Verification of a novel atrial fibrillation cryoablation dosing algorithm guided by time-to-pulmonary vein isolation: Results from the Cryo-DOSING Study (Cryoballoon-ablation DOSING Based on the Assessment of Time-to-Effect and Pulmonary Vein Isolation Guidance)

Arash Aryana, MS, MD, FHRS,* David N. Kenigsberg, MD, FHRS,† Marcin Kowalski, MD, FHRS,‡ Charles H. Koo, MD,§ Hae W. Lim, PhD,¶ Padraig Gearoid O'Neill, MD, FHRS,* Mark R. Bowers, MS, MD,* Robert B. Hokanson, BA,¶ Kenneth A. Ellenbogen, MD, FHRS,‖ Cryo-DOSING Investigators

*From the *Mercy General Hospital and Dignity Health Heart and Vascular Institute, Sacramento, California, †Florida Heart Rhythm Specialists, PLLC, Plantation, Florida, ‡Staten Island University Hospital, Northwell Health, Staten Island, New York, §Jersey Shore University Medical Center, Neptune, New Jersey, ¶Medtronic, Inc, Minneapolis, Minnesota, and ‖Virginia Commonwealth University Medical Center, Richmond, Virginia.*

BACKGROUND There are no recommendations on the optimal dosing for cryoablation of atrial fibrillation (Cryo-AF).

OBJECTIVE The purpose of this study was to develop and prospectively test a Cryo-AF dosing protocol guided exclusively by time-to-pulmonary vein (PV) isolation (TT-PVI) in patients undergoing a first-time Cryo-AF.

METHODS In this multicenter study, we examined the acute/long-term safety/efficacy of Cryo-AF using the proposed dosing algorithm (Cryo-AF_{Dosing}; n = 355) against a conventional, nonstandardized approach (Cryo-$AF_{Conventional}$; n = 400) in a nonrandomized fashion.

RESULTS Acute PV isolation was achieved in 98.9% of patients in Cryo-AF_{Dosing} (TT-PVI = 48 ± 16 seconds) vs 97.2% in Cryo-$AF_{Conventional}$ (P = .18). Cryo-AF_{Dosing} was associated with shorter (149 ± 34 seconds vs 226 ± 46 seconds; P <.001) and fewer (1.7 ± 0.8 vs 2.9 ± 0.8; P <.001) cryoapplications, reduced overall ablation (16 ± 5 minutes vs 40 ± 14 minutes; P <.001), fluoroscopy time (13 ± 6 minutes vs 29 ± 13 minutes; P <.001), left atrial dwell time (51 ± 14 minutes vs 118 ± 25 minutes; P <.001), and total procedure time (84 ± 23 minutes vs 145 ± 49 minutes; P <.001) but similar nadir balloon temperature (–47°C ± 8°C vs –48°C ± 6°C; P = .41) and total thaw time (43 ± 27 seconds vs 45 ± 19 seconds; P = .09) as compared to Cryo-$AF_{Conventional}$. Adverse events (2.0% vs 2.7%; P = .48), including persistent phrenic nerve palsy (0.6% vs 1.2%; P = .33) and 12-month freedom from all atrial arrhythmias (82.5% vs 78.3%; P = .14), were similar between Cryo-AF_{Dosing} and Cryo-$AF_{Conventional}$. However, Cryo-AF_{Dosing} was specifically associated with fewer atypical atrial flutters/tachycardias during long-term follow-up (8.5% vs 13.5%; P = .02) as well as fewer late PV reconnections at redo procedures (5.0% vs 18.5%; P <.001).

CONCLUSION A novel Cryo-AF dosing algorithm guided by TT-PVI can help individualize the ablation strategy and yield improved procedural endpoints and efficiency as compared to a conventional, nonstandardized approach.

