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Dispersion-guided ablation in conjunction with circumferential pulmonary vein isolation is superior to stepwise ablation approach for persistent atrial fibrillation☆

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ABSTRACT

Background: Due to the lack of optimal ablation strategy, the success rate of persistent atrial fibrillation (AF) is still low. We hypothesize that a strategy that targeting pulmonary triggers and dispersion areas in atria improves prognosis of persistent AF.
Methods: We prospectively enrolled 142 persistent AF patients admitted for catheter ablation. These patients were randomly assigned in a 1:1 ratio to ablation with circumferential pulmonary vein isolation (CPVI) + ablation of electrogram dispersion areas (71 patients, group A) or stepwise ablation strategy (71 patients, group B).
Results: Procedural time and fluoroscopy time did not differ between group A and group B (204.6 ± 26.9 min vs 207.8 ± 26.3 min and 7.3 ± 1.3 min vs 7.1 ± 1.3 min, respectively, $P > 0.05$), however, radiofrequency delivery time in group A was significantly shorter than that in group B (70 ± 7.2 min vs 83.2 ± 9.1 min, $P < 0.001$). In total, 265 electrogram dispersion areas were identified in 67 patients, and the most prominent areas were roof, bottom, and inferoposterior wall. The rates of acute AF endpoint (including AF termination and AFCL elongation >30 ms) and termination in group A were significantly higher than that in group B (97.2% vs. 71.8% and 70.4% vs. 15.5%, respectively, $P < 0.001$). During a follow-up period of 204 ± 67 days, both AF-free and AF/AT-free survival in group A were significantly higher than that in group B ($P = 0.012$ and $P = 0.014$, respectively).
Conclusion: Dispersion-guided ablation in conjunction with CPVI is efficient, personalized, and accurate for persistent AF.

1. Introduction

Due to the lack of optimal ablation strategy, catheter ablation for persistent atrial fibrillation (AF) is still challenging. Emerging evidence clearly supports a major role for rotors as the drivers of AF. Recently, it is reported that rotor ablation achieved a high success rate of AF termination and substantially improved outcomes of AF patients [1,2]. Nevertheless, these results were unrepeatable in other centers [3,4]. More recently, Seitz et al. reported that ablation of dispersion areas yielded a high AF termination rate [5]. This study indicated that these areas were AF drivers. Previous studies have confirmed that circumferential pulmonary vein isolation (CPVI) is the cornerstone of AF ablation [6–8]. Nonetheless, it is unclear whether ablation of dispersion areas in conjunction with CPVI would be more helpful.

In the present study, we compared two strategies for persistent atrial fibrillation ablation: CPVI + ablation of electrogram dispersion areas and stepwise ablation strategy.

2. Methods

2.1. Patients

Between July 2017 and April 2018, 142 consecutive patients underwent catheter ablation of drug refractory and symptomatic persistent AF were included.

The inclusion criteria were as follows: (1) patients aged 18 to 80 years; (2) patients with persistent or long-lasting persistent AF.

Patients were excluded if they had left atrial thrombi, severe structural cardiac disease, sick sinus syndrome, renal failure, thyroid dysfunction, left ventricular ejection fraction (LVEF) <45%, or a history of ablation procedures to treat atrial arrhythmia.

All participating patients provided written informed consent and were randomized using a computerized randomization process. This study was approved by the institutional review board of Shanghai Chest Hospital, Shanghai Jiao Tong University.

2.2. Electrophysiological study and mapping

All oral anticoagulants and antiarrhythmic drugs (AADs) were stopped for an appropriate period before ablation. Low molecular-weight heparin according to individual body weight was injected subcutaneously twice a day and withdrawn 12 h prior to ablation. Transesophageal echocardiography was performed before the ablation procedure to rule

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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out any intracardiac thrombi, and transthoracic echocardiography was performed to evaluate cardiac structure and function.

Patients were randomized into two ablation groups: group A (n = 71): CPVI + ablation of electrogram dispersion areas; group B (n = 71): stepwise ablation strategy.

