REVIEW

Troponin in critically ill patients

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ABSTRACT

Assays of cardiac troponin have become a cornerstone in the diagnosis of myocardial infarction across a broad range of clinical settings. In critically ill patients, cardiac troponin is detectable in the plasma in up to 60% of cases, and this incidence may increase further as assays become more sensitive. Troponin rises in critical care are commonly unrelated to pathology in the coronary arteries, but are frequently associated with conditions such as sepsis and respiratory failure. Such non-coronary troponin release is a significant, independent predictor of poor patient outcomes, and can be incorporated into risk scoring systems. Despite adding prognostic value, treatment for non-coronary troponin rises remains limited to management of the underlying cause, and restoration of a favourable balance between myocardial oxygen demand and supply. Conversely, troponin rises secondary to myocardial infarctions are amenable to the same interventions as in any other setting, albeit with additional diagnostic and therapeutic challenges. In this review, we will explore the utility of troponin as a biomarker in critical care, and we will outline a pragmatic management strategy for this patient population. *(Minerva Anestesiol 2012;78:1039-45)*

Key words: Troponin - Biological markers - Critical care - Myocardial Infarction.

Elevated plasma levels of the cardiac troponins (cTn) I and T are highly sensitive and specific biomarkers of myocardial necrosis, and are firmly established in the diagnosis and risk assessment of acute coronary syndrome (ACS).[1] The universal definition of myocardial infarction (MI) published in 2007, requires an increasing or decreasing pattern of cTn measurement with at least one value exceeding the 99th percentile of a normal population (with a coefficient of variation <10% for that assay).[2] In addition, the rise in troponin must be accompanied by symptoms suggestive of myocardial ischemia, with at least one additional factor such as ECG changes or imaging evidence of new loss of viable myocardium.

In critically ill patients, the incidence of raised serum cTn is high. A meta-analysis by Lim reported the following frequencies; 43% across all patient groups (IQR 21%-59%), 60% in septic patients, 53% in medical ICUs, 43% in mixed medical and surgical ICUs and 32% in mixed surgical and trauma ICUs.[3, 4] The majority of these patients (approximately 70%) do not have flow limiting coronary artery disease as judged by stress echocardiography or postmortem diagnosis.[5] Such non-coronary cTn rises are most commonly associated with sepsis [6] and respiratory failure,[7] as well as chronic kidney disease,[8, 9] pulmonary embolism,[10] heart failure,[11-13] stroke [14] and atrial fibrillation.[15] Although the mechanisms of myocardial injury are poorly understood and multifactorial, the end result of a rise in cTn is universally predictive of poor patient outcomes (Table I).[16-43] There are currently no proven therapeutic interventions for this patient cohort. The authors of the above reviews in general take a common sense approach of treating the underlying condition, improving the myocardial oxygen demand and supply balance and remaining vigilant for objective evidence of an MI.

Table I.—*Overview of literature assessing prognostic value of troponin in high-risk patients*