KEYWORDS Algorithm; Atrial fibrillation; Catheter ablation; Cryoablation; Cryoballoon; dosing

ABBREVIATIONS **AF** = atrial fibrillation; **Cryo-AF** = cryoablation of atrial fibrillation; **PV** = pulmonary vein; **RF** = radiofrequency; **TT-PVI** = time-to-pulmonary vein isolation

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Introduction

Contemporary studies of cryoablation of atrial fibrillation (Cryo-AF) using the currently available cryoballoon have adopted shorter and fewer cryoapplications while still demonstrating acceptable clinical efficacy.[1–3] Although a greater emphasis has recently been placed on directing this procedure through objective and quantifiable procedural

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and biophysical markers,[4,5] currently there are no consensus or uniform guidelines regarding optimal Cryo-AF dosing. Several studies have identified the time-to-pulmonary vein (PV) isolation (TT-PVI) as a critical procedural variable.[4–8] Not only has this entity emerged as a powerful marker of acute[4] and durable[5,6] PV isolation, but it has been instrumental in reducing the need for the number of cryoapplications as well as the procedural duration and fluoroscopic utilization.[9,10] In this prospective, multicenter study, we analyzed the procedural characteristics and acute/long-term safety and efficacy of Cryo-AF in a large cohort of patients with symptomatic paroxysmal and persistent atrial fibrillation (AF) using a novel dosing protocol guided by TT-PVI (Cryo-AF_{Dosing}). These outcomes were then compared to those derived from a cohort of consecutive control patients who underwent Cryo-AF using a conventional, nonstandardized method of cryoballoon dosing (Cryo-$AF_{Conventional}$).

Methods

Study patients

The study cohort consisted of consecutive patients undergoing a first-time Cryo-AF for symptomatic paroxysmal or persistent AF. The procedures were performed by 6 experienced operators (Cryo-DOSING Investigators) at 5 centers between August 2013 and November 2015. Approval for this study was granted by each institution's institutional review board.

Procedural details

Briefly, diagnostic electrophysiology catheters including a coronary sinus decapolar and a right atrial quadripolar catheter were positioned for recording and pacing, followed by single transseptal catheterization. Intravenous heparin was administered at the time of transseptal puncture, followed by an infusion (activated clotting time target ≥300 seconds). All patients underwent PV isolation using a 28-mm cryoballoon catheter (Arctic Front Advance, Medtronic, Inc, Minneapolis, MN) inserted through a 12F steerable sheath (FlexCath; Medtronic). Optimal cryoballoon positioning was confirmed by PV angiography. In general, the cryoapplication was terminated if the cryoballoon temperature fell below –65°C, and the balloon was repositioned to avoid ultra-cold temperatures. Luminal esophageal temperature was monitored throughout ablation. Esophageal temperatures <15°C were avoided. During cryoablation of the right-sided PVs, high-output right phrenic nerve stimulation (10–25 mA; 1000–1200 ms) was performed using the diagnostic quadripolar catheter from within the superior vena cava. Whenever diminished or loss of pacing capture was observed, cryoablation was immediately terminated. Phrenic nerve palsy was classified as either transient or persistent. Transient phrenic nerve palsy was defined as diminished/absence of pacing capture during phrenic nerve stimulation at the time of ablation with eventual resolution before the end of procedure. Persistent phrenic nerve palsy was characterized by continued loss of phrenic nerve function that persisted during follow-up. If phrenic nerve palsy was encountered, the cryoapplication was terminated and no further ablation was performed using the cryoballoon.

