

Troponin Testing After Cardiac Surgery

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ABSTRACT

Single biomarker measurements can predict outcome after cardiac surgery, and may assist in decision making about diagnostic and therapeutic steps following surgery. Although comparative data are relatively lacking some data exist to suggest that among markers of myocardial necrosis, results from cardiac troponin (cTn) measurement may be superior for risk prediction after cardiac surgery to those from the MB isoenzyme of CK (CK-MB). Loss of cardiac troponins from necrotic myocardium is not replenished through re-expression of genes that might increase protein synthesis, and release of cTn appears to represent irreversibly damaged myocardium.

Not every cardiac surgical procedure is associated with the same degree of cTn elevation and forms of cardioprotection may importantly affect concentrations of cTn after coronary artery bypass grafting. Similarly, less cardiac injury may occur depending on the form of anesthesia used during surgery. Great caution must be exercised when utilizing cTnT or cTnI for diagnosis of post-cardiac surgery regional acute myocardial infarction: in this context clinical factors must be applied at the risk of a false diagnosis. On the other hand, concentrations of both cTnT and cTnI have repeatedly and unequivocally been shown to be prognostic for delayed recovery, intensive care unit utilization, as well as short- and longer-term mortality following cardiac surgery.

Keywords: *coronary artery bypass grafting surgery, troponin, myocardial infarction.*

Multiple methods exist for stratifying patient risk for complications after cardiac surgical procedures.

Including complex risk scoring systems such as the EUROSCORE (1), as well as more simple approaches such as single biomarker measurements, the ability to judge risk following potentially life-threatening open-heart procedures is of considerable importance.

The ability to accurately judge prognosis for adverse outcome not only provides important information regarding risk for the clinician to discuss with the patient both pre- and post-operatively, but also may as-

sist in decision making about diagnostic and therapeutic steps following surgery in the context of a post-operative complication (such as detection of acute loss of bypass grafts in the setting of a coronary artery bypass graft (CABG) procedure); furthermore, knowledge of impending complications allows for decision making regarding intensive care unit (ICU) bed availability, as those patients predicted to have complications are more likely to have prolonged ICU lengths of stay (LOS).

As noted, options for risk assessment include accurate, albeit complicated risk scoring systems.

On the other hand, more discrete, single-measure risk tools have been examined for post-cardiac surgery risk assessment, including biomarker testing. The attractiveness of biomarker-based risk assess-

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sment of patients either pre-operatively or post-operatively is intuitively attractive, as measurement of biomarkers such as natriuretic peptides, creatine kinase (CK), or the cardiac troponins (cTn) allows for an objective assessment of the underlying biology of the patient, rather than focusing on more subjective measures. Although each of these biomarkers have been shown to be predictive of risk following cardiac surgical procedures, their use is limited by a relatively poor understanding of the factors that lead to their release during and after cardiac surgery, as well as the optimal mode for their measurement and interpretation.

Although comparative data are relatively lacking with respect to the value of biomarkers for risk prediction after cardiac surgical procedures, some data exist to suggest that among markers of myocardial necrosis, results from cTn measurement may be superior for risk prediction after cardiac surgery to those from the MB isoenzyme of CK (CK-MB) (2-5). This is consistent with the superiority of cTn for diagnosis and risk stratification across the wide spectrum of cardiac syndromes. With this in mind, recent consensus guidelines

have adopted measurement of serum cTn as the “gold standard” for diagnosis of myocardial injury and risk stratification in the setting of cardiovascular diseases (6). Among the situations considered in consensus guidelines for cTn use is excessive myocardial necrosis following cardiac surgery, including CABG; referred to as a “Type 5” myocardial infarction (MI), the use of cTn is endorsed in manner depicted in *Table 1*.

CARDIAC TROPONIN BIOLOGY

The distribution of Tn in muscle tissue is best considered as a “two compartment” model. The contractile proteins of the myofibril contain the majority of the protein, which is a complex of three protein subunits: Tn C (the calcium-binding component; molecular mass 18 kDa), TnI (the inhibitory component; molecular mass 22.5 kDa), and TnT (the tropomyosin-binding component; molecular mass 37 kDa); the myofibril is thought to contain about 95% of the Tn present in muscle, while a smaller cytosolic component is also known to exist (7).

