Cardiac biomarkers continue to play a prominent role in the diagnosis and management of patients who present to the emergency department with symptoms suggestive of acute cardiovascular disease. The use of cardiac troponin was reaffirmed in 2007 by the European Society of Cardiology, American College of Cardiology, American Heart Association, and World Heart Federation as the single most important biomarker for diagnosis of acute myocardial infarction (1).

For acute decompensated heart failure (ADHF), the American College of Cardiology and American Heart Association have opined that “measurement of B-type natriuretic peptide (BNP) can be useful in the evaluation of patients presenting in the urgent care setting in whom the clinical diagnosis of heart failure is uncertain (level of evidence: A)” (2). Despite these advances, some clinical needs are not met by measurement of troponin and the natriuretic peptides. For acute coronary syndrome, novel biomarkers are needed for the early diagnosis of acute myocardial infarction, e.g., at the time of emergency department presentation. Biomarkers are also needed for risk stratification for future short-term (30 days) adverse cardiac events (death and acute myocardial infarction). For acute heart failure, new laboratory tests are needed to complement B-type natriuretic peptide and N-terminal pro–B-type natriuretic peptide, because these markers are influenced by obesity, renal failure, and pulmonary disease (3).

In general, 2 strategies are employed for the discovery of novel biomarkers. The proteomic/metabolomic approach compares tissue and blood samples from diseased patients with similar samples from healthy or nondiseased individuals (4, 5) and investigates differences in the expression of proteins or breakdown products resulting from degradative enzyme leakage. This approach does not presume knowledge of the disease process or the identity or function of putative markers that are promising. The pathophysiology approach selects markers based on their role in signifying particular events known to occur in the cardiovascular disease process (6). For example, the weakening of the fibrous cap is an important facet of acute coronary syndrome (7), whereas apoptosis occurs in cardiomyopathies (8). Inflammation is a key component in both acute coronary syndrome and HF, and C-reactive protein is an example of a biomarker that is increased in both diseases.

One novel biomarker that has received significant research and commercial interest is myeloperoxidase (MPO). This enzyme is found in the azurophilic granules of promyelocytes, myelocytes, and neutrophils. MPO produces hypochlorous acid and other reactive molecules from hydrogen peroxide, a process that leads to lipid peroxidation and scavenging of nitric oxide. Because increases in these activities are found within atherosclerotic lesions, MPO is a marker of inflammation and plaque vulnerability. Several studies have documented the utility of MPO as a marker in risk stratification and in HF. Brennan and coworkers found that increased MPO was predictive of major adverse events occurring within 30 days and 6 months in patients whose laboratory results were negative for troponin T (9). In patients with chronic HF, MPO was also found to be highly diagnostic (10) and predictive of future long-term clinical outcomes (11), findings that remained significant in multivariate models after adjustment for age and B-type natriuretic peptide concentrations.

Few if any trials have been conducted to investigate the value of MPO in ADHF. Given that the natriuretic peptides are considerably increased in ADHF, one would expect similar findings for MPO. In this issue of Clinical Chemistry, however, Shah and coworkers report that in a cohort of patients presenting to an emergency department with dyspnea no differences in MPO were observed between patients with ADHF and those with either structural heart disease (chronic HF) or apparently healthy hearts (12). Such an apparent discrepancy in findings warrants a closer examination.

A starting point is the comparison of the methods used in these reported studies. Tang and coworkers (10, 11) used the Prognostix assay, which has been licensed to Abbott Laboratories, Inverness Medical, and Siemens Medical Solutions. The Siemens Dimension Rxl® was used in the study performed by Shah and coworkers. Although different antibodies are used in each method, a comparison of methods showed good correlation (Dimension = 1.03Prognostix + 32).
pmol/L; \( r = 0.977 \) \((13)\), suggesting that these antibody differences do not account for the discordances seen. Sample processing and stability are also potential sources of error. Shih and coworkers recently showed that MPO is reasonably stable and that EDTA is the preferred anticoagulant \((14)\). Fortunately, the samples used for MPO testing in each of these reports were collected in EDTA tubes.

Assuming that there is no analytical reason for this discordance, it becomes important to investigate other reasons to explain why MPO showed no diagnostic or prognostic value in patients presenting with acute dyspnea. A critical issue is the cutoff concentration used to determine abnormal results. In both of the reports by Tang and coworkers, MPO concentrations were divided into quartiles and tertiles in correlating results with clinical outcomes. Interestingly, the reported upper quartile limit at 400 pmol/L \((10)\) and upper tertile limit of 385 pmol/L \((11)\) were each below their respective upper 95th percentile limits for healthy individuals, 539 and 482 pmol/L, respectively, suggesting that diagnostic utility is conferred by MPO concentrations that are within the reference interval, a situation similar to what was observed when high-sensitivity C-reactive protein was implemented for cardiovascular risk assessment. Prognostix lists 640 pmol/L as the upper reference limit \((\text{http://www.prognostix.com/inner.aspx?PAGE_ID=15})\), further complicating the interpretation of these results.

In the study by Shah and coworkers on patients with acute HF symptoms \((12)\), mean reported MPO concentrations for all study patients were considerably higher (566 pmol/L) than those reported on chronic HF mentioned above. Although no reference interval was given, the manufacturer lists 633 pmol/L as the 95th percentile (R. Bauer, Siemens, personal communication, October 15, 2008), which is consistent with the correlation data observed previously between the 2 assays. Therefore when these reference limits are used, a larger fraction of patients who present with acute dyspnea would have abnormal MPO results compared to patients with chronic HF. Because MPO increases observed in the Shah et al. study occurred in all dyspneic patients, these data suggest that any disorder associated with shortness of breath is sufficient to stimulate MPO release, not just HF. A major limitation of most novel biomarkers previously studied has been their lack of specificity for a cardiovascular disease etiology. The findings of the study by Shah and coworkers confirm this notion for MPO and suggest that increases may not be directly linked to the remodeling within HF itself, but to the underlying inflammatory process leading to failure. One might also argue that MPO would have limited utility in chronic HF, unless all sources of non-cardiac acute or chronic inflammation are absent. A similar limitation has also been noted for the use of high-sensitivity C-reactive protein for primary risk stratification of cardiovascular disease \((15)\).

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