Perioperative Troponin Elevation

GA Redfern

Commentator: L Ryan
Moderator: B Biccard

Department of Anaesthetics
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1. INTRODUCTION

Peri operative myocardial infarction (PMI) remains a significant cause of morbidity and mortality; especially in the vascular surgical patient.\textsuperscript{1-3} The diagnosis of MI in this period is often difficult. Troponin surveillance in the post operative period has shown that many patients experience silent myocardial ischaemia.\textsuperscript{4} Although any elevation of troponin beyond a normal reference range is diagnostic of myocardial injury\textsuperscript{5}, small postoperative rises are often disregarded.

The following talk will focus on the work done by myself, Dr B Biccard and Dr RN Rodseth on the outcomes associated with a postoperative troponin leak which was not elevated to the diagnostic threshold of myocardial infarction. We are in the process of producing a meta-analysis on all cause mortality focusing on vascular surgical patients.

2. TROTONIN – A BRIEF BACKGROUND

![The troponin complex](image)

\textbf{Figure 1} The troponin complex
The cardiac troponins (cTn) are sensitive\(^6\) and specific\(^7\) markers of myocardial necrosis. Both troponin I (cTnI) and T (cTnT) are used worldwide in the diagnosis of MI. Both are almost undetectable in normal populations.

Diagnosis of troponin elevation has changed as the test assays have evolved. Professional societies recommended the 99th percentile (i.e., a positive test for 1 in 100 persons in the reference group) as more conservative than the 97.5th percentile.\(^8\)

Since 2000, cardiology and laboratory guidelines have endorsed a single cut-off value for the diagnosis of myocardial infarction at the 99th percentile for each assay.\(^8\)

A meta-analysis performed in 2000 to determine the predictive value of troponins showed marginal differences between the operating characteristics of cTnI and cTnT but this did not approach statistical significance.\(^9\)

Until further evidence-based investigations demonstrate compelling evidence of the superiority of one form of troponin testing over another, the current consensus appears to be that cTnI and cTnT are equivalent for both diagnostic and prognostic applications.

It is important to note that troponin elevations may also occur in the setting of septic shock, renal failure, or pulmonary embolism.

3. THE DIAGNOSIS OF MI

In the distant past, a general consensus existed for the clinical entity designated MI. In studies of disease prevalence by the World Health Organisation (WHO), MI was defined by a combination of two of three characteristics:

- typical symptoms (i.e. chest pain)
- enzyme rise
- and a typical ECG pattern involving the development of Q waves.\(^{10}\)

With the advent of troponin assays, the diagnosis needed to be re-evaluated. In 2000, the Joint European Society of Cardiology with the American College of Cardiology published a consensus document to redefine MI.\(^8\)
They are as follows:

*Criteria for acute, evolving or recent MI.*

Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:

1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:

   a) ischaemic symptoms;
   b) development of pathologic Q waves on the ECG;
   c) ECG changes indicative of ischaemia (ST segment elevation or depression); or
   d) coronary artery intervention (e.g., coronary angioplasty).

2) Pathologic findings of an acute MI.

The document went on to categorise myocardial infarctions temporally from clinical and other features, as well as according to the pathological appearance, as evolving (<6 h), acute (6 h–7 days), healing (7–28 days), and healed (29 days and beyond).

This refocus on biomarkers allowed for the identification of the entity known as non-ST elevation MI (NSTEMI), which is particularly relevant in the postoperative period.

In 2007, the ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction published a further consensus document. It classified MIs into various clinical classification as seen in Table 1.
4. MI IN THE PERIOPERATIVE PERIOD

Arterial thrombosis is the precipitant for the majority of non-operative MIs. The pathophysiology of post-op MI is less certain. Post mortem studies done after fatal postoperative MI showed an incidence of left main stem or 3-vessel disease of 66%. However, only about one third of these patients demonstrated intracoronary thrombus at autopsy. Importantly, very few showed signs of active plaque instability as evidenced by plaque fissuring.