A decapolar mapping catheter (Biosense Webster, Diamond Bar, CA, USA) was positioned in the coronary sinus (CS) via left femoral vein. Two SL1-type Swartz sheaths (St. Jude Medical, St. Paul, MN, USA) were advanced into the left atrium after two successful transseptal punctures. After transseptal catheterization, systemic anticoagulation was achieved with intravenous heparin (100 IU/kg) to maintain an activated clotting time between 270 s and 350 s. Selective PV venography was performed to identify all PV ostia prior to ablation. PentaRay multispline catheter (group A, Biosense Webster, Diamond Bar, CA, USA) or Lasso (group B, Biosense Webster, Diamond Bar, CA, USA) was used as a navigational catheter.

The definition of dispersion areas was as follows. (1) A reference atrial fibrillation cycle length (AFCL) was calculated by averaging 10 consecutive beats at three different times in the left atrial appendage (LAA), right atrial appendage (RAA), and prior and distal electrodes of the CS catheter. (2) The PentaRay catheter was maintained in a stable position in atria for a minimum of 10 s at each location during mapping procedure. (3) As is shown in Fig. S1A, all measurements were done at the minimum of three adjacent bipolar electrodes. When the electrogram dispersion >AFCL and was stable for 2.5 s, the area was defined as a dispersion area. (4) Exclusion. The continuous, low-voltage (<0.05 mV) fractionated electrograms and the fast electrograms (CL <120 ms) were not included in dispersion analysis. If these electrograms were recorded during mapping procedures, the areas were marked and the PentaRay catheter was moved slightly to an adjacent area.

The definition of complex fractionated atrial electrograms (CFAEs) was as follows: (1) fractionated atrial electrograms composed of ≥2 deflections and/or perturbation of the baseline with continuous deflection of a prolonged activation complex over a 5-second recording period or (2) atrial electrograms with a very short CL (<120 ms) averaged over 5 s.

2.3. Ablation protocol

Ablation was performed using irrigated-tip catheter under the guidance of an electroanatomical mapping system (CARTO, Biosense Webster, Diamond Bar, CA, USA). A contact force of 7 g was considered a minimum to deliver RF energy at any location. Radiofrequency power output was 35 W, temperature was 43 °C, the ablation time for each lesion was 20–30 s, and the saline infusion rate was 20–25 ml/min.

Detailed information of ablation strategy was as follows.

Group A: CPVI was the first step of this approach. After CPVI, mapping and ablation of electrogram dispersion areas would be performed in the LA and RA if AF persisted. If AF converted to atrial tachycardia (AT) during the procedure, AT was mapped and ablated. If AT cannot be abolished, direct current cardioversion (DCC) was performed. If AF did not terminate after CPVI after ablation of all the electrogram dispersion areas, DCC was performed.

Group B: stepwise ablation strategy was used in this group. In brief, CPVI was performed as the first step. If AF was not terminated by CPVI, linear ablation across the left atrial roof, mitral valve isthmus and cavotricuspid isthmus was performed. If AF persisted after creation of linear lesions, ablation of CFAEs was followed. If AF did not terminate, DCC was performed.

Fig. S1B and C show the flowchart and graphical demonstration of two ablation strategies.

2.4. Follow up

All patients were hospitalized for at least 3 days, the cardiac rhythm was continuously monitored during the first 48 h. After the procedure, patients continued anticoagulation with warfarin (maintaining an INR of 2–3) or novel oral anticoagulant (NOAC) for at least 3 months. A blanking period of 3 months after the initial ablation was applied in the present study. In all patients, AADs were used during the blanking period, and all class I and III AADs were to be discontinued at the end of blanking period. Patients were followed in the outpatient clinic at 1, 3, 6, and 12 months post-ablation. A 12-lead ECG and 48 h Holter recording was performed at each visit and for any symptoms suggesting arrhythmia. Monthly telephone interviews were also done during the follow-up period. A 'recurrence' of atrial arrhythmias was considered any episode lasting >30 s detected by ECG and/or Holter.

2.5. Study endpoints

The primary short-term endpoint was AF termination or >30 ms AFCL elongation. Secondary short-term endpoints included: (1) conversion to SR or AT, (2) procedure time, (3) fluoroscopy time, (4) radiofrequency delivery time, (5) incidence of procedural complication. The primary long-term endpoint was AF recurrence rate after a single procedure. Secondary long-term endpoint was AF/AT recurrence rate after a single procedure.

2.6. Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median with interquartile range and compared using independent sample *t*-tests or non-parametric tests. Categorical variables were expressed as n (%) and compared using the chi-square test or Fisher exact test as appropriate.

