‘Paradox’ of troponin elevations after non-cardiac surgery

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Dr Noordzij and colleagues1 report in this issue of BJA that after major abdominal surgery, elevations in troponin, measured with a high-sensitivity assay, predict non-cardiac complications. This may seem to be an apparently paradoxical result. How can a very sensitive and specific diagnostic assay for myocardial injury and infarction predict postoperative non-cardiac rather than cardiac complications? However, those who carefully follow the literature on postoperative troponin elevations should not find this surprising at all.

In a study published in 20032 from a cohort of 447 patients who underwent major vascular surgery, we showed that even low-level troponin elevations, measured with earlier cardiac troponin (cTn) assays during the first 3 days after surgery, presaged mortality at 5 yr, while more marked elevations predicted higher mortality. The vast majority of postoperative troponin elevations were asymptomatic. In fact, among patients with low-level troponin elevations, who were the majority, only 18% had signs or symptoms that could be attributable to myocardial infarction and only 32% had ST-segment depression lasting longer than 15 min on continuous 12-lead ECG monitoring. Even fewer ischaemic events would have been detected if only daily samples of ECGs had been used, which is the common practice of most clinicians. Among the fewer patients with higher postoperative troponin elevations, the incidence of signs or symptoms possibly related to myocardial infarction increased incrementally to 40–60%, and the chance of finding even short (15 min) episodes of ischaemia on continuous 12-lead ECG monitoring increased to 80–90%.

The recent VISION study3 has rediscovered this phenomenon. In VISION, even minor cTnT elevations detected with the fourth-generation assay for cTnT during the first 3 days in 15 065 patients predicted 30 day postoperative mortality, and more marked elevations were incrementally associated with higher mortality. In that study, as in ours, out of 115 patients with troponin elevations who died, only 22 (19%) had cardiac symptoms and only 31 (27%) had ischaemic ECG findings (ST-elevation/depression, new Q-waves or left bundle branch block) on daily ECGs.

Similar results were reported by Beattie and colleagues4, who studied 51 701 patients retrospectively and found that 20.4% had postoperative troponin I elevations. These elevations incrementally predicted 30 day postoperative all-cause mortality. Importantly, only 34% of postoperative deaths in low-risk patients were cardiac deaths, although the proportion of cardiac deaths increased to 42 and 60% in higher-risk patients.

Finally, Van Waes and colleagues5 recently studied 2216 consecutive patients after major non-cardiac surgery using high-sensitivity troponin I measurements during the first 3 days after surgery. They too confirmed that postoperative troponin elevations strongly and incrementally predicted 30 day mortality. Of the 315 (19%) patients with troponin elevations, 27 (8.6%) died but only 10 (3.2%) had typical chest pain and only 30 (9.5%) had new ischaemic ECG changes.

It is clear from the above summary that while postoperative troponin elevations in the first days after surgery are common and strongly predict both 30 day and long-term mortality, they are not strongly associated with cardiac signs or symptoms. Higher postoperative troponin concentrations are better associated with cardiac signs or symptoms, but low-level troponin elevations, although prognostically important, are rarely associated with overt signs of cardiac abnormalities.

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The publication by Noordzij and colleagues, although a small report of only 203 patients, focuses on non-cardiac complications, which is something that previous studies did not. Postoperative fifth-generation high-sensitivity troponin T (hs-cTnT) elevations ≥14 ng litre⁻¹ (the 99th% upper reference limit for the hs-cTnT assay) in the study by Noordzij and colleague’s occurred in 106 (52%) patients. Only 39 (19%) had hs-cTnT >30 ng litre⁻¹ and only 33 (16%) had a marked (100%) increase from baseline preoperative hs-cTnT concentrations. These troponin elevations are in the very low range compared with those in previously published papers but are consistent with the preliminary report of Kavak and colleague with the high-sensitivity troponin T assay.

Combining all the studies together, one may conclude that the low range of postoperative troponin elevations is associated with postoperative non-cardiac complications, while the higher ranges of troponin elevations correlate better with cardiac signs and complications, although all troponin elevations incrementally predict mortality. Hence, the paradox with which we started can now be rephrased; how come low-level postoperative troponin elevations correlate mainly with non-cardiac complications and higher levels of troponin concentrations correlate incrementally with cardiac complications, while both predict early and late mortality? To understand this paradox, we must understand the pathophysiology of postoperative troponin elevations (i.e. the concept of type II myocardial injury and infarction).

