Comparison of the Safety and Efficacy of Automated Annotation-Guided Radiofrequency Ablation and 2nd-Generation Cryoballoon Ablation in Paroxysmal Atrial Fibrillation

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Background: Automated ablation lesion annotation with optimal settings for parameters including contact force (CF) and catheter stability may be effective for achieving durable pulmonary vein isolation.

Methods and Results: We retrospectively examined 131 consecutive patients who underwent initial catheter ablation (CA) for paroxysmal atrial fibrillation (PAF) by automatic annotation system (VISITAG module)-guided radiofrequency CA (RFCA) (n=61) and 2nd-generation cryoballoon ablation (CBA) (n=70) in terms of safety and long-term efficacy. The automatic annotation criteria for the RFCA group were as follows: catheter stability range of motion ≤1.5 mm, duration ≥5 s, and CF ≥5 g. We ablated for >20 s with a force-time integral >150 gs at each site, before moving to the next site. Each interlesion distance was <6 mm. Procedural complications were more frequent in the CBA group (1.6% vs. 10.0%, P=0.034). Across a median follow-up of 2.98 years, 88.5% and 70.0% of patients in the RFCA and CBA groups, respectively, were free from recurrence (log-rank test, P=0.0039). There was also a significant difference in favor of RFCA with respect to repeat ablations (3.3% vs. 24.3%, log-rank test, P=0.0039).

Conclusions: RF ablation guided by an automated algorithm that includes CF and catheter stability parameters showed better long-term outcomes than CBA in the treatment of patients with PAF without increasing complications.

Key Words: Ablation; Paroxysmal atrial fibrillation; Pulmonary vein isolation
patients underwent initial PAF ablation by 2 experienced operators between July 2014 and August 2015. We excluded from the study 5 patients who underwent LA linear ablation in addition to PVI. The remaining 131 PAF patients who underwent an initial PVI procedure using an automated annotation-guided RFCA (RFCA group, n=61) or 2nd-generation CB (CBA group, n=70) were examined in this study. The 2 operators selected RFCA or CBA based on the patient’s characteristics and preferences. We preferred to use RFCA if patients had uncommon atrial flutter or atrial tachycardia in addition to PAF. Adequate oral anticoagulation was maintained for at least 1 month before the procedure. Warfarin was interrupted 1 day before the procedure and was restarted in the evening after completion of the procedure. Dabigatran, rivaroxaban, apixaban, and edoxaban were omitted only on the morning of the procedure. The absence of thrombus in the LA was confirmed by transesophageal echocardiography the day before PVI. Antiarrhythmic drugs were stopped for at least 5 half-lives before the procedure and patients taking amiodarone were excluded from this study. All patients gave informed consent for the ablation procedures and the use of their clinical data in a retrospective study. The study protocol was approved by the institutional ethics committee.

LA Imaging Acquisition by Multidetector Computed Tomography (MDCT)
All patients underwent MDCT with a 160-detector row, dynamic volume scanner for 3D reconstruction of the LA and PVs in the week prior to the ablation procedure using a 64-slice MDCT scanner (Brilliance CT 64, Phillips Medical Systems, Cleveland, OH, USA). A bolus of non-ionic iodinated contrast (Iopamirone 370, Bayer Yakuhin, Osaka, Japan) was injected through an antecubital vein at a flow rate of 0.67 mL/min/kg for 15 s, followed by a saline bolus flush. The scan was initiated according to the bolus-tracking method (6 s after a threshold of 120 Hounsfield units in the descending aorta). Cardiac images from the carina to the apex of the heart were acquired during a single breath-hold at the end-tidal position. The 3D CT images were reconstructed at 50% of the R-R interval and recorded as DICOM data. Attending operators selected RFCA or CBA depending on the patient’s PV anatomy on MDCT and preference. We preferred RFCA in patients whose PV diameter was >25 mm.

