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IMPACT OF RACE AND GENDER ON CLINICAL OUTCOMES OF CATHETER ABLATION IN PATIENTS WITH ATRIAL FIBRILLATION

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Abstract

Background—Radiofrequency catheter ablation (CA) is an effective treatment of drug-refractory atrial fibrillation (AF). However, the efficacy of CA by race and gender has not been well characterized. We sought to determine the impact of ethnicity and gender on clinical outcome following CA in patients with AF.

Methods—Patients who underwent CA for AF from September 2013 to April 2016 were included in this study. Patients were identified retrospectively and followed prospectively.

Results—A total of 118 patients (15.3% black and 78.8% white, 33% female) comprised the cohort, with mean age at ablation 63.4 $\pm$ 10.4 years. Black patients were older at time of the procedure (65.4 vs 63.4 years old) and had more prevalent comorbidities, including hypertension (77.8 vs 63.4%), diabetes (33.3 vs 15.0%), chronic kidney disease (22.2 vs 7.5%) and lower left ventricular ejection fraction (51.8 vs 56.2%). Blacks also had significantly larger left atrial size ($p=0.03$). Late recurrence of AF was similar between blacks and whites (33.3 vs 34.4%, $p=1$) as well as between women and men (28.2 vs 36.7%, $p=0.41$). Early recurrence was predictive of late recurrence in men ($p<0.001$) but not in women ($p=0.48$). Enlarged left atrium and early recurrence of AF were significant predictors for late recurrence of AF in the cohort.

Conclusions—CA for AF is equally effective in black patients despite more prevalent comorbidity and increased left atrial size. Early recurrence of AF after CA was not predictive of late recurrence of AF in women but was in men.

Keywords

Atrial fibrillation; Race; Gender; Catheter ablation

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INTRODUCTION

There is a high prevalence of atrial fibrillation (AF) in both genders and across all ethnicities.¹ AF is increasingly common with advanced age and associated with significant morbidity and mortality.^{1–5} Gender-based differences in presentation of AF have been reported as the incidence of AF is lower in women. Heart failure and underlying valvular heart disease are more common in women, while men more often have AF associated with coronary artery disease (CAD). Overall, women with AF are older and have lower quality of life, more symptoms and more significant comorbidities compared with men.⁶ Similarly, there are race-based differences in presentation and characteristics of AF. It is reported that black patients have less AF despite more traditional risk factors and that European ancestry is associated with greater AF risk.^{7–9} Blacks with AF have been shown to have higher incidence of stroke, heart failure, CAD and even sudden cardiac death than whites.^{10–12} However, impact of race and gender on overall clinical outcome and efficacy of catheter ablation (CA) for the treatment of AF have not been well documented.

Pulmonary vein isolation by CA has been demonstrated to be an effective treatment to restore and maintain normal sinus rhythm in patients with AF.^{13–15} Women with AF, however, are generally treated less aggressively with fewer cardioversions and CA.^{16–18} Recent studies have differed in answering whether women have similar or higher long-term AF recurrence rates after CA, with the matter yet to be definitively settled.^{19,20} There is also evidence of higher post-procedure complication rates in women, such as increased rates of cardiac tamponade.²¹ Further, there is a significant racial disparity in use of CA as a treatment modality in patients with AF. Compared to whites, black and hispanic patients have a lower rate of CA when hospitalized for AF.^{16–18} These race and gender differences persist despite correcting for age, medical comorbidities and income. Notably, prior studies have shown nearly equal use of CA with respect to race in the management of other arrhythmias, such as atrial flutter (AFL).²² One factor possibly accounting for these differences is that clinical outcomes following CA in patients with AF have not been well demonstrated by ethnicity and gender.

Thus, we aimed to determine the impact of gender, ethnicity and gender-specific ethnicity on early and late recurrence of AF following first CA for AF. All patients who underwent single CA procedure for paroxysmal and persistent AF in our institution were included in analysis to characterize the gender- and ethnicity- based disparity, investigate the clinical outcome and evaluate predictors for differences.

METHODS

Study population

All patients who underwent catheter-based pulmonary vein isolation for AF between October 2013 and April 2016 at the University of Chicago were included in this study. The study cohort included patients with only single CA procedure for paroxysmal and persistent AF. Those patients who had previously undergone CA for AF before the study dates were excluded. Patients were identified retrospectively and followed prospectively. Patients lost to

follow up or with no demographic information provided were also removed from the study cohort. The study was approved by the Institutional Review Board.

