Effect of Left Atrial Enlargement on Success Rates of Catheter Ablation for Atrial Fibrillation in Women

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ABSTRACT: Background: Catheter ablation (CA) is a well-established therapeutic option for patients with recurrent symptomatic atrial fibrillation (AF). Data on gender-related differences are limited with regard to baseline characteristics and long-term success rates of catheter ablation for AF.

Methods: We analyzed a cohort of 251 consecutive patients who underwent a first catheter ablation for AF in our institute during the period 2008 through 2015. All patients were followed by regular annual clinic visits, electrocardiograms, periodic 24-48 hour Holter monitoring, and loop recorders. The primary endpoint was first recurrence of AF during 1 year of follow-up.

Results: The cohort comprised 26% women (n=65), who were older (62.1 ± 9.6 vs. 54.4 ± 11.3 years, P < 0.01) and had a higher proportion of diabetes mellitus (23.1 vs. 5.4%, P < 0.001) than male patients. No other significant differences were evident. At 1 year follow-up, the cumulative survival free of AF was significantly higher in women compared with men (83% vs. 66%, respectively, log rank P value = 0.021). Subgroup analysis showed an interaction between female and small indexed left atrial diameter (LADi < 23 mm/m²).

Conclusions: Our findings suggest that women experience a significantly lower rate of AF recurrence post-CA compared with men. This gender-related advantage appears to be restricted to women without significant left atrial enlargement. It further implies that left atrial enlargement has a stronger negative impact on post-CA AF recurrence in females than in males. Due to the relatively small sample number of females further research is warranted to validate our conclusions.

KEY WORDS: atrial fibrillation (AF), catheter ablation (CA), gender, left atrial enlargement

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A trial fibrillation (AF), the most common sustained arrhythmia, is associated with a significant burden of morbidity and mortality [1]. Epidemiological studies have demonstrated gender-related differences in the clinical manifestations, management and prognosis of AF patients [2]. While the incidence of AF is higher in men (estimated number of new cases per year 2.7 million for men and 2.0 million in women) [1], the risk of stroke and mortality rates are higher in women with AF [3] and related strokes tend to be more severe and debilitating [4]. Catheter ablation (CA) is a well-established therapeutic approach to symptomatic patients with recurrences of AF. It was endorsed after failure of or intolerance to anti-arrhythmic drug therapy and increasingly favored as first-line treatment in selected cases. However, several studies have shown that women are treated more conservatively and are less likely to be referred to CA compared to men [2]. Moreover, women are referred to CA at a later stage [5]. These findings are particularly surprising in light of the higher incidence of side effects experienced by women treated with anti-arrhythmic drugs [6]. Moreover, delayed intervention may have a detrimental effect on atrial remodeling and the likelihood of maintaining sinus rhythm [7].

Studies regarding gender-related differences in long-term success rates of CA and procedure-related complications are limited and show inconsistent results. While some reported similar outcomes, others found a higher incidence of complications and recurrence of the arrhythmia in women [5,8]. It is possible that prior conflicting data may be related to baseline differences in clinical and echocardiographic parameters between men and women prior to the index CA. Specifically, differences in baseline left atrial (LA) sizes may contribute to variances in AF recurrences in both groups. Therefore, we sought to evaluate differences between men and women referred to their first CA for the treatment of AF as well as the long-term success rates of these procedures in a contemporary cohort of unselected patients. Furthermore, we sought
to relate those possible gender differences in outcomes to baseline clinical and echocardiographic parameters.

**PATIENTS AND METHODS**

The study cohort comprised 251 consecutive patients who underwent a first CA procedure for the treatment of symptomatic AF, despite anti-arrhythmic drug therapy, at the Sheba Medical Center during the period 2008 through 2015 and were included in a prospective registry. All patients with a follow-up of more than 90 days (i.e., after the blanking period) were included. Subjects were recruited and followed prospectively according to a standard protocol. Pre-specified standard forms were used to record demographics, clinical data, history and characteristics of AF, as well as history of prior treatments. The study was approved by the local institutional review board. No individual consent was required.

**THE ABLATION PROCEDURE**

Patients underwent pulmonary vein isolation using either radiofrequency energy delivered by a catheter with an open irrigated tip or Arctic Front Advance™ Cardiac CryoAblation Catheter (Medtronic, MN, USA). No additional ablation beyond pulmonary vein isolation was performed. When appropriate a three-dimensional mapping system (EnSite Velocity, St. Jude Medical, MN, USA; CARTO 3, Biosense Webster, CA, USA) was used for navigation. Anti-arrhythmic medications were permitted during the first 90 days following ablation (during the post-ablation blanking period), thereafter their use was discouraged but retained at the physician’s discretion. Anticoagulation was continued following ablation for a minimum of 90 days. After 90 days, anticoagulation treatment was administered at the discretion of the treating clinician.

