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ORIGINAL ARTICLE

A Novel Visually Guided Radiofrequency Balloon Ablation Catheter for Pulmonary Vein Isolation

One-Year Outcomes of the Multicenter AF-FICIENT 1 Trial

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BACKGROUND: A multielectrode saline-irrigated radiofrequency balloon catheter with an integrated camera system was designed to perform single-shot pulmonary vein (PV) isolation. To optimize ablation, simultaneous circumferential radiofrequency energy can be delivered, albeit with power output that is tailored to individual electrodes based on direct visualization of tissue-electrode contact. In a first-in-human multicenter clinical trial, we studied the feasibility, performance, safety, and efficacy of PV isolation using this novel ablation catheter to treat atrial fibrillation.

METHODS: AF-FICIENT-1 was a prospective, 5-center, single-arm study. After transseptal puncture, the radiofrequency balloon was positioned over the wire at each pulmonary (PV) ostium using a 13.3F sheath. Radiofrequency energy was titrated based on visual contact (6–10 W; up to 60 seconds per ablation). Electrical PV isolation was confirmed using either, (1) sensing mini-electrodes situated on the RF balloon itself or (2) a circular mapping catheter. Patients were clinically assessed for recurrent atrial arrhythmias lasting >30 s over 12 months, after a 3-month blanking period.

RESULTS: Six operators performed de novo PV isolation in 99 patients (95 paroxysmal/4 persistent; age, 58±11; men, 67.7%). Median times, including procedure, fluoroscopy, ablation (time from first RF to last RF application), and balloon (time elapsing between catheter introduction to removal from the body) times, were 85 (interquartile range, 62–118), 14 (interquartile range, 9–23), 31 (interquartile range, 20–53), and 43 minutes (interquartile range, 32–70), respectively. The 12-month Kaplan-Meier estimates of freedom from any atrial arrhythmia (atrial fibrillation, atrial flutter, or atrial tachycardia) or atrial fibrillation alone were 77.5% (95% CI, 67.6%–84.7%) and 84.1% (95% CI, 74.9%–90.1%), respectively. There were no device-related serious adverse events.

CONCLUSIONS: The novel radiofrequency balloon catheter allowed visually guided, directional titration of ablative energy to safely isolate PVs with short procedure times.

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Key Words: atrial fibrillation ■ catheter ablation ■ catheters ■ electrodes ■ punctures

Electrical pulmonary vein (PV) isolation (PVI) forms the cornerstone of the catheter ablation procedure for atrial fibrillation (AF).[1] Because of its technical complexity, a multitude of technological advancements have been developed to facilitate the procedure. Three of these have received regulatory approval in the United

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WHAT IS KNOWN?

- Electrical isolation of the pulmonary veins remains the cornerstone of ablation therapy for atrial fibrillation with a multitude of technological advancements developed to facilitate the procedure.
- The most commonly used ablation modalities include point-by-point radiofrequency ablation allowing operators flexibility to tailor each lesion and single-shot cryoballoon ablation.

WHAT THE STUDY ADDS

- In a first-in-human, multicenter clinical experience, novel visually guided radiofrequency balloon catheter ablation was demonstrated to be feasible in achieving pulmonary vein isolation in patients with paroxysmal atrial fibrillation.
- The ablation system allowed the operator to optimize a circumferential ablation path with integrated cameras to visually identify electrodes in contact with tissue and deliver individually titrated ablative energy simultaneously from all selected electrodes.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
AFL	atrial flutter
AT	atrial tachycardia
IQR	interquartile range
PV	pulmonary vein
PVI	pulmonary vein isolation
RFA	radiofrequency ablation
RFB	radiofrequency balloon
SAE	serious adverse event

States: spot radiofrequency ablation (RFA) catheters for point-by-point ablation, cryoballoon ablation for one-shot PVI, and visually guided laser balloon ablation.[2–4] The first of these, the most commonly used AF ablation modality, retains the greatest flexibility in allowing power titration according to tissue thickness and safety considerations. Furthermore, point-by-point RFA has been improved by the advent of saline irrigation to improve lesion safety and efficacy and force sensing to facilitate tissue contact during ablation.[2,5,6] However, these advances have largely focused on improving the quality of individual lesions and less so on the technical ease of creating contiguous, electrically durable point-by-point lesion sets. Hence, this ablation modality remains technically challenging.

The single-shot PVI capability of the cryoballoon catheter provides for technical simplicity and speed and results in an identical amount of ablative energy delivery circumferentially.[3] This necessarily translates to either underablation of thicker tissue or overablation of thinner tissue, often the posterior left atrial wall potentially overlying the esophagus. The laser balloon is also a single-shot PVI tool in the sense that it provides a platform to allow visually guided placement of contiguous lesions.[4] While this sequential placement of lesions permits the operator to tailor the energy to the tissue, it can be laborious to place the multiple 20-s lesions required to isolate each PV. Thus, while the clinical safety and efficacy data with the laser balloon are favorable, its utilization is substantially less than other technologies.

In an effort to coalesce the strengths of these various ablation tools into a single ablation technology, a multielectrode saline-irrigated radiofrequency balloon (RFB) catheter with an integrated camera system was designed to perform single-shot PVI. This RFB catheter has (1) a balloon design to allow a stable platform without going into the vein for delivering RF energy irrespective of whether the catheter is perpendicular to the long axis of the PV, (2) an array of 18 saline-irrigated RFA electrodes, arranged to optimize a circumferential ablation path, (3) integrated cameras such that the operator can visually identify which electrodes are in contact with tissue, and (4) the ability to simultaneously deliver ablative energy from all of these electrodes, with independent power output control for each electrode. In a first-in-human multicenter clinical trial of first-time ablation for paroxysmal AF, we studied the performance, safety, and efficacy of PVI using this novel RFB catheter.

METHODS

This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committees and local regulatory agencies at all participating sites/countries. Informed consent was obtained from all subjects before enrollment. The authors had full access to and take responsibility for the integrity of the data and have read and agree with the manuscript as written.

