Original Article

Comparison of Cryoablation and Radiofrequency Ablation Areas Demarcated by Postprocedural Electroanatomic Mapping in Patients with Atrial Fibrillation Treated by Pulmonary Vein Isolation

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Background: Circumferential pulmonary vein isolation (CPVI), achieved by cryoballoon ablation (CBA) or by irrigated-tip radiofrequency catheter ablation (RFA), has been used to isolate the area surrounding the pulmonary veins (PVs) in patients with paroxysmal atrial fibrillation (AF). Although studies have shown circumferential RFA to be comparable to CBA in terms of arrhythmia-free survival and the overall complication rate, there has been no reported comparative quantification of the resulting acute ablated areas of the left atrial endocardial surface. Therefore, we conducted such a study.

Methods and Results: The study involved 40 patients (32 men, 8 women; mean age, 62.2 ± 10.4 years) who were undergoing CBA or circumferential RFA for AF (paroxysmal AF, $n = 24$; persistent AF, $n = 16$). A detailed 3-dimensional electroanatomic map of the left atrium (LA) was created and merged onto the pre-procedural computed tomography (CT) of the LA, and the ablation areas, interpreted as low voltage areas, were quantified and compared between the 2 CPVI methods. The low voltage areas were significantly larger in the CBA patient group than in the circumferential RFA patient group (40.6 ± 13.8 vs. 31.46 ± 15.8 cm², respectively, $p = 0.00287$).

Conclusions: Our acute phase data indicate that CBA produces a larger PV-LA surface isolation area compared with point-by-point circumferential CF-based RFA.

Key words: atrial fibrillation, pulmonary vein isolation, left atrial voltage, cryoablation, radiofrequency ablation

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1. Introduction

Catheter ablation is recognized as an effective therapeutic option for atrial fibrillation (AF) and has been given the highest level recommendation (class I, level A) for the treatment of drug refractory and symptomatic paroxysmal AF^{1–3)}. A cornerstone of AF ablation is electrical isolation of the pulmonary veins (PVs)¹⁾. After the development of segmental PV isolation (PVI), various other PVI approaches were developed, including circumferential PVI (CPVI) and PV antrum ablation/isolation, and these approaches resulted in comparatively better clinical outcomes^{4, 5)}. Cryoballoon ablation (CBA) has recently emerged as an alternative to radiofrequency (RF) ablation for PVI and has proven to be effective in patients with paroxysmal AF⁶⁾. Quantification of the acute and chronic ablated surface areas after second-generation CBA has been reported^{7, 8)}, but there has been no reported quantification of the isolation area achieved by means

of circumferential point-by-point RF ablation (RFA) in comparison to that achieved by “single-shot” CBA. The aim of the study described herein was to quantify and compare the acute-phase isolation area after CPVI achieved by means of circumferential RFA, i.e., creation of a single circumferential lesion around the ipsilateral PVs, and that after CPVI achieved by CBA with a 28-mm cryoballoon to clarify whether a difference exists between the 2 technologies in the resulting isolation areas.

2. Material and methods

2.1. Study patients

The study involved 40 consecutive patients (32 men, 8 women; mean age: 62.2 ± 10.4 years) scheduled for their first catheter ablation of AF. First 20 patients were selected for RFA group and next 20 patients were selected for CBA group because CBA became available in our hospital at that time. No patient with cardiomyopathy, valvular heart disease, or congenital heart disease was included

in the study. Adequate oral anticoagulation therapy was given for at least 1 month before the ablation procedure, and all antiarrhythmic drugs were discontinued for at least 5 half-lives before the procedure. Transesophageal echocardiography and transthoracic echocardiography were performed upon admission, and the following baseline echocardiographic values were obtained: left atrium (LA) dimension, maximum LA volume by the prolate ellipsoid method, and left ventricular ejection fraction (LVEF) by the Teichholz method. Multi-slice computed tomography was performed with a 320-detector row, dynamic volume scanner (Aquilion ONE; Toshiba Medical Systems, Tokyo, Japan) in all patients for 3-dimensional (3D) reconstruction of the LA and PVs before ablation.