**FOLLOW-UP AND OUTCOME MEASURES**

All patients were evaluated at pre-determined 3 and 12 monthly clinic visits, and annually thereafter. Each visit included a review of the medical history, a 12-lead electrocardiogram and a 24-hour Holter monitor recording. Echocardiography results were also reviewed. Specifically, left atrial diameter (LAD), representing the LA anteroposterior length, measured in the parasternal long axis view using M-mode of 2D was recorded for each patient. Both the absolute values and index-to-body surface area values were recorded. Normal values for LAD, and the definition of LA enlargement, were based on the American Society of Echocardiography (≥ 4.1 cm for males and ≥ 3.9 cm for females), as was the normal value for LADi (1.5–2.3 cm/m²) [9]. In addition, during the first 6 months following the ablation procedure, patients were supplied with an external loop recorder and were encouraged to use a telemetry service daily as well as during palpitation episodes or any other symptoms. Thereafter, in patients complaining of palpitations, external loop recorders were used as well as other standard measuring devices. The primary endpoint of the study was first event of AF or atrial flutter > 30 seconds after the blanking period and during 1 year of follow-up.

**STATISTICAL ANALYSIS**

A descriptive analysis was performed by presenting data as mean ± standard deviation (SD), median and interquartile range or frequency and percentage, when appropriate. All data were compared by gender, using Chi-square analysis for categorical variables, Student’s t-test or Wilcoxon rank sum for continuous variables, as appropriate. The cumulative probabilities of AF recurrence over 2 years of follow-up by gender were graphically displayed according to the Kaplan-Meier method, with comparison of cumulative events by the log-rank test. The association between the primary endpoint and all relevant variables was evaluated by a univariate Cox proportional hazard regression analysis. Multivariate analysis aimed at identifying independent predictors of the primary endpoint was performed using Cox proportional hazards regression modeling. This included a pre-specified model controlling for gender, age above 65, non-paroxysmal AF, large left atrial diameter [upper quartile of indexed left atrial diameter (LADi)], and hypertension introduced both via single iteration and in a stepwise manner. A secondary multivariate analysis was based on the univariate analysis and included all covariates that showed a trend (P < 0.15) associated with AF recurrence. Lastly, we performed an interaction-term analysis to evaluate the efficacy of CA in women compared to men in pre-specified subgroups. All analyses were performed using SPSS 21.0 software (SPSS Inc., Chicago, IL). A two-sided P value < 0.05 was used for determining statistical significance.

**RESULTS**

Our study cohort comprised 251 patients aged 56 ± 11 years, of whom 65 (26%) were women. Most patients presented with paroxysmal AF (85%) and had a preserved left ventricular ejection fraction (LVEF) (55 ± 11%). A comparison of baseline characteristics between men and women is presented in Table 1. Aside from a few notable exceptions, the groups were generally well balanced: (a) women, compared to men, were generally older (62 ± 10 vs. 54 ± 11 years, P < 0.01) and had a higher proportion of diabetes mellitus (23 vs. 5%, P < 0.001); (b) at the time of the index procedure, fewer women were treated with anti-arrhythmic drugs (48 vs. 37%, P = 0.017); (c) no significant differences between the groups were found in terms of body mass index, past history of myocardial infarction and concomitant morbidities such as hypertension, cerebrovascular accident or hypothyroidism; (d) men and women were similar with regard to AF type, LA diameter, LVEF, and systolic pulmonary atrial pressure (SPAP).
The rates of treatments with anti-arrhythmic drugs progressively declined over the follow-up in both men and women (P for trend < 0.001). Notably, there was no statistically significant difference in the proportion of patients treated with anti-arrhythmic drugs between the two groups [Figure 1]. Similarly, the intensity and quality of follow-up was similar in both groups, with similar rates of attendance at each follow-up visit and monitoring test (Holter and loop recorder P > 0.05 for all, data not shown).

### Table 1. Baseline characteristics by gender and predictors of atrial fibrillation recurrence

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n=186)</th>
<th>Women (n=65)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.4 ± 11.3</td>
<td>62.1 ± 8.6</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>60.3</td>
<td>80.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Basal metabolic index (kg/m²)</td>
<td>28.6 ± 4.2</td>
<td>28.2 ± 5.2</td>
<td>0.746</td>
</tr>
<tr>
<td>Obesity</td>
<td>31.8</td>
<td>33.3</td>
<td>0.003</td>
</tr>
<tr>
<td>Past myocardial infarction</td>
<td>2.2</td>
<td>0</td>
<td>0.233</td>
</tr>
<tr>
<td>Hypertension</td>
<td>40.3</td>
<td>35.4</td>
<td>0.482</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5.4</td>
<td>23.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>14.5</td>
<td>3.1</td>
<td>0.013</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>3.2</td>
<td>3.1</td>
<td>0.953</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>4.8</td>
<td>0</td>
<td>0.071</td>
</tr>
<tr>
<td>Severe COPD</td>
<td>4.3</td>
<td>4.6</td>
<td>0.915</td>
</tr>
<tr>
<td>Heart failure</td>
<td>20</td>
<td>21.2</td>
<td>0.871</td>
</tr>
<tr>
<td>CHADS2, median (IQR)</td>
<td>1 (0-2)</td>
<td>1 (0-1)</td>
<td>0.613</td>
</tr>
<tr>
<td>CHADS2, mean ± SD</td>
<td>0.72 ± 0.75</td>
<td>0.85 ± 0.75</td>
<td>0.261</td>
</tr>
</tbody>
</table>

