A Novel Technology for Measuring Cumulative Cardiac Biomarker Exposure over Time: What Happened When We Weren’t Looking?

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Cardiac troponin testing is front and center for the diagnosis of acute myocardial infarction (MI) in patients with signs and symptoms suggestive of an acute coronary syndrome, and in the absence of an ST-segment elevation on their electrocardiogram. For at least 15 years, the troponin concentration on presentation or the peak value during hospitalization has been recognized to carry both short- and long-term prognostic information. More recently, longitudinal follow-up of biomarkers after an MI has led to the recognition that patients with persistent increases in cardiac troponin or natriuretic peptide concentrations also have a poor prognosis compared with post-MI patients who have a decrease in concentrations (1, 2). With the recent evolution to “high-sensitivity” cardiac troponin assays, which can achieve a 10-fold increase in low-end sensitivity compared with their contemporary counterparts, detectable troponin concentrations can now be measured in 25%–67% of the general population, depending on the patient’s age (3, 4). Even these low-level increases are not benign in these seemingly asymptomatic individuals, because such increases are associated with an increased risk of adverse cardiovascular events, including MI. Although cardiac imaging can provide some insight into the cardiac pathology underlying a persistent biomarker increase after an MI or in the general population, imaging still provides limited insight into a longitudinal process, given the cross-sectional nature of an imaging study. For example, in a patient with a high coronary calcium score according to computed tomography and an increased left ventricular mass by echocardiography, it is difficult to determine whether a detectable cardiac troponin concentration is due to a clinically unrecognized MI or to a persistent increase caused by myocardial pathology. Examples of 2 possible post-MI patterns for patients identified with a chronic troponin increase are shown in Fig. 1. Over an extended period of time, the patient with a second, now clinically silent MI would release more cardiac troponin in total than the patient with low-level chronic increases due to a nonacute coronary syndrome etiology, despite their having similar concentrations on retesting at a later time. Given that 22%–40% of MIs in the general population are clinically unrecognized (5), a percentage that is likely higher after a recent MI, a technology that could differentiate these high-risk patients from others with persistent small troponin increases could provide the opportunity to initiate disease-modifying therapy.

Differentiating a clinically silent or an atypical MI from nonacute coronary syndrome etiologies of increased troponin concentrations is only one of several scenarios in which interpretation by occasional spot checks of cardiac biomarker concentrations is problematic for clinicians. Another scenario that is occurring with increased frequency because of the evolution of chemotherapy is chemotherapy-related cardiac toxicity. The appropriate timing and frequency of cardiac biomarker measurements necessary to make this diagnosis is a source of debate. Lastly, there is increasing interest in the use of cardiac biomarkers, specifically the natriuretic peptides, to guide heart failure therapy in order to reduce hospitalizations and ultimately mortality. One of the limitations to the use of natriuretic peptides to guide therapy has been not only determining the optimal target for therapy but also deciding the frequency of testing, because the measurement-to-measurement variation can be substantial. One approach has been to increase the frequency of measurement, such as by including a home-testing approach. Even with such a system, which would be similar to the finger-stick glucose meter checks of diabetics, discerning the long-term efficacy of heart failure management may remain difficult.

Currently, there is no serum marker analogous to glycohemoglobin that would reflect the cumulative long-term release of markers of cardiac injury or their hemodynamics. A new technology may overcome this limitation, however, and make measurement of the total release of a biomarker over time a clinical reality. To address the conundrum posed by the clinical scenarios outlined above, Ling et al. have carried out an intriguing proof-of-concept study of a novel technology for

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measuring the cumulative biomarker exposure over an extended time that would be independent of the specific release kinetics of that biomarker (6). To accomplish this task, this group developed a subcutaneously implantable receptor that uses a new class of nanoparticle-based magnetic resonance contrast agents. These superparamagnetic iron oxide nanoparticles aggregate around analyte molecules and alter the transverse relaxivity surrounding water protons. The particles can be used to detect small molecules, including proteins, nucleic acids, oligonucleotides, peptides, receptors, ligands, and antibodies, and this technology is capable of quantifying small molecules that occur in blood at concentrations as low as the picogram-per-milliliter range. To prove the feasibility of their technology, the authors used an in vivo murine model to measure markers of myocardial injury (myoglobin, creatine kinase isoenzyme MB, and cardiac troponin I) that involved subcutaneous placement of a sensor containing the nanoparticles within a semipermeable membrane placed in the animal’s flank. They subsequently quantified the biomarkers via either sensor implantation or in situ interrogation for minimally invasive measurement of the cumulative “dose” of the biomarker present at different time points. Each sensor was specifically designed to measure a concentration interval of the biomarker of interest on the basis of the aggregate release expected after an MI. For example, in this murine model of left anterior descending coronary artery ligation, the sensor’s interval of detection was 100–1000 μg/L for creatine kinase isoenzyme MB and 10–100 μg/L for cardiac troponin I. The authors’ proof-of-concept experiments demonstrated that (a) the markers were present in the subcutaneous space at adequate concentrations shortly after their increase in the serum following an experimentally induced MI, (b) all 3 biomarkers detected by the sensors occurred at higher concentrations in animals with an MI than in the control animals, and (c) the biomarker concentration measured by the sensor was proportional to the size of the MI.

In summary, the experiments described by Ling et al. hold out the tantalizing clinical possibility of measuring cumulative cardiac biomarker release and potentially detecting new markers that cannot be measured reliably at the very low concentrations that may be present in the blood at any given time. As with any new technology and potentially new paradigm, however, multiple questions remain. The first question concerns the technology itself. As a clinician who would often like to think of high-precision immunoanalyzers as “magical” black boxes that can endlessly deliver reproducible measurements at single-digit picogram-per-milliliter concentrations, I am often brought back to the reality of the moment by an aberrant result that does not fit a clinical scenario. Technological limitations are common, particularly with respect to smaller point-of-care devices, and this novel technology for biomarker quantification will need to withstand the rigors of demonstrating continuously reproducible results with very good precision as it moves from “bench to bedside.” Second, because this sensor technology represents a new paradigm by changing cardiac biomarker measurement from an in vitro activity to an in vivo activity, there will be a host of new issues to consider, including ease of implant placement and recovery, safety, comfort, and reproducibility of measurements according to patient age, body habitus, and clinical scenario. Third, clinician and patient acceptance will also depend on the “added” value of quantifying cumulative biomarker release over time. Although several potential clinical scenarios were outlined above, acceptance of this implantable diagnostic device will most likely occur only if measurement of cumulative biomarker release can be shown to guide therapy to improve outcomes, compared with other competing technologies. Such a demonstration would include showing superiority to intermittent long-term measurements with high-sensitivity cardiac troponin assays to follow trajectories of concentrations in post-MI and other high-risk patients, or superiority to home testing of B-type natriuretic peptide with finger-stick technology in directing the therapy of patients...
with chronic heart failure. Overall, this nanoparticle-based magnetic resonance contrast agent sensor represents a fascinating opportunity to rethink the assessment of cardiac biomarkers with cumulative-release assessment. It is hoped that the developers will be able to further develop this technology so that its implications for patient care can be tested.

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References


