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Original Article

Long-term observation of fibrillation cycle length in patients under angiotensin II receptor blocker therapy for chronic atrial fibrillation

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ABSTRACT

Introduction: The long-term effect of angiotensin II receptor blockers (ARBs) on atrial fibrillation (AF) is unclear. In this study, we evaluated the change in the fibrillation cycle length (FCL) in patients under long-term ARB therapy for chronic AF.

Methods and results: The study population consisted of 25 chronic AF patients who were prescribed the same medication for more than 6 years and in whom specific ECG recording for FCL evaluation could be performed before and after the 6-year observation period. The patients were divided into 2 groups: those with and without ARB (ARB group and non-ARB group and $n=15$ and 10 , respectively). FCL was calculated by the spectral analysis of the fibrillation waves in the surface ECG. There was no significant difference in the clinical characteristics between the 2 groups. In the ARB group, the mean FCL was prolonged from 154 ± 20 ms to 187 ± 37 ms ($p=0.005$), whereas it remained unchanged in the non-ARB group (150 ± 12 ms vs. 149 ± 10 ms). In the comparison between patients with and those without FCL prolongation (> 30 ms; $n=6$ and 19 , respectively), a significant difference was observed only in those prescribed ARBs.

Conclusion: In cases of chronic AF, FCL might be prolonged under long-term ARB treatment.

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1. Introduction

Several experimental studies utilizing animal models of atrial fibrillation (AF) have shown a suppressive effect of angiotensin II receptor blockers (ARBs) on the process of atrial remodeling serving as the arrhythmogenic substrate for AF [1,2]. We have previously reported that olmesartan suppresses the increase in AF inducibility in a canine AF model by the suppression of tissue fibrosis and down-regulation of connexin 43. Even in clinical patients with AF, several sub-analyses of mega-trials have highlighted

the potential of using ARBs as upstream therapeutic agents for the suppression of AF [3–5]. However, recent prospective clinical trials on ARBs with suppression of AF as the primary endpoint have failed to document positive results [6,7]. These results clearly indicate that the suppression of AF using upstream ARB therapy is complicated and that its effect should be evaluated by a specific method of determining whether there is any positive effect in clinical AF cases.

In the present study, we focused on the long-term effect (in years) of ARBs on the AF substrate. However, evaluation of the atrial electrophysiological properties of clinical patients is technically difficult because an invasive cardiac electrophysiological study using electrode catheters cannot be repeated frequently. Instead, we measured the fibrillation cycle length (FCL) by the spectral analysis of the fibrillation waves in the surface electrocardiogram

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(ECG) [8–11] since it is a non-invasive and easy method for evaluating the electrophysiological properties of the atria [12–16]. Therefore, factors influencing the atrial electrophysiological properties, if present, might be detected by the observation of the FCL. In this study, we evaluated a change in the fibrillation cycle length (FCL) in patients with chronic AF under long-term, i.e., 6-year, ARB therapy, and FCL and clinical data were compared between patients with and without ARB therapy.

2. Method

2.1. Study population

The study population consisted of 25 patients with chronic AF. They were retrospectively recruited from 198 consecutive patients with chronic AF who visited the outpatient clinic of Kitasato University Hospital, between January and December 2010. The following criteria were used for patient selection: (1) diagnosis of chronic AF made 6 years back; (2) FCL measurement using spectral analysis performed 6 years back; (3) prescription unchanged during the last 6 years; (4) clinical symptomatic level scored as class 1 or 2 of the New York Heart Association classification; (5) no documented ischemic heart disease, revascularization, or cardiac surgery in the previous year; (6) no antiarrhythmic drug use; and (7) no history of catheter ablation therapy. Concomitant control of the ventricular rate with β -adrenergic receptor antagonists, calcium-channel blockers, and digitalis was permitted. All patients were prescribed an optimal dose of warfarin as anticoagulation therapy to prevent any cardiogenic embolisms. The retrospective observation period was 6.0 ± 0.8 years, and specific surface 12-lead ECG recording for the spectral analysis was performed to evaluate the FCL. All patients underwent transthoracic echocardiography and physical examination before and after the observation period to exclude serious heart disease, and the left atrial dimension (LAD) was measured in the long axis view (Hewlett-Packard, SONOS-5500, Tokyo, Japan). The index for the change in the LAD during the follow-up period (Δ LAD) was calculated by subtracting the baseline LAD from that obtained at the follow-up. All study protocols were approved by the permission of the Ethics Committee of Kitasato University, and written informed consent was obtained from all patients.

