

# Effect of Left Atrial Enlargement on Success Rates of Atrial Fibrillation Ablation in Women: A Wake-Up Call for Early Ablation

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**T**oday, catheter ablation for atrial fibrillation (AF) is a mainstream non-pharmacological therapy for symptomatic patients with intolerance/failure of antiarrhythmic drugs, patients with heart failure, and as first-line therapy in selected cases [1]. Successful AF catheter ablation enables left atrium (LA) structural and potential electrical reverse remodeling [2,3]. Delayed referrals for catheter ablation may negatively affect procedural success rates through atrial remodeling and fibrosis [4,5].

There is a gender difference in clinical outcome after catheter ablation. Most studies show that female gender is an independent predictor of AF recurrence after catheter ablation. In a national population-based cohort study in the United States, 16.5% of the 37,360 patients who had AF catheter ablation were readmitted within 90 days, mostly for arrhythmia. Female gender was one of the independent predictors of AF recurrence [6]. Risk scores for predicting AF recurrence after a first catheter ablation procedure were developed and validated (e.g., ATLAS-score, CAAP-AF score). All included female gender as an independent predictor of AF relapse [7,8].

The recently published FIRE and ICE trial also revealed that female gender independently predicted AF recurrence and readmission after catheter ablation.

Among the 750 patients with drug-refractory paroxysmal AF enrolled in FIRE and ICE, female gender was associated with an almost 40% increase in the risk of atrial arrhythmia recurrence and cardiovascular rehospitalization [9].

Yu et al. [10] evaluated the association between gender and clinical recurrence after catheter ablation in 1060 relatively young (< 60 years old) AF patients (71% paroxysmal type). During  $24.5 \pm 18.9$  months of follow-up, women showed significantly higher clinical recurrence of AF than men, and female gender was independently associated with post-ablation clinical recurrence of AF. This positive association was seen in the comparison between propensity score-matched groups. Moreover, they compared the outcome of second ablation in 111 patients with AF recurrence during  $22.9 \pm 15$  months of follow-up and showed again that women had higher recurrence even after a second procedure, despite no difference between genders for acute procedural success. Importantly, they showed that women had a higher proportion of left ventricular (LV) diastolic dysfunction, a higher prevalence of heart failure, greater LA volume index, lower LA endocardial voltage, and higher parasympathetic nervous activity than men. These factors may be potential mechanisms underlying gender differences in catheter ablation outcomes of early-onset AF.

A recent study investigated gender differences in fibrosis remodeling in patients with long-standing persistent AF [11]. Since it has been shown that fibrosis promotes AF and its recurrence, thereby

substantially reducing the efficacy of catheter ablation in AF patients, the authors hypothesized that fibrosis may contribute to gender differences in the outcomes of AF catheter ablation. Histological analysis of pulmonary vein sleeves obtained from 166 patients with and without long-standing persistent AF revealed that the AF female group, rather than its male counterpart, had a higher degree of fibrosis when compared to the non-AF group. Further analysis using microarray, immunohistochemistry and Western blot displayed that gender differences in fibrosis remodeling of AF were mainly due to the inherent differential expression of fibrosis-related genes and proteins. Especially, those related to the transforming growth factor- $\beta$ /Smad3 pathway appeared to be up-regulated in the AF female group, thus promoting an aggravation of fibrosis remodeling.

In this issue of *IMAJ*, Sabbag and fellow-researchers [12] report their study of a single-center cohort of 251 consecutive patients who underwent their first AF catheter ablation. They investigated gender differences in AF-free survival after 1 year of follow-up. In this cohort women were older and had a higher proportion of diabetes mellitus than the male patients. Nevertheless, the authors showed a gender-related advantage in AF-free survival in the subgroup of women without significant LA enlargement ( $LADi < 23 \text{ mm/m}^2$ ).

Despite the small sample size of women in this study, the retrospective nature of the analysis and the inherent limitations of subgroup analysis, the clinical significance of this study is its implication that once

LA remodeling had occurred women no longer have the gender protective effect, whereas other factors probably dominate and underlie their worse outcome as compared to men from this stage on (LV diastolic dysfunction, endocardial atrial fibrosis, vagal tone, etc., as discussed above).

Other studies showed a similar motif. In a post-hoc analysis of the AFFIRM trial, LA diameter was an independent predictor of cardiovascular death in female AF patients [13]. Yoshida et al. [14] showed a significant negative association between global LA function and CHADS2 score only among women, which may be a reason for the higher prevalence of embolic stroke in women versus men.

Women are referred for AF ablation later, with a more complex clinical preoperative presentation than in men [15,16]. Thus, although a larger prospective study is warranted to validate the results, current accumulating data are a wake-up call to refer women for early AF ablation, before extensive LA remodeling occurs, thereby giving them at least an equal (if not a greater) chance as men for AF-free survival, lower cardiovascular death risk, and lower stroke rates.

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**Capsule**

**Why are Behçet’s disease patients always exhausted?**

Patients with Behçet’s disease (BD) constantly complain of fatigue and many have problems of poor sleep. This situation ultimately has a major impact on all aspects of normal living. Attempting to understand this, **Senusi** et al. used artificial intelligence (AI) to identify potential biomarkers, including alpha-melanocyte stimulating hormone (α-MSH), vasoactive intestinal peptide (VIP), and some inflammatory cytokines. The authors assessed the association of fatigue, quality of sleep, and disease activity with circulating concentration of α-MSH, VIP, and inflammatory cytokines. The study included 127 participants: 97 BD patients and 30 healthy controls (HC). All subjects completed the Multi-Dimensional Assessment of Fatigue questionnaire (MAF) and the Pittsburgh Sleep Quality Index (PSQI) on the day of their clinical assessment. Enzyme-linked immunosorbent assays (ELISA) were used to evaluate the serum concentrations of α-MSH, VIP and cytokines (IL-1β,

IL-6, IL-10, and TNF-α). Of BD patients, 64% experienced high fatigue scores and 63% had poor quality of sleep. When BD and HC were compared, the MAF and PSQI scores, as well as the serum concentrations of α-MSH, VIP, and IL-6, were significantly higher in BD (*P* values were 0.001, 0.001, 0.001, 0.004, and 0.036, respectively). Both α-MSH and IL-6 had a significant impact on MAF and PSQI. Interestingly, VIP had a significant influence on PSQI and disease activity, but not on MAF. The authors concluded that a better understanding of these complex clinical and biochemical interactions with α-MSH, VIP, and IL-6 might lead to the development of novel approaches to manage fatigue and sleep disorders as well as disease activity in BD patients.

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