Atrial fibrillation (AF) is a highly prevalent arrhythmia associated with significant morbidity and mortality because of the hemodynamic impairment and thromboembolic events. AF affects 1–1.5% of the population worldwide; it has been estimated that 2.2 million people in the USA and 4.5 million in Europe have paroxysmal or persistent AF. The estimated prevalence of AF was 0.6% in the Japanese general population in 2005, and it will increase to 1.1% in the 2050s. AF is often associated with structural heart disease; however, a substantial proportion of patients with AF have no detectable structural heart disease.

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AF has a complex pathophysiology, showing both electrical and structural remodeling. Over the past 10 years, great progress has been made in understanding the electrical remodeling caused by AF. Numerous studies have confirmed that atrial electrical remodeling occurs within a wide range of atrial tachyarrhythmias, and leads to shortening of the atrial effective refractory period and decreases in the atrial conduction velocity. Subsequent work has revealed that many of the AF-promoting effects of atrial tachycardia-induced electrical remodeling are mediated by alterations in ion channels. Rapid atrial pacing leads to progressive decreases of the L-type calcium channel (I_{CaL}). The results of electrophysiological studies of the action potential suggest that the reduction in I_{CaL} is an important determinant of atrial action potential shortening and refractoriness changes observed in response to AF. There is evidence that the sodium channel (I_Na) is also decreased during AF. The reduction in I_{Na} may contribute to the atrial conduction delay commonly associated with AF. By decreasing the wavelength, the atrial conduction delay may also favor multiple-circuit reentry. Therefore, the role of electrical remodeling in AF has significant potential relevance for AF therapy.

On the other hand, the structural remodeling in AF, including atrial dilatation and fibrosis, occurs in parallel with the changes of electrical remodeling. Studies of patients and animal models suggest the importance of atrial fibrosis in the development of AF. It is reported that the selective atrial fibrosis induced by cardiac overexpression of a constitutively active form of TGF-β1 is sufficient to increase AF inducibility. Atrial fibrosis might lead to subsequent impairment of atrial conduction and increase AF vulnerability by creating a substrate for atrial re-entry circuits. In the transgenic mouse with selective atrial fibrosis, vulnerability to AF is increased in the absence of a change in the atrial effective refractory period. The alterations in atrial structure lead to increased conduction heterogeneity in the atrium and a decrease in conduction velocity. Therefore, the alteration in atrial conduction produced by atrial interstitial fibrosis, persists, is sufficient to induce AF. There is increasing evidence that AF is associated with inflammation, with previous studies identifying a potential link between inflammation and AF. AF is frequently associated with inflammatory conditions, such as cardiac surgery, myocarditis and pericarditis. The concept that inflammation contributes to AF is supported by the frequent occurrence of AF after cardiac surgery. The temporal course of AF occurring after cardiac surgery closely follows the activation of the complement system and release of proinflammatory cytokines. There is evidence of atrial myocarditis in patients with lone AF, and results of atrial biopsies taken from patients with AF compared with controls have demonstrated evidence of inflammatory infiltrates and oxidative damage within the atrial tissue. In this issue of the Journal, Yamashita et al. investigate the active adhesion and recruitment of macrophages across the endocardium in human fibrillating atria, thereby supporting a concept of a local immunologic inflammatory responses around the atrial endocardium in AF. Inflammation and oxidative injury promote structural remodeling, so inflammation appears to be involved in the early phase of structural or electrical remodeling and thus promotes AF. Furthermore, abnormal changes in systemic inflammation have been related to prothrombotic indices, suggesting that inflammation could also drive the hypercoagulable state in AF. The relationship between inflammation and AF is further evidenced by the increase in C-reactive protein (CRP), interleukin-6 and tumor necrosis factor-α in both paroxysmal and persistent lone AF. Compared with subjects in the first CRP quartile (<0.97 mg/L), subjects in the fourth quartile (>3.41 mg/L) had more AF (adjusted odds ratio: 1.8). In both the cross-sectional and the longitudinal studies, CRP remained a significant predictor of AF, even after adjustment for multiple risk factors for AF, including hypertension and coronary heart disease.

The association of inflammation with AF has potential therapeutic implications. There are various therapeutic strategies for modulating CRP levels, including statin treatment. Numerous subsequent studies have shown that interventions that affect inflammation or oxidative stress, such as statins, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, may reduce the occurrence of AF. How-
ever, treatment with valsartan or rosuvastatin was not associated with a reduction in the incidence of AF in recent reports.\textsuperscript{11,12} Although inflammation may be a pathogenic factor for AF, the clinical role of antiinflammatory drugs remains controversial.

References