Early Tissue Reaction After Second-Generation Cryoballoon Ablation Evaluated with Intracardiac Echocardiography
Evidence of Acute Tissue Edema After Cryoballoon Ablation

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Summary
Radiofrequency energy applications immediately produce tissue edema. This study aimed to investigate the acute tissue reaction immediately after second-generation cryoballoon applications using 3-dimensional intracardiac echocardiography (ICE) imaging technology.

This study consisted of 10 patients with paroxysmal atrial fibrillation who underwent pulmonary vein isolation (PVI) using second-generation cryoballoons. Ablation was performed with a single 3-minute freeze strategy and exclusively 28-mm balloons. The left atrial and right pulmonary vein (PV) antra geometries were created with 3-dimensional ICE technology before and immediately after the PVI.

Out of 20 right PVs, 19 were isolated exclusively with cryoballoons, and one right inferior PV (RIPV) required touch-up ablation. All 10 right superior PVs (RSPVs) were isolated by single cryoballoon applications, and RIPVs were isolated by a mean of 1.2 ± 0.4 applications. The total application time was 171 ± 19 and 203 ± 71 seconds, and nadir balloon temperature was −56.0 ± 4.9 and −53.8 ± 5.4°C for the RSPVs and RIPVs, respectively. In all patients, diffuse wall thickening of the antra and ostium of the right PVs was observed as compared to baseline. The wall thickening was 0-0.25 mm in 3 patients, and 0.25-0.5 mm in the remaining 7. During the median follow-up of 13 [10.2-17.2] months, 8 (80%) patients were free from arrhythmia recurrences. Nine (90%) patients underwent repeat cardiac computed tomography at a median of 6.0 [4.5-12.0] months after the initial procedure, and no PV stenosis was observed in all.

Tissue edema and wall thickening appeared in the human left atrium immediately after second-generation cryoballoon ablation.

Key words: Cryoablation, Pulmonary vein isolation, Atrial fibrillation

Paroxysmal atrial fibrillation (AF) is often triggered by spontaneous ectopic beats of pulmonary venous (PV) origin, and the observation has led to the emergence of PV isolation (PVI) as an effective treatment for AF. Radiofrequency (RF) ablation has been the standard energy source to perform electrical PVI, however, PV reconnections after PVI are a common finding and the main cause of arrhythmia recurrence. Since RF energy applications immediately produce acute tissue edema, the reversible tissue edema temporarily provides electrical isolation during the acute phase, which makes it difficult to create durable lesions during ablation procedures.

Recently, cryoballoon (CB) ablation has emerged as an alternative strategy for PVI. Animal studies have shown that cryoablation accompanied with minimal disruption of the endothelium, creates relatively discrete lesions, and preserves the myocardial architecture, followed by replacement with fibrous tissue. It is believed that acute tissue edema would be less during cryoablation than RF ablation, however, little evidence is available. The present study aimed to prospectively evaluate the acute tissue reactions after CB ablation using recently introduced 3-dimensional intracardiac echocardiography (ICE) (CartoSound technology).

Methods

Study population: This study consisted of 10 patients with paroxysmal AF who underwent PVI using a second-generation CB (Arctic Front Advance, Medtronic, Minneapolis, MN, USA). The CB ablation was performed with a single 3-minute freeze strategy, without a routine bonus application, and exclusively 28-mm balloons. Geometries of the left atrium (LA) and right PVs were created before and immediately after the PVI using CartoSound technology. AF was classified according to the latest guidelines. All patients provided written informed consent. The study protocol...
Figure 1. A representative case. A, B: Pre-procedural cardiac CT showing a normal PV anatomy. C, D: A single CB application successfully isolated the RSPV and RIPV. E: No PV stenosis was observed 17 months after the procedure. LSPV indicates left superior PV; LIPV, left inferior PV; LA, left atrium; RSPV, right superior PV; RIPV, right inferior PV; PA, postero-anterior; AP, antero-posterior; and RAO, right anterior oblique view.

was approved by the hospital’s institutional review board. The study complied with the Declaration of Helsinki.

**Mapping and ablation protocol:** All antiarrhythmic drugs were discontinued for at least 5 half-lives prior to the procedure. Contrast-enhanced cardiac computed tomography (CT) was performed to evaluate the PV and LA anatomy (Figure 1A, B). The surface electrocardiogram and bipolar intracardiac electrograms were continuously monitored and stored on a computer-based digital recording system (LabSystem PRO, Bard Electrophysiology, Lowell, MA, USA). The bipolar electrograms were filtered from 30-500 Hz. A 7 Fr 20-pole 3-site mapping catheter was inserted through the right jugular vein for pacing, recording, and internal cardioversion.

