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Editorial

When the Myocardium Gets MIFfed: Macrophage Inhibitory Factor as a Biomarker in Acute Coronary Artery Disease

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See article by Zhao et al., pages 1366–1376 of this issue.

Survival after acute myocardial infarction has improved significantly in the past years and decades. Besides the developments in interventional treatment options, the increasing public awareness of typical symptoms has contributed to a reduced time lag between the onset of symptoms and intervention. However, the differential diagnosis of acute or chronic myocardial ischemia in patients who present with atypical symptoms can be much less straightforward.[1] Despite current guidelines that allow for 1-hour ruling in or out of non–ST-elevation myocardial infarction for certain high-sensitivity troponin assays, patients are often left anxious and stressed during the waiting period for the second troponin measurement. For other disorders like coronary microvascular disease, diagnostic plasma or serum markers have not yet been identified.

In contrast, diagnosing ST-elevation myocardial infarction (STEMI) is mostly straightforward on the basis of the electrocardiogram changes typical of acute myocardial ischemia, even when markers of myocardial damage (ie, creatine kinase [CK], CK-MB, or troponins), have not yet risen. Accordingly, biomarkers are less relevant for making a STEMI diagnosis despite unprecedented sensitivity and specificity. Nonetheless, these biomarkers have a rightful place in predicting secondary adverse events (eg, mortality or development of heart failure), despite being less sensitive and specific in this case. In addition to supporting the identification of high-risk patients, novel biomarkers might also provide new mechanistic insights and thus drive development of innovative therapeutic avenues.

In this issue of the *Canadian Journal of Cardiology*, Zhao and colleagues[2] set off to study the role of macrophage migration inhibitory factor (MIF) as a predictor of clinical prognosis in STEMI patients. Although its name suggests otherwise, MIF mostly displays proinflammatory effects.[3] MIF was one of the first cytokines described. When discovered in 1966, in the context of delayed hypersensitivity reactions, MIF was considered a cytokine of the adaptive immune system with T cells as its main source.[4,5] Besides T cells, various myeloid lineage cells but also other tissues, including endocrine organs involved in stress responses, have since been shown to produce MIF.[6] Although most cytokines are produced in response to internal or external triggers, MIF is constitutively expressed. This enables a rapid response comparable with that of the innate immune system. Indeed, accumulating evidence shows that MIF forms an integral part of the innate immune system, among others upregulating Toll-like receptor 4 expression.[7] Accordingly, MIF has been associated with numerous inflammatory processes and disorders, including atherosclerosis and acute myocardial infarction.[8,9]

The current study of Zhao et al.[2] in this issue of the *Canadian Journal of Cardiology* addresses the important issue of patient outcome, for which appropriate biomarkers are still lacking. In their cohort of 498 STEMI patients, MIF did not improve prediction of short-term outcomes such as in-hospital mortality, when corrected for confounders. However, MIF was associated with long-term major cardiovascular events, a relationship that could not fully be explained by high-sensitivity troponin, CK-MB, or N-terminal prohormone of brain natriuretic peptide (NT-proBNP) peak levels in a multivariable model (adjusted hazard ratio, 1.2 [95% confidence interval, 1.06-1.33]; $P = 0.003$). Because MIF is secreted by a multitude of cells, its origin is difficult, if not impossible, to pinpoint. Nevertheless, it seems reasonable to speculate that leukocytes and especially neutrophils form the main source in this population, because of their pivotal role in myocardial ischemia and early reperfusion damage and the early MIF concentration peak. Although the findings of Zhao et al.[2] might not be of immediate clinical value to treating physicians, because diagnostic assays for MIF meeting the In Vitro Diagnostic Regulation (IVDR) requirements are not yet available, they add to the growing body of evidence supporting the role of the immune system in atherosclerosis and the diagnostic potential of peripheral blood cells in coronary artery disease.[10] In coronary angiography patients, hematological biomarkers, including leukocyte count, percentage of neutrophils, percentage of monocytes, and the coefficient of variance of neutrophil complexity obtained before

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angiography is predictive of mortality and, comparable with the study of Zhao et al.,[2] performed better than high-sensitivity troponin I or NT-proBNP, alone or combined.[11]

Despite the similar kinetics of leukocyte numbers and MIF concentrations after admission, the mechanism that results in increased MIF concentrations in STEMI patients remains unclear. Cardiac ischemia has been shown to induce rising MIF levels.[12] C-reactive protein (CRP) correlated with MIF concentrations 1-2 days after STEMI in the study of Zhao and colleagues,[2] suggesting that MIF might either reflect myocardial infarct size or proinflammatory status. Although MIF levels did not correlate with other typical inflammatory markers such as increased white blood cell count or CRP at admission, it correlated with the myocardial injury marker CK-MB. This led the authors to the conclusion that the observed early rise of MIF level in their cohort can most likely be ascribed to the ensuing myocardial injury rather than reflecting the patient's inflammatory status. However, this conclusion might be premature, because inflammation and extent of tissue damage are closely interwoven and probably not separable from each other.

Inflammatory biomarkers (eg, neutrophil to lymphocyte ratio[13] or lymphocyte to monocyte ratio[14]) have been shown to associate with unfavourable outcome in comparable studies. Another biomarker that has frequently been reported to predict increased mortality or secondary events in various diseases is red blood cell distribution width (RDW). Although counterintuitive at first sight, because it is derived from red blood cells rather than white blood cells, RDW correlates with low-grade inflammation and CRP and not only associates with long-term mortality in coronary artery disease patients, but also predicts other complications like postoperative pneumonia in cardiovascular surgery patients.[15] Furthermore, hematological parameters including RDW, immature reticulocyte fraction, coefficient of variation of neutrophil lobularity, and mean lymphocyte cell size were associated with higher coronary artery calcification scores in cardiac computed tomography.[16] Identifying cause and result or the contribution of inflammatory status and the extent of tissue damage to (inflammatory) biomarker concentrations might prove to be as difficult as finding the answer to the proverbial question: "what came first, the chicken or the egg?" Although finding the answer to the latter generally does not affect our daily life, unraveling the intertwined mechanisms of injury and inflammation could very well affect clinical routine in the future, difficult as this might be.

Considering these challenges, one might wonder: do we really need yet another biomarker in cardiovascular medicine that will not make it into routine clinical application? Probably not. However, we still need a broadly applicable and cost-effective prognostic biomarker for secondary cardiovascular events to better predict the clinical outcome of our STEMI patients, and—most importantly—we need biomarkers that provide actionable insights. Although a single biomarker like MIF is unlikely to fulfil these ambitious goals, the results of Zhao et al.[2] might help to further unravel the intricate role of the immune system in coronary artery disease patients and put into perspective existing literature on the role of leukocytes in myocardial infarction. At the very least, this study again underscores the predictive value of blood-based markers.

Disclosures

The authors have no conflicts of interest to disclose.

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