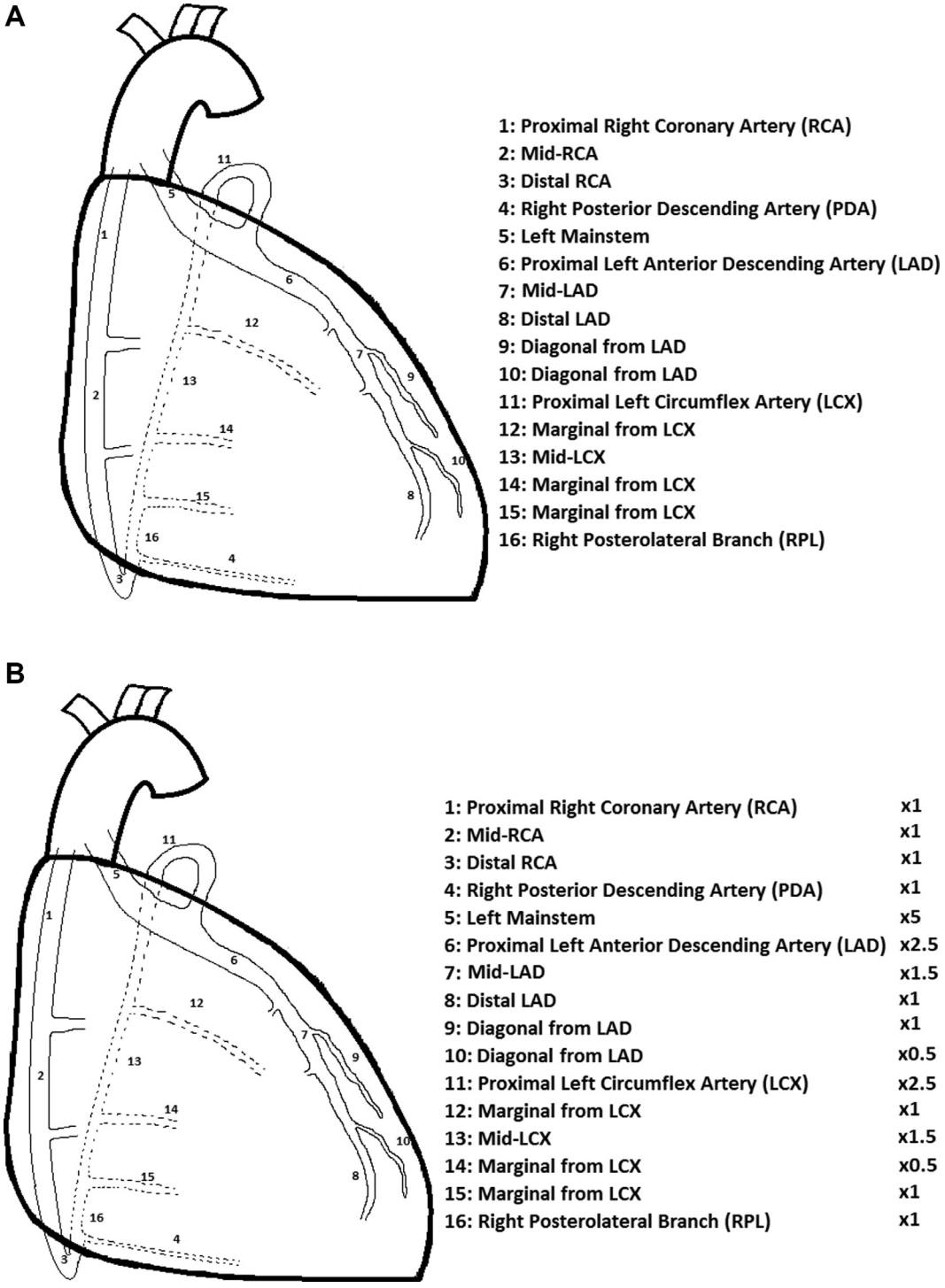

Fig 1. Cardiac vessel segments and multiplication factors. (A) Vessel segments used for scoring diffuse coronary atherosclerosis and number of significant stenoses, seen from the right side of the heart. (B) Multiplication factors for segments in the Modified Gensini score.

(Pavulon; Organon, Oss, Netherlands) was used. Anesthesia was maintained with isoflurane (Forane; Abbott, Abbott Park, IL) and additional doses of fentanyl, and propofol (Actaris, Oslo, Norway) were used during cardiopulmonary bypass (CPB). Before CPB, patients received heparin (300 U/kg) (Leo, Copenhagen, Denmark) to achieve a kaolin-activated coagulation time (Medtronic, Minneapolis, MN) of at least 480 seconds. Additional heparin was administrated when needed. The CPB circuit was primed with 1,500 mL of Ringer's acetate and 7,500 U of heparin. A coated oxygenator membrane was used. Crystalloid cardioplegia was used routinely during CPB. For practical reasons, blood cardioplegia was used for a small number of patients. The type of cardioplegia was not registered in the database. Tranexamic acid (Leo), 30 mg/kg, was given

routinely before CPB. Blood in the circuit was collected and retransfused to the patient after CPB. Protamine sulfate (Leo) was given to achieve a kaolin-activated coagulation time within 10% of baseline. There were no major changes in surgical or anesthetic management between the 2 cohorts.