Survival analyses were performed to compare endpoints at the end of follow-up: Kaplan–Meier estimates for AF rate and AF/AT rate after a single procedure. Kaplan–Meier was assessed and compared using log-rank tests. The time recorded was the time needed for the event (recurrence of AF/AT) to occur. The outcome was unknown in patients who did not reach the event before the end of follow-up. In all such cases, time of follow-up was recorded and interpreted as censored data. Cox regression was used to identify risk factors of AF recurrence. All tests of significance were two-sided, with a probability <0.05 considered significant. All statistical analyses were performed using SPSS version 25.0 and GraphPad software.

3. Results

3.1. Baseline characteristics

The baseline characteristics with comparison between group A and group B are displayed in Table 1. Mean age of the 142 participants was 63.1 ± 9.8 years; 88 patients male (62%). No significant differences were found between the two groups in the age, AF history, left atrial diameter (LAD), left ventricular end diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF) and CHA_2DS_2-VASc Score (P > 0.05). In addition, there were no statistical significances in the frequency of hypertension, coronary artery disease (CAD), stroke, diabetes mellitus (DM), NYHA classification and the usage of antiarrhythmic drugs (P > 0.05) between group A and group B.

The follow up period was 204 ± 67 days and no patient dropped out during the follow-up period.

3.2. Procedural characteristics

At the beginning of the procedure, all of participants were in AF.

In group A, 4 AF was terminated and restored sinus rhythm (SR) after CPVI. Electrogram dispersion areas were then mapped using PentaRay in the remaining 67 patients. Electrogram dispersion areas were seen in all of these patients. In total, 265 dispersion areas were identified, and there was an average of 4 ± 1.4 dispersion areas per patient. The distribution of electrogram dispersion areas is shown in Fig. 1A. The most prominent areas were the roof (n = 61, 91%), bottom (n = 44, 65.7%), and inferoposterior wall (n = 41, 61.2%). 262 electrogram dispersion areas were in left atrium and 3 were in right atrium. During the ablation, AF endpoint and AF termination were achieved in 65 and 46 patients, respectively. Among patients obtained AF termination, 11 restored SR, 35 patients converted to AT. 7 patients converted to SR after ablation of AT. 28 patients with AT that could not convert to SR received DCC and all of them restored SR. 21 patients remained in AF after ablation of all the dispersion areas and received DCC. All of them restored SR after DCC. We simultaneously marked CFAEs in group A. Although some CFAEs overlapped with dispersion areas, most CFAEs existed in the periphery of the driver regions (Fig. 1B). Procedural outcomes of patients in group A are shown in Table 2 and Fig. 1C.

In group B, after CPVI, AF termination occurred in 4 of these patients. 2 restored SR and 2 were AT. Both of these patients restored SR after ablation of AT. We performed linear ablation with or without CFAE ablation in the remaining patients. After completion of linear ablation, 1 patient restored SR. CFAEs were mapped and ablated in patients without AF termination. AF was terminated in 6 patients during CFAE ablation. 2 patients restored SR and 4 patients were AT. 3 patients restored SR after ablation of AT, 1 patient remained in AT after ablation and received DCC. 60 patients who were in AF after CFAE ablation received DCC, all of these patients converted to SR. At the end of ablation, 51 patients achieved AF endpoints. The acute results for patients in group B are shown in Table 2 and Fig. 1D.

In summary, the rate of AF endpoint and AF termination was significantly higher in group A than that in group B (97.2% vs 71.8%, P < 0.001 and 70.4% vs 15.5%, P < 0.001, respectively). Moreover, more patients in group A converted to SR by ablation than group B during the procedure (31% vs 14.1%, P = 0.016). Procedure outcomes by catheter ablation are shown in Table 2 and Fig. 1E.

Table 1
Baseline characteristics of group A and group B.