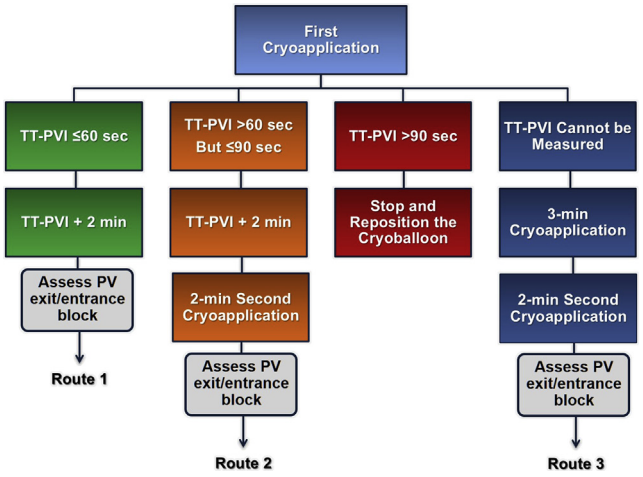

Figure 1 The proposed cryoballoon ablation dosing protocol: The decision tree. Between 1 and 2 effective cryoapplications were delivered to each pulmonary vein (PV) during cryoablation of atrial fibrillation, based on the proposed dosing algorithm. A single cryoapplication was delivered to a PV if time-to-PV isolation (TT-PVI) measured ≤60 seconds (Route 1). The duration of this application consisted of TT-PVI + 2 minutes. If TT-PVI was >60 seconds but ≤90 seconds, then an additional (bonus) 2-minute application was delivered to the same PV (Route 2). However, if TT-PVI could not be achieved within 90 seconds, the cryoapplication was abandoned and the cryoballoon catheter repositioned to achieve a suitable TT-PVI. Lastly, if TT-PVI could not be measured at all, then an empiric 3-minute followed by a 2-minute cryoapplication was delivered to the PV (Route 3). It should be emphasized that PV isolation was always confirmed at the end of each arm of the algorithm by testing for entrance/exit block and after administration of intravenous adenosine.

Whenever the PVs could not be successfully isolated using cryoablation, point-by-point radiofrequency (RF) ablation was used to achieve this acute endpoint. Furthermore, arrhythmias other than AF (eg, atrial flutters/tachycardias) inducible at the time of procedure were also targeted using RF energy. RF ablation was performed using an externally irrigated ablation catheter (ThermoCool SmartTouch, Biosense Webster, Inc, Diamond Bar, CA; or FlexAbility, St. Jude Medical, Inc, St. Paul, MN), guided by 3-dimensional electroanatomic mapping (CARTO, Biosense Webster; or NavX, St. Jude Medical). Whenever linear ablation was required (i.e., for ablation of cavotricuspid isthmus-dependent atrial flutter), bidirectional block across the line of conduction was confirmed following ablation before and after administration of intravenous adenosine. Additionally, arrhythmia induction was routinely performed at the end of the procedure by rapid atrial pacing (no less than 220 ms).

Meanwhile, the principal ablation approach evaluated in this study consisted of a prespecified novel dosing protocol guided by TT-PVI (Cryo-AF_{Dosing}). The outcomes were then compared in nonrandomized fashion to those derived from a cohort of consecutive control patients who underwent Cryo-AF using a conventional, nonstandardized method (Cryo-$AF_{Conventional}$).

Dosing protocol approach

The cryoballoon catheter was inserted over a 20-mm circular inner lumen mapping catheter (Achieve, Medtronic). In the Cryo-AF$_{Dosing}$ cohort, attempts were made to specifically record TT-PVI during ablation of each PV in every case. Between 1 and 2 effective cryoapplications were delivered to each PV using the suggested Cryo-AF dosing protocol (Figure 1). In brief, a single cryoapplication was applied to a given PV if the TT-PVI measured $\leq$60 seconds (Route 1). The duration of that application consisted of TT-PVI + 2 minutes. If TT-PVI was >60 seconds but $\leq$90 seconds, then a second (bonus) 2-minute cryoapplication was delivered to the same PV (Route 2). Those cryoapplications that did not achieve TT-PVI $\leq$90 seconds were abandoned, and the cryoballoon was repositioned in order to achieve a suitable TT-PVI. Lastly, if TT-PVI could simply not be measured, then a 3-minute followed by a 2-minute cryoapplication was empirically delivered to the PV (Route 3). At the end of all 3 arms of the dosing algorithm, PV isolation was always confirmed by testing for entrance/exit block and after administration of intravenous adenosine.