The study protocol was approved by the Institutional Review Board of Nihon University Itabashi Hospital (May 25, 2016; RK-160614-10), and all patients provided written informed consent for their participation.

2.2. Mapping and ablation procedure

Electrophysiologic study was performed in all patients under conscious sedation achieved with dexmedetomidine, propofol, and fentanyl, as described previously^{9,10}.

In all patients who underwent CBA, 2 SL0 long sheaths (St. Jude Medical, Inc., St. Paul, MN, USA) were inserted into the LA through a puncture hole¹¹. The 3D geometry of the LA and PVs was reconstructed with an EnSite NavX mapping system (St. Jude Medical) from data obtained with a 20-pole circular mapping catheter (4-mm interelectrode spacing; Inquiry AFocus II EB catheter; St. Jude Medical) or a 10-pole mapping catheter with 5-mm interelectrode spacing (Snake, Japan Lifeline, Inc., Tokyo, Japan) advanced through 1 of the 2 SL0 sheaths. An exchange length (0.035 inch) guidewire was introduced into the left superior (LS) PV, over which another SL0 sheath was exchanged for a 15Fr deflectable sheath (Flexcath steerable sheath, Medtronic, Inc., Minneapolis, MN, USA). An Arctic Front Advance 28-mm cryoballoon (CB-Adv, Medtronic) with an Achieve inner lumen mapping catheter (Medtronic) was placed in the LA through the steerable 15Fr sheath. The CB-Adv was then inflated and advanced successively to each PV ostium to establish optimal PV occlusion, determined by the absence of contrast leakage. To avoid vigorous wedging of the balloon inside the PVs, we used the “proximal-seal” technique for each PV, i.e., withdrawing the inflated cryoballoon until a small leak was observed and then slightly repositioning the cryoballoon¹². Cryoenergy was delivered to each PV after occlusion was established. Ablation of each PV antrum was performed with a 180-s application of cryoenergy followed by a 120-s or 180-s application. Continuous monitoring of the phrenic nerve during ablation of the right superior and inferior PVs (RSPV and RIPV, respectively) was systematically performed by pacing

the right phrenic nerve from the superior vena cava (at a cycle length of 1000 ms, current of 10–25 mA, and pulse width of 2 ms)¹¹. After each CBA procedure, PVI was confirmed with the 20-pole circular mapping catheter. If residual PV potentials were recorded, additional cryoenergy was delivered. In patients with PV reconnection(s), PVI was achieved with minimal focal ablation where the earliest PV potential was recorded with a 4-mm irrigation catheter (Therapy Cool Flex Ablation Catheter, St. Jude Medical).

The RFA was based on contact force (CF) and guided by 2 Lasso (Biosense Webster, Inc., Diamond Bar, CA, USA) catheters and a 3D geometric map reconstructed with use of the CARTO mapping system (Biosense Webster), as previously reported [13]. Point-by-point ablation was performed with a CF-sensing irrigated tip catheter with 2-5-2 mm spacing (ThermoCool Smart Touch; Biosense Webster) under VisiTag system guidance. RF energy was delivered at a maximum power output of 25–30 W and a target CF of 10–20 grams with a force-time integral of > 400 gs. The upper temperature limit was set to 43°C at a saline irrigation rate of 17–30 mL/min (CoolFlow Pump; Biosense Webster). PVI was confirmed with use of the Lasso catheters. If a PV remained connected, additional touch-up CF-guided ablation lesions were created until PVI was achieved.

After complete PV antrum isolation was achieved by CBA or RFA, a 30-mg bolus of adenosine triphosphate was injected to unveil any dormant PV conduction. If dormant PV conduction was detected, RF ablation was repeated until the dormant PV conduction disappeared.

