Magnetic resonance imaging–guided cryoballoon ablation for left atrial substrate modification in patients with atrial fibrillation

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Abstract

Background: Cryoballoon ablation (CBA) for pulmonary vein isolation (PVI) is an established modality for the treatment of atrial fibrillation (AF). We report feasibility of left atrial (LA) substrate modification in addition to PVI both using the cryoballoon.

Methods: LA substrates and CBA-induced scar were assessed at baseline and 3 months after ablation using late gadolinium enhancement magnetic resonance imaging (LGE-MRI). Common periprocedural data including postablation LGE-MRI for evaluation of esophageal thermal injury, and CBA-associated complications were collected. Freedom from AF recurrence at 12 months was assessed using Holter and 30-day rhythm monitors.

Results: In 26 patients (64 ± 11 years, 69% male; 27% persistent AF, CHADSVASC score: 2.3 ± 1.5; left ventricular ejection fraction: 56 ± 10%, oral anticoagulation with warfarin/direct oral anticoagulants: n = 11/15), referred for first-time AF ablation, CBA of the pulmonary veins and extrapulmonary LA substrates was performed (median: 12 [interquartile range {IQR}: 7–14] freezes over 1675 seconds [IQR: 1168–2160]). On LGE-MRI, significant postablation cryoballoon-induced LA scar (median: 19.4% [IQR: 13.4–24.7] in comparison to baseline preablation LA-LGE (median: 10.6% [IQR 3.1–13.1]; P = .01) was found. Freedom from AF recurrence at 12 months was 74.5% with median time-to-recurrence of 242 days (IQR: 172–298). In 15 of 26 (58%) patients, esophageal enhancement on the postablation MRI was present with full recovery after 3 months. No major periprocedural complications were observed.

Abbreviations: 3D, three-dimensional; AF, atrial fibrillation; CBA, cryoballoon ablation; DOAC, direct oral anticoagulants; EGD, esophagogastroduodenoscopy; ETI, esophageal thermal injury; ICE, intracardiac echocardiography; IQR, interquartile range; LA, left atrium/left atrial; LGE-MRI, late gadolinium enhancement magnetic resonance imaging; LVEF, left ventricular ejection fraction; OAC, oral anticoagulation; PV, pulmonary vein; PVI, pulmonary vein isolation; PWI, posterior wall isolation; RF, radiofrequency; TIA, transient ischemic attack.
1 | INTRODUCTION

Pulmonary vein isolation (PVI) using cryoballoon ablation (CBA) is an established catheter-based technique for the treatment of atrial fibrillation (AF).\(^1\) However, the use of CBA in recent clinical trials has been limited to PVI solely. Patients with paroxysmal AF have been the main recipients of this technology. Over time, our understanding of pathophysiologic AF drivers has evolved. As such, AF ablation targets have expanded from pulmonary vein (PV) triggers to additional extrapulmonary arrhythmogenic substrate modification within the entire left atrium (LA) that can be found in both paroxysmal and persistent AF patients.\(^2\)

In patients with significant extrapulmonary LA substrates, the utility of CBA is less than straightforward. In such patients, the choices are to either use CBA in a PVI-only approach or alternatively, use CBA for PVI followed by the use of radiofrequency (RF) ablation for additional substrate modification. The ability to use CBA for LA substrate modification in addition to PVI would therefore provide a promising advantage.

Three-dimensional (3D) late gadolinium enhancement magnetic resonance imaging (LGE-MRI) has emerged as a unique noninvasive approach to quantify LA substrates as well as ablation-induced scar formation.\(^3\) Substrate modification by targeting MRI-detected LA-LGE is an increasingly popular approach that might be effective to decrease the risk of AF recurrence.\(^4\) In this study, we report our initial clinical experience of LGE-MRI-guided LA substrate modification in addition to PVI using CBA.

2 | METHODS

This was a retrospective observational study of consecutive patients who underwent first-time CBA for AF at the University of Utah between June, 2014 to August, 2016. The study was approved by the University of Utah Institutional Review Board.

