ECGI targeted ablation for persistent AF not responding to pulmonary vein isolation: Results of a two-staged strategy (TARGET AF2)

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BACKGROUND Mechanisms sustaining persistent atrial fibrillation (AF) remain unclear.

OBJECTIVES The study sought to evaluate both the clinical outcomes and response to ablation of potential drivers in patients with recurrent persistent AF recurrence following pulmonary vein isolation (PVI).

METHODS A total of 100 patients with persistent AF of <2 years' duration underwent cryoballoon PVI (ECGI phenotyping of persistent AF based on driver burden and distribution to predict response to pulmonary vein isolation). Patients with documented recurrence of atrial arrhythmia within 12 months were recruited and underwent repeat PVI (if needed) followed by ablation of potential drivers (PDs) identified by electrocardiographic imaging (ECGI). PDs were defined as rotational activity >1.5 revolutions or focal activations. Cycle lengths were measured pre- and postablation. The primary outcome was freedom from atrial arrhythmia off antiarrhythmic drugs at 1 year as per guidelines.

RESULTS Of 37 patients recruited, 26 had recurrent AF and underwent ECGI-guided ablation of PDs. An average of 6.4 ± 2.7 PDs were targeted per patient. The mean ablation time targeting PDs was 15.5 ± 6.9 minutes. An ablation response occurred in 20 patients (AF termination in 6, cycle length prolongation ≥10% in 14). At 1 year, 14 (54%) of 26 patients were free from arrhythmia, and 12 (46%) of 26 were off antiarrhythmic drugs. Considering the 96 patients who completed follow-up out of the original cohort of 100 patients undergoing cryoablation in this staged strategy, freedom from arrhythmia at 1 year following the last procedure was 72 (75%) of 96, or 70 (73%) of 96 off antiarrhythmic drugs.

CONCLUSIONS In patients with recurrent AF despite PVI, ECGI-guided ablation caused an acute response in a majority with reasonable long-term outcomes.

KEYWORDS ECGI mapping; Persistent AF mechanisms; Noninvasive mapping; Drivers of AF; Ablation of drivers

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Introduction

The underlying mechanisms of persistent atrial fibrillation (AF) remain unclear. Pulmonary vein isolation (PVI) has been proven to be as effective as any other strategy as an index procedure for persistent AF.[1,2] For those with recurrent arrhythmia, the strategy for repeat ablations beyond PVI remains unclear.

Growing evidence from recent studies suggest persistent AF is maintained by localized sources termed drivers.[3–6] These drivers have been described as either focal or rotational activation patterns that can originate in either atria, the PVs or vena cavae.[4,7] Further evaluation is required to define them and to fully understand the role of these drivers in maintaining persistent AF.

The electrocardiographic imaging (ECGI) system (CardioInsight; Medtronic, Minneapolis, MN) is a noninvasive mapping system that panoramically maps both atria. Studies have demonstrated its potential to panoramically map potential drivers (PDs) of AF.[7–10] We and others have reported on ECGI-guided ablation of persistent AF with some success.[6,9] We hypothesized that ECGI-guided PD ablation for AF that had recurred despite PVI would result in high rates of acute AF termination and subsequent freedom

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KEY FINDINGS

- This 2-step approach (pulmonary vein isolation at index procedure followed by redo catheter ablation guided by electrocardiographic imaging if required) led to freedom from atrial fibrillation at 1 year following their last procedure of 75% and 73% off antiarrhythmics.
- Ablation of drivers guided by electrocardiographic imaging at the redo procedure led to an acute ablation response in 77% of patients.
- Potential drivers were identified in all patients with atrial fibrillation recurrence, with the majority being rotational (77.6%). The majority of potential drivers were mapped to the left atrium, followed by the right atrium and then the septum.

from AF. Furthermore, evaluation of the cohort initially undergoing PVI alone would enable us to report the outcome of a 2-stage strategy, with PVI as a first procedure followed by ECGI-guided PD ablation at a second procedure for those with recurrent AF despite PVI.

Materials and Methods

Patient populations

Initial PHENOTYPE-AF cohort

Patients undergoing first time catheter ablation for persistent AF of <2 years' duration were prospectively enrolled in the ECGI phenotyping of persistent AF based on driver burden and distribution to predict response to pulmonary vein isolation (PHENOTYPE-AF) study between January and December 2018. The study was approved by the national ethics committee and was prospectively registered on ClinicalTrials.gov (NCT03394404).

Patients underwent cryoballoon PVI at their index procedure; our methodology has been published previously.[7] Patients were then evaluated clinically at 3, 6, 9, and 12 months, with 24-hour ECG Holter monitoring at 6 and 12 months.[11]

The current study: TARGET AF2

Patients who had documented atrial arrhythmia within 12 month follow-up from their index PHENOTYPE-AF cryoballoon PVI procedure were prospectively enrolled in the current study (ECGI targeted ablation for persistent AF not responding to pulmonary vein isolation: results of a two-staged strategy [TARGET AF2]) as shown in Figure 1. This study was approved by the national ethics committee and prospectively registered on ClinicalTrials.gov (NCT04633265). All participants provided written informed consent. The research in this study was conducted according to the Helsinki Declaration guidelines on human research.

