Cardiac Troponin
Friend of the Cardiac Physician, Foe to the Cardiac Patient?

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Troponin, an important regulatory protein of the thin filament (actin) of striated muscle, is a complex of 3 subunits: C, T, and I. Troponin T and I isoforms from the heart are structurally different from the corresponding forms found in skeletal muscle. Because of this distribution, the measurement of cardiac troponin T and I isoforms is superior to other serum biomarkers of cardiac disease such as creatine kinase (CK)-MB and myoglobin because these proteins are released in patients with skeletal muscle disease or injury, as well as the heart. Recently, the European Society of Cardiology (ESC) and American College of Cardiology (ACC) have redefined acute myocardial infarction (AMI) to be predicated on the finding of increased concentrations of cardiac troponin in the clinical context of myocardial ischemia.1 These and other clinical practice guidelines2–4 have led to a steady decline in the use of CK-MB and myoglobin as diagnostic laboratory tests for MI. Because there is a high tissue content of troponin within myocytes, measurement of troponin T and I has become important for risk stratification of patients for short-term adverse events (cardiac death, MI, readmission for recurrent ischemia, and need for revascularization).

Autoantibodies and Macromolecular Complexes

Despite the widespread use of cardiac troponin as a cardiac biomarker for diagnosis and risk stratification, there are still several unanswered biochemical and pathophysiological questions with reference to the release and detection of troponin and the clinical consequences of its circulation in blood. With regard to troponin release, most cardiology and laboratory medicine experts believe that troponin appears in blood only after irreversible injury to the myocyte, given the size of the T (37 kDa) and I (24 kDa) molecules.5 However, Western blot analysis using denaturing gels has shown that much lower-molecular-weight N-terminal and C-terminal troponin T and I fragments appear in blood very early after the onset of AMI, before they are detected by commercial troponin assays.6 It is unknown whether these proteins originate from the breakdown of intact troponin after irreversible damage or reflect in situ degradation during reversible ischemia, as suggested by Murphy et al.7 Can low-molecular-weight peptides traverse across ischemic membranes to indicate ischemic injury, with the myocytes recovering their contractile function with restoration of coronary artery blood flow? If so, then detection of reversible ischemia by measurement of cardiac troponin will make this blood test even more useful than it is today. In an effort to improve the clinical utility of troponin and to meet the current recommendations of the ESC/ACC for assay precision, many manufacturers are formulating new troponin assays with detection limits that are 10- to 100-fold lower than current commercial tests. The use of more than the traditional 2 antibodies in the immunobod assay kit also may enable detection of additional troponin molecules in blood, including unstable fragments, and provide freedom from interferences such as unusual antibodies. These new generations may reopen this question of whether troponin can be released during reversible injury, particularly if these assays are directed toward the stable and the unstable epitopes of the troponin molecule.

Another complicating issue is the discovery that the release of cardiac troponin into blood can stimulate the production of autoantibodies.8 Although only recently discovered for troponin, autoantibodies to other serum biomarkers have been known for decades. Macromolecular complexes (autoantibodies bound to enzymes) have been described for many biomarkers such as salivary amylase,9 CK-BB,10 lactate dehydrogenase,11 and aspartate aminotransferase.12 These complexes have been found in healthy subjects, although they are detected more often in elderly subjects. The mechanism for autoantibody production is unknown. For amylase and CK, the specific salivary and BB isoenzymes are infrequently found, and it may be possible that they are recognized as foreign entities by the immune system. Macromolecular enzymes tend to have persistently abnormal activities in blood because of the reduced clearance rate of these high-molecular-weight complexes. As such, their presence can lead to false-positive test results. None of the studies on macrocomplexes has suggested that these biomarkers contribute to human pathology and are detrimental to human health.

In contrast to these macro forms, Eriksson et al13 have shown that troponin autoantibodies can produce false-negative results by blocking the binding of troponin antibodies used in analytical assays to the target protein. The effect is more pronounced at low troponin concentrations because the autoantibody titers can be overcome by release of high quantities of troponin.14 It may be possible that autoantibodies can mask any minor release of troponin in reversible injury, but this possibility has not been studied. In addition to the analytical interference to assays, troponin autoantibodies

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may have an undesired clinical consequence. Using mice deficient in the immunoregulatory receptor PD-1, Okazaki et al.\(^6\) showed that troponin autoantibodies induced dilation and cardiac dysfunction by the chronic stimulation of calcium influx in cardiomyocytes. These research studies have stimulated other investigations.