Routine Electrophysiological Settings in Both Groups
The surface and intracardiac ECGs were digitally recorded and stored (Lab System™ Pro EP Recording System, Bard Clearsign™, Boston Scientific Corp.). The bipolar electrograms were filtered from 30 to 500 Hz. A 6-Fr 20-pole 3-site mapping catheter (BeeAT, Japan Lifeline, Tokyo, Japan) was passed through the right brachial or jugular vein for pacing, recording, and internal cardioversion. A single 150 μg/kg bolus of heparin was administered after the transseptal puncture and was repeated to maintain an activated clotting time >300 s. The endpoint of the PVI was achieving a bidirectional conduction block between the LA and PVs. After the completion of the PVI, we routinely administered high-dose isoproterenol (4–20 μg/min) after a waiting time of at least 20 min. Additional ablation was strongly encouraged to eliminate non-PV triggers, which were defined as ectopies that initiated AF originating from non-PV origins both in the RFCA and the CBA groups. The superior vena cava (SVC) was isolated in cases of frequent ectopic foci within the SVC or ectopies initiating AF from the SVC. When atrial flutter or atrial tachycardia was induced with rapid atrial pacing, we eliminated it by performing linear ablation of the cavitricuspid isthmus, left atrial roof, and mitral valve isthmus using a bidirectional conduction block as the endpoint. We did not perform empiric linear ablation or defragmentation. The procedures were performed under mild sedation with pentazocine, thiamylal sodium, and dexmedetomidine hydroxyzine. Patients’ respiration was controlled using bi-level positive airway pressure in all cases.

Specific Electrophysiological Studies and Catheter Ablation in the RFCA Group
A 20-pole catheter was placed in the right atrium or SVC and a SoundStar ultrasound catheter (Biosense Webster, Diamond Bar, CA, USA) was inserted into the right atrium via the femoral vein. Anatomic mapping of the LA was performed using the CartoSound module of the CARTO3 system (Biosense Webster). Intracardiac echocardiography (ICE) images were displayed through the CartoSound module using an echocardiography system (Vivid i, GE). ICE LA plane images were obtained at the end-tidal position and at the end of the T wave; 5–8 contours were sampled between the ostia of the right PV and the left PV, all of which were registered as the LA ICE image. These 2 images were integrated with the installed surface registration system. Next, 2 long sheaths (SLO, AF Division, SJM, Minneapolis, MN, USA) were introduced into the LA using a single transeptal puncture technique via the femoral vein. PVI was performed by integrating the 3D image using an open-irrigated ThermoCoolSmartTouch catheter (Biosense Webster) and a circular mapping catheter (adjustable circumference 15–25 mm, interelectrode pacing 1–2 mm Lasso; Biosense Webster) in all patients. We performed ipsilateral circumferential PVI using the single-lasso technique in sinus rhythm in all subjects except those in which AF occurred despite repeated electrical cardioversion. The automated ablation annotation system (Carto 3 System, VISITAG Module, Biosense Webster) parameters were as follows: (1) catheter stability range of motion ≤1.5 mm, (2) catheter stability duration >5 s, and (3) force over time (CF ≥5 g, time ≥25%). Tag size was 6 mm in diameter. We ablated thickly so that the interlesion distance was <6 mm. We set the minimum force-time integral as 150 g·s, and attempted to meet or exceed this level at each ablation site. We ablated for at least 20 s at each site, and continued the ablation until the force-time integral exceeded 150 g·s. Detailed electrophysiological studies and ablation methods have been described previously.a Elimination of PV potentials was confirmed with the 20-pole circular mapping catheter >20 min after the initial PV isolation.

Specific Electrophysiological Studies and Catheter Ablation in the CBA Group
A 14-Fr deflectable sheath (FlexCath, Medtronic) was advanced into the LA through the transseptal puncture. The 3D geometry of the LA and PVs was reconstructed using an EnSite NavX mapping system (St. Jude Medical) from data obtained with a 20-pole circular mapping catheter (4-mm interelectrode spacing, adjustable circumference 15–25 mm; Reflection Spiral Catheter, St. Jude Medical). The Arctic Front Advance CB was subsequently introduced into the sheath, inflated, and advanced to the ostium of each PV. The procedure was performed using the 28-mm
CB in all cases. Before cryoenergy delivery, the occlusion of each PV was assessed using venous angiography. Ablation of PV antra was performed using 2×180-s applications per vein. Continuous monitoring of the phrenic nerve during ablation of the right PVs was systematically performed by pacing the right phrenic nerve with a circular mapping catheter. If electrical isolation was not achieved, touch-up ablation was performed using a 10-mm-tip cryocatheter (Freezor MAX, Medtronic) for 2 min for each application or an irrigated-tip RF catheter. After each CBA procedure, elimination of PV potential was also confirmed with the 20-pole circular mapping catheter >20 min after the initial PV isolation.