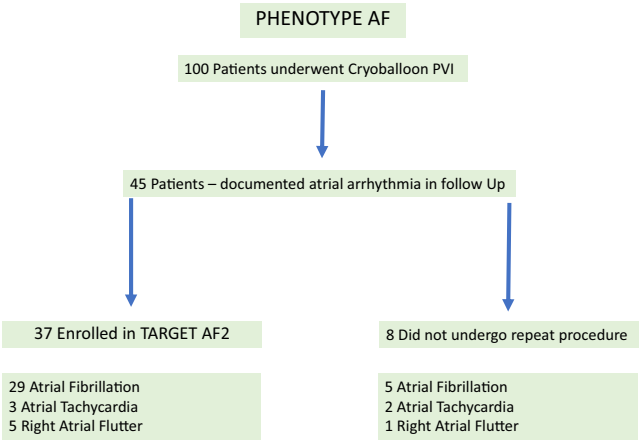

Figure 1 Flow chart showing the flow of enrolled patients from the ECGI phenotyping of persistent AF based on driver burden and distribution to predict response to pulmonary vein isolation (PHENOTYPE-AF) study into the electrocardiographic imaging ECGI targeted ablation for persistent AF not responding to pulmonary vein isolation: results of a two-staged strategy (TARGET AF2). PVI = pulmonary vein isolation.

Catheter ablation

Procedures were performed under conscious sedation or under general anaesthesia. Patients did not routinely undergo transesophageal echocardiography. Right femoral venous access was guided by vascular ultrasound. Patients continued uninterrupted oral anticoagulation throughout the perioperative period. Patients were heparinized with a target activated clotting time of 300 to 350 seconds.

All procedures were guided by CARTO 3 (Biosense Webster, Diamond Bar, CA) with LabSystem Pro (Boston Scientific, Marlborough, MA) used to record and display electrogram data. A decapolar mapping catheter was placed in the coronary sinus. After transseptal puncture, a multipolar steerable mapping catheter (Pentaray; Biosense Webster) and a smart touch ablation catheter were passed into the left atrium.

Atrial tachycardia and atrial flutter

Patients with atrial tachycardia (AT) or atrial flutter underwent conventional mapping and ablation using contact electrograms and the CARTO 3D mapping system (Biosense Webster). In all patients, a transseptal puncture was performed, and the PVs were evaluated for entrance and exit block. Further ablation was delivered if necessary to reisolate the PVs.

Noninvasive ECGI mapping

Patients who had recurrent AF following cryoballoon PVI in the PHENOTYPE-AF study underwent ECGI mapping intraprocedurally. Our ECGI mapping methods and evaluation of PDs have described previously but are outlined subsequently.[7]

If patients were in sinus rhythm at the start, then AF was induced through burst atrial pacing and left to stabilize for 10 minutes prior to mapping and repeat PVI if needed. If patients terminated to sinus rhythm with repeat PVI, no further ablation was performed. If patients remained in AF

post-PVI, then ECGI mapping was used to guide ablation at sites identified as PDs. Fifteen seconds of cumulated atrial intervals, each of a minimum duration of ≥840 ms, were collected to generate a biatrial map of PDs. Intravenous beta-blockers and/or calcium-channel blockers were administered if the ventricular rate required slowing. If this failed to slow the rate adequately, then adenosine was administered. ECGI maps were reviewed to identify PDs. Focal drivers were defined as centrifugal activation originating from a point. Rotational drivers were defined as ≥1.5 revolutions around a spatially stable core (in an area of <2 cm^2) on phase maps.[2,3,9] Drivers occurring in the same region of an 18-segment model of the atria[9] were assumed to be occurrence of the same driver. Drivers were targeted in order of those with the most frequent occurrence during the 15-second mapping period.

Targeted ablation

Following PVI, a 20-minute waiting period was observed before ablation of PDs was commenced in the left atrial (LA) and right atrial (RA) bodies. This was to avoid any delayed effect potentially attributable to PVI, which might influence AF cycle length (CL) during ablation at the sites of PDs. To monitor the effect of ablation at the PD sites as identified on the post-PVI maps, CLs were recorded before and after ablation within a region from the Pentaray catheter sited at the left atrial appendage (LAA) in which electrograms are clear and CL is clear. Cycle lengths were measured manually over 30 cycles by a single operator blinded to the ECGI findings. Confirmed drivers were defined as sites where ablation resulted in ≥10% slowing of the CL or terminated AF. If AF persisted despite ablation of all localized drivers identified on the post-PVI maps, a further ECGI map was created. If any new localized drivers were identified, these were ablated. If patients remained in AF following ablation of these localized drivers, patients were cardioverted with a direct current shock.

Ablation at driver sites was delivered with a contact force of 5 to 40 g, with a power of 30 to 40 W. Ablation at sites with either focal or rotational activation was delivered as discrete focal points, aiming for the center of the focal or rotational activation. Further ablation was delivered in a cluster of lesions surrounding the first point. Ablation in any region was stopped if the endpoint was met (ie, AF terminated or CL slowed) or once there was no remaining signal. Care was taken not to form a linear lesion with clusters, so as not to impact any AF mechanisms in this way. Beyond isolating PVs and targeting PDs, no additional ablation was performed in AF. If the AF organized into an AT, this was mapped using local activation times and entrainment and ablated. The ECGI mapping system was not used to map AT.

