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The extent of complex fractionated atrial electrograms in the left atrium reflects age-related electrical remodeling in patients with persistent atrial fibrillation

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Abstract

Backgrounds: Alterations in the atrial structure and function associated with aging result in electric remodeling of the left atrium (LA) in patients with persistent atrial fibrillation (AF). We performed this study to evaluate the influence of age on electric remodeling as assessed by the extent of complex fractionated atrial electrograms (CFAEs) in the LA.

Methods: A total of 122 patients (mean age, 55.9 ± 10.4 years; range, 31-79; 106 males) who underwent catheter ablation for drug-refractory persistent AF were included in the study. The extent of CFAE was measured by CFAE area and its index (CFAE area/LA surface area × 100) using three-dimensional automated software of NavX system.

Results: The mean value of CFAE extent was significantly different among age groups; the CFAE area decreased significantly with increasing age (30 seconds [43.2 ± 14.5 mm^2] vs 40 seconds [28.6 ± 6.0 mm^2] vs 50 seconds [22.8 ± 3.4 mm^2] vs 60 seconds [15.3 ± 2.6 mm^2] vs 70 seconds [10.3 ± 3.2 mm^2]; $P = .010$). A similar significant decrease was observed in the CFAE area index (30 seconds [22.9 ± 7.4] vs 40 seconds [14.9 ± 3.4] vs 50 seconds [10.4 ± 1.6] vs 60 seconds [6.9 ± 1.2] vs 70 seconds [4.6 ± 1.4]; $P = .002$). Age had a significantly negative correlation with the CFAE area ($r = -0.322$, $P < .001$) and CFAE area index ($r = -0.357$, $P < .001$).

Conclusions: Increasing age is associated with electric remodeling in the LA characterized by a decrease in the extent of CFAE area and its index.

KEYWORDS
aging, atrial fibrillation (AF), complex fractionated atrial electrograms (CFAEs)

1 | INTRODUCTION

Aging is the most frequently attributable risk factor for atrial fibrillation (AF).[1] Alterations in atrial structure and function associated with aging provide electroanatomic remodeling of the left atrium (LA) and consequently plays an important role in the genesis and progression of AF.[2] Several studies to characterize electric remodeling were conducted in patients with and without AF.[3–7] The major electrophysiologic characteristics that develop after AF are reduction in the atrial refractory period and loss of action potential duration adaptation

to rate, and increased fibrillatory rates.[5,8] Electric remodeling of the LA also occurs, such as decreased voltage and prolonged atrial conduction, which is crucial for the maintenance of AF.[9] However, electrophysiologic changes of LA in association with aging remain to be determined in persistent AF. Complex fractionated atrial electrograms (CFAEs) are atrial electrograms with fractionations and a short cycle length (≤120 milliseconds)[10] reflecting the electric activity of LA in persistent AF. This study undertook to evaluate the influence of age on electric remodeling in the LA as assessed by the extent of CFAEs.

2 | PATIENTS AND METHODS

2.1 | Patients

This is a retrospective study and patients with persistent AF who were referred for their first ablation were included in this study. All patients had previously failed to respond to antiarrhythmic drugs and had symptomatic AF. Persistent AF was defined according to the 2014 AHA/ACC/HRS guideline for the management of patients having AF with duration longer than 7 days.[11] Totally, 122 patients were enrolled in the study, with age ranging from 31 to 79 years. The patients were categorized into five groups based on 10 years of age: 30 seconds (31-40 years, n = 8), 40 seconds (between 41 and 50 years, n = 24), 50 seconds (51-60 years, n = 47), 60 seconds (61-70 years, n = 30), and 70 seconds (71 years and above, n = 13). All patients provided written informed consent.

