



Opinion

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The Evolution of Improved Diagnosis of Coronary and Vascular Disorders



Larry H Bernstein*

Triplex Medical Diagnostics, USA

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*Corresponding author: Larry H Bernstein, Triplex Medical Diagnostics, 54 Firethorn Lane Northampton, MA 01060, USA, Email: larry.bernstein@gmail.com

Opinion

The diagnosis of myocardial infarction leaped forward when Arthur Karmen [1] devised the spectrophotometric method for measuring aspartate aminotransferase (AST) in serum in 1954. Prior to this, there was only the electrocardiogram and characteristic chest pain. In these studies, Karmen [1] demonstrated that acute myocardial infarct and also hepatic necrosis can be determined by measuring the serum elevation of either AST or on the other hand, alanine aminotransferase. He also measured the NADH linked lactate and malate dehydrogenases, of which Kaplan [2] found had enzymes, of which H-type LD was used for the diagnosis of myocardial infarct and the M-type for the diagnosis of hepatic or muscle injury. The H-type LD was elevated to a peak on the second day after infarct. But these tests were followed by creatine kinase (CK) and the CK-MB isoenzyme, which had an earlier rise to peak and which Burton Sobel [3] demonstrated had additional value for measuring infarct size which drove a related goal to reduce infarct size by early intervention. This led to enormous and rapid advances in coronary artery vascular interventions.

The troponins I and T (cTn I or T) were introduced in the last decade of the 20th century. These proteins are cTnI, cTnT and cTnC the last of which is of no concern to this discussion. The troponins are located on the actin filament and are involved in skeletal and cardiac muscle contraction. Hugo Katus [4] first developed the cTnT, which has been measured exclusively on the Roche instruments by immunoassay. Consequently, the cTnI was introduced to satisfy the needs of a broad diagnostic market. The troponins are proteins that are found in cardiac muscle as part of the contractile apparatus and they are released into the circulation within 2-3hrs after onset of ischemia [5]. The percentage of troponin released that reaches the blood after cardiac injury is greater for troponin than for CK-MB, but ctns persist in the blood owing to the slow release and degradation of the structural pool [5] and the half-life of either cTn is 2hrs.

The measurement of the cTns has had an evolution through three major phases. In the original assays, the diagnostic cutoff for the first generation elevated markers was 0.08mg/ml for cTnT and 1mg/ml for cTnI. The first generation cTnT assay had a nonspecific tag antibody that cross-reacted with troponin T in skeletal muscle [5]. However, the TNT assay and its 99th percentile cutoffs and the 10% CV are well established. But even then, there was much variability for the cTnI diagnostic cutoff obtained on different analyzers that had to be reduced [6]. Further, in the Gusto IV trial the laboratory cTnT [6] assay identified an additional 96 (28%) of 337 patients with a positive TNT result but negative point-of-care TnI; these patients had higher rates of death or MI at 30 days. The above led to 2nd and then 3rd generation assays for both cTns to increase the sensitivity of both assays and to also reduce the assay variability to obtain the highest sensitivity. This came at a price, a biological variability unrelated to assay variability, which also was associated with decreased specificity. The symptoms of acute myocardial infarction (AMI) may be atypical or nonexistent and electrocardiogram changes may be absent or nonspecific. Consequently the 2000 joint committee of the European Society of Cardiology and the American College of Cardiology (ESC/ACC) issued new criteria [5] that emphasized that elevations in biomarkers are fundamental to the diagnosis of AMI.

Minor elevations in troponin levels have significant prognostic value [5]. Diagnostic elevations of troponin invariably have prognostic and therapeutic significance for patients with acute coronary syndromes and, increasingly, other entities such as heart failure and pulmonary embolism. There are more acute and more complex plaques, more extensive disease, more thrombi and reduced Thrombolytic in Myocardial Infarction (TIMI) flow grades when troponin levels are elevated [5]. Troponin elevations identify a group of patients who will benefit from therapy with delteparin and enoxaparin.

Patients with elevated troponin levels but negative creatine kinase MB (CK-MB) values are classified as non-ST segment elevation MI (NSTEMI), even in the absence of diagnostic electrocardiogram (ECG) changes. Similarly, only 1 elevated troponin level above the established cutoff is required to establish the diagnosis of acute MI, according to the ACC guidelines for NSTEMI. ACC/American Heart Association (AHA) guidelines recommend immediate reperfusion therapy for qualifying patients with ST-segment elevation MI (STEMI), without waiting for cardiac marker results [6]. It is important to keep in mind that myocardial necrosis can be a product of predominantly no ischemic myocardial injury, as occurs in association with heart failure, arrhythmia, myocarditis, renal failure, pulmonary embolism and percutaneous or surgical coronary procedures [5-8].

The National Academy of Clinical Biochemistry (NACB) working with the ACC/ESC guidelines has recommended adoption of the 99th percentile upper reference limit as the recommended cutoff for a positive troponin result. Ideally, the precision of the assay at this cutoff level should be measured by a CV that is less than 10%. But most TnI assays are imprecise at the 99th percentile reference limit [5]. In addition the true 99th percentile cutoff for a healthy patient population is actually a factor of 10-50 lower. In addition to its use in the diagnosis of MI, an elevated troponin level can identify patients at high risk for adverse cardiac events. The TnI-Ultra (cTnI assay) detects plasma cTn levels as low as 0.006mg/ml with an assay range that spans 4 orders of magnitude (0.006-50mg/ml) [8]. Similarly, the ElecsysTnT-hs (Roche Diagnostics; approved for clinical use in Europe) is as low as 0.005mg/ml. With high-sensitivity troponin assays, circulating cTnT or cTnI can be found in the plasma as a result of transient ischemic or inflammatory myocardial injury. Elevated cTn may be detected in conditions other than ACS, including heart failure, cardiomyopathies, myocarditis and renal failure, tachy arrhythmias and pulmonary embolism and even after strenuous exercise in healthy individuals [5-9]. Multiple randomized studies and several meta-analyses have substantiated the adverse prognostic risk associated with elevated cTn [10]. For example the meta-analysis by Ottani et al. [10]. Found that the odds ratio for death and MI was 3.44-fold at 30 days in the cTnT-positive group compared to patients with unstable angina. In addition, numerous randomized trials have found that patients with a positive troponin result benefit from a more intense ant thrombin or ant platelet treatment and also from an early invasive strategy and with respect to post percutaneous angioplasty (PCI), cTnI elevation following PCI correlated with an increased risk of adverse events at 18 months and a threefold elevation of cTnI after successful elective PCI was predictive for future cardiac events, especially for early repeat vascularisation. The universal definition of MI includes the typical rise and/or fall of cTn with at least one value above the 99th percentile of a healthy reference population accompanied by at least one of the following clinical factors: presence of ischemic

symptoms; electrocardiographic changes or imaging evidence of loss of viable myocardium or a new wall motion abnormality.

In view of the biological variability of cTn at the 99th percentile of a healthy reference accompanied by associated risks with non-AMI conditions, there is a residual opportunity to improve the use of these tests. This requires a more serious attention to the functionality of the electronic medical record which would substantially relieve an overload burden on the physician. There are two components that need to be considered. One component is the library of the patients, their laboratory records, their known conditions, their past medical and surgical histories, the radiological findings and the pharmacotherapy. The second component is an engine that analyzes the data in real time and lists the expected interpretation and presents the probability of the findings to the attending physician. It is all the more important to attend to this today in view of the current workload burdens physicians have. There is no question that this can be done and the task at hand will require a large database. Considerable work done with respect to this has not come into the mainstream. There are limited examples from work I have done with superb collaboration [11-20].

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