2.1 | Patient selection

Patients were included in the study if they were more than 18-years old, had symptomatic paroxysmal or persistent AF, and were referred for first-time AF ablation. All patients underwent a preablative LGE-MRI followed by scans within 24 hours after ablation and at 3 months. The 24-hour LGE-MRI assessed acute postablation complications including esophageal thermal injury (ETI) while the preablative and 3-month scans assessed LA substrate and CBA-induced scar formation, respectively. All patients were admitted for overnight observation and discharged the next day after their 24-hour LGE-MRI scan. The admission was extended if follow-up studies such as repeat MRI or an esophagogastroduodenoscopy (EGD) was required based on the extent of esophageal enhancement on the acute LGE-MRI. Patients who had a contraindication for LGE-MRI were not included.\(^5\) Other exclusion criteria were recent (within last 3 months) coronary artery syndrome, cardiac surgery, or transient ischemic attack (TIA)/stroke, presence of known LA thrombus, or the inability to remain on continuous anticoagulation postoperatively. All patients were followed up within 8 weeks in clinic.

2.2 | Magnetic resonance imaging procedures

Patients underwent 3D LGE-MRI evaluation before ablation obtained on a 1.5-Tesla Avanto or 3-Tesla Verio clinical scanner (Siemens Medical Solutions, Erlangen, Germany) acquired 15 minutes after injection of 0.01 mmol/kg of gadolinium contrast (Multihance; Bracco Diagnostics Inc, Princeton, NJ) using a 3D ECG-gated, respiratory-navigated, inversion-recovery prepared gradient-recalled echo pulse sequences as previously described.\(^3\) Quantification of LA-LGE and scarring were defined using dedicated software (Corview; Marrek, Salt Lake City, UT). Patients were assigned to one of four groups of increasing LA-LGE stages: Utah stage 1 (minimal: <10%), Utah stage 2 (mild: 10%-20%), Utah stage 3 (moderate: 20%-30%), and Utah stage 4 (extensive: >40%).\(^3\) A substrate map displaying areas of LA-LGE was generated and used during the ablation procedure. Similar images were acquired 3 months later to determine the levels of postablation scarring created by CBA.\(^5\) Immediately 24 hours after ablation, all patients underwent MRI to assess ETI. Any delayed enhancement in this area was considered to be esophageal enhancement secondary to ETI and categorized as none (no detectable enhancement), mild (focal enhancement), moderate (transmural or near transmural enhancement), and severe (transmural enhancement involving more than 5 mm of esophageal tissue or present in more than one location).\(^6\) Presence of atrioesophageal fistula was also assessed. Patients with severe enhancement had to repeat an MRI study within 24 hours. Patients with moderate esophageal enhancement had a repeated study within 7 days. All patients with persistent enhancement on their repeat study

**Conclusion:** LA substrate modification in addition to PVI using LGE-MRI-guided CBA is feasible but still experimental. The efficacy and safety have to be investigated in a prospective randomized trial.

**KEYWORDS**

ablation, atrial fibrillation, cryoballoon, LA substrate, late gadolinium enhancement, magnetic resonance imaging
were referred for EGD. A repeat MRI was performed at 3 months after ablation in all patients. Ablation scar size as well as presence of PV stenosis were assessed and correlated to regions of LA substrate measured before ablation.

2.3 | Ablation procedure

All patients were continued on their home oral anticoagulation (OAC) agent periprocedurally. Patients who had AF as their presenting rhythm at the time of ablation underwent transesophageal echocardiography to exclude presence of LA thrombus. A weight-based bolus of heparin was given immediately before transeptal puncture and intermittently every 10 minutes thereafter to achieve a target activated clotting time of 350 to 450.

