Postoperative Troponin Screening: a Cardiac Cassandra?

Running title: Beckman; Troponin: Barometer or Weather-vane?

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The cardiovascular management of the patient undergoing non-cardiac surgery has been in evolution for the last 35 years. Over this time frame, two secular trends have advanced in parallel but provided contrary practice implications for the care of the surgical patient. First, cardiovascular event rates have been dropping significantly over time. In 1977, Goldman and colleagues created a risk evaluation system that predicted a 22% rate of “life-threatening” cardiovascular events and more than 50% mortality in the highest risk group in 1001 patients undergoing surgery. These rates of events have dropped each decade since significantly. Finks and colleagues reported 2 years ago a mere 2.8% national mortality rate for open abdominal aortic aneurysm repair; the exemplar of routine, high-risk surgery. These numbers were recapitulated world-wide for high-risk patients undergoing noncardiac surgery in the PeriOperative ISchemic Evaluation (POISE) trial. Improvements in surgical and anesthetic techniques, perioperative medical therapy, and intensive care have each participated in the significant improvement in outcomes.

Second, the sensitivity of testing to detect evidence of cardiovascular disease or ischemia has increased dramatically. In this same time frame, risk assessment has evolved from stress testing, to nuclear – vasodilator testing, inotropic echocardiographic assessment, cardiac magnetic resonance imaging, and positron emission tomographic (PET) scanning. Counterintuitively, the ability to accurately detect smaller and smaller amounts of disease has not improved post-operative cardiovascular event prognostication. Indeed, the positive predictive value for each of these modalities in predicting a cardiovascular event remains below 20% . The poor performance may be attributed to two components. First, improvements in disease detection fosters inclusion of patients previously deemed healthy by less sensitive modalities. Indeed, it is the specific coronary heart disease detection improvement that undermines its prognostic value.
in the stable patient by diminishing the risk of the group with a “positive study.” Second, ever-
dropping event rates largely render the prognostic value of these tests moot. A three-fold hazard
ratio in the setting of a 1-3% surgical mortality provides little insight into patient selection for
higher level therapies beyond medical therapy. Because of the overall low mortality and the
limited value of noninvasive testing to clarify outcome and need for preoperative coronary artery
revascularization, there has been an increase in effort to find patients at heightened risk post-
operatively to stave off severe adverse events. Over the last decade, much of this effort has
focused on biomarkers of myocardial injury, the cardiac troponins.

The troponin complex is co-located with tropomyosin on the actin filament and
participates in cardiac muscle contraction. The complex consists of three peptide components, T, I,
and C. The first two have been used in the measurement of myocardial injury whereas troponin
C, the calcium binding site, is not because of its shared location in skeletal muscle. Measurement
of troponin T was approved by the Food and Drug Administration in 1996 and its uptake into the
medical practice was rapid. Just 4 years later, the cardiology community made troponin the
preferred biomarker to diagnose myocardial infarction as part of the guideline process. By
2007, troponin measurement became the de facto global standard when the first Universal
Definition of Myocardial Infarction was published. Over the last decade, the troponin use has
skyrocketed beyond the limited use for determining the presence or absence of an acute coronary
syndrome and become a nonspecific marker of illness. Indeed, the value of troponin in the
diagnosis of myocardial infarction may have reached its apex in 2001 with the publication of the
Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative
Strategy (TACTICS) study. The investigators showed that early invasive therapy was superior to
a conservative approach in patients presenting to the hospital with chest pain with a troponin T of
> 0.01 ng/ml but not without this troponin T elevation. This led to the wide adoption of troponin in the standard evaluation of patients with chest pain or thought to be at risk of myocardial infarction.

Subsequently, troponin has been measured in a wide variety of settings to provide prognostic information in diseases that do not originate in the coronary arteries. Prognostic information has been generated for diseases that originate with the heart, affect the heart, are remote from the heart, and have extended to patients who aren’t acutely ill. Elevations in troponin associate with worse outcomes in patients with myocarditis, congestive heart failure, and cardiac contusions showing the value of this biomarker in a broad range of cardiac disease. Troponin release provides significant prognostic information for pulmonary disease, presumably because of its direct vascular coupling with the right ventricle. For example, many studies have shown that troponin release during pulmonary embolism is a marker of severity and adverse prognosis. Similarly, elevations in troponin during chronic obstructive pulmonary disease exacerbation are associated with a greater need for ventilator support and worse long-term survival. The release of troponin is thought to result from a direct increase in right ventricular overload and right heart strain.

Perhaps more impressively, release of cardiac troponin has become sensitive enough to act a barometer of the severity of illness unrelated to the heart. Patients with septicemia who have measurable troponin levels suffer worse outcomes than those who do not, even after adjustment for other prognostic markers. Similarly, the release of troponin predicts poorer outcomes in patients admitted with subarachnoid hemorrhage. More recently, investigators have shown that troponin release may occur in the absence of overt illness and provide prognostic data for outcomes in the non-hospitalized person. Using a high-sensitivity troponin T
assay, investigators in the Dallas Heart Study have shown that among 3546 individuals aged 30 to 65 years enrolled between 2000 and 2002, 25% of the cohort had detectable troponin T \(^{21}\). Moreover, when the troponin level was greater than 0.0014 ng/ml, the hazard ratio for all-cause death over the 6.4 years of follow up was nearly 5 five fold higher despite adjusting for age, race/ethnicity, sex, diabetes, hypertension, hypercholesterolemia, low high-density lipoprotein cholesterol level, current smoking, log-transformed values of high-sensitivity C-reactive protein, and chronic kidney disease categories. Moreover, the troponin elevation across the range predicted all-cause mortality and cardiovascular mortality similarly. And, therein, lies the problem. Although certainly originating in the heart, when used to provide prognostic data beyond cardiac-in-origin diseases, troponin elevation no longer provides cardiovascular outcome-specific information. It becomes a nonspecific test of illness that requires interpretation by setting. Indeed, the screening measurement of troponin post-operatively most resembles the use of troponin in the Dallas Heart Study as a screening tool.

