TROPONIN T AFTER CARDIAC SURGERY: WHAT IS NORMAL? A REVIEW OF THE LITERATURE

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Abstract

It is well established that cardiac biomarkers are universally raised post-cardiac surgery. This is due to various preoperative, intraoperative, and postoperative factors. At present, no reliable tool or model considers intraoperative and postoperative factors to predict morbidity and mortality after cardiac surgery. Troponin T as a single or serial measurement to predict postoperative mortality and morbidity, is an attractive diagnostic tool due to the direct relationship to myocardial damage and the availability of testing. Currently, there is no consensus regarding the expected release of troponin T post-cardiac surgery. From a diagnostic and prognostic point of view, troponin T testing could be beneficial in recognising high-risk patients and any imminent complications early. Therefore, this review aims to assess the expected release profile and prognostic value of troponin T after cardiac surgery.

Keywords: troponin T., CABG, MPM, SAPS

Introduction

Perioperative mortality after cardiac surgery has been decreasing over the last few decades, highlighting the advancements in technology and healthcare. According to the 2019 national annual report published by The Australian and New Zealand Society of Cardiac and Thoracic Surgery, the thirty-day mortality post isolated Coronary Artery Bypass Graft (CABG) was 0.4%, 1.5% and 7.8% for elective, urgent and emergency patients, respectively. Additionally, 30-day mortality for aortic valve replacement (AVR) was 1.4%, and for mitral valve surgery was 1.0% (mitral valve replacement (MVR): 1.8% and mitral valve repair: 0.2%) [1]. However, the incidence of postoperative morbidity remains significant and is reported to be between 4.3% - 36% [2], leading to prolonged intensive care unit (ICU) stay and worse long-term outcomes. Consequently, these patients require a greater allocation of resources, resulting in higher health care costs. Thus, identifying and preventing postoperative morbidity early will improve patient care and reduce the health care burden [2, 3].

Multiple risk-stratifying models such as; EuroSCORE II, Cardiac Anaesthesia Risk Evaluation (CARE) score, Parsonnet score, and Society of Thoracic Surgeons' risk model are available to predict morbidity and mortality after cardiac surgery. EuroSCORE II is a widely used model, which uses preoperative patient factors to predict mortality

post-surgery [4, 5]. While these models are important to assess preoperative risk and subsequently evaluate patients for suitability of surgery, they fail to take into account intraoperative and postoperative factors to identify high-risk patients after surgery [6].

Other risk-stratifying models used for general ICU patients such as; Acute Physiology and Chronic Health Evaluation (APACHE) III score, Mortality Prediction Models (MPM) II & III and the Simplified Acute Physiology Score (SAPS) III do not apply well to cardiac surgery patients. Moreover, cardiac surgery patients were excluded while developing these models because complex surgical and anesthetic management that cardiac surgery patients require resulted in falsely elevated mortality rates in these patients [6, 7].

Presently, no reliable tool or model considers intraoperative and postoperative factors to predict morbidity and mortality after cardiac surgery. Cardiac biomarkers as a single or serial measurement, to predict postoperative mortality and morbidity, is attractive due to the direct relationship to myocardial damage and the availability of testing. It is well established that cardiac biomarkers are universally raised post-cardiac surgery. This is due to various preoperative, intraoperative, and postoperative factors [8-10]. However, there is no consensus regarding the expected level or range of cardiac

biomarkers after various cardiac surgeries. Furthermore, studies to validate the universal definition of myocardial infarction (MI) post-cardiac surgery (type 5 MI) have reported inconsistent cardiac biomarker levels, higher than the arbitrarily set level of >10 times the upper range limit (URL) [9, 11-15].

Identifying an expected release pattern of cardiac biomarkers post-surgery would be beneficial; This would enable clinicians to identify postoperative complications such as MI and manage any relevant adverse events expectantly. Additionally, using various intra-operative and postoperative determinants, clinicians may be able to predict the postoperative pattern of biomarker release and the associated complications early. This may provide an opportunity to offer early intervention such as a postoperative echocardiogram, angiogram and cardiac monitoring [16, 17]. Furthermore, knowledge of imminent complications will allow efficient resource allocation decisions such as ICU and monitored cardiac beds [18].