Although multiple Tn isoforms exist in muscle, cardiac-specific isoforms of TnT (cTnT) and TnI (cTnI) have been identified, and assays for their measurement are now widely available.

Mechanistically, the release of cTn is thought to occur whenever myocardial injury occurs, irrespectively of the mechanism. The best studied situation, of course, is acute MI from an ischemic cause; in this setting a 40-80% decrease of tissue cTnT and cTnI may be documented, which is directly reflective of release of either peptide in the peripheral blood. Furthermore, in pig hearts with severe left ventricular remodeling two months postinfarction, both cTnI and cTnT were decreased 80% and

Table 1 - Consensus guidelines for application of cTn testing following cardiac surgery (6).

- For patients with normal baseline cTn values, elevations above the 99th percentile upper reference limit (essentially any measurable cTn) are indicative of peri-procedural myocardial necrosis.
- A type 5 MI is defined as:
 - Increases of cTn greater than five times the 99th percentile upper reference limit, plus
 - New pathological Q waves/new left bundle branch block or
 - Angiographically documented new graft or native coronary artery occlusion or imaging evidence of new loss of viable myocardium

40%, respectively, compared with nondiseased normal myocardium (8). These data demonstrate that loss of cardiac troponins from necrotic myocardium is not replenished through re-expression of genes that might increase protein synthesis, and release of cTn appears to represent irreversibly damaged myocardium.

Some debate exists about whether transient ischemia without cell death may lead to release of cTn from efflux of the cytosolic component, however this has not been proven, and only speculative at present.

In the setting of acute ischemic injury, detectable concentrations of cTn may be found in peripheral blood within 4 hours; with the advent of higher sensitivity cTn (hsTn) methods, a change in the concentration of cTn may be found even earlier, perhaps within an hour of injury.

Following acute MI, depending on the size of the infarct as well as whether revascularization occurred, peak concentrations of cTnT or cTnI tend to be seen within 24-48 hours, and fall over a period of days.

It is not well known if other mechanisms of myocardial cell death lead to a different set of release kinetics.

For example, unusual patterns of cTn release may be seen after endurance exercise. On the other hand, following cardiac surgery - where a multiplicity of mechanisms for cTn elevation may exist (see below) - it has been established that cTn kinetics are largely similar to that of acute MI.

cTn ELEVATION AFTER CARDIAC SURGERY: WHY DOES IT OCCUR?

It is very well-established that cTn elevation is nearly universal after cardiac surgical procedures (3, 9-12); there are multiple mechanisms proposed to explain the finding of myocardial injury after cardiac

Table 2 - Selected variables predictive of cTn concentrations after cardiac surgery.

	Effect on post-operative cTn
Age	↑
Estimated glomerular filtration rate	↑
Acute MI within a week of surgery	↑
Pre-operative need for IABP	
Total number of distal anastomoses	↑
Bypass time	↑
Number of intra-operative defibrillations	↑
Need for placement of intra/post-operative IABP	↑
Higher core temperature during surgery	↓
Beating heart surgeries	↓
Warm cardioplegia	↓
Desflurane, sevoflurane anesthesia	↓

IABP denotes: intra-aortic balloon pump

surgery: pre-operative elevation of cTn may persist into the post-operative setting, intra-operative injury may occur related to cardiac manipulation, inadequate myocardial protection, intra-operative defibrillation or acute post-bypass hemodynamic instability, while post-operative injury may be associated with acute loss of bypass grafts. In one recent study, each of these mechanisms were supported as a cause of cTnT elevation in the post-operative setting (11) (Table 2).