Study Design

AF-FICIENT 1 (https://www.anzctr.org.au; unique identifier: ACTRN12615001340527) was a first-in-human, prospective, multicenter, single-arm, clinical study of the RFB ablation catheter (developed by Apama Medical, Inc; later acquired by Boston Scientific, Inc) for the treatment of symptomatic paroxysmal AF. The study enrolled patients in Paraguay, New Zealand (2 sites), Czech Republic, and Lithuania. Subjects were followed for 12 months post-procedure. The clinical data were collected and recorded in an electronic database and monitored at regular intervals.

This study was originally designed as a first-in-human protocol to assess its feasibility and safety in 30 patients. An interim analysis of the study data from the initial series (phase I, March to December 2016) confirmed a favorable safety profile and superior performance in achieving PVI. Accordingly, the protocol was amended to increase the sample size: a first amendment to increase the sample size to 50 patients and a

subsequent amendment to increase to 100 patients, along with the addition of a statistical plan including hypothesis testing.

The safety and effectiveness of the RFB catheter system was assessed in 2 phases. Phase I was the first-in-human experience to evaluate device safety (patients 1–18). Within phase I, the system was enhanced by addition of a bidirectional sheath and incorporation sensing electrodes into the RFB catheter. After completing phase I, the number of patients was increased as above (phase II, patients 19–100).

Patient Enrollment Criteria

Briefly, eligible patients were adults undergoing a first-ever ablation procedure for symptomatic paroxysmal AF. Key exclusion criteria included left ventricular ejection fraction <30%, left atrium >55 mm, hypertrophic cardiomyopathy, stroke within 3 months, severe chronic obstructive airways disease, severe renal impairment, and severe valvular dysfunction (see Table I in the Data Supplement for detailed criteria).

RFB Catheter Description

The RFB ablation system consists of a bidirectional steerable, multielectrode, irrigated, luminal RFB catheter (Luminize; Apama Medical/Boston Scientific, Inc, Marlborough, MA). It is an over-the-wire catheter introduced into the heart using a 13.5F deflectable sheath (Luminize Steerable Sheath; Apama Medical/Boston Scientific, Inc). The catheter interfaces with the Ablation Console, which is designed to deliver multipolar (>2 electrodes selected for ablation) or bipolar (2 electrodes selected for ablation) radiofrequency energy. In the case of multipolar ablation, power is delivered from selected source electrodes to all active sink electrodes. The distribution of power is based on the number of and distance to neighboring electrodes. With this system, bipolar ablation only occurs when a single source and sink electrode is selected. The original device (2016) was upgraded to an enhanced version, which was used to perform all subsequent ablations beginning in 2017. In the enhanced version, activated sensing electrodes were added, and sheath steerability was increased from 90 to 125 degrees.

The RFB catheter incorporated the following features (Figure 1A and 1B): (1) a conformable 28-mm diameter balloon that is inflated with saline, (2) a series of 18 ablation electrodes (6 forward facing, 12 equatorial) on the outside surface of the balloon, (3) irrigation holes within each RF electrode to provide for saline-based cooling of the electrodes, (4) 12 sensing mini-electrodes, and (5) a series of 4 CMOS cameras inside

