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ORIGINAL ARTICLE

Atrial Fibrillation Catheter Ablation Improves 1-Year Follow-Up Cognitive Function, Especially in Patients With Impaired Cognitive Function

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BACKGROUND: Although atrial fibrillation (AF) has a risk of cognitive dysfunction, it is not clear whether AF catheter ablation improves or worsens cognitive function. This prospective case-control study sought to assess the 1-year serial changes in the cognitive function with or without AF catheter ablation.

METHODS: We evaluated the Montreal Cognitive Assessment score in 308 patients (71.4% male, 60.6±9.1 years of age, 34.1% persistent AF) who underwent AF ablation (ablation group) and 50 AF patients on medical therapy who met the same indication for AF ablation (control group), at baseline and 3 and 12 months after enrollment. Cognitive impairment was defined as a published cutoff score of <23 points. To exclude any learning effects, we used the practice-adjusted reliable change index for assessing the cognitive changes.

RESULTS: Preablation cognitive impairment was detected in 18.5% (57/308). The Montreal Cognitive Assessment score significantly improved 1 year after radiofrequency catheter ablation in both overall ablation group (24.9±2.9–26.4±2.5; $P<0.001$) and the propensity-matched ablation group (25.4±2.4–26.5±2.3; $P<0.001$), but not in the control group (25.4±2.5–24.8±2.5; $P=0.012$). Preablation cognitive impairment (odds ratio, 13.70; 95% CI, 4.83–38.87; $P<0.001$) was independently associated with an improvement in the 1-year post-ablation cognitive function. In the reliable change index analyses, 94.7% of propensity-matched ablation group showed an improved/stable cognitive function at the 1-year follow-up.

CONCLUSIONS: Catheter ablation of AF, at least, does not deteriorate the cognitive function, but rather improves the performance on 1-year follow-up neurocognitive tests, especially in patients with a preablation cognitive impairment.

VISUAL OVERVIEW: A visual overview is available for this article.

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Key Words: atrial fibrillation ■ brain infarction ■ catheter ablation ■ cognitive function ■ dementia

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WHAT IS KNOWN?

- Atrial fibrillation (AF) is associated with a higher risk of cognitive impairment and dementia independently of a history of a clinical stroke.
- AF ablation reduces the burden of AF and improves the cardiac output and cerebral perfusion.
- There have been conflicting results where AF ablation has been shown to reduce the risk of dementia, while another study has indicated a higher prevalence of postoperative cognitive dysfunction during the short-intermediate period after AF ablation.

WHAT THE STUDY ADDS?

- AF catheter ablation does not cause postoperative cognitive dysfunction 3-months after the ablation procedure but rather improves the 1-year follow-up cognitive performance.
- Cognitive improvement is more pronounced among patients with a mild cognitive impairment before ablation.
- Patients with sustaining AF after catheter ablation show a significantly lower improvement in the 1-year follow-up cognitive function than those maintained in sinus rhythm.

Atrial fibrillation (AF) is a prevalent arrhythmia especially among the elderly, and an independent predictor associated with a nearly 5-fold increased risk of a stroke.[1] Because the stroke increases the risk of dementia and a cognitive decline,[2] it is consequently not surprising that AF is significantly associated with cognitive impairment.[3,4] Recently, many studies have shown that AF may be a risk factor for cognitive impairment independent of a stroke, suggesting that AF itself has additional adverse effects on the cognitive function.[5–7] However, the impairment of the cognitive function is influenced by various factors: age, sex, family history, educational level, and the comorbid factors of cerebrovascular disease, such as hypertension and diabetes mellitus.[3] Thus, it remains controversial how AF directly affects the human cognitive function. AF may increase the risk of an impaired cognitive function through a silent brain infarction,[8] brain hypoperfusion due to a reduced cardiac output,[9] or inflammation and platelet dysfunction.[10,11] Moreover, cerebral microbleeds during anticoagulation can also contribute to an impairment of the cognitive function.[12] Although AF contributes directly to a cognitive decline independent of a stroke, it is unclear whether restoring sinus rhythm and reducing the AF burden could attenuate a cognitive impairment. Previously, ablation-related ischemic brain lesions were detected on diffusion-weighted magnetic resonance imaging in 14%.[13] However, there are controversies regarding whether the patients with AF undergoing radiofrequency catheter ablation (RFCA) face a lower risk of dementia[14] or higher postoperative cognitive dysfunction.[15] No eligible studies have addressed whether patients with AF treated with catheter ablation differ in regards to the long-term cognitive outcomes.

In this prospective case-control study, we hypothesized that RFCA of AF may improve the cognitive function, mainly by reducing the AF burden and improving the brain hemodynamic perfusion. Additionally, we measured the plasma concentrations of the biomarkers known to be associated with the cognitive function or inflammatory process, including adiponectin and leptin, to explore the predictors of a cognitive improvement. The purposes of this study were (1) to evaluate the 1-year changes in the cognitive function after catheter ablation of AF, as compared with patients under medical therapy alone and (2) to explore the clinical variables and biomarkers associated with an improvement in the post-RFCA cognitive function.