	Group A (n = 71)	Group B (n = 71)	p Value
Age, yrs	63.2 ± 9.2	63.1 ± 10.5	0.95
Male	42 (59.2)	46 (64.8)	0.49
AF type			0.7
Persistent	52 (73.2)	54 (76.1)	
Long-lasting persistent	19 (26.8)	17 (23.9)	
Months since first diagnosis of AF	18 (9–24)	17 (5–36)	0.35
Hypertension	40 (56.3)	33 (46.5)	0.24
CAD	7 (9.9)	10 (14.1)	0.44
Stroke	11 (15.5)	7 (9.9)	0.31
DM	9 (12.7)	5 (7)	0.26
NYHA			0.83
I	7 (9.9)	5 (7)	
II	56 (78.8)	58 (81.7)	
III	8 (11.3)	8 (11.3)	
IV	0 (0)	0 (0)	
Failed AAD			
Class I	29 (40.8)	32 (45.1)	0.61
Class III	25 (35.2)	22 (31)	0.6
β-Blockers	50 (70.4)	45 (63.4)	0.37
LAD, mm	43.4 ± 4.4	44.4 ± 5	0.19
LVEDD, mm	48.2 ± 5.1	47.9 ± 4	0.72
LVEF, %	61.4 ± 5.7	61.2 ± 5.1	0.84
CHA_2DS_2-VASc score	2.3 ± 1.7	1.9 ± 1.7	0.24

AF indicates atrial fibrillation; AAD, antiarrhythmic drugs; CAD, coronary artery disease; DM, diabetes mellitus; LAD, left atrial diameter; LVEDD, left ventricular end diastolic diameter, LVEF, left ventricular ejection fraction and NYHA, New York Heart Association.

The procedure time and fluoroscopy time were similar in the two groups (204.6 ± 26.9 min vs 207.8 ± 26.3 min, P = 0.47, 7.3 ± 1.3 min vs 7.1 ± 1.3 min, P = 0.45, respectively). However, the radiofrequency delivery time in group A was significantly shorter than that in group B (70 ± 7.2 min vs 83.2 ± 9.1 min, P < 0.001). The procedural characteristics are displayed in Table S1.

3.3. Follow up

AADs were continued during the first 3 months after ablation, and at the end of 3 months, Class I and Class III AADs were discontinued in all of the participants. At 3 months after ablation, a documented recurrence of AF/AT occurred in 3 patients from group A (all of them were AT) and 12 patients from group B (5 were AF and 7 were AT). The rate of SR maintenance at 3 months is significantly higher in group A than that in group B (95.8% vs 83.1%, P = 0.014). During a follow-up period of 204 ± 67 days, 12 patients experienced recurrence of AF, 2 from group A and 10 from group B. 15 patients experienced recurrence of AT, 6 from group A and 9 from group B. Survival analyses revealed that the rates of AF-free and AF/AT-free survival in group A were significantly higher than those in group B (P = 0.012 and P = 0.014, Fig. 2). In univariate and multivariate analysis, it was revealed that types of AF and the strategies used during the procedure were associated with the outcomes (Table S2).

3.4. Subgroup analysis

We divided patients in group A into 2 subgroups according to the termination of AF during the procedure (group 1: patients with AF termination, group 2: patients without AF termination). According to the procedural characteristics, participants were categorized into two group sets: AFCL ≤ 160 ms, AFCL > 160 ms; LA volume ≤ 160 ml, LA volume > 160 ml. We compared epidemiologic data and procedural characteristics between group 1 and group 2. Results are displayed in Table S3. No significant differences were found in age and AF history, as well as in the frequency of sex (P > 0.05). There was a significantly lower proportion of patients with a history of long-lasting persistent AF, AFCL ≤ 160 ms or LA volume > 160 in group 1. (18% vs 47.6%, P = 0.01, 38% vs 71.4%, P = 0.01, 44% vs 71.4%, P = 0.035, respectively).

3.5. Complications

1 patient experienced groin hematomas and was treated by physical compression. No major adverse events, such as pericardial effusion, cardiac tamponade, stroke, pulmonary stenosis, esophageal injury, or major bleeding events, occurred.

4. Discussion

In the present study, we aimed to investigate a new ablation strategy to improve prognosis of persistent AF. We compared effectiveness of CPVI + ablation of electrogram dispersion areas and stepwise ablation strategy. Procedural outcomes demonstrated that CPVI + ablation of electrogram dispersion areas achieved a significantly higher success rate without excessive ablation. During a follow-up period of 204 ± 67 days, the novel strategy substantially improved outcomes of persistent AF patients. To the best of our knowledge, this is the first clinical trial to compare these 2 strategies, and our results suggested that the novel strategy is effective, individualized and accurate.