2.2. Analysis of the fibrillation wave

Spectral analysis was performed using data from the surface ECG recording in lead V_1 (customized ECG-recorder FDX-6531, Fukuda Denshi, Co. Ltd., Tokyo, Japan), which was digitally stored offline on a microcomputer at a sampling rate of 1 kHz, and the QRS-T complexes were subtracted using a template-matching algorithm [12]. To minimize the influence of circadian change in FCL data, all ECG recordings were performed between 9:00 am and 12:00 am. Frequency analysis was performed offline on the microcomputer (BIMUTUS II, Kissei Comtec Co. Ltd, Matsumoto, Japan). Frequency analysis of the subtracted ECG involved 3 steps: (1) band-pass filtering, (2) application of the Hamming window, and (3) 4096-point fast

Fourier transformation. The 50% overlap of adjacent spectral analyses allowed the use of an average of 20 epochs of analyses within a single 44-s data set [12]. After spectral analysis, recordings were displayed as power spectra, which were quantified by measuring the peak frequency signal with the maximum magnitude derived from each epoch. The peak frequency of the spectrum in the 3–12 Hz range was converted to a cycle length (CL in ms = $1000/\text{frequency}$), defined as FCL, and was calculated as an average of 20 epochs. The reproducibility of the FCL data was confirmed by repeating the specific ECG recording for FCL analysis at least twice in each patient [12]. The index for the change in FCL during the follow-up period (Δ FCL) was calculated by subtracting the baseline FCL from that obtained at the end of the follow-up period.

2.3. Grouping and comparison of the data

First, the 25 patients were divided into 2 groups: those with and those without ARB therapy, and the FCL and clinical data were compared between the groups. Second, the 25 patients were divided into 3 groups by the change in the FCL during the 6-year observation period (Δ FCL), i.e., prolonged, unchanged, or shortened FCL groups, and the clinical parameters, including ARB prescription, were compared among the groups. The presence of the change in FCL was determined by $|\Delta\text{FCL}| > 30$ ms, which is calculated as twice the mean of the standard deviations of raw FCL data of 20 epochs in each patient.

2.4. Statistical analysis

All values were expressed as the mean \pm standard deviation. Statistical analysis was performed using one-way ANOVA. A *P* value of less than 0.05 was considered significant.

3. Results

3.1. Clinical characteristics of the study population

The mean age of the study population was 66 ± 10 years; the female: male ratio was 4:21; and none of the patients had structural heart disease. The medical prescriptions are outlined in Table 1. Oral anticoagulation therapy using vitamin K antagonists was administered to all patients. Of the 25 patients, 22 had comorbid hypertension, and all the 15 patients in the ARB group were prescribed ARB for the management of hypertension. The incidence of hypertension as a comorbidity with chronic AF was higher in the ARB group than in the non-ARB group (100% vs. 70%, $p=0.024$). ARBs used in the ARB group were candesartan (4–12 mg) in 7 patients, olmesartan (10–20 mg) in 3, valsartan (40–80 mg) in 2, losartan (25–50 mg) in 2, and temisartan (20 mg) in 1. Five of the 15 patients in the ARB group were prescribed calcium-channel blockers as additional therapy for hypertension, but none of the 10 patients in the non-ARB group received calcium-channel blockers ($p=0.041$). Hypertension was treated with β -blockers and/or diuretics in the remaining patients in the non-ARB group. No difference was noted in the level of hypertension control between the

Table 1
Clinical characteristics of the patients of the ARB and non-ARB groups.