Cardiac biomarkers:

Three common cardiac biomarkers in clinical use are creatine kinase – MB (CK-MB), troponin (cTn) T (cTnT) and I (cTnI). Cardiac biomarkers are structural proteins and enzymes that are specific to cardiac muscle. These are released into the blood when there is underlying cardiac muscle injury or necrosis [19]. Troponin T and I are components of the contractile apparatus of myocardial cells and are expressed almost exclusively in the heart. CK-MB is primarily cytosolic and plays an important role in cellular metabolism. CK-MB is less specific than troponin because of its production by skeletal muscle, tongue, diaphragm, small intestines, uterus and prostate. Hence, troponin is the preferred biomarker for evaluation of the myocardial injury. [11, 13, 14, 20, 21]. Newer assays can detect small levels of troponin earlier with higher sensitivity and specificity. Hence, high-sensitive troponin (hs-cTn) assays are recommended for routine clinical use [11, 14, 22, 23].

Troponin T elevation in acute cardiac syndrome

Cardiac troponins are regulatory proteins with cytosolic and structural pools. Following myocardial injury, there is an early release of cTnT from the free cytoplasmic proteins and a slower prolonged rise with the subsequent breakdown of structural muscle fibres. Troponin T elevation begins 2-4 hours after onset of myocardial injury and remains elevated for several days (cTnT 5-14 days)[24, 25]. The Peak concentration of troponin T is seen within 24-48 hours. With the introduction of high sensitive troponin T (hs-cTnT) assays, the detection of troponin elevation as early as one-hour post-myocardial injury has been reported. The new hs-cTnT is an improvement to the fourth-generation assay. Due to a lower limit of detection of hs-cTnT (0.003 ng/ml) compared to standard cTnT (0.01 ng/ml) and increased precision, hs-cTnT assays can detect

more subtle elevations of troponin after cardiac injury[26, 27]. Troponin T has been investigated extensively for the diagnosis of myocardial infarction. In the emergency department setting, hs-cTnT significantly improved the early diagnosis of acute myocardial injury compared to standard troponin T assay [27]. According to the diagnostic criteria of AMI, a hs-cTnT level > 99th percentile (0.014 ng/ml) has a sensitivity, specificity, negative predictive value, and positive predictive value of (95% confidence interval [CI] of 95% [90%- 98%], 80% [77%- 83%], 99 [97% - 100%], 50 [43% - 56%], respectively [11, 28]. While the diagnostic and prognostic value of troponin T at detecting myocardial injury is well established, there is still much contention regarding the interpretation of troponin T after cardiac surgery.

Troponin T elevation post-cardiac surgery

Myocardial injury and the consequent troponin T release is universal after cardiac surgery. Mechanisms that are proposed to explain these findings include preoperative elevation of troponin may persist into the postoperative period. Intraoperative injury may be due to myocyte death from insufficient myocardial protection, surgical manipulation (suture placement or arteriotomy), defibrillation, ischaemia related to low perfusion, length of surgery (prolonged cardiopulmonary bypass time and aortic cross-clamp time) and reperfusion injury. Whereas the postoperative injury may be related to acute graft failure after CABG, acute pericarditis, acute heart failure and sepsis [8, 9, 12, 16, 17, 23, 29]. A procedure dependent level of myocardial injury and subsequent hs-TnT can be expected after various cardiac surgical procedures [16]. Therefore, the postoperative release of troponins can be complicated with the interplay of various factors; thus there is significant variability in the release profile of hs-cTnT.

