13. Goobie SM. Tranexamic acid: still far to go. *Br J Anaesth* 2017; **118**: 293–5
14. Bolliger D, Gorlinger K, Tanaka KA. Pathophysiology and treatment of coagulopathy in massive hemorrhage and hemodilution. *Anesthesiology* 2010; **113**: 1205–19
15. Ivanciu L, Stalker TJ. Spatiotemporal regulation of coagulation and platelet activation during the hemostatic response in vivo. *J Thromb Haemost* 2015; **13**: 1949–59
16. Sakharov DV, Nagelkerke JF, Rijken DC. Rearrangements of the fibrin network and spatial distribution of fibrinolytic components during plasma clot lysis. Study with confocal microscopy. *J Biol Chem* 1996; **271**: 2133–8
17. Bolliger D, Szlam F, Levy JH, Molinaro RJ, Tanaka KA. Haemodilution-induced profibrinolytic state is mitigated by fresh-frozen plasma: implications for early haemostatic intervention in massive haemorrhage. *Br J Anaesth* 2010; **104**: 318–25
18. Chee YE, Liu SE, Irwin MG. Management of bleeding in vascular surgery. *Br J Anaesth* 2016; **117**: i85–94
19. Skagius E, Siegbahn A, Bergqvist D, Henriksson AE. Fibrinolysis in patients with an abdominal aortic aneurysm with special emphasis on rupture and shock. *J Thromb Haemost* 2008; **6**: 147–50
20. Moore HB, Moore EE, Gonzalez E, et al. Hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown: the spectrum of postinjury fibrinolysis and relevance to antifibrinolytic therapy. *J Trauma Acute Care Surg* 2014; **77**: 811–7
21. Pabinger I, Fries D, Schochl H, Streif W, Toller W. Tranexamic acid for treatment and prophylaxis of bleeding and hyperfibrinolysis. *Wien Klin Wochenschr* 2017; **129**: 303–16
22. Bolliger D, Seeberger MD, Tanaka KA. Principles and practice of thromboelastography in clinical coagulation management and transfusion practice. *Transfus Med Rev* 2012; **26**: 1–13
23. Chiesa R, Tshomba Y, Psacharopulo D, et al. Open repair for infrarenal AAA: technical aspects. *J Cardiovasc Surg* 2012; **53**: 119–31
24. McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. *J Clin Epidemiol* 2014; **67**: 267–77
25. Sukeik M, Alshryda S, Haddad FS, Mason JM. Systematic review and meta-analysis of the use of tranexamic acid in total hip replacement. *J Bone Jt Surg Br* 2011; **93**: 39–46
26. Myles PS, Smith JA, Forbes A, et al. Tranexamic acid in patients undergoing coronary-artery surgery. *New Engl J Med* 2017; **376**: 136–48
27. Lin Z, Xiaoyi Z. Tranexamic acid-associated seizures: a meta-analysis. *Seizure* 2016; **36**: 70–3
28. Lecker I, Wang DS, Whissell PD, Avramescu S, Mazer CD, Orser BA. Tranexamic acid-associated seizures: causes and treatment. *Ann Neurol* 2016; **79**: 18–26
29. Lecker I, Wang DS, Romaschin AD, Peterson M, Mazer CD, Orser BA. Tranexamic acid concentrations associated with human seizures inhibit glycine receptors. *J Clin Invest* 2012; **122**: 4654–66
30. Morrison GA, Koch J, Royds M, et al. Fibrinogen concentrate vs. fresh frozen plasma for the management of coagulopathy during thoraco-abdominal aortic aneurysm surgery: a pilot randomised controlled trial. *Anaesthesia* 2019; **74**: 180–9

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Elevated cardiac troponin before surgery: perhaps not so benign

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Cardiac troponin is a biomarker for myocardial necrosis and part of the standard diagnostic pathway for the diagnosis of acute myocardial infarction. Until the recent introduction of high-sensitivity cardiac troponin assays, contemporary cardiac troponin assays were relatively insensitive and often interpreted clinically as either 'negative' or 'positive', in essence treating cardiac troponin more like a pregnancy test than a laboratory test with a continuous range of values.[1] In the era before high-sensitivity cardiac troponin assays, using cardiac troponin measurement as a screening tool to improve preoperative risk stratification thus did not make sense: only a small number of patients would have measurable cardiac troponin concentrations, even in high-risk patients, and the test would likely miss patients at elevated risk of major adverse cardiac events.[2]

However, the clinical relevance of troponin testing completely changed with the introduction of high-sensitivity

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cardiac troponin assays a few years ago.[3] Cardiac troponin concentrations are now detectable and measurable in most adult patients, even in the absence of coronary artery disease symptoms or an acute cardiac event. Measuring actual cardiac troponin concentrations before surgery, and not simply in a 'positive' or 'negative' fashion, became a distinct possibility, as did use of cardiac troponin as a preoperative screening tool to identify patients at high risk of adverse cardiac events.