**Patient Follow-up**

All patients were hospitalized under continuous rhythm monitoring for 3 days after the ablation procedure. All patients were scheduled for visits to the outpatient clinic at 1, 3, 6, 9, and 12 months after ablation. They visited the outpatient clinic every 6 months thereafter. ECG was obtained at each visit. Holter ECG was performed at 6 months after the procedure. Additional monitoring was performed depending on the patients’ symptoms. A 3-month blanking period after ablation was used. We instructed patients to check their pulse rate and rhythm 3 times daily and to visit the outpatient clinic if they experienced a persistent irregular pulse. In such cases, inspection by an external loop recorder was performed. Antiarrhythmic drugs were discontinued at 3 months after the procedure. Freedom from atrial tachyarrhythmia was defined as the documentation of AF, atrial flutter, or atrial tachycardia lasting >30 s while not taking antiarrhythmic drugs.

**Statistical Analysis**

Descriptive statistics are reported as mean±SD for continuous variables and as absolute frequencies and percentages for categorical variables. Continuous variables were compared using parametric and non-parametric testing based on the distribution of the data. Categorical variables were compared using the chi-squared or Fisher’s exact test. Event-free survival is reported as the crude event rate and estimated using the Kaplan-Meier survival function. Pairwise comparisons of survival rates were made using the log-rank test. A multivariable Cox proportional hazards analysis was applied to adjust for other established risk factors of recurrence. All statistical analyses were performed using JMP13.2.1. (SAS Institute, Inc., Cary, NC, USA).

**Results**

**Patients’ Characteristics**

Patient characteristics at baseline are summarized in Table 1. All patients had PAF. There were no significant differences in age, the proportion of male patients, left ventricular ejection fraction, or LA diameter between the groups. There were 3 patients whose PV was larger than 28 mm (1 in LSPV, 2 in RSPV) in the RFCA group.

**Procedural Parameters**

All PVs were successfully isolated in all patients. Successful PVI at the completion of the initial anatomical line was achieved in the majority of ipsilateral pairs of PV (73.0%)}
Two patients experienced temporary phrenic nerve injury and another 2 patients experienced persistent phrenic nerve injury in the CBA group. There were no severe procedural complications in either group (Table 2).

**Clinical Recurrence of Arrhythmia**

Median follow-up duration was 2.98 years. The 3-year single procedure success rate while off antiarrhythmic drugs was 54/61 (88.5%) in the RFCA group and 49/70 (70.0%) in the CBA group. As shown in Figure 2, the log-rank test confirmed that the RFCA group had a statistically significantly lower rate of arrhythmia recurrence than the CBA group (hazard ratio [HR]=0.31, 95% confidence interval [CI] 0.12–0.69, P=0.0035). One patient in the RFCA group and 2 patients in the CBA group did not have AF recurrence, but had atrial tachycardia.
patients received SVC isolation because of frequent ectopic foci or ectopies initiating AF from the SVC in the CBA group at the second procedure, although no cases of ectopic activities initiating AF from the SVC were observed in these patients at the first CBA session despite isoproterenol infusion. The log-rank test confirmed that the RFCA group had a statistically significantly lower rate of repeat ablation than the CBA group (HR=0.10, 95% CI 0.017–0.37, P=0.0003).

