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REVIEW

Troponin in critical care patients and outcomes

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Abstract

Myocardial infarction is common in the critically unwell population with pre-existing cardiovascular disease and is associated with a greater overall mortality. This article explores guidelines for diagnosing myocardial infarction, and research into the use of troponin as both a diagnostic and prognostic tool.

Currently, the majority of patients in the intensive care unit with acute myocardial infarction go unrecognised. The underlying cause is predominantly oxygen supply–demand imbalance, therefore identifying those at risk is important as there is the potential to modify elements of their care and reduce their overall mortality.

Key words: Cardiovascular disease; Critical care; Mortality; Troponin

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Introduction

Troponin is a biomarker commonly used in the diagnosis of myocardial infarction. It can also be released in response to ischaemia without evidence of myocardial necrosis, and levels are commonly elevated in the critically ill population. This article explores research into the use of troponin as a diagnostic and predictive tool in intensive care, including potentially modifiable outcomes for those at risk of worse outcomes secondary to myocardial injury.

Troponin

The troponin complex is a group of three regulatory proteins found in skeletal and cardiac muscle that allow calcium to bind, resulting in muscle contraction (Gomes et al, 2002). The three subunits of troponin are troponin I (TnI) and T (TnT), which are specific to cardiac muscle, and troponin C (TnC), which is expressed in both cardiac and skeletal muscle.

Cardiac troponin is primarily bound within the myocyte cytoskeleton, with approximately 5–8% unbound in the cytosol (White, 2011). It is this unbound proportion of troponin that is released into the bloodstream first, a process that is independent of the mechanism of injury. The mechanisms of troponin release are outlined in Table 1.

Diagnosis of myocardial infarction

The fourth universal definition of acute myocardial infarction is used when there is acute myocardial injury with clinical evidence of acute myocardial ischaemia (Thygesen et al, 2019). The criteria for this includes detection of a rise or fall in cardiac troponin level with at least one value above the 99th percentile upper reference limit, together with one or more of:

- Symptoms of myocardial ischaemia
- New ischaemic electrocardiogram changes
- Development of pathological Q waves
- Imaging evidence of new loss of viable myocardium or new regional wall abnormality in a pattern consistent with an ischaemic aetiology
- Thrombus on angiography or autopsy (not for type 2 or 3 myocardial infarction).

Myocardial injury is the term used when there is evidence of elevated cardiac troponin levels with at least one value above the 99th percentile upper reference limit. This is considered acute if there is a rise and/or fall of cardiac troponin values and chronic if the troponin level is statically elevated, for example in patients with heart failure (Ooi et al, 2000).

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Table 1. Mechanisms of troponin release	
Myocyte necrosis (French and White, 2004)	Ischaemia, inflammation, trauma and toxins
Apoptosis (Narula et al, 1996)	Associated with activation of caspases that cleave structural proteins, potentially releasing troponin
Normal myocyte turnover (Bergmann et al, 2009)	Cardiac myocytes regenerate, with almost half of cells exchanged in a human lifetime. This may be associated with release of troponin into the systemic circulation
Cellular release of proteolytic troponin degradation products (Gao et al, 1997; Feng et al, 2001)	Proteolysis to create small fragments may allow passage of troponin degradation products through a normal cell membrane. As little as 15 minutes of mild ischaemia causes development of troponin I degradation products
Increased cellular wall permeability (Hessel et al, 2008)	Reversible injury to the myocyte cell membrane (without ischaemia or necrosis) allows leakage of troponin from the cytosol
Formation and release of membranous blebs (Hickman et al, 2010)	During ischaemia, blebs (vesicles) occur on the surface of cardiac myocytes. In prolonged ischaemia the blebs rupture, leading to myocardial necrosis. Resolution of ischaemia before rupture may lead to shedding into the circulation and release of the cytoplasmic contents, without necrosis of the myocyte

Myocardial infarction can be subcategorised into those related to intraluminal thrombus in one or more coronary arteries (type 1) or myocardial infarction secondary to ischaemic imbalance (type 2) (Thygesen et al, 2012). There are other sub-categories related to interventions such as percutaneous coronary intervention or coronary artery bypass grafting, which will not be considered further in this article.

