Current controversy

Triage of acute onset chest pain: now a biochemical rule-out test?

SJ Wilson, P Bloomfield, PO Collinson

The management of coronary disease has moved forward with the application of more sensitive blood biomarkers for early detection alongside more structured symptom assessment, examination and serial ECG measures. However every episode of exertional chest pain isn’t symptomatic coronary disease and given massive public awareness campaigns we now face a different management issue with undiagnosed chest pain sent as a ‘rule-out’ activity. These urgent referrals are often justified based on the management of the minority with unstable coronary disease without preliminary medical review or examination. Avoiding delay which is valuable in coronary patients may be irrelevant to the majority. The overall effectiveness of this pathway is unclear where the patient does not have coronary disease but also where superficial interpretation can be misleading through non-specificity. Do biomarker assays become the answer to every chest pain patient and has the basic assessment of the individual patient and a prior probability of disease no role to play? Does this activity represent a burden or an irrelevant dead end for non-coronary patients? We have asked for comment from two leading authorities on the evolving role and application of cardiac biomarker technologies in managing this considerable and common clinical dilemma.

KEYWORDS Troponin, cardiac troponin T, cardiac troponin I, chest pain, triage

DECLARATION OF INTERESTS No conflict of interests declared.

The exclusion of acute chest pain by biochemical markers will never be possible

SJ Wilson, P Bloomfield

Chest pain is a major burden on healthcare resources in the UK, with the potential for significant morbidity and mortality. It is one of the most common referrals to hospital, accounting for around 5% of presentations to the Emergency Department and one-third of unplanned admissions. In medicine, the traditional approach to assessment has been careful history taking and physical examination, formulation of a differential diagnosis, and the application of investigations to establish the diagnosis. Assessment of chest pain can be difficult, with a wide differential diagnosis including potentially life-threatening conditions. Symptoms and clinical signs are inadequate discriminators in many patients such that biomarkers are already heavily relied upon in some instances. It is proposed that the traditional medical approach to assessment has become redundant. That is, a more direct and streamlined approach can be adopted by utilising ever improving biomarkers as a rule-out test. This is clearly not possible for all causes of chest pain. Suspected pathologies such as pneumothorax or aortic dissection for example will inevitably need radiological evaluation. Furthermore, despite newer high sensitivity D-dimer assays, diagnosis of pulmonary embolism (PE) remains reliant on clinical appraisal and pre-test probability; a normal D-dimer cannot reliably exclude PE in intermediate/high risk individuals. On the other hand, suspected acute coronary syndrome (ACS) which is the cause of greatest burden in chest pain assessment has biomarkers that would appear much more promising.

ACUTE CORONARY SYNDROME

A substantial proportion of patients presenting with chest pain have suspected acute coronary syndrome. Of those shown to have ACS only a quarter are ST elevation myocardial infarction (STEMI), with the majority either non-ST elevation myocardial infarction (NSTEMI) or unstable angina (UA). Individuals with NSTEMI or UA may be at considerable risk but the diagnosis is often difficult on clinical or electrocardiogram (ECG) results alone. Prognosis can be improved by early identification and treatment. Dual antiplatelet therapy such as aspirin and clopidogrel or prasugrel, and percutaneous coronary intervention have been shown to reduce the risk of future coronary thrombosis, myocardial infarction (MI) and death. The UK Registry reports the six-month mortality for non-ST elevation
TROTONIN

Troponin is a structural protein released into the circulation from myocyte necrosis with the cardiac isoforms TnT and TnI virtually specific to cardiac muscle. Detection of troponin in blood is an exquisitely sensitive marker of myocardial cell death, and therefore MI. Furthermore, higher levels of troponin are associated with increased thrombus burden within the coronary arteries, greater complexity of coronary artery lesions and reduced perfusion of the coronary bed. Troponin elevation therefore identifies patients who benefit from more potent anti-platelet/anticoagulant and early invasive strategies. Perhaps even more important in considering a rule-out test for ACS, the value of troponin extends beyond diagnostic and therapeutic decision making. Troponin is a strong and independent marker of future adverse events and prognosis.

