Interleukin-8 and atrial fibrillation

Vojtech Melenovsky1* and Gregory Y.H. Lip2

1Department of Cardiology, Institute of Clinical and Experimental Medicine (IKEM), Vidsenska 1958/9, 140 21 Prague 4, Czech Republic; and 2Haemostasis, Thrombosis and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham, England, UK

Online publish-ahead-of-print 3 June 2008

This editorial refers to 'Source of inflammatory markers in patients with atrial fibrillation' by I. Liuba et al.,† on page 848

A large number of studies have now documented that atrial fibrillation (AF) is often associated with inflammation.1 Given that AF predisposes to stroke and thrombo-embolism and is associated with a hypercoagulable or prothrombotic state, the causal relationship among these 'partners-in-crime'—that is, inflammation and thrombosis—is still a matter of intense debate. Besides its intellectual thrill, this quest may have very practical implication in pinpointing specific targets for the prevention of AF or stroke.

The relationship between AF and inflammation is evident when studied locally in atrial tissue or at the level of 'whole' organism, using biomarkers in the systemic circulation. Examination of atrial biopsies from subjects with paroxysmal AF but without other cardiovascular disease documented myocarditis confined to atria in almost 2/3 of cases.1 Another example is AF in post-thoracotomy patients where inflammatory pericarditis is a significant contributor. Indeed, sterile pericarditis induced by talcum dust in dogs when studied locally in atrial tissue or at the level of 'whole' organism, AF patients often demonstrate signs of low-grade systemic inflammation as evidenced by the elevation of inflammatory biomarkers in the systemic circulation, such as C-reactive protein or interleukin-6 (IL-6).1,3,4 In large cohorts, the linkage between the presence of AF and elevations of inflammatory biomarkers seems rather strong given that C-reactive protein elevation is proportional to AF burden and the persistence of AF4 as well as the future risk of AF development.3

In most patients, AF does not exist on its own, but may be part of a broader cardiovascular ailment, such as hypertension, atherosclerosis, or heart failure. Because each of these disease entities associates itself with inflammation, it remains uncertain whether observed elevation of C-reactive protein stems from AF itself or from co-morbid conditions. Indeed, adjusting for potential confounding clinical variables, such as the presence of vascular disease, blurs the difference in C-reactive protein between patients with chronic AF and controls.5 In contrast, complete elimination of supraventricular arrhythmia (e.g. atrial flutter) by means of isthmus ablation leads to significant fall of C-reactive protein and IL-6 at 6 months after the procedure, which provides a good argument for independent role of tachyarrhythmia per se as a cause of inflammation.6

An interesting contribution to this debate is the paper by Liuba et al. in which the authors measured C-reactive protein, IL-6, and interleukin-8 (IL-8) in samples obtained from multiple sites of the circulation in patients with paroxysmal or permanent AF with a low burden of concomitant disease. Their findings that C-reactive protein and IL-6 levels were not significantly elevated in either form of AF when compared with controls is in line with a report from larger set of patients with lone AF.7 In contrast, they were able to demonstrate significant elevations of IL-8 in the femoral vein, right atrium, and coronary sinus in patients with permanent AF when compared with controls or paroxysmal AF. As IL-8 levels were not elevated in coronary sinus blood and IL-8 levels were lower in the pulmonary veins, the source of this cytokine is presumably extracardiac and extrapulmonary.

This interesting observation clearly raises several questions. First, it suggests that there may be more specific humoral factors associated with AF or actually 'driving' the prothrombotic inflammatory state, rather than the 'traditional' ones such as C-reactive protein or IL-6. Previous studies comparing chronic AF and controls showed that levels of tissue factor in patients with AF persisted even after statistical adjustments for co-morbid conditions, in contrast to C-reactive protein or IL-6 that fell off as non-significant after adjustments;5 a similar case might be seen here with IL-8. After all, statistical adjustment cannot account for all biological processes and pathophysiology.

Second, why there is a difference between these two cytokines? Although often 'put together' into one simplistic...
category of ‘inflammatory mediators’, IL-6 and IL-8 may differ in their sources, biological effects, and prognostic role. Although IL-6 is a key activator of the acute phase response and a major determinant of C-reactive protein synthesis in the liver, IL-8 belongs to different family of CXC chemokines whose members serve as chemo-attractants for neutrophil granulocytes. Interestingly, the capacity of elevated IL-8 to predict future risk of coronary artery disease was confirmed in EPIC-Norfolk study, and importantly, was completely independent of C-reactive protein levels, which suggest some divergence of IL-8 and IL-6-mediated effects.

Third, what are the sources of IL-8 release in systemic circulation? In the absence of infection, significant amounts of IL-8 and other cytokines can be released from adipocytes and macrophages in adipose tissue, particularly in obese subjects. In this study, there was no significant difference in body mass index between the groups, so the source of IL-8 lies probably elsewhere, or so we hope. Besides macrophages, IL-8 is also synthesized by endothelial cells where is stored in Weibel-Palade bodies, thin organelles of endothelial cells that are laden mainly with von Willebrand factor and P-selectin. Upon endothelial activation, these substances are rapidly emptied onto endothelial surface, helping white blood cells to slow down, roll on endothelium, attach to it, and then cross the endothelial cell barrier. The observed increase of IL-8 in patients with concurrent AF might be therefore related to endothelial activation, perhaps due to local perturbations in shear stress related to the irregular or fast heart rate. Lastly, IL-8 may be directly involved in the modulation of platelet–platelet and platelet–leukocyte interactions.

Due to low number of participants, the result of the study should be interpreted with some caution but the many intriguing questions it raises clearly show that more research is needed. The study is also hampered by the absence of additional parameters which would help to interpret the sources of IL-8 elevation. However the study remains unique, given the observations that point towards possible relation between lone AF and systemic IL-8 release.

Conflict of interest: none declared.

Funding
V.M. is supported by grant MZO-00023001 from the Czech State Department of Health, Czech Republic.

References