Conventional approach

All the PVs were ablated using a cryoballoon catheter inserted over a guidewire. Although no standardized ablation dosing protocol was followed in the Cryo-AF$_{Conventional}$ arm, the operators typically administered between 2 and 3 cryoapplications to each PV, with each application lasting between 2 and 4 minutes in duration. The duration and the number of applications were left to the discretion of the operator and depended on subjective quality measures of the application (i.e., degree of PV occlusion, balloon nadir temperature, etc). PV isolation was always confirmed postablation by testing for entrance/exit block and after administration of intravenous adenosine.

Postprocedural management

Patients were discharged from the hospital within 1 day of the procedure. Oral anticoagulation was typically held on the morning of the procedure, resumed later that evening, and continued for a minimum of 3 months postablation. Antiarrhythmic therapy was discontinued within 6 weeks of ablation. In addition to obtaining routine electrocardiograms during each follow-up visit, 2- to 4-week ambulatory electrocardiographic monitoring was also performed at 6 weeks, 3 and 6 months. Freedom from recurrent atrial arrhythmias was defined as >30 seconds on any cardiac rhythm recording after a 90-day postablation blanking period. In patients who opted for redo ablation, repeat computed tomographic angiography was performed to exclude PV stenosis. In those with persistent or unexplained pulmonary symptoms (eg, persistent cough or dyspnea), cardiac computed tomographic angiography was also performed. Patients with persistent phrenic nerve palsy underwent outpatient serial chest radiography for reassessment during follow-up.

Statistical analysis

Data are given as percentage or mean $\pm$ SD. Baseline patient demographics and procedural/clinical characteristics were compared between the cohorts. Continuous variables were analyzed using the 2-sample t test or Mann-Whitney test for parametric and nonparametric variables, respectively. The χ^2 or Fisher exact test was used for categorical variables. Time-to-first recurrence of atrial arrhythmias was analyzed using Kaplan-Meier estimates, and overall freedom from atrial arrhythmias was compared between the 2 ablation groups using log-rank testing. Point estimate comparisons at 12 months after the index ablation were evaluated using a 2-sided Z test for difference. For all analyses, P values were 2-sided, and $P < .05$ was considered significant. Analyses were conducted using of Stata 14 (StataCorp LP, College Station, TX), SAS software (version 9.4, SAS Institute, Cary, NC), and the R statistical package (version 3.2.2, www.r-project.org).

Results

Data from 755 consecutive patients who underwent a first-time Cryo-AF were analyzed: 355 patients using Cryo-AF$_{Dosing}$ and 400 patients using Cryo-AF$_{Conventional}$. The cohort did not include patients with long-standing persistent/permanent AF. The breakdown of the cases by operator included 29.9% (DK), 23.7% (AA), 16.6% (GO), 15.2% (MK), 8.5% (MB), and 6.2% (CK). Patient demographics are listed in Table 1. Overall, left atrial size was smaller in Cryo-AF$_{Dosing}$ compared to Cryo-AF$_{Conventional}$. However, the incidences of sleep apnea, stroke, coronary artery disease, myocardial infarction, prior cardioversions, $CHADS_2$ score, and antiplatelet therapy were greater in Cryo-AF$_{Dosing}$ vs Cryo-AF$_{Conventional}$. All other baseline characteristics were similar. Acute PV isolation was achieved in 1410 of 1416 PVs (99.6%) in Cryo-AF$_{Dosing}$ vs 1582 of 1595 PVs (99.2%) in Cryo-AF$_{Conventional}$ ($P = .18$). Specifically, the endpoint of acute PV isolation was attained in 351 patients (98.9%) in Cryo-AF$_{Dosing}$ vs 389 patients (97.2%) in Cryo-AF$_{Conventional}$ ($P = .11$). As such, RF ablation was required to complete isolation of 6 PVs (0.4%) in 4 patients (1.1%) in Cryo-AF$_{Dosing}$ vs 13 PVs (0.8%) in 11 patients (2.8%) in Cryo-AF$_{Conventional}$, with no statistical difference between the cohorts ($P = .26$ and $P = .12$, respectively).

