Factors That Alter the Relationship Between Peak Postoperative CKMB and Troponin T After CABG

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Introduction

Peak postoperative creatine kinase MB fraction (CKMB) and Troponin T (TnT) levels have been measured after cardiac surgery to assess perioperative myocardial damage, evaluate myocardial protective strategies and predict adverse events. Several studies have shown that elevated levels of creatine kinase isoenzyme MB (CK-MB) are associated with adverse postoperative events, especially when peak levels exceed ten times the upper limit of normal during the initial 48 hours after coronary artery bypass graft (CABG) [1].

More recently other markers have emerged, particularly cardiac Troponin T (cTnT) and Troponin I (cTnI). Both have been suggested to be superior to CK-MB in the setting of acute myocardial infarction (AMI), owing to greater specificity for cardiac myocyte damage [2].

In the setting of coronary bypass surgery, open heart surgery such as CABG, cardiac troponin and CK-MB have been well established as biomarkers of myocardial injury. Troponin and CK-MB levels are frequently elevated within 24 hours after most cardiac operations and have generally been associated with poorer clinical prognosis [3].

The release of cardiac enzymes after CABG may relate to graft occlusion, reperfusion injury, inadequate myocardial protection, ischemia during operation, and surgical trauma [4]. However there has been debate surrounding the clinical interpretation and accuracy of the levels of biomarkers postoperatively. Nevertheless, many cardiac surgery programs collect perioperative biomarker data as a quality assurance measure in order to direct management of patients after cardiac surgery and avoid worse outcomes [3]. However, the relationship between peak levels of both enzymes has not been fully established in the setting of coronary artery bypass surgery.

The analysis of cardiac enzyme levels becomes more challenging in cohorts of patients with comorbidities such as renal disease. CK-MB has been widely used to diagnose myocardial infarction (MI) but also has been elevated in patients with chronic renal failure and skeletal muscle injury, which could falsely diagnose a perioperative ischemic event [5]. TnT has proven a highly sensitive and specific indicator of MI yet has also been elevated in some patients with renal insufficiency [6].

Purpose

The purpose of this study was to examine the relationship between peak levels of cTnT and CK-MB following CABG in defined subsets of patients with pre-defined comorbidities to test the hypothesis that patient and operative characteristics influence the correlation between the values of these biomarkers.

This information may enable us to better understand the assessment of the success or failure of cardio protection in specific cohorts of patients undergoing CABG.

Methods

Data were prospectively collected from 602 patients at a single institution undergoing on-pump CABG between July 2011 and September 2016. Peak values were selected from all serum levels of CKMB and TnT collected during the hospital stay following surgery. Clinical variables were collected based on definitions in the STS Adult Cardiac Surgery Database versions 2.73 and 2.81.

Characteristics of the sample were summarized using descriptive statistics. All continuous variables of interest were found to be non-normally distributed; these variables are summarized using medians and ranges. Categorical variables were summarized using frequencies and percentages.

Analysis of covariance (ANCOVA) models were utilized to statistically compare the slope of the linear relationship between peak postoperative CKMB and TnT for the patient cohort. The ANCOVA models were created to compare slopes by pre-defined variables including gender, age (dichotomized at 70), race, smoking status, hypertension, dyslipidemia, diabetes, renal dysfunction (GFR < 60), MI within 21 days, EF (dichotomized at 40%), preoperative use of ACE-inhibitors, beta blockers, and anticoagulants, cross clamp time, CPB time, and whether intra-operative blood products were received. A lower slope implies less change in CKMB relative to the change in TnT.

Statistical significance is indicated by $p < 0.05$.

Results:

Table 1. Characteristics of the sample

Age	59 (26-87)
Sex	
Male	458 (76.1%)
Female	144 (23.9%)
Race	
White, non-Hispanic	221 (36.8%)
Black, non-Hispanic	124 (20.7%)
Hispanic	201 (33.5%)
Other	54 (9.0%)
Diabetes	
Yes	386 (64.4%)
No	213 (35.6%)
Hypertension	
Yes	551 (91.5%)
No	51 (8.5%)
Smoking status	
Current smoker	136 (22.7%)
Former smoker	149 (24.9%)
Never smoked	314 (52.4%)
Prior MI	
Yes	381 (64.8%)
No	205 (35.4%)
ACE inhibitors	
Yes	308 (51.3%)
No	293 (48.8%)
Anticoagulants	
Yes	187 (31.1%)
No	415 (68.9%)
Beta blockers	
Yes	534 (87.0%)
No	78 (13.0%)
EF	53 (4-75)
CPB time (minutes)	107 (31-275)
Cross clamp time (minutes)	68 (15-175)
CKMB	21.8 (1.7-297.5)
Troponin T	0.5 (0.0-16.3)
In-hospital post-op events	
Yes	326 (54.5%)
No	274 (45.5%)
Dyslipidemia	
Yes	558 (92.9%)
No	43 (7.2%)

