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BIOMARKER SPOTLIGHT
Biomarkers

Cardiac troponin T and I: back to basics

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Cardiac troponin T (cTnT) and cardiac troponin I (cTnI) are highly expressed in cardiomyocytes and therefore have become the preferred biomarker for detecting acute myocardial infarction (MI) and other causes of myocardial injury.[1] Currently, high-sensitivity cTnT and cTnI assays are considered equivalent for the diagnosis of MI.[1] Clinical laboratories usually implement either one of the assays, which in practice depends on the vendor of a clinical chemistry analyser used within the clinical laboratory.

The ternary cTnT–cTnI–TnC complex is part of the contractile apparatus of skeletal and cardiac muscle cells, with cTnT and cTnI being different proteins with different roles. In short, cTnT (35 kDa) binds the troponin complex to tropomyosin, cTnI (24 kDa) inhibits the blocking of myosin with actin filaments, and TnC (18 kDa) binds calcium upon stimulation and thereby triggers a conformational change in the interaction of myosin with actin. Both cTnT and cTnI are characterized by a cardiac specific N-terminal extension. In contrast, the same isoform of TnC is found in both cardiac and skeletal muscle. Most of the cTnT and cTnI is tightly bound to the sarcomere. It initially was estimated that around 5–10% of the total cTnT and cTnI content is less tightly bound. Originally, it was said to be 'cytosolic'. However, the experimental procedures of those original studies have been disputed. Recent work of Starnberg *et al.*[2] suggest that besides myofibril degeneration, cardiac troponin (cTn) release might also result from the washout of reversibly bound cTn (complex) to tropomyosin so that the pool of cTn that can be released early, the so-called early releasable pool, may be substantially greater than previously estimated.

Indeed, the kinetics of cTnT and cTnI following MI differ from each other in patients with atherothrombosis.[3] First, in the early hours after symptom onset, cTnI concentrations increase to much higher levels than cTnT. Second, cTnT concentrations follow a biphasic release curve and remain elevated a bit longer than cTnI concentrations (monophasic curve). Third, in contrast to cTnT, there are multiple cTnI assays commercially available, with each their own antibodies and other assay characteristics, and as a result, the dynamic range of cTnI concentrations differs significantly by both assay and vendor. This underlines the importance of assay-specific cut-offs when interpreting cTn concentrations for clinical applications. This is evident when using serial assessments in rapid diagnostic pathways.[1]Nevertheless, it is also important to consider for high-sensitivity point-of-care devices used outside of the emergency department, for example, in the ambulance or in the follow-up of outpatients for risk stratification in patients with chronic coronary syndromes or structural cardiac disease.

In the early days following the introduction of cTn as biomarker, it was perceived that cTn release was exclusively caused by cardiomyocyte necrosis and that the amount of cTn release was an accurate reflection of the degree of necrosis. However, contemporary studies observed significant increases in cTn in the absence necrosis. In some instances, apoptotic cell death is present. Nonetheless, the phenomenon of 'reversible' cell damage due to physiological myocyte turnover, proteolytic degradation, increased cell membrane permeability, and membranous blebs have been suggested as possible alternative mechanisms for cTn release. These may have particular relevance as recently updated in procedure-related MIs following cardiac surgery.[4] Interestingly, recent data have identified a new pathway for the maintenance of myocardial function in the face of an extremely low turnover of cardiomyocytes, whereby defective mitochondria and protein debris are ejected by exopher particles,[5] another potential way in which cTn could escape from cardiomyocytes. It is a fact that most cTn release mechanisms occur simultaneously and with interconnecting pathways.[6] Thus, translation of these new insights from experimental studies into clinical practice is challenging. Nonetheless, these mechanisms if explained may help to further increase the ability of cTn to inform and improve patient care.

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Data availability

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