**Triggers of perioperative MI**

Surgery, with its associated trauma, anaesthesia and analgesia, intubation and extubation, pain, hypothermia, bleeding and anaemia, and fasting, is analogous to an extreme stress test. Figure 2 illustrates how these factors initiate inflammatory, hypercoagulable, stress and hypoxic states which are associated with perioperative elevations in troponin levels, arterial thrombosis and mortality.
Increased stress hormone levels result in increases in blood pressure, heart rate, coronary artery shear stress, relative insulin deficiency and free fatty acid levels. \(^{14}\)

Coronary artery shear stress may be responsible for precipitating plaque fissuring and acute coronary thrombosis. \(^{15}\) The other factors, particularly an increased heart rate, increase oxygen demand and can result in myocardial ischaemia, which is strongly associated with perioperative MI. \(^{17,18}\)

Factors that can initiate a hypoxic state include anaemia, hypothermia (through shivering), and anaesthesia and analgesia (respiratory depression). \(^{19-21}\) These can result in a supply-demand imbalance in the setting of a haemodynamically significant coronary artery stenosis.

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**Figure 2** \(^{14}\) Potential triggers of states associated with the perioperative elevations in troponin levels, arterial thrombosis and fatal myocardial infarction. TNF-α = tumour necrosis factor, IL = interleukin, CRP = C-reactive protein, PAI-1 = plasminogen activator inhibitor-1, BP = blood pressure, HR = heart rate, FFAs = free fatty acids

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Pathophysiology of perioperative MI

With the introduction of troponin surveillance, it has become apparent that PMI is detectable within the first 24 hours post surgery.\textsuperscript{22} The current hypothesis of the pathophysiology behind PMI is based heavily on the work done by Landesberg et al.\textsuperscript{4} Two discreet mechanisms are postulated: acute coronary syndrome (ACS) (type 1 MI) and prolonged myocardial oxygen supply-demand imbalance in the presence of CAD (type 2 MI).

Type 1 PMI/ACS
This shares the same pathogenesis as non-operative MI. Vulnerable or unstable plaques undergo spontaneous rupture, fissuring or erosion with resultant coronary artery thrombosis, ischaemia and infarction.\textsuperscript{24} Whilst intraplaque inflammation is believed to be an essential component in plaque instability and spontaneous ACS, external triggers such as those previously outlined, are believed to contribute.\textsuperscript{24}

Type 2 PMI
Perioperative Holter monitoring in high-cardiac-risk patients undergoing major surgery has shown that silent, heart rate–related ST-segment depression is common postoperatively and is associated with in-hospital\textsuperscript{25} and long-term morbidity and mortality.\textsuperscript{26} Postoperative cardiac complications, including sudden death occurred after prolonged (>30 minutes) silent ST-segment depression.\textsuperscript{24}

These findings were further corroborated by studies that correlated continuous, online 12-lead ST-segment analysis with serial cardiac troponin measurements after major vascular surgery.\textsuperscript{4} Cardiac troponin elevations occurred after prolonged, transient, postoperative ST-segment depression and peak troponin elevations correlated with the duration of ST depression.\textsuperscript{4} ST elevation occurred in <2\% of postoperative ischemic events and was a rare cause of PMI.\textsuperscript{4} Hence, prolonged, ST-depression–type ischemia is the most common cause of PMI.

Furthermore, work done on high-cardiac-risk patients using the currently available highly sensitive troponin assays showed that low-level troponin elevations are common in the postoperative period, even with little or no ECG evidence of ischaemia.\textsuperscript{27} And, importantly, these mild elevations are prognostically significant.