Table 2. ANCOVA results

Variable	N	Slope	St. Err.	p
Age				<0.001
< 70	515	23.6	0.9	
≥ 70	78	16.7	1.2	
Sex				0.019
Male	451	20.6	0.8	
Female	142	25.3	2.1	
Race				<0.001
White	219	22.8	1.1	
Black	121	32.7	1.4	
Hispanic	199	19.1	2.0	
Other	53	13.8	1.5	
Diabetes				<0.001
Absence	213	24.8	1.2	
Presence	377	19.6	1.0	
Hypertension				<0.001
Absence	50	8.9	3.3	
Presence	543	22.5	0.8	
Renal function				0.004
GFR > 60	477	23.5	0.8	
GFR < 60	116	18.3	1.9	
Ejection fraction				<0.001
≤ 40	143	13.2	1.1	
> 40	431	26.7	0.9	
Smoking status				<0.001
Current smoker	135	17.3	1.2	
Former smoker	149	21.2	1.5	
Never smoked	306	29.0	1.3	
ACE inhibitor use				<0.001
Yes	308	30.2	1.3	
No	292	18.9	0.8	
Beta blocker use				<0.001
Yes	515	24.1	0.9	
No	78	16.6	1.3	
Intra-operative blood products				0.013
Yes	358	22.2	1.0	
No	241	15.0	1.5	
Cross clamp time				<0.001
≤ 70 minutes	305	13.4	1.0	
> 70 minutes	250	35.3	1.2	
In-hospital post-op events				0.772
Absence	266	20.9	1.1	
Presence	297	23.7	1.0	

Figure: Renal function

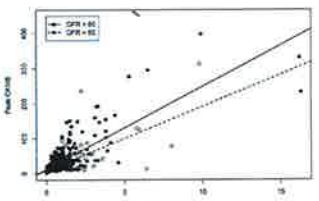


Figure: Intra-operative blood products

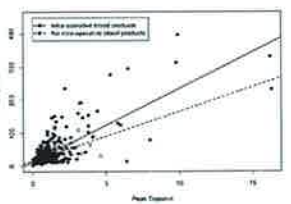


Figure: Cross clamp time

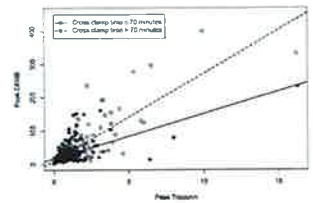
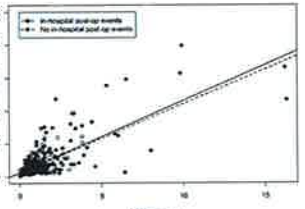


Figure: In-hospital post-op events



Discussion

Overall, the correlation between peak postoperative CKMB and TnT was robust in patients undergoing CABG ($r = 21.7$, $r = 0.756$). However, the slope of the relationship was significantly lower in males, patients > 70 years, diabetics, non-smokers, patients with renal dysfunction, and patients with lower EF. The slope was significantly greater in patients with longer cross clamp times, patients with hypertension, and patients who were receiving beta blockers and ACE-inhibitors (Table 2). In all other models, the slope of the relationship was similar.

Myocardial infarction is a recognized complication of coronary bypass surgery. The "Universal Definition" of myocardial infarction categorizes myocardial infarction related to coronary artery bypass grafting as a "type 5", and a URL (upper range limit of normal) value for troponin and serum CKMB are often determined for an individual lab and population. The definition of perioperative MI following on-pump CABG is 5 times the 99th percentile of that range during the first 72 hours after CABG. This enzyme level reflects significant myocardial cell damage, but the number is not reliable if the patient had an MI in evolution before the operation. New Q waves or new LBBB on ECG, or evidence on imaging of myocardial loss or wall motion defect are supportive of the enzyme elevation criterion.

The definition is important, as identified perioperative myocardial damage can identify patients at risk for early and late complications and may guide subsequent management of these patients to improve outcomes.

Both CKMB and Troponin have been advocated as markers to detect perioperative myocardial infarction, and some feel they are interchangeable. Our data in this study suggest that this concept should be viewed with caution, as patients with certain preoperative conditions and intra-operative characteristics show significant differences in the behavior of these biomarkers after CABG. While some differences might have a predictable biologic mechanism (for example, renal clearance of the two biomarkers may differ in patients with renal dysfunction), the reason behind these variations is not known in most instances.

It is interesting to note that despite the differences observed between different patient subsets, patients that sustained in-hospital postoperative adverse events did not have a different relationship between peak biomarker levels compared to those experiencing no adverse outcomes. This is perhaps consistent with prior studies that have observed that even long-term outcomes (LV ejection fraction 6 months after CABG) were similar between patients who had early significant enzyme elevation and those who did not [6].

Conclusion

The relationship between CKMB and TnT following CABG appears to be influenced by patient and operative characteristics. These data do not assess which enzyme more accurately reflects myocardial injury, but do suggest conclusions about myocardial damage may be affected by the biomarker selected in the presence of certain variables. Further study to assess the association between these biomarkers and patient outcomes is warranted.

References

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