### Anti-arrhythmic therapy

| Amiodarone              | 14.5        | 20.2         | 0.017   |
| Sotalol                 | 13.4        | 12.3         |         |
| Propafenone             | 15.1        | 6.2          |         |
| Flecainide              | 7.5         | 13.8         |         |
| Other                   | 12.4        | 0            |         |
| None                    | 36.6        | 47.7         |         |

### AF type

| Persistent AF | 2.2 | 0 | 0.483 |
| Permanent AF  | 2.2 | 0 | |
| None          | 84.7 | 87.5 | |

### Echocardiography

| LVEF (%)       | 55.8 ± 12.6 | 52.7 ± 17 | 0.199   |
| LVEDd (cm)     | 4.8 ± 5.1   | 4.98 ± 5.4 | 0.027   |
| LVESd (cm)     | 2.96 ± 0.5  | 3.25 ± 0.7 | 0.02    |
| LA diameter (cm)| 4.1 ± 0.5 | 4.3 ± 0.5 | 0.193   |
| LA diameter enlargement* | 65.4 | 79.7 | 0.038   |
| LVEDd indexed (cm²/m²) | 2.48 ± 0.27 | 2.46 ± 0.25 | 0.617 |
| LVESd indexed (cm²/m²) | 1.52 ± 0.27 | 1.59 ± 0.31 | 0.137 |
| LA diameter indexed (cm/m²) | 2.1 ± 0.29 | 2.1 ± 0.29 | 0.556 |
| LA diameter indexed upper quartile (≥ 2.3 cm²/m², %) | 31.5 | 19.3 | 0.079 |
| SPAP (mmHg)    | 32.8        | 32.8        | 0.904   |

### Recurrence of Atrial Fibrillation

The median follow-up was 12.8 months (interquartile range 6.8–31.9 months). During the first year of follow-up, the primary endpoint, recurrence of AF or atrial flutter > 30 seconds was reached by a total of 97 patients (38.6%). When AF recurrence was compared by gender, women were shown to have higher event-free survival compared with men (83% vs. 66% at 1 year, respectively, log rank P = 0.021 for the overall comparison during follow-up) [Figure 2]. Notably, this difference was maintained at 2 years follow-up as well (72% vs. 51%). In a univariate analysis, male gender [hazard ratio (HR) = 1.6, P = 0.03], indexed LA diameter [HR = 2.1, P = 0.03] and hyperlipidemia were associated with recurrence of AF after the first CA [Table 1]. Notably, time from first AF diagnosis or treatment with anti-arrhythmic drugs at 12 months was not significantly associated with its recurrence [Table 1].
DISCUSSION

Our study, based on analysis of 251 unselected subjects with AF who underwent a first CA and were followed for a median of 12.3 months (interquartile range 6.8–31.9), yielded three major findings. First, women appear to be under-represented in this contemporary AF CA cohort, comprising only 26% of the study population. Compared with men, the proportion of women in our cohort was significantly low. Furthermore, this proportion is much lower than the reported rates of women with AF in the general population, indicating underutilization of CA ablation in women with AF. Second, during 1 year of follow-up, women in our cohort had significantly lower rates of AF recurrence after a first CA. Notably, this advantage was maintained at 2 years as well. Third, the reduced risk of AF recurrence following CA among women compared with men in the present study appeared to be confined only to those with a smaller atrial size, suggesting that the protective effect of female gender disappeared once the atria were markedly enlarged.

FEMALE UNDER-REPRESENTATION

A recent study, based on the largest health services organization in Israel, Clalit, which includes most of the adult population in Israel, portrays an intriguing picture of AF patients in Israel: women comprised 50% of incident non-valvular AF cases in 2004–2012, with a similar prevalence of AF in both genders [10]. These data provide a robust estimate of the proportion of women among AF patients in Israel. The fact that our cohort included only 26% female patients strongly implies differences in the management of AF in Israel. Of note, several other previous studies have reported disproportionately lower rates of women among subjects undergoing CA for the treatment of AF [8].