Thus, prolonged postoperative ischaemia, myocardial injury, and type 2 PMI span a spectrum from silent, minor injury with low-level troponin elevations and low frequencies of ECG ischaemia to prolonged, overt ischaemia in multiple ECG leads, marked troponin elevation, and PMI.\textsuperscript{24}

Tachycardia is the most common cause of postoperative oxygen supply-demand imbalance.\textsuperscript{4,28} Heart rates exceeding 90 bpm in patients with significant CAD and a baseline resting heart rate of 50 to 60 bpm can lead to prolonged ischaemia and PMI. This can be compounded in those patients with pre-existing systolic and/or diastolic dysfunction.
A further review article published in 2010\textsuperscript{29} has postulated a third aetiology for PMI. The authors suggest that in a coronary artery with some degree of stenosis from atheromatous plaques, the low flow state resulting from hypotension and poor diastolic blood flow, subjects the intraluminal blood to areas of stasis just distal to the obstruction.

This stasis, combined with the platelet activation that accompanies surgery and the endothelial damage already inherent in these patients can lead to thrombus formation and ischaemia.

Although post mortem studies have shown limited thrombi in patients without plaque rupture, evidence does suggest that thrombolysis occurs in a number of patients before death.\textsuperscript{29}
5. PREOPERATIVE RISK ASSESSMENT

‘Prediction is very difficult, especially about the future.’ -- Niels Bohr

The majority of noncardiac surgeries are elective and an accurate preoperative risk assessment can facilitate informed physician and patient decision making. Choice of surgical technique and the location and intensity of postoperative care can all be influenced by this assessment.

This assessment can be divided into those risks pertaining to surgery and those pertaining to individual patient risk.

**Surgical risk**

The most important risk factors appear to be the urgency of surgery and the operative site. The following table outlines the cardiac risk stratification for noncardiac surgical procedures that has become accepted teaching.

![Table 231 Surgical risk* estimate (modified from Boersma et al)](image)

* Risk of MI and cardiac death within 30 days after surgery.

Surgery time greater than three hours under general anaesthesia was among the independent risk factors associated with perioperative cardiopulmonary complications, according to a retrospective study designed to investigate perioperative complications.

It has also been shown that the choice of general versus regional anaesthesia does not have a significant impact on perioperative cardiac outcome.

**Patient risk**

Several clinical risk indices have been advocated over the years. Lee’s revised cardiac risk index (RCRI) is currently the assessment tool of choice. It has proven to be the most accurate predictive generic risk index, and it is simple to use in clinical practice. It follows on from work done by Goldman *et al.*
It consists of 6 equally weighted cardiovascular risk factors:

- high-risk surgery (intraperitoneal, intrathoracic or suprainguinal vascular surgery)
- history of ischaemic heart disease (history of myocardial infarction, positive exercise test result, current complaint of ischemic chest pain or nitrate use, or electrocardiogram showing pathological Q waves)
- history of congestive heart failure (defined as a history of heart failure, pulmonary oedema or paroxysmal nocturnal dyspnoea; an S3 gallop or bilateral rales on physical examination; or chest radiograph showing pulmonary vascular resistance)
- history of cerebrovascular disease (stroke or transient ischemic attack),
- use of insulin therapy for diabetes
- preoperative serum creatinine level of more than 175 µmol/L (> 2.0 mg/dL).

Table 3 shows the estimated risk of a major perioperative cardiac event based on the number of risk factors met.14

<table>
<thead>
<tr>
<th>No. of risk factors†</th>
<th>Risk of major perioperative cardiac event, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.4 (0.1–0.8)</td>
</tr>
<tr>
<td>1</td>
<td>1.0 (0.5–1.4)</td>
</tr>
<tr>
<td>2</td>
<td>2.4 (1.3–3.5)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>5.4 (2.8–7.9)</td>
</tr>
</tbody>
</table>

*Includes cardiac death, nonfatal myocardial infarction and nonfatal cardiac arrest. Not included in this table are postoperative cardiogenic pulmonary edema and complete heart block, which are included as outcomes in the Lee index.