The procedure was performed under conscious sedation obtained with dexmedetomidine. A 100 IU/kg body weight dose of heparin was administered immediately following the venous access, and heparinized saline was additionally infused to maintain the activated clotting times at 300-350 seconds. A single transseptal puncture was performed using an RF needle (Baylis Medical, Montreal, QC, Canada) and 8.5-Fr long sheath (SL0, AF Division, SJM, Minneapolis, MN, USA). The transseptal sheath was exchanged over a guidewire for a 15-Fr steerable sheath (Flexcath Advance, Medtronic). A spiral mapping catheter (Achieve, Medtronic) was used for mapping the PV potentials, and a complete occlusion was confirmed by injecting contrast medium. This was followed by a freeze cycle of 180 seconds. No 23-mm CBs were used in any cases. No additional applications were performed after the isolation. To avoid bilateral phrenic nerve injury, all CB applications were applied while monitoring the ipsilateral diaphragmatic compound motor action potentials during phrenic nerve pacing. The procedural endpoint was defined as an electrical PVI verified by the 20-mm circular mapping catheter (Lasso, Biosense Webster).

**Mapping with the CartoSound System:** The 7-Fr Soundstar catheter (Soundstar, Biosense Webster) was employed to obtain 3-dimensional structures of the LA and PVs from the right atrium (RA), and then the catheter was inserted into the LA via an 8.5-Fr long sheath to create the geometry. Images were gated to an atrial electrogram recorded by an electrode in the coronary sinus under sinus rhythm or 80% of the R-R interval under AF. The contours collected were collated to re-construct a 3-dimensional rendering of both the LA and PVs. The geometry of the LA was created prior to the CB ablation, then the geometry of the right PVs and antra were again created after the CB ablation using the transducer with the same method for a comparison. The LA endocardial surface was carefully demarcated, and several planes were collected from multiple transducer locations (both from RA and LA) to obtain an accurate image of the right PV antra. Since creating precise 3-dimensional images from
significant difference between the patients with wall thickening was 0-0.25 mm in 3 patients, and 0.25-0.5 mm in the remaining 7 patients (Figures 2, 3). There was no thickening was observed at all patients. In all patients, a diffuse wall thickening immediately after the CB applications appeared after ablation was defined as tissue edema.11) Acute tissue reaction and follow-up data: The wall thickening was 0-0.25 mm in 3 patients, and 0.25-0.5 mm in the remaining 7 patients (Figures 2, 3). There was no significant difference between the patients with wall thickening of < 0.25 mm and those with 0.25-0.5 mm regarding the number of cryoapplications (RSPV: 1.0 versus 1.0, P = 1.0, RIPV: 1.3 ± 0.6 versus 1.1 ± 0.4, P = 0.55), total application time (RPVs: 383 ± 87 versus 370 ± 79 seconds, P = 0.83), and PV diameter (RSPV coronal: 16.6 ± 1.5 versus 18.0 ± 1.6 mm, P = 0.23, RIPV: 14.7 ± 2.1 versus 13.0 ± 2.1 mm, P = 0.28, RIPV: coronal: 13.9 ± 1.8 versus 14.3 ± 2.3 mm, P = 0.78, RIPV: horizontal: 10.2 ± 2.3 versus 13.4 ± 2.3, P = 0.08), except for the nadir balloon temperature (RSPV: −49.3 ± 0.6 versus −58.8 ± 2.0°C, P < 0.01, RIPV: −49.7 ± 6.8 versus −55.5 ± 4.0°C, P = 0.12).

During the median follow-up of 13 [10.2-17.2] months, 8 (80%) patients were free from arrhythmia recurrence. The remaining 2 patients underwent a second procedure 6 and 7 months after the procedure, respectively. No PV reconnections were observed in the first patient, and the LIPV was reconnected in the second patient. In 9 (90%) patients, a repeat cardiac CT was performed at a median of 6.0 [4.5-12.0] months after the initial procedure, and no PV stenosis (> 25%) was observed in all.

Discussion

In the present study, we evaluated the acute tissue reactions after second-generation CB ablation in humans using ICE. We found that diffuse acute tissue edema appeared immediately after the CB applications.

Evaluation of the LA endocardium using ICE: ICE provides high quality images and has been used successfully in other cardiac procedures. A new technology, CartoSound, permits rapid collection of a large quantity of spatial data derived from LA endocardial surfaces, which is apparent on ICE images.26 Schwartzman, et al. validated the use of ICE for assessing the magnitude of cardiac wall swelling in response to RF applications, and characterized the time course of the swelling and correlated it with the underlying histology in an animal study.27 The CartoSound module and Soundstar catheter integrate real-time ICE images into the CARTO mapping system. In the present study, the contours were initially obtained from the RA, then obtained from the LA to create an accurate geometry of the right PV antra. Given the absence of solid tissue barriers that may obscure or attenuate ultrasound signals and/or limit image planes, it is reasonable to expect that the LA transducer location would yield the most comprehensive image of the LA endocardium.