One explanation may be a tendency to treat women more conservatively and less aggressively than male patients. This trend has been noted in several other cardiovascular interventions [11]. In fact, this was also seen in various aspects of AF treatment, including poorer hypertension control [12], undertreatment with oral anticoagulants in post-stroke patients [13], and lower tendency to undergo an electrical cardioversion [14]. Another plausible explanation is that AF symptoms are more likely to be attributed to stress, panic or anxiety in women, and thus they are not treated adequately [15]. Furthermore it is possible that women are less likely to be referred to a specialist (an electrophysiologist), similar to female patients with heart failure [16], a phenomenon that may further contribute to a more conservative management.

As for other therapeutic options, one might argue that women respond to medical treatment, obviating the need for CA. The literature on this matter, however, ranges between reports of similar response to anti-arrhythmic drugs in both genders [17] and studies reporting higher rates of adverse
LA ENLARGEMENT AND ITS INTERACTION WITH FEMALE GENDER

LA enlargement is a well-established risk factor for new onset of AF. LA diameter is a well-validated metric of LA enlargement and has been shown to be strongly associated with AF [20]. According to the Framingham Heart Study, every 5 mm increase in LA diameter is translated to a 39% increase in the risk of AF developing in elderly patients [21]. Furthermore, LA enlargement was shown as an independent risk factor for stroke and death in patients with and without AF [22]. The excess risk of cardiovascular mortality observed in subjects with both AF and LA enlargement is further magnified in females [23]. Of note, the upper quartile of LADI found in our study (> 2.3 cm/m²) is similar to the upper normal limit for LADI endorsed by the American Society of Echocardiography [9]. In addition to its association with the incidence of new-onset AF, LA enlargement also adversely affects the clinical response to various therapeutic options. Patients with enlarged LA have higher rates of AF recurrences when treated with rate control or rhythm control and following electrical or pharmaceutical cardioversions [24]. Specifically, dilated LA has been associated with failure of CA for the treatment of AF [7].

Men and women in our cohort had similar indexed LA diameters and, in accordance with previous research, an enlarged LA did indeed increase the risk of AF recurrence after CA. Interestingly, enlargement of the LA reverted the observed association between patient gender and AF recurrence. It subjected female patients with enlarged LA to more AF recurrences, nullifying the protective effect displayed by those without LA enlargement. Evidently, the interaction between female gender and large LADI (> 75th percentile) indicates the strong impact that enlargement of the LA has on the failure of CA in female patients. LA size is gender dependent, and it is widely accepted that these differences are accounted for when adjusting for body mass index [9]. Nevertheless, previous studies have shown that while this holds true for the general population, gender differences may still persist despite adjustments in cohorts of patients with cardiovascular disease [25]. Both female gender and advanced age are independently associated with larger LA. Women in our cohort were older than men and therefore were expected to have a larger LA. The LADI was, in fact, similar in both groups, implying that women in our cohort might have been subjected to less atrial remodeling or were more resistant to its effect. Both hypothetical mechanisms could explain the more favorable outcome observed in women in our study. Another possible explanation is that women in our cohort had AF over a shorter time period. Since we have no data regarding this explanation remains mere speculation.

LIMITATIONS

This was a single-center study, of modest sample size, with only 65 women. This may limit the generalizability of our results to other populations. In addition, our study has some notable limitations mostly resulting from the retrospective nature of the analysis that are inherent to the use of registries. We could only speculate the reasons for under-representation of women in our cohort. Furthermore, we had limited data regarding the time from initial diagnosis of AF. Clearly, a significant difference between the groups may account for differences in outcomes, although most studies report that women are usually referred to ablation at a later stage [5]. Our evaluation of LA size was based on diameter alone, a less accurate method than echocardiographic estimations and calculation of LA volume. As a result, we may only speculate the actual differences in LA sizes.
in our cohort. Therefore, further study, based on LA volume, is warranted to validate our results. Nevertheless, left atrial diameter is a well-validated predictor of adverse outcome among AF patients. Patient follow-up in our study relied on Holter monitors and loop recorders; therefore, we may have underestimated the recurrence rate because of asymptomatic undocumented arrhythmia episodes. However, it is likely that these unnoticed episodes would be equally distributed in both groups. Lastly, it is essential to acknowledge the statistical limitations of subgroup analysis. While our results are clinically plausible and supported by current literature, further research is required to confirm their validity. A larger study, based preferably on LA volume rather than LAD, would better test the gender-specific effect of LA size on CA success.

CONCLUSIONS

In a cohort of unselected subjects followed after a first attempt of catheter ablation for the treatment of atrial fibrillation, women had higher rates of arrhythmia-free survival despite being older. Significant LA enlargement nullifies the advantage we observed in women. These results may suggest that women should be referred to CA earlier, preferably before extensive left atrial remodeling has occurred.

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References