PD analysis

PD burden was defined as the total number of PD occurrences. To assess the distribution of PDs, we utilized an 18-segment biatrial model described previously.[7] The PD distribution was then defined as the number of segments on the 18-segment model harboring PDs. The temporal stability of rotational activation patterns was defined as the mean number of cycles per PD occurrence. The PD recurrence rate was the number of times the PD occurred during the 15-second recording.

Table 1 Demographics of participants of electrocardiographic imaging TARGET AF2

Number of patients	37
Age, y	60.8 ± 11.9
Male	29 (78.4)
Hypertension	15 (40.5)
Diabetes mellitus	5 (13.5)
Ischemic heart disease	6 (16.2)
Cerebrovascular accident	1 (2.7)
Body mass index, kg/m^2	28.8 ± 4.1
LA diameter, mm	38.0 ± 9.1
LVEF, %	53.8 ± 7.7
Duration of AF: diagnosis to procedure, mo	32.3 ± 57.9
Duration of persistent AF, mo	11.8 ± 7.5
Persistent AF duration <12 mo	18 (48.6)
Persistent AF duration >12 mo	19 (51.4)

Values are n, mean ± SD, or n (%).

AF = atrial fibrillation; LA = left atrial; LVEF = left ventricular ejection fraction; TARGET AF2 = ECGI targeted ablation for persistent AF not responding to pulmonary vein isolation: results of a two-staged strategy.

Follow-up

Patients were evaluated clinically at 3, 6, 9, and 12 months following their repeat procedure. Clinical evaluation included 12 lead ECG and assessment of patient symptoms with 24-hour ECG Holter monitoring at 6 and 12 months.

Study endpoints

The prespecified primary endpoint was clinical success at 1 year defined as freedom from documented atrial arrhythmia lasting ≥30 seconds following a 3-month blanking period off antiarrhythmic drugs as per guidelines.[12]

Prespecified secondary endpoints included freedom from AF at 1 year following a 3-month blanking period after a single procedure off antiarrhythmic drugs (ie, allowing for AT but not AF), rates of AF termination during ablation, and a composite of AF termination and slowing of CL by ≥10% during ablation.

Statistical analysis

Normally distributed data were expressed as mean ± SD or, if not normally distributed, as median and interquartile range (IQR). Student's t test was performed for normally distributed variables and the Mann-Whitney U test was performed for nonparametric variables. All statistical analyses were performed using SPSS (version 25; IBM Corporation, Armonk, NY). A P value of <.05 was taken to indicate statistical significance.

Table 2 Procedure details

Number of patients	37
General anesthesia	7 (18.9)
Rhythm on day	
Sinus rhythm	16
AF	18
Atrial tachycardia	3
Atrial flutter	0
Reconnection of PVs	17 (45.9)
AF ablation	27
Atrial tachycardia ablation	6
Cavotricuspid line	2
Cavotricuspid line and redo PVI	2
Procedure duration	222.6 ± 265.6
Fluoroscopy time, s	106.3 ± 367.8
Fluoroscopy dose, cGy·cm^2	31.4 ± 81.4
RF duration, min	35.6 ± 11.29
Complications	1*

Values are n, n (%), or mean ± SD.

AF = atrial fibrillation; PV = pulmonary vein; PVI = pulmonary vein isolation; RF = radiofrequency.

*A single pericardial effusion that required percutaneous drainage.

Results

A total of 100 patients with persistent AF were recruited into the PHENOTYPE-AF study and underwent cryoballoon PVI. During follow-up of the PHENOTYPE-AF study, 45 patients had documented recurrence of an atrial arrhythmia. Of these 45 patients, 37 underwent ablation and were recruited into the TARGET AF2 study (the remaining 8 had paroxysmal arrhythmia managed medically). Of 37 patients, 4 (11%) underwent cavotricuspid ablation and 6 (16%) underwent AT ablation. A total of 27 (73%) patients underwent catheter ablation for AF. Demographic data of the patients enrolled into this study are shown in Table 1.

Procedure data are shown in Table 2. All 37 patients underwent evaluation of their PVs, and 17 (46%) of 37 patients were found to have PV reconnection (8 had 1 PV reconnected, 7 had 2 PVs reconnected, and 2 had 3 PVs reconnected). All 17 patients underwent reisolation of their PVs.

AF ablation

Of 27 patients with AF, 9 were in sinus rhythm on the day of their procedure requiring induction of AF. One (3%) patient underwent PVI alone, which led to acute termination of their AF. Repeat PVI was required in 14 (54%) of 26, followed by PD ablation guided by ECGI. Outcomes are shown in Figure 2. The procedure time was 196.1 (IQR 172.5–240.3) minutes and fluoroscopy time 13 (IQR 0–34.5) seconds. The total radiofrequency ablation time was 33.9 (IQR 30.1–43.5) minutes. There was 1 acute complication of a pericardial effusion that required percutaneous drainage.

Ablation of PDs

The results of ECGI mapping can be found in Supplemental Table 1. LAA CL was recorded in all patients pre- and postablation at each PD region to evaluate the impact of ablation (Supplemental Table 2).