	Total (n=25)	ARB group (n=15)	Non-ARB group (n=10)	p value
Age	66 ± 2	69 ± 2	61 ± 4	0.07
Sex (M:F)	21:4	12:3	9:1	0.51
AF duration (months)	29 ± 2	32 ± 3	24 ± 4	0.07
sBP (mmHg)	123 ± 1	122 ± 2	125 ± 1	0.20
dBp (mmHg)	74 ± 1	72 ± 2	76 ± 1	0.07
Co-morbidity				
Hypertension	22 (88%)	15 (100%)	7 (70%)	0.024
Hyperlipidemia	7 (28%)	4 (27%)	3 (30%)	0.86
Diabetes mellitus	2 (8%)	2 (13%)	0 (0%)	0.23
Echocardiographic data				
LAD (mm)	49 ± 1	51 ± 2	48 ± 2	0.27
LVEF (%)	63 ± 1	64 ± 2	61 ± 2	0.36
Medication				
Calcium-channel blockers	5 (20%)	5 (33%)	0(0%)	0.041
b-blockers	13 (52%)	7 (47%)	6 (60%)	0.51
Diuretics	10 (40%)	8 (53%)	2 (20%)	0.10
Digitalis	11 (44%)	7(47%)	4 (40%)	0.74
Statins	7 (28%)	4 (27%)	3 (30%)	0.86

HR indicates heart rate; sBP, blood pressure; dBp, diastolic blood pressure; LAD, left atrial dimension; LVdD, left ventricular diastolic dimension; LVdS, left ventricular systolic dimension; LVEF, left ventricular ejection fraction; MR, mitral regurgitation and ARB, angiotensin II receptor blocker.

Table 2
Hemodynamic and echocardiographic data of the patients of the ARB and non-ARB groups.

	ARB group (n=15)			Non-ARB group (n=10)			Comparison between ARB vs. Non-ARB	
	Baseline	After the follow-up	p value	Baseline	After the follow-up	p value	Baseline (p value)	After the follow-up (p value)
Hemodynamic data								
Heart rate (bpm)	70 ± 3	72 ± 3	0.55	77 ± 2	77 ± 3	1.00	0.06	0.24
sBP (mmHg)	122 ± 2	117 ± 2	0.15	125 ± 1	119 ± 3	0.08	0.23	0.54
dBp (mmHg)	72 ± 2	68 ± 2	0.21	76 ± 1	74 ± 3	0.50	0.07	0.11
BNP (pg/mL)	101 ± 20	113 ± 21	0.68	100 ± 17	110 ± 2 9	0.75	0.95	0.93
Echocardiographic data								
LAD (mm)	51 ± 2	53 ± 2	0.29	48 ± 2	50 ± 4	0.51	0.27	0.44
LVdD (mm)	52 ± 1	50 ± 2	0.21	50 ± 2	49 ± 2	0.74	0.40	0.85
LVdS (mm)	32 ± 1	30 ± 1	0.42	36 ± 2	33 ± 2	0.31	0.09	0.29
LVEF (%)	64 ± 2	65 ± 2	0.53	62 ± 3	67 ± 1	0.07	0.36	0.51
Grade of MR (0:I:II:III:IV)	2:3:7:3:0	2:4:8:2:0	0.53	2:2:6:0:0	1:3:6:0:0	0.78	0.27	0.85

sBP, systolic blood pressure; dBp, diastolic blood pressure; LVdD, left ventricular diastolic dimension; LVdS, left ventricular systolic dimension; MR, mitral regurgitation.