2.2 | Electrophysiology study

Antiarrhythmic drugs were discontinued at least five half-lives before the procedure. Amiodarone was discontinued at least 1 month before the ablation procedure. Transesophageal echocardiography was performed within 24 hours before the procedure to exclude the presence of atrial thrombi. The ablation procedure was performed under sedation with intravenous propofol with continuous monitoring of blood pressure and oxygen saturation. The high right atrium, low right atrium, and coronary sinus were mapped with a decapolar catheter (Bard Electrophysiology Inc) and steerable duo-decapolar catheter (St. Jude Medical Inc) inserted through the left femoral vein. A quadripolar catheter was also placed in the superior vena cava. Intracardiac electrograms were recorded using an electrophysiology system (Prucka CardioLab™ ; General Electric Health Care System Inc). After a double transseptal puncture, anticoagulation was started with unfractionated heparin, maintaining an activated clotting time between 300 and 350 seconds. We used three-dimensional (3D) mapping guided geometry (NavX System; St. Jude Medical Inc) for electroanatomic mapping in all patients.

2.3 | Ablation strategy

The stepwise approach for ablation was performed under the guidance of fluoroscopic and 3D mapping. All patients initially underwent circumferential antral ablation of pulmonary vein (PV) with the endpoint being the electric exit and entrance block or dissociation while mapping the PVs with bipolar signals recorded by a 20-pole circular Lasso catheter (Biosense Webster Inc). If AF was sustained following antral ablation of the PVs, further ablation was guided by automated CFAE maps of the LA and subsequently the right atrium (RA), as defined previously.[10] The endpoints of the CFAE-guided ablation were a significant reduction in the CFAE amplitude (>80%), electric silence, organized atrial tachycardia (AT), or termination of AF. CFAEs of the RA were targeted on the persistence of AF after extensive LA ablation. Linear ablation at the cavotricuspid isthmus was performed in all patients either before or after restoring the sinus rhythm, and bidirectional conduction block was confirmed. No antiarrhythmic drugs were used during the ablation procedure. When AF converted to AT, activation mapping and ablation for AT were performed until a sinus rhythm was restored. If a patient had more than one stable AT, an attempt was made to map and ablate all ATs. The endpoint of catheter ablation was the termination of AF or AT[12] and noninducibility of AT (cycle length >280 milliseconds) by burst atrial pacing.[13] If termination of AF or AT was not achieved after ablating all target sites, the sinus rhythm was restored by electric cardioversion. Radiofrequency ablation was delivered at a target temperature of 48°C with power in the range of 25-35 W (Stockert generator; Biosense Webster Inc or IBI 1500T11; St. Jude Medical, Inc) using a 4-mm open irrigated-tip catheter (Thermocool, Biosense Webster, Inc or Cool Path Duo, St. Jude Medical, Inc). The esophagus was visualized by barium swallow before sedation, and radiofrequency power was reduced to 25 W with ablation duration less than 15-20 seconds to minimize the use of radiofrequency energy near the esophagus.

2.4 | Measurements of CFAEs in LA

We defined the CFAEs as previously reported.[10,14] Briefly, CFAEs were (a) atrial electrograms with fractionation and composed of two or more deflections and/or with continuous activity of the baseline or (b) atrial electrograms with a cycle length (CL) ≤120 milliseconds These electrograms were recorded with the mapping catheter in a stable position for at least 6 seconds (to avoid artifacts) using the 3D automated software of the NavX system.[15] This area is coded in white and pink on the CFAE map. CFAE area and LA surface area were measured. The representative examples of CFAE measurements are shown in Figure 1. CFAE area index was defined as CFAE area/LA surface area × 100, as previously reported.[16] The physician was blinded to the clinical characteristics of the patient during all CFAE measurements.

2.5 | Postprocedural management and follow-up

Patients were treated with intravenous heparin and monitored overnight. They were discharged after being prescribed anticoagulants, which were continued for at least 3 months after the procedure. Patients resumed the antiarrhythmic drugs they had been taking

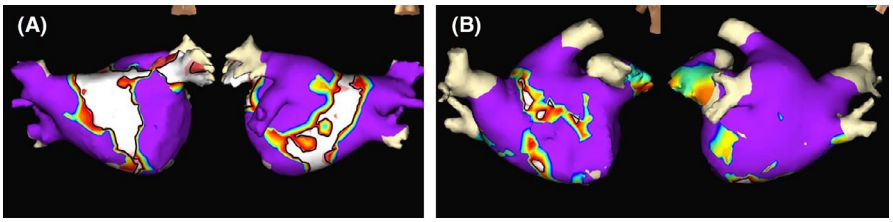

FIGURE 1 CFAEs were recorded using the 3D automated software of the NavX system (St. Jude Medical Inc) and are coded in white and pink. The measured areas encircled within the black line. A, 44-year old patient. The CFAE area was 48.9 mm^2 and CFAE area index was 23.36. B, 74-year old patient. The CFAE area was 2.8 mm^2 and CFAE area index was 1.32. CFAE, complex fractionated atrial electrogram