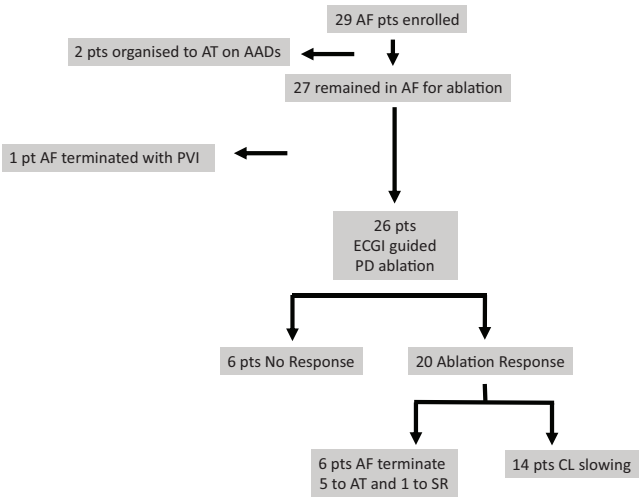

Figure 2 This flow chart shows the flow of patients and their outcomes. The patients are grouped as per the arrhythmia that they had documented prior to enrollment into the electrocardiographic imaging (ECGI) TARGET AF2 study. AAD = antiarrhythmic drug; AF = atrial fibrillation; AT = atrial tachycardia; CL = cycle length; PD = potential driver; pts = patients; SR = sinus rhythm.

ECGI mapping identified 33.0 ± 12.3 PD occurrences per patient with a mean of 11 (IQR 9–13) of 18 segments occupied by PDs. There were 210 PDs identified in total, with 8.1 ± 2.2 PDs identified per patient.

The PDs were predominantly rotational in nature (163 [77.6%] rotational drivers and 47 [22.4%] focal drivers). Out of the 210 PDs, 152 (72.4%) were mapped to the LA, 50 (23.8%) were mapped to the RA, and 8 (3.8%) were mapped to the septum. The most common sites for PDs to be identified in the LA were the posterior wall (46.7%), anterior wall (17.8%), lateral wall (13.8%), and roof (12.5%). In the RA, PDs were predominantly mapped to the lateral wall (26%) and RA appendage (26%), to the posterior wall (18%), and then to the RA roof (12%). The rotational drivers demonstrated an average recurrence rate of 2 (IQR 2–3) during the mapping period and an average temporal stability of 2.3 (IQR 1.9–2.8) revolutions per occurrence. The focal drivers demonstrated an average recurrence rate of 2.4 ± 1.6 and an average temporal stability of 1.2 ± 0.3 cycles per occurrence.

In those patients who underwent AF ablation, there was no difference in freedom from arrhythmia at 12 months in those who required repeat PVI compared with those who did not (9 of 14 vs 5 of 11; $P = .346$). Comparison of the number of PDs identified in patients who required repeat PVI with those who did not was not significant (14 ± 8.1 vs 12 ± 8; $P = .865$), nor was the total number of drivers ablated in patients who required repeat PVI compared with those that did not (14 ± 6.4 vs 12 ± 6.4; $P = .444$).

Figure 3 shows the number of cycles completed per rotational driver occurrence. This reveals that the distribution of cycles per rotational driver is skewed. Figures 4A to 4C show the distribution of cycles per rotational drivers in the LA, in the RA, and on the septum.

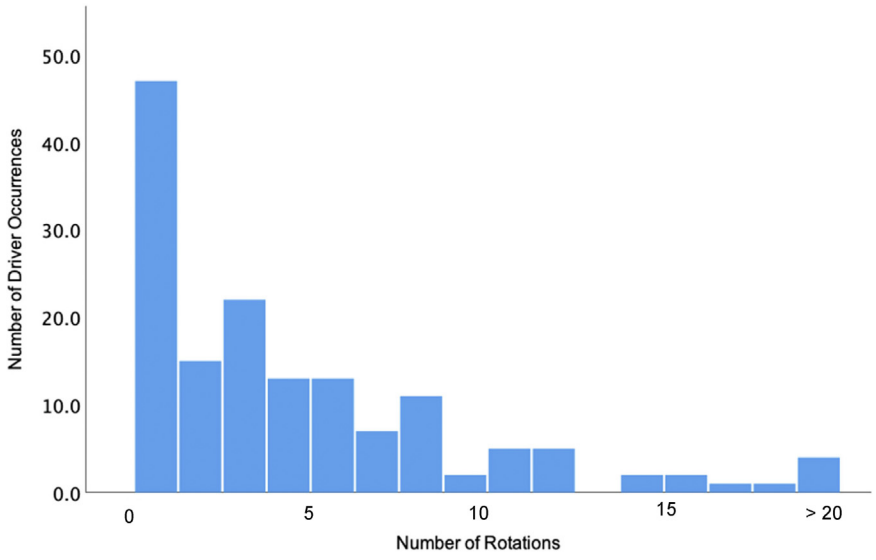

Figure 3 This histogram shows the distribution of the number of cycles per rotational driver.

Response to ablation of PDs

Response on a per-patient basis

An ablation response that met the study criteria (AF termination or CL slowing ≥10%) was achieved in 20 (77%) of 26 patients. PD ablation led to termination of AF in 6 (23%) of 26 patients (AT = 5, sinus rhythm = 1), and CL slowing ≥10% was achieved in 14 (54%) patients. The mean radiofrequency ablation time targeting PDs was 15.5 ± 6.9 minutes.

