Dormant Conduction after Second-Generation Cryoballoon-Mediated Pulmonary Vein Isolation for Atrial Fibrillation: Comparison with Contact Force-guided Irrigated-Tip Radiofrequency Ablation

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Background: Both contact force (CF)-guided radiofrequency ablation (RFA) based pulmonary vein isolation (PVI) and second-generation cryoballoon ablation (CBA) based PVI may improve the procedural outcome. However, the clinical outcome after RFA- and CBA-based PVI remains unclear. Adenosine or adenosine triphosphate (ATP) administration after PVI is useful to detect dormant PV conduction (DC) after the ablation procedure, and the presence of DC has been shown to be related to AF recurrence.

Methods: Out of 100 patients with paroxysmal AF (PAF), 50 underwent CF-guided PVI (25–30 W, 30 sec for each ablation: CF-RFA group), and the remaining 50 patients underwent cryoballoon ablation-based PVI (3 min cooling + 2 min bonus cooling for each PV: CBA group). Thirty minutes after PVI, a 30-mg bolus of ATP was administered. We compared the success rate of PVI, and incidence of DC after PVI between the CF-RFA and CBA groups.

Results: The subsequent response was assessed for each vein using a ring catheter. In the CBA group, 180 (90%) of 200 PVs were isolated and 20 PVs (10%) (2 left superior PV (LSPV), 3 left inferior PV (LIPV), 4 right superior PV (RSPV), 11 right inferior PV (RIPV) from 14 of 50 patients (28%) required additional RFA because of residual potential at the PV or PV antra. After a waiting period of 30 min after the last energy application, acute PV reconduction was observed spontaneously in 13 PVs (6.5%) (6 LSPV, 3 LIPV, 4 RSPV) from 12 patients (24%) in the CF-RFA group. The DC sites provoked by ATP were 13 PVs (6.5%) (5 LSPV, 3 LIPV, 2 RSPV, 3 RIPV) from 8 patients (16%) in the CF-RFA group, compared with 9 PVs (4.5%) (2 LSPV, 4 LIPV, 1 RSPV, 2 RIPV) from 9 CBA patients (18%) (P = 1.000). AF recurred in 6/50 (12%) in both the CF-RFA and CBA groups at 1 year after the ablation (P = 1.000).

Conclusions: There was no significant difference in the incidence of DC after PVI and the 12-month AF-free rate between the second-generation CBA- and CF-based RFA.

Key words: pulmonary vein isolation, contact force-guided radiofrequency ablation, cryoballoon ablation, adenosine triphosphate provocation

Original Article

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1. Introduction

Catheter-based pulmonary vein (PV) isolation (PVI) is recognized as an effective therapeutic option for atrial fibrillation (AF)\(^1\). Recently, Carto 3 system has incorporated contact force (CF) sensor into the system to improve the lesion efficacy and safety. The CF-guided radiofrequency (RF) ablation enables to create more durable lesion formation, substantially improving procedural outcome\(^2,3\). To simplify PVI for AF, cryoballoon (CB) ablation (CBA) has been developed\(^4\), and PVI by a second generation CB is highly effective for paroxysmal AF (PAF). Success rates of both ablation methods are comparable, however, AF recurrence after ablation occurs in approximately 10–30% of patients with PAF and even more in patients with persistent AF. The main mechanism of AF recurrence is the PV reconnections because of failure to create transmural lesions or gaps in the PV encircling ablation lines\(^5\). Adenosine or adenosine triphosphate (ATP) administration after PVI can unmask dormant PV conduction (DC) after ablation procedure, and presence of DC has been shown to be related to AF recurrence\(^6,7\). Characterization of DC provoked by ATP may provide the mechanistic insight into the understanding the effective and ineffective lesion formation by CF-guided RFA and CBA. The purpose of this study, therefore, was to compare the incidence of DC provoked by ATP and AF recurrence between standardized PVI for PAF guided by
CFA (CF-RFA group) and second-generation CBA (CBA group).