The new assays added colour to a previously black and white landscape. In 2011, Kavsak and colleagues[4] first observed that high-sensitivity cardiac troponin T could be detected in approximately 60% of patients before surgery (n=325), with 21% having a cardiac troponin concentration above the 99th percentile (14 ng L^{-1}). Because cardiac troponin assays are not standardised or harmonised across assays or laboratories, no single universal cutoff value distinguishes normal from abnormal. Thus, laboratory medicine established the 99th percentile upper reference limit as the cutoff that defines abnormal for each individual assay. For high-sensitivity cardiac troponin T (only one assay exists in the market) this cutoff is 14 ng L^{-1}. Any cardiac troponin elevation exceeding the 99th percentile is thus referred to as elevated. Subsequent studies have consistently shown that elevated high-sensitivity cardiac troponin elevations before noncardiac surgery are associated with a markedly increased risk of postoperative cardiac morbidity and mortality.[2,5–7]

We can be fairly certain that the association between cardiac troponin elevation before surgery and increased postoperative risk of adverse cardiac events is true. But we do not know why. What causes high-sensitivity cardiac troponin elevation in patients before noncardiac surgery? In a recent issue of the *British Journal of Anaesthesia*, Mol and colleagues[8] suggest a possible mechanism. One might dismiss this small 14-patient study as an insignificant secondary analysis of a largely failed pilot trial. To do so would be a mistake, however, as Mol and colleagues[8] provide one of the first mechanistic insights into what may cause elevated cardiac troponin concentrations before surgery, and the mechanism proposed may not be as benign as many have thought.

The study was originally designed as the Rotterdam Antiplatelet therapy in Vascular patients (RAVE) pilot trial, where high-risk patients undergoing vascular surgery were randomised to either standard aspirin monotherapy, or clopidogrel and aspirin dual antiplatelet therapy for 12 months after surgery. As part of the preoperative workup, high-sensitivity cardiac troponin T was measured before surgery and, if elevated above 14 ng L^{-1}, patients would undergo coronary angiography to diagnose the presence and extent of coronary artery disease, thus allowing a definitive answer whether elevated cardiac troponin before surgery correlated with significant underlying coronary artery disease.

Mol and colleagues[8] screened 164 vascular surgery patients, 14 of whom had elevated preoperative high sensitivity cardiac troponin, and 10 of these 14 underwent coronary angiography. Among these 10 patients, nine had significant obstructive coronary artery disease and only one was free of atherosclerotic coronary lesions. Four patients required percutaneous coronary intervention (stent placement) and one underwent coronary artery bypass grafting before surgery, highlighting the severity of the underlying ischaemic heart disease.

Despite clear methodological limitations such as selection bias, and an enriched but small sample size, the report by Mol and colleagues[8] suggests that one reason for elevated high-sensitivity troponin concentrations before surgery may be previously unrecognised, clinically relevant coronary artery disease. Clearly, larger more definitive studies are required to determine whether preoperative measurement of high-sensitivity cardiac troponin concentrations can lower the risk of perioperative adverse cardiac events, but the first piece of evidence that elevated concentrations can indicate severe coronary artery disease has now been found.

Declaration of interest

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References

1. Apple FS, Sandoval Y, Jaffe AS, Ordonez-Llanos J. IFCC Task Force on Clinical Applications of Cardiac Bio-Markers. Cardiac troponin assays: guide to understanding analytical characteristics and their impact on clinical care. *Clin Chem* 2017; **63**: 73–81
2. 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. *Am Heart J* 2013; **166**: 325–332.e1
3. Sherwood MW, Kristin Newby L. High-sensitivity troponin assays: evidence, indications, and reasonable use. *J Am Heart Assoc* 2014; **3**, e000403
4. Kavsak PA, Walsh M, Srinathan S, et al. High sensitivity troponin T concentrations in patients undergoing noncardiac surgery: a prospective cohort study. *Clin Biochem* 2011; **44**: 1021–4
5. Botto F, Alonso-Coello P, Chan MT, et al. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. *Anesthesiology* 2014; **120**: 564–78
6. 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. *JAMA* 2012; **307**: 2295–304
7. 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 noncardiac surgery. *JAMA* 2017; **317**: 1642–51
8. Mol K, Hoeks SE, van Mieghem N, et al. Preoperative coronary angiography in vascular surgery patients with asymptomatic elevated high-sensitivity troponin T: a case series. *Br J Anaesth* 2019; **123**: 565–9