before the catheter ablation. The patients were seen in an outpatient clinic at one week and at 1, 3, 6, 9, and 12 months after the procedure, and every 6 months thereafter. A 12-lead surface electrocardiogram was performed at every visit. Patients were evaluated by 24- or 48-hour Holter monitoring or a 7-day event recorder during each visit. A detailed history of any symptoms suggesting potential AF or AT recurrence was taken. Recurrence was defined as an episode of an atrial arrhythmia (AF or AT including atrial flutter) of at least 30 seconds that occurred after a blanking period of 12 weeks after ablation.[11]

Antiarrhythmic drugs were discontinued at the 3-month visit if there was no evidence of recurrence. Anticoagulation was discontinued in patients without a previous history of stroke if the electrocardiogram consistently demonstrated sinus rhythm. Success was defined as the absence of any documented atrial arrhythmia or symptoms suggestive of arrhythmia recurrence without antiarrhythmic drugs.

2.6 | Statistical analysis

Patient age ranged from 31 to 79 years; the patients were categorized into five groups based on 10 years of age. Continuous variables are reported as the mean ± SD, while categorical variables are reported as a number or percentage. One-way ANOVA testing compared the continuous variables, while categorical variables were compared using a chi-square test or Fisher's exact test, as appropriate among groups. Pearson's correlation method was used to calculate the relationship between age and the CFAE area, CFAE area index, LA size, and LA volume. All statistical analyses were performed using SPSS 12.0 software (SPSS Inc). All tests were two-tailed and a *P*-value of <0.05 was considered significant.

3 | RESULTS

3.1 | Baseline characteristics

In total, 122 patients were included in the analyses. The mean age was 55.9 ± 10.4 years (range, 31-79) and 106 patients (86.9%) were male. The mean duration of continuous AF before catheter ablation was 6.4 ± 4.9 years. The mean antero-posterior LA diameter measured by transthoracic echocardiography was 44.3 ± 5.9 mm, and the mean LA volume measured by cardiac computed tomography was 130.7 ± 44.3 mL. The mean left ventricular ejection fraction was 53.6 ± 6.7% (range, 25.5-67.5).

Baseline characteristics according to age groups are compared in Table 1. The proportion of female gender and patients with accompanying hypertension were significantly higher in the older age group.

3.2 | Age and electric remodeling

The mean value of CFAE extent was significantly different among the age groups. A significant decrease in CFAE area was observed with increasing age (30 seconds [43.2 ± 14.5 mm^2] vs 40 seconds

TABLE 1 Comparison of characteristics among the age groups

	30 s (N = 8)	40 s (N = 24)	50 s (N = 47)	60 s (N = 30)	70 s (N = 13)	*P*
Age (years)	35.5 ± 2.8	45.4 ± 2.6	54.7 ± 2.8	64.4 ± 3.1	72.9 ± 3.1	**<.001**‡
Male, n (%)	8 (100)	24 (100)	42 (89.4)	23 (76.7)	9 (69.2)	**.023***
AF duration (years)	2.7 ± 2.8	5.5 ± 3.9	6.2 ± 4.3	8.1 ± 6.7	6.5 ± 4.3	.059
HTN, n (%)	0	8 (33.3)	22 (46.8)	16 (53.3)	9 (69.2)	**.019***
CAD, n (%)	0	1 (4.2)	2 (4.3)	2 (6.7)	1 (7.7)	.925
SHD, n (%)	2 (25)	7 (29.2)	19 (40.4)	9 (30.0)	2 (15.4)	.477
Previous embolic events, n (%)	0	0	4 (8.5)	2 (6.7)	3 (23.1)	.119
LVEF (%)	54.0 ± 9.2	55.1 ± 5.7	51.7 ± 7.9	54.9 ± 5.0	54.3 ± 4.2	.187

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; HTN, hypertension; LVEF, left ventricular ejection fraction; SHD, structural heart disease.
*$P < .05$; ‡$P < .001$.
Bold values indicates statistical significance $P < .05$.