2. Material and methods

2.1. Study patient

This study consisted of 100 consecutive patients (64 men, 36 women; mean age, 63.5 ± 10.5 years; median duration of AF, 20 [interquartile range 6–54] months) who underwent PVI from September 2014 until March 2016. Patients were randomly assigned to 1 of 2 ablation procedures: PVI performed by second-generation CBA (CBA group, n = 50) and PVI by CF-guided RF catheter ablation (CF-RFA group, n = 50). The study protocol was approved by our institutional review board (IRB) (IRB approval number: RK-150310-20, approval date: Feb. 3, 2016). Informed written consent was obtained from all patients for the participation of the study. Transesophageal and Transthoracic echocardiography were performed 1 day before ablation with an ACUSON Sequoia C256 echocardiography system (Siemens Medical Solutions USA, Inc., Malvern, PA). LA diameter (LAD) was measured at the end of the T wave, and left ventricular ejection fraction (LVEF) was assessed by means of M-mode echocardiography (Teichholz’s method). Measurements from 3 consecutive beats were averaged.

Exclusion criteria for the study were (1) a previous ablation procedure; (2) valvular heart disease; (3) global or regional LV contraction abnormality; (4) left ventricular hypertrophy; (5) idiopathic cardiomyopathy; (6) chronic pulmonary disease; and (7) thyroid disease. Adequate oral anticoagulation was given for at least 1 month before the procedure, and all antiarrhythmic drugs were withdrawn for at least 5 half-lives prior to ablation. Upon admission, physical examination, routine hematology and biochemistry tests, 12-lead electrocardiography (ECG), chest X-ray, and transthoracic and transesophageal echocardiography were performed. Before ablation, all patients underwent multi-slice computed tomography with a 320-detector row, dynamic volume scanner (Aquilion ONE; Toshiba Medical Systems, Tokyo, Japan) for three-dimensional (3D) reconstruction of the left atrium and PVs.

2.2. Ablation protocol

Electrophysiologic study was performed in all patients under conscious sedation achieved with dexmedetomidine, propofol and fentanyl, as previously described10. In brief, after vascular access was obtained, single transseptal puncture was performed and followed by extensive encircling ipsilateral PVI (EEPVI), guided by double LASSO® catheters (Biosense Webster, Inc., Diamond Bar, CA) and a 3D geometric map generated by a CARTO 3 (Biosense Webster, Inc) mapping system. CF-sensing irrigated-tip catheter (Thermocool Smart Touch™; Biosense Webster) was used for ablation. RF energy was delivered at a maximum power output of 25–30 W and the target CF of 10–20 grams with a force-time integral of > 400 gs, and upper temperature limit was set to 43°C at a saline irrigation rate of 17–30 mL/min (CoolFlowTM Pump; Biosense Webster).

Cryoballoon ablation group (CBA group)

A 15-Fr deflectable sheath (FlexCath Advance, Medtronic) was advanced into the LA through the transseptal puncture. Then, the Arctic Front Advance CB was introduced into the sheath, inflated, and advanced to the ostium of each PV. The procedure was performed using the 28 mm CB, Cryoenergy was delivered after the occlusion of each PV by no leak of contrast agent. Ablation of PV antra was performed with two applications of 180 s and followed by 120 s per vein. Continuous monitoring of the phrenic nerve (CMAP) during ablation of the right PVs was systematically performed by pacing the right phrenic nerve from the superior vena cava (at a cycle length of 1000 ms, current of 25 mA, and pulse width of 2 ms)11, 12. PVI was assessed using the circular Achieve Catheter (Medtronic) during CB freezing, but was confirmed with a 20-pole circular mapping catheter (4-mm interelectrode spacing; Inquiry AFocus II EB catheter; St. Jude Medical) after CBA. If the PV(s) remained connected, touch-up irrigated-tip RFA (Therapy™ Cool Flex™, St. Jude medical) or additional CBA were conducted.