2.3. Testing for dormant PV conduction

For patients undergoing CBA, dormant PV conduction was tested by injection of a 30-mg bolus of adenosine triphosphate after placement of an AFocus II EB catheter and an Achieve mapping catheter and 2 Lasso catheters in the ipsilateral PVs.

2.4. Determining the isolation area

For each patient, after 2 (or 3) cryoenergy applications at each PV or complete CF-based PVI, a 3D LA voltage map was created with the use of CARTO 3 or NavX software^{7,8,14}. The isolation area was taken as the area of low voltage (< 0.5 mV) surrounding the PVs identified by high-density mapping (> 400 points) performed with an Inquiry AFocus II EB catheter (4-mm interelectrode spacing) in patients who underwent CBA or with a 10-pole lasso catheter (4.5-mm interelectrode spacing) in patients who underwent circumferential RFA, as described previously¹⁵. The PV ostium was identified as the point of maximal inflection between the PV wall and LA wall. The PV antrum area was defined as the total antrum surface area excluding the PVs. The isolated surface area

ratio was calculated as follows: isolated surface area of each PV antrum/total LA surface area excluding the left atrial appendage and PVs.

2.5. Post-ablation management and follow-up

Patients were followed up at our hospital's outpatient clinic at 2 weeks, at 3 months, and then every 6 months. Routine electrocardiography (ECG) was performed, and if the patient had symptoms, Holter ECG and/or event ECG monitoring was performed. Any antiarrhythmic drugs administered before the PVI procedure were reinstated after the procedure. Oral anticoagulation was continued for 3 months after PVI, and if sinus rhythm was maintained, the oral anticoagulation therapy was discontinued. The oral anticoagulation therapy was continued for any patient with a CHADS₂ score ≥ 2 .

2.6. Statistical analysis

Values are shown as mean $\pm$ SD unless otherwise indicated. Between-group differences in patients' clinical characteristics and isolation area and percentage were analyzed by Mann-Whitney U test, and between group differences in patient's characteristics were analyzed by chi-square test. All statistical analyses were performed with Stat View 5.0 (SAS Institute, Cary, NC, USA), and $p < 0.05$ was considered significant.

3. Results

3.1. Patient characteristics

Patient's clinical characteristics are shown per group on Table 1. Twenty-four patients had paroxysmal AF (AF lasting less than 7 days), and 16 had persistent AF (AF lasting 7 days or more). There was no significant differ-

ence between the CBA group and the circumferential RFA group in age, sex ratio, body mass index, number of patients with paroxysmal AF, AF duration, LA diameter, LVEF, presence of hypertension, or presence of diabetes mellitus.

3.2. Ablation procedure results

Complete PV antrum isolation was achieved in all patients in both groups. Additional touch-up RF catheter ablation was needed for 14 PVs (3 LIPVs, 3 RSPVs, 8 RIPVs) in 9 patients in the CBA group. Dormant conduction was detected in 3 PVs (3.8%) (1 LSPV, 2 LIPVs) in 3 patients (15%) in the CBA group and in 6 PVs (7.5%) (2 LSPVs, 2 LIPVs, 1 RSPV, and 1 RIPV) in 5 patients (25%) in the circumferential RFA group ($p = 0.695$, with no significant between-group difference in the prevalence of dormant PV conduction (Fig. 1).

Table 1 Baseline patients characteristics

	CBA (n = 20)	RFA (n = 20)	<i>p</i> value*
Age (years)	60.0 $\pm$ 11.7	64.4 $\pm$ 8.5	0.188
Male sex, n (%)	17 (85)	15 (75)	0.695
Body mass index (kg/m ²)	25.0 $\pm$ 4.5	23.8 $\pm$ 3.0	0.307
PAF, n (%)	13 (65)	11 (55)	0.748
AF duration (month)	11 (5.3–36.0)	12 (5.3–51.0)	0.786
LA dimension, mm	40.8 $\pm$ 5.1	39.0 $\pm$ 6.8	0.361
Ejection fraction, %	66.8 $\pm$ 7.0	69.5 $\pm$ 8.0	0.266
Hypertension, n (%)	8 (40)	15 (75)	0.054
Diabetes mellitus, n (%)	7 (35)	3 (15)	0.273

Values are shown as mean $\pm$ SD unless otherwise indicated.

