Troponin I, the Story

Jack H. Ladenson1*


In the early 1980s, David N. Dietzer and I started building a team to develop monoclonal antibodies to the isoenzymes then used for detecting cardiac damage: creatine kinase (CK)3 and lactate dehydrogenase. In the clinical laboratory, these tests, which had become widely used, entailed the use of electrophoretic procedures that took a few hours to perform. Although initially this approach was adequate, the advent of new therapies to open clotted arteries (streptokinase and tissue plasminogen activator, cleared by the US Food and Drug Administration in 1982 and 1987, respectively) placed a premium on prompt treatment. This conflict between the clinical need to treat within 4–6 h after a myocardial infarction (MI) and a laboratory procedure requiring 2 to 3 h led to “interesting” relationships between clinicians and clinical chemists. We were performing up to 7 routine electrophoresis runs of CK-MB isoenzymes a day, and internal medicine residents knew exactly when the cutoff time was for each run.

The laboratory team was Vonnie Landt (nee Maynard), who joined the laboratory in 1983 as research laboratory manager; Sharon Porter, who joined the laboratory as a technologist in 1986; and Hemant Vaidya, who began as a postdoctoral fellow in 1984. The laboratory expanded further when 3 additional postdoctoral fellows, Geza Bodor (1988), Emad Daoud (1989), and David Silva (1987) joined the laboratory.

The work with CK and lactate dehydrogenase proceeded well, and projects with additional cardiac proteins were started. Dave Silva developed a myoglobin assay that used 2 monoclonal antibodies, which is still used clinically (1). Emad Daoud worked on myosin light chains, which had been reported to be a specific cardiac marker (2). Emad’s work and later reports by Katus and others showed that the myosin light chains in skeletal and cardiac muscle were actually identical and therefore not a specific marker for cardiac damage. Geza Bodor worked with cardiac troponin I (TnI), which Cummins and coworkers had shown in the late 1970s to hold promise as a marker and which was known to be 40% dissimilar to skeletal TnI.

The work with TnI initially went a bit slowly owing to the “stickiness” of purified TnI. We even tried siliconizing our glassware. In the assay described in the featured report, we kept purified TnI in TnI-depleted serum, which resolved the problem. Another issue since resolved was our use of the Bradford protein assay to measure the concentration of purified TnI. We later changed to the more appropriate Lowry protein assay, which led to a downward shift in patient values.

As noted in the report, TnI in blood increases after an MI similarly to CK-MB, but it remains increased for a considerably longer time than CK-MB. Later work showed the half-lives of CK-MB and TnI to be similar, and we also found that cytoplasm contains 5% of the cellular TnI. The current thought is that the release of cytoplasmic troponin leads to the initial release of troponin and that the troponin complex is cleared from the myofibrils over time after an MI, which explains why it takes about 9 days to reach baseline.

Clinical validation of the assay was challenging because we now knew that CK-MB was not a true gold standard. Fortunately, I had excellent cardiology clinical researchers to collaborate with, in particular Allan Jaffe, Victor G. Dávila-Román, and Jessie Adams III. Allan and Victor devised a means of detecting an MI with serial echocardiograms, thus avoiding the need to use CK-MB as a gold standard. Once the specificity was established, a series of studies showed the value of TnI in many situations in which CK-MB was not sufficient (3).

The further development of TnI assays has led to high-sensitivity assays and has led to troponin in the blood being one of the requirements for the definition of MI (4), a relatively common, serious condition.

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1 Departments of Pathology and Medicine, Washington University School of Medicine, St. Louis, MO.

* Address correspondence to the author at: Departments of Pathology and Medicine, Washington University School of Medicine, Box 8118, 660 S. Euclid Ave., St. Louis, MO 63110. Fax 314-454-5208; e-mail ladenson@labmed.wustl.edu.

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2 This report has been cited more than 260 times since publication.

3 Nonstandard abbreviations: CK, creatine kinase; MI, myocardial infarction; TnI, troponin I.
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References