Cardiac troponins: their use and relevance in anaesthesia and critical care medicine

Juliet A Wolfe Barry BSc FRCA
Julian H Barth MD FRCP FRCPath
Simon J Howell FRCA MD

Cardiac markers were first recommended as part of diagnostic criteria for myocardial infarction (MI) by the World Health Organization in 1979.1 The cardiac troponins (cTn) have become the preferred biochemical markers (or biomarkers) of cardiac injury as they are more cardiac-specific than the MB fraction of creatine kinase (CK-MB) and have a very high sensitivity, detecting even microscopic areas of myocardial necrosis.

Cardiac muscle and troponin

The contractile complex in cardiac muscle contains the contractile proteins actin and myosin, and the regulatory proteins troponins and tropomyosin. Troponin is necessary for the calcium mediated regulation of skeletal and cardiac muscle contraction. The troponin complex is a heteromeric protein located with tropomyosin on the actin filament. It consists of three single chain polypeptides: troponin T (cTnT), which binds the other troponin components to tropomyosin; troponin I (cTnI), which inhibits ATP activity when bound to actin; and troponin C (cTnC), which contains binding sites for calcium. Most troponin is found as this three unit complex but there is also a small percentage (2–8%) of unbound troponin in the cytoplasm of the cardiac muscle cell. When myocyte damage occurs, cTn is released from cardiac myocytes. Both troponin I and T exhibit biphasic release kinetics. Release from the cytosolic pool gives increase to blood concentrations rising 4–6 h after the onset of damage and peaking at 12–24 h after myocardial injury. Structural protein release leads to a second peak 2–4 days after injury. Continuing breakdown of myofibrillar-bound complex explains the prolonged elevation of both troponins for up to 10 days after infarction. This accounts for increased detection of cardiac events using troponin and its increased sensitivity but can make diagnosis of reinfarction more difficult (CK-MB has valuable role here).

Troponin as a biomarker

Detectable increases in the troponin biomarkers are indicative of cardiac injury but do not determine the mechanism. The Joint European Society of Cardiology and American College of Cardiology Committee have recommended the cTn as the biomarkers of choice in the diagnosis of MI.3 cTn have nearly absolute myocardial tissue specificity and reflect even microscopic zones of myocardial necrosis but cTn elevations are not always attributable to acute coronary syndromes (ACSs) and a troponin increase in isolation cannot be used to diagnose MI.

Key points

Cardiac troponins reflect myocardial damage but do not indicate its mechanism. In the absence of other evidence of ischaemia, another cause should be sought.

cTn is currently the biomarker of choice in the diagnosis of acute MI.

Commercial assays for cTn are improving; however, there are still limitations because of the lack of international standardization.

No standard diagnostic criteria for perioperative MI exist and the role of postoperative cTn surveillance remains unclear.

Not all cTn release is in the setting of coronary artery disease.

Whatever the clinical setting, cTn elevation has prognostic significance

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There are tissue-specific isoforms of troponin I, T, and C. Troponin C is not useful for diagnosing cardiac injury because the cardiac isoform is shared by skeletal muscle. Multiple cTnT isoforms are expressed in the human heart (predominantly cTnT3) whereas TnC and TnI are expressed as single isoforms. There are substantial differences between the amino acid sequences of the cardiac isoforms of TnI and TnT and other isoforms and it has been possible to produce highly specific monoclonal antibodies without cross reactivity with other non-cardiac forms.

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After myocardial cell damage, unbound cytoplasmic troponin is released from cardiac myocytes. Both troponin I and T exhibit biphasic release kinetics. Release from the cytosolic pool gives increase to blood concentrations rising 4–6 h after the onset of damage and peaking at 12–24 h after myocardial injury. Structural protein release leads to a second peak 2–4 days after injury. Continuing breakdown of myofibrillar-bound complex explains the prolonged elevation of both troponins for up to 10 days after infarction. This accounts for increased detection of cardiac events using troponin and its increased sensitivity but can make diagnosis of reinfarction more difficult (CK-MB has valuable role here).
Troponin assays

A number of commercial troponin assays are available and their diversity has been a source of considerable confusion for cTnI measurements. Owing to international patenting restrictions, there is only one manufacturer of TnT assays (Roche diagnostics). There are multiple immunoassays for cTnI produced by different manufacturers and the different immunoassays use antibodies directed at different epitopes on the troponin molecule. Owing to the current lack of an international standard troponin I preparation, values for cTnI using different manufacturers’ assays are not comparable and the cut off value for the diagnosis of myocardial injury varies from assay to assay.

Confusion over the ‘cut off’ value for cTn has been created by the introduction of two definitions by the 2000 consensus panel: (i) 99th centile value of a normal population; and (ii) a measure of analytical precision, the 10% CV. Until recently no commercial assays were capable of measuring troponin in normal individuals with sufficient analytical precision. This has now (2006) been rectified and the latest generation of assays can measure low concentrations of cTn and it is possible to use 99th centile values as a ‘cut off’ for acute coronary syndromes (ACSs).