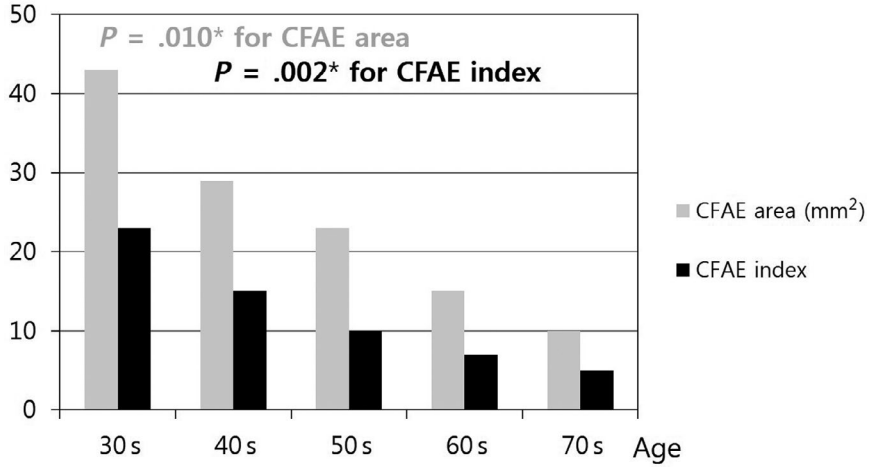

FIGURE 2 The CFAE area decreases significantly with increasing age (30 s [43.2 ± 14.5 mm^2] vs 40 s [28.6 ± 6.0 mm^2] vs 50 s [22.8 ± 3.4 mm^2] vs 60 s [15.3 ± 2.6 mm^2] vs 70 s [10.3 ± 3.2 mm^2], P = .010). Similarly, significant decrease in the CFAE area index is observed with increasing age (30 s [22.9 ± 7.4] vs 40 s [14.9 ± 3.4] vs 50 s [10.4 ± 1.6] vs 60 s [6.9 ± 1.2] vs 70 s [4.6 ± 1.4], P = .002). CFAE, complex fractionated atrial electrogram. *P < .05

[28.6 ± 6.0 mm^2] vs 50 seconds [22.8 ± 3.4 mm^2] vs 60 seconds [15.3 ± 2.6 mm^2] vs 70 seconds [10.3 ± 3.2 mm^2], P = .010). Similarly, CFAE area index decreased significantly with age (30 seconds [22.9 ± 7.4] vs 40 seconds [14.9 ± 3.4] vs 50 seconds [10.4 ± 1.6] vs 60 seconds [6.9 ± 1.2] vs 70 seconds [4.6 ± 1.4], P = .002) (Figure 2). Representative examples of CFAE area measurements in 40s and 70s are shown in Figure 1. Age revealed a significantly negative correlation with the CFAE area (r = −0.322, P < .001) and CFAE area index (r = −0.357, P < .001) (Figure 3) which was not altered even after controlling possible confounding covariates including female gender, the presence of hypertension, and LA size and volume (r = −0.277, P = .003 for CFAE area, and r = −0.302, P = .001 for CFAE area index).

3.3 | Age and structural remodeling

In contrast to CFAE extent, the LA size (30 seconds [39.4 ± 4.8 mm] vs 40 seconds [42.7 ± 6.9 mm] vs 50 seconds [44.6 ± 5.7 mm] vs 60 seconds [45.9 ± 5.2 mm] vs 70 seconds [45.4 ± 5.9 mm], P = .040) and LA volume (30 seconds [92.7 ± 40.9 mL] vs 40 seconds [114.5 ± 34.9 mL] vs 50 seconds [139.5 ± 44.2 mL] vs 60 seconds [136.0 ± 38.5 mL] vs 70 seconds [144.9 ± 46.5 mL], P = .009) significantly increased with increasing age (Figure 4). The LA size (r = 0.307, P = .001) and LA volume (r = 0.295, P = .001) significantly and positively correlated with age (Figure 5).

