Gender Difference in the Association Between Uric Acid and Atrial Fibrillation

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The association between hyperuricemia and atrial fibrillation (AF) is well established, but not whether the relationship is causal or not. The first report regarding the relationship between serum uric acid (SUA) and permanent AF was from Greece and published in 2010. So far, more than 100 articles regarding this issue have been published. Some large-scale cohort studies report that hyperuricemia is associated with the development of AF, and meta-analysis also has shown a positive relationship between increased SUA and AF. Moreover, a high SUA level is a risk for AF recurrence after catheter ablation and left atrial thrombus or spontaneous echo contrast detected by echocardiography. However, the SUA level is easily influenced by many other factors such as gender, meals, drink (e.g., alcohol, fructose), lifestyle, obesity, metabolic syndrome, hypertension, diabetes, dyslipidemia, chronic kidney disease, and use of medications such as diuretics. When any UA study is conducted, these factors and comorbidities have to be taken into account. Our previous study of subjects without comorbidities, such as hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, and current medications for hyperuricemia and/or gout showed that hyperuricemia is an independent competing risk factor for AF in both men and women. However, we cannot tell whether UA alone induces AF, because there has not been a large-scale intervention study to confirm whether SUA-lowering therapy is effective for AF prevention.

The article by Kawasoe et al in this issue of the Journal is well written and designed to evaluate the relationship between SUA and new onset AF. The study included 111,566 subjects with data from annual health checkups, and all the analyses were stratified by gender to investigate

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Activation of the Kv1.5 channel is one of the main factors for the provocation and recurrence of AF. The accumulation of intracellular UA via activation of urate transporters enhances Kv1.5 protein expression to shorten the atrial action potential duration, which contributes to the reentry circuit for AF.

Pertinently, and interestingly, Kawasoe et al demonstrate a gender difference regarding the effects of SUA on new-onset AF. The gender difference observed in this study is consistent with a previous study by Suzuki et al, which could be explained by the unique feature of SUA levels in women associated with aging. Female hormones such as estrogen decrease the SUA level; thus, the SUA level increases after menopause. Interestingly, the expression of urate transporters such as SLC2A9 is known to be regulated by estrogen.

Thus, the gender-dependent effects of SUA on new-onset AF observed in Kawasoe et al’s article may be attributed to the estrogen-induced modification of the expression level of atrial urate transporters, which could facilitate the accumulation of intracellular UA via enhanced expression of urate transporters by female hormones.

We have to pay attention to aging as the most important risk factor for AF. However, not only the prevalence of AF but also the SUA level increases with aging after menopause in women. Although this study by Kawasoe et al adjusted age as well as other comorbidities in the multivariate analysis, it could be difficult to adjust these cofactors through the urate transporter to induce AF. Activation of the Kv1.5 channel is one of the main factors for the provocation and recurrence of AF. The accumulation of intracellular UA via activation of urate transporters enhances Kv1.5 protein expression to shorten the atrial action potential duration, which contributes to the reentry circuit for AF.

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completely.
There are some experimental findings on why hyperuricemia induces AF, but little clinical evidence showing that SUA-lowering therapy could prevent AF provocation. We need further high-quality clinical intervention studies to clarify whether SUA-lowering therapy for hyperuricemic patients can prevent new-onset AF.

Name of Grant
None.

References