Response on a per-driver basis

A per-driver analysis of response to ablation is shown in Supplemental Table 2. In 26 patients, 166 PDs were targeted with ablation, with an average of 6.4 ± 2.7 PDs targeted per

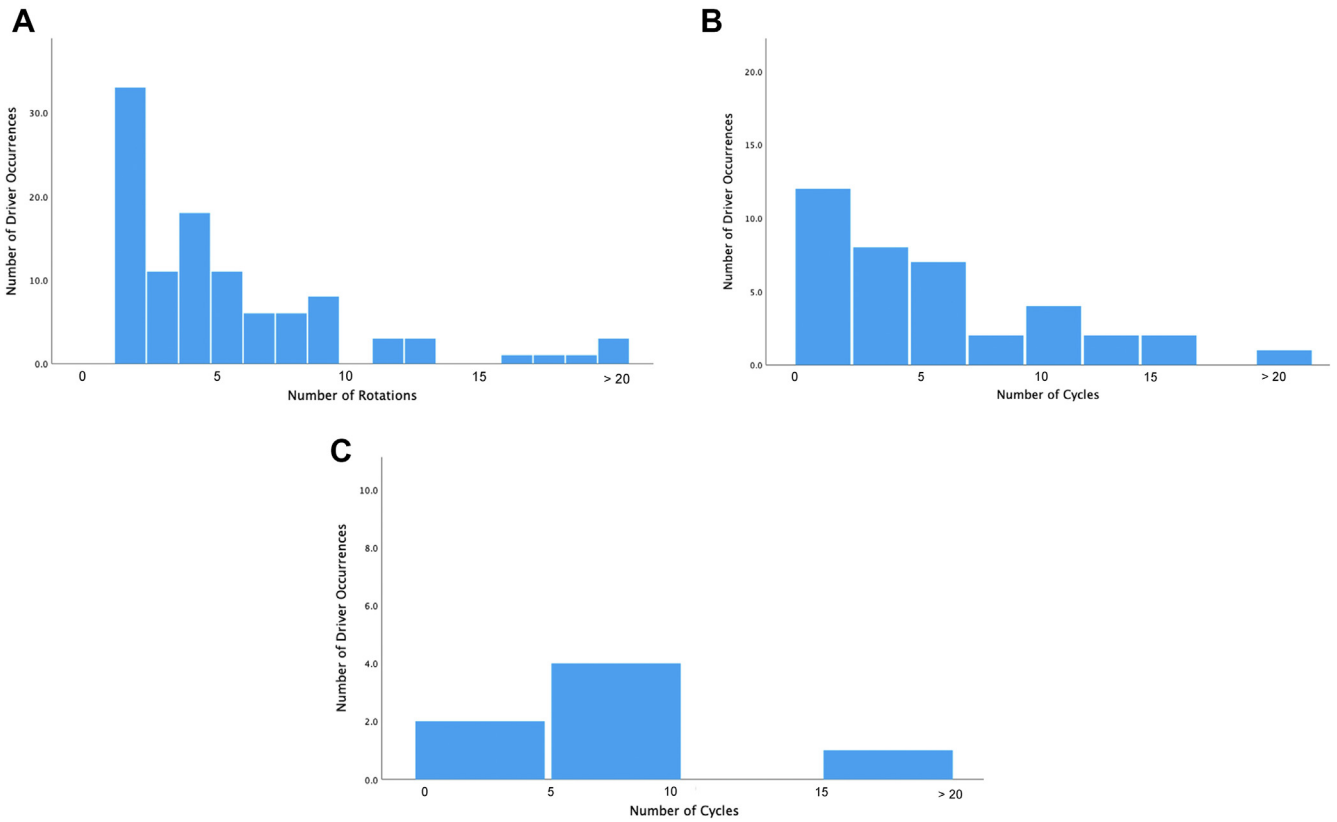

Figure 4 **A–C:** Histograms of the number of cycles per rotational driver in the left atrium **(A)**, in the right atrium **(B)**, and on the septum **(C)**.

