Myocardial Infarction and Inflammation

Lost in the Biomarker Labyrinth

Michael Hristov, Christian Weber

atherosclerosis as a persistent arterial disease is characterized by an imbalanced lipid metabolism and maladaptive immune response, resulting in subendothelial lipoprotein retention and endothelial activation with continuous migration of leukocytes and smooth muscle cells to the inflamed intima. Over decades, this leads to the formation of stable atheromas that induce chronic tissue ischemia or of vulnerable plaques that cause acute occlusive atherothrombotic complications, such as myocardial infarction and stroke. As such, atherosclerosis and its consequences remain the leading causes of mortality and morbidity in Western countries. Acute myocardial infarction (AMI) often occurs as the first and fatal manifestation of atherosclerotic coronary artery disease. In general, AMI represents a typical sterile inflammation with release of inflammatory cytokines, platelet activation, leukocytosis, and hyperglycemia. The pathophysiological and laboratory parameters of AMI are monitored at admission after confirming the diagnosis only; however, this hampers any consideration and distinction of the very critical interval between initiation of myocardial ischemia, with the first symptoms of AMI of- ten being imprecise or rather nontypical, and hospitalization. Numerous animal studies have provided detailed experimental and clinical atherosclerosis becomes increasingly characterized by an imbalanced lipid metabolism and maladaptive immune response, resulting in subendothelial lipoprotein retention and endothelial activation with continuous migration of leukocytes and smooth muscle cells to the inflamed intima. Over decades, this leads to the formation of stable atheromas that induce chronic tissue ischemia or of vulnerable plaques that cause acute occlusive atherothrombotic complications, such as myocardial infarction and stroke. As such, atherosclerosis and its consequences remain the leading causes of mortality and morbidity in Western countries. Acute myocardial infarction (AMI) often occurs as the first and fatal manifestation of atherosclerotic coronary artery disease. In general, AMI represents a typical sterile inflammation with release of inflammatory cytokines, platelet activation, leukocytosis, and hyperglycemia. The pathophysiological and laboratory parameters of AMI are monitored at admission after confirming the diagnosis only; however, this hampers any consideration and distinction of the very critical interval between initiation of myocardial ischemia, with the first symptoms of AMI often being imprecise or rather nontypical, and hospitalization.

In this issue of the journal, Liebetrau et al provide intriguing evidence in humans by taking advantage of ethanol-based transcoronary ablation of septal hypertrophy (TASH) in 21 patients with hypertrophic obstructive cardiomyopathy as a clinical model to induce AMI. This model allows for precise definition of the exact time point of myocardial ischemia. By using TASH, the authors intended to screen early release kinetics of some soluble inflammatory biomarkers and leukocyte subsets within 24 hours of myocardial injury. They found a sustained elevation in interleukin (IL)-6, C-reactive protein, neutrophils and classical CD14+CD16− monocytes, whereas sCD40L levels were decreased (Figure).

In fact, the same group has recently published studies with identical design and on the same patient collective. Their results revealed the release kinetics of additional early ischemic biomarkers in the setting of TASH-induced AMI, such as cardiac troponin-T, NT-proBNP, s-Fit1, microRNAs, ischemia-modified albumin, and heart-type fatty acid–binding protein. A common conclusion implied that all these biomarkers may harbor a certain diagnostic value in the setting of AMI. Yet, the questions remained unanswered which of the biomarkers has a major effect and whether a single biomarker or rather the combination of >1 biomarker (eg, in a panel) are useful for routine measurement during the onset of AMI? This clearly mandates the need for more conclusive research with solid prospective data on outcome and correlation to cardiac function and the extent of myocardial necrosis in larger patient collectives.

Given that TASH is an elective even though forceful catheter intervention, the AMI evolving after alcohol-induced myocardial ablation seems reminiscent but not identical to atherosclerosis-related AMI, which usually results from acute atherothrombosis after plaque erosion or rupture and is accompanied by profound platelet activation. Unfortunately, the current study does not provide evidence on platelet function, but the lack of increased sCD40L may indeed indicate that platelets are much less affected during TASH. Moreover, most of the patients with AMI display a history of multivessel coronary artery disease and are often preconditioned with statins that are well-known to exert not only cholesterol lowering but also anti-inflammatory effects. This medication may substantially attenuate the early increase in inflammatory biomarkers of AMI. Yet, the questions remained unanswered which of the biomarkers may harbor a certain diagnostic value in the setting of AMI. Yet, the questions remained unanswered which of the biomarkers has a major effect and whether a single biomarker or rather the combination of >1 biomarker (eg, in a panel) are useful for routine measurement during the onset of AMI? This clearly mandates the need for more conclusive research with solid prospective data on outcome and correlation to cardiac function and the extent of myocardial necrosis in larger patient collectives.