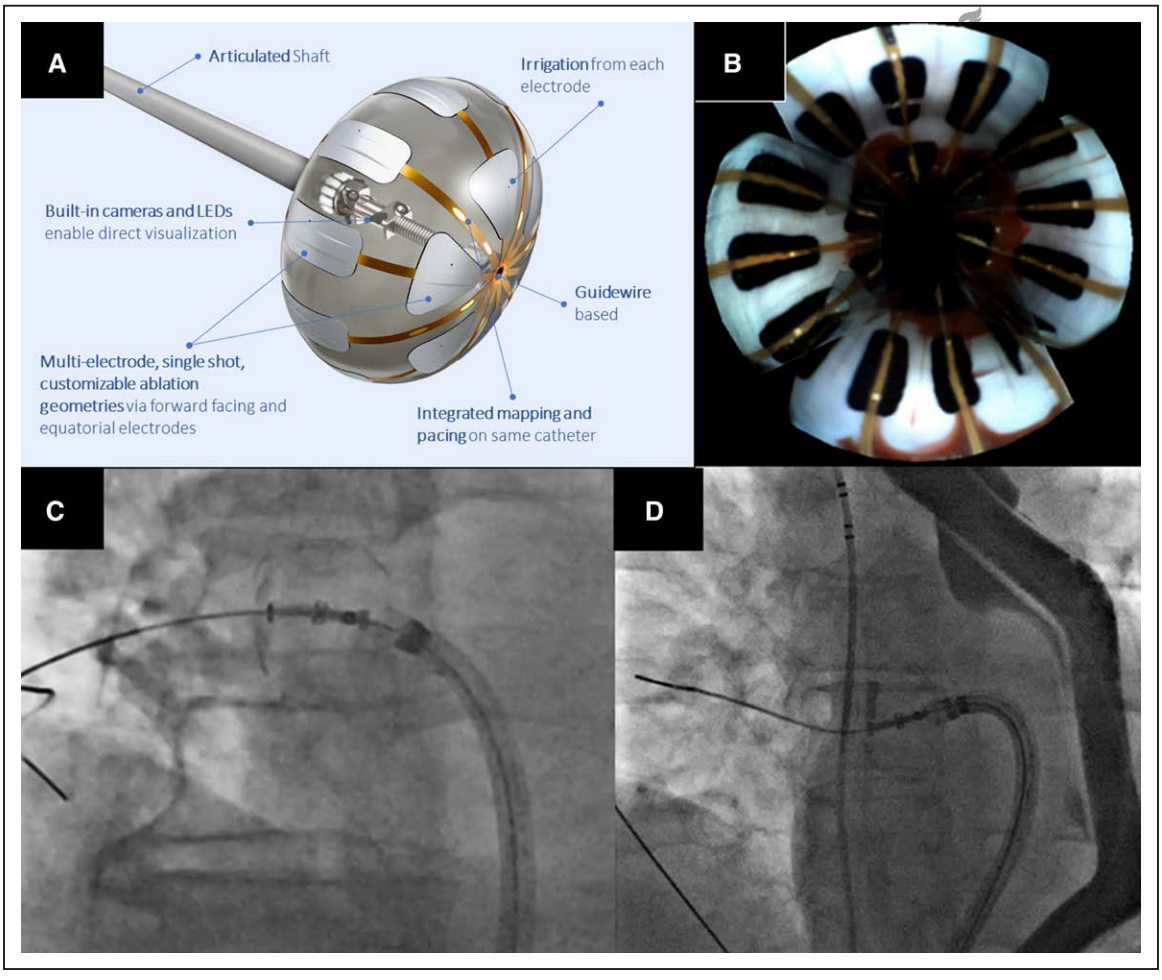


Figure 1. The radiofrequency balloon (RFB) ablation catheter.
A, Various aspects of the RFB catheter are shown. **B**, The internal composite image is generated by the built-in cameras. **C** and **D**, The catheter is positioned at the pulmonary vein (PV) ostia either without (**C**) or with (**D**) mechanical esophageal deviation. Also note a pacing catheter situated within the superior vena cava to pace the right phrenic nerve during right PV ablation.

the balloon, looking outward to provide a composite video image of the balloon inner surface, in particular, the 18 ablation electrodes and any tissue in contact with the conformable balloon membrane. The console's user interface is used to visualize tissue contact, select the ablation pathway, display real-time impedance for reach RF electrode, and is able to control the irrigation pump. The generator provides independently titratable radiofrequency energy (6–10 W) to any of the selected electrodes during ablative treatment. The generator receives and passes through electric signals to an external recording system.

Procedural Workflow

Patients received either warfarin or nonwarfarin oral anticoagulation for a minimum of 1 month before the procedure and were withheld for 0 to 3 days pre-procedure. Preprocedure in all patients included transthoracic echocardiography and either computed tomography or magnetic resonance imaging to define PV anatomy. The AF ablation procedures were performed under either general anesthesia (33/99, 33.3%) or sedation (66/99, 66.7%), either using no esophageal monitoring (86/99, 86.9%), esophageal temperature monitoring (13/99, 13.1%), or mechanical esophageal deviation (DV8; Manual Surgical Sciences, Minneapolis, MN) without temperature monitoring (26/99, 26.3%; Figure 1C and 1D).[7]

Following standard femoral venous access, a decapolar catheter was placed in the coronary sinus, and as per operator preference, an intracardiac echocardiography catheter (8F AcuNav; Siemens Healthcare, Mountain View, CA) was placed to help guide the procedure. After single transseptal puncture, the ACT was maintained at >350 s. The standard transseptal sheath was exchanged over a guidewire to place the custom 13.3F deflectable sheath, and after thorough aspiration to evacuate any trapped air bubbles, the RFB catheter was advanced through the sheath into the left atrium. The RFB catheter preparation included a dedicated flush and sonication of the balloon to remove any trapped air bubbles before being inserted into the sheath.

Using the guidewire (0.032 or 0.035) as an anchor within each target PV, the RFB catheter was positioned sequentially at each vein ostium. Under visual guidance from the internal cameras, the balloon was manipulated to maximize electrode-tissue contact, and a circumferential path of electrodes was selected for the ablation path, regardless of whether the balloon was centered at the PV ostium or askew (Figure 2A and 2B). Radiofrequency energy was delivered between electrodes for up to 60 s. PV electrograms and RF electrode impedance were continuously monitored throughout each radiofrequency application to assess electrical isolation (Figure 2C). If circumferential contact and electrical isolation was not achieved with the initial balloon position, the RFB was repositioned and further applications were administered. During ablation of the right PVs, 1 of 2 strategies was used to avoid phrenic nerve palsy: (1) pacing the phrenic nerve using a catheter positioned within the superior vena cava (Figure 1D) or (2) pacing the phrenic nerve directly through the RFB ablation electrodes, if the phrenic nerve was stimulated, either the ablation pathway or balloon position were adjusted. After electrical isolation, PV entrance block was reconfirmed after either adenosine administration or a 30-minute observation period, and vascular sheaths were removed and hemostasis achieved.

Follow-Up

After the procedure, patients were typically observed overnight and discharged the following day. The follow-up schedule included patient visits at 30 days and 3, 6, and 12 months (Table II in the Data Supplement; Figure I in the Data Supplement). Computed tomography or magnetic resonance imaging was repeated at 3 months to assess for PV stenosis. In addition to symptom-driven ECG telemetric monitoring, all patients received 24-hour Holter monitoring at 6 and 12 months post-ablation.

Study End points

As detailed in Table III in the Data Supplement, the primary safety end point was freedom from device or procedure-related major adverse events at 30 days post-procedure including stroke/transient ischemic attack, cardiac tamponade, PV stenosis, atrioesophageal fistula, diaphragmatic paralysis, major