ATP testing

In each group, after waiting time for 30 min after PVI, a bolus of 30 mg of ATP was injected intravenously to provoke dormant PV conduction29. Sites of DC were verified with double LASSO catheters positioned at the ipsilateral right or left PVs ostia. The breakthrough site(s) of DC was categorized based on the PV anatomy, i.e., anterior, posterior, or superior aspect of the right or left superior PVs (RSPVs or LSPVs, respectively), anterior or posterior carina of the PVs, or anterior, posterior, or inferior aspect of the right or left inferior PVs (RIPVs or LIPVs, respectively) (Figure 1A). RFA or CBA was performed to the conduction gaps until disappearance of the DC provoked by ATP (Figure 1B). Cavo-tricuspid isthmus ablation was performed when typical atrial flutter was induced by burst atrial pacing or observed clinically.
Comparison of the incidence of dormant conduction after Pulmonary Vein Isolation with contact force guided radiofrequency ablation and cryoballoon ablation

2.3. Post-ablation follow-up
Follow-up was performed for at least 12 months after ablation with ECG, 24-h Holter ECG recording, and symptom questionnaire at three monthly intervals. All documented AF episodes of > 30 seconds duration on the standard ECG, ECG event monitor, or 24-hour Holter recording were defined as recurrence.

2.4. Comparison between the CF-RFA group and the CBA group
Data were compared between the CF-RFA group and the CBA group. The variables included in the comparison were as follows: baseline clinical characteristics, transthoracic echocardiographic variables, the prevalence and distribution of the DC provoked by ATP, and outcomes after ablation.

2.5. Statistical analysis
Continuous variables are expressed as mean ± SD or median values and interquartile ranges. Differences in continuous variables between the CF-RFA group and the CBA group were analyzed by unpaired t-test or Mann-Whitney U-test. Differences in categorical variables were analyzed by chi-square test. A p value < 0.05 was accepted as statistically significant. All statistical analyses were performed with JMP 10 software (SAS Institute, Cary, NC).

3. Results
3.1. Patient characteristics
Patient characteristics and transthoracic echocardiographic variables are summarized in Table 1. There was no significant difference in patients’ clinical characteristics, LAD and LVEF between the CF-RFA group and the CBA group.

3.2. PV isolation and dormant PV conduction provoked by ATP
Acute PVI was achieved in all 200 PVs of 50 patients (100%) in the CF-RFA group. In CBA group, 180 (90%) of 200 PVs were isolated with a total CBA number of 2.2 ± 0.78 times or a total freezing time of 328.4 ± 96.2 seconds for each PV, and 20 PVs (10%) (2 left superior PV (LSPV), 3 left inferior PV (LIPV), 4 right superior PV (RSPV), 11 right inferior PV (RIPV)) among 14 of 50 patients (28%) required additional RFA because of residual potential at the PV or PV antra. The majority of these residual PV potentials (12/20 [60%] PVs) were located at the floor of the RIPV or LIPV. After a waiting period of 30 min after last energy application, acute PV reconduction was spontaneously observed in 13 PVs (6.5%) (6 LSPV, 3 LIPV, 4 RSPV) among 12 patients (24%) in CF-RFA group.

The breakthrough sites of DC provoked by ATP were in 13 PVs (6.5%) (5 LSPV, 3 LIPV, 2 RSPV, 3 RIPV) of
8 patients (16%) in the CF-RFA group, while they were in 9 PVs (4.5%) (2 LSPV, 4 LIPV, 1 RSPV, 2 RIPV) of 9 CBA patients (18%) ($P = 1.000$). Distribution of the DC sites per group is illustrated in Figure 2. DC at PV carina regions in CF-RFA group was more prevalent than the CBA group (11/13 [85%] PVs vs. 4/9 [44%] PVs, $P = 0.0467$). To eliminate the ATP-provoked DC, patients in the CF-RFA group required a median of 5 (4–6) focal RF applications along the previous ablation lines, whereas the median number of additional RFA or CBA in the CBA group was 1 (1–3.5) ($P < 0.01$).

### Table 1: Patient characteristics between contact force guided radiofrequency ablation (CF-RFA) and cryoballoon ablation (CBA).