2 groups ($122 \pm 7/72 \pm 7$ vs. $125 \pm 4/76 \pm 4$ mmHg, $p=0.07$). The other parameters, including transthoracic echocardiographic data, did not show significant differences between the ARB and non-ARB groups. Table 2 summarizes the hemodynamic and echocardiographic data of the patients in the ARB and non-ARB groups. Significant differences were absent between the 2 groups before and after the observation period.

3.2. Analysis of the fibrillation waves and FCL

Fig. 1 shows a representative example of the results of spectral analysis of the fibrillation waves. The 2 panels show frequency powers of 20 consecutive epochs in

the same patients before and after the 6-year follow-up period. In the provided example, the mean of the peak frequency powers was 6.67 Hz, and FCL was calculated as 150 ms at the baseline analysis; the respective values were 5.71 Hz and 175 ms in the analysis at the end of the follow-up period.

Fig. 2 shows the FCL data of the 2 groups. In the graph, each thin line indicates FCL data obtained for each patient before and after the follow-up period, and the means and zones of standard deviations are shown on both sides of these lines. At baseline analysis, there was no difference in the FCL data between the 2 groups ($p=0.62$). With regard to FCL data before and after follow-up, the ARB group exhibited significant prolongation ($p=0.005$), whereas the

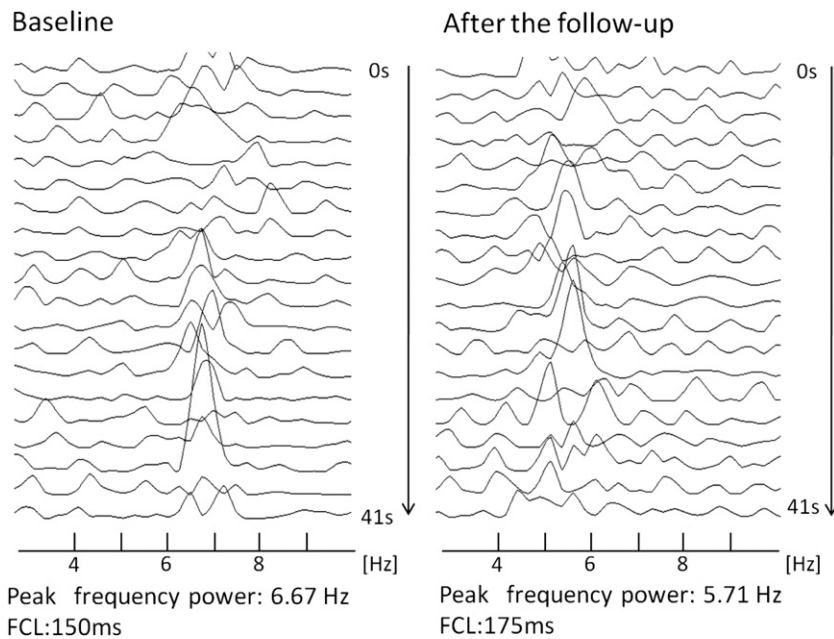


Fig. 1. An example of spectral analysis of the fibrillation waves in a surface ECG. A representative example of the results of spectral analysis of the fibrillation waves. The 2 panels show frequency powers of 40 consecutive epochs in the same patients before and after the 6 year follow-up period. The horizontal axis indicates the frequency and each trace indicates the power spectrum of the fibrillation wave in each 4-s window. Time-series spectral analysis of the fibrillation waves are shown by 3-dimensional plots of the power spectra during a 41-s period. In this example, the mean of the peak frequency powers was 6.67 Hz and FCL was calculated as 150 ms at baseline analysis; these values were 5.71 Hz and 175 ms in analysis at the end of the follow-up period.