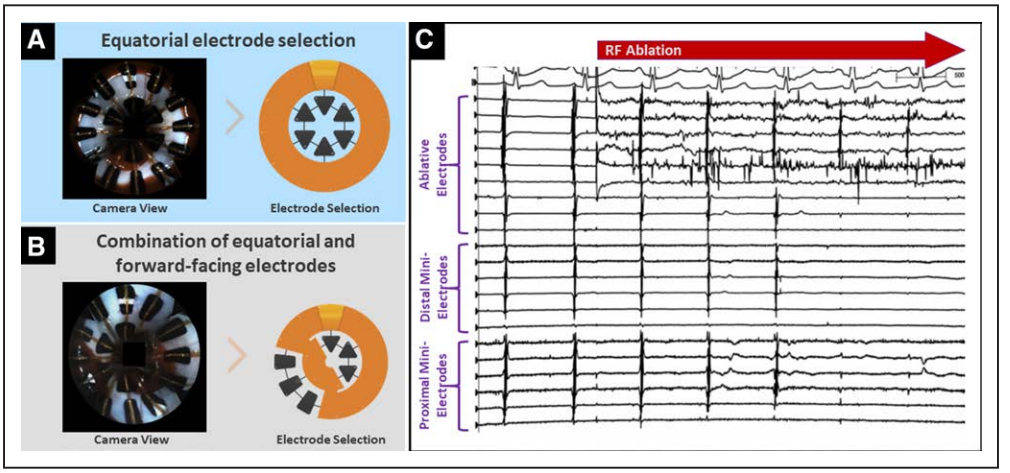


Figure 2. Pulmonary vein isolation (PVI) with the radiofrequency balloon catheter.
Shown are 2 balloon positions and the strategies used to achieve PVI: (**A**) the radiofrequency balloon (RFB) catheter is centered along the pulmonary vein (PV) long axis so the 12 equatorial electrodes are selected for ablation, and (**B**) because the RFB is askew to the center of the PV, a combination of 9 equatorial and 3 forward-facing electrodes is selected. **C**, Electrical PVI is observed in real time during ablation: shown are the ablation electrodes, as well as the distal and proximal pairs of mini-electrodes. Note the significant artifact on the ablation electrodes but not on the mini-electrodes. In this example, the PV is electrically isolated within 2 s of commencing energy delivery.

bleeding or other device-related complication requiring surgical intervention, or death. The primary performance end point was the rate of successful PVI as confirmed by entrance conduction block; a sensitivity analysis was performed comparing the results of patients enrolled during phase 1 versus phase II.

There were a number of secondary end points including (1) procedural performance parameters such as total procedure time, total fluoroscopy time, ablation time, and balloon time, (2) any serious adverse events (SAEs) during 12 months post-procedure, and (3) freedom from symptomatic or asymptomatic episodes of AF/atrial flutter (AFL)/atrial tachycardia (AT) recurrences at 12 months following ablation. Ablation time was defined as the time transpiring from the start of the first application to the end of the last application in the lesion set. Balloon time was defined as the time elapsing between when the catheter was introduced into the body till when it was removed from the body.

Statistical Analysis

The study was designed to demonstrate noninferiority of the study primary end points as compared with historical rates from standard of care ablation devices. For the primary safety end point, using an objective performance criterion of freedom from major adverse events being 97%, a noninferiority margin of 10%, and a 1-sided type I error probability threshold of 0.05, 56 subjects would provide 88% power to refute the null hypothesis. For the primary performance end point, a clinically reasonable performance goal for acute PVI success was estimated to be 98% as reported for paroxysmal AF ablation studies, evaluated on the vein level using the exact binomial distribution. In the analysis, each vein is treated independently. Assuming that 4 veins would be evaluated per subject and accounting for a 20% illegible data loss, a sample size of 19 subjects (60 PVs) provided 96% power to test the primary performance end point hypothesis, again assuming a noninferiority margin of 10% and a 1-sided type I error probability threshold of 0.05.

Since AF-FICIENT I was a first-in-human study for a new technology, it was decided to enroll a total of 100 subjects to not only fulfill the goals of the primary end points but also provide a reasonably large data set to assess clinical outcomes. The study was not powered for any secondary end point, so descriptive statistics were used to characterize these outcomes. Continuous variables are reported as mean±SD (or median and range as appropriate), and categorical variables are reported as number and percentage.

RESULTS

Patient Enrollment and Compliance

Between March 2016 and September 2018, 100 patients were enrolled. Patient disposition with respect to procedure and follow-ups is presented in Figure 3. One patient dropped out before the procedure, and 4 patients from one site were excluded because they presented with persistent, not paroxysmal, AF per study inclusion criteria; these patients were not included in the primary analyses or long-term follow-up. Therefore, the study population available for the primary end point analysis was comprised of 95 patients. One patient was treated

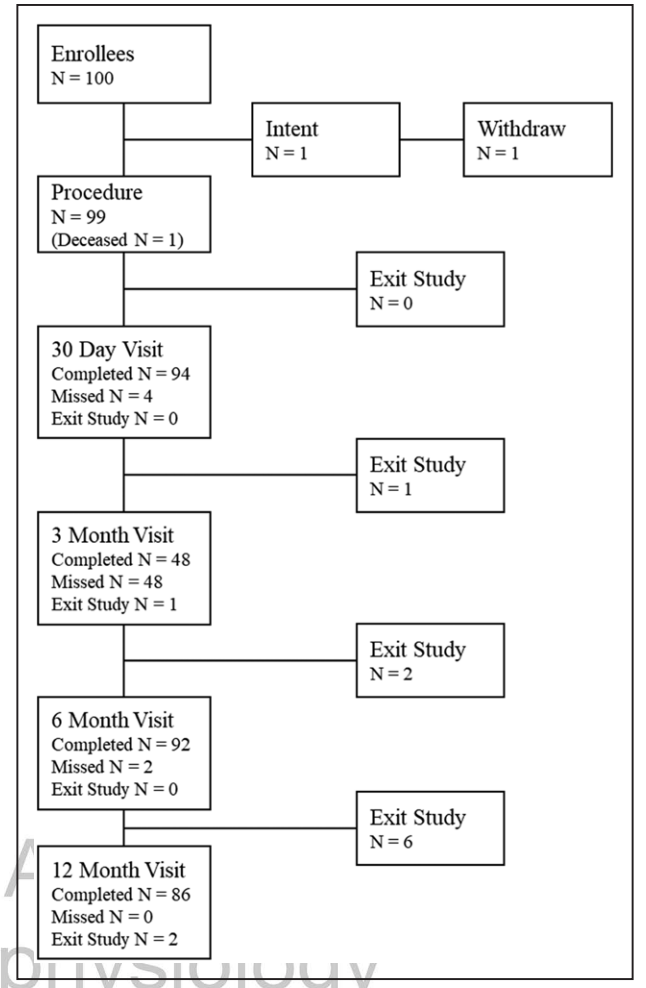


Figure 3. Consort diagram for AF-FICIENT I.
This patient flowchart shows the disposition of subjects in the AF-FICIENT I study and the timing of subject withdrawals, deaths, and patients lost to follow-up (or others) for all enrolled subjects.

with the RFB catheter without achieving PVI; accordingly, ablation was completed using an RFA commercial catheter. This patient was exited from the study at 1 month, in accordance with the protocol.

