Acta Cardiol Sin 2017;33:486–488
Editorial Comment
doi: 10.6515/ACS20170731A

Profiling the Evolution of Inflammatory Response and Exploring Its Prognostic Significance in Acute Myocardial Infarction: The First Step to Establishing Anti-Inflammatory Strategy

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Acute myocardial infarction (AMI) is defined as myocardial tissue necrosis owing to abrupt decrease in coronary arterial blood supply, of which the most common cause is atheroma-mediated thromboembolism. From the onset of acute tissue necrosis to the later healing process, a myriad of inflammatory reactions are involved in the pathophysiology of AMI.[1] Through up-regulation of pro-inflammatory cytokines [such as tumor necrosis factor (TNF), interleukin (IL)-6, and IL-1β] and activation of toll-like receptor/p38 mitogen-activated protein kinase (MAPK) signaling pathway,[2] necrotic tissue triggers innate immune responses and leukocyte infiltration to remove tissue debris for the following tissue repair. While timely reperfusion to viable, but ischemic myocardial tissue has been demonstrated to be effective in confining the extent of myocardial necrosis in acute phase,[3] experimental evidence has shown that, prolonged and over-reactive necrotizing inflammation could worsen myocardial damage and cause detrimental left ventricular (LV) remodeling.[1] For restraining necrotizing inflammatory reactions in a timely manner, anti-inflammatory subsets of leukocytes are then recruited and transformed to avoid excessive myocardial damage and to facilitate healing process, including CD14+CD16+ monocyte,[4] reparative M2 macrophages, and regulatory T lymphocytes. Of note, transforming growth factor β has been recognized as the key mediator to activate anti-inflammatory process and profibrotic reparative pathways.[1] Epidemiological evidence has indicated that in AMI patients, elevated serum levels of TNF and IL-6 raised the risk of mortality, and increased IL-1β was associated with developing heart failure.[5] Hence, great interest has been taken in anti-inflammatory strategies for limiting over-reactive necrotizing inflammation. However, clinical studies did not, thus far, provide consistent evidence that suppressing inflammatory reactions with specific or non-specific drugs could reduce the infarct size or improve prognosis in AMI.[3] Recently, a large phase 3 trial enrolled 3,503 AMI patients receiving losmapimod, a P38 MAPK inhibitor, or placebo before coronary revascularization or reperfusion therapy, to investigate whether suppression of necrotizing inflammation in acute phase could lead to prognostic benefit.[6] The disappointing results showed that 12-week use of losmapimod, as an anti-inflammatory agent, did not reduce the risk of major cardiovascular events, though levels of C-reactive protein and N-terminal pro-BNP were significantly reduced.[6] The failure to translate anti-inflammatory therapy into a favorable clinical outcome might be partly due to the failure to identify high-risk patients with over-reactive inflammatory status and the appropriate timing for anti-inflammatory treatment administration to restrain necrotizing inflammation and to facilitate reparative process. Given that, much effort is required to establish biomarker-based assessments germane to distinct inflammatory pathways for effectively profiling temporal evolution of complex inflammatory reactions.

Systemic inflammatory response syndrome (SIRS) is characterized by a constellation of basic clinical and laboratory features in patents with sepsis.[7] SIRS is defined if two of the four readily available features are present: 1) body temperature less than 36 °C, or greater than 38 °C;

Received: July 13, 2017 Accepted: July 31, 2017
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2) heart rate greater than 90 per minute; 3) respiratory rate greater than 20 per minute; 4) white blood cell (WBC) count less than 4,000 per mm^3, or greater than 12,000 per mm^3. The four features of the syndrome indicate the severity of systemic inflammation induced by sepsis, and subsequent pathophysiological responses caused by imminent septic vasodilatory shock. Afterwards, the SIRS assessment of systemic inflammation and relevant pathophysiological reactions are also applied to non-infectious conditions, such as pancreatitis, burns, and trauma.[8] Similarly, prior research has demonstrated the course of AMI and post-infarct LV remodeling involves complex inflammatory reactions.[1,5] Therefore, Huang WC and his colleagues conducted a retrospective study to explore the association between AMI prognosis and the severity of inflammation assessed by SIRS.[9] The retrospective study included 330 AMI patients, of which 116 were diagnosed with ST-elevation MI (STEMI). In the Issue of the Journal, the authors showed that, in patients with AMI, the presence of SIRS was significantly associated with increased risk of all-cause mortality and cardiovascular events at one year, though the association between SIRS and cardiovascular events attenuated after confounding factors were taken into consideration. Their findings were consistent with previous reports that the AMI patients with the presence of SIRS were more likely to have poor prognosis.[10,11]

However, there are some concerns on applying SIRS assessment for risk-stratification in AMI. First, assessment criteria of SIRS are not specifically designed to assess inflammatory status in AMI. The construct of SIRS is aimed at assessing the severity of sepsis-related inflammation and impending vasodilatory shock, which is distinct from the pathophysiological and hemodynamic alterations in AMI. Relative to the other three criteria, WBC count is more relevant to inflammatory status, and it has been reported that the risk of heart failure and mortality in AMI is raised with increasing WBC counts.[12] Although increased heart rate is also a prognostic predictor in patients sustaining AMI,[13] the relevant cause of tachycardia might be cardiogenic rather than inflammation. The concern has been evidenced by the findings of an early study analyzing a pooled data from the COMplement inhibition in Myocardial infarction treated with Angioplasty (COMMA) trial and the COMPlement inhibition in myocardial infarction treated with thromboLYtics (COMPLY) trial.[11] The study enrolled 1,843 patients with STEMI, of which 296 were classified as having SIRS. The findings showed that, among the four criteria, only WBC count and heart rate were associated with increased risk of 90-day death, cardiogenic shock, heart failure, and stroke after adjusting confounding factors. The authors also pointed out that WBC count and heart rate together accounted for 94.6% of SIRS-associated risk for poor prognosis. Provided the evidence above, it would be warranted to establish specific criteria dedicated to assessing inflammatory reactions in AMI, other than the non-specific SIRS. Second, lack of specific biomarkers in SIRS criteria results in inability to accurately profile temporal evolution of discrete inflammatory pathways. It would limit the application of biomarker-guided anti-inflammatory treatment in a timely manner. Third, SIRS assessment has uncertain discriminatory performance with regard to risk-stratification in AMI patients, as compared with the established prediction models like the Global Registry of Acute Coronary Events or the Thrombolysis In Myocardial Infarction risk models.[14-16]

For improving LV remodeling and preserving LV contractility, there is an urgent need to develop novel therapies to restrain prolonged and excessive inflammatory reactions after AMI. Constructing specific assessments for temporal profiling of inflammatory status, and establishing their relationships with clinical prognosis would be the fundamental steps to formulating effective strategies to modulate over-reactive necrotizing inflammation in AMI. As a result, we will be able to identify high-risk patients who could benefit most from anti-inflammatory therapies.

DISCLOSURES

All authors have nothing to disclose.

CONFLICT OF INTEREST

None declared.

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