Patient population	First author (Year)	Troponin cut-off(s)	Positive test	Hospital mortality; troponin raised vs normal (unless stated otherwise)
All ICU patients	Lim (2006) [3]	Meta-analysis using variable cut-offs	43%	Odds ratio for death =2.5 [95% CI 1.9-3.4, P<0.001]*
ICU patients (non-coronary rises only)	Stein (2008) [35]	cTnI>100ng/L, <1490ng/L	38%	28% *vs.* 5%, P<0.0001*
Sepsis in ICU	Mehta (2004) [6]	cTnI>1000ng/L	43%	56% *vs.* 24%, P=0.04
Sepsis in ICU	Rosjo (2011) [36]	cTnT>10ng/L HScTnT >14ng/L	cTnT = 60% HScTnT = 100%	HScTnT higher in non-survivors; 54 *vs.* 35 ng/L, P=0.047
Sepsis in ICU (non-coronary rises only)	Ravindranath (2012) [37]	cTnI>100ng/L	56%	36.1% *vs.* 15%, P<0.01
Acute respiratory disease in ICU	Vasile (2010) [7]	cTnT>10ng/L	42%	21% *vs.* 1.5%, P<0.0001*
Vascular surgery	Redfern (2011) [38]	Meta-analysis using variable cut-offs	16%	30 day mortality: NSTEMI=21.6%, non-coronary rise =11.6%, normal =2.3%, P=0.000001
End stage renal failure	Hickson (2008) [39]	cTnT>10 ng/L	61%	Mortality waiting for kidney transplant: hazard ratio =1.729 [95% CI 1.25-2.39, p=0.01]*
End stage renal failure	Deegan (2001) [40]	cTnT>100ng/L	27%	Mortality at 15 months: 65% *vs.* 15%, P<0.00001*
End stage renal failure	Apple (2002) [41]	cTnT>10/30/100 ng/L cTnI>100/400/600 ng/L	0-82%	Relative risk of death: cTnT=3.9 [95% CI, 1.9-7.9; P<0.001], cTnI=2.1 [95% CI, 1.3-3.3, P=0.007]*
Atrial fibrillation (excluding patients with STEMI)	Van den Bos (2011) [15]	cTnI>650ng/L	19%	Hazard ratio of all cause mortality; 3.77 [95% CI 1.42-10.02]*
Pulmonary hypertension (ACS excluded)	Heresi (2012) [42]	cTnI>1ng/L	25%	Hazard ratio for death (3 year follow up); 4.74 [95% CI 1.89-11.89, p<0.001]*
Acute heart failure	Peacock (2008) [12]	cTnT>100ng/L or cTnI>1000ng/L	6.2%	8.0% vs 2.7%, P<0.001*
Pulmonary embolism	Lankeit (2010) [10]	HScTnT>14ng/L	64%	HScTnT higher in patients with at least one 30-day adverse outcome (71.7 *vs.* 26.4, P=0.027)
Stroke	Sandhu (2008) [14]	cTnI>400ng/L	14-21%	Ischemic stroke; 65% *vs.* 4% (P<0.001), Intracerebral haemorrhage; 64% *vs.* 28% (P<0.005), subarachnoid haemorrhage; 40% *vs.* 11% (P<0.005)
Traumatic brain injury	Salim (2008) [43]	cTnI>300ng/L	30%	44% *vs.* 29%, P<0.05*

*Raised troponin is an independent predictor of mortality using multivariate analysis

For intensive care patients who have cTn release secondary to an MI (approximately 30%),[5] there are established treatment pathways. Regular troponin tests of high sensitivity may lead to earlier detection of this cohort.[16] This is particularly true in critical care, as the symptoms of ischaemia are often masked by analgesic drugs and low consciousness levels, and subtle ECG changes can be missed by continuous cardiac monitoring. When a MI is detected by troponin screening there are often barriers to early commencement of anti-platelets, anticoagulants, beta-blockers and ACE inhibitors, because of concomitant conditions. Thus, the potential to improve outcomes may be unfulfilled.[17]

Despite the limitations of troponin as a biomarker in critical care, it also has enormous utility, and the medical establishment has con-

tinued to drive improvements in the sensitivity of troponin assays. As a consequence, more patients will be identified as high-risk and the impetus for appropriate interpretation increases. In this review we aim to additionally address some of the uncertainty surrounding the utility of troponin assays in the intensive care setting, and we will outline a pragmatic strategy aimed towards improving patient outcomes.

High sensitivity troponin assays

High sensitivity (HS) troponin assays represent the 5th generation of their class. There is a limit of detection 10-100 fold less than conventional assays, and they have been successfully developed to facilitate earlier detection of acute myocardial infarction.[18] Even in a largely cardiovascular disease free population, the prevalence of a positive HS troponin test is between 19-24.8%,[19, 20] and this is associated with a greater 5-year mortality. The improved sensitivity is such that there may be a role for troponin assays in the primary prevention of cardiovascular disease or as a chronic marker of established illness.[21]

The introduction of HS troponin assays into clinical practice has lead to an increase in the number of patients diagnosed with MIs, and a reduction in morbidity and mortality.[22, 23] This was observed in parallel with an increase in cardiology referrals, coronary angiography and dual antiplatelet therapy. The impact on the intensive care population is less clear, as few studies utilise the HS tests. Indeed, there is considerable heterogeneity in the assays employed in the literature, making across study comparisons difficult. In a move towards standardisation, Apple proposed that two criteria must be met to qualify an assay as high sensitivity;[18, 24] 1) the coefficient of variation at the 99th percentile be ≤10%; and 2) the measurable concentrations below the 99th percentile should be attainable with an assay at a concentration value above the assay's limit of detection for at least 50% of healthy individuals. In addition, Apple recommended that concentrations should be measured in nanograms per litre (ng/L). Adherence to these criteria will assist future appraisal of the evidence base.