The mean enrollment per site was 33 patients, with 3 of 5 sites enrolling >25 patients per site (Table IV in the Data Supplement). Compliance with the protocol-required study visits was good, with overall compliance at 88.6% for all visits completed within the visit window (Table V in the Data Supplement). Of note, compliance was >95% for all visits except the 3-month visit, since the initial version of the protocol did not require the 3-month visit; compliance was >95% for this visit for subjects enrolled after the protocol was modified to make this a requirement.

Patient Characteristics

The baseline clinical characteristics are presented in Table 1. The age of the cohort was 58±11 years, with

Table 1. Baseline Patient Characteristics

Characteristics	Full cohort (n=100)
Age, y; mean±SD (range)	58±11 (26–77)
Men/women, %	68%/32%
Modified EHRA classification, %	
1: none	10%
2a: mild (normal daily activity not affected)	20%
2b: moderate (normal daily activity not affected)	39%
3: severe (normal daily activity affected)	27%
Medical history	
Paroxysmal/persistent AF, %	96%/4%
Hypertension, %	55%
Diabetes, %	10%
Dyslipidemia, %	29%
Permanent pacemaker, %	6%
Coronary artery disease, %	9%
Chronic pulmonary disease, %	4%
Stroke or transient ischemic attack, %	2%
Left ventricular ejection fraction, %; mean±SD	60±6.9 (n=66)
Left atrial dimension, mm; mean±SD	39±12 (n=67)
Medications	
Oral anticoagulants, %	98%
Class I or III antiarrhythmic medications, %	86%

AF indicates atrial fibrillation.

68% of the subjects being male. Just over half the cohort (55%) had a history of hypertension, 10% had a history of diabetes, and 2% had a history of a cerebrovascular event. The left ventricular ejection fraction was preserved at 60±6.9%, and the left atrial size was 39±12 mm. The majority of the cohort (86%) had previously been treated with a class I or III antiarrhythmic medication, and most had been receiving an oral anticoagulant (84%).

Primary End points

Of the 95 subjects analyzed for the primary safety end point, 94 subjects were free from device/procedure-related major adverse events. Accordingly, the primary safety success rate was 98.9%, with the 95% lower confidence bound being 97.2%, thereby rejecting the null hypothesis and meeting the primary safety end point. The single patient with a major adverse event had sustained a perforation into the aorta during the transseptal puncture procedure (using nonstudy equipment) resulting in cardiac tamponade and ultimately culminating in death during an attempt at emergency surgical repair; this event was adjudicated as procedure related but not device related (Table 2).

In evaluating the primary performance end point, from among 381 targeting PVs, 372 veins were electrically isolated using the RFB catheter alone, translating to a success rate of 97.6%. The 95% lower confidence bound

Table 2. Primary Safety End Point Events

Characteristics	Incidence (n=95)
Stroke/transient ischemic attack	0 (0%)
Major bleeding requiring surgical intervention	0 (0%)
Cardiac tamponade	1 (1.1%)*
PV stenosis	0 (0%)
Myocardial infarction	0 (0%)
Pulmonary edema	0 (0%)
Pericarditis	0 (0%)
Diaphragmatic paralysis	0 (0%)
Atrioesophageal fistula	0 (0%)
Valvular damage	0 (0%)
Intraprocedural device–related complication requiring surgery	0 (0%)
Death	1 (1.1%)*
Any other device or procedure-related SAEs	0 (0%)
Composite safety end point	1 (1.1%)†

PV indicates pulmonary vein; and RFB, radiofrequency balloon.

*One patient sustained a myocardial perforation with cardiac tamponade at the time of the transseptal procedure, before any introduction of the RFB catheter. During the resuscitation attempt, the patient expired.

†xxx.

was 96.4%, which exceeded the 10% noninferiority margin of the 98% performance goal, thereby rejecting the null hypothesis and meeting the primary performance end point ($P<0.0001$). On a per-patient basis, all PVs were electrically isolated using the RFB catheter alone in 90 of 95 subjects (94.7% [95% CI, 88.1%–98.3%]). A sensitivity analysis of the primary performance end point was performed, including only the 81 patients included in phase II of enrollment (activated sensing electrodes and enhanced sheath steerability). On a per-vein and per-patient basis, the success rates were 322 of 324 PVs (99.4% [95% lower CI, 98.7%]) and 79 of 81 patients (97.5% [95% CI, 91.4%–99.7%]), respectively.

Procedural Performance Parameters

All patients underwent a PVI procedure; in 2 patients, an additional cavotricuspid isthmus line was placed using a standard RFA catheter to treat typical AFL. As shown in Table 3, in the majority of cases (83.8%), a single RFB catheter was utilized; for technical reasons, additional RFB catheters were used in the remaining cases. Ultimately, a mean of 9 applications were delivered per patient, each lasting no more than 60 s with RF power of 8 to 10 W. The total transpired ablation time was a median 31 (interquartile range [IQR], 20–53) minutes. The total balloon time for the RFB catheter was a median 43 (IQR, 32–70) minutes; the total procedure time, 85 (IQR, 62–118) minutes; and the fluoroscopy time, 14 (IQR, 9–23) minutes.