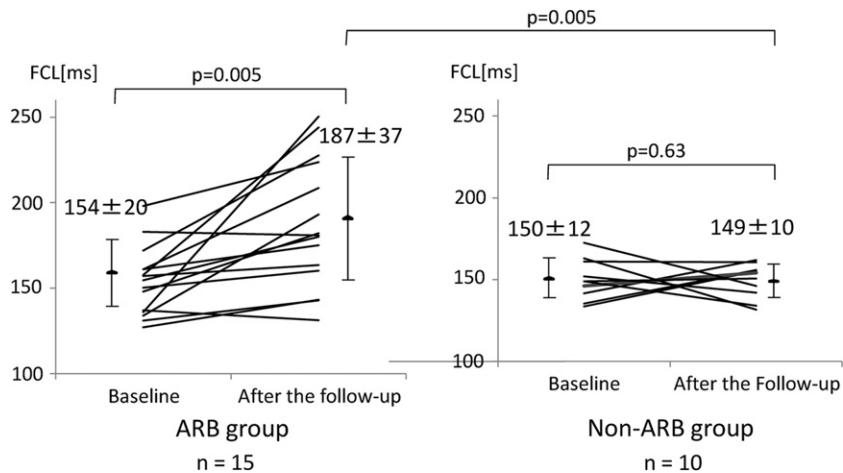


Fig. 2. FCL data of the 2 groups. This figure displays FCL data of the 2 groups. In the graph, each thin line indicates FCL data of each patient before and after the follow-up period, and the means and zones of standard deviations are shown on both sides of these lines. At baseline analysis, there was no difference in FCL data between the 2 groups ($p=0.62$). With regard to FCL data before and after follow-up, the ARB group exhibited significant prolongation ($p=0.005$) whereas the non-ARB group exhibited no difference ($p=0.63$). At analysis after follow-up, FCL was longer in the ARB group than in the non-ARB group ($p=0.005$).

non-ARB group exhibited no difference ($p=0.63$). At the end of the follow-up period, the FCL was longer in the ARB group than in the non-ARB group ($p=0.005$).

3.3. Relationship between FCL and transthoracic echocardiographic data

As shown in Table 2, transthoracic echocardiographic data did not exhibit any differences between the 2 groups or before and after the observation period. Fig. 3 shows

the relationship between Δ LAD and Δ FCL during the 6-year follow-up period. No significant relationship was noted between the 2 parameters even between the ARB sub-groups and the non-ARB group.

3.4. Comparison of patients with and without changes in FCL

Among the 25 patients, 6, 19, and no patients exhibited prolonged, unchanged, and shortened FCL at the end

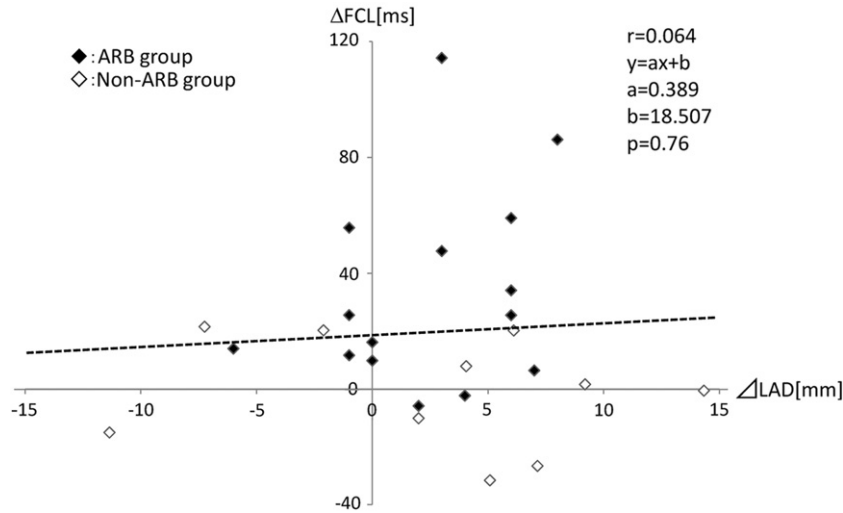


Fig. 3. The relationship between Δ LAD and Δ FCL. This figure displays the relationship between Δ LAD and Δ FCL during the 6-year follow-up period. There was no significant relationship between the 2 parameters, even among the ARB sub-groups and the non-ARB group.