Not every cardiac surgical procedure is associated with the same degree of cTn elevation, an important fact to be kept in mind. In a cohort of 224 subjects undergoing a wide range of cardiac surgeries, including CABG but also valve repair or replacement, heart transplantation, ventricular

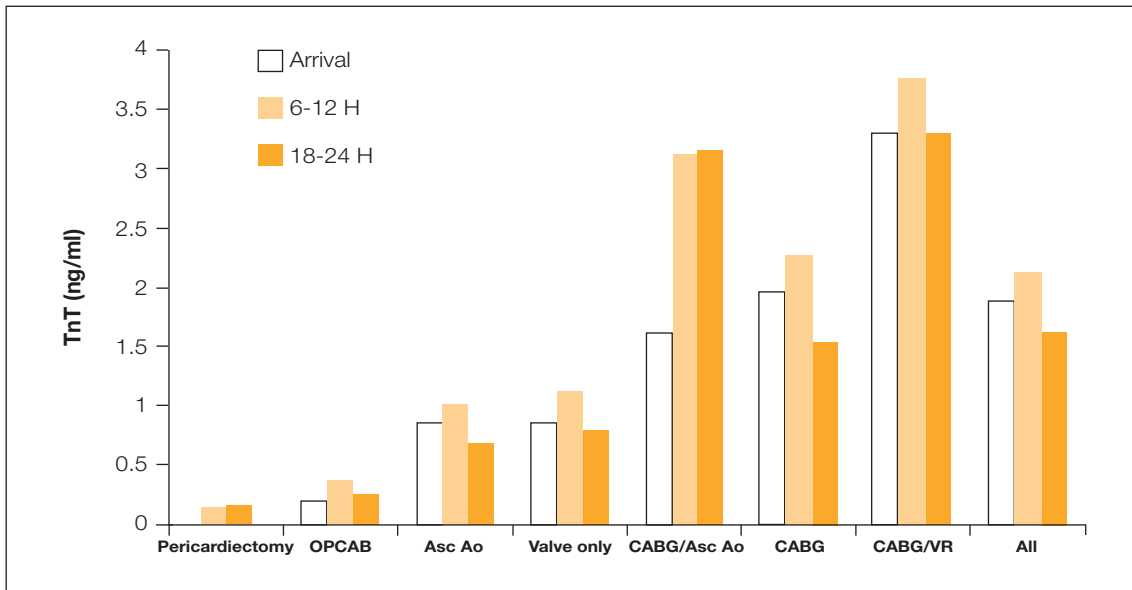


Figure 1

Concentrations of cTnT at various time points (arrival to ICU, 6-12 hours and 18-24 hours) for different forms of cardiac surgery. Of note, pericardiectomy, off-pump CABG (OPCAB), and non-CABG procedures were generally associated with lower post-operative cTnT values (3).

assist device implantation, or more minor procedures such as pericardial stripping, a wide range of cTnT values were observed (3) (Figure 1), with the higher concentrations of the marker seen in those patients that underwent coronary revascularization; this implies - supported by the data in Table 2 - that a significant percentage of circulating cTn following cardiac surgery is related to an ischemic mechanism. This is further borne out in studies of patients with excessive cTnI elevation after CABG, where a higher prevalence of acute graft loss was detected (4), as well as longer-term follow up of patients after CABG, where excessive post-operative cTnT release was associated with a higher likelihood for death and need of revascularization at one year (13), implying more complex coronary anatomy and higher risk for intra-operative ischemic necrosis. Nonetheless, the association between coronary disease

and cTn after surgery is not absolute: notably, cTnT and cTnI have both been shown to be useful after pediatric cardiac surgical procedures in the absence of coronary atherosclerosis. While the association between cTn and the presence/severity of coronary artery disease (CAD) in patients undergoing CABG is necessary to keep in mind, other caveats are important to consider when measuring cTn in this setting. Firstly, while less well understood, there are certain forms of cardiac surgery associated with surprisingly high levels of cTn in the absence of CAD or obvious complications, in particular surgical maze procedures for atrial fibrillation management. In addition and perhaps more importantly, it is also well-known that forms of cardioprotection may importantly affect concentrations of cTn after CABG, such that a wide range of release might be expected to occur depending on the form of cardio-

plegia utilized. For example, those patients undergoing revascularization with cardiopulmonary bypass are expected—even in the absence of obvious complication—to have considerably higher concentrations of cTn (5, 9, 14-19).