Non-coronary troponin rises

In 70% of critical care patients with a troponin rise, there is no demonstrable coronary artery pathology.[5] A diagnosis of a non-coronary troponin rise can be made when ECG and echocardiography changes do not meet the criteria for the universal definition of MI. The aetiology of troponin leak in these circumstances is complex and poorly understood.[4] A final common pathway must involve myocardial cell damage, necrosis or apoptosis, leading to cTn release into the plasma. The antecedents to this pathway are broad and include sepsis, respiratory failure, pulmonary embolism, atrial fibrillation, renal failure, heart failure, stroke and high-risk surgery.

Despite HS tests leading to greater detection of non-coronary troponin rises, there are still no evidence-based interventions shown to improve outcomes. Thus, most critical care physicians are limited to addressing the underlying condition and applying sound clinical principles. A recent nationwide survey in the USA revealed broad differences in approach amongst 310 intensivists.[25] The most common treatments implemented were aspirin or clopidogrel (76%), beta blockers (68.7%), high dose statins (48.9%), low molecular weight or unfractionated heparin (47.4%) and an ACE inhibitor (37.6%). A large proportion would request a cardiology consultation (72.7%) and many would refer for a coronary angiogram once stable (51.3%). The authors concluded that more research is required to determine the treatment for elevated troponins in cases not associated with ACS.

Although therapeutic options are limited, making a diagnosis of a non-coronary troponin rise may be useful for prognostic purposes. In many conditions plasma troponin levels are strongly predictive of short and long-term mortality (Table I). For example, intensive care patients with acute respiratory disease and a raised troponin, have up to a 30-fold increase in their observed short, medium and long-term mortality, compared to a very low death rate when cTn is not raised.[7] In these patients a history of coronary artery disease was not a predictor of mortality, suggesting a predominantly non-coronary aetiology for the troponin release. Thus,

non-coronary troponin rises have significant prognostic value, and this may be enhanced in studies employing the higher sensitivity assays.

Myocardial infarction

Patients in intensive care are at high risk of MI and there are specific diagnostic and therapeutic challenges compared to other settings. Northern European studies suggest the incidence of ischemic heart disease (IHD) for those admitted to a critical care unit is approx 29%, which is nearly double that of a comparable age and sex matched cohort for the general population.[26] Furthermore, critical illness predisposes to physiological stress, stimulation of prothrombotic pathways, hypoxia, tachycardia and imbalances in oxygen consumption and delivery. In addition to a high incidence of MI, the standard alert processes are often removed, as sedation and analgesia preclude the patient from reporting symptoms. Clearly, an ST elevation infarct (STEMI) should be detected on continuous cardiac monitoring, and primary PCI or thrombolysis can be considered. It is the non-ST elevation MIs (NSTEMI), with only subtle ECG changes or regional wall motion abnormalities, that may be missed in this population. As NSTEMIs carry a worse long-term prognosis than STEMIs there is a considerable opportunity to improve outcomes.[27]

To address these issues, Lim *et al.* conducted a prospective study of patients admitted to a mixed medical and surgical ICU (N.=112).[17] All patients underwent systematic screening with frequent cTn measurements and ECGs, and were classified as having had an MI (35.9%), an isolated troponin rise (14.6%), or no troponin rise (49.5%). The ICU team were blinded to the screening results, and correctly diagnosed 14 patients (12.5%) as having a MI on clinical grounds. Although the screening programme was clearly effective at identifying additional patients with MIs, the outcomes for those identified by routine clinical practice were similar. This equivalence in outcomes may reflect the challenges to appropriate and timely medical intervention for MIs in this population. Ultimately, larger trials will be necessary to further evaluate the utility of screening programmes.

In terms of prognostic value, troponin rises as part of a diagnosis of MI are highly predictive of poor outcomes. In the same prospective study described above, Lim reported that patients with MIs had a longer duration of mechanical ventilation (4 days [0.5-12.5]) compared to patients with isolated troponin rises (2 days [0-3]) or normal levels (1 day [0-2]), P<0.0001. They also had a longer duration of ICU stay (5[2-14] *vs.* 4[3-7] *vs.* 2 [1-4] days respectively, P=0.002), and a higher hospital mortality (43% *vs.* 26.7% *vs.* 2% respectively, P>0.0001).

