EDITORIAL

Cardiac troponins

S Sharma, P G Jackson, J Makan

Benefits and pitfalls for diagnosing myocardial infarction

The diagnosis of myocardial infarction has conventionally relied on the presence of chest pain or typical ST segment and T wave abnormalities on the 12 lead electrocardiogram (ECG) and a rise in the serum concentrations of cardiac muscle enzymes. Whereas most patients with ST segment elevation also invariably have high serum cardiac muscle enzyme values, indicating myocardial damage, a considerable proportion of patients with less specific ST segment changes may not have increased cardiac muscle enzymes, and in the past have been diagnosed as having either stable angina or non-cardiac chest pain. Cardiac troponin T (cTnT) and troponin I (cTnI) are cardiac regulatory proteins that control the calcium mediated interaction between actin and myosin. The cardiac forms of these regulatory proteins are coded by specific genes and theoretically have the potential of being unique to the myocardium. Indeed, cTnI has not been identified outside the myocardium.[1] Cardiac troponin T is expressed to a small extent in skeletal muscle; however, the current cTnT assay does not identify skeletal troponins.[2]

> ''Cardiac troponin T and troponin I are cardiac regulatory proteins that control the calcium mediated interaction between actin and myosin''

The measurement of serum cTnI and cTnT is superior in terms of sensitivity and specificity to cardiac muscle enzyme measurements in the identification of cardiac muscle damage.[3] Raised cardiac troponin concentrations are now accepted as the standard biochemical marker for the diagnosis of myocardial infarction.[4 5]

Cardiac troponins are detected in the serum by the use of monoclonal antibodies to epitopes of cTnI and cTnT. These antibodies are highly specific for cardiac troponin and have negligible crossreactivity with skeletal muscle troponins.[6] Cardiac troponins may not be detected in the serum for up to four hours after the onset of an acute coronary event and should be repeated after 12 hours if the troponin concentration on admission is not raised in an individual presenting with chest pain. Troponin T is measured using a single assay, so that results for cTnT can be compared from one laboratory to another, and generally a cutoff value of 0.1 μg/litre is indicative of myocardial damage. In contrast, there are several cTnI assays with differing sensitivities and cutoff values. The European Society of Cardiology and American College of Cardiology consensus document recommends that each laboratory should determine its cutoffs for each test at the 99th centile of normal with $\leqslant$ 10% coefficient of variation.[7] Using these criteria, serum cTnI values indicative of myocyte necrosis/myocardial damage range from 0.1 to 2 μg/litre.

The paper by Jishi *et al* in this issue highlights that the measurement of cardiac troponins as markers of myocardial damage in the investigation of patients with chest pain has had two important beneficial effects on clinical practice.[8] First, more patients with chest pain who would not have been diagnosed as having myocardial damage with conventional muscle enzyme assays are being diagnosed with myocardial infarction, even in the absence of ST segment elevation. Many of these patients are at high risk of full thickness myocardial infarction or even death in the ensuing six month period,[9–12] and have been shown to benefit prognostically from early treatment with low molecular weight heparins,[13] platelet glycoprotein IIb/IIIa receptor blockers,[14] and coronary revascularisation.[15] In the setting of a typical UK district general hospital, where facilities for coronary angiography are often absent, raised cardiac troponins in patients with chest pain but without ST segment elevation (now termed non-ST segment elevation myocardial infarction) identify patients who are at high risk of an adverse cardiac event and who should be referred to a tertiary referral for coronary angiography and revascularisation before discharge home.

Conversely, the absence of cardiac troponins in the blood 12 hours after the onset of chest pain is associated with a low risk of an adverse outcome, with respect to myocardial infarction and death, and permits early discharge in patients who do not have electrocardiographic evidence of myocardial ischaemia.[16] Based upon conventional protocols involving cardiac muscle enzyme concentrations, many patients in this group would stay in hospital for up to 72 hours, placing unnecessary burden on hospital bed occupancy.

A raised cardiac troponin concentration is not just confined to myocardial injury from coronary plaque rupture or occlusion (primary ischaemic myocardial injury). Indeed, cardiac troponins are also raised in, and have been shown to be of prognostic importance in, many other conditions associated with secondary ischaemic injury,[17] such as coronary intervention and spasm, cardiac arrhythmias, large pulmonary emboli,[18] heart failure caused by idiopathic dilated cardiomyopathy,[19 20] hypertrophic cardiomyopathy,[21] and in conditions causing non-ischaemic myocardial injury, such as myopericarditis,[22 23] septicaemia,[24] cardiac trauma, and chemotherapy.[25] Cardiac troponins are also raised in and are of prognostic importance in some patients with renal failure,[26] although many such patients do not present with pain that is typical of myocardial ischaemia. There is currently no evidence that increases in cardiac troponins in patients with renal failure represent a ''false positive'' result[27]; however, the precise mechanism for raised cardiac troponin concentrations in this group of patients is uncertain. It remains unclear whether raised troponins outside the clinical context of acute coronary syndrome are representative of reversible or irreversible myocardial damage.

Although cardiac troponin measurements are of diagnostic and prognostic importance in patients with acute coronary syndromes, the broad range of conditions associated with raised cardiac troponin values has the potential for causing diagnostic confusion and generating clinical dilemmas in patient management. For example, should all renal failure patients with raised cardiac troponin concentrations be referred for coronary angiography, or should patients with a raised troponin after an episode of rapid atrial fibrillation or supraventricular tachycardia be diagnosed as myocardial infarction and undergo risk stratification investigations and be enrolled on a cardiac rehabilitation programme? Similarly, should patients on the intensive care unit with septicaemia or multiorgan failure and raised cardiac troponin be initiated on antithrombotic agents? These questions regarding clinical management emphasise the fact that sole reliance on raised cardiac troponin measurements for the diagnosis of myocardial infarction could

lead to inappropriate investigations and treatments that are potentially harmful and expensive. These issues are particularly relevant when one considers that up to 30% of patients with raised cardiac troponins do not have conventional acute coronary syndromes.[17]

> ''The broad range of conditions associated with raised cardiac troponin values has the potential for causing diagnostic confusion and generating clinical dilemmas in patient management''

Raised serum concentrations of cardiac troponins represent myocardial damage; however, this does not necessarily equate to myocardial infarction. It remains for the clinician to distinguish whether a raised cardiac troponin concentration is the result of coronary plaque rupture/occlusion or whether it has another cause. The specific diagnosis of the cause of myocardial damage can only be made after detailed clinical assessment, which should include a clinical history and serial ECG recordings. A raised cardiac troponin alone will never result in a clinical diagnosis, although one cannot detract from the fact that cardiac troponin measurements have been an invaluable step forward in the identification of high risk patients with acute coronary syndromes.

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