Up to 2007, the most dominant recognized cause for myocardial infarction was acute coronary event, namely coronary plaque rupture, fissuring, or erosion, and subsequent acute coronary thrombosis. Stable, although severe, coronary artery disease was thought, according to that paradigm, to be the cause of ischaemia, angina pectoris, or heart failure, but rarely if ever the cause of myocardial infarction. This situation has changed dramatically since the introduction of the troponin assays, which have markedly increased the sensitivity and specificity for detection of cardiac injury, and numerous studies have repeatedly shown that an increase in cTn values has major prognostic importance even in the absence of acute coronary thrombosis. In 2007, the Universal Definition for Myocardial Infarction guidelines reclassified myocardial infarction and, for the first time, defined spontaneous primary coronary event caused by plaque rupture, rupture fissuring, or dissection and subsequent acute coronary thrombosis as type I myocardial infarction. In contrast, myocardial infarction secondary to ischaemia resulting from an imbalance in myocardial oxygen supply–demand in the absence of a primary coronary event was defined as type II acute myocardial infarction. The recognition that a prolonged imbalance in supply and demand was by far the most common mechanism of postoperative myocardial infarction and injury had already been noted by us in 2003, based on the observations that ST-segment elevation-type myocardial infarction, which is pathognomonic for acute plaque rupture and coronary thrombosis, rarely occurs in high-risk cardiac patients undergoing major surgery, despite the immense postoperative physiological and emotional stresses.

The observation that myocardial injury occurs after prolonged imbalance in myocardial oxygen supply and demand in response to the stress of surgery, particularly in patients with limited coronary or limited myocardial structural reserve, also explains why these patients are at increased risk of mortality from any critical illness or postoperative complication. Critically ill patients admitted to the intensive care unit who have cTnT elevations have a markedly increased rate of both short- and long-term mortality. This has been shown for patients with acute respiratory failure, gastrointestinal bleeding, or sepsis. What a cTn elevation marks in each individual situation is unclear, but it is undeniable that when one has critical illness and troponin elevations, whether detected acutely or after prolonged stress such as surgery, mortality is increased. This is most likely to be the reason for the increased mortality seen in the study by Noordzij and colleague’s. We have recently shown that diastolic dysfunction is common and strongly associated with troponin elevations and mortality in patients with severe sepsis and septic shock. The challenge now is to understand how to modify our treatment of these patients to take these data into account and improve outcomes.

There are important caveats in this area that we need to keep in mind. The first is that acute events, such as acute myocardial infarction requires a rising and falling pattern of cTn values and not only isolated cTn elevations. In addition, there are many things that might cause isolated cTn elevations after surgery other than ischaemia, such as pulmonary embolism, infection, the effects of renal dysfunction, structural heart disease, or a combination of these. Thus, clinical integration is essential, lest we fall into the trap of attributing all postoperative cTn elevations to ischaemic heart disease, leading to the potential for excessive intervention.

There has been considerable confusion about some of the causes for cTn elevations, and clarifying all of them is beyond the scope of this editorial. Nevertheless, there are several issues that are important to mention in this context. There are frequent elevations of cTn in patients with renal disease, and these elevations are a result of cardiac injury and are a potent risk factor for mortality. However, as best we can tell, this is not a result of reduced renal clearance, because cTn is not cleared renally. There is only one report of cTnI and cTnT in urine, and that was in patients with massive proteinuria. Thus, cTn elevations in kidney disease probably reflect the metabolic effects of renal failure, structural myocardial changes (e.g. left ventricular hypertrophy) and the association of renal disease with coronary artery disease. It is likely that the renal metabolic milieu changes the degradation pathways so that small fragments of cTn persist, and because the epitopes for binding are so close together (two to six amino acids), the signal persists. Given that the antigen epitopes for cTnl are further apart (50–50 amino acids), that signal is lost with cTnl.

In addition, as with any test, there can be analytical false positives. One can have false positives as a result of cross-reacting or heterophilic antibodies, which usually cause marked elevations of cTn that do not change over time, or so-called ‘fliers’, which are usually attributable to fibrin interference. These are rare and can be unmasked by good laboratory practices. The other situation is one where there is re-expression of presumably fetal proteins in response to skeletal muscle injury. That is unique to cTnT.

In summary, postoperative non-cardiac and cardiac complications correlating with low-levels and higher-levels postoperative troponin elevations, respectively, are two sides of the same spectrum of events. Non-cardiac complications pose a higher demand on the patient’s heart, and thus, it is not surprising that mortality is increased in those with underlying heart disease, which is often marked by an elevated cTn. Conversely, primary cardiac injury may lead to cardiac failure and a deterioration in other important systems, such as the kidneys, leading to what may appear to be a non-cardiac cause of death. Our important role in the future is to develop ways to understand the specifics of both situations so that we can devise treatment strategies that take both cardiac and non-cardiac issues into account and improve patient care.
Declaration of interest

A.S.J. has been consultant to many companies dealing with diagnostics.

References