Markman et al. [16], with a prospective data set, plotted the observed release profile of hs-cTnT prospectively after off-pump coronary artery bypass surgery (OPCAB), CABG, AVR, MVR and transfemoral aortic valve implantation (TAVI) [16]. They found that, in the absences of MI, hs-cTnT peak was at 4-8 hours post-surgery. Not surprisingly, the extent of hs-cTnT release correlated with the extent of myocardial injury from surgery. Procedures that avoided cardiopulmonary bypass (OPCAB and TAVI) had the lower peak values (58 [50 – 136] ng/L and 115 [112 – 275] ng/L, respectively) earlier (4 hours after surgery). On-pump procedures (CABG and MVR), due to cardiac arrest and prolonged procedural time, showed higher peaks values (241 [99 – 566] ng/L and 918 [604 – 1166] ng/L) at a later time (6-8 hours after surgery) [16]. An important observation in this study was the large interpatient variability of hs-TnT in each procedure. In the CABG group, there was a six-fold difference between the highest and the lowest peak of troponin. Additionally, In OPCAB group, the patient with the highest hs-TnT received four

coronary grafts suggesting an association with longer surgical time and more cardiac manipulation [16].

Furthermore, Ge et al. [30] have evaluated the release profile of troponin T in patients who underwent OPCAB with a normal postoperative course. They observed a peak hs-cTnT at 24 hours with a subsequent steady decline until 120 hours. This is very different from the 4 hours peak previously seen after OPCAB [16, 30]. Swaanenburg et al. [31], have also shown the difference in troponin T release profile after cardiac surgery. In their study, patients who underwent valvular surgery (AVR and MVR) showed a higher level of troponin T compared to CABG with cardiopulmonary bypass [31]. This is expected after valvular surgery, especially after MVR, due to the extent of myocardial damage involved. They also reported a peak troponin T value between 4-6 hours [16, 31].

In general, higher hs-TnT levels are seen in a patient with EuroSCORE ≥ 2 [30], males compared to females [30], in a patient receiving five or more bypass grafts after OPCAB [30] or > 4 after grafts after CABG [16], longer cardiopulmonary bypass times, longer cross-clamp time, intraoperative defibrillation, postoperative or intraoperative intra-aortic balloon pump requirement [8, 16].

There are important limitations in the available literature to evaluate the expected release profile of troponin T after cardiac surgery [16, 30, 31]. Firstly, the sample size used is small with large inter-patient variability of troponin T post cardiac procedures [16, 31]. This makes the clinical applicability of these studies challenging. Secondly, one study evaluated the release profile of hs-cTnT in 398 patients after the single procedure (OPCAB); while this provides a guide for the expected troponin T raise after OPCAB, this cannot be adapted to other cardiac surgical procedures [30]. Finally, there is a large variation in the peak release time of troponin after surgery (4 hours [16] vs 24 hours [30] after OPCAB) [16].

Prognostic value of troponin T

Myocardial infarction post-cardiac surgery is of great clinical and research interest, as early diagnosis and intervention could prevent significant postoperative complications. Depending on the criteria used, the incidence of MI is reported between 2% – 10% post-CABG and 4-after heart valve surgery between 4% - 10.9% [32-34]. According to the current guidelines from the fourth universal definition of MI, after cardiac procedures, MI is defined arbitrarily as a cardiac troponin level >10 times the 99th percentile URL (hs-cTnT: >140 ng/L) within the first 48 hours after cardiac surgery and one of the following: development of new pathological Q waves; angiographic documented new graft occlusion or new native coronary artery occlusion; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a

pattern consistent with ischemic aetiology [11]. Numerous studies have attempted to validate this definition. However, it has been challenging to find a consistent troponin T value to diagnose MI post-CABG (type 5 MI) with high sensitivity as well as high specificity. [16, 33]. Most studies have found a value much greater than ten times the upper range limit (URL) and have noted that the cut-off value of troponin T recommended by the fourth definition of MI resulted in large false-positive results [8, 9, 13-15, 35]. Mohammed et al. [8] have reported 100% sensitivity and 4.2% specificity to diagnose type 5 MI using the cut-off value of 10 times the URL [8]. Additionally, Cubero-Gallego et al. [33] have found that in patients post valvular surgery, hs-TnT of 1057 pg/mL (ng/L) at 16 hours post-procedure had the greatest sensitivity (97.7%) and specificity (93.3%) to diagnose MI post-procedure. This is significantly higher than the level recommended by the fourth universal definition of MI of 140ng/L [11, 33]. Moreover, they included all patients with valvular surgery in their analysis (including patients who underwent AVR, MVR, double valve and triple valve surgeries), despite evidence showing larger troponin T release post mitral valve surgery (due to the nature of the procedure and the myocardial damage involved) [16, 33].