Current controversies centre on the absolute level of troponin that is necessary to be detected in blood to diagnose MI or exclude risk. Additionally, whether the measurement of very small amounts of the specific protein will enable us to detect myocardial ischaemia or improve outcomes is unclear. The current European/American definition of MI is a rise in troponin above the 99th percentile of a healthy reference population in the clinical context of myocardial ischaemia. To prevent misdiagnosis, it is recommended assays achieve this with a coefficient variation (CV) of less than 10%. Across the UK, few assays in practice are able to realise this. Instead, laboratories have to adopt a cut-off above the 99th percentile but below the recommended 99th percentile let alone beyond. At lower troponin concentrations there is an escalating prevalence of non-ACS causes of troponin elevation. In any case, further research is required to determine evidence-based thresholds particularly before any greater reliance on troponin is made. It may be there is no universal cut-off, instead thresholds may vary according to the information required, whether diagnostic, prognostic or therapeutic.

In considering a lower troponin cut-off, which may be appropriate particularly for a rule-out test, the overall clinical impact and practicalities must also be considered. They have yet to be fully understood at the 99th percentile let alone beyond. At lower troponin concentrations there is an escalating prevalence of non-ACS causes of troponin elevation. This causes progressive difficulty in troponin interpretation for a growing number of ‘positive’ individuals and increases the risk of misinterpretation (Table 1). It may be argued this is irrelevant, as any troponin rise no matter what the underlying cause is significant and therefore worthwhile detecting. While this is true, the value of such a diagnosis and allocation of resources in doing so may be limited if the risk cannot be modified as a result e.g. chronic heart failure or left ventricular hypertrophy.

Another difficulty is biological variability. Serial troponin testing can be helpful in ACS diagnosis particularly with lower troponin concentrations. A dynamic rise occurs to a greater degree with MI. At the 99th percentile, the
recommendation is a rise or fall in troponin of at least 20%. However, with progressively lower troponin levels the influence of biological variability in an individual’s baseline troponin steadily increases. Thus, at levels below the 99th percentile a change in troponin greater than 50% or perhaps higher may be necessary to be sure a clinically significant rise has occurred.28–27 Similarly the precision of healthy reference populations used to establish normal troponin values will be ever more decisive, such that sex, race and age may need to be considered. In fact, existing reference population ranges for many of the assays may overestimate the true 99th percentile for various subgroups, so that assay performance appears more favourable. It is clear that further research is required before lower cut-offs can be considered. This will include determining what constitutes a significant dynamic troponin rise for a given concentration and healthy reference ranges for differing individuals. Perhaps more importantly, the benefit of early MI detection or safe discharge of some patients would also have a positive test. This is reassuring and not referred for further investigation or treatment. Alternatively, patients whose symptoms are related to underlying coronary disease not ACS. However she might unnecessarily be subjected to invasive coronary angiography, a procedure with some risk to the patient and considerable cost to the Health Service. Similarly a middle-aged woman with a small pulmonary embolism might present with chest pain, minor ECG changes and a positive troponin. If labelled ACS she would receive antiplatelet and anticoagulant treatment and be subjected to invasive coronary angiography, associated with lifelong hypertensive heart disease might present with palpitation and have a ‘positive troponin’. This increase would be related to arrhythmia and hypertensive heart disease not ACS. However she might unnecessarily be given dual antiplatelet and anticoagulant treatment and possibly coronary angiography, when a careful assessment would have revealed the accurate diagnosis and initiation of the correct potentially life-saving treatment. Alternatively, patients whose symptoms of chest pain were related to underlying coronary disease but who had no rise in troponin due to lack of assay sensitivity or myocardial ischaemia, may be falsely reassured and not referred for further investigation or given important secondary preventive medication.