Catheter ablation is effective in restoring and maintaining SR in AF patients [9]. However, the success rate of catheter ablation in persistent AF is only 50% even after repeat ablation procedures in a 5-year follow-up [10,11]. Therefore, it is necessary to find out an optimal ablation strategy.

Recently, rotor has received more and more attention from researchers. Rotor, or alternatively, spiral wave, is a form of functional reentrant activity with curved wavefront and wavetail meet each other at a phase singularity [12,13]. Mechanistic studies have confirmed that rotor is essential in sustaining persistent AF, and clinical trials demonstrated that AF can be terminated once the rotor areas were ablated [1,14]. However, subsequent trials failed to confirm the high success rates of these techniques [3,4]. Contemporary rotor ablation is likely limited by two main factors. Firstly, the shape of human atrium is highly irregular, therefore, an oval or spherical basket-shaped electrode is difficult to achieve a satisfactory contact with human atria. Secondly, insufficient resolution of basket catheter limits the accuracy of the rotor identification. It is estimated that only 63.1% of the interelectrode distances were less than the most stringent spatial resolution requirement for identification of rotors in human AF [15].

More recently, Seitz et al. used high-density mapping tool, PentaRay to map spatiotemporal dispersion areas [5]. This technique achieved a significantly higher AF termination rate and AF/AT-free survival rate when compared with conventional ablation approach. Mechanistic study showed that wavefront shape in dispersion areas was highly curved and impulse propagation was impaired. The characteristics of dispersion areas were similar to that of rotor areas. Therefore, these dispersion areas might represent rotor regions that sustained AF. However, Seitz et al. did not performed CPVI, which is recommended for AF ablation [5]. Since numerous studies have demonstrated that CPVI is the cornerstone of AF treatment [6,9,16–18], we speculated that CPVI + electrogram dispersion area ablation could substantially improve outcomes of persistent AF and was superior to conventional stepwise ablation strategy.

To test this possibility, we prospectively recruited 142 patients with persistent AF, and divided them into two groups: CPVI + electrogram dispersion area ablation (Group A) and stepwise ablation strategy (Group B). CPVI was the initial ablation approach and achieved only 8 (5.6%) AF termination. Evidence accumulated in the last two decades indicated the vital importance of pulmonary veins in persistent AF, nevertheless, in the present study, only a small portion of persistent AF could be terminated by CPVI. This result questioned the real role of pulmonary veins in persistent AF maintenance. We subsequently targeted drivers in LA and RA. Procedural outcomes and follow up demonstrated that the novel strategy was more efficient than the conventional one. More importantly, the radiofrequency delivery time was significantly shorter

in group A than that in group B. These results indicated that the novel strategy obtained satisfactory outcomes but avoid unnecessary ablation.

Mechanisms involved in AF are sophisticated [19]. Uncertainty in AF mechanism culminates in diverse ablation strategies. Nevertheless, some of these strategies failed to find out ideal targets, resulting in increased procedural complications, deteriorated atrial functions and a high recurrence rate of AF/AT [20]. In the present study, we targeted sites that were reminiscent of rotor areas. Procedural outcomes and follow up suggested that these sites were drivers that sustained AF. These results were consistent with previous reports [1,5], and support the conception that rotor was the main mechanism involved in AF maintenance. Taken together, we think this novel strategy represents an optimal electrophysiological approach to treat persistent AF and provides evidence for accurate treatment of AF.

We analyzed the regions mapped during the procedure, and found that the most prominent driver regions were the roof (n = 61, 91%), bottom (n = 44, 65.7%), and inferoposterior wall (n = 41, 61.2%). These areas are common sites for ablation in conventional procedures. Our results offered insight into why these sites were worthy ablation targets in some studies. Previous studies showed that RA sources were found in a certain portion of AF patients (ranging from 15% to 30%) and were important in the maintenance of AF [1,21]. However, in our study, electrogram dispersion areas were identified in only 3 (4.2%) patients, we compared characteristics of patients included in our study and previous studies, and supposed this difference was due to the smaller portion of patients with a long history of AF.

We also analyzed the characteristics of patients in group A. It was revealed that patients with a history of long-standing persistent AF, short AF cycle length or large LA volume achieved a significantly lower AF termination rate. These results indicated that history of AF, AFCL and LA volume reflected the complexity of AF mechanisms and offered hints in patient selection.