| Characteristic                  | CF-RFA group (n = 50) | CBA group (n = 50) | $P$ value* |
|--------------------------------|-----------------------|-------------------|-----------|
| age (years)                    | 63.3 ± 11.3           | 65.1 ± 9.4        | 0.3999    |
| Male sex, n (%)                | 33 (66)               | 31 (62)           | 0.8352    |
| Body mass index (kg/m$^2$)     | 24.5 ± 4.4            | 23.3 ± 3.9        | 0.1781    |
| Paroxysmal AF, n (%)           | 38 (76)               | 42 (84)           | 0.4539    |
| AF duration, months            | 24 [6–60]             | 12 [5–48]         | 0.0979    |
| LAD, mm                        | 39.6 ± 5.6            | 38.6 ± 6.4        | 0.4165    |
| LVEF, %                        | 67.1 ± 8.1            | 68.0 ± 9.76       | 0.6441    |
| Hypertension, n (%)            | 26 (52)               | 23 (46)           | 0.6893    |
| Diabetes mellitus, n (%)       | 5 (10)                | 10 (20)           | 0.2623    |
| Ischemic heart disease, n (%)  | 0 (0)                 | 3 (6)             | 0.2424    |
| CHADS2 score                   | 0.9 ± 0.90            | 1.1 ± 1.0         | 0.4038    |

Values are mean ± SD, median [interquartile range], or n (%).
*CF-RFA group vs. CBA group.

AF: atrial fibrillation, LAD: left atrial diameter, LVEF: left ventricular ejection fraction

CHADS2 score indicates the score adding congestive heart failure (1), hypertension (1), age ≥ 75 years (1), diabetes mellitus (1), and prior stroke or transient ischemic attack (2).

3.3. Determinants for the patients with residual PV conduction, spontaneous acute PV reconduction and dormant PV conductions in CF-RFA and CBA groups

We sought to characterize the patients with residual conduction gap(s) in the CBA group, touch-up ablation(s) site(s) for the spontaneous acute PV reconduction(s) in CF-RFA group or DC were evaluated in terms of age, sex, body mass index, LAD, LVEF, and the prevalence of PAF, hypertension, diabetes, and ischemic heart disease. CBA patients requiring additional ablation to residual conduction gap(s) were significantly younger (57.9 ± 12.2 years vs. 67.9 ± 6.4 years, $P = 0.0004$), and had a higher prevalence in male (86% vs. 53%, $P = 0.0312$) and a smaller percentage in patients with PAF (64% vs. 92%, $P = 0.0304$) than those without residual conduction gap(s).

In CBA group, only the LVEF was significantly higher in the patients with DC than those without it (74.5 ± 7.0% vs. 66.6 ± 9.8%, $P = 0.0258$). Nonetheless, there were no clinical characteristics regarding the presence of spontaneous acute PV reconduction and DC in the CF-RFA group.

3.4. Ablation results and post-ablation outcome

CMAP identified intermittent reduction of diaphragm movement in 2 (4%) of the 50 CBA group, but all were recovered during the procedure. Except that, no complications were observed between the two groups. AF recurred in 6/50 (12%) in both CF-RFA and CBA groups at 1 year after the ablation ($P = 1.000$). Post-ablation AF recurrence was related to the ATP-provoked DC (50% [3/6] vs. 11% [5/44], $P = 0.0444$), but not to the spontaneous acute PV reconnections (17% [1/6] vs. 25% [11/44], $P = 1.000$).

Fig. 2  Comparison of the incidence of dormant conduction after pulmonary vein isolation with contact force guided radiofrequency ablation and cryoballoon ablation.
in the CF-RFA group. However, residual PV potential sites (33% [2/6] vs. 27% [12/44], \( P = 1.000 \)) and ATP-provoked DC (0% [0/6] vs. 18% [9/44], \( P = 0.5786 \)) were not related to the AF recurrence in the CBA group.

4. Discussion

4.1. Major findings

In the present study, we showed that DC sites provoked by ATP were differently distributed, however no significant difference was found on the incidence of total DC per patient and atrial tachyarrhythmia recurrence over the 1-year follow-up period between CBA and CF-RFA based PVI.

