Cardiac troponin in cerebral injury: understanding your laboratory reports

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that elevated cTn indicates AMI.
It does not.'

Cardiac troponin (cTn) is now the 'gold standard' biochemical test for the diagnosis of acute coronary syndrome (ACS). This clinical spectrum of ischemic heart disease includes stable and unstable angina through to acute myocardial infarction (AMI). The growing evidence base for the diagnostic and prognostic use of cTn in ACS has resulted in the redefinition of AMI [1].

With increasing popularity owing to ease of measurement, the presence of a tick box on a laboratory request form and a reduction in test price, cTn is a common request in many clinical scenarios outside the remit of ACS. This has resulted in the identification of a plethora of elevated cTn in other conditions, often creating clinical confusion. With the redefinition of AMI, many emergency physicians could not adequately distinguish between a primary acute coronary syndrome and secondary ischemic or nonischemic disease states [2], plainly from ignoring the clinical history. A common misconception is that elevated cTn indicates AMI. It does not. All cTn elevations indicate myocardial cell necrosis [3] but not the pathological mechanism of release. Anecdotal data from a London teaching hospital demonstrate as many as 30% of all medical noncardiac admissions with elevated serum cTn do not have a final diagnosis of ACS [2].

Cardiac troponin T (cTnT) and cardiac troponin I (cTnI) are expressed in the cardiac myocyte. A small circulating pool exists in the cytosol, but greater than 90% is bound to the thin filament of the contractile apparatus. The cardiac isoforms are distinctly different in amino acid sequence from those expressed in skeletal muscle. Monoclonal antibodies have been raised against cTnT and cTnI and form the basis of immunoassay tests that have been in commercial use since the early 1990s [4].

Patients presenting to the emergency department with an acute cerebral injury may be cognitively impaired or exhibit severe speech

impediments. This hampers obtaining a full clinical history, including concomitant chest pain symptoms. Many of the risk factors for cardiovascular disease also contribute heavily towards the risk of developing acute cerebral ischemic disease states. The economic consequences of cerebral ischemia are extensive, consuming approximately 3% of total healthcare budgets [5] and a more crippling wider financial burden, with strokes costing the UK economy £7–8 billion in 2005 [6].

Cerebral injury commonly manifests as stroke, of which 87% are ischemic [7]. Elevated cTn occurs in approximately 10–30% of stroke patients [8–12]. Generally, elevated cTn during stroke episodes is prognostic; however, there is a lack of consensus between studies. This probably reflects the inappropriate cut-off used to define a positive cTn. Many studies quote an AMI cut-off value for cTn. This was based on the epidemiologically derived WHO definition of AMI, where 'enzyme' concentrations were deemed positive if they were twice the upper limit of normal. Many noncardiology-based studies adopting cTn since 2000 have continued to use this concentration to define a positive cTn.

Myocardial damage (myocytolysis) during stroke may result from intense activation of the sympathoadrenal system [13], resulting in cardiac arrhythmia [14]. cTn-positive patients demonstrate statistically higher blood adrenaline concentrations [12]. However, the increases in cTn are not correlated with the extent of insular damage [9,12]. This is contradictory to the findings of Ay and colleagues who demonstrated a correlation between cTnT and insular infarctions found in the right posterior insular cortex and inferior parietal lobule [15]. In this study, imaging was performed using diffusion-weighted magnetic resonance, which is superior to conventional CT; however, they also adopted a high cTn cut-off value derived from the WHO-derived definition.

The dogma has been that the concentration of cTn in the healthy individual was effectively zero, given the intracellular location of the molecule within the myocyte and its release from tissue during cellular necrosis. The 'normal' concentration of cTn in a healthy person theoretically

could be truly undetectable or at best below the detection limit of the assay employed. Recently an ultra-sensitive flow-based microparticle immunoassay with single-molecule counting has been developed. Using this assay, a normal distribution of cTnI in a healthy population has been observed [16]. This assay has determined the 99th percentile of 100 healthy subjects to be 8 ng/l. With the most sensitive commercial immunoassay on the market to date, the 99th percentile value can range from 0.02 to 0.04 ng/ml ($\mu\text{g/l}$), which is a number of orders of magnitude higher than the ultra-sensitive method. Therefore, current cTnI assay performance characteristics are determined by the limit of the detection methodology.

cTnT is manufactured by a single supplier owing to patent ownership, therefore direct comparison between studies is possible. However, cTnI is available from a number of manufacturers. The use of different antibodies directed against different epitope-binding regions does not allow direct comparison. A standardization program is currently underway and a reference material has been assigned to act as the calibrator for all cTnI methods [17]. Even with the success of the ongoing standardization program, each troponin assay should be validated in terms of its analytical performance as well as its diagnostic and prognostic clinical utility.

An updated universal definition of AMI was published in October 2007 with the aim of eliminating the clinical confusion surrounding diagnosis [18]. The use of cTn remains integral to the diagnosis, with a rise and/or fall in the kinetics. At

least one value in the sequence of measurement should exceed the 99th percentile of the upper reference limit, but this should occur in the appropriate clinical context, that is, in conjunction with evidence of myocardial ischemia.

Studies have demonstrated that patients with serum values above the 99th percentile confer a poor outcome for both cTnT [19] and cTnI [20]. These studies have been performed in chest pain populations. It is crucial that the 99th percentile value is adopted as the cut-off point to define a positive cTn assay in favor of the redundant WHO-derived AMI cut-off. This translation from the cardiology world to other clinical disciplines is essential in order to truly assess myocardial cell necrosis in patients with non-ACS primary pathology. Further studies of such patient groups are required using the sensitive cTn methods, adopting the appropriate cut-off points to assess the prognostic value of such elevations.

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