Acute edema after RF ablation: Tissue heating with RF energy is a result of resistive heating at the interface between the catheter and tissue. This heating is a direct function of the current density between the catheter ablation electrode and the myocardial interface extending a few millimeters into the tissue. There is evidence from animal studies that tissue edema causes wall thickening after RF ablation.22 A few studies have observed edema in humans with ICE imaging. Schwartzman, et al. initially demonstrated a reduction in the PV lumen cross-sectional area together with PV wall swelling immediately after a selective segmental PV ostial isolation with a non-irrigated RF catheter.23 Weerasooriya, et al. elegantly showed the early appearance (within 15 seconds) of

### Table. Characteristics of the Study Population

| Characteristic                  | Value               |
|--------------------------------|---------------------|
| Age, years                     | 57.2 ± 16.9         |
| Paroxysmal AF, n (%)           | 10 (100 %)          |
| Female, n (%)                  | 5 (50.0 %)          |
| Hypertension, n (%)            | 2 (20.0 %)          |
| Body mass index, kg/m²         | 25.4 ± 3.2          |
| LA diameter, mm               | 37.8 ± 4.3          |
| LV ejection fraction, %        | 67.6 ± 4.8          |
| Pro-Brain Natriuretic Peptide, pg/mL | 125 ± 143    |
| Estimated GFR, mL/minute/1.73m² | 74.0 ± 17.2        |

AF indicates atrial fibrillation; LA, left atrial; LV, left ventricular; PV, pulmonary vein; and GFR, glomerular filtration ratio.

Multiple contours requires a long mapping time, we did not create the geometry of the left PV antra post-ablation. After the procedure, we looked for identical cross sections before and after the ablation, and found the sites where the wall thickness could be reliably compared on the cross sections. The morphologic changes in the PV wall were analyzed, and hypoechogenic abnormal tissue that newly appeared after ablation was defined as tissue edema.11) Then, the thickness of the hypoechogenic tissue was measured on the cross section.

**Statistical analysis:** Continuous data are expressed as the mean ± standard deviation for normally distributed variables or the median [25th, 75th percentiles] for non-normally distributed variables.

**Results**

Clinical characteristics and procedural results: The baseline patient characteristics are summarized in the Table. In 10 patients, a total of 40 PVs were identified. Overall, 37 of 40 (92.5%) PVs were isolated successfully using exclusively 28-mm CBs (Figure 1C, D). The total number of CB applications was 1.4 ± 1.3, 1.3 ± 0.7, 1.0, and 1.2 ± 0.4 for the left superior (LSPV), left inferior (LIPV), right superior (RSPV), and right inferior (RIPV) PVs, respectively. The total application time was 175 ± 14, 233 ± 110, 171 ± 19, and 203 ± 71 seconds for the LSPV, LIPV, RSPV, and RIPV, respectively. The nadir balloon temperature was −50.7 ± 5.8, −44.4 ± 5.3, −56.0 ± 4.9, and −53.8 ± 5.4°C for the LSPV, LIPV, RSPV, and RIPV, respectively. The remaining 3 (7.5%) PVs (LSPV, LIPV, and RIPV in 1 each) required touch-up ablation with an irrigation-tip catheter. In total, all 40 PVs were successfully isolated. No complications were observed during the procedure.

Acute tissue reaction and follow-up data: Three-dimensional ICE images of the LA and right PV antra pre- and post-CB ablation were successfully obtained in all 10 patients. In all patients, a diffuse wall thickening (hypoechogenic tissue newly appeared) was observed at the antra and ostium of the right PVs after the CB ablation as compared to that before the CB ablation. The wall thickening was 0-0.25 mm in 3 patients, and 0.25-0.5 mm in the remaining 7 patients (Figures 2, 3). There was no significant difference between the patients with wall thickening.
edema during RF energy deliveries using irrigated-tip catheters at the mitral isthmus. Steel, et al. demonstrated LA edema produced by RF ablation using CT images. More recently, an MRI study revealed that LA edema most likely occurs during and immediately after AF ablation, as evidenced by an increase in the atrial wall thickness, and resolves within 1 month. Arujuna, et al. showed that MRI could identify a reversal of the tissue injury after an acute PVI, which seems to represent tissue edema, and that the acute PVI was achieved by a combination of reversible and irreversible circumferential tissue injury at the PV-LA junction.