Clinical management

Not withstanding the limitations of troponin as a basis for improving outcomes, we believe there is sufficient evidence to justify a degree of screening in most critical care units. The frequency of such screening should be determined at a local level based on knowledge of the patient population, access to cardiology services and cost. In our practice, we currently perform daily troponin assays as part of our routine ICU profiles. A retrospective review of our unit before HS tests were introduced, demonstrated that 38% patients had a positive troponin on admission (cTnI>40ng/L), rising to 52% when the whole ICU stay was considered, with even small increases in troponin (50-120 ng/L) being associated with increased mortality.[28]. As we now use HS tests as standard, we expect the current incidence of troponin rises to be even higher.

The next step is to develop cardiology services that can react promptly to a positive troponin result with clinical assessment, ECG and echocardiography investigations as required. Thus, patients can be quickly categorised into MI and non-coronary groups. The MI patients should then be discussed in a multi-disciplinary environment to ensure optimal medical management and follow up are implemented, taking into account each patients risk profile and contraindications.

Finally, patients in the non-coronary group should be identified as an at-risk population, and have an urgent clinical review by a senior critical care doctor. An emphasis should be placed on optimal treatment of the underlying condition

and consideration of any other hitherto unrecognised diagnoses *e.g.* pulmonary embolism. In addition, parameters such as heart rate, afterload, inotropes, haemoglobin and oxygen levels should be optimised. Extra vigilance for the evolution of an MI is appropriate and may require daily ECGs or interval echocardiography. A comparison of the incidence of raised troponin on admission and for the whole ICU stay may form the basis of a global quality measurement for each local unit.

Discussion

As troponin rises in critical-care are frequent and carry a poor prognosis, there is a clear impetus for further evaluation of the utility of this biomarker. A pressing question for local units is whether to introduce a screening programme based on current evidence. Using public health criteria, screening is appropriate when a condition is important, there is a suitable test, there is an accepted treatment for patients with the disease, and the costs of case finding are justified[29]. We believe that these criteria are met for patients with MIs that would otherwise go undetected. A by-product of this approach is the identification of a large cohort of non-coronary troponin rises, which raises further challenges.

The difficult interpretation of non-coronary troponin rises reflects the limited understanding of the aetiology of myocardial cell injury. It is clear how an acute coronary event or an oxygen supply-demand imbalance can render heart cells ischaemic, and how the subsequent necrosis leads to troponin release into the plasma. It is less clear how a diverse group of disease processes can result in troponin leaks with no evidence of coronary disease, and why this should be such a consistent predictor of poor outcomes. The mechanisms of such non-coronary troponin rises are in urgent need of investigation. Recently proposed hypotheses include paracrine mediated (e.g. natriueretic peptides) increases in cell membrane permeability, direct toxicity from inflammatory cytokines and catecholamine-induced cellular injury.[30] In addition to elucidating the mechanisms involved, it will be important to understand why troponin release carries such a poor prognosis. It may be that myocardial damage leads to relative heart failure and subsequent organ dysfunction. Alternatively, cardiac function may be preserved and outcomes are simply related to the severity of the underlying disease.

The evolution of the cardiac troponin assays has been driven by the quest for quicker, more reliable diagnoses of acute MI, and has accentuated the dilemmas of interpretation in critical care. As the sensitivity of assays has increased, several interesting observations have come to light. For example, a number of healthy individuals have raised troponins,[31], as do nearly all marathon runners after strenuous exercise.[32] As yet, these results have not been associated with poor outcomes, and may reflect a degree of physiologically mediated cardiac remodelling.[33] Drawing a distinction between physiological and pathological aetiologies will be of clear importance. There are suggestions that the speed and magnitude of troponin rises measured by HS tests may illuminate this issue.[34]

Overall, the use of troponin as a biomarker across many clinical settings is the subject of intense investigation. In critical care there is a role for early detection of MI and improved risk modelling. Larger trials are necessary to evaluate whether troponin based clinical algorithms lead to an improvement in patient outcomes.

In the meantime, we recommend a pragmatic approach based on troponin screening, close liaison with cardiology services and an experienced clinician review for the non-coronary cohort. The primary intention is to replicate the improvements in detection and outcomes of MIs that have been achieved in non-critical care settings. In our opinion, future studies in critical care patients should differentiate between non-coronary troponin rises and MI, and should focus on novel therapeutic interventions guided by the results of mechanistic studies.

Key messages

— Troponin rises occur in up to 60% of critically ill patients and are strong, independent predictors of poor outcomes.

— Screening programmes are successful in detecting more patients with MIs, but the potential outcome benefits of this effect are unproven.

— There are no specific therapeutic options available for non-coronary troponin rises, and their utility is currently limited to improved prognostication.

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