Statistics

Statistical analyses were performed using Stata, version 14 (StataCorp, College Station, TX). Data are provided as numbers (%), means, or medians with 95% confidence interval (CI), as appropriate. Wilcoxon rank sum test was used for between-group comparisons. A p value < 0.05 was considered to be statistically significant.

To use cTnT to diagnose a postoperative MI, a clinician would evaluate the rise-and-fall pattern in serial measurements. This pattern shows large individual variation. The aim of the analysis therefore was to identify variables explaining the variations in cTnT measured preoperatively and on the first and second postoperative mornings, thus establishing a mathematical expression (ie, a statistical model) that would permit evaluation of statistical significance for potential explanatory variables. In other words, the model would point to variables other than an MI that need to be considered when the clinician evaluates the cTnT pattern observed in patients. To this end, mixed model analysis was used because simpler methods such as analysis of variance for repeated measures are based on strong assumptions that were violated in the clinical setting of the present study. Mixed models allow for time-related correlations within each study participant because cTnT was measured at several time points. They also take into account the cTnT concentration curves being individual for each patient instead of assuming that all patients with the same values for the variables in the model must have an identical curve, and they consider time-varying covariates (eg, an effect of CPB only on the postoperative measurements). cTnT and creatinine concentrations were transformed logarithmically to achieve appropriate model fit. Aortic cross-clamping time was highly correlated with CPB time ($r = 0.86$) and therefore was not included in the study models.

To identify variables explaining the cTnT patterns in the data, the authors started with a full clinical model including variables potentially associated with the cTnT concentration course. Variable selection was based on clinical knowledge, previous publications, and a hypothesis of their potential influence on the cTnT concentration course (Table 1). Per protocol, the number of potential explanatory variables was limited to <30 to avoid overfitting, ensuring >20 cases per potential explanatory variable. The actual list assembled before statistical analysis (Table 1) included fewer variables. The clinical model was then reduced by removing clearly nonsignificant factors, evaluated with likelihood ratio tests. Thereafter, the Modified Gensini score was added to assess whether the score was associated with the cTnT concentration course. Finally, predefined interactions (see Table 1) to achieve the best-fitting models were investigated (ie, where the observed cTnT concentrations and those calculated by the model are in agreement).

Table 1
Predefined Variables and Interactions

Preoperative	
Age*	Years (continuous)
Female sex†	(yes/no)
Body mass index†	kg/m^2 (continuous)
Body surface area*	m^2 (continuous)
C-reactive protein*	mg/L (continuous)
Creatinine*	μmol/L (continuous)
Hemoglobin†	g/dL (continuous)
Previous heart disease and/or surgical procedures†	(yes/no)
Kidney disease†	Creatinine >140 μmol/L, kidney transplanted, or preoperative dialysis (yes/no)
Chronic obstructive pulmonary disease†	Preoperative use of bronchodilators or forced expiratory volume 1 <75% (yes/no)
Hypertension†	Preoperative use of antihypertensive drugs or diastolic blood pressure >90 mmHg (yes/no)
Diabetes mellitus†	Receiving medication (yes/no)
New York Heart Association functional classification*	Class I-III versus IV (yes/no)
Left ventricular ejection fraction*	Normal (>50%), reduced (>30%-50%), pathological (≤30%)
Intraoperative	
Number of anastomoses†	n (continuous)
Red blood cell transfusion*	On clinical indication during surgery (yes/no)
Inotropic treatment during surgery*	On clinical indication during surgery (yes/no)
Duration of cardiopulmonary bypass*	Minutes (continuous)
Postoperative	
Intraoperative or postoperative myocardial infarction*	Diagnosed based on electrocardiogram and cardiac markers (yes/no)
Predefined interactions	
Recent myocardial infarction versus time for measurement*	Grounds: Preoperative heart injury may introduce another cTnT concentration course into the course related to surgery
Inotropic treatment during surgery versus time for measurement*	Grounds: Intraoperative decision, will not affect the preoperative measurement

Abbreviation: cTnT, cardiac troponin T.
* Included in clinical model.
† Nonsignificant variable excluded from the model.