A single transeptal puncture was performed using intracardiac echocardiography (ICE) guidance (SoundStar®; Biosense Webster, Diamond Bar, CA). Using a multipolar catheter (Lasso® or PentaRay®; Biosense Webster) and ICE integration, a 3D electroanatomic map of the LA was created (CartoSound®; Biosense Webster) and PV ostia were marked. The transeptal sheath was then exchanged with a 12-Fr steerable sheath (FlexCath Advance™; Medtronic, Minneapolis, MN) over a guidewire (Amplatz Super Stiff™; Boston Scientific, Marlborough, MA) placed in the superior PV. A second-generation 28 mm cryoballoon catheter (Arctic Front; Medtronic) was then advanced into the LA and into the PV ostia over the circular inner lumen mapping catheter (Achieve; Medtronic). The Arctic Front balloon was inflated and positioned to occlude the vein ostium. The balloon was cooled to a freezing target temperature of −30°C with an application time of up to 120 seconds. Freezing was halted if recorded temperature reached −60°. Repeat freezes (up to a total of four freezes) were done if needed. After achieving PVI, the catheter was pulled back slightly and directed either anteriorly or posteriorly to cover the periosial regions of atrial substrates. This process was repeated sequentially for all PVs. When freezing right-sided veins, phrenic nerve activity was monitored by ensuring phrenic capture from a pacing catheter placed in the superior vena cava. Freezing was stopped immediately with weakening of loss of phrenic nerve capture. The Arctic Front catheter was then maneuvered posteriorly to have the balloon cover areas of LGE on the posterior wall. A freezing temperature of −30°C and application time of 80 to 120 seconds was applied when targeting areas of atrial LGE. We used ICE to ensure the alignment of the cooling zone of the balloon with the LA tissue. In cases where extensive LGE was present in the anterior wall, the catheter–tissue alignment was ensured by anchoring the Achieve catheter in the LA appendage.

Information from MRI with preablation LGE was integrated into a 3D mapping system. Alignment with landmarks from fluoroscopy or ICE was extensively used to navigate to extrapulmonary areas of LA-LGE and to guide catheter positioning as well as to ensure overlapping of lesions without any gaps. Esophageal temperature was monitored at all times by maneuvering a temperature probe in the esophagus and stopped freezing if the temperature was decreased bellow 20°C. Ablation ended if PVI was achieved by entrance block and noninducibility by rapid atrial pacing as well as homogenization of LA-LGE outside the PVs by CBA. During and at the end of the procedure, the LA was surveyed with ICE and presence of any pericardial effusion was checked.

2.4 | Postoperative management and follow-up

All patients were kept in the hospital overnight after ablation with cardiovascular monitoring for at least 24 hours and were assessed for immediate postablation and late postablation complications such as access complications (eg, bleeding, infection, aneurysm, fistula, thrombosis), complications from catheter manipulation (eg, perforation, tamponade), postprocedure PV stenosis, phrenic nerve injury, atroesophageal fistula, or TIA/stroke. If applicable, prior antiarrhythmic medication was stopped. Anticoagulation was continued postoperatively in all patients. All patients were started on a proton pump inhibitor for a month. All patients received either 30-day or 60-day event monitors immediately following ablation and at the 3-month follow-up. The first 90 days after ablation were considered as blanking period. Patients were followed at 3-, 6-, and 12-month intervals. If patients complained of AF symptoms, additional home monitoring was ordered. Recurrence was defined as sustained (≥30 seconds) AF or flutter on event monitors, AF or flutter on electrocardiogram, or the need for additional ablation and/or cardioversion.

2.5 | Data analysis and statistical methodology

Data are expressed as number (percentage) or median with interquartile range (IQR). Continuous variables were analyzed using the two-sample t-test when distribution was normal or Mann–Whitney test with a non-normal distribution. The χ² test or Fisher exact test was used to analyze categorical variables. Time to first recurrence of atrial arrhythmias was analyzed using Kaplan–Meier estimates. A two-sided probability of P ≤ .05 was considered significant. Statistical analyses were performed using R software (R Core Team, Vienna, Austria; URL: http://www.R-project.org/).

3 | RESULTS

3.1 | Patient population

Twenty-six patients (64 ± 11 years, 69% male; CHADSVASC score: 2.3 ± 1.5) with mainly paroxysmal AF type and normal left ventricular ejection fraction (LVEF) were eligible for analysis. Regular PV anatomy was present in the majority of patients (four veins, n = 20/26; 77%). Common ostium (n = 2/26; 8%) or accessory PVs (five veins, n = 4/26; 15%) were frequently found. Detailed baseline demographics are given in Table 1.
3.2 | Evaluation of left atrial substrates and ablation-induced scar by LGE-MRI

Median preprocedure LA-LGE burden from 3D-MRI analysis measured 10.6% (IQR: 3.1-13.1), Utah stage II. Postinterventional reassessment after 3 months showed a significant CBA-induced median LA scar lesion formation measuring 19.4% (IQR: 13.4-24.7; P = .01) of the LA surface in comparison to baseline with an absolute change by 9.3% ± 3.7%.