This difference in “expected” cTn might be problematic if the marker is used for post-operative risk stratification, but it turns out that in the context of complications, use of the same cTn cut-point is associated with similar prognostic value whether a patient was revascularized using on-pump (ONCAB) or off-pump (OPCAB) methods (11, 20) (see below for more details). Similarly, less cardiac injury may occur depending on the form of anesthesia used during surgery (21-28).

In recognition of the multiple reasons for cTnT or I elevation after cardiac surgery, it should not be surprising that values for these biomarkers are elevated very soon after surgery, often upon arrival to the ICU; prognostic associations will be discussed later, yet both the value of cTn on arrival to the ICU as well as later values may be prognostically meaningful. Thus, sampling at ICU arrival, as well as 18-24 hours may provide unique prognostic information (3, 11).

cTn CONCENTRATIONS AFTER CARDIAC SURGERY: WHAT IS TRULY ABNORMAL?

Keeping in mind the multiple reasons for elevation of cTnT or I after cardiac surgery, it should become obvious to the reader that use of these markers for diagnosis of “acute MI” after CABG is incrementally challenging. One can appreciate the efforts of consensus recommendations to incorporate other variables into the equation for definition of post-cardiac surgery MI, such as electrocardiogram (ECG) findings,

documentation of bypass graft loss or imaging findings suggesting loss of myocardial function. However, associations between the presence of Q-waves or LBBB and acute graft loss following CABG are weak at best, and cTn concentrations do not clearly elevate more excessively when such ECG changes are found (11). Furthermore, coronary and graft angiography after CABG is rarely performed, and imaging studies for myocardial dysfunction are variably specific for MI.

Thus, an inevitable reliance on biomarker results for post-operative risk assessment could theoretically occur, and if misinterpreted, could lead to an excessive percentage of patients diagnosed with an “acute MI”; this becomes a particularly thorny issue when considering the cut-points endorsed by consensus guidelines, which are rather low. For example, in a recent study of patients undergoing CABG, the median cTnT was 1.08 ng/mL.

Among these subjects, 99.4% had a cTnT ≥ 0.01 ng/mL (the 99th percentile concentration for a normal healthy population), and 96.6% had a cTnT ≥ 0.15 ng/mL (the consensus recommended cut-point), most often in the absence of obvious complication. Using consensus cut-points for cTn, a 100% sensitivity for post-CABG MI was observed, but this was associated with a specificity of 4.2% and a dreadfully high misclassification rate (11).

Although the utility of cTn testing for secure diagnosis of regional acute MI after cardiac surgery is in question (particularly given the robust data suggesting that significant elevation of cTnT and cTnI is very common after these procedures in the absence of such a syndrome), the results of numerous analyses would argue that troponin testing after cardiac surgical procedures may add important prognostic value nonetheless. Indeed, it is now well-established that cTn concentrations following

cardiac surgery are strongly predictive of impending adverse cardiovascular events including post-cardiac surgery instability (4, 5, 12, 14, 17, 29-46), ICU length of stay (LOS) (30, 40), ICU utilization (such as duration of ventilator use and need for and number of vasopressors) (3, 11), shock, post-operative quality of life (2), and both short and longer term mortality (4, 5, 12, 14, 17, 29-46).

Interestingly, although current guidelines accept a very low upper reference limit for cTn testing after cardiac surgery, the results of numerous studies would suggest the true inflection point in cTn values for risk prediction is considerably higher (Table 3).

For example, in a prospectively gathered cohort of patients undergoing a wide range of surgical procedures, the optimal cut-point for cTnT to predict adverse outcomes was 1.58 ng/mL (3); this cut-point, more than 10 times above the currently endorsed upper reference limit for cardiac surgery, was recently validated among a larger group of more than 800 subjects undergoing CABG (11) (Table 4).