*per Student's *t* test or chi-square test.

PAF = paroxysmal atrial fibrillation.

Fig. 1 Dormant pulmonary vein conduction sites after cryoballoon ablation (blue dots) and circumferential pulmonary vein isolation by radiofrequency ablation (red dots).

RPV: right pulmonary vein, LPV: left pulmonary vein, SPV: superior pulmonary vein, IPV: inferior pulmonary vein. RFA: radiofrequency ablation, CBA: cryoballoon ablation

3.3. Isolated surface area

The LA surface area was $126.6 \pm 28.8 \text{ cm}^2$ in the CBA group and $123.8 \pm 27.0 \text{ cm}^2$ in the CPVI group and did not differ significantly ($p = 0.7536$). The isolated surface area after CBA ($40.6 \pm 13.8 \text{ cm}^2$) was significantly larger than the isolation area enclosed by the circumferential RFA line ($31.4 \pm 15.8 \text{ cm}^2$, $p = 0.00287$) (Table 2, Fig. 2). In addition, the %LA ablated area was significantly greater after CBA than after CPVI ($32.6 \pm 1.1\%$ vs. $25.3 \pm 1.2\%$, respectively, $p = 0.0263$). The isolated right PV antrum area was significantly larger in the CBA group ($18.0 \pm 7.4 \text{ cm}^2$) than in the CPVI group ($13.7 \pm 6.8 \text{ cm}^2$, $p = 0.0338$), but there was no significant between-group difference in the isolated left side PV antrum area (Table 2).

3.3. Rhythm outcome

The AF recurrence rate after a mean follow-up period

Table 2 Ablated areas produced by CBA and circumferential RFA

	CBA	RFA	p value
Total isolated area (cm ²)	40.6 ± 13.8	31.4 ± 15.8	0.002
% total isolated area	32.6 ± 1.1	25.3 ± 1.2	0.026
LSPV antrum (cm ²)	7.3 ± 3.8	7.5 ± 5.1	0.883
LIPV antrum (cm ²)	6.4 ± 2.5	7.6 ± 4.4	0.285
RSPV antrum (cm ²)	10.3 ± 5.8	8.1 ± 4.4	0.201
RIPV antrum (cm ²)	7.7 ± 3.7	5.6 ± 3.6	0.038
LPVs antrum (cm ²)	13.7 ± 5.7	15.1 ± 8.0	0.518
RPVs antrum (cm ²)	18.0 ± 7.4	13.7 ± 6.8	0.034

CPVI: circumferential pulmonary vein isolation, CBA; cryoballoon ablation, LSPV: left superior pulmonary vein, LIPV: left inferior pulmonary vein, RSPV: right superior pulmonary vein, RIPV: right inferior pulmonary vein, LPVs: left superior + inferior pulmonary veins, PRV: right superior + inferior pulmonary veins

of 7.3 ± 4.3 months was 5% (1/20) in the CBA group and 5% (1/20) in the CPVI group and thus did not differ significantly ($p = 0.1347$).

4. Discussion

4.1. Major findings

We found in our study of CPVI that CBA produced a greater LA/PV antrum isolation area and greater %LA/PV antrum isolation area than those produced by means of point-by-point CF-based circumferential RFA. We also found that CBA and circumferential RFA were comparable in terms of the post-procedural incidence of dormant PV conduction.

