Sex Differences in Atrial Fibrillation

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It is well known that there are significant sex differences in the epidemiology of cardiac arrhythmia and electrophysiological features of the myocardium. Numerous previous studies have indicated significant sex differences in the epidemiology, pathophysiology, and therapeutic outcome of atrial fibrillation (AF; **Table**).^{1,2} In general, AF is more prevalent in men than in women in age-matched observations, and this is also the case in Japan.^{1,3} Conversely, among patients with diagnosed AF, women are more likely to have the persistent form of AF at presentation, heart failure, and stroke, and thus a poorer prognosis.⁴ Importantly, the outcome of AF ablation also differs between men and women, with a higher recurrence rate in women.⁵ The reasons for these clinically important sex differences in AF are not entirely clear; however, it has been reported that women are more likely to have complex pro-arrhythmic substrates and non-pulmonary vein (PV) triggers of AF.⁵⁻⁷

How Do We Treat Persistent/Recurrent AF in Women?

In this issue of the Journal, using the database from their previous prospective study, namely the EARNEST-PVI trial, Sato et al tested the hypothesis that an extensive ablation strategy in addition to PV isolation may be more effective for women than men among patients with persistent AF.⁶ Since the hypothesis was unexpectedly rejected based on the study results, the authors concluded that the

Article p????

superiority of an extensive ablation strategy for persistent AF was consistent across both sexes.⁶ As in previous studies, the women undergoing AF ablation were older than the men, tended to have higher CHA₂DS₂-VASc scores, and had larger left atrial size considering differences in body height and weight, all of which were related to tougher arrhythmogenic substrates. Most of the extensive ablation groups across men and women underwent additional linear ablations and only few (<20%) underwent complex fractionated atrial electrogram (CFAE) ablations. Thus, the favorable outcomes of the extensive ablation groups may generally be attributable to the favorable effect of linear ablations both in men and women. Sato et al speculated that the linear ablations could exert a back-up blocking effect to the PV isolation (PVI) line,⁶ and were thus effective in men even if their atrial arrhythmogenic substrate was not extensive, which may have diminished the differences in the efficacy of extensive ablations between the sexes. Another possibility is that CFAE ablation may have suppressed the arrhythmogenic substrates, especially in women, because CFAE ablation was related to a lower recurrence rate only in women even though the number of cases of CFAE ablation among women was small. The precise reason for the comparable effect of extensive abla-

Table. Characteristics of AF in Women Compared With Men

Epidemiology

- Less prevalent than in men in the general population, but increases with advanced age
- More associated with heart failure, as both a predisposing factor and outcome
- Higher incidence of stroke

Pathophysiology

- Anti-arrhythmic estrogen effect on atrial myocardium (less prevalent in younger women)
- A series of pathophysiological and electrical changes after menopause
- Enlarged and fibrotic atria

Electrophysiological study and ablation outcomes

- More complex arrhythmogenic substrate
- More prevalent non-PV AF triggers
- Higher recurrence rate after catheter ablation

AF, atrial fibrillation; PV, pulmonary vein.

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tion across both sexes in the study of Sato et al is not clear. It should be noted that no advantages of extensive ablation strategies, especially for women, were reported in subgroup analyses of a previous randomized clinical trial (STAR-AF II) assessing the efficacy of extensive ablation strategies.⁸

Another important confounding factor in the study of Sato et al is the high prevalence of non-PV triggers in women. Indeed, non-PV triggers were more than threefold more prevalent in women than in men.⁶ Non-PV triggers were allowed to be mapped and ablated in the study, but vigorous induction and mapping of non-PV triggers may be difficult in a procedure when attempting extensive substrate ablations. This may rather favor the PVI-alone group. Indeed, it seems that more patients in the PVI-alone group had documentation and treatment of non-PV triggers among both men and women, which may have affected the study results in both men and women. Finally, it should be again emphasized that no extensive ablation strategy beyond PVI has been established to date for persistent/recurrent AF regardless of sex.

Future Perspectives

Sex-oriented ablation strategies for AF remain to be established despite significant pathophysiological differences in AF between men and women.⁹ As suggested in the study of Sato et al,⁶ it may be possible that different kinds of strategies beyond PVI, targeting either triggers or substrates, differently affect clinical outcomes. Future studies are needed to clarify this important issue.

Disclosures

None declared.

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