Table 2 provides an overview of the ablation/procedural characteristics and the adverse events for the 2 groups. In the Cryo-AF$_{Dosing}$ arm, PV isolation was most commonly achieved using Route 1 (51%), followed by Route 3 (40%) and Route 2 (9%). Meanwhile, Cryo-AF$_{Dosing}$ was associated with a reduction in the total number of cryoapplications, duration of cryoapplications, and total cryoablation time as compared to Cryo-AF$_{Conventional}$. Biophysical parameters including nadir temperature and balloon thaw times did not differ between the 2 groups, nor did the requirement for RF ablation or the RF duration. Conversely, Cryo-AF$_{Dosing}$ was associated with shorter left atrial dwell time, fluoroscopic time, and total

Table 1 Baseline patient demographics and characteristics

Characteristic	Cryo-AF$_{Dosing}$ (n = 355)	Cryo-AF$_{Conventional}$ (n = 400)	*P* value
Age (y)	64 ± 11	63 ± 11	.15
Male	244 (69%)	294 (74%)	.17
Body mass index (kg/m^2)	30 ± 6	30 ± 5	.32
Hypertension	242 (68%)	272 (68%)	.99
Diabetes mellitus	81 (23%)	75 (19%)	.18
Sleep apnea	104 (29%)	68 (17%)	<.001*
Stroke/transient ischemic attack	42 (12%)	9 (2%)	<.001*
Left atrial diameter† (mm)	43 ± 7	48 ± 6	<.001*
Left ventricular ejection fraction† (%)	55 ± 9	56 ± 10	.22
Coronary artery disease	74 (21%)	50 (13%)	.002*
Myocardial infarction	30 (8%)	9 (2%)	<.001*
PCI or CABG	44 (12%)	49 (12%)	.99
Cardiac implantable electronic device	52 (15%)	47 (12%)	.28
Paroxysmal AF	254 (72%)	297 (74%)	.41
Prior cardioversion	252 (71%)	206 (52%)	<.001*
No. cardioversions/patient (n)	1.0 ± 0.9	0.7 ± 0.9	<.001*
$CHADS_2$ score	1.5 ± 1.0	1.2 ± 0.9	<.001*
Antiplatelet therapy†	1.2 ± 0.7	0.7 ± 0.8	<.001*
Oral anticoagulation therapy†	304 (86%)	343 (86%)	.99

Values are given as mean ± SD or n (%), unless otherwise indicated.

AF = atrial fibrillation; CABG = coronary artery bypass graft; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes, and stroke/transient ischemic attack; Cryo-AF = cryoablation of atrial fibrillation; PCI = percutaneous coronary intervention.

*Significant *P* value.

†Baseline data before catheter ablation.

procedure time as compared to Cryo-AF$_{Conventional}$. Adverse events such as groin vascular complications, pericardial effusion, and persistent phrenic nerve palsy were similar in both groups. Furthermore, all patients with persistent phrenic nerve palsy exhibited complete PV isolation. There were no incidences of cardiac tamponade, stroke, atrioesophageal fistula, or death during follow-up.

The mean study follow-up was 15 ± 3 months which did not differ significantly between the 2 groups (Table 3). Moreover, there were no discernible differences in freedom from recurrent atrial arrhythmias at 3, 6, 9, or 12 months between Cryo-AF$_{Dosing}$ and Cryo-AF$_{Conventional}$. Figure 2 shows a Kaplan-Meier curve illustrating similar cumulative freedom from recurrent atrial arrhythmias after cryoablation in Cryo-AF$_{Dosing}$ vs Cryo-AF$_{Conventional}$ (log-rank $P = .13$). In contrast, the incidence of atrial flutters/tachycardias at 12 months was significantly lower in Cryo-AF$_{Dosing}$ vs Cryo-AF$_{Conventional}$ (Table 3).