Table 2
Patient Characteristics and Perioperative Variables (n = 626)

Variable	Definition	Mean (95% CI) or Percentage (yes)
Preoperative		
Age (y)	Continuous	66 (65-67)
Sex	Female (%)	130 (20.8%)
Body mass index (kg/m^2)	Continuous	27.3 (27.1-27.4)
Body surface area (m^2)	Female	1.78 (1.77-1.80)
	Male	2.03 (2.02-2.04)
Troponin T concentration (ng/L)	Median (95% CI)*	
	Preoperative	10 (10-10)
	first postoperative day	218 (204-235)
	second postoperative day	143 (130-150)
New York Heart Association class, n (%)		
	I	24 (3.8%)
	II	196 (31.3%)
	III	339 (54.2%)
	IV	67 (10.7%)
Urgent surgery (within 2 wk), n (%)	Yes (%)	349 (55.8%)
Myocardial infarction last 4 wk, n (%)	Yes (%)	218 (34.8%)
Kidney disease, n (%)	Yes (%)	20 (3.2%)
Pulmonary disease, n (%)†	Yes (%)	67 (10.7%)
Left ventricle ejection fraction‡	≤30	28 (4.5%)
	>30-50	223 (35.6%)
	>50	325 (59.9%)
Previous myocardial infarction	Yes (%)	372 (59.4%)
Previous percutaneous coronary intervention	Yes (%)	96 (15.3%)
Congestive heart failure preoperatively	Yes (%)	52 (8.3%)
Treated for diabetes mellitus	Yes (%)	98 (15.7%)
Treated for hypertension	Yes (%)	394 (62.9%)
Smoker or quit <6 mo ago	Yes (%)	151 (24.3%)
Cerebrovascular disease	Yes (%)	41 (6.6%)
Preoperative hemoglobin concentration (g/dL)		
Female	Mean (95% CI)	13.1 (13.0-13.2)
Male	Mean (95% CI)	14.4 (14.3-14.4)
Intraoperative		
Inotropic support during surgery	Yes (%)	110 (17.6%)
Vasoconstrictor treatment during surgery	Yes (%)	593 (94.7%)
Plasma transfusion during surgery	Yes (%)	24 (3.8%)
Red blood cell transfusion during surgery	Yes (%)	81 (12.9%)
Cardiopulmonary bypass time (min)	Median (95% CI)*	62 (61-64)
Aortic cross-clamp time (min)	Median (95% CI)*	38 (37-38)
EuroSCORE II§	Median (95% CI)*	1.7% (1.6%-1.8%)
Time in intensive care unit, n (%)	≤2 d	613 (97.9%)
	3-6 d	9 (1.4%)
	≥7 d	4 (0.6%)
Number of anastomoses/bypasses	Mean (95% CI)	3.51 (3.47-3.54)
	Median (95% CI)*	4 (3-4)
Postoperative		
Postoperative myocardial infarction	Yes (%)	19 (3.0%)
Reoperation	Yes (%)	31 (5.0%)
Postoperative renal failure¶	Yes (%)	30 (4.8%)
Heart failure	Yes (%)	27 (4.3%)
Postoperative intubation time (min)	Median (95% CI)*	204 (200-205)
Postoperative intubation time >24 h	Yes (%)	1 (0.2%)

* Non-normally distributed data are presented as median with 95% confidence interval of the median.
† Using bronchodilator or forced expiratory volume 1 <75%.
‡ Patients considered having "good" ejection fraction were not evaluated further and were categorized as >50 (n = 135).
§ EuroSCORE II: Risk assessment tool for calculating predicted mortality in patients undergoing cardiac surgery.
¶ Postoperative renal failure defined as new dialysis treatment or creatinine >140 μmol/L.

Model fit was compared using the Akaike information criterion (AIC) and Bayesian information criterion (BIC). These criteria indicate how well different models in the same data set (relatively to each other) represent the patterns in the data, while also penalizing the inclusion of many variables and interactions (ie, high complexity). Lower AIC and BIC indicate better model fit. Any significant variable that contributes to lower AIC and BIC in the mixed model explains some of

the variation in the data. By including this variable, the independent contribution from other variables may be assessed, similarly to using adjustment in linear regression. To evaluate the independent contribution from the explanatory variables of interest, the variables preoperative or postoperative MI (yes/no) therefore were included as adjustment in the models to account for the MI-related cTnT release. A sensitivity analysis excluding the 19 patients diagnosed with a definite postoperative MI also was performed in order to evaluate whether inclusion of these patients could have biased the results regarding the remaining variables in the model. Overall explanatory ability of the models was assessed using the Snijders/Bosker *R2*, which is one of the most common methods for mixed models.[10]

To examine whether recent changes in patient selection or procedures had reduced the relevance of the model, a validation model with patients undergoing isolated primary CABG from 2015 through 2017 (n = 686) was calculated using the same variables as in the first model. For these patients, data concerning coronary atherosclerosis were not available owing to lack of resources to perform the scoring. Thus, the models were compared excluding the Modified Gensini score. New routines of measuring cTnT on the 4th postoperative morning instead of on the 2nd postoperative morning were introduced during the years for inclusion of the validation cohort. Thus, the validation model contained 4 different time points.