Not surprisingly, there were improvements in these procedural parameters between phase I and phase

Table 3. Procedure Details

	Outcome*
Successful pulmonary vein isolation, n/total (%)	
Full cohort (n=95 patients)	372/381 PVs (97.6%)
Phase II cohort (n=79 patients)	322/324 PVs (99.4%)
Total procedure time	85 (62–118) min
Transpired ablation time†	31 (20–53) min
Total balloon time‡	43 (32–70) min
No. of radiofrequency applications per patient (mean±SD)	9±4
No. of RFB catheters used per patient, n (%)	
1	83 (83.8%)
2	9 (9.1%)
3	7 (7.1%)
Fluoroscopy time	14 (9–23) min
Total heparinized saline infused, mL (mean±SD)	1230±1102

PV indicates pulmonary vein; and RFB, radiofrequency balloon.
*Unless otherwise indicated, values are median (IQR).
†Defined as the time transpiring from the start of the first application to the end of the last application in the lesion set.
‡Defined as the time elapsing between when the catheter was introduced into the body till when it was removed from the body. Data available for 91 (of 99) patients—15 and 76 from phases I and II, respectively.

II (Figure 4): radiofrequency applications per patient (median [IQR], 12 [9–15] versus 8 [6–10]), ablation time (median [IQR], 92 [59–145] versus 29 [19–40]), total procedure time (median [IQR], 157 [132–213] versus 71 [59–101]), and fluoroscopy time (median [IQR], 43 [35–53] versus 13 [8–18]).

Clinical Follow-Up

Over the 12 months of follow-up, SAEs occurred in a total of 15 patients, so the freedom from SAEs was 84.9% ([95% CI, 77.8%–91.9%] see Table VI in the Data Supplement). However, only one of these SAEs was adjudicated as possibly related to the device (a patient who developed pericarditis), and beyond the aforementioned patient who sustained aortic perforation/tamponade/death, only 2 SAEs were adjudicated as possibly procedure related: the patient with pericarditis and a patient with recurrent symptomatic AF requiring reablation. Follow-up cardiac imaging with either computed tomography (n=47) or magnetic resonance imaging (n=14) was performed between the 3- and 12-month time points: there was no evidence of PV stenosis.

By the 12-month time point, 58.3% of the cohort was taking class I or III antiarrhythmic medications. Initiation of antiarrhythmic medications after the 3-month blanking period was individualized and at the treating physician discretion. As shown in Figure 5, the 12-month Kaplan-Meier estimates for freedom from AF/AFL/AT and AF were 77.5% (95% CI, 67.6%–84.7%) and 84.1% (95% CI, 74.9%–90.1%). For those patients not taking class I or III antiarrhythmic medications (n=35), the 12-month Kaplan-Meier estimates for freedom from AF/AFL/AT and AF were 85.7% (95% CI, 69.0%–93.8%) and 94.3% (95% CI, 79.0%–98.5%), respectively. If only including those patients enrolled in phase II of the study, the 12-month Kaplan-Meier estimates for freedom from AF/AFL/AT and AF were 78.1% (95% CI, 67.2%–85.8%) and 85.9% (95% CI, 76.1%–92.0%).

DISCUSSION

In this first-in-human clinical experience of the treatment of patients with paroxysmal AF using the novel visually guided RFB ablation catheter, we observed an acceptable acute safety profile, excellent procedural performance, and promising clinical efficacy. There were no serious complications related to the RFB ablation catheter itself. The procedural performance was favorable: in phase II, 99.4% of PVs were electrically isolated with the RFB catheter alone, with a median balloon time of only 40 minutes. And the 1-year estimated clinical efficacy of freedom from AF/AFL/AT was 77.5%.

This balloon-based ablation system offers several theoretical advantages over traditional ablation technologies.

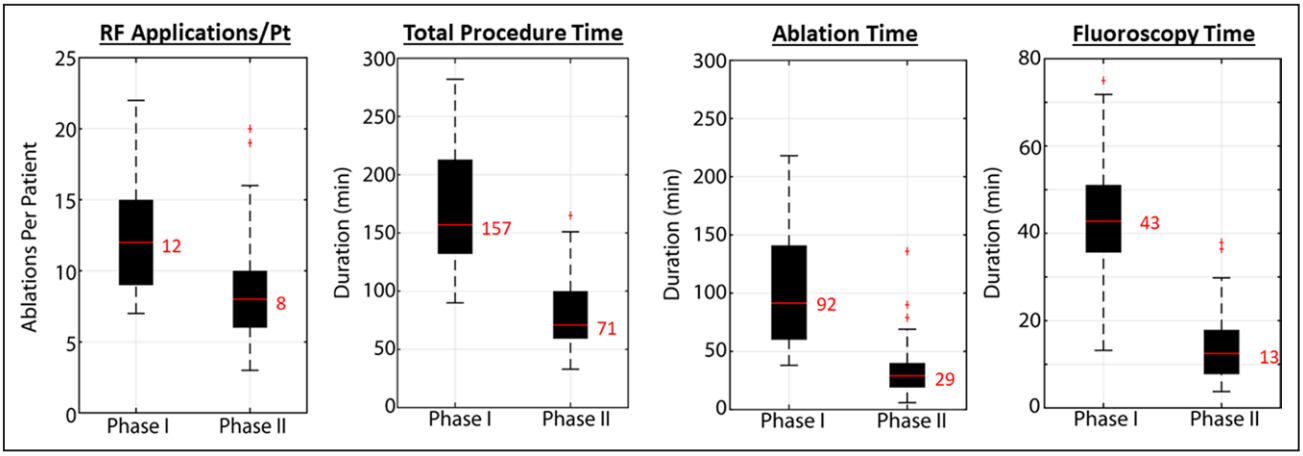
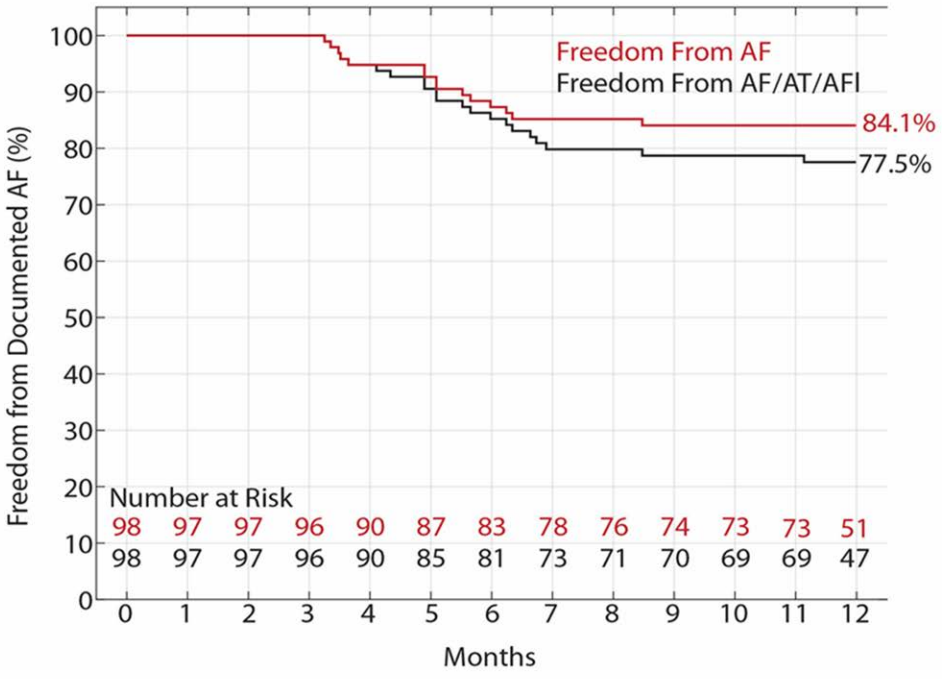