Table 3

Clinical parameters of the patients of the FCL prolonged and unchanged groups.

	Total (n=25)	FCL prolonged group (n=6)	FCL unchanged group (n=19)	p value
Age	66 ± 2	69 ± 3	65 ± 2	0.07
Sex (M:F)	21:04	5:01	16:03	0.96
AF duration (months)	29 ± 2	29 ± 4	29 ± 3	0.97
HR (bpm)	72 ± 2	69 ± 4	73 ± 2	0.31
sBP (mmHg)	123 ± 1	123 ± 2	123 ± 2	0.84
dBp (mmHg)	74 ± 1	72 ± 1	74 ± 2	0.45
BNP (pg/mL)	101 ± 13	88 ± 17	105 ± 17	0.57
Co-morbidity				
Hypertension	22 (88%)	6 (100%)	16 (84%)	0.3
Hyperlipidemia	7 (28%)	2 (33%)	5 (26%)	0.74
Diabetes mellitus	2 (8%)	1 (17%)	1 (5%)	0.37
Echocardiographic data				
LAD (mm)	49 ± 1	51 ± 2	48 ± 2	0.27
LVDd (mm)	51 ± 1	53 ± 1	51 ± 1	0.43
LVDs (mm)	33 ± 1	31 ± 2	34 ± 2	0.32
LVEF (%)	63 ± 1	65 ± 2	62 ± 2	0.52
Grade of MR (0:I:II:III:IV)	4:5:13:3:0	1:2:2:1:0	1:4:12:2:0	0.59
Medication				
ARB	15 (60%)	6 (100%)	9 (47%)	0.02
Calcium-channel blockers	5 (20%)	2 (33%)	3 (16%)	0.35
b-blockers	13 (52%)	3 (50%)	10 (53%)	0.91
Diuretics	10 (40%)	2 (33%)	8 (42%)	0.7
Digitalis	11 (44%)	3 (50%)	8 (42%)	0.73
Statins	7 (28%)	2 (33%)	5 (26%)	0.74

HR, heart rate; sBP, blood pressure; dBp, diastolic blood pressure; LAD, left atrial dimension; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; LVEF, left ventricular ejection fraction; MR, mitral regurgitation and ARB, angiotensin II receptor blocker.

of the 6-year observation period, respectively. Table 3 compares the clinical parameters among these groups. As shown, ARB prescription was the only parameter that differed significantly among the groups.

4. Discussion

The present evaluation of Δ FCL in chronic AF patients over a long-term observation period revealed a few

interesting findings. First, at the end of the 6-year observation period, the mean FCL had prolonged from 154 ± 20 ms to 187 ± 37 ms in patients with ARB therapy ($p=0.005$), but remained unchanged (150 ± 12 ms vs. 149 ± 10 ms, NS) in patients without ARB therapy. To the best of our knowledge, this is the first study on the change in FCL data over a long-term observation period, during which the patients received the same medical therapy. Furthermore, the prescription of ARB was the only

parameter that differed significantly between the patients with and without FCL prolongation. Differences in the clinical background of the patients, such as age or comorbidity, did not contribute to FCL prolongation in this study, but this lack of influence may be attributable to the small study population and therefore warrants further reevaluation in a larger study population.