Results

Patient characteristics are summarized in Table 2. As described, 19 patients were diagnosed with a postoperative MI. Most patients (n = 589 [97.0%]) had a cTnT concentration greater than the 2007 biomarker (cTnT) criterion for diagnosing MI after CABG.[4] When applying the fourth universal definition for MI (ie, a cTnT concentration >10 times the 99th percentile upper reference limit),[1] 467 patients (76.9%) demonstrated a cTnT concentration greater than the biomarker criterion.

Associations of cTnT With Coronary Atherosclerosis Score

The Modified Gensini score ranged from 10.5 to 66. The mean score was 38.6 (95% CI 38.1-39.0). The score was not associated with the cTnT concentration course (p = 0.35).

Associations of cTnT With Clinical Variables

The median (95% CI) observed cTnT concentration on the first postoperative day in patients diagnosed with MI was 1,090 ng/L (785-1,242 ng/L) versus 215 ng/L (202-229 ng/L) in patients not diagnosed with MI ($p < 0.001$) (Fig 2). In the sensitivity analysis excluding patients with a postoperative MI diagnosis, the coefficients for the remaining variables in the model were essentially unchanged, documenting that the main model was not biased owing to these patients. Observed preoperative cTnT concentrations for patients with and without a postoperative MI were comparable (p = 0.64).

Two hundred eighteen patients (34.8%) had an MI diagnosis within the last 4 weeks before surgery (see Table 2). Among these patients, 114 (54.3%) had a preoperative cTnT concentration elevated above the 99th percentile upper reference limit (median 17 ng/L [95% CI 13-23 ng/L]). In comparison, 50 (12.6%) of the patients without a recent MI had preoperative cTnT concentrations above this limit (median 10 ng/L [95%

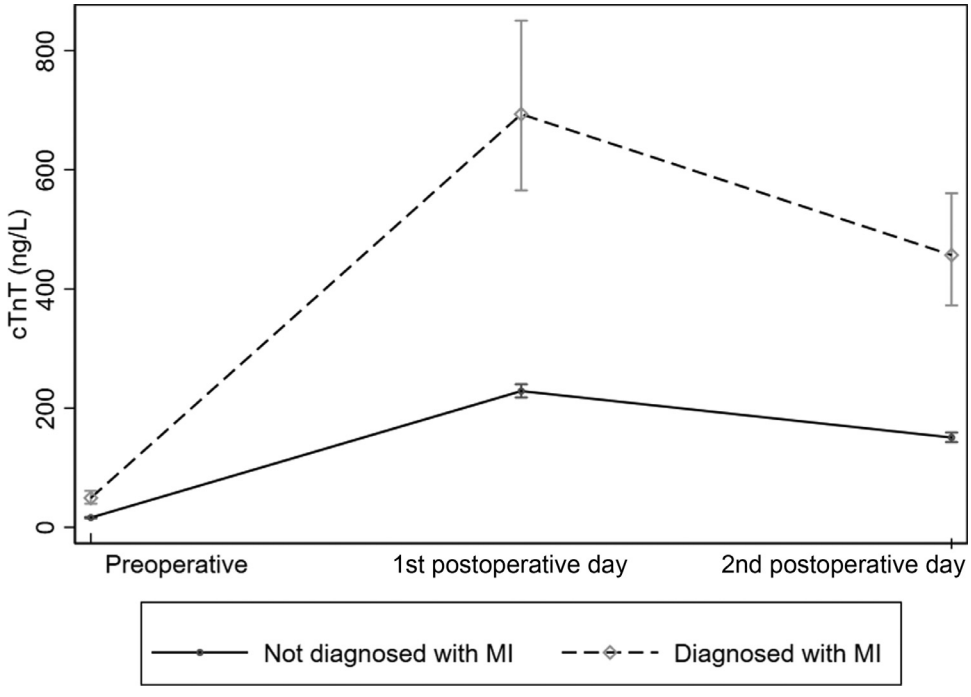

Fig 2. Cardiac troponin T concentrations in patients with and without postoperative myocardial infarction. Average concentrations in patients undergoing coronary artery bypass grafting in 2008-2010. Data are presented as mean and 95% confidence intervals. Cardiac troponin T was back-transformed to the original scale, and overlap of confidence intervals cannot be used to evaluate statistical significance. cTnT, cardiac troponin T; MI, myocardial infarction.