Data Collection

Data were collected from a centralized system electronic medical record that contained complete records of all patients treated and followed at the University of Chicago during the range of study dates. These records contain detailed histories and diagnoses for all inpatient and outpatient encounters including emergency room visits, diagnostic tests and clinical follow up. Charts were reviewed for baseline characteristics including demographic information, medical history, electrocardiogram (ECG), Holter recording, echocardiogram, event monitor and procedural details.

Follow-up

The follow-up period for the patients who underwent ablation began at the time of the procedure and ended July 2016. Patients had clinic visits within one month of the procedure, and at regular three- to six-month intervals thereafter. ECG and symptom assessment were performed in all patients during those follow-up visits. Holter recording was performed if symptoms were suggestive of recurrence but this was not captured on ECG. Early recurrence was defined as AF detected within three months of ablation, while late recurrence was defined as AF detected between three months post-ablation and most recent follow-up.

Catheter Ablation

All patients underwent standard CA using radiofrequency energy for pulmonary vein isolation.^{1,6,14} CA was performed using an endpoint of entrance and exit block. Additional ablation such as roof line or mitral isthmus line was performed in a minority of patients (7.6%) and was based on patient-specific conditions and operator.

Statistical analysis

Baseline characteristics were compared between groups using the Fisher's test of independence for categorical variables and Student's t-test for continuous measures. To evaluate for differences in AF rates after ablation, we used Fisher's test with relevant race and gender combinations. Within race and gender groups, Fisher's test was also used for comparison of early and late rates of AF recurrence. Univariate and multivariate associations were assessed by means of logistic regression model. The following variables were considered as potential prognostic factors for both univariate and multivariate analysis: age, race, gender, comorbid conditions (hypertension, diabetes, thyroid disease, obstructive sleep apnea (OSA), chronic kidney disease (CKD) and CAD), type of AF, left ventricular ejection fraction (LVEF), and left atrial (LA) size. For late recurrence, early recurrence was also included as a predictor. Statistical analyses were performed using R version 3.3.2.

RESULTS

Demographic Characteristics

A total of 118 patients (79 men and 39 women) were included in this study. All patients underwent first-time CA for pulmonary vein isolation during the study period. Overall, 93 patients (78.8%) were white, 18 patients (15.3%) black, 2 patients (2%) hispanic, 3 patients (3%) asian/pacific-islander and 2 patients (2%) mixed race. Mean follow up after CA was 18.2 ± 8 months (median 18.2 months, range 3.4 to 34.5 months) in the total cohort. Approximately two-thirds of the patients had paroxysmal AF while one-third had persistent AF. The baseline characteristics of the entire study cohort and as stratified by race and gender are summarized in Table 1.

There were several race and gender based differences in the baseline characteristics of the cohort. Women had significantly more thyroid dysfunction (23.1 vs 5.1%, $p=0.008$) and higher LVEF (58.6 vs 53.6%, $p=0.03$). OSA was more prevalent in men (27.8 vs 10.3%, $p=0.03$). Women had more hypertension (71.8 vs 60.8%) and diabetes (20.5 vs 15.2%), while men had more CAD (15.2 vs 7.7%) and CKD (11.4 vs 5.1%). None of these latter differences were significant.

LA size was significantly larger in blacks as compared to their white counterparts ($p=0.03$). Syncope was also more common in blacks (16.7 vs. 2.2%, $p=0.03$). There were no other significant baseline differences between blacks and whites, but black patients had older age at time of procedure (65.4 vs 63.4 years old) and notably higher rates of comorbidities including hypertension (77.8 vs 63.4%), diabetes (33.3 vs 15.0%), and CKD (22.2 vs 7.5%). Blacks also had lower baseline LVEF (51.8 vs 56.2%). Whites had higher rates of OSA (22.6 vs 16.7%) and CAD (15.1 vs 5.6%).

Recurrence of AF by gender

During a median of 18.2 months of follow-up, early recurrence of AF for overall cohort was 39%, with men having a rate of 36.7% and women having 43.6% recurrence ($p=0.55$). The average late recurrence was 33.9%, with men having 36.7% recurrence and women 28.2% recurrence ($p=0.41$). The recurrence of AF after CA in the early and late period is demonstrated in Figure 1A. There were also no statistical differences in rates of early and late recurrences within gender groups.