METHODS

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population

The study protocol adhered to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the Yonsei University Health System. All patients provided written informed consent for inclusion in the Yonsei AF Ablation Cohort Database (URL: https://www.clinicaltrials.gov. Unique identifier: NCT02138695). This prospective case-control study included 308 consecutive patients with AF (71.4% male, 60.6±9.1 years of age, and 34.1% with persistent AF) who underwent RFCA as the ablation group. We also included 50 patients on medical therapy who met the same indication for AF ablation (78.0% male, 60.3±7.5 years of age, and 66.0% with persistent AF) as the control group. There was no any participant dropout during the follow-up period.

The study's exclusion criteria were as follows: (1) a history of a recent stroke or transient ischemic attack within 1 year, (2) moderate-to-severe valvular heart disease, (3) associated structural heart disease other than left ventricular hypertrophy, and (4) a history of prior RFCA. Before the ablation, the absence of a left atrial thrombus was confirmed by transesophageal echocardiography. All patients were imaged using 3-dimensional spiral computed tomography (64 Channel, Light Speed Volume CT, Philips, Brilliance 63, Amsterdam, the Netherlands) to visually define the anatomy of the left atrial and pulmonary veins. All antiarrhythmic drugs were discontinued at least 5 half-lives, and amiodarone was stopped at least 4 weeks before the procedure.

Cognitive Function Assessment

The Montreal Cognitive Assessment (MoCA) is a brief cognitive screening tool with a high sensitivity and specificity for

detecting a mild cognitive impairment,[16] and the Korean version of the MoCA has been shown to be valid and reliable as a screening tool for cognitive impairment in outpatient clinic settings.[17] MoCA scores range from 0 to 30 and are divided into 7 cognitive domains: visuospatial/executive (5 points), naming (3 points), attention (6 points), language (3 points), abstraction (2 points), short-term memory (delayed recall; 5 points), orientation (6 points), and an additional 1 point is given to each subject with an educational experience of 6 years or less. Cognitive impairment was defined as a MoCA score <23 according to a previous study.[17] All subjects underwent a prospective assessment of their cognitive function using the MoCA at 1 day before (baseline) and 3 months (intermediate term) and 1 year (long term) after the ablation procedure. The examiner was blinded to the patients' previous MoCA scores. To eliminate any learning and practice effect, we used the reliable change index (RCI) adjusted for the practice effects to measure the cognitive changes after the RFCA, while taking measurement errors and practice effects into account. The practice-adjusted RCI was defined as described by Chelune et al[18]: (X2–X1)–(M2–M1)/SED, where X1=observed pretest score; X2=observed post-test score; M1=group mean first test score; M2=group mean second test score; SED=$\sqrt{2}(SEM)^2$, where SEM=SD1$\sqrt{(1-r_{xx})}$, with SD1=SD of the pretreatment experimental group and r_{xx}=test–retest reliability coefficient. For all RCIs, the reliable change was calculated by setting α to 0.10 (2-tailed) with reliable improvement defined as values exceeding +1.645 and reliable deterioration defined as values below −1.645. We measured the global cognitive function by the total MoCA score and, thus, defined a cognitive improvement as an RCI >1.645 and cognitive deterioration as an RCI <−1.645 for the total MoCA score.[19–21]

Biochemical Analysis

A total of 2 circulating biomarkers were measured: adiponectin and leptin. Venous blood samples were collected just before the procedure in an overnight fasting status, and all samples were stored at −80°C until the assays were performed in the laboratory. The measurements of the plasma level of the adipokines (total adiponectin-Acrp30 and leptin) were performed by an ELISA (R&D Systems, Inc, Minneapolis, MN), according to the manufacturer's instructions, with intra-assay and interassay coefficients of variation below 5%.

Electrophysiological Mapping and RFCA

The details regarding the electrophysiological mapping and RFCA technique and strategy were as described in the previous studies.[22] In brief, we used an open irrigated-tip catheter (Celsius, Johnson & Johnson Inc; Diamond Bar, CA; Coolflex, St Jude Medical Inc, Minnetonka, MN; 30–35 W; 47°C) to deliver RF energy for the ablation. All patients initially underwent a circumferential pulmonary vein isolation and bidirectional block of the cavo-tricuspid isthmus. For the patients with persistent AF, we added a roofline, posterior inferior line, and anterior line[23] as the standard lesion set. The operator could opt to perform additional ablation in the superior vena cava or of non-PV foci or conduct a complex fractionated electrogram-guided ablation at his discretion. If mappable AF triggers or atrial premature beats remained, we carefully mapped and ablated those non-PV foci as much as possible. All catheter ablation procedures were conducted by 2 operators with over 10 years of experience, according to the specific protocol described above.

Anticoagulation Strategy

For peri-procedural anticoagulation, we used uninterrupted vitamin K antagonist (VKA) in 41.9% (129/308) and single morning dose skips nonvitamin K antagonist in 58.1% (179/308). All patients received oral anticoagulation therapy with VKA or nonvitamin K antagonist at least 1 month before and 3 months after the procedure. In patients who received VKA, VKA was started at least 8 to 10 weeks before the ablation, and a therapeutic international normalized ratio of 2 to 3 for at least 4 weeks was required before the procedure. Patients underwent ablation procedures with uninterrupted warfarin therapy. Systemic anticoagulation was performed with intravenous heparin to maintain an activated clotting time of 350 to 400 seconds throughout the procedure. In uncomplicated procedures, oral anticoagulation was maintained/restarted with the previous schedule before the procedure and was continued for at least 3 months. After 3 months of AF ablation, the antithrombotic strategy was determined based on the CHA_2DS_2-VASc score.[24]