CI 10-10 ng/L]). Patients with a recent preoperative MI had a cTnT concentration course with a falling pattern in their postoperative measurements when adjusting for other variables. These patients also had higher postoperative cTnT concentrations, but this postoperative elevation was associated with the other variables related to surgery and not the recent preoperative MI. These results remained the same when excluding patients with a postoperative MI.

Increasing BSA was associated with a lower cTnT concentration course ($p < 0.001$), indicating that a small person had higher cTnT concentrations than a larger person (Fig 3, A). In models including sex instead of BSA, cTnT concentrations were higher in women than in men, but sex became nonsignificant ($p = 0.40$) if BSA also was included. Model fit was clearly better using BSA instead of sex.

Longer duration of CPB was associated with higher increases in postoperative cTnT concentrations ($p < 0.001$) (Fig 3, B). Patients with higher preoperative creatinine concentrations had higher postoperative cTnT concentrations ($p < 0.001$) (Fig 3, C). Inotropic treatment during surgery was associated with a small, but statistically significant, reduction of cTnT concentrations postoperatively in the model excluding patients with postoperative MI ($p = 0.028$), but there was no statistically significant association in the model including patients with postoperative MI nor in the validation model.

New York Heart Association (NYHA) class IV was also associated with a higher postoperative cTnT concentration course compared with classes I to III ($p = 0.005$). A reduced LVEF (ie, ≤ 50) ($p = 0.017$) was associated with higher postoperative cTnT concentrations compared with a normal LVEF. Remaining clinical adjustment variables associated with an increase in postoperative cTnT concentrations were older age ($p = 0.045$) (Fig 3, D) and elevated preoperative CRP ($p = 0.049$) (Fig 3, E). Because it may be difficult to evaluate how simultaneous differences in several variables were related to cTnT concentrations, Table 3 contains realistic examples of how differences in 3 important variables in the main model affected the average cTnT concentration observed in the patients.

The model showed good overall explanatory ability (Snijders/Bosker $R2 = 0.74$ for the between-person effects and $R2 = 0.55$ for the within-person effect). The validating model for patients undergoing CABG in 2015-2017 showed essentially the same results as those in the first model. The 95% CIs for the coefficients of all variables were overlapping, which indicates that the coefficients were not significantly different (Fig 4). Thus, the findings in the first model were essentially similar for patients undergoing surgery during recent years. The overall explanatory ability for the validation model was slightly lower than for the main model but still high (Snijders/Bosker $R2 = 0.67$ for the between-person effects and $R2 = 0.50$ for the within-person effect). The full main model before removal of nonsignificant variables is provided in the Supplement (Table S1). The coefficients for variables in the reduced model were essentially unchanged when comparing them with those in the full model, and the Snijders/Bosker $R2$ was similar, indicating minimal overfitting by model reduction.

Discussion

The present study's main findings were that higher concentrations of cTnT were associated with older age, higher preoperative CRP concentrations, higher creatinine concentrations, reduced LVEF, longer duration of CPB, and NYHA class IV, when adjusting for preoperative and postoperative MI. A larger BSA was associated with lower postoperative cTnT concentrations. A higher extent of diffuse coronary atherosclerosis and a larger number of significant stenoses were not associated with perioperative cTnT concentrations in patients undergoing CABG when quantified with the Modified Gensini score. Overall explanatory ability as shown by the Snijders/Bosker $R2$ was high. The results were validated in a model containing patients undergoing CABG in 2015-2017. As is usually the case, the overall explanatory ability was somewhat lower for the validation model. However, the 95% CIs of the coefficients of the 2 models were overlapping (ie, they were not significantly different). This indicates that the variables found to most strongly influence cTnT concentrations were still relevant even with changes in, for example, patient demographics and MI definitions over the years.

Importantly, the present study was of an exploratory nature and associations do not prove causation. Unless all causative factors can be included during statistical modeling, the variables that are selected will be those that best explain the variation in the data, independently of whether they are truly causative. Significant variables therefore may substitute for unmeasured causes. Thus, identifying biologically credible reasons for significance of a specific variable may be impossible. The models should not be used to predict cTnT concentrations, which should be measured in accordance with clinical practice.

The usefulness of the present study lies in the ability to point at factors—causative or not—that need to be considered when evaluating whether a patient really has a postoperative MI. Furthermore, this study provides additional insight into which clinical and perioperative factors are associated with myocardial injury in the course of CABG. In the fourth universal definition for MI, the distinction between myocardial injury and MI is emphasized.[1] cTnT is not an ideal marker but still is widely used during diagnostic workup, thus improved knowledge about factors influencing the concentrations is crucial. However, it cannot be excluded that use of novel, and even more sensitive, troponin measurement methods would have given other results.

cTnT and Coronary Atherosclerosis Scores

The main model using the Modified Gensini score showed no associations with the cTnT concentration course. This may be because no association exists between the degree of coronary atherosclerosis and cTnT changes after CABG. Alternatively, the grading or weighting of the score may have been inappropriate.