Recurrence of AF by race

As summarized in Figure 1B, white patients had 39.7% early recurrence and 34.4% late recurrence. Black patients had 33.3% in both early recurrence and late recurrence. There were no significant differences in rates of early or late recurrences between whites and blacks or within racial groups. When stratified by LA size, all the early recurrences in blacks were seen in those with severely dilated LA (6/12 or 50% of these patients had early recurrences), while the late recurrence rate was 5/12 or 41.7%. Only one black patient with moderately dilated LA had a late recurrence. For the 76 white patients who had LA size data available, the rate of early and late recurrence generally increased with LA size as follows:

normal (22.7 early vs 13.6% late), mild (55 vs 35%), moderate (40 vs 50%) and severe (58.3 vs 54.2%).

Recurrence of AF by gender- and race- specific analysis

Combined race- and gender-specific recurrence of AF is presented in Figure 1C. The study cohort included 64 white men, 10 black men, 29 white women and 8 black women. Black women had higher rates of chronic kidney disease compared to white women (25 vs 0%, $p=0.04$) and white men had a lower rate of diabetes compared to black men (13 vs 40%, $p=0.05$). Early recurrence was as follows: white men 36%, black men 30%, white women 48% and black women 38%. Late recurrence was as follows: white men 36%, black men 40%, white women 31% and black women 25%. White women had the highest rate of early recurrence of AF but differences were not statistically significant. Late recurrence was comparable among the groups.

Predictors of early recurrence

In univariate analysis, CAD was associated with early recurrence in the overall cohort ($p=0.008$) and in men ($p=0.01$), while thyroid disease ($p=0.03$) was associated with early recurrence in women. CAD was associated with early recurrence in white patients ($p=0.003$) as well. In multivariate analysis, LA size (OR 1.13, 95% CI 1.01–1.27, $p=0.04$) was predictive in men while age (OR=1.03, 95% CI 1.00–1.05, $p=0.02$), CAD (OR 1.67, 95% CI 1.13–2.47, $p=0.02$) and CKD (OR 2.25, 95% CI 1.14–4.44 $p=0.03$) were predictive in women. Subgroup analysis showed no significant predictors of AF recurrence in black patients in either univariate or multivariate analysis.

Predictors of late recurrence

With respect to late recurrence, LA size ($p=0.01$) and having early recurrence ($p<0.001$) were univariate predictors in the overall cohort. Early recurrence also emerged as a univariate predictor in men ($p<0.001$) and white ($p<0.001$) patients but not in women or blacks. Additionally, LA size ($p=0.02$) was a predictor in white patients. Table 2 demonstrates the multivariate predictors of late recurrence among the entire cohort and gender subgroups. Multivariate analysis demonstrated that LA size (OR 1.11, 95% CI 1.03–1.20, $p=0.01$) and early recurrence (OR 1.60, 95% CI 1.33–1.92, $p<0.001$) were associated with late recurrence in overall cohort. Early recurrence was predictive in men (OR 2.09, 95% CI 1.71–2.56, $p<0.001$) but not women ($p=0.48$). Further, gender demonstrated a significant interaction with early recurrence ($p=0.004$). Early recurrence of AF preceded late recurrence in 76% of men but only in 35% of women. Only LA size (OR 1.26, 95% CI 1.10–1.43, $p=0.002$) was significantly associated with late recurrence in women. Among whites, early recurrence (OR 1.51, 95% CI 1.22–1.87, $p<0.001$) and LA size (OR 1.11, 95% CI 1.02–1.22, $p=0.02$) were predictive. In comparison, there were no predictors in black patients, including LA size.

DISCUSSION

This study investigated the overall impact of ethnicity and gender on the efficacy of CA for AF. The main finding in our cohort is that race and gender differences do not adversely

impact the clinical outcomes of CA for AF. Despite blacks having more co-morbidities and larger LA size at baseline, CA was similarly effective in maintaining sinus rhythm. Additionally, early recurrence of AF after CA was not predictive of late recurrence of AF in women but was in men.

