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Editorial

Behçet's disease: A (silk) route to atrial fibrillation?

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Atrial fibrillation (AF) is the most common sustained arrhythmia closely associated with inflammation [1]. The development of AF involves an array of electrophysiological and structural changes including shortened refractoriness, slow conduction, triggered activity, fibrosis, and enlarged atrial size, etc. as well as dysfunction of multiple ion channel proteins at either transcriptional or posttranslational levels [2]. Multiple canonical inflammatory signaling pathways including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and 'NACHT, LRR, and PYD domains-containing protein 3' (NLRP3) inflammasome have been linked to arrhythmogenic mechanisms underlying AF development [1,3]. Behçet's disease (BD), predominantly found in people with ancestors from the ancient Silk Road countries, is a chronic and multisystemic vascular inflammatory disorder affecting mucocutaneous, genital, ocular, and vascular organ systems along with others [4]. Although BD has been linked to various inflammation-related disorders, its association with AF has not been established. In the current issue of *International Journal of Cardiology*, Lee et al. performed the first nationwide population study to evaluate the potential correlation between BD and the risk of AF [5]. Lee et al. showed that the risk of AF was doubled in BD patients compared to non-BD individuals. History of heart failure and stroke, age, cardiovascular co-morbidities, male sex and number of admissions are independent risk factors of AF in the patients with BD. Cardiovascular complications camouflaged the effect of BD on AF exhibiting a weaker correlation between BD and AF in patients with cardiac abnormalities. This study goes in corroboration with other reports published by the same group where they have established the higher incidence of AF with inflammatory bowel disease and ankylosing spondylitis using the Korean National Health Insurance Service database [6,7]. Such growing evidence makes the association between chronic inflammatory diseases and increased risk of AF even stronger.

Several considerations need to be kept in mind when evaluating this study. Since this is an observational cohort study and the findings were extrapolated from the patient data collected between 2010 and 2014, several potentially useful biochemical data were not available at the time of analysis. Levels of the sensitive inflammatory biomarkers such as C-reactive protein (CRP), IL-6, etc. in BD patients were not measured; therefore, the correlation between AF incidence and the inflammatory status and severity of BD cannot be directly established. Due to the rare nature of BD in European countries and the United States, case-control or retrospective cohort study could be designed to learn epidemiology of BD in the future to overcome this drawback. Additionally, the current study provides limited insights into the causative mechanisms underlying AF development as a consequence of BD. A previous study has shown that the left atrial (LA) volume (a predictor of AF) is increased in BD patients [8], suggesting the structural remodeling caused by BD could provide a reentry substrate for AF development. Future experimental studies with animal models should be designed to determine the key molecular pathways altered by BD that can promote LA remodeling and AF. Furthermore, it is well established that AF risk increases with aging [9]. However, one very interesting finding from this study is that the effect of BD on AF risk is more prominent in young men (≤40) than older men (≥ 65). Aging did not exert additional risk or synergistic effect on AF incidence in BD patients. This suggests a non-aging related cause could be the direct link between BD and AF pathology. It would be remarkable to find out plausible reasons for the development of AF at a young age in the context of BD.

It is worth pointing out that Lee et al. found immunosuppressant and TNF-α inhibitor therapy increases AF risk in BD patients [5], which corroborated with their ankylosing spondylitis study showing similar results [7]. Meanwhile, several anti-inflammatory and immunosuppressive medications like methotrexate, etanercept, and azathioprine have been associated with AF in patients with rheumatoid arthritis and psoriasis [10]. These evidences together indicate the potential challenge of targeting inflammatory signaling or inflammation as a new frontline anti-AF strategy. Because of the dynamic nature of inflammation processes and the complexity of multiple inflammatory signaling pathways, a cell-specific or tissue-specific approach would be much more appreciated in investigating the mechanisms of inflammation-caused AF and developing more effective and safer anti-AF target. Since the pathophysiology of AF is multifaceted, seeking a nodal signal that potentially modulates multiple arrhythmic events perhaps can provide a desirable target for drug development. In conclusion, patients with BD or any other chronic inflammatory disorders, especially those on TNF-α inhibitor therapy and with cardiovascular risk factors, should be screened periodically for early signs and symptoms of AF to improve their quality of life.

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