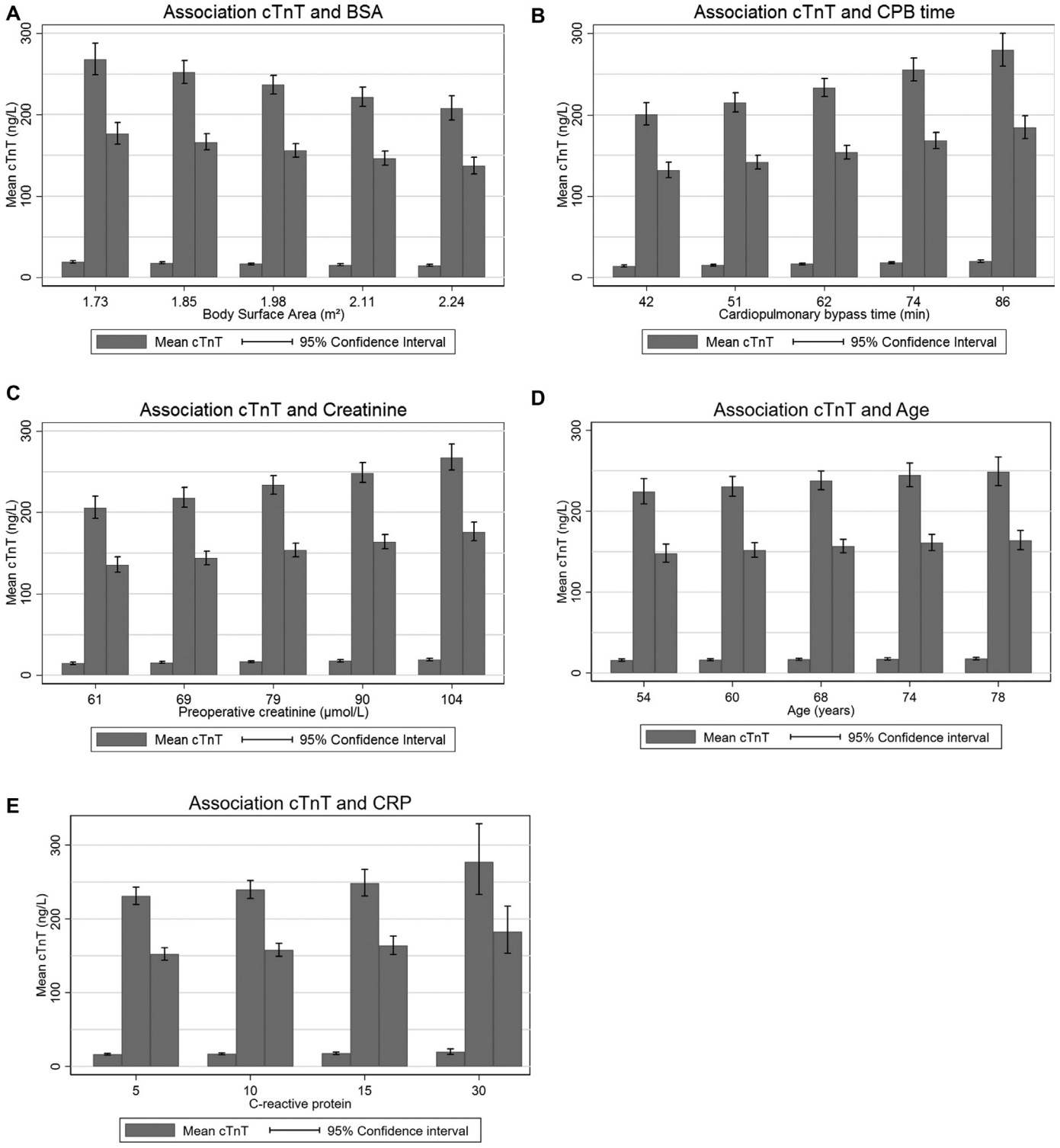

Fig 3. Associations of cardiac troponin T concentrations with patient and surgical variables. *First shaded bar,* preoperative measurement; *second shaded bar,* first postoperative morning; *third shaded bar*, second postoperative morning. The model was adjusted for clinical variables. Cardiac troponin T was back-transformed to the original scale. (A) Body surface area. Larger persons had lower cardiac troponin T concentrations. Body surface areas are shown at the 10th, 25th, 50th, 75th, and 90th percentiles. (B) Duration of cardiopulmonary bypass. Cardiopulmonary bypass duration is shown at the 10th, 25th, 50th, 75th, and 90th percentiles. (C) Preoperative creatinine concentrations. Creatinine concentration are shown at the 10th, 25th, 50th, 75th, and 90th percentiles. Cardiac troponin T and creatinine were back-transformed to their original scales. (D) Age. Age is shown at the 10th, 25th, 50th, 75th, and 90th percentiles. (E) C-reactive protein concentrations. C-reactive protein concentrations are shown at the 50th, 85th, 90th, and 95th percentiles. BSA, body surface area; CPB, cardiopulmonary bypass; CRP, c-reactive protein; cTnT, cardiac troponin T.