In this issue of *Circulation*, Van Waes and colleagues are to be commended for reporting the largest single-center study of post-operative troponins yet published. The investigators studied 2,232 consecutive intermediate to high risk noncardiac surgery patients aged >60 years who underwent surgery in 2011 \(^{22}\). Of the total surgical population, all-cause mortality was 3%, troponin T release was detected in 19%, and elevations predicted death in a dose-related manner, consistent with past work. Also consistent with past work and similar to the Dallas Heart Study was a stronger association with all-cause mortality than myocardial infarction. In this cohort, myocardial infarction (based on the universal definition) was diagnosed in 10 subjects or 0.6% of the total.

Other studies have demonstrated both a similar relationship between troponin elevation
and mortality after surgery and the relative infrequency of myocardial infarction by the universal definition in this setting, however, it is the Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study that puts the whole picture in perspective. The VISION investigators measured troponin T levels 6 to 12 hours after surgery and on days 1, 2, and 3 after surgery in patients older than 45 years who required at least a one-night stay in the hospital. Overall, the 30-day mortality rate was 1.9% and troponin T was measurable in 11.6% of the patients. Across a narrow range of troponin T elevation, the hazard for mortality rose quickly, with a 10-fold mortality risk noted in patients with troponin elevations ≥ 0.30 ng/ml. Despite the fact that the vascular death category included nontraditional elements like pulmonary embolism, hemorrhage, and death from unknown causes, the number of vascular deaths remained smaller than non-vascular deaths. The VISION investigators reported that increases in troponin T predicted cardiovascular and non-vascular death equivalently. Thus, post-operative troponin elevation has become a non-specific marker of hazard.

In this author’s opinion, practitioners underappreciate this lack of specificity of post-operative troponin testing. For example, the authors of the Third Universal Definition of Myocardial Infarction recommend “routine monitoring of cardiac biomarkers in high-risk patients, both prior to and 48–72 h after major surgery” because “most patients who have a perioperative MI will not experience ischemic symptoms. Nevertheless, asymptomatic perioperative MI is as strongly associated with 30-day mortality, as is symptomatic MI.” They then go on to recommend close clinical scrutiny, but without any specific recommendation for care. I favor an approach to testing as advocated by Laine in posing certain questions prior to ordering a test. First, will the test change the care of my patient? In the asymptomatic patient without ECG changes, a troponin elevation does not predict any specific kind of death, thus the
test provides no direction for care and clinicians should continue to treat patients individually. Second, what are the probability and potential adverse consequences of a false positive result? For this, I would refer to the vanishingly small number of type 1 myocardial infarctions diagnosed and worry that management for plaque rupture events (antiplatelet therapy, anticoagulation, and possibly catheterization) would be provided for patients with hemodynamic (type 2 myocardial infarction) events. None of these interventions is likely beneficial for the vast majority of patients, particularly early after major surgery when the troponin is likely to be elevated. As noted by Van Waes and the VISION investigators, the majority of troponin T release occurs by the end of post-operative day 1, a high-risk period for bleeding. Third, is the patient in potential danger over the short term if I do not perform this test? Although it is certainly true that an elevation in troponin portends adverse outcome, the lack of specificity concerning the mechanism of adverse outcome suggests that the test will not foster a change or modification of therapy. In a small study of patients over aged 60 years undergoing emergency orthopedic surgery, the addition of cardiovascular care to troponin positive patients did not affect in-hospital cardiovascular complications or 1 year mortality. Most telling, however, is that the cardiologists did little to alter care. No coronary angiography was performed and only 1 in 6 patients seen by cardiologists had the addition of aspirin, beta blockers, or both.

It is the author’s opinion that improvements in troponin T assay sensitivity have created a condition in which the biomarker is so easily measured that it now culls out patients at higher risk for any adverse event more than diagnoses cardiac-specific events. Indeed, one may suggest that the results are similar to the Dallas Heart Study, but instead of free-living individuals, the perioperative patient population represents an asymptomatic group exposed to surgical stress, and the elevation in troponin similarly indicates a high-risk group for all-cause death. In the
absence of any demonstrated beneficial treatment strategy, the possibility of harm in applying the standard treatment for type 1 myocardial infarction, and the potential to divert attention from a true cause of adverse event (non-vascular morbidity) to a false one (myocardial infarction), the author believes that routine measurement of troponin is more likely to cause harm than provide benefit and should not be used as a screening modality.

Currently, low rates of overall perioperative mortality in the setting of guidelines based care\(^28\) have made risk prediction difficult and largely limited the task of risk assessment to ferreting out patients with active cardiac conditions, severe pulmonary disease, or severe underlying medical illness. These factors may or may not be related to the features seemingly most predictive of troponin release, such as intra-operative hypotension, pre-operative hypertension, and the presence of atherosclerosis\(^29-31\). Studies are ongoing to determine response strategies to elevations of troponin post-operatively, but until a specific strategy or treatment is identified, the ontogeny of troponin testing makes unlikely patient benefit from its routine measurement after noncardiac surgery.

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