Follow-Up After Ablation

All patients in the ablation group were followed with the antiarrhythmic drugs discontinued after the catheter ablation. Patients were asked to attend scheduled outpatient follow-up appointments 1 and 3 months after the RFCA and every 6 months thereafter. We evaluated the follow-up MoCA score at 3 months and 1 year after the RFCA follow-up visit. An ECG was obtained during each visit, and additional ECGs were performed when patients' symptoms were suggestive of AF. A 24-hour Holter ECG monitor or an event recorder was worn by the patients at 3, 6, and 12 months at a minimum, according to the Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society Expert Consensus Statement guidelines.[25] Additionally, whenever patients reported symptoms of palpitations, Holter monitor or event monitor recordings were obtained and evaluated for possible recurrence of the arrhythmia. We defined a recurrence of AF as any episode of AF or atrial tachycardia lasting longer than 30 seconds.[24]

Statistical Analysis

Continuous variables are expressed as the mean±SD, and categorical variables are expressed as frequencies (percentage). Normality tests were performed for each variable to determine whether a data set was well-modeled by a normal distribution. Continuous variables were compared by Student *t* tests or a Mann-Whitney *U* test, whereas categorical variables were compared using a χ^2 test or Fisher exact test. To compare the serial changes in the cognitive function over time, we used a linear mixed-model analysis. Response variable was the longitudinal change of MoCA test (total and subdimension scores) at 3 months and 1 year after

Table 1. Baseline Characteristics of the Overall and Matched Populations

	Overall Population			Propensity Score-Matched (3:1) Population		
	Ablation (n=308)	Contro (n=50)	*P* Value	Ablation (n=150)	Control (n=50)	*P* Value
Age	60.6±9.1	60.3±7.5	0.837	60.1±7.9	60.3±7.5	0.824
Male, n (%)	220 (71.4)	39 (78.0%)	0.334	118 (78.7%)	39 (78.0%)	0.921
BMI, kg/m^2	24.7±3.2	25.7±3.1	0.040	24.9±3.1	25.7±3.1	0.113
Nonparoxysmal AF, n (%)	105 (34.1)	33 (66.0%)	<0.001	95 (63.3%)	33 (66.0%)	0.734
Comorbidities						
Heart failure, n (%)	49 (15.9)	5 (10.0%)	0.201	17 (11.3%)	5 (10.0%)	0.794
Hypertension, n (%)	148 (48.0)	24 (48.0%)	0.977	75 (50.%)	24 (48.0%)	0.806
Diabetes mellitus, n (%)	52 (16.9)	10 (20.0%)	0.653	31 (20.7%)	10 (20.0%)	0.919
Stroke/TIA, n (%)	52 (16.9)	4 (8.0%)	0.070	13 (8.7%)	4 (8.0%)	1.000
Vascular disease, n (%)	52 (16.9)	2 (4.0%)	0.009	12 (8.0%)	2 (4.0%)	0.524
Chronic kidney disease, n (%)	24 (7.8%)	2 (4.0%)	0.553	7 (4.6%)	2 (4.0%)	1.000
Anemia, n (%)	27 (8.8%)	3 (6.0%)	0.781	9 (6.0%)	3 (6.0%)	1.000
CHA_2DS_2-VASc score	2.0±1.6	1.5±1.3	0.016	1.6±1.4	1.5±1.3	0.710
Baseline MoCA score	24.88±2.99	25.39±2.53	0.771	25.36±2.39	25.39±2.53	0.903
Baseline cognitive impairment	57 (18.5%)	5 (10.0%)	0.100	16 (10.6%)	5 (10.0%)	0.894
Echocardiography						
LA diameter, mm	41.9±6.8	43.6±6.7	0.082	43.2±7.0	43.6±6.7	0.723
LA volume index, mL/m^2	39.0±15.4	40.5±13.1	0.532	41.5±14.8	40.8±13.1	0.787
LVEF, %	62.9±8.6	62.4±7.1	0.713	62.7±6.6	62.4±7.1	0.597
E/E′	10.6±4.5	9.5±2.8	0.021	9.9±4.5	9.5±2.8	0.327
LVEDD, mm	50.1±4.7	49.6±4.0	0.505	50.2±4.2	49.5±4.0	0.826

Values are expressed as an (%) or the mean±SD. Cognitive impairment was defined as a total MoCA score of <23 points. Chronic kidney disease was defined as an eGFR <60 mL/min per 1.73 m^2. Anemia was defined as a hemoglobin concentration of <13 g/dL for men and <12 g/dL for women.