Acute edema after cryoablation: In contrast to RF, cryoenergy removes heat from tissues, lowering the molecular movement and stored kinetic energy, which results in tissue cooling and ice formation. With cryoballoon catheters, a rapid and intense cooling leads to ice formation on the tissues in contact with the balloon. However, the mechanism of the lesion formation is highly complex, and there is still disagreement on whether direct cellular injury or vascular failure is the primary cause of injury from cryoablation. Microcirculation is damaged directly within the probe/ice ball contact area, and coagulative necrosis at the ice ball site typically leads to edema that can cause adjacent vessel cells to swell and rupture. Theoretically, the magnitude of the tissue edema is likely less in cryoablation than RF ablation. However, given that PV reconnections could be observed during the chronic phase even after CB ablation, it is not surprising that acute tissue edema could be observed after cryoablation. The temporal tissue edema likely has an impact on the electrical PVI and area of a low voltage during the acute phase. Our study showed that diffuse acute tissue edema appeared immediately after the CB applications, and also showed that the nadir balloon temperature was lower in patients with a greater magnitude of tissue edema. However, given this comparison between small populations, further study is necessary to identify the factors associated with acute tissue edema.

The comparison of the acute tissue reaction between RF and CB ablation seemed to be interesting. However, since RF ablation created linear lesions, but not area lesions like the CB, delineating the entire RF lesion with CartoSound was more difficult than that with CB ablation. Moreover, it is likely that the RF lesion was influenced by many other factors (contact force, power, application duration, inter-lesion interval, operator experience, and so on).

Study limitations: This study was a single center study and the study population was relatively small. However, the data was consistent and acute tissue edema was observed in all cases. Although several planes were collected from multiple transducer locations to obtain accurate images, a detailed quantitative analysis of the edema distribution was challenging due to the limited ICE window and image quality. We did not compare the magnitude of the tissue edema after CB and RF ablation, and further
study is necessary to elucidate this point.

Conclusions

Tissue edema and wall thickening appeared in the human LA immediately after second-generation CB ablation.

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Disclosure

Conflicts of interest: None.

References

1. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. J Arrhythm 2017; 33: 369-409.
2. Schwartzman D, Ren JF, Devine WA, Callans DJ. Cardiac swelling associated with linear radiofrequency ablation in the atrium. J Interv Card Electrophysiol 2001; 5: 159-66.
3. Schwartzman D, Kanzaki H, Bazaz R, Gorcsan J. Impact of catheter ablation on pulmonary vein morphology and mechanical function. J Cardiovasc Electrophysiol 2004; 15: 161-7.
4. Arujuna A, Karim R, Caulfield D, et al. Acute pulmonary vein isolation is achieved by a combination of reversible and irreversible atrial injury after catheter ablation: evidence from magnetic resonance imaging. Circ Arrhythm Electrophysiol 2012; 5: 691-700.
5. Kojodjojo P, O’Neill MD, Lim PB, et al. Pulmonary venous isolation by antral ablation with a large cryoballoon for treatment of paroxysmal and persistent atrial fibrillation: medium-term outcomes and non-randomised comparison with pulmonary venous isolation by radiofrequency ablation. Heart 2010; 96: 1379-84.
6. Kacker DL, Kowal RC, Wheelan KR, et al; STOP AF Cryoablation Investigators. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. J Am Coll Cardiol 2013; 61: 1713-23.
7. Coulombe N, Paulin J, Su W. Improved in vivo performance of second-generation cryoballoon for pulmonary vein isolation. J Cardiovasc Electrophysiol 2013; 24: 919-25.
8. Khairy P, Chauvet P, Lehmann J, et al. Lower incidence of thrombus formation with cryoenergy versus radiofrequency catheter ablation. Circulation 2003; 107: 2045-50.
9. Schwartzman D, Zhong H. On the use of CartoSound for left atrial navigation. J Cardiovasc Electrophysiol 2010; 21: 656-64.
10. Sacher F, Monahan KH, Thomas SP, et al. Phrenic nerve injury after atrial fibrillation catheter ablation: characterization and outcome in a multicenter study. J Am Coll Cardiol 2006; 47: 2498-503.
11. Baran J, Lewandowski P, Smarz K, et al. Acute Hemodynamic and Tissue Effects of Cryoballoon Ablation on Pulmonary Vessels: The IVUS-Cryo Study. J Am Heart Assoc 2017; 6: e005988.
12. Weerasooriya R, Jais P, Sanders P, et al. Images in cardiovascular medicine. Early appearance of an edematous tissue reaction during left atrial linear ablation using intracardiac echo imaging.
13. Steel KE, Roman-Gonzalez J, O’Bryan CL 4th. Images in cardiovascular medicine. Severe left atrial edema and heart failure after atrial fibrillation ablation. Circulation 2006; 113: e659.
14. Avitall B, Kalinski A. Cryotherapy of cardiac arrhythmia: From basic science to the bedside. Heart Rhythm 2015; 12: 2195-203.
15. Takayama K, Hachiya H, Iesaka Y, et al. Early Recurrence after Longstanding Persistent Atrial Fibrillation Ablation. Int Heart J 2018; 59: 321-7.