

EDITORIAL

The role of routine postoperative troponin measurement in the diagnosis and management of myocardial injury after non-cardiac surgery

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Postoperative troponin elevation strongly predicts major complications and death after cardiac and non-cardiac surgery [1, 2]. Myocardial injury after non-cardiac surgery (MINS) is the term given to postoperative troponin elevation without a clear non-cardiac cause. Myocardial injury after non-cardiac surgery is predominantly silent, occurring in 5–25% of patients recovering from non-cardiac surgery, depending on baseline risk [1,3-5]. More than 90% of MINS is asymptomatic, and 30-day mortality is only slightly less in asymptomatic than symptomatic patients [4-8].

Myocardial injury after non-cardiac surgery is thought to be consequent to myocardial demand-supply mismatch which may result from factors, including: haemodynamic instability, especially hypotension rapid fluid shifts; acute blood loss during surgery; and other peri-operative demands on the cardiovascular system [9-12]. Since these circumstances are more likely to occur in the setting of emergency surgery, it is unsurprising that MINS is more likely in patients having urgent or emergent operations [1,13].

Some patients have troponin elevation due to silent acute coronary events following non-cardiac surgery without meeting the diagnostic criteria for acute myocardial infarction per the Fourth Universal Definition of Myocardial Infarction [5]. Specifically, MINS is defined by troponin elevation believed to be of ischaemic origin, whereas myocardial infarction additionally requires symptoms or signs such as electrocardiographic or echocardiographic changes. The pro-inflammatory and pro-thrombotic states consequent to surgery predispose patients to both MINS and myocardial infarction.

Risk assessment

Patients \geq 65 years of age and those \geq 45 y old with cardiovascular risk factors (especially known cardiovascular disease), are at relatively high risk of MINS [6,14]. Several well-established clinical stratification tools have been used to evaluate the peri-operative risk of mortality and cardiovascular events in non-cardiac surgery. One that is well validated and universally recognised is the Lee index or the revised cardiac risk index [15]. The 2014 American College of Cardiology /American Heart

Association, along with the 2014 European Society of Cardiology/European Society of Anaesthesiology guidelines on peri-operative cardiac evaluation and management of patients having non-cardiac surgery, advocate use of risk-assessment tools such as the revised cardiac risk index, the American College of Surgeons National Surgical Quality Improvement Project (ACS NSQIP) surgical risk calculator [16], or the ACS NSQIP MICA (myocardial infarction and cardiac arrest) score calculator [17,18].

Nearly all guidelines recommend a stepwise approach to evaluation of patients scheduled for non-cardiac surgery. This approach includes assessing functional capacity in patients at moderate-to-high risk of poor outcomes based on risk stratification estimates, and further evaluation for the presence of severe obstructive coronary artery disease in those with a poor functional status [17, 18].

The Canadian Cardiovascular Society guidelines on peri-operative evaluation and management favour use of the revised cardiac risk index as the tool for risk stratification because both the ACS NSQIP and the ACS NSQIP MICA underestimate peri-operative cardiovascular risk since troponin was not routinely measured in their test and validation datasets [19]. Other risk stratification models such as the Portsmouth Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (P-POSSUM) and APACHE (Acute Physiology and Chronic Health Evaluation)-2 have been used to predict peri-operative mortality risk, but are not specific for predicting cardiovascular events such as MINS and peri-operative myocardial infarction [20,21].

Pre-operative elevation of specific cardiac biomarkers can help identify patients at greatest risk of MINS. Patients with an elevated baseline pre-operative troponin are at higher risk of MINS [5]. Furthermore, pre-operative N-terminal pro-B-type natriuretic peptide concentrations are strong predictors of both MINS and vascular death [22]. N-terminal pro-B-type natriuretic peptide can be combined with other risk stratification models, and doing so improves assessment by properly reclassifying patients into both lower and higher risk categories than the revised cardiac risk index alone [22].

Diagnosis of MINS

Since more than 90% of patients with MINS have no symptoms of myocardial ischaemia, MINS can only be reliably detected by routine postoperative troponin screening. The 2014 American College of Cardiology /American Heart Association as well as the European Society of Cardiology/European Society of Anaesthesiology guidelines recommend that peri-operative troponin measurement should be measured in high-risk patients. However, this class-2b recommendation preceded much important recent work [17,18]. The more recent Canadian Cardiovascular Society Guidelines recommend routine measurement of troponin for the initial 2 to 3 days after non-cardiac inpatient surgery in patients with an elevated baseline risk for cardiovascular death and non-fatal MI > 5% within 30 days of surgery, and in patients who have a revised cardiac risk index score ≥ 1 , are age 45 to 65 years with known cardiovascular disease, and all patients ≥ 65 years old [19].