Table 2 Procedural characteristics and adverse events between the 2 groups

Variable or outcome	Cryo-AF$_{Dosing}$ (n = 355)	Cryo-AF$_{Conventional}$ (n = 400)	*P* value
Ablation variables			
TT-PVI (s)	48 ± 16	N/A	N/A
TT-PVI recorded	1,145 (81%)	N/A	N/A
Total cryoapplications/PV (n)	1.7 ± 0.8	2.9 ± 0.8	<.001*
Cryoapplication duration (s)	149 ± 34	226 ± 46	<.001*
Cryoballoon nadir temperature (°C)	−47 ± 8	−48 ± 6	.41
Cryoballoon thaw time (s)	43 ± 27	45 ± 19	009
Total cryoablation time (min)	16 ± 5	40 ± 14	<.001*
RF ablation	53 (15%)	76 (19%)	.14
Total RF ablation time (min)	20 ± 17	19 ± 17	.79
Procedural variables			
Left atrial dwell time (min)	51 ± 14	118 ± 25	<.001*
Fluoroscopy time (min)	13 ± 6	29 ± 13	<.001*
Total procedure time (min)	84 ± 23	145 ± 49	<.001*
Adverse events	7 (2.0%)	11 (2.7%)	.48
Groin vascular complications	3 (0.8%)	2 (0.5%)	.56
Pericardial effusion	2 (0.6%)	4 (1.0%)	.50
Persistent phrenic nerve palsy	2 (0.6%)	5 (1.2%)	.33

Values are given as mean ± SD or n (%), unless otherwise indicated.

Cryo-AF = cryoablation of atrial fibrillation; N/A = not available; PV = pulmonary vein; RF = radiofrequency; TT-PVI = time-to-pulmonary vein isolation.

*Significant *P* value.

Table 3 Comparison of freedom from recurrent atrial arrhythmias between the two groups.

Freedom from atrial arrhythmias	Cryo-AF$_{Dosing}$ (n = 355)	Cryo-AF$_{Conventional}$ (n = 400)	*P* value
At 3 months	93.2%	90.8%	.23
At 6 months	89.0%	84.8%	.09
At 9 months	84.2%	81.5%	.34
At 12 months	82.5%	78.3%	.14
Atrial fibrillation at 12 months	9.0%	8.3%	.89
Atrial flutter/tachycardia at 12 months	8.5%	13.5%	.02*
Mean follow-up, months	15 ± 2	16 ± 3	.54

Cryo-AF = cryoablation of atrial fibrillation.
*Significant *P* value.

Lastly, during the course of this study, 35 patients (9.9%) in Cryo-AF$_{Dosing}$ and 63 patients (15.7%) in Cryo-AF$_{Conventional}$ underwent a repeat catheter ablation procedure. The incidence of PV reconnection detected at redo procedure is shown in Table 4. The incidence of patients with PV reconnection and the rate of PV reconnection were both found to be lower in Cryo-AF$_{Dosing}$ vs Cryo-AF$_{Conventional}$.

Discussion

Main findings

This study represents the first large, multicenter analysis of the acute and long-term outcomes of Cryo-AF in patients with symptomatic AF using a novel ablation dosing algorithm guided by TT-PVI compared to a conventional, nonstandardized approach. As such, this study provides several important insights. First, it shows that TT-PVI may be effectively used to guide and individualize the ablation dosing strategy during Cryo-AF. Second, ablation dosing guided by TT-PVI yielded an equivalent and high rate of acute PV isolation. Moreover, this approach was associated with improved durability of PV isolation at repeat procedures and a lower incidence of atypical atrial flutters/tachycardias during long-term follow-up. Although equivocal, the authors believe that this characteristic was likely a consequence of a more tailored ablation strategy. Third, the TT-PVI–guided dosing algorithm improved the procedural efficiency, allowing for not only fewer and shorter cryoapplications but also reduced left atrial dwell, ablation, and procedure times. However, the biophysics of ablation including balloon nadir temperature and thaw time, adverse event rates and freedom from recurrent AF during long-term follow-up were equivalent between the 2 ablation strategies.

