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Editorial

Chronic Osteomyelitis and Atrial Fibrillation: Revisiting the Link Between Inflammation Burden and Arrhythmia

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See article by Hsiao et al., pages 1388–1395 of this issue.

Inflammation has long been established as part of the pathophysiology of atrial fibrillation (AF) development.[1] The prevalence and prognosis of AF is associated with various inflammatory biomarkers.[2] The mutual inter-relationship between inflammation and AF is complex, with multiple inflammatory pathways involved in AF initiation and perpetuation, often in the context of underlying comorbidities. In addition, abnormal atrial fibrosis has been well documented in patients with AF, with added contributions from inflammation, with monocytes/macrophages playing a significant role.[3,4]

A large body of evidence points to atrial fibrosis as a major factor contributing to the structural remodelling that takes place in AF.[5] This is further emphasized by the presence of inflammatory infiltrates in atrial tissue of patients with AF.[6] Progressive atrial fibrosis leads to increased frequency of AF paroxysms, which in turn increase the likelihood of progression toward permanent AF. With subsequent irreversible structural changes that occur within the atria secondary to inflammation and fibrosis, the role of antiarrhythmic drugs for rhythm control becomes less effective.

Of the inflammatory mediators evidenced in AF, monocytes appear to play a central role. In 1 recent study, there was a significantly higher proportion of $CD14^{++}CD16^{+}$ monocyte subsets (Mon2) compared with controls, with Mon2 being independently associated with the presence of AF.[7] Also, Mon2 is the main producer of reactive oxygen species and has been found to be a predictor of future cardiovascular events.[8] However, it is unclear what the exact mechanism is by which Mon2 contributes to AF, although a possible link is through its modulating atrial remodelling and fibrosis. In samples of left atrial appendage, monocyte-derived macrophage migration is found to be greater in patients with AF vs patients with sinus rhythm, together with adhesion molecules and cytokines.[9]

In this issue of the *Canadian Journal of Cardiology,* Hsiao et al.[10] highlight the role of inflammation as a risk factor for the development of new-onset AF. In this retrospective cohort study, patients with newly diagnosed osteomyelitis were identified, and subsequent cases of AF, death, or withdrawal were recorded from the well-validated Taiwan National Health Insurance database. In this analysis of 19,002 patients with osteomyelitis and 76,008 controls, AF developed in 2.2% of patients with chronic osteomyelitis (COM). The study showed a significant predisposition to the development of AF in the COM cohort (hazard ratio, 1.33; 95% confidence interval, 1.18-1.49; $P < 0.0001$). Interestingly, young patients with COM had a higher risk of permanent AF developing compared with their non-COM counterparts. Furthermore, Hsiao et al.[10] demonstrate that the association between COM and the occurrence of new-onset AF remained in a frequency-matched population for all variables. Moreover, patients with COM and new-onset AF had a higher incidence of stroke and mortality than did the non-COM cohort.

There are important limitations to the study by Hsiao et al.,[10] 1 being the detection of asymptomatic AF. Recent large-scale cohort studies have highlighted the impact of "silent" AF on risk of stroke and increased mortality, likely because of the reduced uptake of oral anticoagulation agents.[11] Much focus is now on AF screening programs, given the promising results for improving the uptake of stroke prevention.[12]

In a wider context, the study by Hsiao et al.[10] further expands our knowledge about the contribution of inflammation to the development of new AF. Indeed, recent studies have shown the role of Mon2 monocytes in patients with AF when compared with controls.[13] The availability of sophisticated flow cytometry analyses provides more evidence for various inflammatory cells that link inflammation with multiple cardiovascular disease states (eg, atherogenesis and

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coronary ischemia, heart failure, and AF), and chronic inflammatory conditions such as COM.[14-16]

Can inflammation burden improve risk stratification in patients with AF? Various inflammatory biomarkers have been studied in AF, and the addition of any biomarker is likely to improve risk stratification (whether for thromboembolism or bleeding) of clinical scores based on clinical factors alone.[17] Nonetheless, the improved prediction of inflammatory biomarkers over clinical risk scores is still modest (although statistically significant) but raises major issues about simplicity and practicality for "quick" decision-making when used in busy clinics or wards.[17]