The diagnosis of MINS relies on postoperative troponin elevation. For troponin T, the fourth-generation threshold is $\geq 0.03 \text{ ng.ml}^{-1}$ [13]. For high-sensitivity (generation five) troponin, the threshold is an increase of at least 5 ng.l^{-1} to a concentration of at least 20 ng.l^{-1} or any postoperative concentration exceeding 65 ng.l^{-1} [1]. Since up to a third of non-cardiac surgical patients have detectable high-sensitivity pre-operative troponin, a pre-operative sample is needed to complement postoperative samples. Because 94% of myocardial injury after non-cardiac surgery occurs within two postoperative days, blood for troponin usually only needs to be sampled pre-operatively and on the first and second postoperative days.

Prevention and management

There are no known safe and effective prophylactic measures for preventing myocardial infarction after non-cardiac surgery. Beta-blockers reduce myocardial infarction risk by 30% but increase the risk of devastating strokes and overall mortality [23]. Avoiding nitrous oxide neither decreases nor increases the risk of cardiovascular events [24]. Clonidine does not reduce infarction risk but

promotes clinically important hypotension and bradycardia; similarly, aspirin does not reduce infarction risk, while promoting life-threatening bleeding [25, 26].

Patients who have been stable on beta-blocker and statin therapy before surgery should continue with these medications to reduce the risk of cardiovascular events as per the 2014 American College of Cardiology /American Heart Association (ACC/AHA) guidelines on peri-operative cardiovascular evaluation and management [17]. Statins can be started in patients undergoing vascular surgery or if otherwise indicated based on their 10-year cardiovascular risk profile [17]. Consistent with MINS being due to oxygen supply-demand mismatch, hypotension during and after surgery is strongly associated with myocardial injury, acute kidney injury, and death [9-11]. One small trial supports avoiding peri-operative hypotension [27]. In contrast, data for the association between tachycardia and MINS is conflicting [9,28]. Consequently, if treated at all, tachycardia should be managed in a way that does not promote hypotension.

Patients with troponin elevation should have electrocardiogram(s) and echocardiographic evaluation for left ventricular regional wall motion changes. When MINS is accompanied by a strong suspicion of coronary ischaemia, stress testing or coronary angiography may be appropriate. Coronary angiography may especially be indicated when MINS is accompanied by high-risk features such as haemodynamic instability, heart failure, persistent clinical symptoms, or arrhythmia such as ventricular tachycardia/fibrillation [6].

Patients with myocardial infarction should be treated per national/international treatment protocols for type-1 myocardial infarction including percutaneous coronary intervention when indicated (as per respective guidelines for ST-elevation and non-ST-elevation acute coronary syndrome), taking into account the risk and of bleeding and acute kidney injury in postoperative patients. Outcomes of peri-operative myocardial infarctions are often poor despite percutaneous coronary intervention, possibly from the adverse effects of bleeding and acute kidney injury associated with percutaneous intervention after non-cardiac surgery [29].

Only one treatment has specifically been tested for postoperative myocardial injury. Dabigatran anticoagulation for one to two postoperative years reduces the hazard for cardiovascular complications (mostly re-infarction) by 28% without increasing the risk of major bleeding [30]. Although aspirin, statins, and angiotensin-converting enzyme inhibitors have not been specifically tested in postoperative patients, there is overwhelming evidence of benefit for non-operative infarctions. These drugs should therefore be seriously considered in MINS patients. Myocardial injury also constitutes a 'teachable moment' and an opportunity to discuss smoking cessation, healthful eating, and exercise. More research and clinical trials are clearly needed to guide management of MINS.

Conclusion

Troponin elevation after non-cardiac surgery is strongly associated with death. Identification of patients with MINS remains challenging since presentation is usually silent. It is therefore helpful to identify patients at risk of MINS. Clinical risk stratifications tools such as the modified revised cardiac risk index are useful, but NT-Pro BNP better identifies high-risk patients likely to benefit from scheduled post-operative troponin measurement. Clearly, many more patients should have troponin screening. A potential strategy is to measure troponin pre-operatively and on the first and second postoperative days in surgical inpatients ≥ 45 years of age with at least one cardiovascular risk factor, and in all surgical inpatients ≥ 65 years old.