3.4 | Procedural characteristics according to age groups

Procedural characteristics are summarized in Table 2. Patients requiring additional RA ablation to achieve an endpoint were similar among all groups. Also, the proportion of acute procedural success by means of AF termination, either converting to sinus rhythm or AT during catheter ablation, was not significantly different. Ablation time during procedure and total procedural time among groups showed no significant difference.

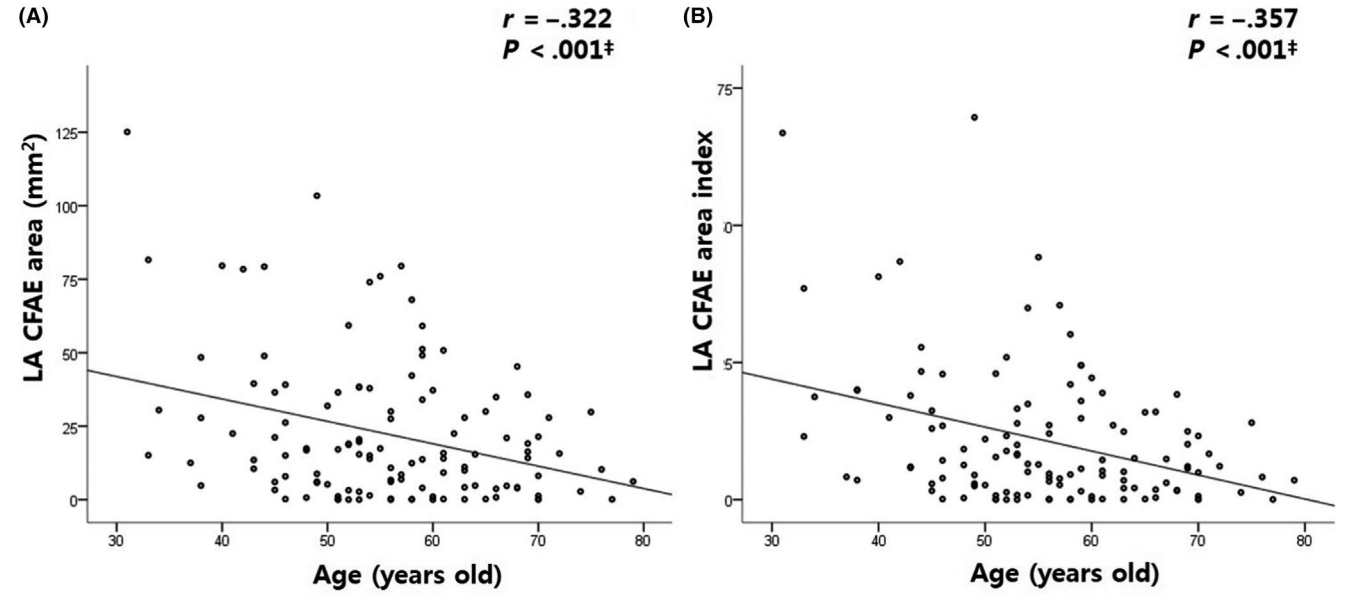

FIGURE 3 Age significantly and negatively correlates with CFAE area (r = −0.322, P < .001) and CFAE index (r = −0.357, P < .001). CFAE = complex fractionated atrial electrogram; LA, left atrial. ‡P < .001

