Chasing myocardial outcomes: perioperative myocardial infarction and cardiac troponin

À la poursuite de critères d'évaluation myocardiques: infarctus du myocarde périopératoire et troponine cardiaque

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Abstract *Perioperative myocardial infarction represents the most common cardiovascular complication following non-cardiac surgery, but frequently presents without the usual clinical signs and symptoms consistent with acute coronary syndrome. Given the silent nature of this event, a clinician's reliance on risk stratification tools and cardiac specific biomarkers to assist in the identification of at-risk individuals is heightened in the perioperative setting. Although cardiac troponin elevations following non-cardiac surgery have been consistently linked to increased mortality, uncertainty remains over how to clinically intervene to prevent harm. This decision is further complicated by the increasing sensitivity of the newest generation of cardiac biomarker immunoassays. In this narrative review, the growing body of evidence surrounding cardiac troponin elevations in the perioperative setting, how the evidence has been integrated into recent clinical practice guidelines, and its implications for the detection of perioperative myocardial infarction are discussed.*

Résumé *L'infarctus du myocarde périopératoire représente la complication cardiovasculaire la plus fréquente après chirurgie non cardiaque, mais il se présente fréquemment sans les signes et symptômes cliniques usuels du syndrome coronarien aigu. Compte tenu de la nature silencieuse de cet événement, les cliniciens doivent pouvoir se fier d'autant plus à des outils de stratification du risque et à des biomarqueurs cardiaques spécifiques pour les aider à identifier les individus à risque dans le cadre périopératoire. Bien qu'une augmentation de la troponine cardiaque après une chirurgie non cardiaque ait été constamment liée à une augmentation de la mortalité, des incertitudes persistent sur la façon d'intervenir cliniquement afin d'éviter tout préjudice. Cette décision est encore compliquée par la sensibilité croissante de la nouvelle génération de dosages immunologiques des biomarqueurs cardiaques. Dans cette étude narrative, nous discuterons la masse croissante de données probantes concernant l'élévation de la troponine cardiaque dans un cadre périopératoire, la façon dont les données probantes ont été intégrées dans les lignes directrices de pratique clinique récentes et leurs conséquences sur la détection de l'infarctus du myocarde périopératoire.*

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Despite 40 years of cumulative interest in the cardiovascular management of the patient undergoing non-cardiac surgery, the subject matter remains as relevant as ever. Estimations of global surgical volume indicate that more than 200 million operations are performed worldwide each year.¹ As the elderly have been shown

to require surgery at a rate four times greater than that of the general population, global aging trends suggest further growth in the surgical realm.² Accompanying this influx of an older population, providers can expect to see similar increases in patient comorbidities, the greatest of these being cardiovascular disease.³

With overall complication rates that average as high as 17% and mortality rates that exceed 2% for patients presenting for non-cardiac surgery, the perioperative management of this population represents a significant opportunity for harm reduction.⁴⁻⁶ Closer examination of the morbidity and mortality associated with non-cardiac surgery shows that a substantial percentage of the precipitating events are cardiovascular in origin.⁷ As perioperative myocardial infarction (PMI) represents the most common cardiovascular complication following non-cardiac surgery, significant emphasis has been placed on identifying such events.⁸ Noting that these ischemic events often lack the clinical signs and symptoms of acute coronary syndrome, our reliance on cardiac biomarkers is elevated in the perioperative setting. Consequently, efforts to drive outcomes in this cohort begin first with the determination of risk.

Attempts at evaluating the risk of a cardiovascular event date back to the 1970s when Tarhan *et al.* described predictors of postoperative myocardial infarction (MI) in a single-institution cohort of over 32,000 patients.⁹ Later that decade, Goldman, *et al.* proposed a risk index specific to postoperative cardiovascular complications that stratified patients into four distinct risk categories.¹⁰ Although the rates of cardiovascular events following non-cardiac surgery have fallen over the past 40 years, risk stratification remains a pillar of perioperative evaluation.¹¹ The Revised Cardiac Risk Index (RCRI), the most commonly used and broadly validated tool in practice today, consists of six independent predictors of major cardiac complications. These specific cardiovascular endpoints were identified in the initial study population using creatine kinase-MB as a biomarker, yet subsequent studies have validated the tool to continue to discriminate risk when using the more modern cardiac troponin assay.^{12,13} While the RCRI is specific to cardiovascular risk, it encompasses a wide breadth of clinical outcomes: cardiac death, nonfatal MI, nonfatal cardiac arrest, postoperative cardiogenic pulmonary edema, and complete heart block.¹⁴ This composite set of clinical outcomes, often referred to as major adverse cardiovascular events, encompasses multiple endpoints of varying degrees of relatedness.¹⁵ But despite its design to predict a composite outcome, given the relative frequency of MI in relation to other major adverse cardiac events, this preoperative risk stratification tool has specific utility for focusing the detection of PMI.⁸