AF indicates atrial fibrillation; BMI, body mass index; LA, left atrium; LV, left ventricle; LVEDD, LV end-diastolic dimension; LVEF, LV ejection fraction; MoCA, Montreal Cognitive Assessment; and TIA, transient ischemic attack.

ablation or the equivalent time in the control group. Two fixed effects were included: one between-subjects ablation effect (ablation versus control) and one within-subject time effect (time: baseline, 3 months, and 1 year). Possible differenced in the ablation effect for over time (from baseline to 1 year) were analyzed according to time×group interactions. Analyses of the mixed model were adjusted for age, sex, prior stroke/transient ischemic attack, and baseline MoCA score. A multivariable linear regression analysis was used to explore the associated variables of a pre-RFCA impaired cognitive function, and a multivariable logistic regression analysis was used to identify any predictors of an improvement of cognitive function. Propensity scores were used to match the ablation group to the control group to reduce the potential confounding factors. Ablation and control groups were then matched according to the propensity score in a 3:1 ratio, without a replacement. A matching caliper of 0.1 standard deviations of the logic of the estimated propensity score was enforced to ensure that matches of poor fit were excluded. For the in-group comparison of cognitive changes after AF ablation, we analyzed using data of overall patients in the ablation group. Statistical analysis was performed using Statistical Package for Social Sciences version 23.0 (SPSS Inc, Chicago, IL) and R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

The final sample size for the longitudinal study was 308 and 50 in the ablation and control groups, respectively. The baseline characteristics of the ablation and control groups are shown in Table 1. Among the ablation group, pre-RFCA cognitive impairment (total MoCA score <23) was found in 18.5%. The patients with a baseline cognitive impairment were older (*P*<0.001), were more likely to be female (*P*<0.001), had higher CHA_2DS_2-VASc scores (*P*<0.001), and had a past history of a stroke/transient ischemic attack (*P*=0.004) and anemia (hemoglobin <13 g/dL for men and <12 g/dL for women; *P*=0.016) more often than in those without a baseline cognitive impairment (Table I in the Data Supplement). Although we did not quantify AF burden accurately, baseline MoCA scores were lower (24.6±3.1 versus 25.0±2.8) and proportions of baseline cognitive impairments (MoCA <23) were higher (21.9% versus 16.7%) in patients with persistent AF compared with those with paroxysmal AF without statistical significance. The plasma levels of leptin were significantly

Table 2. Linear Regression Analysis for the Clinical Variables Predictive of the Baseline MoCA Score

	Univariable Analysis		Multivariable Analysis	
	β (95% CI)	*P* Value	β (95% CI)	*P* Value
Age	−0.119 (−0.153 to −0.085)	<0.001	−0.111 (−0.162 to −0.059)	<0.001
Male	1.836 (1.122 to 2.550)	<0.001	0.888 (−0.590 to 2.367)	0.238
BMI, kg/m^2	−0.076 (−0.181 to 0.030)	0.158		
AF type (nonparoxysmal)	−0.526 (−1.232 to 0.180)	0.144		
Heart failure	−0.245 (−1.163 to 0.672)	0.599		
Hypertension	−1.056 (−1.718 to −0.395)	0.002	−0.509 (−1.348 to 0.329)	0.232
Diabetes mellitus	−0.827 (−1.719 to 0.064)	0.069		
Prior stroke/TIA	−1.059 (−1.947 to −0.170)	0.020	−0.557 (−1.587 to 0.474)	0.288
Vascular disease	−0.434 (−1.329 to 0.461)	0.341		
Chronic kidney disease	−1.768 (−3.004 to −0.531)	0.005	−1.124 (−2.697 to 0.450)	0.161
Anemia	−4.031 (−3.528 to −1.214)	<0.001	−2.630 (−4.190 to −1.070)	0.001
LA diameter, mm	−0.022 (−0.071 to 0.028)	0.392		
LVEF (%)	−0.014 (−0.053 to 0.025)	0.492		
E/E′	−0.143 (−0.218 to −0.067)	<0.001	0.007 (−0.088 to 0.102)	0.891
Leptin, ng/mL	−0.148 (−0.226 to −0.070)	<0.001	−0.107 (−0.203 to −0.010)	0.031
Adiponectin, μg/mL	−0.085 (−0.179–0.008)	0.073		

Multivariable analysis to adjust for the age, sex, hypertension, stroke/TIA, chronic kidney disease, anemia, LA diameter, leptin, and adiponectin. AF indicates atrial fibrillation; BMI, body mass index; LA, left atrium; LVEF, left ventricle ejection fraction; MoCA, Montreal Cognitive Assessment; and TIA, transient ischemic attack.

lower in the patients with an impaired cognitive function than in their counterparts (*P*=0.028). Multivariable linear regression analyses showed that old age (β, −0.11 [−0.16 to −0.06]; *P*<0.001), high plasma leptin levels (β, −0.11 [−0.20 to −0.01]; *P*=0.031), and anemia (β, −2.63 [−4.19 to −1.07]; *P*=0.001) were independently associated with a low preablation baseline MoCA score (Table 2).

Cognitive Function Changes Over 1 Year After AF Ablation

There was no major cardiovascular cerebral event or death during the follow-up period in either the ablation group or control group. Table 3 summarizes the changes in the MoCA scores over time and compares the overall ablation group, propensity score-matched ablation group, and control group. Significant improvements in the cognitive performance were observed in propensity score-matched ablation groups (25.4±2.4 at baseline, 26.6±2.3 at 3 months, and 26.5±2.3 at 1 year; *P*<0.001 for the time effect). In contrast, the control group did not exhibit any significant changes in the total MoCA score (25.4±2.5 at baseline, 25.2±2.3 at 3 months, and 24.8±2.5 at 1 year; *P*=0.064 for the time effect). The cognitive trajectory significantly differed between the propensity score-matched ablation group and control group (*P*=0.005; Figure 1A). The changes of 1-year follow-up total MoCA scores ($\Delta MoCA_{1yr}$) were a mean of 1.1 in the matched ablation group, but −0.7 in the control group (*P*<0.001; Figure 2). Ablation group resulted in a significant improvement of the total MoCA score (*P*<0.001), whereas control group showed in a significant reduction in the total MoCA score (*P*=0.012) from baseline to 1-year follow-up (Figure I in the Data Supplement).