In our cohort, single CA showed efficacy in preventing recurrence of AF in all patients with paroxysmal and persistent AF during average 18 months follow up. Notably, this rate was similar between blacks and whites even as black patients had more underlying co-morbidity as potential triggers of AF recurrence, including enlarged LA, hypertension, diabetes, CKD and lower ejection fraction. Given LA size was a predictor of late recurrence in the overall cohort, it is notable that blacks still had similar ablation outcomes. This indicates that black patients with normal and mildly increased LA size might have had lower recurrence than comparable white patients. At moderate and severely increased LA size, recurrence rates were comparable between ethnicities. These results would be consistent with what is already known about the racial prevalence of AF, namely that blacks generally have lower rates of AF despite having high rates of traditional risk factors.^{7,9}

The two variables LA size and early recurrence of AF were most strongly associated with late recurrence in this study group. This finding is consistent with previous report as both factors have been shown to affect AF ablation outcome.^{23,24} The effect of LA size on recurrence of AF was more prominent in women than in the overall cohort. LA size was not an independent predictor for late recurrence in black patients based on multivariate analysis in our cohort. This finding was likely due to the higher prevalence of severe LA dilation in the small sample size of black patients. It is also known that a substantial proportion of patients with early recurrence have long-term maintenance of sinus rhythm.^{25,26} In our cohort, both white and black women had an early recurrence rate that was higher than the late recurrence rate. Early recurrence was predictive of late recurrence in men but not in women. More generally, gender was shown to have a significant interaction with early recurrence.

It has previously been suggested that early recurrences in women may involve non-pulmonary vein triggers.^{25,27} The results of this study support the notion of additional factors influencing early recurrence that do not have long-term significance. Women had more thyroid dysfunction and this was shown to be a significant univariate predictor of early recurrence in that group. In addition to the well-documented transient stimulatory effect of the PVI procedure²⁸, a higher inflammatory state may have contributed to early recurrences in women that had little impact on the long-term success of the procedure. Subclinical as well as overt hyperthyroidism has been linked to increased risk of AF²⁹, suggesting this as a possible mechanism.

While the role of early recurrence of AF following CA in predicting long-term outcomes has been shown broadly, data regarding gender dependence is not readily apparent. Previous studies have shown early recurrence to be strongly associated with lower long-term success rate, but also that a significant proportion of patients with early recurrence will have no further AF episodes.²⁵ The presence of structural heart disease and lack of successful anatomic ablation of all targeted pulmonary veins were shown to be independent predictors

of early recurrence.³⁰ Other factors such as age, hypertension, duration of AF and persistent-permanent AF have also been linked to early recurrence.³¹ Our study shows that not only do clinical factors such as CAD and chronic kidney disease remain important considerations, gender also has a strong impact on the long-term significance of early recurrences.

Recently published studies continue to show different results regarding the efficacy of CA by gender. Our study results are similar to work by Singh et. al. that evaluated the one-year efficacy of initial CA in patients undergoing treatment for persistent AF. Despite women being older than men in the study, single procedure drug-free atrial arrhythmia recurrence occurred in 53% of the cohort with no difference between men and women (54 vs. 53%, $p=1.0$).¹⁹ In contrast, Zylla et. al. performed a large-scale retrospective study showing that at one year women may have higher AF recurrence rates (women 50 vs men 45%, $p=.017$)²⁰ after CA. Women were also older at the time of ablation and exhibited a higher prevalence of paroxysmal AF in the study. Neither of the two studies compares early and late recurrence rates such as in our study. Overall, this shows the need for large, prospective trials to further study the factors that affect outcomes of CA in women.

The gender differences in management of AF remain consistent throughout various studies. Schnabel et. al. performed a retrospective study of patients diagnosed with AF and found that women were initially less likely to undergo PVI or electrical cardioversion, but more likely to undergo pharmacological cardioversion at 1 year.³² Kaiser et. al. published a large-scale retrospective study evaluating gender differences in 30-day safety and 1-year effectiveness of CA for AF, noting women had higher rates of vascular complications and trended towards increased rates of all-cause hospitalization at 30 days. They also had increased rate of all-cause hospitalization and hospitalization with AF at 1 year, but were notably less likely to undergo repeat ablation or cardioversion.³³ This indicates that barriers persist with regards to increased utilization of invasive procedures in women.

