Atrial fibrillation (AF) is one of the most common arrhythmias in clinical practice, and is associated with an increased risk of stroke, heart failure, and overall mortality. The occurrence of AF increases with age, with prevalence rising from 0.5% of people in their 50s to nearly 10% of the octogenarian population. Several cardiac disorders predispose to AF, such as mitral valve disease, coronary artery disease, pericarditis, congestive heart failure, and thyrotoxic and hypertensive heart diseases. Many of these are thought to promote AF by increasing atrial pressure and/or by causing atrial dilation. AF also occurs in individuals without any other evidence of heart or systemic disease, known as ‘lone AF’.

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Recent multicenter studies have demonstrated no difference in mortality between AF patients who were treated by rhythm-control drugs and those taking rate-control drugs, but rhythm control is preferable for patients with symptomatic paroxysmal AF in terms of quality of life. Because the efficacy of antiarrhythmic drugs is limited, catheter ablation has been used for rhythm-control therapy in patients with drug-refractory AF. For catheter ablation of lone paroxysmal AF, circumferential electrical isolation of the 4 pulmonary veins (PV) is effective because the triggered firing and arrhythmogenic substrate of the AF is usually located in and/or around the ostium of the PVs. On the other hand, additional ablation in the atria is required in patients with persistent AF, because structural remodeling in the left atrium (LA) plays an important role when AF is persistent.

In this issue of the journal, Kim et al report that high plasma concentrations of transforming growth factor-β (TGF-β) and tissue inhibitor of metalloproteinase-1 (TIMP-1) and low ejection fraction were closely related with electroanatomical remodeling. Accumulation of ECM proteins has been documented in biopsy specimens of the LA from patients with AF, and experimental studies using animal models have indicated that interstitial deposition of dense ECM proteins causes separation of the bundles of atrial myocytes and disturbs cell-to-cell impulse propagation. Dense and disorganized collagen deposition with apoptosis or necrosis of cardiomyocytes reduces the voltage of the contact atrial electrogram and enlarges the LA volume; that is, electroanatomical remodeling.

Thus, electrical remodeling and structural remodeling are not independent of each other and together may promote and maintain AF, as Kim et al term it ‘electroanatomical remodeling’. In addition, atrial fibrosis potentially exaggerates myocardial ischemia by impeding oxygen diffusion and alters the electrophysiological and biomechanical properties of atrial myocytes, allowing the initiation and perpetuation of AF.

**TGF-β**

The development of adverse structural remodeling within the course of AF is mainly characterized by an interplay between...
fibroblasts and paracrine signaling proteins such as TGF-β1, which is secreted by both cardiomyocytes and fibroblasts and acts as a primary downstream mediator of angiotensin II effects in both autocrine (influencing the cells that produce angiotensin II/TGF-β1) and paracrine (influencing adjacent cells) manner. Angiotensin II induces TGF-β1 synthesis, which potently stimulates fibroblast activity. In turn, TGF-β1 reciprocally enhances the production of angiotensin II and additional profibrotic factors to create positive feedback. Profibrotic signals such as angiotensin II and TGF-β proceed ECM remodeling. The profibrotic signals induce a local inflammatory process and proliferation of myofibroblasts, resulting in collagen deposition and a barrier to impulse propagation. TGF-β1 acts primarily through the SMAD protein pathway to stimulate fibroblast activation and collagen deposition. Cardiac over-expression of constitutively active TGF-β1 causes selective atrial fibrosis, atrial conduction heterogeneity, and AF promotion. Moreover, it has been reported that LA diameter, but not left ventricular function, significantly correlates with the TGF-β1 serum level, which supports the hypothesis that the blood level of TGF-β1 may be associated with LA enlargement as a consequence of chronic AF. In accordance with that report, Kim et al showed that a high plasma concentration of TGF-β1 was related to a low mean LA voltage and enlarged LA volume. The greater the extent of cardiac fibrosis the higher the chance of developing recurrent or even permanent AF alongside heart failure.

**TIMP-1**

Inflammatory infiltrates have been observed in the atrium of AF patients and in animal models. Furthermore, inflammatory biomarkers, such as C-reactive protein, are elevated in AF patients and associated with the presence of AF and the future development of AF. However, it remains to be fully elucidated how inflammation is linked to the development of structural remodeling in a susceptible AF substrate in the stressed heart.

The matrix metalloproteinases (MMPs) constitute a family of zinc-dependent proteinases that participate in the degradation of ECM components. They are mainly regulated by TIMP. Decreased concentrations of MMP-1 (the most important enzyme in the extracellular degradation of collagen) and raised levels of its inhibitor, TIMP-1, have been noted in hypertensive patients, and appear to be associated with depressed extracellular degradation of collagen type I, especially in patients with left ventricular hypertrophy. It has been proposed that inflammation promotes the increased MMP activity that leads to left ventricular and atrial dilatation, but with chronic inflammatory signaling there is a decrease in the MMP/TIMP ratio and consequently greater collagen content. These findings suggest diminished collagen degradation, which could be interpreted as more myocardial fibrosis. Plasma TIMP-1 (the molecule that inhibits collagen degradation) has been proposed as a non-invasive marker of interstitial fibrosis. The results of Kim et al’s study are in accordance with those from a previous study which found a decreased level of MMP-1 and an increased level of TIMP-1 in plasma samples from patients suffering from AF compared with a control group in sinus rhythm. Thus, the balancing of MMP and its antagonist TIMP may regulate ECM turnover, even though Kim et al failed to show a correlation between the plasma concentrations of MMP-1, 2, 9 and the degree of atrial structural remodeling.

This study by Kim et al emphasizes the importance of diagnosing electroanatomical remodeling of the LA in AF patients, and draws physicians’ attention to the relationship between it and clinical decisions on rhythm control strategies. Pre-determination of electroanatomical remodeling by non-invasive parameters, such as the plasma concentrations of TGF-β and TIMP-1, may be useful for clinical decisions on rhythm control strategies and thus improve the clinical outcome.

**References**