4.2. Impact of different technique of CB ablation vs. CF-guided RF ablation on ATP-provoked dormant PV conduction and clinical outcome

Recurrence of atrial tachyarrhythmias after PVI has sown to relate to PV reconnection\(^5\), therefore creation of durable PV antrum lesions may decrease the incidence of future PV reconnections and atrial tachyarrhythmias recurrence. The difficulty to create consistent durable lesions has evolved the development and refinement of navigation systems incorporated force or contact sensing into the system. There have been increasing the evidence that the CF-based RF provides a substantial increase of success rate after AF ablation compared to non-CF-based RFA\(^2,3\). On the other hand, balloon-based ablation technology has been evolved to simply PVI, and clinical efficacy was established especially in the CBA. Compared with the first-generation CB (Arctic Front\(^\text{TM}\)), the second-generation CB (Arctic Front Advance\(^\text{TM}\)) has double number of freezing pores (8 instead of 4) with their more distal location, leading to more uniform ablation of PVs. This technology improved the procedural parameters such as procedure duration, fluoroscopy time, time to PVI, and had better clinical outcomes than first-generation CB\(^24\).

Both ablation technologies have a similar clinical success rate ranging from 73% to 88%\(^2,3,13–15\), however, there are few reports on the incidence and characteristics of DC provoked by ATP or adenosine between the CF-based RFA and CBA. In the present study, the incidence of ATP-provoked DC was infrequent in both the CF-RFA group and CBA group, but the distribution of the DC was different. ATP-provoked dormant PV conduction was observed at the carina regions of the PV in the CF-RFA group, but it was located at the inferior PVs in the CBA group. DC in our point-by-point CF-RFA group was relatively low (in 13 PVs [6.5%] in 8 patients [16%]) because we used not only CF but also the VisiTag module, which includes catheter stability information. We reported previously that use of this module reduced the commonly reported incidence of DC which was 8–15% of initial isolated PVs\(^5\). The CB patients had DC in 9 PVs (4.5%) of initially isolated PVs in 9 patients (18%), which was consistent of recent reported incidences by using second-generation CB of approximately 0–4.5% of the PVs in 0–12% of patients\(^18–20\). Although cryothermal energy is a milder and safer form of energy than RF energy, cryothermal energy creates well-delineated wider lesions with preservation of tissue structure as compared to RF which causes tissue disruption from excess heating and generation of inhomogeneous lesions\(^21,22\). Therefore, good quality of lesions by cryothermal energy may confer an infrequent incidence of ATP-provoked DC.

We found a relatively higher incidence of additional ablation for residual PV potentials requiring for complete PVI (20/200 PVs [10%] among 14/50 patients [28%]) in the CB A. In recent reports, additional ablation for residual PV potentials after CBA has been reported for 0–17% of PVs\(^18–20\). The residual PV sites in the present study were observed mainly at floor of RIPV. These residual PV conduction sites were related to younger patients, male and non PAF patients. These patient characteristics suggests the difficulty of anatomical characteristics to establish CB-tissue contact-based effective lesion formation such as larger PV antra and thicker PV-LA junction\(^23\) especially in the inferior PVs. Although CBA has residual PV potentials due to a poor balloon-tissue contact, CBA patients did not have any spontaneous acute PV reconnection. In contrast, one fourth of the CF-based RFA patients experienced spontaneous acute PV reconnections even after the creation of encircling ablation lines around the PV. Although the incidence of DC was equivalent between the two groups, CF-RFA group required a larger number of applications to DC sites than the CBA group. Furthermore, AF recurrence was associated with the occurrence of DC in CF-RFA group, but it was not related to the DC sites in the CBA group. All of these results partially suggest an inferiority of ability to prevent PV reconnection in point-by-point based RFA as compared to CBA. In fact, a recent study of CBA have documented wide and antral ablation lesions\(^24\), and the incidence of PV reconnection in the chronic phase was higher in RFA than in CBA. Nonetheless, clinical 1-year success rate was 88% in our CF-RFA group and 88% in our CBA group, respectively. Recent studies comparing CF-guided RFA with CBA have shown statistical equivalence between the 2 technologies\(^25\). This may relate to the fact that even focused lesions may eliminate triggers and that not for all transmural continuous lesions around the PVs are needed\(^26–29\).

4.3. Limitation

Our study has some limitations. First, this is a single-center study with a relatively small number of patients. Second, repeat procedures were not analyzed to assess long-term durability of the PVI. Although some difference-
5. Conclusion

Incidence of ATP-provoked DC after PVI was very low using second-generation CBA and CF-based RFA. The 1-year success rate was also equivalent between two groups.

Conflict of interest

All authors declare no conflict of interest related to this study.

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