**Discussion**

**Major Findings**

To our knowledge, this is the first study to assess the long-term efficacy and safety of PVI performed with either RFCA guided by automated annotation or 2nd-generation CBA. We found that (1) the long-term procedural success rate was better in the automated annotation RFCA group than in the CBA group; (2) the automated annotation RFCA group had a lower rate of repeat ablation; and (3) CBA led to more phrenic nerve palsies. There were no major complications during or after PVI in either group. Importantly,
PVI-Guided Novel Annotation

PVI-Guided Novel Annotation

irrigated catheters in RFCA, although the issue of whether CF-guided PVI improves arrhythmia outcome is still controversial. In a multicenter study, Squara et al compared procedural parameters and arrhythmia recurrence between CF-guided RFCA without automated annotation and second-generation CBA. They revealed that the procedural time was shorter in CBA, while fluoroscopy duration, overall complications, and arrhythmia recurrence rates were similar between the groups. As the outcome of AF ablation changes according to the type of cryoballoon and catheter used for RFCA, data comparing the clinical outcomes of these 2 methods for AF ablation should be updated when new technologies become available.

Lesion Formation and Catheter Stability

The size of the lesion created by RF catheters correlates with CF, RF duration and power. In addition to these factors, the stability of the RF catheter during energy delivery is important from a clinical perspective because the catheter position may be unstable because of movement caused by the heart beat and respiration, and position

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**Table 4. Procedures in the 2nd RFCA**

| Procedure                              | RFCA group (n=2) | CBA group (n=17) | P value |
|----------------------------------------|------------------|------------------|---------|
| Re-isolation of reconnected PVs, n (%) | 2 (100)          | 13 (76)          | 0.32    |
| -Common LPV isolation                  | 0 (0)            | 1 (50)           |         |
| -LSVP re-isolation                     | 2 (100)          | 5 (33)           | 0.047   |
| -LIPV re-isolation                     | 0 (0)            | 5 (33)           | 0.22    |
| -RSPV re-isolation                     | 1 (50)           | 3 (18)           | 0.33    |
| -RIPV re-isolation                     | 1 (50)           | 8 (47)           | 0.94    |
| CTI ablation                           | 1 (50)           | 2 (12)           | 0.22    |
| LA linear ablation                     | 0 (0)            | 1 (6)            | 0.63    |
| SVC isolation                          | 0 (0)            | 5 (29)           | 0.25    |
| Non-PV foci ablation except SVC        | 1 (50)           | 5 (29)           | 0.57    |

Abbreviations as in Tables 1, 2.
instability will lead to insufficient lesion formation. VisiTag is an automatic annotation system that evaluates the positional stability of the ablation catheter during energy delivery. With this system, a site at which the catheter position is determined to be unstable during the energy delivery is not counted as an ablated point. In our current study, RFCA guided by automated annotation including CF and catheter stability parameters resulted in comparable procedure time, shorter fluoroscopy duration, lower X-ray dose, lower arrhythmia recurrence rates and less frequent repeat ablation after an index procedure compared with 2nd-generation CBA.

Isolation Area Difference Between RFCA and CBA
A wide ablation line encircling the entire PV antrum from the LA side targets both AF triggers and the perpetuating substrate. Several studies have reported that a larger isolation area is associated with a significantly lower AF recurrence rate in RFCA. CBA cannot specifically control an isolated area of PV, suggesting that the area is defined by the LA and PV anatomy. In contrast, attending operators can design tailormade isolation lines in RFCA cases, which would enable larger isolation areas compared with CBA cases. Miyazaki et al reported that the quantitative isolation area in the chronic phase after 2nd-generation CBA using 28-mm balloons was significantly smaller than the expected isolation area defined by the estimated ablation line of the ipsilateral PV tagged by a CF catheter. We found in 2 cases AF resources were identified outside the CBA isolation area but inside the circumferential PV line in the 2nd procedure. These cases highlighted the importance of the LA antrum isolation area, and a wider isolation area in the RFCA group than in the CBA group could potentially explain the difference in outcomes.