The main objective of this study was to establish a simple, easy-to-follow, but highly effective cryoablation "decision tree" that could be replicated reliably and implemented effortlessly during Cryo-AF across various cardiac electrophysiology laboratories and different practitioners. In theory, there might be several benefits to such an algorithm. First, it may provide a more uniform and homogeneous approach to Cryo-AF across various operators. Furthermore, not only could it improve the effectiveness and the procedural efficiency of Cryo-AF, but it has the potential to enhance the technical safety of the procedure by minimizing the need for multiple, redundant cryoapplications and reducing left atrial dwell and procedure times. To elaborate, it is conceivable that any measures that minimize the need for superfluous cryoapplications will directly reduce the possibility of not only common adverse events, such as phrenic nerve palsy, but also infrequent complications, such as stroke and atrioesophageal fistula. Along these lines, both the extent and the duration of Cryo-AF have been associated with increased risk of collateral injury, including the bronchial tree, as recently reported in an *in vivo* study.[11]

In creating the intended algorithm, an assortment of previously reported procedural and biophysical makers and predictors of acute and durable PV isolation were carefully scrutinized.[5] Ultimately, based on the available data, we designed the proposed dosing protocol, which hinges exclusively on TT-PVI. It should be emphasized that TT-PVI has been described as the single most critical parameter of Cryo-AF. As such, several studies have established the utility and significance of monitoring TT-PVI during Cryo-AF. Early on, Chierchia et al[7] showed that early PV reconnection was associated with longer TT-PVI (117 ± 25 seconds vs 59 ± 25 seconds). Similarly, Chun et al[4] demonstrated that

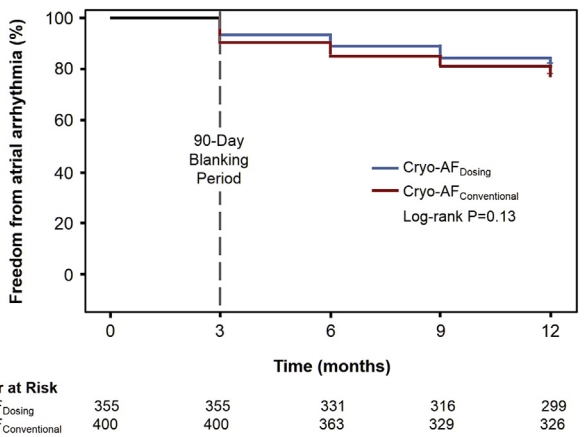

Figure 2 Kaplan-Meier estimates showing the cumulative freedom from all recurrent atrial arrhythmias after cryoballoon ablation of atrial fibrillation using the prespecified dosing protocol guided by time-to-pulmonary vein isolation (Cryo-AF$_{Dosing}$) vs the conventional, nonstandardized approach (Cryo-AF$_{Conventional}$). Freedom from all recurrent atrial arrhythmias did not differ between the 2 groups when compared by log-rank testing (*P* = .13).

Table 4 Comparison of PV isolation durability between the two groups: Analysis from repeat ablation procedures.

Variable	Cryo-AF$_{Dosing}$ (n = 35)	Cryo-AF$_{Conventional}$ (n = 63)	*P* value
Patients with PV reconnection	6/35 (17.1%)	26/63 (41.3%)	.01*
No. of PVs with reconnection	7/140 (5.0%)	46/249 (18.5%)	<.001*
Left superior PV	1/140 (0.7%)	11/249 (4.4%)	.03*
Left inferior PV	3/140 (2.1%)	6/249 (2.4%)	.88
Left common PV	N/A	3/249 (1.2%)	N/A
Right superior PV	0/140 (0%)	12/249 (4.8%)	.006*
Right inferior PV	3/140 (2.1%)	14/249 (5.6%)	.09

Values are given as n (%), unless otherwise indicated.

Cryo-AF = cryoablation of atrial fibrillation; N/A = not available; PV = pulmonary vein.