Table 3
Average Postoperative cTnT Concentrations

	BSA (m^2)	Creatinine (μmol/L)	CPB Time (min)	Estimated cTnT (ng/L)	
				First Postoperative Day	Second Postoperative Day
Example 1	1.80	70	60	234	154
Example 2	1.80	70	80	272	179
Example 3	1.80	105	60	284	187
Example 4	1.80	105	80	330	218
Example 5	2.11	70	60	201	132
Example 6	2.11	70	80	233	154
Example 7	2.11	105	60	243	160
Example 8	2.11	105	80	283	186

NOTE. Examples of the combined influence on average postoperative cardiac troponin T concentrations for 3 important preoperative and intraoperative variables when other variables are set to mean, based on main model including patients from 2008-2010. Body surface area is shown at the 25th and 75th percentiles (1.80 m^2 and 2.11 m^2, respectively) and renal function as normal or impaired (creatinine = 70 [ie, 25th percentile] or creatinine = 105 [ie, 90th percentile], respectively). Time on cardiopulmonary bypass is shown as average (60 min [ie, mean]) or long (80 min [ie, 80th percentile]). Cardiac troponin T concentrations given these values are shown for the first and second postoperative days. For comparison, the cardiac troponin T concentration criteria for diagnosing myocardial infarction after coronary artery bypass grafting are set to 140 ng/L.[1]
Abbreviations: BSA, body surface area; CPB, cardiopulmonary bypass; cTnT, cardiac troponin T.

cTnT and Clinical Variables

The present study's findings demonstrate that differences in several clinical variables are associated with a substantial difference in the observed postoperative cTnT concentrations. Importantly, most of the patients with a cTnT concentration greater than the 2018 cTnT criterion of 140ng/L[1] did not fulfill the criteria for MI and should be classified as having myocardial injury. Including or excluding patients diagnosed with a postoperative MI did not change the associations for the remaining variables in the model, indicating that evaluation of the other variables in the main model was not biased by these patients.

Lower LVEF and higher NYHA functional class are both factors indicating poorer heart function. Thus, the present study's results imply that reduced preoperative left ventricular function is associated with higher cTnT concentrations after CABG, indicating that these patients are more vulnerable to myocardial injury. This suggests that with reduced left ventricular function, cardiac protection during surgery should be optimized.

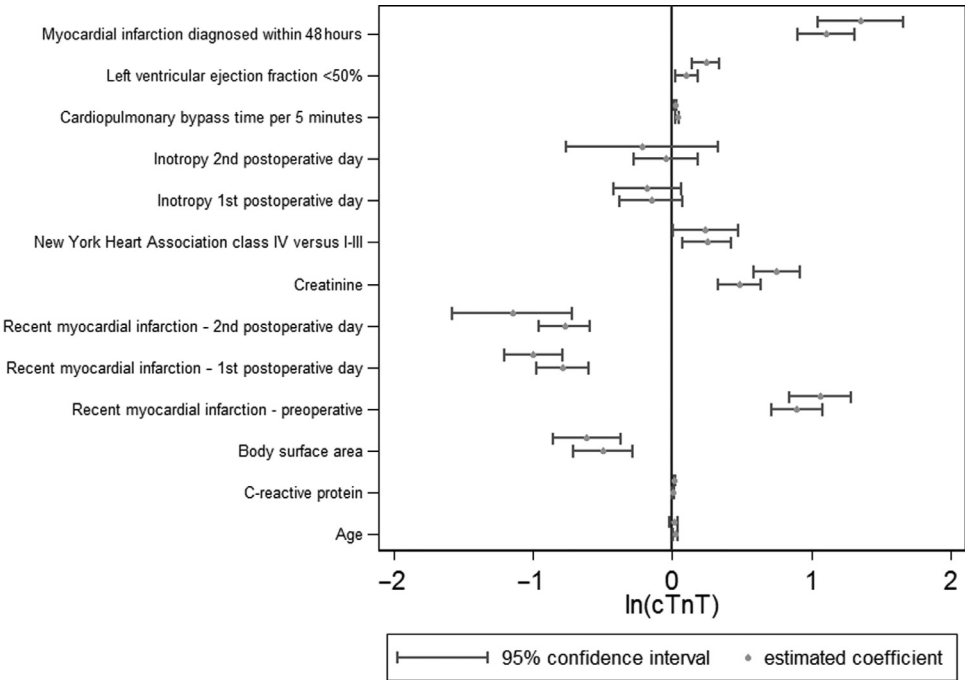

Fig 4. Comparison of results in main cohort and validation cohort. The figure shows coefficients for ln(cTnT) *(diamond)* and 95% confidence interval *(line)* for the same variables from the models for the 2 patient cohorts undergoing coronary artery bypass grafting in 2008-2010 (*lower line* in each pair) and 2015-2017 (*upper line*). Variables mentioned separately on 1st and 2nd postoperative days have 2 coefficients owing to different associations on different days. Due to the logarithmic scale, some variables have values close to zero. The 95% confidence intervals are overlapping for all variables, indicating no significant difference.