The European Society of Cardiology recommends using high-sensitivity cardiac troponin assays as part of clinical pathways to improve the 'rule-in' and 'rule-out' of myocardial infarction at the time of presentation (Roffi et al, 2016). The High STEACS trial (High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome; Shah et al, 2018) looked at whether using a high-sensitivity cardiac troponin assay would reduce myocardial infarction or death from cardiovascular disease in patients presenting to hospital with suspected acute coronary syndrome. The study applied thresholds of less than 5 ng/litre to rule out myocardial infarction, and a rule-in threshold greater than the 99th centile. The trial demonstrated that early sampling of cardiac troponin I (within 3 hours of acute coronary syndrome symptoms) has a positive predictive value for the diagnosis of myocardial infarction of 56.2% for patients presenting to hospital with suspected acute coronary syndrome, but a negative predictive value of 99.5% (Chapman et al, 2018b; Shah et al, 2018), making it a potentially very valuable 'rule-out' test for myocardial infarction in those presenting with signs and symptoms of acute coronary syndrome.

In critically unwell patients, sepsis is the most common non-cardiac cause of troponin elevation (Sheyin et al, 2015). There is an association between this and poorer cardiac function (lower stroke index and left ventricular ejection fraction), higher inotrope or vasopressor requirements and higher overall mortality (Rudiger and Singer, 2007). Research suggests that up to half of all patients with sepsis will have evidence of ventricular dysfunction, with the cardiac troponin level correlated with its severity (Mehta et al, 2004). Whether this is the cause of the ventricular dysfunction or a consequence is unclear.

Diagnosing myocardial infarction in critically unwell patients is challenging, in part as a result of the use of sedation, which may mask the clinical symptoms such as chest pain and breathlessness which usually trigger investigation. Electrocardiograms are often not routinely performed and can be challenging to interpret with concurrent arrhythmias related to the presenting illness (Mehta et al, 2011). Troponin levels may also be raised in the context of critical illness, making the potential relevance of increased levels difficult to interpret (Lim et al, 2010). Table 2 details some cardiac and non-cardiac causes of an elevated troponin level, demonstrating how challenging it can be to interpret. A multicentre prospective cohort study investigating the incidence of myocardial infarction in intensive care unit patients with co-existing cardiovascular disease has shown that nearly a quarter of such intensive care unit patients experience clinically undiagnosed myocardial infarction and that this was associated with lower long-term survival (Docherty et al, 2018).

Table 2. Causes of elevated levels of troponin

Cause		References
Cardiac	Myocarditis, endocarditis or pericarditis	Lauer et al (1997); Brandt et al (2001)
	Post-intervention, such as percutaneous coronary intervention or coronary artery bypass grafting	Tricoci (2017); Pegg et al (2011)
	Heart failure	Horwich et al (2003)
	Hypertrophic cardiomyopathy	Gommans et al (2013)
	Tachyarrhythmia or bradyarrhythmia	Agewall et al (2011)
	Trauma	Lippi et al (2016)
	Aortic valve disease	Nunes et al (2003)
	Aortic dissection	Rapezzi et al (2008)
Non-cardiac	Pulmonary embolism	Giannitsis et al (2000)
	Pulmonary hypertension	Torbicki et al (2003)
	Burns	Chen et al (2000)
	Renal failure	Jacobs et al (2009)
	Stroke or subarachnoid haemorrhage	Jensen et al (2007; Bruder and Rabinstein (2011)
	Sepsis-related	Bessiere et al (2013; Sheyin et al (2015)
	Cardiotoxic drugs	Wallace et al (2004)

Outcomes of myocardial infarction and myocardial injury

Outcomes for both type 1 and type 2 myocardial infarction are poor. Within the hospital setting, excluding critical care, patients with type 2 myocardial infarction or myocardial injury have worse outcomes compared to those with type 1 injury (Shah et al, 2015; Chapman et al, 2016). In a group of 2165 unselected consecutive patients admitted to a cardiac centre with an elevated troponin level, 54% were classified as having a type 1 myocardial infarction, 20% a type 2 myocardial infarction and 24% a myocardial injury (the remaining 2% had a type 3–5 myocardial infarction). Those with a type 2 myocardial infarction were more likely to die, with a 1-year mortality of 37% compared to 16% for type 1, although they had a lower risk of having a recurrent myocardial infarction (6% vs 12%) (Shah et al, 2015). The results were similar for patients with myocardial injury.

A second study at the same centre (Royal Infirmary, Edinburgh) of 2122 consecutive patients looked at long-term outcomes and risk stratification of patients with type 2 myocardial infarction or myocardial injury (Chapman et al, 2018a). Nearly two-thirds of patients (62.5%) with type 2 myocardial infarction had died at 5 years compared to approximately one-third of patients (36.7%) with type 1 myocardial infarction. These results reflect all-cause mortality, although there were the same number of crude major cardiovascular events in those with type 1 and type 2 myocardial infarction (30.6% vs 32.6% respectively). These findings suggest that there may be the potential to implement secondary prevention strategies and modify risk if this subgroup with coronary artery disease is identified.