PVI Durability in RFCA and CBA
AF recurrence after ablation for PAF is associated with resumption of conduction between the previously isolated PV and LA in most re-ablation cases. Reversible tissue injury stems from incomplete lesion formation, resulting in temporary electric uncoupling without cell death. Some studies have compared the PVI durability between RFCA and CBA. A large multicenter, retrospective study comparing the incidence of late PV reconnection following an index CA for AF using the open-irrigated, non-CF RF catheter with that using 2nd-generation CB, Aryana et al revealed that more PVs had reconnected in RFCA cases compared with CBA cases (34.6% vs. 18.8%, P<0.001) at repeat ablation. In a small single-center study investigating the incidence of late PV reconnection following index PVI initially achieved with CF-guided RFCA without automated annotation and the incidence of late PV reconnection with second-generation CBA, Ciccone et al reported that the PV reconnection rate was significantly lower in CBA cases than in RFCA cases (1.2 vs. 1.8 PVs per patient, P=0.01). We previously reported that PVI guided by an automated ablation lesion annotation system reduced the acute resumption of LA-PV conduction and possibly led to improved durability of PVI. The VISITAG system may have improved the durability of PVI in the RFCA group and may underlie the improved rhythm outcome in this study.

Procedural Data and Safety
Overall, complications were more frequent with CBA, mainly phrenic nerve injury (5.7%). A previous study reported that the incidence of cardiac tamponade was low in PVI using CBA (0.3%). In comparison, other studies showed that PVI using a CF-sensing catheter without an automated annotation system was associated with a 1.3–2.5% incidence of cardiac tamponade. In the current study, no severe complications, including cardiac tamponade, were observed in either group. A previous study likewise did not observe cardiac tamponade among 200 patients who underwent PV guided by a VISITAG module. The VISITAG system may decrease insufficient energy application caused by catheter instability and avoid excessive ablation, which might contribute to the reduced occurrence of cardiac tamponade.

Usefulness of VISITAG Module
Our previous study showed that use of the VISITAG module in PVI cases was associated with a shorter procedure time, lower X-ray dose, lower frequency of conduction gaps after completion of the initial anatomical PV line, and lower rate of spontaneous PV reconnection. The 1-year ablation success rate was better in patients in whom VISITAG was used, possibly because of improvements in the durability of PVI. In a recent prospective, multicenter, observational registry, Zucchelli et al reported that RFCA for PAF using the VISITAG module led to shorter RF time, shorter fluoroscopy time, and a lower atrial tachyarrhythmia recurrence rate at 12-month follow-up compared with manual annotation. Although these 2 studies used different predefined parameters in the VISITAG module, they set similar predefined stability maximum range (1.5–2.5 mm) and minimum force (5 g) values. The automated annotation ablation system enables visualization of the location and intensity of ablation at each ablated point, which can influence an operator’s manipulation of the catheter. When the settings are optimal, this system would therefore be helpful in achieving durable PVI. These 2 studies provide strong evidence that PVI guided by the VISITAG module with optimal settings improves PVI durability and the arrhythmia-free rate.

Study Limitations
First, it was a retrospective observational study, which is associated with potential bias. Second, the recurrence rate of AF may have been underestimated because asymptomatic short-duration AF episodes may have gone undetected. However, we likely overestimated the arrhythmia success rate to a similar extent in both groups because they had the same monitoring protocol. Third, the results were based on a relatively small sample of patients. Fourth, the proportion of patients requiring SVC isolation because of AF triggers was higher in the CBA group (7 in the CBA group, 1 in the RF group). This could be a bias that might possibly affect the result. Finally, although this study involved 2 experienced operators, they did not conduct many CBA procedures during the study period because 2nd-generation CB became available in Japan just before the beginning of this study. As with any new technology, a learning curve is expected. This might have influenced the result of relatively high PV reconnection rates at the 2nd procedure in the CBA group, although the AF recurrence rate in the CBA group was comparable to that in other CBA studies. This is in contrast with RF in which the outcomes of AF ablation are considered to be more operator-dependent than those of CBA. As noted previously, the AF ablation
procedures in this study were performed by 2 experienced operators, which might have influenced the ablation outcome, especially in the RFCA group. To ensure that automated annotation-based RFCA is efficacious and safe, our results should be confirmed in a multicenter study with a larger sample size.

Conclusions

In PVI procedures, the use of RF ablation guided by an automated algorithm that includes CF and catheter stability parameters was associated with a better long-term outcome and lower frequency of repeat ablations compared with CBA, without increasing complications in patients with PAF.

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