Previously, CFAEs were supposed to be ideal target sites of persistent AF and that ablation of these sites yielded an acute termination rate of 95% and a success rate of 91% in one-year follow-up [22]. Disappointingly, in 2015, a large-scale randomized clinical trial demonstrated

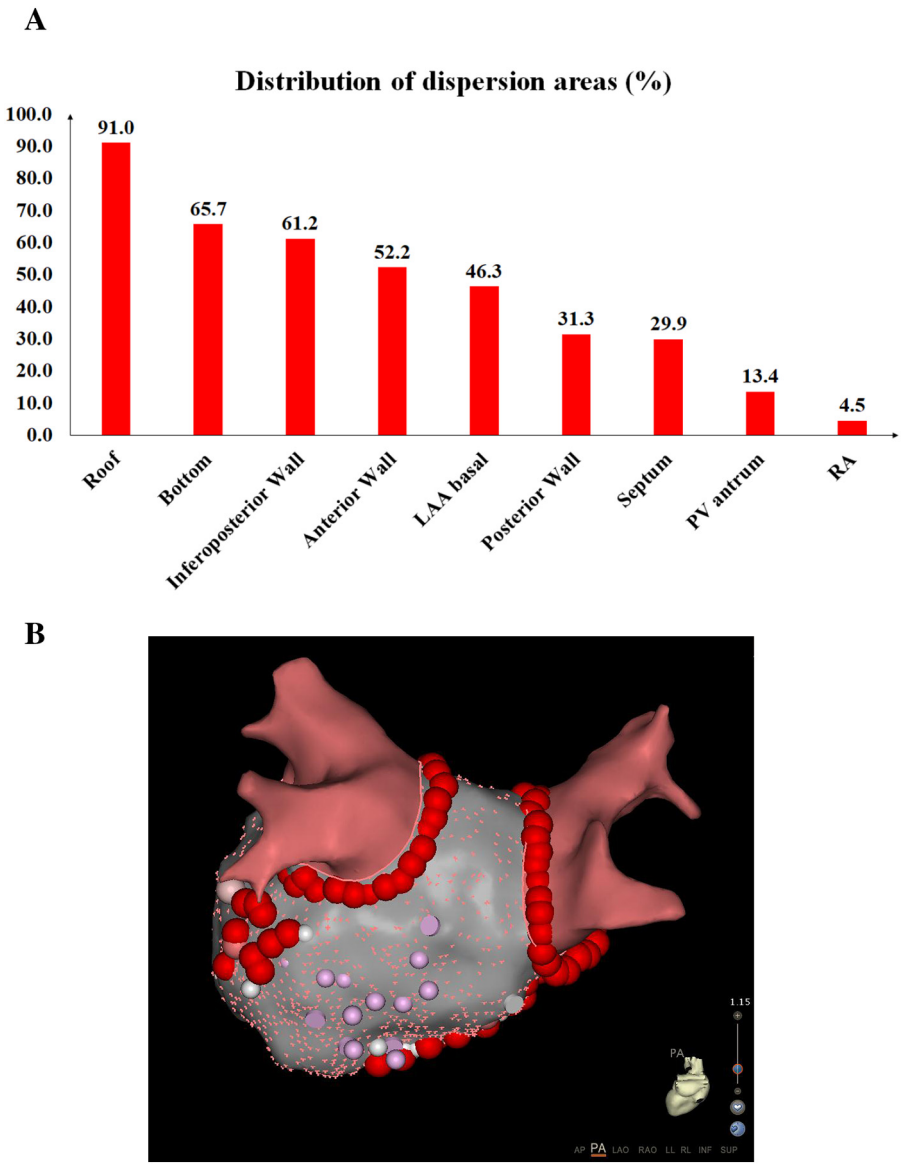

Fig. 1. Procedural outcomes. A. Distribution of electrogram dispersion areas in group A. B. The distribution of dispersion areas (white dots) and CFAEs (pink dots). C. Procedural outcomes in group A. D. Procedural outcomes in group B. E. Procedure outcomes by catheter ablation. AF indicates atrial fibrillation; AT, atrial tachycardia; CFAE, complex fractionated atrial electrograms; CPVI: circumferential pulmonary vein isolation; DCC, direct current cardioversion; LAA, left atrial appendage; peAF, persistent atrial fibrillation; PV, pulmonary vein and SR, sinus rhythm.