Figure 1 shows the changes in the total MoCA scores over the 1-year period after the ablation with respect to the various clinical situations. The improvements in the 1-year post-RFCA MoCA score were consistent, regardless of the age, sex, a previous stroke, AF type, and there was no difference in $\Delta MoCA_{1yr}$ between VKA group (1.6±2.2) and nonvitamin K antagonist group (1.4±2.1; *P*=0.453). However, patients with preablation cognitive impairment (MoCA scores <23) showed a more improved cognitive performance over time than their counterparts (*P*<0.001; Figure 1B). Their total MoCA scores improved to over ≥23 in 65% (37/57) at 3 months and in 70% (40/57) at 1 year after the ablation, respectively.

Cognitive Function According to Recurrence After the Ablation

Among 308 patients who underwent RFCA, 25.3% (78/308) showed early recurrence, and 15.2% (47/308) showed clinical recurrence. However, more than half of recurred patients restored sinus rhythm after taking antiarrhythmic drugs and did not show recurrence within a year (8.8%; 27/308). Remaining 6.5% (20/308)

Table 3. Changes in the Total Score and Each Neuropsychological Domain of the MoCA Between Baseline, 3 Month, and 1 Year After Ablation in the Ablation and Control Groups

MoCA Dimensions	Baseline	Post-3 mo RFCA	Post-1 y RFCA	Overall *P* Value*	Baseline vs 3 mo*	Baseline vs 1 y*	3 mo vs 1 y*
Overall ablation group (n=308)							
Total MoCA score	24.88±2.92	26.30±2.67	26.36±2.49	<0.001	<0.001	<0.001	0.803
Visuoexecutive/5	4.15±0.92	4.42±0.82	4.35±0.80	<0.001	0.001	0.003	0.497
Naming/3	2.78±0.52	2.83±0.46	2.89±0.42	0.069	0.314	0.001	0.019
Attention/6	5.36±0.89	5.55±0.81	5.41±0.89	0.060	0.001	1.000	0.078
Language/3	2.64±0.54	2.79±0.43	2.92±0.31	<0.001	0.001	<0.001	0.001
Abstraction/2	1.70±0.52	1.85±0.42	1.86±0.39	0.069	0.053	0.021	0.971
Short-term memory/5	2.29±1.43	2.91±1.36	2.94±1.25	<0.001	<0.001	<0.001	0.962
Orientation/6	5.96±0.22	5.98±0.15	6.00±0.06	0.540	0.449	0.125	1.000
Matched ablation group (n=150)							
Total MoCA score	25.36±2.39	26.57±2.29	26.47±2.26	<0.001	<0.001	<0.001	1.000
Visuoexecutive/5	4.29±0.76	4.44±0.77	4.37±0.74	0.152	0.096	1.000	0.848
Naming/3	2.83±0.42	2.89±0.34	2.95±0.34	0.021	0.393	0.039	0.269
Attention/6	5.51±0.78	5.61±0.67	5.40±0.91	0.069	0.463	0.845	0.070
Language/3	2.66±0.55	2.79±0.41	2.92±0.34	<0.001	0.053	<0.001	0.008
Abstraction/2	1.78±0.43	1.89±0.31	1.88±0.37	0.019	0.017	0.111	1.000
Short-term memory/5	2.29±1.34	2.96±1.26	2.96±1.19	<0.001	<0.001	<0.001	1.000
Orientation/6	5.99±0.09	5.99±0.09	6.00±0.00	0.608	1.000	0.958	0.958
Control group (n=50)							
Total MoCA score	25.39±2.53	25.24±2.31	24.82±2.47	0.064	1.000	0.100	0.147
Visuoexecutive/5	4.04±0.87	3.78±1.01	3.78±0.90	0.026	0.095	0.053	1.000
Naming/3	2.92±0.34	2.96±0.21	2.84±0.42	0.036	1.000	0.344	0.031
Attention/6	5.06±1.12	5.02±1.04	4.75±1.20	0.056	1.000	0.111	0.108
Language/3	2.78±0.42	2.80±0.45	2.84±0.37	0.751	1.000	1.000	1.000
Abstraction/2	1.90±0.36	1.86±0.47	1.88±0.33	0.814	1.000	1.000	1.000
Short-term memory/5	2.75±1.23	2.78±1.03	2.67±0.95	0.161	1.000	1.000	0.183
Orientation/6	6.00±0.00	6.00±0.00	6.00±0.00	…	…	…	…

Values are mean±SD. MoCA, Montreal Cognitive Assessment; RFCA, radiofrequency catheter ablation; and TIA, transient ischemic attack.
*Overall *P* value is from a linear mixed-model repeated measures analysis adjusted for the time, age, sex, prior stroke/TIA, and baseline MoCA score, and the *P* values for pairwise comparisons are Bonferroni-corrected.

sustained AF during follow-up period. Although there was no difference in $\Delta MoCA_{1yr}$ between no recurrence group and restoring sinus rhythm after clinical recurrence group (1.5±2.2 versus 1.4±1.9; *P*=0.767), the patients with sustaining AF after clinical recurrence showed significantly lower $\Delta MoCA_{1yr}$ (0.5±1.8; *P*=0.039; Figure II in the Data Supplement).