Furthermore, elevated levels of troponin T has been associated with short-term and medium-term mortality and morbidity [15, 21, 29, 35-37]. In an extensive meta-analysis of 17 studies conducted by Laurati et al. [29], the estimated diagnostic odds ratio (OR) of elevated cTn after cardiac surgery for midterm (≥ 12 months) all-cause mortality was 5.46 (95% CI: 2.0 – 14.6) and for short-term mortality (≤ 30 days) was 6.57 (95% CI: 4.3 – 10.1), in this study the level of troponin T varied considerably between studies (0.8 – 2.0 $\mu\text{g/L}$) or (800 – 2000 ng/L). Significant limitations from this analysis include large between-study variability of study populations, follow up, and different degrees of completeness of data collected. Furthermore, the timing of blood sample collection varied (0-96 hrs postoperatively), as well as troponin subunit used (T and I) were different [29].

Ghal et al. [35] further tested the prognostic value of hs-cTnT and showed that post CABG, every 200 ng/L increase in cTnT and hs-TnT measured between 6 and 12 hours is associated with an increase in an odds ratio of in-hospital major cardiac or cerebrovascular event (MACCE) [35]. More recently, using a large dataset from our institution, peak hs-cTnT greater than 400ng/L, measured within 24 hours after CABG surgery, was associated with major adverse cardiac and cerebrovascular events, 30-day mortality, and ICU stays >48 hours [38].

While the prognostic value of cTnT post-CABG is being recognised [8, 13, 21, 35, 38-41], few studies evaluate the prognostic significance of cTnT after isolated valvular surgery and other cardiac surgical procedures [33, 42]. Saito

et al. [42] have reported that a statistically significant difference in the occurrence of MACE (the composite event of heart failure, fatal arrhythmia and all-cause death) between groups who have normal preoperative hs-cTnT (<0.014 ng/ml) and raised hs-cTnT (>0.014 ng/ml) (Log-rank test, $X^2 = .24$, $P=0.004$). Furthermore, they reported a mean preoperative elevated hs-TnT of 0.306 ± 0.263 ng/ml (306 ± 263 ng/L) is associated with MACE post AVR (Hazard ratio (95%CI) 3.71 (1.16 – 11.9)[42].

The challenge with identifying a universally accepted cut off value of troponin T post-cardiac surgery lies in the complex nature of cardiac surgery and the preoperative, intraoperative and postoperative factors that affect the release profile of troponin T. Since large variability exists in the currently available literature regarding the time of measurement of troponin T and cut off level of significant prognostic value, it is difficult to make any meaningful deductions [11, 29].

Conclusion

Elevation in cTnT is universal after cardiac surgery. This can be attributed to multiple preoperative, intraoperative and postoperative factors. While the prognostic value of troponin T is being evaluated in recent studies, there is still a large disparity in the literature regarding the optimal cut-off value and the time of measurement of troponin T after cardiac surgery. Most studies that attempted to validate the fourth universal definition of MI have found a troponin T value much higher than the recommended cut off value. Caution must be exercised while using this criterion due to the high number of false-positive results. There is limited data on the expected release profile of troponin T postcardiac surgery, particularly valvular surgery, for clinical applicability. Evaluating myocardial injury and subsequent troponin rise and clearance after cardiac surgery could be beneficial to prevent mortality, morbidity and decrease health care costs. It would also enable clinical to predict the trend of troponin T, based on individual patient risk factors, and intervene early. Major limitations for effective evaluation of troponin release after cardiac surgery are a large number of cases needed for statistical evaluation and an appropriate statistical model to accurately calculate the expected troponin release profile while accounting for the multifaceted interplay of risk factors associated with cardiac surgery. A nationwide collaboration to evaluate hs-cTnT would be of great value in assessing the importance of troponin T post cardiac surgery.

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