A recent iteration of the universal definition of MI, published in 2012, defines MI as necrosis in a clinical setting consistent with acute myocardial ischemia. Within this conditional framework, an elevation and/or decline of the cardiac biomarker, namely, troponin with at least one value above the 99th percentile upper reference limit, will fulfill diagnostic criteria when paired with symptoms of ischemia, changes in the electrocardiogram (ECG), or imaging suggestive of loss of viable myocardium or intracoronary thrombus.¹⁶ Nevertheless, the challenge in detecting MI in the perioperative setting is that the majority of these cardiovascular events are silent and lack the traditional signs and symptoms that would raise clinical suspicion.¹⁷

Current thinking suggests two distinct mechanisms by which a PMI may occur. The first, often referred to as a type-1 PMI, represents the spontaneous rupture of an unstable plaque causing acute coronary thrombosis, ischemia, and infarction. The second, and more common cause of PMI, represents a prolonged imbalance of the supply and demand of myocardial oxygen. This type-2 PMI, which may represent > 65% of the MIs suffered in the perioperative setting, generally presents as silent heart rate-related ST-segment depression on an electrocardiogram (ECG).^{8,18} Given that the majority of these patients will not experience ischemic symptoms, detection of these events are often late and beyond the time frame of meaningful intervention.⁸ As such, the utility of cardiac biomarker surveillance is of particular interest.

Since the first cardiac troponin I and T immunoassays were introduced in the late 1980s, sensitivity and precision continue to improve. Several generations of assays have entered commercial application, with the newest iterations displaying nearly 100 times greater sensitivity than those initially introduced.¹⁹ These newest high-sensitivity assays have the capacity to detect cardiac troponin levels in the majority of healthy individuals, trading to some extent on the test's specificity for identifying acute MI.²⁰ Given the rapidly improving precision of these tests and the lack of consistency in the units of measurement, a growing consensus is emerging to suggest the standardization of units of detection as ng·L⁻¹.^{21,22}

Although these technological advances may have implications for the interpretation of cardiac troponin assays in the future, there is a growing body of evidence linking the elevation of perioperative troponin to increased mortality. In their study of 1,136 patients undergoing abdominal aortic surgery, Le Manach *et al.* showed that elevated levels of cardiac troponin I postoperatively were independently predictive of in-hospital mortality.²³ Levy *et al.* further amalgamated the prognostic capability of an elevated troponin assay through the meta-analysis of 14 studies investigating perioperative mortality following

non-cardiac surgery. Despite substantial heterogeneity among the trials, increased postoperative troponin measurements were independent predictors of mortality (odds ratio [OR], 3.4; 95% confidence interval [CI], 2.2 to 5.2). This risk was categorized as intermediate-term (< 12 mth) mortality (OR, 6.7; 95% CI, 4.1 to 10.9; $I^2 = 0\%$) and long-term (>12 mth) mortality (OR, 1.8; 95% CI, 1.4 to 2.3; $I^2 = 0\%$; $P < 0.001$ for test of interaction).²⁴ In a retrospective review of 51,701 patients undergoing non-cardiac non-transplant surgery, Beattie *et al.* identified that postoperative troponin I elevations incrementally predicted 30-day postoperative all-cause mortality.²⁵ Van Waes *et al.* also confirmed that postoperative troponin elevations during the first three days after surgery predicted 30-day mortality in their study of 2,216 patients following major non-cardiac surgery.²⁶

The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Study examined major complications after non-cardiac surgery in a prospective international cohort of 15,133 patients and has since served as the basis of several publications of merit on the utility of measuring cardiac biomarkers postoperatively. An initial investigation correlated peak troponin T (TnT) measurement in the first three days following non-cardiac surgery with 30-day mortality, finding that peak TnT values of $0.02 \mu\text{g}\cdot\text{mL}^{-1}$, $0.03\text{--}0.29 \mu\text{g}\cdot\text{mL}^{-1}$, and $\geq 0.30 \mu\text{g}\cdot\text{mL}^{-1}$ were all independently associated with an increased risk of mortality from both cardiovascular and non-cardiovascular origins.²⁷ This specific illustration that such low detected levels of troponin—previously perceived as not being detrimental to cardiac well-being—are associated with an increased risk of cardiac events has spawned closer examination of the thresholds we utilize to identify myocardial injury.