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References

1. Devereaux PJ, Biccard BM, Sigamani A, et al. Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-Day mortality among patients undergoing non-cardiac surgery. *Journal of the American Medical Association* 2017; **317**: 1642-51.
2. Thielmann M, Sharma V, Al-Attar N, et al. ESC joint Working Groups on cardiovascular surgery and the cellular biology of the heart position paper: perioperative myocardial injury and infarction in patients undergoing coronary artery bypass graft surgery. *Eur Heart J* 2017; **38**: 2392-407.
3. Reed GW, Horr S, Young L, et al. Associations between cardiac troponin, mechanism of myocardial injury, and long-term mortality after non-cardiac vascular surgery. *Journal of the American Heart Association* 2017; **6**.
4. Puelacher C, Lurati Buse G, Seeberger D, et al. Perioperative myocardial injury after non-cardiac surgery: incidence, mortality, and characterization. *Circulation* 2018; **137**: 1221-32.
5. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of myocardial infarction. *Journal of the American College of Cardiology* 2018; **72**: 2231-64.
6. Devereaux PJ, Szczeklik W. Myocardial injury after non-cardiac surgery: diagnosis and management. *European Heart Journal* 2019. Epub ahead of print 16 May. <https://doi.org/10.1093/eurheartj/ehz301>
7. Lowe MJ, Lightfoot NJ. The prognostic implication of perioperative cardiac enzyme elevation in patients with fractured neck of femur: a systematic review and meta-analysis. *Injury* 2020; **51**: 164-73.
8. Nagele P, Brown F, Gage BF, et al. High-sensitivity cardiac troponin T in prediction and diagnosis of myocardial infarction and long-term mortality after noncardiac surgery. *American Heart Journal* 2013; **166**: 325-32 e1.
9. Abbott TEF, Pearse RM, Archbold RA, et al. A prospective international multicentre cohort study of intraoperative heart rate and systolic blood pressure and myocardial injury after non-cardiac surgery: results of the VISION study. *Anesthesia and Analgesia* 2018; **126**: 1936-45.
10. Mascha EJ, Yang D, Weiss S, Sessler DI. Intraoperative mean arterial pressure variability and 30-day mortality in patients having non-cardiac surgery. *Anesthesiology* 2015; **123**: 79-91.
11. Salmasi V, Maheshwari K, Yang D, et al. Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after non-cardiac surgery: a retrospective cohort analysis. *Anesthesiology* 2017; **126**: 47-65.
12. Sessler DI, Meyhoff CS, Zimmerman NM, et al. Period-dependent associations between hypotension during and for four days after non-cardiac surgery and a composite of myocardial infarction and death: a substudy of the POISE-2 trial. *Anesthesiology* 2018; **128**: 317-27.
13. Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Study I, Devereaux PJ, Chan MT, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *Journal of the American Medical Association* 2012; **307**: 2295-304.
14. Sessler DI, Devereaux PJ. Perioperative troponin screening. *Anesthesia and Analgesia* 2016; **123**: 359-60.
15. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999; **100**: 1043-9.
16. Bilimoria KY, Liu Y, Paruch JL, et al. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. *Journal of the American College of Surgeons* 2013; **217**: 833-42 e1-3.

17. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *Journal of the American College of Cardiology* 2014; **64**: e77-137.
18. Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: the Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *European Heart Journal* 2014; **35**: 2383-431.
19. Duceppe E, Parlow J, MacDonald P, et al. Canadian Cardiovascular Society guidelines on perioperative cardiac risk assessment and management for patients who undergo non-cardiac surgery. *Canadian Journal of Cardiology* 2017; **33**: 17-32.
20. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Critical Care Medicine* 1985; **13**: 818-29.
21. Prytherch DR, Whiteley MS, Higgins B, Weaver PC, Prout WG, Powell SJ. POSSUM and Portsmouth POSSUM for predicting mortality. Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity. *British Journal of Surgery* 1998; **85**: 1217-20.
22. Duceppe E, Patel A, Chan MTV, et al. Preoperative N-terminal pro-B-type natriuretic peptide and cardiovascular events after non-cardiac surgery: a cohort study. *Annals of Internal Medicine* 2019.
23. Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008; **371**: 1839-47.
24. Myles PS, Leslie K, Chan MT, et al. The safety of addition of nitrous oxide to general anaesthesia in at-risk patients having major non-cardiac surgery (ENIGMA-II): a randomised, single-blind trial. *Lancet* 2014; **384**: 1446-54.
25. Devereaux PJ, Mrkobrada M, Sessler DI, et al. Aspirin in patients undergoing non-cardiac surgery. *New England Journal of Medicine* 2014; **370**: 1494-503.
26. Devereaux PJ, Sessler DI, Leslie K, et al. Clonidine in patients undergoing non-cardiac surgery. *New England Journal of Medicine* 2014; **370**: 1504-13.
27. Futier E, Lefrant JY, Guinot PG, et al. Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. *Journal of the American Medical Association* 2017; **318**: 1346-57.
28. Ruetzler K, Yilmaz HO, Turan A, et al. Intra-operative tachycardia is not associated with a composite of myocardial injury and mortality after noncardiac surgery: A retrospective cohort analysis. *Europea Journal of Anaesthesiology* 2019; **36**: 105-13.
29. Parashar A, Agarwal S, Krishnaswamy A, et al. Percutaneous intervention for myocardial infarction after non-cardiac surgery: patient characteristics and outcomes. *Journal of the American College of Cardiology* 2016; **68**: 329-38.
30. Devereaux PJ, Duceppe E, Guyatt G, et al. Dabigatran in patients with myocardial injury after non-cardiac surgery (MANAGE): an international, randomised, placebo-controlled trial. *Lancet* 2018; **391**: 2325-34.