Figure 4. Procedural parameters–phase I versus II.
Shown is a comparison of various procedural parameters of patients enrolled in phase I vs phase II.



Patient Cohort	# of Recurrences	# of Patients	Recurrence Free Rate (95% CI)
Freedom from AF			
Phase II only (n = 81)	11	81	85.9% (76.1%, 92.0%)
Phase I & II	15	99	84.1% (74.9%, 90.1%)
Freedom from AF/AFl/AT			
Phase II only (n = 81)	17	81	78.1% (67.2%, 85.8%)
Phase I & II	21	99	77.5% (67.6%, 84.7%)

Figure 5. Freedom from atrial arrhythmias.
Shown in the panel on **top** are Kaplan-Meier curves of freedom from either atrial fibrillation (AF; red line) or AF/atrial flutter (AFL)/atrial tachycardia (AT; black line). **Bottom**, The data are also separated by patients enrolled in phase I vs phase II.

First, by using circumferential ablation electrodes around the balloon, it allows the simultaneous delivery of ablative radiofrequency energy around each PV. In addition to a marked reduction of both ablation and overall procedure times, simultaneous energy delivery has the potential for a synergistic interaction between the adjacent heat sources generated by the electrodes, thereby improving efficacy. Second, real-time direct contact visualization through the inbuilt cameras provides accurate positional information to allow the operator to both (1) make small adjustments to optimize balloon position, in a nonfluoroscopic manner, and (2) quickly and easily select the electrodes in contact with tissue to efficiently deliver multipolar or bipolar radiofrequency energy in a circumferentially contiguous manner. Importantly, this ability to tailor energy delivery to each electrode also allows for the possibility to deliver less energy in proximity to the esophagus or if near the phrenic nerve, while yet delivering higher energy in areas of thick tissue. This feature caters to important safety and efficacy concerns lacking in some of the single-shot technologies currently in use. Third, the integrated mapping and pacing abilities of the RFB catheter further aid in reducing procedure times. In addition, while not specifically addressed in this clinical study, it is possible that by actively monitoring for electrical entrance block during ablation, one may be able to

better tailor energy delivery. For example, the time to isolation during cryoballoon ablation can predict the efficacy of a single cryolesion, thereby guiding the operator as to how long an individual lesion should be delivered and whether to place bonus lesions.[8] Further clinical studies with the integrated sensing electrodes of this RFB catheter may prove similarly useful.

The RFB catheter proved to be safe in our experience. The only serious complication was related to the transseptal puncture resulting in aortic perforation, cardiac tamponade, and death. However, this was an unfortunate complication of the transseptal puncture step, before the introduction of the RFB catheter. It is likely that cardiac tamponade related to the RFB catheter itself will prove to remain infrequent because (1) the RFB catheter is introduced over a guidewire and has a flat, atraumatic front face to the tissue, and (2) compared with traditional RFA catheters, the large surface area of the electrodes results in a relatively low current density during radiofrequency energy delivery. This low current density, combined with saline irrigation of the ablation electrodes, also likely explains the absence of thromboembolic phenomena, including no strokes or transient ischemic attacks. The relatively flat face of the balloon likely accounts for the absence of phrenic nerve injury and PV stenosis, since this characteristic would force the RFB to be situated outside the PV ostium.

The absence of esophageal damage, such as atrioesophageal fistula or gastric dysmotility, is encouraging. In contrast to most other RFA systems, the RFB catheter delivers energy in a bipolar fashion between adjacent electrodes. This may have contributed to the safety of the system by reducing the risk of deep ablation, damaging the esophagus. However, in AF-FICIENT I, routine endoscopy to assess the esophageal mucosa was not performed. Furthermore, 26% of the procedures in our study were performed using mechanical esophageal deviation. Clearly, many more patients must be treated before one makes conclusions about the potential for esophageal damage with the RFB catheter.

One of the standout observations in AF-FICIENT I was the short procedure times. After the introduction of sensing electrodes and enhanced sheath deflection, the phase II case procedure times were short and compared favorably with other single-shot ablation systems currently in use.[8–12] By the end of the study, the total procedure times averaged just over an hour, and the balloon time was only ≈40 minutes. The favorable fluoroscopy time, 13 minutes in phase II, reflects some of the advantages of visual guidance from within the balloon.