The VISION investigators returned to this clinical registry more recently to inform their proposal of a new prognostic category, myocardial injury after non-cardiac surgery (MINS). By evaluating troponin elevations until day 30 after surgery and adjusting for perioperative complications, a peak postoperative TnT measurement $\geq 0.03 \text{ ng}\cdot\text{mL}^{-1}$ proved to be the greatest indicator of MINS and 30-day mortality.²⁸ Despite interesting clinical implications, MINS remains a surrogate outcome. Although perioperative myocardial injury due to documented non-ischemic etiologies were excluded from this analysis, the cause of a troponin release was not tracked prospectively in the initial VISION trial registry, essentially framing the criteria of MINS as a diagnosis of exclusion. Furthermore, baseline resting troponin levels were not obtained in the initial cohort. In the Dallas Heart Study by Wallace *et al.*, the investigators examined 3,557 subjects in the non-surgical population and correlated detectable cardiac TnT levels with many of the risk factors

contained in the RCRI, namely, congestive heart failure, diabetes mellitus, and chronic kidney disease.²⁹ Nagele *et al.* have shown that over 98% of high-risk surgical patients have detectable cardiac troponin T levels preoperatively, and 41% of these exceed the 99th percentile upper reference limit of the immunoassay.³⁰ Given the heightened ability to detect measureable troponin levels in various patient populations, preoperative baseline values may serve as important clinical reference points as the discriminative threshold of proposed clinical prognosticators falls.

With this focused interest surrounding the utilization of cardiac troponin in the perioperative setting, the recent clinical practice guidelines offered by the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology/European Society of Anaesthesiology (ESC/ESA) make brief mention of their assessment of the utility of this specific biomarker. The ACC/AHA Guidelines question the value of postoperative troponin screening in patients at high risk for PMI who do not display signs or symptoms suggestive of myocardial ischemia or infarction, noting that there is a lack of established risks and benefits of a defined management strategy (Class IIb recommendation; level of evidence B). They further comment that indiscriminate routine postoperative troponin screening in patients without signs or symptoms suggestive of myocardial ischemia or infarction is not useful for guiding perioperative management (Class III recommendation; level of evidence B).³¹ The ESC/ESA Guidelines, however, suggest that cardiac troponin measurement in high-risk patients may be considered both before and 48–72 hr after major surgery (Class IIb recommendation; level of evidence B). These recommendations are cautioned with the mention that troponin elevations can be observed in other clinical conditions and that the diagnosis of non-ST-elevation MI should never be made on the basis of biomarkers alone.³²

While the majority of attention in the realm of cardiac biomarkers focuses on the utility of troponin, the ESC/ESA Guidelines also comment on evidence identifying B-type natriuretic peptide (BNP) and N-terminal-proBNP (NT-proBNP) as preoperative prognosticators for long-term mortality and the likelihood of cardiac events after major non-cardiac vascular surgery. A recent systematic review and meta-analysis showed that an elevated preoperative BNP measurement was predictive of cardiovascular outcomes at 30 days postoperatively (OR, 19.3; 95% CI 8.5 to 43.7; $I^2 = 58\%$).³³ Based on these findings, the recommendation of the ESC/ESA Task Force is that preoperative BNP and NT-proBNP measurements may be considered for high-risk patients (Class IIb recommendation; level of evidence B).³² With studies underway to

clarify this linkage further, the number of validated biomarkers available to facilitate risk stratification of patients undergoing non-cardiac surgery may be expanding.