*Significant *P* value.

TT-PVI associated with durable PV isolation in patients was significantly shorter than in those with electrical reconnection (66 ± 56 seconds vs 129 ± 76 seconds). Kühne and et al[8] further corroborated these findings by identifying a mean TT-PVI of 61 seconds in PVs exhibiting permanent isolation compared to 184 seconds in those with conduction recovery. More recently, a multicenter analysis established that of all the procedural and biophysical variables of Cryo-AF, TT-PVI ≤60 seconds represents the most powerful indicator of PV isolation durability during long-term follow-up.[5] Similar findings were also reported by Ciconte et al,[6] who found that late PV reconnection was independently predicted by a longer TT-PVI and the inability to achieve a nadir balloon temperature of –40°C within 60 seconds of the ablation onset. Additionally, these authors observed that TT-PVI ≤60 seconds was able to predict PV isolation durability following Cryo-AF with a 96% negative predictive value.

Meanwhile, as one would expect, the proposed TT-PVI–based algorithm evaluated in the current study proved highly valuable at streamlining the approach to Cryo-AF. Not only did this dosing protocol yield fewer and shorter cryoapplications and reduced left atrial dwell, ablation, and procedure times, but it was associated with improvements in PV isolation durability and occurrence of atypical atrial flutters/tachycardias during follow-up. This is not entirely surprising. In fact, the authors believe that the likely reason underlying this observation is associated with the more tailored ablation approach afforded by the suggested dosing algorithm. In other words, any ablation approach that takes into account an objective and quantifiable measure of effective energy application will likely enhance the efficacy of the ablation lesion sets and ultimately lead to improved clinical outcomes. For instance, the same is observed with respect to contact force in the setting of RF ablation, which has been shown to greatly augment the efficacy of ablation lesions and thereby increase the incidence of acute and durable PV isolation.[12] Hence, the authors strongly believe in the notion that both the duration and the frequency of cryoapplications delivered during Cryo-AF should be tailored and directed accordingly through a systematic approach based on quantifiable and objective measures of cryoablation. This is likely critical to the assurance of quality and the consistency in practices among various operators. As such, it may impact not only the efficacy of the procedure but perhaps also its safety.

Study limitations

First, this study represents a large, nonrandomized double-arm analysis of consecutive patients undergoing Cryo-AF using a prespecified dosing algorithm compared to the conventional approach. As such, because the treatment allocation was nonrandomized, we cannot exclude unknown confounding variables. Second, because this was a multicenter study, slight variations in ablation strategy and periprocedural management and monitoring may have existed among operators and centers. Third, because TT-PVI was systematically not measured in the conventional arm, relevant but uncharacterized anatomic differences as causes of difference in the outcomes could not be entirely excluded. Fourth, subclinical manifestation of certain complications, such as esophageal ulceration or PV stenosis, could not be excluded because routine diagnostic studies were not performed to investigate for such adverse events. Fifth, the data presented on PV reconnection only pertain to those patients who underwent repeat ablation and were unavailable for the entire cohort. Sixth, the authors cannot entirely exclude the possibility of temporal bias, that is, during the initial period of the analysis, all the Cryo-AF cases were consecutively performed by the conventional approach, whereas all the cases in the second phase of the analysis were performed using the proposed dosing algorithm. Seventh, recurrent asymptomatic episodes of atrial arrhythmias following Cryo-AF could have occurred without detection during follow-up. However, it would seem unlikely that this would have served as a significant source of bias specifically favoring one or the other treatment arm. Lastly, it should be emphasized that the observed benefits associated with Cryo-AF$_{Dosing}$ were predominantly related to procedural outcomes and not recurrence of AF, itself.

Conclusion

A proposed novel Cryo-AF dosing algorithm guided exclusively by TT-PVI can greatly help to individualize the ablation strategy. Furthermore, this approach yielded improved procedural endpoints and efficacy as compared to a conventional, nonstandardized approach.

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