However, despite the complexity of adopting inflammatory biomarkers in the clinical decision-making for AF management, this remains a targeted area of research with therapeutic potential. We have known for the past 25 years from initial work analyzing tumor necrosis factor α in patients with chronic heart failure that inflammatory cells (and more specifically, cytokines) play key roles in the pathogenesis of cardiovascular disease.[18] Building on these facts, positive correlations have now been found with nuclear factor-κB and interleukin-6 cells in AF. Biomarkers more specific for fibrosis are now well established, including matrix metallopeptidase 9, type III procollagen, and high-sensitivity C-reactive protein, all of which are raised in relation to left atrial volume and atrial remodelling.[19] Furthermore, postmortem analysis of atrial tissue shows monocyte-derived macrophages that are highly localized to the subendocardium of atrial tissue in patients with AF.[20]

We should also be aware that inflammation and thrombogenesis are also intimately linked. Unsurprisingly, inflammation has been implicated in multiple stages leading to AF-related thrombogenesis. Three key areas have been highlighted by which inflammation increases thrombogenesis, as follows: endothelial damage, platelet and endothelial cell activation, and coagulation cascade activation. The key to all 3 mechanisms is the disturbance in endothelial integrity that initiates an inflammatory cascade and subsequent thrombogenic response.[21,22]

Despite such convincing evidence for the role of inflammation in AF, anti-inflammatory interventions have yielded disappointing results thus far. For example, statin drugs have cardiovascular benefits beyond that of cholesterol lowering, and animal models of AF have shown a reduced incidence of AF, hypothesized to result from a suppression of oxidative and inflammatory stress on endothelial function.[23] Further research has also pointed to a beneficial role of statin drugs as having an antithrombotic effect.[24] Antioxidant vitamins (namely, vitamins C and E) may have beneficial effects on atrial remodelling, but long-term animal studies have not been able to reproduce the suppression of adenosine triphosphate—induced electrical remodelling found in shorter-duration animal studies.[23] Other more sophisticated methods of suppressing specific cytokine release (which have been successful in many systemic inflammatory conditions) have failed to provide a successful transition to cardiovascular disease and in some cases signalled harm.[25] Hence, more needs to be done to establish a clinical role for suppressing inflammation associated with AF.

In line with therapeutic aims, inflammatory conditions such as COM often coexist with the recognized risk factors for stroke, which mandate the initiation of oral anticoagulation. Although the possibility of heightened stroke risk with COM does exist, the options for "enhanced" oral anticoagulation under such circumstances are lacking. Thus, despite intriguing studies such as that by Hsiao et al.,[10] the fundamental role of stroke prophylaxis remains the cornerstone of AF management. After initially identifying patients at low risk of stroke who do not require any antithrombotic therapy, the next step is to offer stroke prevention to those with ≥ 1 stroke risk factors, given the positive net clinical benefit of oral anticoagulation, even with a single risk factor.[26,27] This is irrespective of whether we have a CHA_2DS_2-VASc (**C**ongestive Heart Failure, **H**ypertension, **A**ge [≥ 75 years], **D**iabetes, **S**troke/Transient Ischemic Attack, **Va**scular Disease, **A**ge [65-74 years], **S**ex [Female] **sc**ore) of 2, or 8 or 9, or whether we add 1 or even 10 inflammatory biomarkers to improve risk prediction (at least statistically): the therapeutic decision to offer stroke prevention has already been made.

In summary, there is extensive evidence for inflammation as an underlying pathophysiological mechanism in AF. However, AF may be the cause or indeed the consequence of inflammation. As yet, inflammatory biomarkers are not well established in AF risk stratification, and their practical value for everyday decision-making is probably questionable. Studies such as that by Hsiao et al.[10] confirm the role of chronic inflammation in AF, but with anti-inflammatory agents providing disappointing results, the way forward remain uncertain.

Disclosures

G.Y.H.L. is a consultant for Bayer/Janssen, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo and is a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo. The other authors have no conflicts of interest to disclose.

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