Can Anti-inflammatory Therapy Prevent Atrial Fibrillation in Myocardial Infarction Patients?

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diovascular diseases still remain one of the greatest health challenges. While the incidence and case-fatality rate of acute myocardial infarction (AMI) have decreased with the development of medications and reperfusion therapy, the disease burden of complications has increased. Arrhythmia in the setting of AMI is an adverse prognostic factor, and atrial fibrillation (AF), the most frequent supraventricular arrhythmia, is associated with the increased risk of short-term and long-term mortality. In addition, AMI patients with AF have more comorbidities as compared to patients in sinus rhythm, which relate to a higher re-infarction rate, higher stroke rate, and higher risk for heart failure. The presence of AF requires anti-coagulant therapy for the prevention of strokes, although anticoagulant drug administration plus dual anti-platelet therapy after percutaneous coronary intervention would increase the risk of bleeding and a variety of clinical trials have been conducted to evaluate alternative regimens. Hence, the prediction and prevention of atrial fibrillation as a complication of AMI could be a meaningful strategy. In patients with left ventricular dysfunction secondary to AMI, treatment with an angiotensin-converting-enzyme (ACE) inhibitor could reduce the incidence of AF in the chronic phase. Carvedilol has been shown to suppress AF and atrial flutter in a similar patient population, according to a sub-analysis in the the CAPRICORN study. Additionally, atorvastatin significantly reduced the incidence of postoperative AF after elective cardiac surgery. However, there is limited evidence suggesting that upstream medical therapy reduces the incidence of AF as primary endpoint. It is deemed desirable to provide preventive therapy tailored to risk stratification with respect to new-onset AF associated with AMI.

Zhang, et al. investigated the expression of Toll like receptors (TLRs) on the surface of peripheral blood mononuclear cells (PBMCs) in AMI patients. They collected blood samples before any reperfusion therapy within two hours after AMI onset, and divided the clinical subjects into two groups: patients with new-onset AF in 1 month after AMI (AFMI group) or without (MI group). The results showed that the expressions of both TLR2 and TLR4 in PBMCs in the MI group were higher than that in healthy volunteers, and much higher in PBMCs in the AFMI group. Protein assay and flow cytometry analysis also showed a significant difference in TLR2 and TLR4 expression. With respect to the TLR adaptor proteins, myeloid differentiation factor 88 (MyD88) and TIR domain-containing protein-β antibody (TRIF-β), their protein levels were significantly higher in the AFMI group than in the MI group as well, indicating that the TLR2 and TLR4 pathway was surely augmented in PBMCs in the AFMI group. Of note, these differences were already found in the very rapid phase of AMI onset.

Evidence to support the involvement of the inflammatory process in the pathophysiology of AF has been increasing for decades. Several epidemiological studies have reported that higher levels of inflammatory markers such as C-reactive protein (CRP), interleukin (IL)-6, and IL-8 could predict the development of AF. With respect to AF in the setting of AMI, a higher level of CRP in an early phase (within 24 hours) was also associated with its occurrence. However, one large prospective cohort study revealed that increases in CRP levels due to genetic polymorphisms did not increase the incidence of AF. This result suggests that CRP per se does not have a pathophysiological role. On the other hand, comorbid systemic inflammation was related to AF onset in the same cohorts. With regards to cellular components, myocardial biopsies of patients with lone AF showed that activated lymphocytes infiltrated the atrial myocardium with necrosis of the adjacent myocytes, which was compatible with myocarditis. In peripheral blood as well, activation of T lymphocytes was observed in patients with paroxysmal or persistent AF more often as compared to healthy control individuals. Concerning monocytes, it was reported that TLR2 levels in PBMCs of the AF group were significantly higher than those in the control
AMI induces eflux of inflammatory monocytes from the spleen. Zhang, et al. showed that the number of TLR2^hi^ TLR4^hi^ monocytes in the bloodstream predicted AF occurrence associated with AMI even at an early phase.

In another case-control study, flow cytometric analysis of monocyte subpopulations revealed that lone AF patients had a higher proportion of circulating intermediate CD14^+^CD16^+^ monocytes than the controls,23) although several papers have recently revealed that the cell counts of intermediate CD14^+^CD16^+^ monocytes independently predicted cardiovascular events.24) Pre-existing inflammation does not only initiate AF, but these inflammatory processes also further enhance the structural remodeling of atrial myocardium to perpetuate arrhythmia. At the same time, activated vascular endothelial cells promote the attachment of white blood cells, which subsequently contributes to the development of a proinflammatory and prothrombotic environment.16) That is to say, inflammation could be both a cause and a consequence of AF, which would be one of the explanations of the so-called “AF begets AF”. It can be stated without doubt that inflammatory cascades are implicated in the initiation and sustainment of AF associated with AMI, although its pathophysiology could be different from that of lone AF.

It is now obvious that an inflammatory response characterized by an influx of immune cells is induced in atherosclerotic plaque. It is also reported that “MI begets MI”. Heart attacks promote inflammatory monocyte production in the spleen via activation of the sympathetic nervous system, and activated monocytes move to an atherosclerotic lesion to form vulnerable plaque.25) The latest evidence showed that therapeutic antibody targeting IL-1β led to a significantly lower rate of recurrent cardiovascular events.26) Diseases subject to anti-inflammatory therapy will prevail in the cardiovascular field. From that perspective, the present findings are promising for discerning the risk of AF in the setting of AMI at an early phase. In this article, the expression of TLR2 and TLR4 in PBMCs of AMI patients had an association with AF onset,40) but it is uncertain whether PBMCs expressing high levels of TLR2 and TLR4 themselves are initiators of AF, and whether high TLR2 and TLR4 PBMCs are the same population as low TLR2 and TLR4 cells. In any event, further studies will be needed to develop a novel strategy against AF in the setting of AMI, and anti-inflammatory therapy to inhibit AF will be one of the candidates for improving the mortality of AMI and suppressing its burden.

**Disclosures**

**Conflicts of interest:** None.

**References**


