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Editorial

Soluble ST2 in Paroxysmal Atrial Fibrillation: a New Biomarker that Predicts Recurrence?

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▸ See the article "Fibrosis Marker Soluble ST2 Predicts Atrial Fibrillation Recurrence after Cryoballoon Catheter Ablation of Nonvalvular Paroxysmal Atrial Fibrillation" in volume 48 on page 920.

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Despite the success of catheter ablation in the rhythm control of atrial fibrillation (AF), a significant proportion of patients will suffer a recurrence of the arrhythmia.[1] AF recurrence may occur early, in the first three months after catheter ablation. This is known as the blanking period when assessing for recurrence, because the recurrence is usually due to transient factors. Late recurrence after six months is more likely to be due to reconnection of the pulmonary veins, and very late recurrence over 12 months may be due to the progression of the underlying arrhythmic substrate.[2] Attempts to identify predictors of AF recurrence have been met with mixed results. A systematic review of twenty-five studies, that performed multivariable analysis for predictors of AF recurrence, failed to identify an independent predictor of AF recurrence.[3] However, this likely reflects the heterogeneity of the different populations included with regard to ablation technique and the definition of AF recurrence. Persistent and long-standing persistent AF are associated with a lower success rate of catheter ablation.[2] This may be due to the presence of non-pulmonary vein triggers. In patients with paroxysmal atrial fibrillation (PAF), only a large left atrial (LA) size has been shown to predict AF recurrence with relative consistency but LA size may be normal in a significant proportion of PAF.[4] Therefore, the need for a readily measurable biomarker of AF recurrence is clear.

Suppression of tumorigenicity 2 (ST2) is a member of the interleukin-1 family of receptors that is markedly up-regulated after increased strain and stress of the myocardium.[5] Elevated soluble ST2 levels have been associated with poor outcomes in patients with heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). In a meta-analysis of seven studies of patients with chronic HFrEF, with a population of 6,372 patients, elevated soluble ST2 was associated with an increase in all-cause mortality (hazard ratio [HR], 1.75; 95% confidence interval [CI], 1.37–2.22) and cardiovascular mortality (HR, 1.79; 95% CI, 1.22–2.63).[6] Similarly, in a meta-analysis of ten studies enrolling 4,835 patients with acute heart failure, the HRs were calculated for the log of soluble ST2 at admission: all-cause death, 2.46 (95% CI, 1.80–3.37); cardiovascular death, 2.29 (95% CI, 1.41–3.73; p<0.001); HF hospitalization, 1.54 (95% CI, 1.03–2.32).[7] In addition, in comparison to N-terminal prohormone of brain natriuretic peptide (NT-proBNP), changes in soluble ST2 were better able to predict cardiovascular admission or worsening renal function in patients with HFrEF on optimal medical therapy.[7] Soluble ST2 has also been associated with right ventricular pressure overload and dysfunction, as well as systemic congestion in HFpEF.

Soluble ST2 also has a role in atherosclerosis. Soluble ST2 levels are elevated early in non-ST elevation acute coronary syndromes and predict 1-year mortality independently of clinical risk indicators (odds ratio, 2.3; 95% CI, 1.1–4.6).[8] However, the role of soluble ST2 in AF had not been previously explored.

In this issue of the *Korean Circulation Journal*, Okar and colleagues[9] investigated the association between the fibrosis marker soluble ST2 and the recurrence of AF in patients with nonvalvular PAF who have undergone cryoballoon catheter ablation. All patients underwent pulmonary vein isolation with elimination of all pulmonary veins' potentials recorded. In their prospective cohort study of 100 consecutive patients, Okar et al.[9] reported soluble ST2, as measured prior to the ablation procedure, to be the only independent parameter for predicting AF recurrence. Every 10-unit increase in soluble ST2 was found to be associated with a two-fold increase in the risk of AF recurrence. In addition, the authors report a sensitivity of 77.3% and a specificity of 79.5% for the prediction of AF recurrence.[9]

However, several limitations of this work must be acknowledged. The authors excluded patients with non-paroxysmal AF, LA diameter >55 mm, left ventricular ejection fraction <45, sleep apnea and did not analyze LA fibrosis by cardiac magnetic resonance imaging. Therefore, we are unable to draw conclusions as to whether ST2 may be a marker associated with these changes. In addition, though the study exclusively enrolled patients with PAF, the duration of AF was not shown; ST2 may have been a marker of the remodeling due to AF following the adage that AF begets AF. Similarly, patients with higher ST2 had larger LA diameters, a relationship that necessitates further exploration. Lastly, ideally longer and more intensive attempts at detecting AF recurrence are needed to fully clarify the role of ST2. The authors state that soluble ST2 may be useful to distinguish patients with AF originating from only pulmonary vein triggers, who will get more benefit from ablation methods, from patients with AF originating from larger areas of the atrium. Based on the currently presented data, this statement would be premature but should generate interest for future studies.

This is an exciting time in the age of biomarkers. Following the success of cardiac troponins and brain natriuretic peptide in the diagnosis and prognosis of acute coronary syndrome, heart failure and perioperative cardiac risk amongst others, attention has turned toward other biomarkers, including ST2. Okar et al.,[9] in this issue, of the *Korean Circulation Journal* have demonstrated the possible utility of ST2 in predicting AF recurrence. The results of this study should be considered preliminary and should provide the impetus for additional studies to validate these findings and further our understanding of ST2 in AF.

Further work needs to be done to fully elucidate the role of ST2 in AF. A multifaceted approach is required. Is ST2 elevation a marker of increased cardiac remodeling that leads to AF recurrence? In patients with elevated ST2, does AF recur because of pulmonary vein reconnection or is it related to non-pulmonary vein triggers? This knowledge may aid in refining our approach to AF ablation.

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