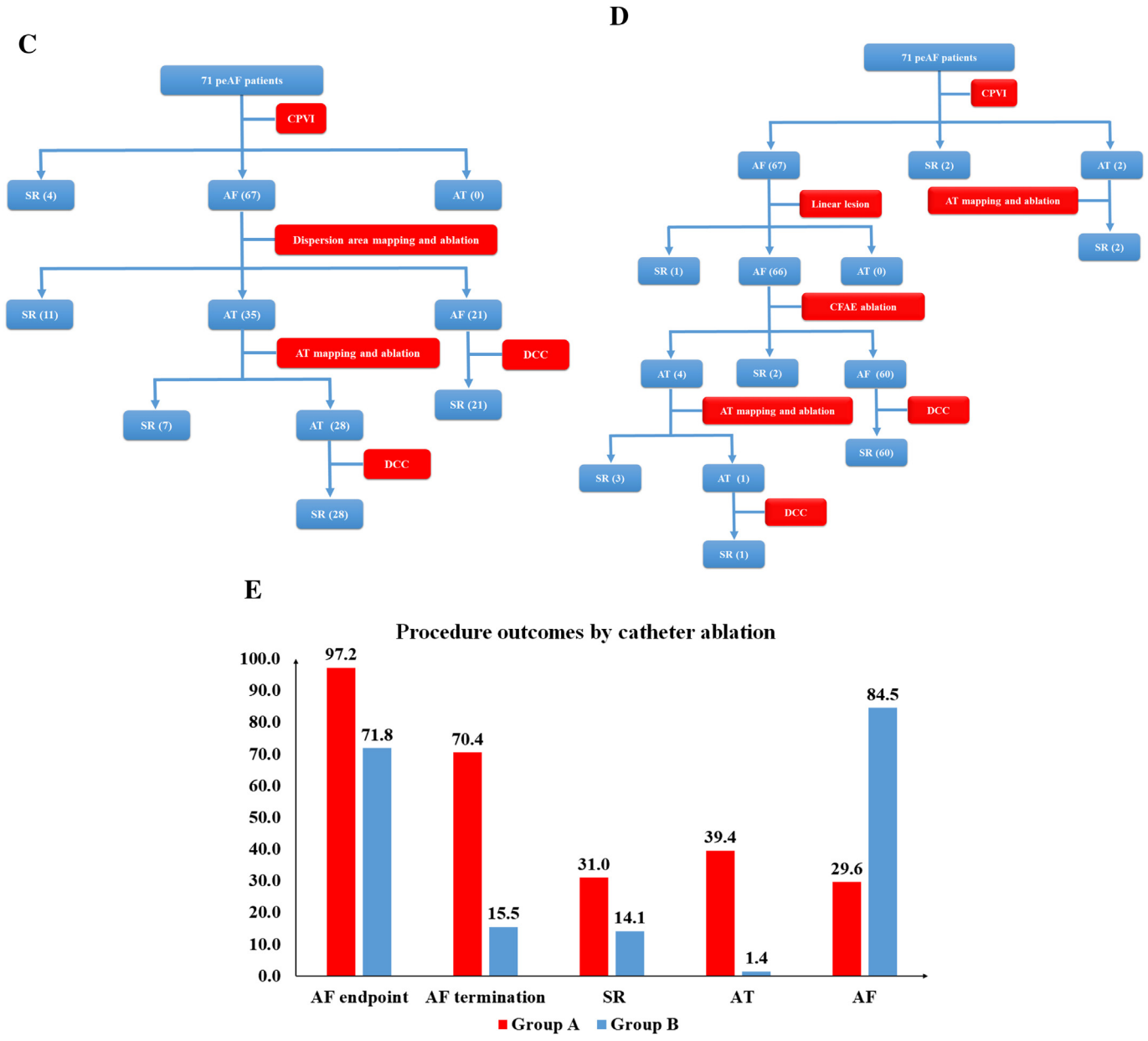

Fig. 1 (*continued*).