**CONCLUSIONS**

Troponin is the most validated biomarker in clinical use with regard to ACS but over-dependence must be avoided. It does not reliably exclude myocardial ischaemia and therefore UA and current assays are not sensitive enough to meet the recommended 99th percentile cut-off for MI. Furthermore, an evidence-based cut-off particularly regarding risk has yet to be established. In considering a lower troponin threshold, the overall clinical benefit has to be determined and difficulties with assay imprecision, biological variability and appropriate reference populations overcome. Utilising troponin as a rule-out test may have a negative impact by discouraging proper assessment. A patient’s presenting symptoms of chest pain might be falsely diagnosed as an ACS. Thus an elderly lady with a new onset of atrial fibrillation associated with longstanding hypertensive heart disease might present with palpitation and have a ‘positive troponin’. This increase would be related to arrhythmia and hypertensive heart disease not ACS. However she might unnecessarily be given dual antiplatelet and anticoagulant treatment and be subjected to invasive coronary angiography, a procedure with some risk to the patient and considerable cost to the Health Service. Similarly a middle-aged woman with a small pulmonary embolism might present with chest pain, minor ECG changes and a positive troponin. If labelled ACS she would receive antiplatelet therapy and possibly coronary angiography, when a careful assessment would have revealed the accurate diagnosis and initiation of the correct potentially life-saving treatment. Alternatively, patients whose symptoms of chest pain were related to underlying coronary disease but who had no rise in troponin due to lack of assay sensitivity or myocardial ischaemia, may be falsely reassured and not referred for further investigation or given important secondary preventive medication.
The exclusion of acute chest pain by biochemical markers will never be possible considering the range of potentially life-threatening aetiologies. In suspected ACS we believe that sensitive markers such as plasma troponin are an extremely important and useful adjunct to diagnosis and assessing prognosis. Improvement in current assays and development of alternative biomarkers will increasingly support but never replace a careful history and clinical assessment of patients.

REFERENCES

Triage of acute onset chest pain is now a biochemical rule-out test?

PO Collinson

**Triage:** The assignment of degrees of urgency to wounds or illnesses to decide the order of treatment of a large number of patients or casualties.1

Patients with chest pain constitute the largest single category of patients attending emergency departments (ED) and admitted to hospitals in the UK.2 Although the electrocardiogram (ECG) is an excellent tool to select those patients who will benefit most significantly from revascularisation, it is a poor diagnostic test for acute myocardial infarction (AMI). When post-mortem studies are used as the ultimate 'gold standard' diagnosis, the ECG has a sensitivity of only 41–61%.3,4 Similarly using a consensus final diagnosis based on all available clinical data, the diagnostic sensitivity of the ECG has been found to be 57%.5 Even in patients presenting with ST segment elevation, diagnostic accuracy for AMI is not 100%6 and confirmatory testing is required. The measurement of biochemical markers of myocardial injury, originally referred to as 'cardiac enzymes' and now referred to as cardiac biomarkers has been accepted as a necessity since the 1970s. Cardiac enzymes are included within the diagnostic criteria of the original World Health Organization (WHO) definition of myocardial infarction (MI).7

The differential diagnosis of patients presenting with acute chest pain is challenging. It has been a consistent finding that 3–7%8 of patients with AMI are inappropriately sent home from the ED. The challenge for the laboratory has been to deliver a rapid biomarker-based confirmation or exclusion of significant myocardial injury. Although strategies based on rapid serial measurement of conventional cardiac enzymes such as creatine kinase (CK)9 and its MB isoenzyme10 can significantly reduce time to confirmation or exclusion of AMI,11 neither of these tests are cardiac specific. The ability to measure the protein components of the cardiac contractile apparatus, the cardiac troponins cardiac troponin T (cTnT)12 and cardiac troponin I (cTnI)13 represented a significant breakthrough in the field of cardiac biomarker measurement. The development of rapid automated immunoassays for cTnT and cTnI resulted in a paradigm shift in the ability of a laboratory to provide cardiac biomarker information as part of the workup of the chest pain patient.

Early studies demonstrated that measurement of cTnT and cTnI was superior to measurement of CK14 or CK-MB15 in patients with chest pain and suspected AMI. In particular, it was demonstrated that in patients where AMI had been ruled out by conventional testing, an elevated cTnT or cTnI diagnosed missed myocardial injury with an adverse prognosis. The demonstration that troponin elevations could be linked to treatment strategies16–19 was the final confirmation of the utility of biomarkers in the emergency department.