Table 3 - Examples of recently reported optimal cTn cut-points for prediction of risk following cardiac surgery.

Marker	Cut-point	Reference
cTnT	0.46 ng/mL	Lehrke, et al. (36)
	0.80 ng/mL	Nesher, et al. (12)
	1.0 ng/mL	Brown, et al. (20)
	1.58 ng/mL	Januzzi, et al. (3)
	1.60 ng/mL	Mohammed, et al. (11)
cTnI*	8.49 ng/mL	Croal, et al. (34)
	13.0 ng/mL	Lasocki, et al. (48)
	13.0 ng/mL	Papparella, et al. (18)
	14.0 ng/mL	Hashemzadeh et al. (49)
	19.0 ng/mL	Benoit, et al. (31)
	23.8 ng/mL	Fellahi, et al. (35)
	25.0 ng/mL	Immer, et al. (50)

*Various assays for cTnI were used in these various studies, so reference ranges may not entirely correlate.

Table 4a - Percentage of cTn elevation as a function of upper reference limit among patients undergoing CABG, including off-pump CABG (OPCAB) (11).

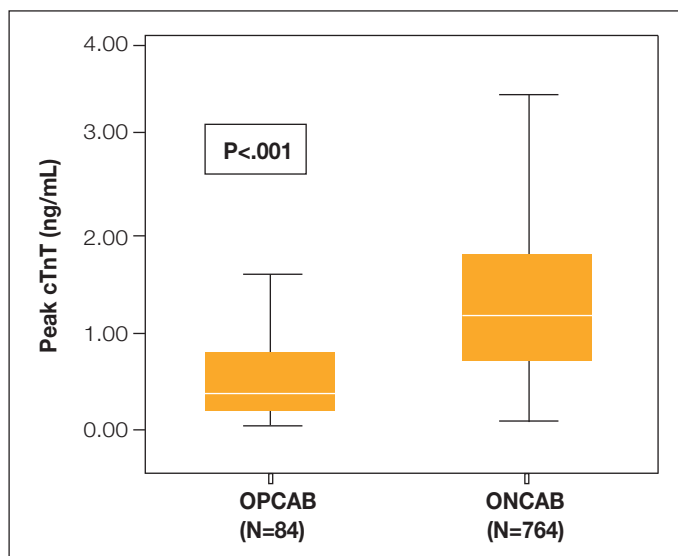
cTnT cut-point	Value	Elevated, all	Elevated, OPCAB
99th percentile for a healthy population	0.01 ng/mL	99.4%	96.4%
10% coefficient of variation	0.03 ng/mL	98.9%	84.0%
Consensus cut-point	0.15 ng/mL	96.6%	72.6%
Januzzi et al.	1.60 ng/mL	36.7%	13.1%

Table 4b - Performance of different potential cut-points for predicting risk following CABG.

cTnT cut-point	Value	NPV	Misclassification
Consensus cut-point	0.15 ng/mL	100%	96%
Januzzi et al.	1.60 ng/mL	99%	28%

Importantly, in a multivariable logistic regression model adjusted for the Society for Thoracic Surgery risk score, cTnT values significantly predicted early post-operative complications of death (OR=3.20; 95% CI=1.5-6.9; $P=.003$), death/heart failure (OR=2.04; 95% CI=1.2-3.5; $P=.008$), death/vasopressor need (OR=2.70; 95% CI=2.0-3.6; $P<.001$), and the triple composite of death/heart failure/vasopressor need (OR=2.57; 95% CI=1.9-3.4; $P<.001$) (11), results similar to those from Simon et al (41).

This suggests that excessive cTn release after surgery adds to the prognostic merit of an already complex risk stratification model and should be considered an independent predictor of bad outcomes independent of other variables considered in this setting.

**Figure 2**

Off-pump CABG (OPCAB) is typically associated with lower median concentrations of cTn than in patients operated on the pump (ONCAB). Nonetheless, the prognostic value of cTn is preserved in OPCAB patients, using the same cut-points as ONCAB patients (11).