3.3 | Extrapulmonary cryoablation procedure characteristics

Total procedure time of PVI with additional targeting of extrapulmonary areas of LA-LGE, both using CBA was performed over a median of 150 minutes (IQR: 130-174) without intraprocedural or periprocedural complications. At median, 12 (IQR: 7-14) cryoballoon freezes over a total freezing time of 1675 seconds (IQR: 1168-2160) and 42 minutes (IQR: 27-56) of fluoroscopy time were required. Median temperature during PVI was −37°C (IQR: −27 to −60). Median temperature during ablation of atrial fibrosis was −29°C (IQR: −24 to −39). In three patients, we had to terminate freezing of left upper PVs due to a less than −60°C temperature. A total case synopsis of LA-LGE and scar evaluation by MRI preablation and postablation with reconstruction of the intraprocedural cryoballoon locations and endocardial contact area during ablation is given in Figure 1. More examples from the studied cohort are given in Figure 2.

3.4 | Rhythm outcome and clinical course

Freedom from AF recurrence at 12 months measured 74.5% (n = 19/26) with a median time to first AF recurrence of 172 days (IQR: 46-221; Figure 3). In 10 of 26 (38%), 14 of 26 (54%), and 1 of 26 (4%) patients, either non, mild, or moderate esophageal LGE on the immediate 24-hour postablation MRI scan was present showing full recovery in all

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**Table 1** Baseline demographic data

|                          | n  | %  | Median | IQR  |
|--------------------------|----|----|--------|------|
| Age, y                   | 26 | 100| 66     | 58-73|
| Sex (male)               | 18 | 69 |        |      |
| BMI (%)                  | 26 | 100| 31     | 25-33|
| Persistent AF (n/%)      | 7  | 27 |        |      |
| CHA2DS2-VASC score       | 26 | 100| 2      | 1-3  |
| LVEF (%)                 | 26 | 100| 60     | 51-66|
| Prior AAD therapy        | 7  | 27 |        |      |
| Beta-blocker/Ca-channel-blocker | 14/6 | 54/23 |
| OAC with warfarin/DOAC   | 11/15 | 42/58 |
| Utah stage I             | 10 | 38 |        |      |
| Utah stage II            | 16 | 62 |        |      |
| Alcohol/Tobacco          | 17/8 | 65/31 |
| Hyperlipidemia           | 9  | 35 |        |      |
| Diabetes mellitus type 2 | 4  | 15 |        |      |
| Arterial hypertension    | 19 | 73 |        |      |
| Mitral valve regurgitation | 0  | 0  |
| Chronic kidney disease   | 2  | 8  |        |      |
| Thyroid disease          | 7  | 27 |        |      |
| Coronary artery disease  | 7  | 27 |        |      |
| Peripheral artery disease| 0  | 0  |        |      |
| Chronic obstructive pulmonary disease | 1 | 4 |
| Sleep apnea              | 13 | 50 |        |      |
| Pulmonary hypertension   | 1  | 4  |        |      |
| TIA/stroke               | 1  | 4  |        |      |

**Abbreviations:** AF, atrial fibrillation; BMI, body mass index; DOAC, direct oral anticoagulants; IQR, interquartile range; LVEF, left ventricular ejection fraction; OAC, oral anticoagulation; TIA, transient ischemic attack

**Figure 1** Case synopsis: three-dimensional left atrium (LA) model in blue from late gadolinium enhancement magnet resonance imaging (LGE-MRI) showing (A) LA-LGE distribution as green/white area, (B) intraprocedural location of the cryoballoon freezing hemispheres, and (C) preablation induced scar after 3 months. (D) Fusion of B and C highlighting the correlation between the cryoballoon location and the corresponding ablation-induced scar
patients on the 3-month scan. Need of EGD with conventional treatment was reported in only one patient with confirmed nonbleeding 5 mm H. pylori positive esophageal ulcer. No major complications, such as pericardial effusion, phrenic nerve injury, atrioesophageal fistula, PV stenosis, deep lower extremity vein thrombosis, lower extremity groin arteriovenous fistula/pseudoaneurysm, bleeding requiring transfusion, TIA, or stroke have been observed.