Table 3\textsuperscript{14} Estimated risk of a major perioperative cardiac event\textsuperscript{*} based on predictors of the Lee Index

Patient risk is also linked with functional capacity. This should be documented for all patients meeting any of Lee’s criteria. Functional capacity is measured in metabolic equivalents (METs). One MET equals the basal metabolic rate. The following table outlines the bedside estimation of functional capacity.
The inability to climb two flights of stairs or run a short distance (<4 METs) indicates poor functional capacity and is associated with an increased incidence of post-operative cardiac events.\textsuperscript{31} When functional capacity is not limited, the post-op risk is low, even in the presence of stable IHD or risk factors.\textsuperscript{31} A patient who can achieve >4 METs rarely requires cardiac evaluation and surgery can continue as scheduled.

For those patients not able to achieve 4 METs, preoperative non-invasive testing is advised. This allows assessment of left ventricular function, myocardial ischaemia and valvular abnormalities. Initial assessment is always done at rest and should myocardial ischaemia be a focus, a stress ECG or other non-invasive imaging techniques can be used.\textsuperscript{31}

The non-invasive strategies currently utilised to assess inducible ischaemia include radionucleotide ventriculography, ambulatory ECG, exercise ECG, myocardial perfusion scintigraphy, dobutamine stress echocardiography (DSE) and dipyridamole stress echocardiography.\textsuperscript{14}

There is limited robust evidence to suggest which of these methods are superior. And, more worrying, the utility of noninvasive tests in patients undergoing nonvascular, noncardiac surgery is uncertain.\textsuperscript{14}
Currently, the choice of test is made on what is available in the centre concerned and what limitations to exercise the patient exhibits. For those high risk patients undergoing high risk surgery, cardiopulmonary exercise testing (CPET) should be the gold standard of risk assessment.\textsuperscript{31}

6. CURRENT AHA/ACC GUIDELINES FOR THE PERIOPERATIVE WORKUP FOR THE CARDIAC PATIENT FOR NON-CARDIAC SURGERY

Multiple members of the surgical disciplines recently canvassed, stated that the entire purpose of an anaesthetist is to cancel a patient on the basis of incomplete preoperative investigations.\textsuperscript{37} This is particularly true should the patient have any background history of a “cardiac problem”.

In 2007, the guidelines for the work up of said patients was revised.\textsuperscript{39} Lee’s revised cardiac risk index (RCRI) has been incorporated to identify patients truly at risk and the active cardiac conditions have been refined to include:

- ACS
- Current cardiac failure
- Severe valvular lesions
- Life threatening arrhythmias

The amended flow chart is included below. Importantly, the need for preoperative workup has been limited substantially from the previous version. It should be noted that this algorithm was not derived from a prospective study; rather, it was derived from the interpretation of data from various studies and the judgements of the committee’s members.\textsuperscript{14}
Figure 5.31 Summary of preoperative cardiac risk evaluation and perioperative management
7. OUR WORK

After establishing the pathophysiology behind PMI and those patients at risk, we can now focus on the significance of perioperative troponin elevation.

- Patients experiencing an MI after noncardiac surgery have a hospital mortality rate of 15%–25%.¹⁴
- Nonfatal perioperative MI is an independent risk factor for cardiovascular death and nonfatal MI during the 6 months following surgery.²⁵
- Patients who have a cardiac arrest after noncardiac surgery have a hospital mortality rate of 65%.³⁹
- Nonfatal perioperative cardiac arrest is a risk factor for cardiac death during the 5 years following surgery.⁴⁰

A recent review article⁴¹ found that perioperative troponin elevation, whether in combination with ST segment changes or not, has been linked with adverse short-, mid-, and long-term outcomes across multiple studies. The review goes on to elaborate that this is also appears true for endovascular abdominal aortic aneurysm surgery.

Work done by Winkel et al⁴² showed that after a 2.9 year follow up of 220 patients, patients with asymptomatic troponin elevation had a mortality rate of 49% in comparison with the 15% mortality rate for those patients without any myocardial damage (p <0.001).