Cognitive Function Changes According to the RCI Analyses

To exclude any learning or practice effects, we evaluated the changes in the MoCA scores according to the RCI analyses (Figure III in the Data Supplement). When comparing the baseline to the 3-month post-RFCA total MoCA score, 6.7% of the matched ablation group and 4.0% of the control group had improved, although 4.7% of the matched ablation and 6.0% of the control group showed deteriorated MoCA scores (*P*=0.746 for comparisons between groups). At 1 year, increases in the MoCA score were observed in 6.0% of the matched ablation group and 4.0% of the control group, and deteriorations were noted in 5.3% of the matched ablation and in 10.0% of the control group (*P*=0.318 for comparisons between groups).

Factors Associated With a Cognitive Function Improvement

On the basis of RCI of total MoCA score, 26 patients (8.4%) had cognitive improvement, and 19 patients (6.2%) had cognitive deterioration at 1 year in the overall ablation group. In the logistic regression analysis, a preablation cognitive impairment defined by a

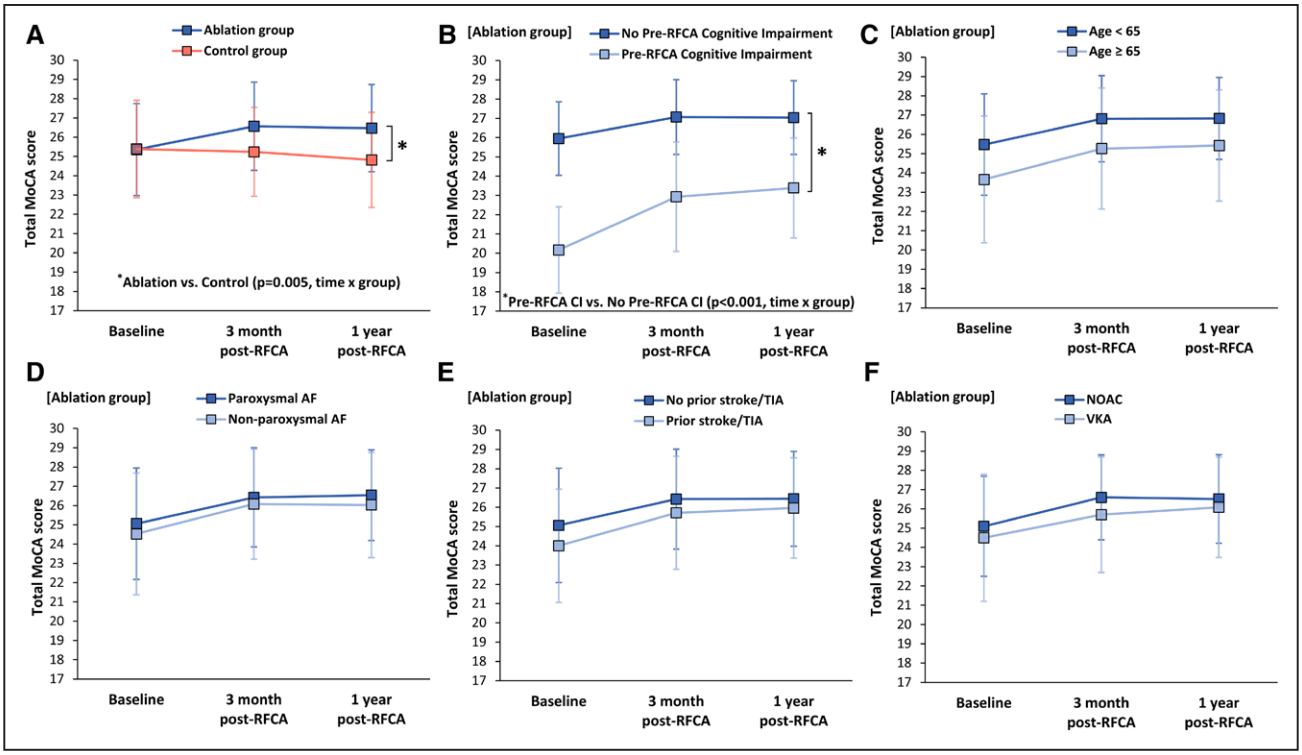

Figure 1. Comparison of the cognitive trajectory over 1 year after atrial fibrillation (AF) ablation with respect to various clinical situations. **A**, Propensity score-matched ablation group vs control group (*P*=0.005, time×group). **B**, Patients with baseline cognitive impairment vs those without among the total ablation group (*P*<0.001, time×group). Cognitive trajectories with respect to the (**C**) age, (**D**) AF type, (**E**) presence of a prior stroke before ablation, and (**F**) kind of peri-procedural anticoagulation. MoCA indicates Montreal Cognitive Assessment; RFCA, radiofrequency catheter ablation; TIA, transient ischemic attack; and VKA, vitamin K antagonist.

total MoCA score of <23 was significantly associated with a cognitive function improvement after AF ablation (odds ratio, 13.70; 95% CI, 4.83–38.87; *P*<0.001; Table 4). Although the plasma levels of leptin were associated with a baseline impaired cognitive function (Table 2), it did not predict an improvement in the MoCA score at 1 year after AF ablation. Sustained AF after recurrence following the ablation was significantly associated with a cognitive deterioration after the procedure (odds ratio, 4.96; 95% CI, 1.39–17.76; *P*=0.014; Table 5).