Acute coronary syndromes

The clinical presentation of unstable angina, non-ST-segment elevation MI (NSTEMI) and ST-segment elevation MI (STEMI), collectively known as the ACSs, results from variations of the same pathological processes: plaque rupture and coronary thrombosis. ACS range from unstable angina with ischaemia without detectable myocardial necrosis and normal troponin concentrations to ACS with variable degrees of myocardial necrosis with raised troponin concentrations. The definition of MI from the European Society of Cardiology/American College of Cardiology is given in the following table.

Revised definition of MI from the European Society of Cardiology/American College of Cardiology

One of the following criteria necessary for the diagnosis of acute, evolving or recent MI:

1. Typical increase and gradual decrease (troponin) or a more rapid increase and decrease (creatine kinase MB isoenzyme) of biochemical markers of myocardial necrosis with at least one of the following:
   - ischaemic symptoms
   - development of pathological Q waves on the ECG
   - ECG changes indicative of ischaemia
   - coronary artery intervention
2. Pathological findings of acute MI

One of the following criteria necessary for the diagnosis of established MI

1. Development of new pathological Q waves on serial ECGs
2. Pathological findings of a healed or healing MI.

As any troponin increase above the lower detection limit of the assay may be sufficient for the diagnosis of acute MI (ACC/ESC task force document), a greater number of patients with a lesser volume of myocardial damage will now be labelled as having an acute MI. The document has ignited debate, many believing that the term acute MI should not necessarily be applied to all patients with evidence of myocardial ischaemia and a cTn increase. The diagnosis of MI has a significant impact on the patient with psychological, social, and occupational consequences. In addition, simply dividing patients into troponin positive and negative groups could lack sensitivity when it comes to predicting risk in ACS. It has been suggested that a diagnostic threshold consistent with more significant myocardial injury be defined.

In ACSs, elevated cTnI and cTnT are adverse prognostic indicators, even after adjustment for clinical predictors and ECG findings. Regardless of treatment, an elevated troponin on admission in patients with STEMI is an independent predictor of death at 30 days. In both STEMI and NSTEMI, there is a relationship between extent of increase in troponin concentration and adverse events. The prognostic value of cTnT and cTnI appear equivalent in ACS.

Perioperative setting

Major perioperative cardiac events (cardiac death, non-fatal MI, and non-fatal cardiac arrest) occur in 3.9% of patients with an established diagnosis of coronary artery disease or risk factors for coronary artery disease undergoing major non-cardiac surgery.

A recent review suggested a 10% mortality for perioperative MI, similar to that of NSTEMI in non-surgical patients and
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long-term survival after perioperative infarction is significantly impaired in line with what occurs after ACS in non-surgical patients. However, the clinical diagnosis of perioperative MI is often difficult. Only 14% of patients who have a perioperative MI have chest pain and up to 50% of perioperative MIs may go unrecognized if physicians rely on clinical signs and symptoms. The formal diagnostic criteria require the presence of two of the three classical findings: ischaemic symptoms; ECG changes; and biomarker release. Perioperative MIs may go unrecognized for a number of reasons. The majority occur in the first 3 postoperative days, when patients may be affected by sedation or residual anaesthesia, be receiving strong analgesics which mask ischaemic chest pain or have a distracting painful surgical incision. Signs and symptoms of AMI have other plausible explanations in the postoperative setting and AMI may not even be considered. In the absence of typical signs and symptoms of perioperative MI, the diagnosis has to rely on increases in biomarkers.

The consensus document of the ESC/ACC makes no mention of MI occurring after non-cardiac surgery and currently there are no standard diagnostic criteria for perioperative MIs in these patients. Three criteria have recently been proposed by Devereaux and colleagues; any one satisfies the diagnosis of perioperative MI in non-cardiac surgical patients:

- Ischaemic signs or symptoms (e.g. chest, arm or jaw discomfort, shortness of breath, pulmonary oedema) and/or development of pathological Q waves on an ECG, and/or ECG changes indicative of ischaemia and/or coronary artery intervention and/or new or presumed new cardiac wall-motion abnormality on echocardiography, or new or presumed new fixed defect on radionuclide scanning accompanied by a typical increase in troponin level or a typical reduction of an elevated troponin level detected at its peak after surgery in a patient without a documented alternative explanation for an elevated troponin concentration (e.g. pulmonary embolism); or a rapid increase and decrease of CK-MB only if troponin measurement is unavailable.
- Pathological findings of an acute or healing MI.
- Development of new pathological Q waves on an ECG if troponin concentrations were not obtained or obtained at times that could have missed the clinical event.

