



## Troponin rise in sepsis...who gets an angiogram?

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### Introduction

Cardiac troponin I (cTnI) and T (cTnT) are sensitive and specific biomarkers of myocardial injury. As cardiac regulatory proteins they control the calcium-mediated interaction between actin and myosin.<sup>(1)</sup> There is now established consensus that elevated serum levels above the 99<sup>th</sup> centile of normal is indicative of myocardial necrosis.<sup>(2,3)</sup> However elevated troponin does not always equate to myocardial infarction caused by coronary plaque rupture or occlusion. Acute pulmonary embolism, heart failure, myocarditis, renal disease, aortic dissection, strenuous exercise, cardiac contusion, cardiotoxic chemotherapy and sepsis have all been shown to cause troponin leak<sup>(4)</sup>.

High-sensitivity troponin assays (hsTn) have gained almost universal adoption in UK hospitals. They represent an important advance with increased sensitivity

for detection of cardiac myocyte necrosis.<sup>(5)</sup> They are able to detect the same proteins as the conventional assays, but at much lower concentrations;<sup>(6)</sup> as low as 0.003 µg/L (3ng/L).<sup>(7)</sup> Compared to the previously used cutoff values of 0.05–0.1 µg/L for third-generation cTnT, the Roche Elecsys troponin T (hsTnT) has an upper limit of normal (99<sup>th</sup> centile) of 14ng/L.<sup>(7)</sup> This markedly increased sensitivity led to a significant reduction in decision-making time after chest pain presentations. At such a low detection level, they are frequently elevated at time of presentation with acute myocardial infarction (AMI). If sampling is taken 3-6 hours after admission for at-risk

### Take Home Messages

- Elevated high-sensitivity troponin is associated with increased mortality in sepsis and is frequently due to non-thrombotic mechanisms.
- This editorial outlines the mechanisms underpinning myocardial dysfunction in sepsis and what patients should be selected for coronary investigation.
- In the era of high-sensitivity troponin, more critically unwell patients have significantly elevated levels. More research is required to determine which factors increase the likelihood of high troponin being attributable to thrombotic causes.

patients, sensitivity increases from 90-95% to 99-100%.<sup>(8)</sup> This is reflected in recently updated European Society of Cardiology (ESC) guidance.<sup>(9)</sup>

The downside to this is the increased detection of circulating troponin in patients who are not suffering from AMI. In emergency departments, access to hsTn testing is widespread. Increasingly, early pharmacological treatment for suspected myocardial infarction is being instituted based on an elevated level, even if the clinical context is not suggestive.

### **Sepsis and elevated troponin**

Sepsis is one of the most common reasons for emergency admissions in the UK with approximately 274,000 cases per year.<sup>(10)</sup> The prevalence of elevated troponin in the context of sepsis is estimated to be 61%. In almost all studies it is associated with a higher mortality.<sup>(11)</sup> In the majority of cases, significant coronary artery disease has been ruled out, suggesting other mechanisms underlie the rise in biomarker. While the mechanism of myocyte damage in sepsis is not fully understood, several pathophysiologic explanations have been hypothesised.

Common manifestations of sepsis including hypotension, microcirculatory dysfunction, anaemia and direct hypoxemia, which can all result in reduced oxygen delivery. Coronary perfusion is often reduced, while fever and tachycardia mandate increased myocardial oxygen demand. This demand-supply mismatch causes myocyte damage and a rise in detectable serum troponin which is exacerbated by the presence of existing coronary artery disease<sup>(12)</sup>. In addition, cytokine and endotoxin release from the bacteraemia leads to microvascular dysfunction. This may cause a direct bacterial myocarditis leading to depressed myocardial function and increased myocardial cell membrane permeability.<sup>(12)</sup> The formation of free radicals generated by the activation of NADPH oxidases complexes in sepsis is associated with myocardial cell apoptosis and consequently myocardial micronecrosis.<sup>(12)</sup>

Studies have correlated troponin elevation in severe sepsis with abnormal cardiac function. Left ventricular dysfunction assessed by transoesophageal echocardiography in those with septic shock was significantly greater in TnI positive patients.<sup>(13)</sup> Post-mortem examination of patients in the same study revealed contraction band necrosis was present in only 50% of those with elevated TnI and in one TnI-negative patient, suggesting leakage from the cardiac myocyte membrane rather than myocardial necrosis was the cause of the troponin release. A further study of 225 septic patients defined left ventricular diastolic dysfunction and right ventricular dilatation as the echocardiographic variables that correlate best with hsTnT concentrations, and best explain the increased mortality seen.<sup>(14)</sup>

However there is a small group of patients for whom elevated troponin, even in the context of a sepsis presentation could be a harbinger of significant coronary artery disease. Small studies looking at the cause of troponin rise in septic patients found only between 4.5-6% were related to coronary artery disease (diagnosed on stress echocardiography, coronary angiography or post mortem).<sup>(15,16,17)</sup>

### **Who do we investigate?**

The challenge for Cardiologists looking after this cohort of patients is to determine whose troponin rise is indeed due to significant coronary artery disease and how they should be investigated. There is little evidence to guide practice in this scenario.

Those classed as high risk due to significant risk factors for coronary disease warrant further investigation. Particular attention should be paid to those with a prior history of coronary revascularisation, known established coronary artery disease, episodes of chest pain at the time of presentation, electrocardiographic (ECG) changes, diabetics and those with a significant smoking history.

The degree of troponin leak can be a useful guide in this setting. Recent ESC guidance suggests hsTn levels should be used as a quantitative marker (i.e. the higher the level, the greater the likelihood of myocardial infarction).<sup>(9)</sup> It concedes that elevations above 5 times the upper limit have a high (>90%) positive predictive value (PPV) for myocardial infarction, while anything up to 3 times the upper limit carries only a moderate PPV (50-60%) and is more likely to be due to another cause (in this case, sepsis). Furthermore the rise and fall of the biomarker is significant. The more pronounced the change, the increased likelihood of an AMI.

Initial investigation begins with a transthoracic echocardiogram looking particularly for new regional wall motion abnormality. However the sensitivity of this in the context of septic shock is indeterminate. Studies show 37% of troponin positive patients with septic shock displayed a wall motion abnormality,<sup>(18)</sup> however this may be a reflection of the myocardial dysfunction that is often seen in sepsis.

Further decisions should focus on coronary investigation. This should be based on the clinical context as well as risk stratification. Factors that would favour inpatient coronary angiography include very high levels of hsTn, new or dynamic ECG changes, episodes of chest pain during admission and significant new regional wall motion abnormality. The timing of angiography is based on the clinical context and is typically once the index infection has settled. More conservative methods of coronary investigation are reserved for low to medium risk patients and include outpatient stress testing or computed tomography coronary angiography (CTCA).

## Conclusion

More and more in my clinical practice I am being asked to assess septic patients with incidentally significantly elevated troponins. The management of this cohort can be tricky. An individualised approach to determining who needs further cardiac investigation must be used, which takes into account coronary risk factors, ECG changes, degree and fluctuations in serum troponin and presence of new regional wall motion abnormalities. Further research is required into what factors and variables increase the likelihood of sepsis-troponin rise being attributable to thrombotic coronary artery disease.

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