DISCUSSION

In this study, we demonstrated the beneficial effect of AF catheter ablation in the relatively long-term (1 year) cognitive function assessed by the MoCA score. A preprocedural cognitive impairment (MoCA <23) was detected in 18.5% of patients and was associated with old age, anemia, and high plasma leptin levels. At 1 year after the AF ablation, the MoCA score increased with statistical significance, especially in patients with an impaired cognitive function before the AF ablation, but not in the control group. In the RCI analyses, AF ablation did not at least adversely affect the cognitive function over 1 year after the catheter ablation of AF.

Mechanism of an AF-Related Cognitive Impairment

Although data have emerged showing that AF is associated with a cognitive impairment and dementia

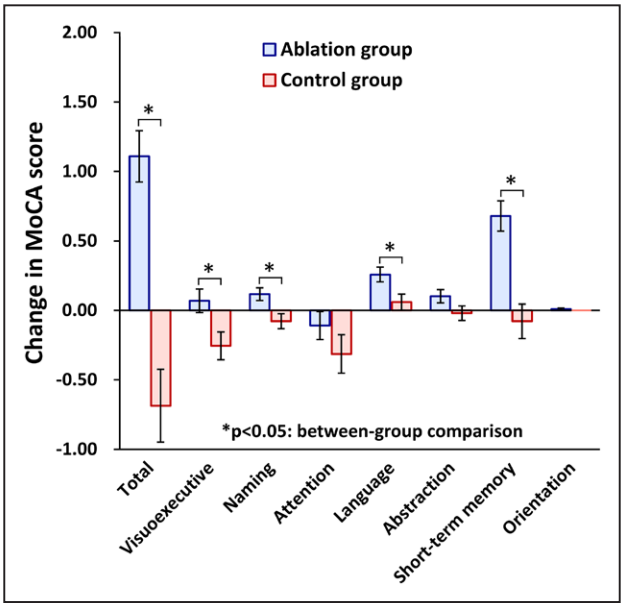

Figure 2. Detailed analysis of changes in total and subtest Montreal Cognitive Assessment (MoCA) scores from baseline to 1-year follow-up between propensity score-matched ablation and control groups.

Table 4. Logistic Regression Analysis for the Clinical Variables Predictive of a Cognitive Improvement 1 Year After AF Ablation

	Univariable Analysis		Multivariable Model 1*		Multivariable Model 2†	
	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Age	1.043 (0.997–1.091)	0.069	0.998 (0.944–1.054)	0.931	0.989 (0.935–1.046)	0.697
Male	0.430 (0.191–0.972)	0.043	0.850 (0.337–2.146)	0.731	0.896 (0.352–2.281)	0.818
AF type (Nonparoxysmal AF)	0.848 (0.356–2.020)	0.709			0.593 (0.223–1.575)	0.295
Heart failure	0.958 (0.315–2.911)	0.939				
Hypertension	1.818 (0.798–4.145)	0.155				
Diabetes mellitus	0.620 (0.179–2.147)	0.620				
Prior stroke/TIA	1.190 (0.427–3.316)	0.739			0.671 (0.216–1.575)	0.490
Baseline cognitive impairment	11.428 (4.766–27.399)	<0.001	11.044 (4.148–29.406)	<0.001	13.704 (4.831–38.872)	<0.001
AF rhythm at baseline test	2.071 (0.893–4.801)	0.090				
Recurrence after the ablation	1.011 (0.332–3.078)	0.985			1.103 (0.328–3.714)	0.874
Sinus restored after recurrence	0.544 (0.068–4.123)	0.530				
Sustained AF after recurrence	1.402 (0.392–5.012)	0.603				
Leptin, ng/mL	1.015 (0.936–1.101)	0.723				
Adiponectin, μg/mL	1.005 (0.905–1.116)	0.924				

Cognitive improvement defined as a value exceeding +1.645 and cognitive deterioration defined as a value below −1.645 on the basis of a reliable change index. AF indicates atrial fibrillation; OR, odds ratio; and TIA, transient ischemic attack.

*Model 1; adjusted for the age, sex, and baseline cognitive impairment.

†Model 2; adjusted for the age, sex, AF type, prior stroke/TIA, baseline cognitive impairment, and recurrence after the ablation.

independent of a stroke,[5,6,26,27] the association is only independent of a clinically manifested stroke and the possibility of an association with a silent micro-infarction cannot be ruled out. However, several recent studies that used detailed cerebral imaging to exclude patients with silent strokes also showed an association between AF and a cognitive impairment.[7,9] Consequently, various mechanisms have been suggested to explain the association between AF and a cognitive impairment. The other potential, but unproven, mechanism is brain hypoperfusion following a reduced stroke volume and cardiac output attributable to a beat-to-beat variability in the length of the cardiac cycle.[9,28] Since 2 landmark studies in the 1980s demonstrated that patients with AF had a reduced regional cerebral blood flow compared with controls,[28] and that the cerebral blood flow increased after electric cardioversion of AF,[29] Jefferson et al[30] showed that a decreasing cardiac index followed by cerebral hypoperfusion were associated with brain aging and a lower brain volume. Furthermore, Stefansdottir et al[5] recently reported that AF was associated with a lower total brain volume, and that the association was stronger with an increasing burden of AF independent of a stroke, suggesting a cumulative negative effect of AF on the cognitive function. Other small studies have reported that anti-inflammatory therapy with cholesterol-lowering agents could improve the neurocognitive function and modify the loss of the brain volume.[10,31] A higher number of cerebral microbleeds, which may be induced by both ischemic strokes and chronic anticoagulation, also have been reported to be associated with a lower cognitive performance.[12] Therefore, the precise causality between AF and a cognitive decline and dementia has not yet been proven, and all of these mechanisms could have an impact on the brain and cognitive function.