SPECIAL CIRCUMSTANCES: CARDIAC OPERATIONS WHERE CTN VALUES ARE LOW

As noted, cTn values are nearly universally elevated among those patients who undergo cardiac surgical procedures, but this is not entirely the case. In a very small percentage of patients, normal or even unmeasurable cTn values may be observed. As already demonstrated in Figure 1, a wide range of cTn values are observed after cardiac surgical procedures, largely dependent on the use of cardiopulmonary bypass as well as the presence and extent of CAD. Accordingly, those patients who are expected to have the lowest concentrations of cTn after cardiac surgery include those patients who undergo non-bypass, beating heart surgeries, such as pericardiectomy. Interestingly, even in the presence of CAD, when beating heart, off-pump CABG (OPCAB) is utilized for revascularization, cTn concentrations are considerably lower than in on-pump CABG (CABG) patients (Figure 2) (11, 15-20). This naturally has raised concerns about whether the same cTn cut-points could be used for both ON-

CAB and OPCAB patients. Fortunately, it would appear that despite concentrations of cTn are lower in OPCAB patients in general, in the context of a complication, values for cTn are similar to ONCAB patients with complications (11, 20), and when cut at similar levels as for ONCAB patients (e.g. 10-15 times the upper reference limit), the marker has comparable negative predictive value (91-97%) for excluding complications, irrespective of cardioprotection strategy (11).

cTn TESTING: POTENTIAL FUTURE APPLICATIONS

In addition to being adopted in a more widespread fashion simply for post-cardiac surgical risk stratification, cTn testing in this setting may have other logical applications in the future. For example, with more widely available non-invasive imaging options such as computed tomography angiography, an elevated cTn might trigger early graft angiography to ensure patency (4, 46); such an approach has been suggested to be of value to “save” potentially th-

reatened grafts in the early post-operative period (47). Furthermore, given the clear association between cTn concentrations and cardioprotection, it is quite clear that these markers may be considered as a surrogate endpoint for the value of novel cardioplegia agents, as well as other forms of intra-operative myocardial protection strategies (21-28).

cTn TESTING AFTER CARDIAC SURGERY: SUMMARY AND LOGICAL APPLICATION

Based on the available data in the literature, cTnT and cTnI are superior to CK-MB as a biomarker for post-cardiac surgery patient evaluation. Elevation in both cTnT and cTnI is expected nearly universally after cardiac surgery, particularly in ONCAB patients, and those undergoing CABG with associated valve replacement surgery. These elevations are due to multiple causes, including presenting syndromes, intra-operative management and post-operative events.

Given the multiplicity of causes for cTn elevation after cardiac surgery, and the particular rarity of a regional MI, in this context, the use of cTnT or cTnI for the diagnosis of regional MI after cardiac surgery is problematic. Furthermore, consensus recommended cut-points for diagnosis of the so-called "Type 5" MI are so low as to render the application of cTnT and cTnI quite problematic, given the expected over-reliance on objective measures - such as biomarkers - for the diagnostic evaluation of the post-operative patient, in whom other means for evaluation (such as ECG or echocardiography) are either non-specific or not easily delivered/interpreted in the ICU setting. Thus, great caution must be exercised when utilizing cTnT or cTnI for diagnosis of post-cardiac surgery regio-

nal acute MI: in this context clinical factors must be applied at the risk of a false diagnosis.

On the other hand, concentrations of both cTnT and cTnI have repeatedly and unequivocally been shown to be prognostic for delayed recovery, ICU utilization, as well as short- and longer-term mortality following cardiac surgery.

The optimal cut-points for this application are considerably higher than consensus guideline cut-points for "Type 5 MI", typically in the range of 10-15 times the upper reference limit.

Data would suggest that a cTn below this threshold on ICU arrival and/or at 18-24 hours provides sufficient prognostic information for identifying those patients with a low likelihood for a complicated course.

For those patients with excessive cTnT or cTnI elevation, an adverse outcome is more likely and more assiduous evaluation and management for such patients is suggested.

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