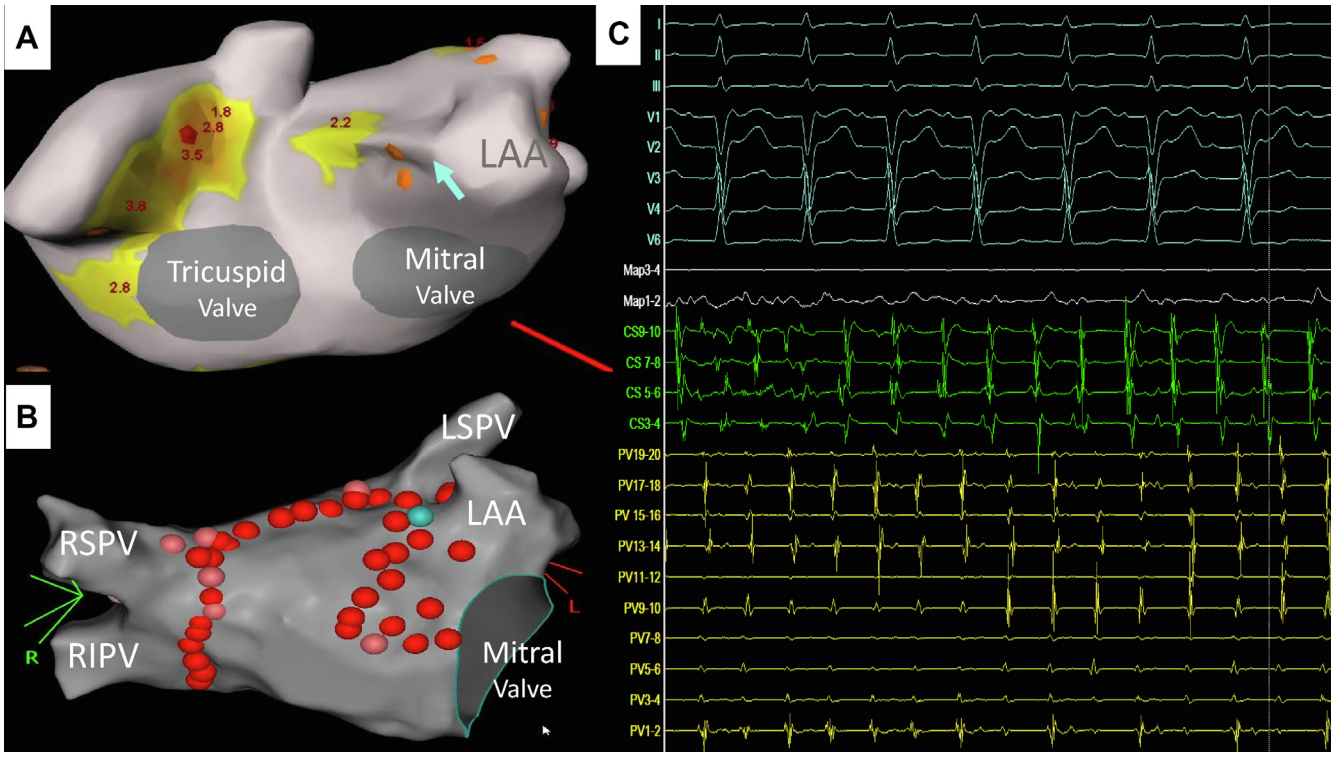

Figure 5 Electrocardiographic imaging–guided driver ablation causing organization of atrial fibrillation. **A:** An electrocardiographic imaging composite map of the atria in an anteroposterior view. The yellow area shows rotational activations, and the orange balls show focal activations at the anterior border of the left atrial appendage (LAA) and at the top of the appendage ridge. **B:** An end-procedure CARTO map in a similar view. The red balls are visitags that are automated marking of lesions. The right pulmonary veins were reisolated at the start. There is a cluster of lesions on the anterior wall where rotational drivers were detected, then an overlapping cluster of lesions at the border of the left atrial appendage and at the top of the appendage ridge. The green ball is where the cycle length change in panel **C** occurred. Following organization into an atrial tachycardia, ablation was required on the left atrial roof, and further ablation of a focal tachycardia anterior to the left atrial appendage was required. LSPV = left superior pulmonary vein; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein;

patient. The mean radiofrequency ablation time per PD was 2.5 ± 0.4 minutes. An ablation response that met the study criteria was achieved with 28 (16.9%) drivers out of the 166 PDs ablated. This included CL slowing that met study criteria with 22 (13.3%) of 166 PDs and termination of AF in 6 (3.6%) of 166 PDs. For those PDs in which ablation was associated with a change in CL that met the study criteria, the mean change in CL was 26.4 ± 4.1 ms. Figure 5 shows a patient in whom targeted ablation led to termination of AF.

Factors determining response to ablation of PDs

Comparing rotational with focal drivers, there was no significant difference in ablation response, with 20 (16%) of 127 rotational drivers vs 8 (21%) of 39 focal drivers ($P = .487$). There was no significant difference in temporal stability (the mean number of consecutive cycles) when comparing rotational PDs that led to an ablation response with those that did not (2.2 [IQR 1.8–2.8] vs 2.2 [IQR 1.8–2.6]; $P = .537$). Comparing the sum of rotations of PDs with an ablation response with those with no response did not reveal a significant difference (5 [IQR 2.3–8.1] vs 3.9 [IQR 2.1–7.3]; $P = .467$), nor was there a difference comparing the number of PD occurrences (2 [IQR 1–3] vs 2 [IQR 1–3]; $P = .534$).

There was no significant difference in temporal stability (the mean number of consecutive cycles) when comparing focal PDs that led to an ablation response with those that did not (2 [IQR 1–3] vs 2 [IQR 2–3]; $P = .325$), nor was there a significant difference when comparing the recurrence rate in terms of the number of focal PD occurrences (2 [IQR 1–3] vs 2 [IQR 1–3]; $P = .527$).

Comparison of patients with and without AF termination

Comparison of noninvasive mapping pre-PD ablation in the 6 patients in whom AF terminated with PD ablation compared with those in whom it did not revealed no significant difference in the total number of PDs (Supplemental Table 3).

Twelve-month clinical outcomes

A total of 36 (97%) of 37 patients successfully completed follow-up. One patient who underwent AF ablation died of COVID pneumonitis at 6 months postprocedure with no documented atrial arrhythmia. No complications were reported postprocedure during follow-up.