Despite somewhat conflicting opinions from the ACC/AHA and ESC/ESA regarding the usefulness of troponin measurement, there is clearly an established linkage between postoperative troponin elevations and increased mortality. Proponents of the use of cardiac biomarkers perioperatively suggest that monitoring troponin after non-cardiac surgery may afford physicians the means for better risk stratification and management of those patients with the greatest likelihood of suffering a cardiovascular event. Consensus is lacking surrounding the timing of troponin measurements in the perioperative period when used as a surveillance tool; however, many of the studies supporting the mortality link have tracked troponin at 6–12 hr postoperatively and daily on postoperative days 1, 2, and 3.^{26,27,30} Those who challenge the broad application of the biomarker caution that, as the precision of high-sensitivity troponin assays improves to allow the detection of very low levels of circulating cardiac troponin, confusion and uncertainty emerge around the interpretation of those values. Specifically, elevations in troponin have been associated with poorer outcomes in cardiac conditions unrelated to ischemia and infarction, namely, myocarditis, congestive heart failure, and cardiac contusions.^{34–36} Troponin has also been linked to the prognosis of disease originating outside the heart, with pulmonary embolism, chronic obstructive pulmonary disease, subarachnoid hemorrhage, and sepsis all showing poorer outcomes associated with elevated troponin measurements.^{36–39}

The issue at hand is that only 14% of patients who experience a PMI will have chest pain, and only 53% of patients will exhibit clinical signs or symptoms of ischemia.⁴⁰ This large percentage of patients who will experience a PMI without the traditional diagnostic features highlights the need for a tool to capture this perioperative event. Nevertheless, as Beckman has suggested, postoperative troponin elevation has become a nonspecific marker of hazard, whereby a troponin elevation does not predict any specific kind of mortality in the asymptomatic patient without ECG changes.⁴¹ Consequently, the additional information is of questionable clinical utility, leaving providers without a distinct treatment strategy and little evidence to support the risks or benefits of intervention.

In our current dichotomous risk stratification system whereby patients are tiered at a lower or higher risk of experiencing a perioperative cardiovascular event, a significant grey zone exists for clinical management and surveillance of PMI. Little controversy surrounds the utility of a troponin measurement in patients presenting with signs or symptoms of ischemia, irrespective of risk. Nevertheless, in the postoperative population without symptoms, our ability to hone efforts on identifying a

PMI currently places a great deal of weight on our preoperative assessment tools. Given the aforementioned association of troponin elevations with comorbidities unrelated to myocardial ischemia, it is unlikely that screening low-risk individuals in the postoperative setting will provide any actionable information to clinicians.

On the other end of the spectrum, the ESC/ESA Guidelines diverge from the ACC/AHA recommendations in suggesting that there may be clinical utility in screening all high-risk patients for troponin elevations following major surgery. This consensus statement highlights that there are facets of the specific surgery being performed that may be of predictive value. Kheterpal *et al.* have shown that particular intraoperative events, namely, significant hypotension or tachycardia, are associated with a greater likelihood of postoperative cardiac adverse events.⁴² Furthermore, the surgical Apgar score, which examines estimated blood loss, lowest mean arterial pressure, and lowest heart rate in the operating room, has been validated to predict major complications following non-cardiac surgery.⁴³ Although the ESC/ESA Guidelines may be interpreted as an endorsement of indiscriminate troponin screening in all patients deemed high risk preoperatively, it appears that incorporating an assessment of intraoperative events may help yield greater value from postoperative troponin surveillance. Ultimately, preoperative assessments of risk can be very different from the postoperative likelihood of developing a PMI. As such, preoperative risk stratification alone may not offer enough information to warrant unfocused troponin screening in asymptomatic patients deemed high risk, or otherwise.

The shift in terminology from PMI to MINS underscores the profound advances in our ability to detect cardiac stress. Yet, our interpretation of a postoperative troponin elevation as anything more than a signal for mortality risk should be greeted with caution. In the right patient population, it seems intuitive that perioperative measurement of cardiac-specific biomarkers may be of great clinical value. Nevertheless, when that biomarker describes very little in terms of a disease or event-specific etiology, as is the case for troponin elevations in isolation, tailoring an intervention remains a challenge. While the exact postoperative population to benefit from screening and intervention remains uncertain, there is mounting evidence that risk stratification tools that combine pre-existing comorbidities with intraoperative events will offer the greatest prognostic value. Until we determine which population would most benefit from our focused efforts, we are left with little guidance on how to interpret an elevation in troponin. As we expand on the current evidence base linking postoperative troponin elevations and increased mortality, more investigation is needed to clarify whether interventions improve outcomes, and if they do, which

patient populations will represent the greatest opportunity for focused care.

Conflicts of interest None declared.

Disclosures None.

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