Editorial

Troponin—Keep Up or Be Left Behind

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The dawn of the new millennium ushered in a new era for cardiac marker testing. The European Society of Cardiology (ESC) and the American College of Cardiology (ACC) redefined myocardial infarction (MI) as "myocardial necrosis caused by ischemia" and designated troponin (Tn) as the "preferred" biomarker (1). The upper reference limit (URL) of Tn was specified to be at the 99th centile of a reference population, and the assay imprecision at this level should be 10% or less. Furthermore, the National Academy of Clinical Biochemistry (NACB) and the International Federation of Clinical Chemists (IFCC) recommend that Tn results should be available within 60 minutes (2). The ESC/ACC reiterated this position in their "universal definition of myocardial infarction" (3). The American Heart Association published a monograph on "Biomarkers in Heart Disease" in 2008 (4).

A review of the historic developments in Tn testing is informative (5). Tn comprises 3 subunits: T, I, and C, each with differing action (6). TnT and TnI are cardio-specific, but TnC is also present in skeletal muscle. TnT interacts with tropomyosin, while TnI promotes the binding of myocardial actin and myosin, and TnC enhances calcium binding in the Tn complex to produce myocyte contraction. The mechanism of Tn clearance from circulation remains unclear. Renal clearance, previously implicated because elevated Tn is often found in chronic renal failure, is now deemed unlikely (7). However, the reticuloendothelial system remains a possible candidate (8).

Until recently, laboratories struggled to meet the ESC/ACC 2000 criteria for Tn assay quality, and users assumed that detectable levels of Tn indicated myocardial injury, while undetectable Tn levels implied that no MI had occurred. That paradigm has shifted (9–11). Although the TnT assay is only available from one vendor (Roche Diagnostics) and is popular in Europe, the TnI assay is available from several manufacturers and is widely used in the USA. Both are equivalent in diagnostic utility for acute MI (AMI) and risk stratification. High-sensitivity (hs) Tn assays are superior to conventional Tn assays in the early detection of AMI (12,13). In patients with definite myocardial injury but negative TnI results by conventional assay, 64% had detectable TnI values in an assay with improved detection limits (14). Moreover, hs-TnT was able to predict evolving non-ST elevation MI (NSTEMI) earlier than a standard TnT assay in patients with suspected acute coronary syndrome (ACS) and negative troponin upon admission (15). Lest doctors be lulled into treating the Tn test result rather than the patient, it is important to adhere to NACB practice guidelines (16) for using Tn assays together with the clinical symptoms, ECG changes, or imaging evidence of cardiac ischemia. It is also prudent to recall the need for a temporal rise or fall in Tn levels in MI diagnosis (2,3,5). Hs-Tn assays also detect non-ischemic causes of myocardial injury or stress, and clinicians should be mindful of this fact to institute the appropriate diagnostic and therapeutic measures (17). The issue of Tn elevations after exercise, especially in marathon runners, needs to be re-examined with hs-Tn assays, as it might indicate the need to screen such subjects. Peri-operative and post-operative care should also include hs-Tn measurements for proper interpretation and risk assessment.

In stable coronary artery disease with preserved left ventricular function (n = 3679), hs-TnT levels were correlated with poorer outcomes (cardiovascular deaths and heart failure) over 5 years of follow-up (19). In middle-aged (mean 44 years) Japanese men without overt cardiovascular risk, elevated hs-TnT levels were positively correlated with cardiovascular risk factors (20).

The current challenges in assessing troponin levels are rapid analysis and high sensitivity. Moreover, we need to meet the desired door-to-balloon time (DBT) of less than 60 minutes (2) because outcomes (30-day and 1-year) are worse in those with prolonged DBT and are particularly poor when DBT exceeds 90 minutes. This service standard requires many other coordinated steps beyond analysis. The service experience in our 800-bed acute-care general hospital is as follows. Samples drawn from the emergency room (ER) or ward are sent to the lab, along with the lab request form, via pneumatic tubes. Samples are processed immediately on receipt. After order entry into the lab information system (LIS) and a 5-minute high-speed centrifugation (more than 2500 g), samples are analysed on an automated immunoassay system (Cobas 6000, Roche Diagnostics, Mannheim, Germany). The Cobas 6000 has a new 9-minute protocol, replacing the previous 18-minute assay. With 2 identical analysers in service, we achieve work standardisation, process simplification, and 100% up-time. We found the functional sensitivity of the assay (10% inter-assay coefficient of variation) to be 11.5 pg/mL. The 99th centile cut-off in our normal ambulatory subjects (n = 380) is 15 pg/mL for hs-TnT versus 30 pg/mL for the standard TnT assay. Once available, all results are transmitted to the requesting unit via the LIS, printed locally, and also deposited into the electronic medical record (EMR). Our mean turn-around-time (TAT) for hs-TnT is now 30 minutes versus 40 minutes with the previous 18-min protocol. For Tn samples received from the emergency department, 99% of the results are available within 60 minutes.

Another issue laboratories face is whether to report hs-Tn results in ng/mL or pg/mL. With the standard TnT assay, the units used were ng/mL and the cut-points were 0.03 ng/mL, as these were the units most clinicians reading US literature were familiar with. However, hs-TnT has improved lower limits of assay detection at 0.003 ng/mL with a cut-point of 0.015 ng/mL. There is a danger of clerical or typographical error occurring with so many decimal points. We recommend the use of whole numbers to reduce the chance of error: 3 pg/mL (lower limit of detection) and 15 pg/mL (99th centile URL). In addition, the improved hs-Tn assays now require an estimate of what constitutes a real significant change in Tn values given its inherent biological and analytical variation. Clinicians need to know how their hospital Tn assays perform, and laboratories must relay this information to the clinician.

More work remains to be done. However, new information is coming out fast and furiously. We must keep apace or risk being left behind.

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