Debate continues as to whether there should be an optimal cTn diagnostic threshold for the diagnosis of perioperative MI or whether any cTn increase, however small, should lead to this diagnosis.

In several non-cardiac surgery studies, troponin release has been shown to be a statistically significant independent predictor of intermediate and long-term outcomes (i.e. mortality and major cardiac events). Kim and colleagues measured cTnI on the first 3 postoperative days in patients undergoing major vascular surgery; 12% had an elevated cTnI on routine postoperative surveillance although only 3% had AMI according to WHO criteria. They found that a raised cTnI was associated with a six-fold increased risk of death and a 27-fold increased risk of MI in the 6 months following surgery. There was a dose–response relationship between postoperative cTnI concentration and mortality.

Landesberg and colleagues demonstrated a substantial increase in perioperative cardiac risk when even minor elevations in cTn occur in patients having undergone vascular surgery. A relationship existed between the finding of ischaemia with continuous ECG monitoring and elevations of troponin; the more prolonged the ischaemia the greater the cTn increase. Those with the greatest cTn concentrations had increased chance of a subsequent cardiac event and worse long-term mortality. Even minor elevations in cTn during first three postoperative days predicted increased risk of long-term mortality (1–5 yr follow up period for this study).

Le Manach and colleagues reported data on 1136 patients undergoing abdominal aortic surgery. They identified two types of postoperative MI differing in timing and cTnI release. The early postoperative MI group had a sudden increase of cTnI to >1.5 μg litre\(^{-1}\). In the delayed postoperative MI group, the increase in cTnI to >1.5 μg litre\(^{-1}\) was more gradual (>24 h), occurred later in the postoperative period and was preceded by a long (>24 h) period of myocardial damage when cTnI concentrations were abnormal but lower than MI threshold. These two types of postoperative MI could reflect different pathophysiology in these two subgroups. The early group resembles acute non-surgical MI and most likely because of acute coronary artery occlusion from plaque rupture and thrombus formation. The delayed postoperative MI group is consistent with postoperative ischaemia and has a similar pattern of cTnI release to prolonged unstable angina leading to MI. Again even lower postoperative cTnI concentrations were associated with higher mortality and some of these patients went on to develop delayed postoperative MI. Monitoring cTnI postoperatively in these patients may allow institution of early aggressive intervention to prevent delayed postoperative MI. The study highlights the significance of low cTnI values after vascular surgery and the potential to identify those at risk of delayed postoperative MI by measuring cTnI immediately postoperatively.

Up to 60% of patients undergoing vascular procedures have severe coronary artery disease and fewer than 10% have normal coronary arteries. The cause of cTn increase in this subset of surgical patients is therefore likely to be MI (a high pre-test probability). Extrapolating results from vascular surgery populations to different surgical subsets may not be appropriate as there may be other causes for the cTn increase. For example, a cTn increase in the orthopaedic surgical population may be as a result of pulmonary embolus and have different prognostic implications. The question is when, and in whom, should we be measuring postoperative troponins and what diagnostic threshold, if any, should we be using to aid in diagnosis of perioperative MI and risk stratification. This is more than an academic question as cTn increases of any aetiology in the sick patient acts as a prognostic indicator for survival.

In the context of cardiac surgery, release of cTn can be caused by surgical instrumentation of coronary vessels in patients...
undergoing coronary artery bypass grafting. However, there is a direct relationship between extent of enzyme and marker release and subsequent mortality: the higher the value, the greater the damage and the worse the prognosis.

**Critical care setting**

An increase in cTn reflects myocardial cell damage. Abnormal values have been found in almost all forms of cardiac injury or dysfunction including: heart failure, myocarditis, pericarditis, pulmonary embolism, stroke, severe renal dysfunction and septic shock. In the critical care population, there is a high frequency of myocardial injury in the absence of ACSs or cardiac dysfunction demonstrated to be as high as 32% (69/217 patients) by Quenot and colleagues in a study in 2005. They measured cTnI in all critically ill patients without clinical evidence of ACS or cardiac dysfunction in the ICU of a university teaching hospital. Those with increased cTnI had a 51% mortality rate compared with only 16% for those without. Elevated cTnI was found to be independently associated with hospital mortality regardless of a simplified acute physiology scale II score and mechanical ventilation.

Several studies report raised cTn in septic patients associated with increased mortality rates and vasopressor requirements. Likely explanations for this cTn release in septic patients include damage to myocardium from inflammatory mediators released in sepsis, septic emboli and use of vasoactive drugs with myocardial oxygen demand–supply mismatch. Myocardial depressive factors could cause degradation of free troponin to smaller fragments and with transient loss in membrane integrity the release of troponin. This may result in reversible cell damage supporting the observation that myocardial depression in sepsis is reversible in survivors.