### 4 | DISCUSSION

#### 4.1 | Main findings

Our initial clinical data suggest, that in AF patients with preserved LVEF and low LA-LGE burden, MRI-guided LA substrate modification in addition to standard PVI using cryoablation was feasible. LA substrates, postablation scar formation, and screening for ETI could be adequately assessed on 3D LGE-MRI. In our small preselected patient cohort, this experimental approach was not associated with any major intraprocedural or postprocedural complications but needs further critical appraisal. This tailored ablation approach led to freedom from arrhythmia recurrence in three out of four LA substrate-positive AF patients at 12 months. Regarding the aforementioned aspects, the following strengths of an LGE-MRI-guided cryoablation approach are summarized in Table 2.

#### 4.2 | Evaluation of LA substrate by LGE-MRI

Homogenization of arrhythmogenic tissue outside the PVs has been suggested as a means to achieve better rhythm outcome after AF ablation. Invasive electroanatomical voltage mapping is currently the most applied technique for substrate evaluation in clinical practice. Since several years, LGE-MRI emerged as noninvasive...
alternative. In the DECAAF study, MRI was used to estimate the extent of LA-LGE as a surrogate of arrhythmogenic fibrotic tissue. Presence and extent of LA-LGE were independently associated with the likelihood of arrhythmia recurrence. However, other tissue pathologies than fibrosis, like fatty infiltration, edema, or amyloid have to be considered if LGE on MRI is present. Whether rhythm outcome can be improved after LGE-MRI-guided LA substrate modification is subject to current investigation in the DECAAF II study (ClinicalTrials.gov Identifier: NCT02529319).

4.3 | Feasibility of extrapulmonary cryoballoon ablation

Cryoballoon ablation or cryoablation outside the PVs has been reported for isolation of the LA roof, the superior vena cava and persistent left superior vena cava, the LA appendage, and posterior wall as well as for LA substrate modification.

In a multicenter nonrandomized study, PVI + posterior wall isolation (PWI) vs standard PVI using CBA (390 patients, persistent AF) achieved significantly more freedom from AF recurrence at 12 months (80% vs 51%; P = .001). However, one-third of patients required additional RF ablation to achieve PWI and every second patient needed additional ablation procedures. In contrast to our approach using LGE-MRI guidance, atrial substrates have been evaluated by high-density voltage mapping. The invasive nature of this approach might have hindered prior appropriate patient selection and ablation procedure planning with potential avoidance to switch to an additional RF approach. It excluded reporting of follow-up data on permanent lesion characteristics. Data regarding the incidence of atrioesophageal injury, PV stenosis, or TIA/stroke were not reported. In concordance with our findings, procedure and fluoroscopy times were prolonged, but PWI by CBA was feasible without major periprocedural complications.

In a comprehensive analysis by Su et al., CBA has been reported feasible and effective with low risk profile at 11 anatomical locations outside the PVs before. However, targeting the individual substrate with the cryoballoon can be challenging and therefore needs execution by an experienced operator who is also aware of the adjacent cardiac structures and potential side-effects during ablation outside the PVs. Possible alterations like sinus node slowing, signs of sinus nodal artery damage, or PR-interval prolongation should be carefully monitored, especially during ablation at the LA roof and septum.