Impact of Catheter Ablation of AF on Cognitive Impairment

Bunch et al[14] previously reported that AF ablation patients (n=4212) had a significantly lower risk of dementia than age-matched and sex-matched patients with AF without ablation (n=16 848) in a retrospective study. In the current study, we evaluated the cognitive function before and after the AF ablation as a prospective design and found an improvement in the cognitive function 1 year after the RFCA. Restoring sinus rhythm after AF ablation improves both the systolic and diastolic function[32] and may help the recovery from cerebral hypoperfusion and a cognitive impairment in patients with AF. However, Medi et al[15] reported that AF ablation had a 13% to 20% incidence of post-procedural neurocognitive dysfunction among 90 patients with AF. They suggested potential subclinical cerebral ischemia, which is reported to be 7% to 14% after AF ablation with an irrigated-tip catheter, as a potential mechanism.[33] They used general anesthesia and replaced warfarin with low-molecular-weight heparin 5 days before the procedure, and their intraprocedural target activated clotting time was 300 to 350 seconds. In contrast, we used conscious seda-

Table 5. Logistic Regression Analysis for the Clinical Variables Predictive of a Cognitive Deterioration 1 Year After AF Ablation

	Univariable Analysis		Multivariable Model 1*		Multivariable Model 2†	
	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Age	0.989 (0.941–1.041)	0.679	0.991 (0.939–1.047)	0.750	1.002 (0.948–1.059)	0.948
Male	1.128 (0.394–3.232)	0.822	1.057 (0.355–3.143)	0.921	0.888 (0.294–2.686)	0.833
AF type (Nonparoxysmal AF)	1.137 (0.434–2.979)	0.794			0.983 (0.973–2.735)	0.983
Heart failure	1.446 (0.459–4.557)	0.529				
Hypertension	1.216 (0.480–3.080)	0.680				
Diabetes mellitus	0.562 (0.126–2.512)	0.451				
Prior stroke/TIA	0.259 (0.034–1.986)	0.194			0.332 (0.045–2.858)	0.358
Baseline cognitive impairment	0.231 (0.030–1.768)	0.158			0.197 (0.030–2.060)	0.250
AF rhythm at baseline test	0.641 (0.242–1.699)	0.371				
Recurrence after the ablation	1.221 (0.449–3.324)	0.696				
Sinus restored after recurrence	0.544 (0.068–4.123)	0.530				
Sustained AF after recurrence	4.250 (1.272–14.197)	0.019	4.505 (1.338–15.167)	0.015	4.963 (1.387–17.764)	0.014
Leptin, ng/mL	1.013 (0.900–1.139)	0.833				
Adiponectin, μg/mL	0.952 (0.772–1.175)	0.650				

Cognitive improvement defined as a value exceeding +1.645 and cognitive deterioration defined as a value below −1.645 on the basis of a reliable change index. AF indicates atrial fibrillation; OR, odds ratio; and TIA, transient ischemic attack.

*Model 1; adjusted for the age, sex, and sustained AF after recurrence.

†Model 2; adjusted for the age, sex, AF type, prior stroke/TIA, baseline cognitive impairment, and sustained AF after recurrence.

tion, an uninterrupted VKA or single morning dose skip nonvitamin K antagonist schedule, and a target activated clotting time of 350 to 400 seconds. Further prospective studies with larger numbers of patients are warranted to explain the contradictory results of the above 3 studies.

Study Limitations

Our study had several limitations. First, as the current study included selective patients referred for AF catheter ablation, the findings cannot be generalized to all types of AF in the general population. Second, this study was a prospective, but not randomized controlled study, and thus, the results of this study should be interpreted with caution. However, all clinical variables were comparable between the ablation and control groups, and the cognitive function improvement in the ablation group (even after an adjustment using the practice-adjusted RCI) itself has an important clinical implication. Third, the small sample size in the control group may have underpowered the analysis, although appropriate sample sizes of cognitive function in patients with AF, particularly in patients undergoing RFCA, have not yet been established. Fourth, the absolute change of MoCA score in the study seemed small compared with wide SD, but the MoCA score has been preferred to detect serial changes in cognitive function, and even small change of the MoCA score was associated with neuropsychological diagnosis transitional status.[34,35] Fifth, we did not evaluate subjective cognitive decline in this study. Finally, we did not perform a brain imaging study before or after the ablation procedure to exclude any potential silent cerebral emboli.

CONCLUSIONS

AF catheter ablation, at least, does not cause a deterioration of the cognitive function, but improves the 1-year follow-up MoCA scores, especially in patients with an impaired cognitive function before ablation. Further randomized controlled studies that utilize larger populations with longer follow-up periods are warranted.

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Disclosures

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