Regarding outcomes in those undergoing repeat catheter ablation of AF in the TARGET AF2 study, of the 26 patients who completed follow-up after catheter ablation of AF, 12 patients had recurrent arrhythmia. The recurrent arrhythmia was AF for 6 and AT for 6. The freedom from atrial arrhythmia was therefore 14 (54%) of 26, and 12 (46%) of 26 were free from arrhythmia and off antiarrhythmic drugs. Freedom from AF in these 26 patients was seen in 20 (77%) of 26 patients, with 14 (54%) of 26 free from AF and off antiarrhythmic drugs.

Regarding outcomes in all of those undergoing repeat ablation (AF and AT), of the 36 patients who completed follow-up, 20 (56%) remained free from AF and atrial arrhythmia, of whom 18 (50%) were off antiarrhythmic drugs. Freedom from AF was achieved in 27 (75%), and 21 (58%) of these patients remained off antiarrhythmic drugs. A total of 16 (44%) had documented atrial arrhythmia recurrence within the 12 months of follow-up. Of these patients, 9 (25%) had documented AF, 6 (17%) had AT, and 1 (3%) had documented typical RA flutter.

Regarding outcomes viewed from the outset for this 2-procedure approach, of the 100 patients who underwent cryoaballoon PVI within the PHENOTYPE-AF study, 97 completed follow-up with 52 (54%) remaining free from arrhythmia and off antiarrhythmic medications at 12 months. A total of 45 (46%) patients had arrhythmia recurrence, and 37 (38%) patients underwent repeat ablation in the current study.

Of the 96 patients who completed follow-up, a combined 72 (75%) of patients were free from atrial arrhythmia, with 70 (73%) free from atrial arrhythmia and off antiarrhythmics at 1 year following their last procedure. Freedom from AF was achieved in 89 (93%), and 69 (72%) were free from AF and off antiarrhythmic drugs.

Discussion

Main findings

This study evaluates ECGI-guided ablation in patients who have failed a PVI-alone strategy at an index procedure. The majority of recurrent arrhythmia following cryoballoon PVI was AF. Only 46% of patients had reconnected PVs. ECGI mapping identified PDs in all patients. Targeting of PDs led to acute termination of AF in 23% of patients, and an ablation response was seen in 77% of patients. At 12 months, 56% of patients remained free from atrial arrhythmia, with 50% free from atrial arrhythmia and off antiarrhythmic drugs. Considering a 2-procedure outcome from the original 100 patients with persistent AF of up to 2 years' duration who underwent cryoballoon PVI in the PHENOTYPE-AF study, this translates to a combined 75% freedom from atrial arrhythmia and 70% free from atrial arrhythmia and off antiarrhythmic drugs at 12 months.

Clinical outcomes

A majority of clinical studies trialing new techniques and technologies have targeted patients with AF undergoing their first procedure.[6,9,13–15] While this is the cleanest cohort to allow interpretation of results, it is arguable that such technologies are most likely to be used predominantly in patients who have failed a PVI procedure, given that this is the industry standard for first procedures currently.[6,9,13–15] This is the first study to report on the use of ECGI-guided ablation in this cohort, and indeed it is the first report of any driver-guided ablation specifically in this cohort.

In total, using this workflow of repeat PVI in which required followed by targeting of drivers guided by ECGI mapping, 56% remained free from atrial arrhythmia (50% off antiarrhythmic drugs). There are few data reporting outcomes for patients with persistent AF of <2 years' duration undergoing repeat ablation after failing a PVI procedure, despite this being a very important cohort clinically. Considering that less than half of patients had PV reconnection, this success rate seems reasonable and suggests a meaningful impact. In the current study, the freedom from AF (ie, allowing for AT) at 1 year off antiarrhythmic drugs was 75% (58% free from AF and off antiarrhythmic drugs), which is comparable to that reported in the Bordeaux experience (80%) and multicentre evaluation of non-invasive biatrial mapping for persistent atrial fibrillation ablation: the AFACART study (77%), albeit with the use of antiarrhythmic drugs accepted in these other studies.[1,3] AT occurrence during follow-up in this study was therefore lower than that reported in the AFACART study (24% vs 38%).[3] Extensive atrial ablation may predispose to re-entry formation, and the greater ablation duration in the AFACART study compared with that in this study may explain the lower rate of AT recurrence during follow-up seen in this study, despite it being a second procedure.

These clinical success rates are fractionally lower than those reported for first-time persistent AF ablation procedures by the Bordeaux group (64%) and by our group in the noninvasive electrocardiographic imaging-guided targeting of drivers of persistent atrial fibrillation: the TARGET-AF1 trial (65%), perhaps reflecting the more resistant cohort.[9,16] However, the results were considerably better than the multicenter experience reported in the AFACART study (34%). There were 2 important differences tested in the current study (TARGET AF2 study) and the TARGET AF1 study. First, PVI was performed first in this study, and ECGI-guided ablation was performed only in those who remained in AF. Second, ECGI mapping was used not just to guide the operator in an attempt to ablate to sinus rhythm, which might be impacted by other information from intracardiac electrograms and operator experience, and ablation was targeted specifically as dictated by the finding of drivers on the CardioInsight system regardless of operator opinion or findings on endocardial signals.