Critically ill patients with co-existing cardiovascular disease

Critical illness alongside cardiovascular disease results in an even higher risk of adverse outcomes. Inflammatory states, such as sepsis or trauma, lead to increasing oxygen requirements, increasing concentrations of cytokines and catecholamines, and a hypercoagulable state (Devereaux et al, 2005). The consequences of this can lead to shear stress and plaque rupture within coronary arteries, resulting in a type 1 myocardial infarction (Gertz and Roberts, 1990; Priebe, 2004). Type 2 myocardial infarction may also occur as a result of an oxygen supply–demand imbalance in the presence of atherosclerosis, causing

narrowing of the vessel. Differentiating between cardiovascular disease and other causes of an elevated troponin level is important to avoid the risk associated with potentially invasive cardiac investigations that may be of little to no benefit to the patient.

The critically unwell population differs from the general hospital population who present with acute chest pain. Patients may not be able to report their symptoms as a result of ventilation, sedation, analgesia, delirium or distracting symptoms as a consequence of their admission diagnosis. As such, the routine practice outwith critical care of testing troponin levels at 6 and 12 hours after the onset of symptoms is unfeasible. Time to peak TnI level after ST-elevation myocardial infarction is approximately 11 hours, after which there is a nearly linear decline (Laugaudin et al, 2016). In the absence of signs and symptoms of myocardial injury or infarction, this is likely to make an elevated troponin level more difficult to interpret, as the sample may have been taken at a time significantly beyond the peak TnI level. The fourth universal definition of myocardial infarction (Thygesen et al, 2019) uses both a TnI value above the 99th percentile upper reference limit and symptoms of myocardial ischaemia as part of the diagnostic criteria. In the absence of one or both of these criteria, the diagnosis becomes inherently more challenging.

Troponin as a risk prediction tool

The Acute Physiological and Chronic Health Evaluation II (APACHE II) model (Knaus et al, 1985) is used by the Scottish Intensive Care Society Audit Group to classify severity of disease, help with prognostication and help with the assessment of new or different therapies within the critical care environment. While TnI is an independent predictor of hospital mortality, after adjustment for potential confounders, it was not shown to improve risk prediction compared to APACHE II (Figure 1). It had the strongest correlation with the acute physiology score component of APACHE II, suggesting it is a reflection of overall physiological derangement in the critically unwell (Docherty et al, 2017). Given the cost of performing the test and there being no clear benefit compared to the current standard, it is not recommended as a routine investigation for all intensive care patients.

The TROPICCAL study (troponin I in cardiovascular patients in critical care; Docherty et al, 2018) was a multicentre prospective cohort study that found that TnI was detectable in all critically ill patients with pre-existing cardiovascular disease: 71% of patients had a peak TnI level over the sex-specific threshold for myocardial infarction or myocardial

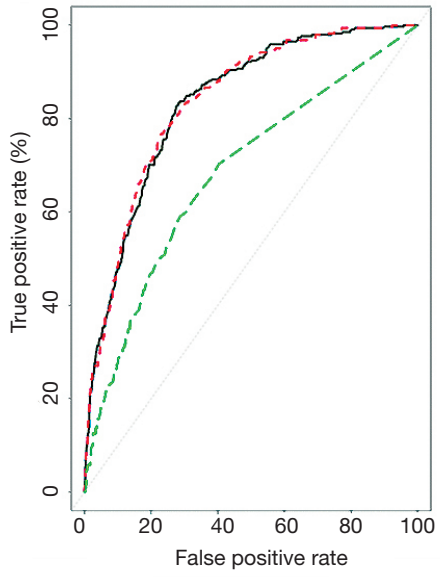

Figure 1. Roc curves comparing the Acute Physiological and Chronic Health Evaluation II score (solid black line), Troponin I (dashed green line) and Acute Physiological and Chronic Health Evaluation+Troponin I (dashed red line).

injury (16 ng/litre in women and 34 ng/litre in men), with peak TnI level occurring within 2–3 days of intensive care unit admission. Nearly all of the patients had a dynamic rise and fall pattern of TnI levels, in keeping with an acute event. The criteria for the universal definition of myocardial infarction were fulfilled by 24% of patients, but more than 95% of these were not recognised by the clinical teams. All patients diagnosed with myocardial infarction were on high doses of vasopressors and had a high lactate level, consistent with oxygen supply–demand imbalance (type 2 myocardial infarction). Both myocardial infarction and myocardial injury were associated with lower 6-month survival. The study results also suggest that the association between myocardial infarction and mortality is greater in patients with less acute physiological derangement. This may therefore be a group of patients who would benefit from routine troponin analysis, on the basis that there are potentially modifiable outcomes and the contribution of myocardial injury to their overall health may be more significant.