Our meta-analysis concluded that the odds ratio for all cause mortality at 30 days for asymptomatic troponin elevation was 5.41 (95% CI 3.13 – 9.33).

8. SO WHAT DOES THIS REALLY MEAN?

If patients with troponin elevation are that much more likely to die than those who do not exhibit this phenomenon, then what does that mean for the anaesthetic community?

Many patients are slipping through the cracks. Without a history of chest pain, cardiac enzymes are never ordered. Until last year, only patients post vascular surgery were having their troponins checked post operatively at Inkosi Albert Luthuli Central Hospital (IALCH) and this is essentially because they were part of a MRC study.

The VISION study, a multi-centre prospective trial, which was initiated last year at IALCH, has shown that many patients show troponin elevation postoperatively, often after what is considered low-risk surgery.
A few questions need to be asked.

1. Who should have routine postoperative troponin evaluation?

Routine testing of all patients post operatively is simply not economically viable. One solution is to test all patients presenting for high-risk surgery. Alternatively, patients with multiple Lee’s criteria should be tested, regardless of the risk of surgery.

Other biomarkers such as c-reactive protein and brain-natriuretic peptide have been shown to be useful surrogate markers of risk if elevated. Perhaps these should be tested in the preoperative period on the previously mentioned groups and then troponin surveillance be instituted for those patients deemed to be at risk.

Another important issue is to decide who implements and oversees this surveillance. The surgeon may see no benefit to being involved in this process. Anaesthetists are loath to leave the theatre complex and enter a ward. Cardiologists often feel ill equipped to deal with a patient that has had surgery. Clearly a multidisciplinary intervention is best but co-operation between all parties may be difficult.

2. What do we do with patients who are troponin positive?

If the ramifications of this phenomenon are so significant, these patients should be started on aspirin and clopidogrel. But what about long term therapy? Should these patients be managed as if they had full thickness infarction? It would seem feasible that they be placed on statins and ACE-inhibitors. And then there is the issue of beta-blockade. Surely decreasing heart rate and increasing diastolic time would improve perfusion to at risk myocardium?

Do we further risk stratify these patients? Non-invasive testing as previously outlined should then be offered to all. But if there is no evidence of ischaemia during these tests, should these patients still be offered coronary angiography?

3. Patients with a history of asymptomatic postoperative troponin elevation.

Does this history automatically allocate a patient one risk factor under the RCRI or should that be limited to the complex of acute coronary syndrome only? Which cardioprotective medications are indicated preoperatively if these patients have not been followed up appropriately? Surely the function of a pre-anaesthetic clinic is not only to assess fitness for surgery but also recommend meaningful preoperative interventions.
It is also important to educate our colleagues about the significance of this phenomenon so that they refer these patients for pre-operative assessment.

Finally, although this is beyond the scope of this lecture, are troponins truly the correct biomarker for screening? Troponins are part of the final common pathway of myocyte death. This may be too late. Possibly the use of a marker of myocyte vulnerability such as BNP will provide more insight into the at-risk patient.

9. IN CONCLUSION

The patient with troponin elevation in the postoperative period presents a diagnostic and treatment dilemma. Most of these patients will not be detected and the opportunity to initiate life-saving interventions will be lost. Until evidence-based surveillance protocols are instituted in all facilities providing anaesthesia for patients with an ASA score greater than 1, this will continue.

10. ACKNOWLEDGEMENTS

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11. REFERENCES


29. Biccard BM, Rodseth RN. The pathophysiology of peri-operative myocardial infarction. *Anaesthesia* 2010; 65: 733-741


31. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery The Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *European Heart Journal* 2009; 30(22): 2769-2812


37. Departments of general surgery, orthopaedic surgery, otorhinolaryngology, gynaecology, urology, neurosurgery, ophthalmology, paediatric surgery et al. Department of Health, UKZN, 2011