**Troponin Autoantibodies as a Contributor to Heart Failure**

In this issue of *Circulation*, Goser and colleagues\(^5\) also have suggested that when cardiac troponin autoantibodies are present, they can contribute to the progression toward heart failure. These investigators prepared and injected recombinant murine cardiac troponin T and I into mice and showed that autoantibodies to these antigens are produced. They further showed that immunized mice developed severe myocardial inflammation with increased expression of inflammatory cytokines. Over the course of 270 days, mice injected with cardiac troponin I, but not cardiac troponin T, developed cardiomegaly, fibrosis, reduced fractional shortening, and a 30% increase in the death rate over controls. One explanation of these apparently discordant findings between the 2 troponin subunits is that cardiac troponin I is found in both the intracellular compartment and the surface of ventricular cardiomyocytes, whereas cardiac troponin T is not found on the myocyte surfaces.

Are the results of these experimental studies in mice applicable to humans, given the observation that cardiac troponin autoantibodies have been independently demonstrated in serum by a separate research group?\(^7\) Goser et al have suggested that troponin autoantibodies are foreign antigens, given their contention that cardiac troponin T or I is not normally found in detectable concentrations in the blood of healthy subjects. This would suggest that the normal human heart does not release troponin into blood during the normal aging process of myocytes. Other organs such as the liver, skeletal muscle, and pancreas do not fit this model; they have measurable (baseline) activities of aspartate aminotransferase, total CK, and amylase, respectively, in the blood of healthy subjects, suggesting that these organs undergo regular turnover. On the other hand, some investigators have been able to reliably detect troponin in the blood of healthy individuals with next-generation assays that have detection limits that are 10- to 100-fold lower than current assays.\(^17\) If healthy subjects have measurable troponin circulating in their blood, then release after MI might not illicit an immune response. Nevertheless, these and other studies provide compelling evidence that autoantibodies do exist and can contribute to disease progression.

The clinical significance of these findings should be the focus of future clinical studies. Why do autoantibodies to troponin I induce myocardial inflammation, but anti-human antibodies to other cardiac proteins such as CK and lactate dehydrogenase do not? If autoantibodies can contribute to heart failure, it would be important to demonstrate that the incidence of these autoantibodies is higher among patients who suffer from AMI and progress to heart failure compared with AMI patients who do not develop heart failure. It is known that a minority of patients with chronic renal failure and other nonischemic origins have increased baseline troponin concentrations.\(^18\) Are these patients at greater risk for autoantibody production and hence heart failure? It also would be important to show that the removal by plasmapheresis, or blockage of their activity by anti-autoantibodies, results in a reduction in the incidence of heart failure caused by acute coronary syndromes. Alternatively, antiinflammatory treatment such as those drugs used to treat autoimmune diseases may be useful. Clearly, more basic and clinical science work is needed before such clinical trials can be conceived and approved by ethics committees.

Currently, there are no commercial analytical methods for detecting cardiac troponin autoantibodies. The commercialization process for a new laboratory test begins with demonstration of the medical utility for such measurement; ie, detection of antibodies leads to the implementation of successful management strategies to avoid or retard heart failure development and progression for patients with acute coronary syndromes. Then, ideally, an automated assay must be developed by manufacturers, validated by clinical laboratories, and cleared for routine use for patients by regulatory agencies such as the US Food and Drug Administration. Along the way, there may be intellectual property issues for the scientific discovery and licensing issues for the technology that must be considered. At the present time, the observations made by Goser and coworkers are interesting and pertinent to the practices of cardiology and laboratory medicine. Although the role of troponin as an aid in the diagnosis of AMI is well established and is a friend to the cardiac physician, this protein also may be a stimulus for troponin autoantibodies that lead to myocardial inflammation and heart failure and thus may be a foe to the cardiac patient.

**Disclosures**

None.

**References**


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