Raised cTn in critically ill patients appears to provide valuable prognostic information. Studies repeatedly demonstrate that elevated cTnI are associated with increased mortality, morbidity and longer hospital stay in non-cardiac critically ill patients.

**Raised troponin in absence of acute MI**

Raised CTn indicates the presence but not the mechanism of myocardial injury and myocardial damage can occur from a variety of other causes other than coronary artery disease.

**Demand ischaemia**

Demand ischaemia without significant coronary artery disease refers to the mismatch between myocardial oxygen demand and supply in the absence of flow limiting coronary artery stenosis. Myocardial oxygen demand increases in sepsis and systemic inflammatory response syndrome, hypotension, hypovolaemia, and tachyarrhythmias. The tachycardia associated with these conditions increases myocardial oxygen demand while the decreasing diastolic time and consequently coronary artery perfusion, results in decreasing oxygen supply. Inflammatory mediators may cause myocardial depression, reduced perfusion pressure and further decreased oxygen delivery to the heart. Even in the absence of significant coronary artery disease and inflammatory mediators, isolated tachycardia can result in cTn increase.

Left ventricular hypertrophy can lead to subendocardial ischaemia from increased oxygen demand from increased muscle mass and less flow reserve. In one study, where acute myocardial ischaemia was excluded, almost one-third of patients with the greatest left ventricular mass had elevated cTn concentrations compared with no patients with least left ventricular mass. In the context of aortic valve disease, elevated cTn was associated with greater left ventricular wall thickness and higher PA pressures.

**Myocardial ischaemia**

Myocardial ischaemia can occur in the absence of thrombotic CAD. Raised troponin concentration can occur in Prinzmetal angina (i.e. vasospasm). Elevated cTn occurs in stoke or intracranial haemorrhage. Up to 27% of patients with acute stroke symptoms and 20% of patients with SAH were found to have raised cTn. Myocardial ischaemia in this setting is likely to be attributable to over activity of the sympathetic autonomic nervous system. In three trials of patients with spontaneous SAH, cTnI was increased in 10% of patients with minimal, 20% of patients with moderate, and 46% with severe neurological deficit ($P < 0.0001$), suggesting that cardiopulmonary dysfunction is more likely to occur with increasing neurological deficit.

**Direct myocardial cell injury**

Direct myocardial cell injury can lead to a troponin increase by several mechanisms. Trauma can be either mechanical (cardiac contusion, cardiac surgery, endomyocardial biopsy, cardiac massage), electrical (cardioversion, ablation, pacing, ICD firings), as a result of cardiac toxicity from chemotherapy, venom, catecholamines or from inflammatory processes. Inflammatory processes include myocarditis, pericarditis and amyloidosis and other cardiac infiltrative disorders causing possible myocyte compression and cTn release.

**Myocardial strain**

Pathological loading conditions of the left and right ventricle resulting in myocardial strain can lead to cTn release in the absence of ischaemia. Myocardial strain is the percentage change in a structure from its initial length with the application of stress. In congestive cardiac failure, this stress is in the form of pressure and volume overload of both ventricles. Close correlation exists between cTnI and B-type natriuretic peptide, a marker of right and left ventricular wall strain. In a study of 238 patients with advanced heart failure referred for cardiac transplantation assessment, 49% had raised cTnI. Those with detectable cTnI had impaired haemodynamics, progressive left ventricular dysfunction and a two-fold increase in mortality rates.

Right heart strain secondary to increased pulmonary vascular resistance in pulmonary embolism causes cTn release. A raised
cTn is more likely to occur in patients with shock and clinical variables associated with poor outcome. In a study by Giannitis, patients with cTnT ≥ 0.1 ng ml⁻¹ in moderate to large PE or massive PE were more likely to have RV dysfunction and those with increased cTn had a 30-fold increase in hospital mortality. Among patients with chronic pulmonary hypertension, 14% have detectable cTn and these were associated with higher heart rates, lower mixed venous oxygen saturation, higher levels of B-type natriuretic peptide and significantly worse 2 yr survival (81% vs 29%). Increased cTn in chronic obstructive airways disease is an independent predictor of in-hospital mortality.

cTn elevation has been described after extreme exercise, possibly because of increased myocardial strain or catecholamine induced vasospasm.

Chronic renal insufficiency

cTns are persistently elevated in patients with chronic renal insufficiency. Increased cTn in chronic renal failure without clinically suspected myocardial ischaemia may be as high as 53%. This may be attributable to silent myocardial necrosis, increased left ventricular mass and impaired renal cTn excretion. Whatever the cause of increased troponin, detectable concentrations in end-stage renal failure is a powerful predictor of increased intermediate mortality. Adjusted for independent risk factors for mortality, the risk of death increases two- to four-fold with increased cTnT and two-fold with cTnI.

Further Reading


References


Please see multiple choice questions 17–21