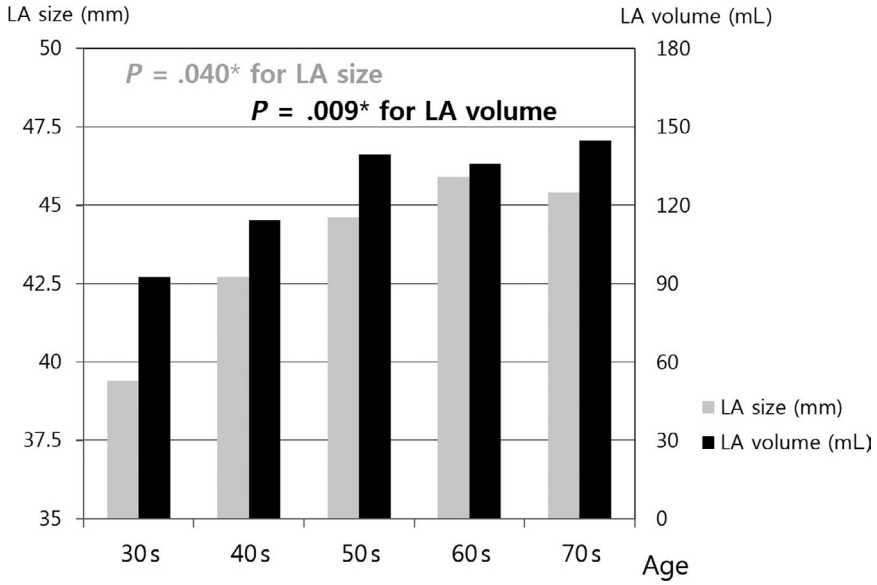

FIGURE 4 LA size (30 s [39.4 ± 4.8 mm] vs 40 s [42.7 ± 6.9 mm] vs 50 s [44.6 ± 5.7 mm] vs 60 s [45.9 ± 5.2 mm] vs 70 s [45.4 ± 5.9 mm], *P* = .040) and LA volume (30 s [92.7 ± 40.9 mL] vs 40 s [114.5 ± 34.9 mL] vs 50 s [139.5 ± 44.2 mL] vs 60 s [136.0 ± 38.5 mL] vs 70 s [144.9 ± 46.5 mL], *P* = .009) increase significantly with age. LA, left atrial. *$P < .05$

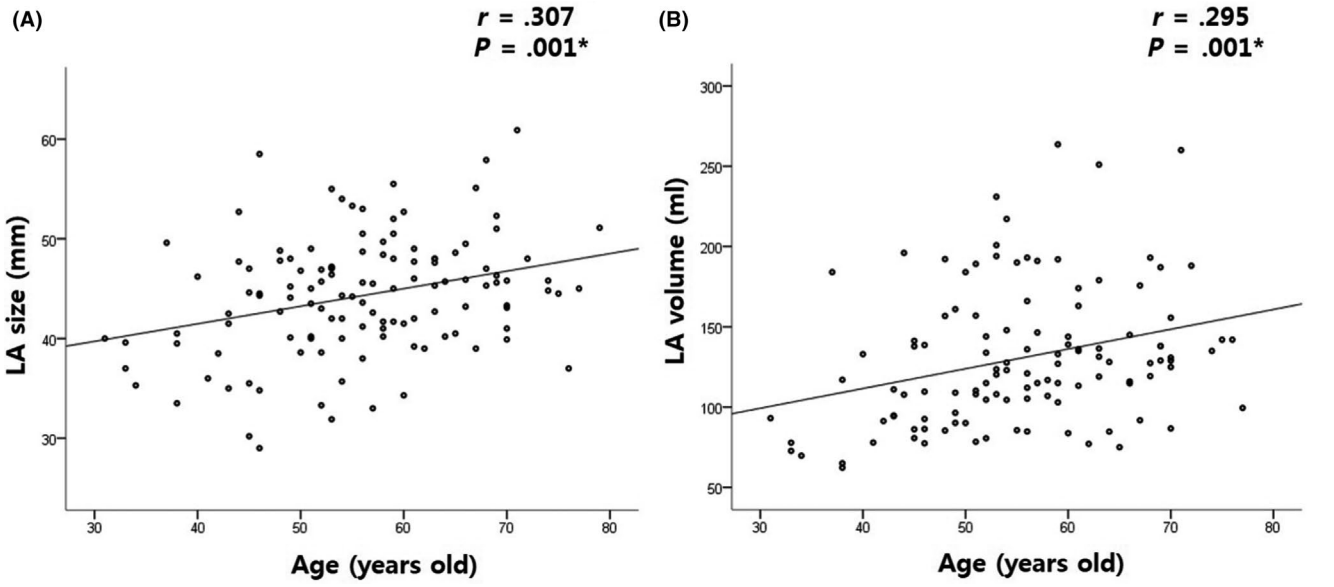

FIGURE 5 LA size (*r* = 0.307, *P* = .001) and LA volume (*r* = 0.295, *P* = .001) are significantly and positively correlated with age. LA, left atrial. ‡*P* < .001