The clinical outcomes were also favorable: the 1-year freedom from AF was 84.1%, while the 1-year freedom from AF/AFL/AT was 77.5%. However, it is important to recognize that just over half the patients had continued class I or III antiarrhythmic medications to the 1-year time point, despite the protocol requiring that these medications be stopped by 3 months. Thus, while favorable, these clinical outcome data need to be corroborated in a large multicenter study in which these membrane-active antiarrhythmics are stopped by the end of the blanking period.

Limitations

AF-FICIENT I is a nonrandomized clinical study which, while multicenter, only included 5 centers. A sizeable percentage of the patient cohort remained on class I/III antiarrhythmic medications at 12 months, largely because they simply failed to stop them at 3 months, rendering it difficult to determine the efficacy of RFB ablation alone in maintaining sinus rhythm. The results reported herein should be reproduced in larger studies with more centers and operators included. Furthermore, additional safety analyses should be conducted, including routine esophageal endoscopy studies and brain magnetic resonance imaging studies to assess for silent cerebral ischemic events. Similarly, invasive remapping studies should be conducted to determine the durability of the PVI lesion sets.

Conclusions

This first-in-human study demonstrated that the visually guided multielectrode RFB ablation catheter is safe, acutely efficacious in achieving PV isolation. This system holds promise for an easy to use, efficient, and time-saving single-shot technology for PVI.

ARTICLE INFORMATION

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Supplemental Materials

Data Supplement Tables I–VI
Data Supplement Figures I–III

REFERENCES

1. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary. *Europace*. 2018;20:157–208. doi: 10.1093/europace/eux275
2. Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, Macle L, Daoud EG, Calkins H, Hall B, et al; ThermoCool AF Trial Investigators. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA*. 2010;303:333–340. doi: 10.1001/jama.2009.2029
3. Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, Dubuc M, Reddy V, Nelson L, Holcomb RG, 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;61:1713–1723. doi: 10.1016/j.jacc.2012.11.064
4. Dukkipati SR, Cuoco F, Kutinsky I, Aryana A, Bahnson TD, Lakkireddy D, Woollett I, Issa ZF, Natale A, Reddy VY; HeartLight Study Investigators. Pulmonary vein isolation using the visually guided laser balloon: a prospective, multicenter, and randomized comparison to standard radiofrequency ablation. *J Am Coll Cardiol*. 2015;66:1350–1360. doi: 10.1016/j.jacc.2015.07.036
5. Natale A, Reddy VY, Monir G, Wilber DJ, Lindsay BD, McElderry HT, Kantipudi C, Mansour MC, Melby DP, Packer DL, et al. Paroxysmal AF catheter ablation with a contact force sensing catheter: results of the prospective, multicenter SMART-AF trial. *J Am Coll Cardiol*. 2014;64:647–656. doi: 10.1016/j.jacc.2014.04.072
6. Reddy VY, Dukkipati SR, Neuzil P, Natale A, Albenque JP, Kautzner J, Shah D, Michaud G, Wharton M, Harari D, et al. Randomized, controlled trial of the safety and effectiveness of a contact force-sensing irrigated catheter for ablation of paroxysmal atrial fibrillation: results of the tacticath contact force ablation catheter study for atrial fibrillation (TOCCASTAR) Study. *Circulation*. 2015;132:907–915. doi: 10.1161/CIRCULATIONAHA.114.014092
7. Bhardwaj R, Naniwadekar A, Whang W, Mittnacht AJ, Palaniswamy C, Koruth JS, Joshi K, Sofi A, Miller M, Choudry S, et al. Esophageal deviation during atrial fibrillation ablation: clinical experience with a dedicated esophageal balloon retractor. *JACC Clin Electrophysiol*. 2018;4:1020–1030. doi: 10.1016/j.jacep.2018.04.001
8. Aryana A, Kenigsberg DN, Kowalski M, Koo CH, Lim HW, O'Neill PG, Bowers MR, Hokanson RB, Ellenbogen KA; Cryo-DOSING Investigators. 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). *Heart Rhythm*. 2017;14:1319–1325. doi: 10.1016/j.hrthm.2017.06.020
9. Kuck KH, Albenque JP, Chun KJ, Fürnkranz A, Busch M, Elvan A, Schlüter M, Braegelmann KM, Kueffer FJ, Hemingway L, et al; FIRE AND ICE Investigators. Repeat ablation for atrial fibrillation recurrence post cryoballoon or radiofrequency ablation in the FIRE AND ICE trial. *Circ Arrhythm Electrophysiol*. 2019;12:e007247. doi: 10.1161/CIRCEP.119.007247
10. Tohoku S, Bordignon S, Chen S, Trolese L, Bologna F, Zanchi S, Bianchini L, Cho D, Chun KRJ, Schmidt B. From point by point to single shot: evolution of visually guided pulmonary vein isolation using the third-generation laser balloon catheter. *J Cardiovasc Electrophysiol*. 2020. doi: 10.1111/jce.14511
11. Reddy VY, Schilling R, Grimaldi M, Horton R, Natale A, Riva S, Tondo C, Kuck KH, Neuzil P, McInnis K, et al. Pulmonary vein isolation with a novel multielectrode radiofrequency balloon catheter that allows directionally tailored energy delivery: short-term outcomes from a Multicenter First-in-Human Study (RADIANCE). *Circ Arrhythm Electrophysiol*. 2019;12:e007541. doi: 10.1161/CIRCEP.119.007541
12. Reddy VY, Neuzil P, Koruth JS, Petru J, Funasako M, Cochet H, Sediva L, Chovanec M, Dukkipati SR, Jais P. Pulsed field ablation for pulmonary vein isolation in atrial fibrillation. *J Am Coll Cardiol*. 2019;74:315–326. doi: 10.1016/j.jacc.2019.04.021