4.1. Atrial remodeling and FCL shortening in chronic AF

Several studies have demonstrated that the persistence of AF would cause shortening of FCL, indicating the shortening of atrial refractoriness due to the progression of atrial electrical remodeling [17,18]. Several methodologies have been proposed for evaluating FCL or atrial refractoriness, but direct measurement utilizing a catheter technique would not be feasible for long-term repetitive evaluation. Several reports have documented that spectral analysis of the fibrillation waves in the surface ECG recorded in AF patients would be useful for evaluating FCL [19–21], and this method should be useful for monitoring the change in FCL or atrial refractoriness in the same patients repeatedly and non-invasively. Using this method, Neuberger et al. showed progressive shortening of FCL in a relatively early phase of persistent AF [17]. Sasaki et al. [19] have reported that this shortening in FCL had a nadir in patients with chronic AF, and it was reported to be around 150–160 ms. It is unclear whether the patients in the present study have shown such nadir of FCL shortening at the baseline evaluation, but because the mean FCLs were 154 ± 20 ms and 150 ± 12 ms in the ARB and non-ARB groups, respectively, their FCLs seemed to be close to their nadir even at the baseline observation.

4.2. Change in FCL and action of ARBs

FCL can be affected by the action of cardioactive medication, especially antiarrhythmic agents. Fujiki et al. reported that class I antiarrhythmic agents result in the prolongation of the FCL immediately before the interruption of AF [15]. Niwano et al. reported that FCL could also be prolonged by the action of pilsicainide or bepridil, even in patients with chronic persistent AF [22]. The precise mechanism of this change in FCL is unclear because FCL is determined not only by atrial refractoriness alone but also by the complexity of plural and random reentries. It is possible that the organization or simplification of plural reentry circuits of AF results in the prolongation of FCL, which can be achieved by the action of class I or III antiarrhythmic agents [23]. In the present study, FCL in the non-ARB group remained unchanged, but it was prolonged in the ARB group at the end of the observation period. Although several experimental studies have shown that ARB would prevent the shortening of atrial refractoriness in the very early phase of atrial electrical remodeling [1,24,25], the effect of ARBs on atrial refractoriness in chronic AF has not been reported. In contrast, several experimental and clinical studies have documented a decrease in cardiac tissue fibrosis by the use of ARBs or angiotensin-converting enzyme inhibitors [26–29]. Because it has been documented that ARBs and angiotensin-converting enzyme inhibitors exert a “reverse

remodeling” effect on the structurally remodeled ventricle or atrium in patients with heart failure, reverse atrial structural remodeling might possibly explain the prolongation of FCL in the present study [30,31]. However, there was no correlation between Δ LAD and Δ FCL, and therefore, the change in FCL could not be explained by the change in the atrial dimension, at least in this study. In contrast, the improvement of atrial fibrosis might be another possible explanation for FCL prolongation. We can speculate that the decrease in intercellular fibrosis may improve electrical intercellular connections and result in an increase in conduction velocity and prolongation of the wavelength. These changes will lead to fusion of smaller reentrant circuits and may result in the organization of the reentrant circuits and prolongation of FCL. The actual structural and electrophysiological changes in the atrial tissues in the ARB group are unknown, but if long-term ARB therapy could induce the decrease in atrial fibrosis, i.e., at least a part of “reverse remodeling”, the FCL prolongation might be partly explained, albeit at a high degree of speculation. Conversely, the mechanism of unchanged FCL in the non-ARB group is also unclear, but this might be explained by the nadir of FCL shortening [19].

4.3. Limitations

This study has several limitations. First, although this study has led to some significant conclusions, the number of patients was limited and the study population may have some selection bias. Second, mainly because of the study design, interpolating data from the 6-year period are missing. Finally, data on various electrophysiological and structural parameters, such as the atrial refractory period, atrial conduction velocity, and atrial tissue fibrosis, were not available because invasive evaluation was not included in this study. These points should be resolved in a prospectively designed study with a larger study population.

5. Conclusion

Long-term (over 6 years) evaluation of FCL data was performed in patients with chronic AF, and prolongation in FCL was observed in some patients. A comparison of the clinical data suggested that ARB prescription might be considered as, at least, a causative factor of the FCL prolongation.

Disclosure

No financial support was received from any specific company for this study and there is no conflict of interest. No specific unapproved use of any compound or product occurred.

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