TABLE 2 Procedural characteristics among age groups

	30 s (N = 8)	40 s (N = 24)	50 s (N = 47)	60 s (N = 30)	70 s (N = 13)	*P*
Additional RA ablation, n (%)	5 (62.5)	18 (75.0)	28 (60.9)	16 (53.3)	7 (53.8)	.556
Conversion to SR, n (%)	6 (75.0)	15 (62.5)	29 (61.7)	20 (66.7)	9 (69.2)	.942
Conversion to AT or SR, n (%)	6 (75.0)	16 (66.7)	38 (80.9)	23 (76.7)	11 (84.6)	.683
Ablation time (minutes)	154 ± 65	172 ± 40	158 ± 48	163 ± 61	157 ± 71	.847
Procedure time (minutes)	376 ± 119	380 ± 91	373 ± 99	394 ± 123	375 ± 123	.953

Abbreviations: AT, atrial tachycardia; RA, right atrial; SR, sinus rhythm.

3.5 | Clinical outcome during follow-up

During a mean follow-up of 18.4 ± 11.6 months after a single ablation procedure, 51 patients (41.8%) maintained sinus rhythm without antiarrhythmic drugs. The proportion of patients with clinical success (30 seconds [37.5%, 3/8] vs 40 seconds [33.3%, 8/24] vs 50 seconds [40.4%, 19/47] vs 60 seconds [56.7%, 17/30] vs 70 seconds [30.8%, 4/13], *P* = .382] was similar across all age groups.

4 | DISCUSSION

4.1 | Main findings

This study demonstrates the effect of age on electroanatomic remodeling in the LA. With increasing age, a significant reduction in CFAE area reflects age-related electric remodeling, whereas an increase in the LA size and volume reflect anatomic remodeling in patients with persistent AF. However, the incidence of a recurrence after catheter ablation was similar across all age groups despite significant differences in the extent of CFAE.

In our study population, there was a significantly higher proportion of hypertension in the older age groups. Hypertension is a common risk factor for developing persistent AF. Hypertension promotes initiation and perpetuation of AF through the enlargement of LA and depression of its contractile function.[17,18] It is possible that hypertension also contributes to electric remodeling; however, there was only a tendency of difference in CFAE area and its index according to the presence of hypertension ($P = .369$ for CFAE area and $P = .240$ for CFAE area index). Controlling with confounding factors (including hypertension) mildly attenuated the associations with no alterations in the statistical significance of aging. Taken together, these results indicate that aging itself is the powerful predictor of CFAE extent.

4.2 | Previous studies on electric remodeling with aging

Prior studies on electric remodeling with aging generally demonstrate the prolongation of an effective refractory period during sinus rhythm.[3,19] An increase in atrial electrogram fragmentation as a marker of slowed conduction was associated with aging in patients without AF or structural heart disease.[19] A prior experimental study demonstrated that aging was associated with increase in interregional dispersion of action potential duration which might render an old dog more susceptible to initiation of AF in comparison to an adult dog that is in sinus rhythm. Chronic AF affects the dispersion of action potential parameters differently in adult and old atria, increasing dispersion in the adult dog while decreasing it in the old dog, suggesting different electric remodeling according to age. The increased dispersion of atrial electrophysiology may be an important contributory factor for AF stabilization in the adult, while the occurrence of fibrosis and slowed conduction of premature beats may be more important in the old.[5] In another study, the younger age group subjects showed higher LA bipolar voltage compared with older patients during sinus rhythm.[7] Patients with chronic AF or atrial flutter showed similar electric remodeling of the human atrial myocardium, as identified by markedly abbreviated action potential duration during steady-state pacing and extrastimulation, as late as 15-30 minutes after cardioversion.[6]

Increasing age is also associated with electric changes in PVs characterized by a significant reduction in PV voltage, conduction slowing, and increasing signal complexity among non-AF patients.[4] Age-related electric remodeling is also observed in RA among patients without prior AF history. A significant reduction was reported in both global and regional bipolar voltage amplitude in the older group, and the heterogeneity of voltage of RA was significantly greater in the older group.[3] Slow conduction and an increase in complex signals in the RA were observed with increasing age, particularly clustered around the crista terminalis during sinus rhythm in patients without AF.[3]

Earlier studies further demonstrated that conduction slowing and increasing signal complexity in either both atrium or PVs occurs with aging during the sinus rhythm. However, to date there are no studies that report on the electric remodeling of the LA during AF rhythm in association with aging in patients with persistent AF. We demonstrate that significant reduction in CFAE area and its index occurs with increasing age.