Potentially modifiable outcomes

Myocardial infarction in patients with pre-existing cardiovascular disease may be on the causal pathway to mortality. Improving the balance in myocardial oxygen supply–demand may therefore improve outcomes. In addition to treating and/or preventing non-cardiac complications, for example major haemorrhage or sepsis, there are other potential avenues for directing treatment. Some of these options are discussed below.

Approximately half of all hospitalised patients are anaemic on presentation (Lin et al, 2013; Stauder and Thein, 2014; Zaninetti et al, 2018). The prevalence is even higher in the critically ill population, with one large study of 3534 patients showing nearly two-thirds of patients had a haemoglobin concentration <120 g/litre and approximately one-third of patients had haemoglobin <100 g/litre (Vincent et al, 2002). Anaemia is associated with worse outcomes in patients with cardiovascular disease (Szachniewicz et al, 2003; Zeidman et al, 2004); meta-analysis of liberal vs restrictive transfusion strategies demonstrates that liberal transfusion (aiming for haemoglobin >80 g/litre) may decrease myocardial infarction rates in patients with cardiovascular disease (Docherty et al, 2016). The use of intensive care unit transfusion protocols to reflect this may help to improve outcomes in this population.

Other strategies include further investigation and/or treatment of the cardiovascular system itself, for example, the continuation or initiation of cardiac medications. Active rate control with beta-blockers, for example, would prolong the diastolic perfusion time, thus prolonging the coronary perfusion time and improving overall myocardial perfusion (Ramanathan and Skinner, 2005). Currently, there is significant variation in practice with regards to primary and secondary interventions. Further studies to clarify best practice in high-risk patients would be beneficial to determine if the benefit from a cardiac perspective outweighs the adverse effects in the critically unwell. High-risk patients may also benefit from coronary imaging to determine if angiography or percutaneous coronary intervention would improve their outcomes. Establishing the cohort of patients who would benefit in the acute phase of their illness requires further investigation.

Determining the patients who have TnI release secondary to myocardial oxygen supply–demand imbalance vs those with global myocardial inflammation as a consequence of critical illness will be an important future target. Computed tomography coronary angiography or cardiac magnetic resonance imaging may help with this (Thygesen et al, 2019).

Conclusions

Patients in critical care with pre-existing cardiovascular disease are at risk of undiagnosed myocardial infarction or myocardial injury, with evidence to suggest that such events are associated with increased short- and long-term mortality. This appears to have a greater proportional impact on outcome in those with less severe overall physiological deficit, suggesting that myocardial infarction may be on the causal pathway to mortality in this patient group.

Troponin is a useful biomarker, particularly as a rule-out test for myocardial infarction. However, elevated levels of TnI in critically unwell patients may reflect other disease processes, such as sepsis, pulmonary embolus or renal failure. While it is independently associated with

Key points

- Nearly a quarter of intensive care unit patients with pre-existing cardiovascular disease suffer from myocardial injury or infarction during their intensive care unit stay, which is associated with worse short- and long-term survival.
- Type 2 myocardial infarction secondary to oxygen supply–demand imbalance is the primary cause of myocardial infarction and often goes unrecognised.
- Measurement of troponin I levels has a good negative predictive value for myocardial infarction and is independently associated with hospital mortality, but does not improve risk prediction compared to Acute Physiological and Chronic Health Evaluation II. It would be recommended for use only if clinically indicated and not as a routine test in critical care patients.
- In critically ill patients with cardiovascular disease and a raised level of troponin I, there may be the potential to modify factors that contribute to oxygen supply–demand imbalance and reduce overall mortality.

hospital mortality, it does not improve existing risk prediction models, for example APACHE II, and as such is not recommended as a routine diagnostic test in all intensive care unit patients. Elevation of TnI levels is likely to be a reflection of their underlying disease severity. Conversely, a sub-set of critically ill patients with pre-existing cardiovascular disease may benefit from routine troponin analysis as part of their admission process. They have a greater overall risk of myocardial injury or myocardial infarction, which is currently under-diagnosed.

The most likely cause for myocardial infarction in these patients is myocardial oxygen supply–demand imbalance (type 2 myocardial infarction). There is potential for targeted investigations and interventions to improve this, and thus improve patient outcomes.

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Conflicts of interest

The authors declare no conflicts of interest.

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