The results regarding CRP show that patients with preoperative inflammation also are more vulnerable to myocardial injury, leading to an increase in cTnT concentration.

BSA is a measure of body size and was a better explanatory variable in the models than was sex (data not shown) or body mass index (similar direction of effect as BSA but weaker effect; data not shown). Increasing BSA was associated with lower postoperative cTnT concentrations. It may be speculated that the association with BSA is an effect of dilution of the released cTnT owing to larger blood volume or body volume in a person with a larger BSA. However, larger BSA also should mean a larger heart and potentially a higher release of cTnT. In addition, there is the possibility that it is easier to perform surgery on larger patients, resulting in lower myocardial injury and cTnT release.[11]

The demonstration of an association between postoperative cTnT concentrations and preoperative renal function is supported by earlier studies.[12] Other studies also have found an elevated cTnT concentration in patients with impaired renal function, with or without coronary disease, despite their disagreement regarding reasons for the elevation.[13,14] Although there are some indications that cTnT is eliminated through the reticuloendothelial system,[14] renal elimination of cTnT and accumulation of cTnT in patients with reduced renal function probably also is a contributing factor and the most plausible explanation for the present study's findings regarding creatinine.[15]

Longer time on CPB was associated with higher cTnT concentrations. The most likely explanation is that a longer surgery with longer ischemia times induced more myocardial injury and a higher release of cTnT. Another possible factor may be that patients undergoing a long procedure are more likely to experience complications that contribute to cardiac injury and therefore to an increased cTnT concentration.

Strengths and Limitations

The present study is based on a large data set including many clinical variables, allowing for broad testing of possible associations. The authors believe it is one of the first to investigate the association of cTnT and several different clinical factors in the same multivariate model, permitting evaluation of independent associations. The use of an advanced statistical method that is based on realistic assumptions about the cTnT patterns observed in cardiac surgery patients adds credibility to the results. The findings also were validated in a more recent patient cohort, indicating that any recent changes in anesthetic methods did not influence the results. Information regarding transfusions, which could lead to dilution of circulating cTnT, or timing of postoperative MI was not available. Such information could have permitted additional fine tuning of the statistical model.

Due to lack of previous data demonstrating the optimal ways to define the coronary atherosclerosis scores, the Modified Gensini score may not have accurately captured the intended information. Patients undergoing isolated CABG is a fairly homogenous group, resulting in less variation in the coronary scores. Exploratory analyses with other weighting of the scores are included in a Supplement. Patients with coronary angiograms not possible to score were excluded, which may have introduced bias. Furthermore, scoring with coronary angiography does not permit assessment of hemodynamic significances or true size or composition of coronary plaques, which may lead to differences in wall stress and blood flow that influence the underlying myocardium and cTnT release.

Cardioplegia type may be associated with the cTnT concentration course because cold blood cardioplegia better protects against perioperative MI than does crystalloid cardioplegia.[16] Due to missing data, the importance of this factor could not be tested in the present study. Owing to missing data for LVEF in some patients, the authors cannot exclude misclassification in the categorical variable for LVEF. Information regarding intraoperative hemodynamic variables was not available. However, such variables are closely monitored and controlled for during cardiac surgery; thus factors such as hypertension, hypotension, or tachycardia, are corrected immediately during anesthesia. Compared with the strong effects of ischemia during cardiac arrest, the authors find it unlikely that such factors would have had much effect on cTnT release.

Clinical Utility

The present study points to factors that need to be considered when assessing cTnT after CABG surgery because they are associated with the rise-and-fall pattern of measured concentrations independent of an MI. A better understanding of associations among cTnT and clinical factors may help physicians in the diagnostic workup of postoperative MI.

Conclusion

The present study demonstrates the complexity of variables associated with the cTnT concentration course after CABG. The tested coronary atherosclerosis scores did not seem to capture much of the variation. Information regarding recent MI, kidney function, inflammation status, BSA, LVEF, and duration of CPB are some of the factors affecting the cTnT concentrations and need to be considered when evaluating the rise-and-fall pattern of cTnT in this setting.

Conflicts of Interest

None declared.

Supplementary Material

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2019.06.029.

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