Furthermore, the findings on the early (15–120 minutes after TASH) and sustained increase of neutrophil numbers are noteworthy. In addition, classical monocytes started to increase 8 hours after ablation with significant rise at 24 hours. These results correspond well to a sequential myeloid response also observed after AMI in mice. In mice, AMI liberated hematopoietic stem and progenitor cells from bone marrow niches via sympathetic nervous system signaling, increasing monocyte recruitment to plaques and exacerbating atherosclerosis. Epidemiological data have also verified leukocytosis as an independent risk factor and predictor of future cardiovascular events. In particular, neutrophilia on admission is associated with impaired left ventricular recovery after AMI, and the overall effect of neutrophils as emerging players in experimental and clinical atherosclerosis becomes increasingly appreciated. Likewise, monocytes negatively correlates...
with ejection fraction and independently predicts heart failure and mortality after AMI. The observed increase in myeloid subsets after AMI can be explained either by augmented mobilization or by attenuated apoptosis. In this regard, one study has reported a pronounced, cytokine-mediated delay of neutrophil apoptosis in acute coronary syndrome.

Liebetrau et al have also monitored IL-6 as a proinflammatory cytokine. IL-6 levels rapidly increased after inducing myocardial ischemia and showed a continuous elevation during all subsequent time points. In this setting, other members of the interleukin family, such as IL-1β and IL-10, would have been of interest as well. For example, IL-1β exerts similar pro-inflammatory actions as IL-6 and orchestrates the production of inflammatory mediators in leukocytes and vascular cells. In contrast, IL-10 rather provides anti-inflammatory effects. Comprehensively monitoring the release kinetics of other relevant anti-inflammatory and homeostatic mediators (eg, TGF-β, CXCL12) should be even more conclusive to unveil the complex balance of inflammation in the context of early myocardial ischemia. Subsequent bioinformatics network analysis may be instructive to further dissect out the most important contributors in a labyrinth of individual and cross-interacting biomarkers.

The general recommendation for the treatment of AMI comprises reperfusion of the target coronary artery, preferably through percutaneous catheter intervention with stent implantation. The accessory routine medical treatment includes analgesia, inhibition of coagulation and platelet aggregation, renin–angiotensin–aldosterone system inhibitors, β-blockers, and high-dose statins. However, these established strategies do not fully cover the inflammatory and immune mechanisms during the onset of AMI. Hence, emerging and innovative concepts in the treatment of AMI are urgently needed. In this regard, more powerful therapeutics, such as cytokine antagonists (eg, against IL-6), specific chemokine receptor blockers, or modulating antimicroRNA strategies, may become instrumental to selectively attenuate local myocardial inflammation during the acute phase, although sustaining the simultaneous influx of regenerative myeloid subsets during the chronic phase of AMI. Such a pioneering drug development requires stringent evaluation of effectiveness, which undoubtedly will have to rely on surrogate biomarkers, such as in the present study.

In summary, the clinical model of TASH-induced AMI used seems to be an interesting and unique alternative to experimental research. Although offering new insights into the release kinetics, the data may help to identify optimal time points for measurements, thereby extending beyond a confirmatory and descriptive nature. Although various soluble and cellular biomarkers have been identified, their predictive value alone or in conglomerate remains largely unknown. Above individual paths in the labyrinth, an aerial perspective on complementary biomarkers suitably covering vascular inflammation should be developed using high-throughput technologies for transcriptional, proteomic, or metabolic profiling. Such comprehensive methods should not only identify new biomarkers of interest but also establish their combination into multiple biomarker panels as an integrated approach with higher predictive and diagnostic potential also after AMI.

**Sources of Funding**

This work was supported by the Deutsche Forschungsgemeinschaft (SFB 1123-A1).

**Disclosures**

None.

**References**


**Key Words:** Editorial ■ cytokines ■ ischemia ■ leukocytes