4.3 | Complex fractionated atrial electrograms as an atrial substrate and targets for atrial fibrillation ablation

CFAEs were mostly observed in areas of slow conduction and/or at pivot points of wavelet turnaround at the end of functional block arcs. They are the active driver and critical sites for AF perpetuation and can therefore serve as target sites for AF ablation. In the current study, a significantly greater area of CFAE with smaller LA seen in the younger age group may reflect electric activity without structural remodeling. Significant reduction in CFAE extent with aging is represented by the attenuation of electric complexity that suggests fibrotic scar change and structural remodeling progressions in the LA. Previous animal studies demonstrated an increase in interstitial fibrosis within the atrium associated with variable conduction slowing with advancing age.[5,20]

In our study, patients had similar procedural characteristics and clinical outcomes across all age groups, although CFAE extents in the LA for target of ablation were significantly different. The endpoint of bi-atrial CFAE-guided ablation in our strategy was a significant reduction in the CFAE amplitude (>80%) or electric silence. After radiofrequency applications over the CFAE areas, most atrial electrograms not only disappeared at the ablation site, but also at neighboring sites, were drastically reduced in amplitude. This resulted in complete elimination of the CFAEs and is often associated with increasing tachycardia cycle lengths before AF termination, even though the cycle lengths were measured from the electric reference of an area remote from the ablation site.[14] Therefore, ablation of all areas showing CFAEs was not required to achieve an endpoint. This may explain similar incidence of additional RA ablation, ablation time and total procedure time across all groups. However, it remains unknown whether complete elimination of CFAE area might cause a similar outcome, or whether age or extent of CFAEs itself are not associated with clinical outcome after catheter ablation. Several recent randomized clinical trials, including the RASTA study, STAR AF II, CHASE AF, and Alster-Lost-AF trial, revealed no clinical benefits of extensive adjuvant ablation at CFAE area beyond PV isolation.[21–24] Nademanee has commented earlier that only very low voltage CFAEs

responsible for scar regions in the atrium are important for targeting. Therefore, in future studies, we need to clarify the real target for ablation among CFAE areas and to further evaluate the best strategy of catheter ablation to achieve better outcomes, especially in older patients with little CFAE areas. Magnetic resonance imaging might also provide benefits for investigating the burden of scar in conjunction with low voltage CFAE to predict ablation outcome.

4.4 | Limitations

There were several limitations in our study. First, the sample size of patients in their 30s and 70s are relatively small because of the limited number of patients who undergo catheter ablation in that age group. Similar clinical outcomes among the groups observed in our study may have resulted from the relatively small population in each group. The mechanism of CFAEs has not been clearly elucidated yet. There is a problem of the spatiotemporal reproducibility and CFAEs can be affected by temporal phenomenon caused by autonomic activity.[25,26] Differences in the baseline characteristics across the groups, such as proportion of female gender and hypertension, are another limitation of this study. Electric remodeling can also be caused by depressed atrial mechanical function due to hypertension. Previously low voltage zone index which might represent fibrosis or scar tissue that may delay or block the conduction significantly correlated with a decreased atrial contraction function.[9] We did not analyze the mechanical function of LA and low voltage area or conduction time which might be associated with increasing age. These issues might be of interest for future work. Further large scale, prospective studies will be required to define the pathophysiology of electric remodeling in the LA and the association with clinical outcome after catheter ablation in persistent AF.

4.5 | Conclusions

Increasing age is associated with electric remodeling in the LA characterized by decrease in the extent of CFAE area and its index.

CONFLICT OF INTERESTS

The authors declare no conflict of interests for this article.

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