There are several limitations to this study. This was a single-center study performed at a tertiary-care academic center. Patients referred to our institution may be more likely to be sicker with refractory disease and to have more comorbidities. Although prior failed therapies were not specifically tracked in this study, only patients who were undergoing first-time CA were included. This was done in an effort to maintain a more uniform cohort of patients. There were also limitations in regards to monitoring of patients post-procedure for AF recurrence. Because patients generally did not have continuous long-term outpatient monitoring, asymptomatic or brief recurrences would have been missed across the cohort. Previously published work, however, has shown that continuous monitoring in patients deemed AF-free at greater than one year identifies only a small number of additional recurrences.³⁴ Lastly, there were a relatively small number of black patients in our study cohort, limiting our ability to determine significant predictors of recurrence.

CONCLUSION

Our study demonstrated no disparity regarding the long-term efficacy of CA between men and women, or between black and white patients. CA should be offered to appropriate patients regardless of gender or race. Further work to determine which factors are more

predictive of success after CA in specific races and between genders would expand on our findings.

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Figure 1.

A) Early and late recurrence among the overall study cohort and then separated by gender.

B) Early and late recurrence among white and black patients. **C)** Early and late recurrence

by gender-specific ethnicity.

Table 1

Baseline characteristics of the study cohort.

Characteristic	All (n=118)	Male (n=79)	Female (n=39)	White (n=93)	Black (n=18)
Age at time of ablation (y)	63.4 ± 10.4	62.3 ± 11	65.5 ± 10	63.4 ± 11	65.4 ± 8.6
Duration of follow up (mo)	18.2 ± 9	18.0 ± 8	18.4 ± 9	17.8 ± 9	21.1 ± 7
Paroxysmal AF (%)	72.0	68.4	79.5	71.0	77.8
Persistent AF (%)	28.0	31.6	20.5	29.0	22.2
LVEF (%)	55.2 ± 12.1	53.6 ± 13	58.6 ± 10	56.2 ± 11	51.8 ± 15
Hypertension (%)	64.4	60.8	71.8	63.4	77.8
CVA (%)	2.5	1.3	5.1	2.2	5.6
Diabetes mellitus (%)	16.9	15.2	20.5	15.1	33.3
Thyroid disease (%)	11.0	5.1	23.1	10.8	11.1
OSA (%)	22.0	27.8	10.3	22.6	16.7
CKD (%)	9.3	11.4	5.1	7.5	22.2
CAD (%)	12.7	15.2	7.7	15.1	5.6
CABG (%)	10.2	13.9	2.6	10.8	11.1
Syncope (%)	4.2	2.5	7.7	2.2	16.7
Atrial flutter (%)	25.4	20.3	35.9	25.8	27.8
Atrial tachycardia (%)	3.4	3.8	2.6	2.2	11.1
AVNRT (%)	1.7	0.0	5.1	1.1	5.6
AVRT (%)	1.7	1.3	2.6	2.2	0.0
VT/VF (%)	1.7	2.5	0.0	1.1	0.0
NSVT (%)	3.4	3.8	2.6	3.2	5.6
Prior non-AF ablation (%)	13.6	10.1	20.5	14.0	11.1
Cardiomyopathy (%)	34.7	39.2	25.6	33.3	38.9
LA mild dilation (%)	18.6	17.7	20.5	21.5	5.6
LA moderate dilation (%)	11.9	13.9	7.7	10.8	11.1
LA severe dilation (%)	32.2	27.8	41.0	25.8	66.7
LVH (%)	55.9	60.8	46.2	58.1	55.6
Valve replacement (%)	4.2	5.1	2.6	4.3	0.0

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Abbreviations: AF, Atrial fibrillation; LVEF, Left ventricular ejection fraction; HTN, Hypertension; CVA, Cerebrovascular accident; DM, Diabetes mellitus; OSA, Obstructive sleep apnea; CKD, Chronic kidney disease; CAD, Coronary artery disease; CABG, Coronary artery bypass graft; AVNRT, Atrioventricular nodal reentry tachycardia; AVRT, Atrioventricular reentrant tachycardia; VT/VF, Ventricular tachycardia/ventricular fibrillation; NSVT, Non-sustained ventricular tachycardia; LA, Left atrial; LVH, Left ventricular hypertrophy

Table 2

Predictors of recurrence of atrial fibrillation.

	Odds Ratio	95% Confidence Interval	P-value
All patients			
Left atrial size	1.11	1.03–1.20	0.01
Early recurrence	1.60	1.33–1.92	<0.001
Women			
Left atrial size	1.26	1.10–1.43	0.002
Men			
Early recurrence	2.09	1.71–2.56	<0.001