that the effect of pulmonary-vein isolation (PVI) + CFAE ablation was not superior to PVI alone [20]. Actually, the electrophysiological origin of CFAEs is not exactly known, and it is accepted that CFAEs may have multiple causes of both physiologic and pathologic origin [23], which means that only some CFAEs are active in the genesis or maintenance of AF. Therefore, ablation of CFAEs without discrimination does not improve success rate of AF but creates massive atrial lesion and causes recurrence of AF/AT. Similar to the mapping of CFAEs, our mapping method was based on the intracardiac electrogram. In order to distinguish between CFAEs and the dispersion areas in our study, we simultaneously marked CFAEs during the procedure. We found that some dispersion areas overlapped with CFAE areas, this phenomenon might explain why CFAE ablation gained successful outcomes in previous reports. Nevertheless, most CFAEs existed in the periphery of the sequential activation areas. This result was consistent with previous reports and further supported the notion that most CFAEs were passive in the process of AF [24]. Furthermore, this phenomenon may help explain the origin of CFAEs: CFAEs occur when meandering drivers encounter heterogeneous substrates or drivers collide with each other.

Table 2
Procedure outcomes by catheter ablation.

	Group A (n = 71)	Group B (n = 71)	p Value
AF endpoint	69 (97.2)	51 (71.8)	<0.001
AF termination	50 (70.4)	11 (15.5)	<0.001
SR	22 (31)	10 (14.1)	0.016
AT	28 (39.4)	1 (1.4)	<0.001
AF	21 (29.6)	60 (84.5)	<0.001

AF indicates atrial fibrillation; AT, atrial tachycardia and SR, sinus rhythm.

5. Study limitations

We acknowledged that there are some limitations in the present study. Firstly, we recognize these data are from a single institution and

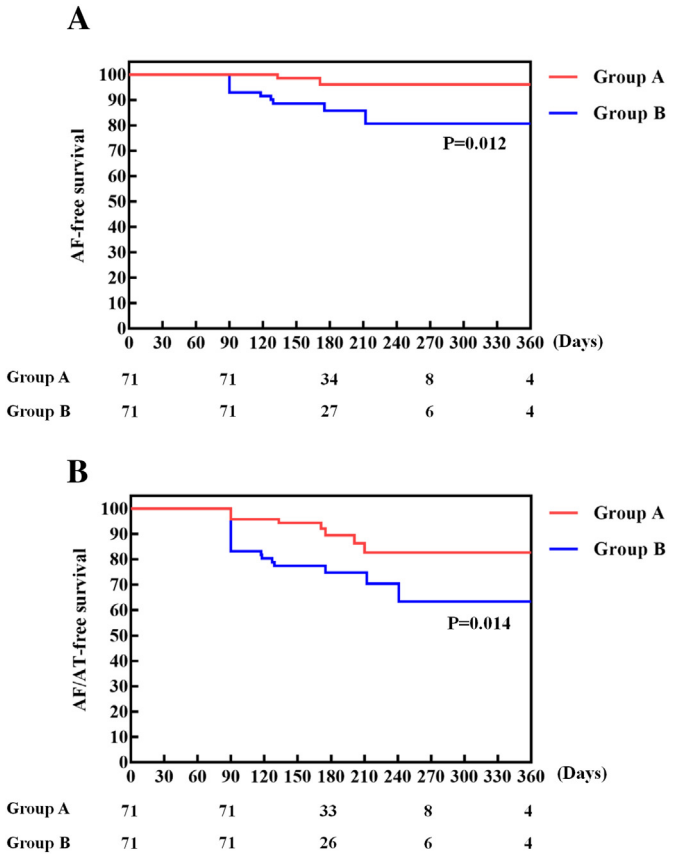

Fig. 2. Long-term clinical outcomes. A. The Kaplan–Meier plot of AF-free survival for patients in group A (red line) and group B (blue line). B. The Kaplan–Meier plot of AF/AT-free survival for patients in group A (red line) and group B (blue line). AF indicates atrial fibrillation and AT, atrial tachycardia.

these results need external validation. Secondly, the number of patients included in this study is relatively small and the follow-up period is relatively short. Finally, data from ex vivo experiment and computer simulation are needed in the future to support our study.

6. Conclusions

We compared the effectiveness of CPVI + dispersion area ablation with stepwise ablation strategy. Results indicated that dispersion areas were ideal target sites for persistent AF and that CPVI + dispersion area ablation is superior to stepwise ablation strategy. We recommend using strategy to perform a safe and successful ablation for persistent AF.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.12.051.

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Conflict of interests

The authors have declared that no competing interests exist.

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