Outcome with a 2-stage strategy

By following an original cohort with persistent AF undergoing cryoballoon PVI in the PHENOTYPE-AF study

and recruiting those with recurrent AF into this study with formal follow-up, it has also been possible to examine the outcome with a 2-stage strategy. Of the original cohort, 75% of patients remained free from atrial arrhythmia for 1 year after their last procedure (70% free from atrial arrhythmia and off antiarrhythmic drugs). This is arguably an encouraging result for a relatively conservative strategy in persistent AF that ought to be highly reproducible. It is a higher success rate than reported in the previous studies with a more aggressive strategy of PVI and driver ablation at a single procedure (accepting that more of those patients may have been successfully treated at a second procedure). It is difficult to compare this systematic data for a specific cohort with the literature, but it is perhaps in line with registry data from leading centers reporting outcomes after repeated ablations for persistent AF.[17]

Response to ablation

Although the majority of patients in this study (77%) responded to ECGI-guided PD ablation, AF terminated in a minority (23%). This is considerably lower than was achieved at a first procedure in the TARGET AF1 study published by our group (91% and 41%) or in the AFACART study (94% and 80%). It remains unclear why there is such a discrepancy seen in terms of AF termination rates. In the AFACART study, the average total driver ablation duration was 46 minutes compared with only 10 minutes of driver ablation in the TARGET AF1 study and 15.5 ± 6.9 minutes in the current study. Furthermore, in the AFACART study, driver ablation was performed pre-PVI compared with post-PVI in the TARGET AF1 study and the current study, which may have organized AF. Ablation was also heavily protocolized in the TARGET AF1 study and the current study, ablating in clusters only where PDs were demonstrated on ECGI maps and then stopping, in a manner perhaps more conservative than the AFACART study. The lower proportion of patients responding to ablation and achieving termination of AF compared with the TARGET AF1 study would be compatible with this cohort being more resistant to treatment.

Although previous studies have reported the proportion of patients responding to ablation guided by ECGI mapping,[1,3] this study also reported the response to ablation on a per-driver basis as in the TARGET AF1 study. In contrast to previous studies using different AF mapping technologies, a lower proportion of localized drivers identified on ECGI maps were associated with an ablation response or AF termination.[2,6,7,18] This may owe to the technical challenges of noninvasive mapping. A lower recurrence rate and temporal stability of PD was observed in the current study compared with the TARGET AF1 study. This may relate to more atrial scarring in this population resistant to PVI and presumably to more advanced disease, making PDs more difficult to map. This may also explain the lower proportion of PDs responding to ablation in the present cohort compared with that in the TARGET AF1 study.

Analysis of the distribution of the number of rotation driver recurrences and number of cycles of rotational PDs were found to be skewed and this is in keeping with similar studies evaluating rotational activation in persistent AF. This supports the suggestion that the mechanisms that maintain persistent AF are intermittent and recurrent.

Limitations

It is recognized that patient numbers are small, and this would be regarded as a pilot study for outcome data. However, the patient numbers are comparable to those of other proof-of-concept studies evaluating novel methods and technologies.[4–6,19]

To determine the mechanistic significance of PDs, we necessarily focused on electrophysiological endpoints because there is arguably no other way to verify that a driver has been ablated. Although termination of AF is clear, the importance of CL prolongation is less certain. Others have used termination of AF or CL prolongation as a surrogate for the interruption of mechanisms important for the maintenance of AF.[2,5,6,11,12]

In this study, CL prolongation was measured solely from the LAA. It is recognized that ablation in the RA may have impacted local CL in the RA, which may have been underrepresented or missed by measuring CL only in the LAA.

The underlying mechanisms of AF remains unclear. Although mapping PDs using the ECGI system focuses on focal and rotational activations, there have been multiple studies using alternative mapping strategies that have all had slightly different findings or indeed not confirmed the presence of these phenomena at all. Alternative hypotheses to explain the mechanisms of AF have included the wandering wavelet hypothesis, fixed or transient re-entry in areas of scar, or dissociation between endocardial and epicardial layers allowing endocardial-epicardial circuits to form.

In order to evaluate the impact of abolition of PDs, we delivered ablation lesion lesions in clusters. Where we identified a potential narrow isthmus, we went on to deliver an linear ablation lesion. By delivering lesions in clusters, we accept that we may delivered lesions that may have been proarrhythmogenic.

Conclusion

ECGI mapping was used to map and ablate localized drivers in patients with recurrent persistent AF despite a PVI strategy at an index procedure. An ablation response occurred in most patients, although AF terminated in a minority. Repeat PVI followed by ECGI-guided localized driver ablation was associated with a reasonable rate of freedom from AF at 1-year follow-up. A staged approach of cryoballoon PVI for persistent AF followed by ECGI-guided driver ablation for those with recurrent AF produced a good success rate. Further study of ECGI-guided ablation is needed to define its place in the ablation of AF.

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Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: All participants provided written informed consent.

Ethics Statement: The study was approved by the national ethics committee and was prospectively registered on ClinicalTrials.gov (NCT03394404). The research in this study was conducted according to the Helsinki Declaration guidelines on human research.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2023.08.004.

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