© 2012 RCPE

**References:**

35 Roy D, Quiles J, Aldama G et al. Ischemia modified albumin for the assessment of patients presenting to the emergency department with acute chest pain but normal or non-diagnostic 12-lead electrocardiograms and negative cardiac troponin T. Int J Cardiol 2004; 97:297–301. http://dx.doi.org/10.1016/j.ijcard.2004.05.042
Very rapidly, measurement of cTnT and cTnl was incorporated into the recommendations of professional societies20 and ultimately into the definition of AMI.22,23

Initially, triage using troponin was for confirmation of diagnosis in patients presenting with ST segment elevation and for the confirmation or exclusion of AMI where the initial presenting diagnosis was uncertain. In patients presenting without ST elevation, a simple dichotomous troponin based classification of AMI was utilised. It was recognised early on that there were a few other conditions apart from AMI, most significantly renal failure, where troponin elevation was seen.24 The sensitivity of the measurement technology used in the laboratory for cTnT and cTnl measurement has progressively improved. As a result, the range of conditions other than suspected ACS where troponin elevations are known to occur has increased. Troponin elevation outside the ACS population has led to the concept that troponin measurement is non-specific. This is untrue. Troponin elevation is 100% specific for myocardial injury. In those conditions where there is follow-up information available, it has been conclusively demonstrated that troponin elevation outside of the ACS population indicates an adverse prognosis. This is perhaps most vividly demonstrated for patients with chronic renal failure. In this group, the majority of the mortality is cardiac and is predicted by the presence of a detectable cardiac troponin.25 Troponin elevation in chronic renal failure patients is associated with evidence of diffuse myocardial injury.24,27

The current generation of troponin assays is able to measure troponin levels in healthy normal individuals. It has been shown that the presence of an elevated troponin above the reference interval, currently defined as the 99th percentile, is associated with other cardiac risk factors28 and with an increased risk of cardiac events such as MP29,30 or risk of development of heart failure.31 The other advantage of these sensitive troponin assays is the ability to achieve diagnostic sensitivity equivalent to the previous assays within one to two hours of admission21,23 and very likely to achieve 100% diagnostic sensitivity by three to six hours from presentation.24

The concept of triage originated in World War I with French doctors who were treating the battlefield wounded, based on concepts originally developed by Dominique Jean Larrey during the Napoleonic Wars. There were three categories:

- Those who are likely to live, regardless of what care they receive;
- Those who are likely to die, regardless of what care they receive;
- Those for whom immediate care might make a positive difference in outcome.

The modern ED environment is not perhaps as extreme as this (although it may feel that way to the ED physician) but the fundamental concept of triage remains risk stratification and effectiveness of intervention. In the chest pain population troponin is the ultimate triage test. In those presenting with ST segment elevation, troponin measurement on admission defines the highest risk group20 and subsequent measurement confirms the diagnosis, although the management pathway is already assigned. In the remaining two ECG categories, chest pain with a non-diagnostic but abnormal ECG or those with a normal ECG, troponin measurement will categorise patients into high-risk or low-risk chest pain.

The ability of small elevations of troponin to predict outcome and the impact of evidence-based therapies has recently been illustrated in a prospective observational study.35 Following a six-month baseline observation period, the diagnostic discriminant for the diagnosis of AMI for cTnl was lowered from 200 nanograms per litre (ng/L) to 50 ng/L. The impact of this change in threshold on diagnosis and prognosis was followed up during the subsequent six months. Patients with troponin in the range 50–200 ng/L had a 39% rate of death or recurrent MI at one year compared to 21% following reduction of the diagnostic threshold. This was accompanied by a significant increase in the number of patients with cTnT in the range 50–200 ng/L group treated with evidence-based cardiac interventions. In a further study the same team examined the outcome of patients with a cTnl in the range from the 99th percentile to the 10% coefficient of variation (CV) cut point of the assay, 14–<50 ng/L.38 They found patients with a cTnl in this range were four times more likely to have had an adverse cardiac event than those with a cTnl <14 ng/L.

In the chest pain population, failure of troponin to increase defines outcome, irrespective of whether the patient has ACS. This triage can be achieved very rapidly. Two large studies, one a randomised controlled trial27 and the other an observational study,38 have shown that failure of troponin to increase during the two-hour period following admission defines a low-risk group which can be safely discharged. Triage of acute onset chest pain is now a biochemical rule-out test based on troponin because it is fast and accurate.

REFERENCES