4.2. CBA, RFA, and outcomes

In comparison to open-irrigated, non-force sensing RFA for PVI, second-generation CBA coupled with RFA (as occasionally required) was recently associated with greater freedom from atrial arrhythmias at 12 months following a single procedure without antiarrhythmic therapy¹⁶. In another recent study, however, second-generation CBA and CF-guided RFA were shown to be comparable in terms of single-procedure arrhythmia-free survival at 18 months, and the overall complication rates were similar¹⁷.

4.3. CBA, RFA, and isolation areas

Kenigsberg et al. reported that the posterior LA wall isolation area produced by the cryoballoon catheter is wide and antral and that the resulting posterior LA wall debulking could in part explain the efficacy of CBA beyond the discrete PVI that is achieved⁷. However, they

Fig. 2 Low voltage areas after pulmonary vein isolation achieved by cryoballoon ablation or circumferential radiofrequency ablation. AP: antero-posterior, PA: postero-anterior, CF: contact, RFA radiofrequency ablation CBA: cryoballoon ablation, PV: pulmonary vein, LA: left atrium, LVA: low voltage area

did not compare the LA ablated areas of the left atrial endocardial surface produced by CBA and by circumferential RFA. Miyazaki et al. reported that the PV isolation areas measured during the chronic phase after second-generation CBA were significantly smaller than the areas encircled by the RFA line, except at the RIPV antrum⁸⁾. However, their RFA areas were derived from estimated ablation lines. We found the LA/PV antrum isolation area to be significantly larger after CBA than after circumferential RFA, and when the isolated area of each PV antrum was compared, the RIPV antrum isolation area was significantly larger than that produced by RFA.

4.4. LA size, PV anatomy, PV diameters and outcome of CBA

LA size, RSPV size, and the number of right PV ostia have been associated with AF recurrence following CBA^{18, 19)}. Therefore, even though CBA may produce a larger LA/PV antrum isolation area and the clinical outcome is similar to that produced by circumferential RFA, the LA anatomy should be considered in the decision to apply CBA for PVI.

4.5. Clinical implications

In the present study, isolation area by CBA was larger than that by RFA. The present data may be explained in part, the results of a recent trial that patients treated with cryoballoon as opposed to non contact force-guided RFA had significantly fewer repeat ablations, direct-current cardioversions, all-cause rehospitalizations and cardiovascular hospitalizations during follow-up²⁰⁾. In the present study, 60% of the patients were paroxysmal AF, and 40% patients were per AF, but the mean left atrial diameter was relatively small (40.1 ± 6.1 mm). The reason that no difference in the outcome in the present study might be 1) small number of patients in each group, 2) shorter follow-up periods, and 3) utilization of contact force- and VisiTag-guided approach for PVI. Pulmonary vein isolation is the most important for the treatment of both PAF and Per AF²¹⁾. A multicenter trial showed that pulmonary vein isolation using contact force-guided RFA and CBA led to comparable single procedure arrhythmia-free survival at up to 18 months¹⁷⁾. Furthermore, another report has shown that freedom from atrial tachyarrhythmias following PerAF ablation with RFA and CBA was comparable at 1-year follow-up after a single procedure. Ablation with CBA was associated with shorter procedure time and radiation exposure as compared with RFA²²⁾.

4.6. Study limitations

Our study was limited by the relatively small number of patients in each group and by the fact that both paroxysmal and persistent AF patients were included. In addition, follow-up was not long-term. In addition, different

mapping systems were used for assessment of the low voltage zones, and the PV isolation area was measured only once, just after CPVI. An additional study is needed that will include a large number of patients and in which the ablation area can be assessed during the chronic phase to confirm the differences we found between CBA and circumferential RFA in terms of the resulting LA/PV antrum isolation area/morphology and PV reconnections.

5. Conclusion

Our acute phase data indicate that CBA, in comparison to point-by-point circumferential CF-based RFA, produces a larger PV-LA surface isolation area.

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Conflict of interest

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

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