4.4 | Rhythm outcome after LA substrate modification using CBA

Histopathological characteristics of cryo-lesions have been intensively studied and described as contiguous, large areas of sharply demarcated,
homogenous, transmural, and durable scar with low arrhythmogenic potential.\textsuperscript{20,23} Thus, low rates of AF recurrence after CBA have been reported.\textsuperscript{24-26} Design adjustments to the second-generation cryoballoon catheter lead to further improved lesion creation. The half dome shape freezing zone allows to target a broader tissue area resulting in larger cryo-lesions. This might have been the prerequisite for quick targeted homogenization of patchy substrates on a specific spot of the LA wall in comparison to a point-by-point isolation of the whole LA wall using an RF approach. On the contrary, lower cryocatheter maneuverability could have resulted in inaccessibility of arrhythmogenic tissue or inadequate tissue contact leaving areas of residual substrates or slowed conduction, that could serve as drivers for AF recurrence or increased arrhythmogenicity. Cryo- and RF-lesions were compared on LGE-MRI before. Number of gaps per patient and arrhythmia recurrence after AF ablation did not differ between both techniques.\textsuperscript{27} However, cryo-lesions were wider and more continuous than RF-lesions.\textsuperscript{28} In our cohort of LA substrate-positive patients, who are prone to worse rhythm outcome, freedom from AF recurrence was 74.5\% and in line with the findings from multisite-wide success rates as well as recently published experiences of PVI+PWI using CBA.\textsuperscript{16,19,29} However, not all AF patients benefit from additional substrate ablation outside the PVs as reported in the STAR-AF II trial.\textsuperscript{30} Evaluation of the individual LA substrate and selection of a tailored ablation approach seem to be crucial for rhythm outcome.\textsuperscript{8,9}

In light of the current results, the value of CBA for LA substrate modification is still experimental and might be promising in well-selected patients. However, this needs critical appraisal in terms of safety and efficacy in a larger number of patients also investigating potential proarrhythmic effects of cryo-lesions outside the PVs. Addressing these questions, the presented concept will be investigated in a prospective single-center, open-label pilot study (ClinicalTrials.gov Identifier: NCT03489096).

4.5 | Assessment of esophageal thermal injury by LGE-MRI

Esophageal thermal injury with deterioration into atrioesophageal fistula remain life-threatening complications after AF ablation. LGE-MRI has been reported a useful screening modality for early detection and further monitoring of ETI.\textsuperscript{6} Esophageal enhancement immediately after ablation is frequently observed in 50 to 80\% of cases but did not predict severe ETI on EGD at such an early stage.\textsuperscript{31,33}

While overall in line with previous reports, the majority (54\%) of our patients presented with mild esophageal enhancement acutely after cryoablation. Only one patient had moderate enhancement without ETI on EGD. As seen before, pathological imaging commonly appeared in the acute postablation period with almost all cases exhibiting complete resolution within 3 months.\textsuperscript{6,33} It seems possible that acute enhancement dissolving within 1 to 3 days, indicates transient procedure-related inflammatory response with edema rather than clinically relevant esophageal tissue necrosis leading to severe complications.

In a recent analysis, only moderate and severe esophageal enhancement exhibited high sensitivity and negative predictive value (100\% each, 78\% specificity) for the detection of ETI confirmed by EGD.\textsuperscript{33} Especially the combination of lasting symptoms and persistent esophageal enhancement of the anterior wall without posterior wall involvement beyond 24-hour postablation were associated with endoscopic ulcer.\textsuperscript{35} Identification of these patients could potentially lead to early treatment and minimization of severe ETI-related complications. Further research is needed to determine the optimal time point of imaging and other predictors within patient’s demographics, mediastinal anatomy, and ablation techniques leading to or preventing of ETI.

4.6 | Limitations

We report about a single-center retrospective initial experience that investigated a small cohort of preselected patients with mainly paroxysmal AF type and low LA-LGE burden. Due to the initial experiences with this new technique, procedural and fluoroscopy times were longer than known from standard CBA procedures but are subject to a steep learning curve. There was no randomization against substrate-positive patients treated with standard PVI by CBA or comparison to an RF approach. Whether LGE on MRI can only be interpreted as arrhythmogenic tissue predicting better rhythm outcome when addressed by CBA is debatable. Challenging catheter maneuverability could have resulted in incomplete substrate modification and PV reconnection as potential reasons for AF recurrence or even increased arrhythmogenicity. The presented techniques may only be reproducible by experienced operators and hold an increased risk of harming sensible cardiac structures during extrapulmonary ablation. Therefore, it is of critical note, that overall statements on efficacy and safety cannot be made. Validation in multicenter randomized trials with review of complication rates and long-term rhythm outcome in a larger number of patients is needed.

5 | CONCLUSION

In preselected AF patients, LA substrate modification in addition to PVI using LGE-MRI-guided cryoablation is feasible but still experimental. Freedom from AF recurrence after 12 months was achieved in three of four LA substrate-positive patients. Efficacy and safety have to be further investigated in a randomized controlled trial and a larger number of patients.

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