Focal source and trigger mapping in atrial fibrillation: Randomized controlled trial evaluating a novel adjunctive ablation strategy

Vijay S. Chauhan, MD,* Atul Verma, MD,† Sachin Nayyar, MD, PhD,* Nicholas Timmerman, MD,* George Tomlinson, PhD,* Andreu Porta-Sanchez, MD, MSc,* Sigfus Gizurarson, MD, PhD,* Shouvik Haldar, MD (Res), MRCP,* Adrian Suszko, MSc,* Don Ragot, MSc,* Andrew C.T. Ha, MD*

*From the *Peter Munk Cardiac Centre, Division of Cardiology, University Health Network, Toronto, Canada, and †Southlake Regional Health Center, Newmarket, Canada.*

BACKGROUND Intraoperative mapping has demonstrated focal activations during human atrial fibrillation (AF). These putative AF sources can manifest sustained periodic bipolar and unipolar QS electrograms (EGMs). We have automated the detection of these EGM features using our validated Focal Source and Trigger (FaST) computational algorithm.

OBJECTIVE The purpose of this study was to conduct a randomized controlled pilot evaluating the feasibility and efficacy of FaST mapping/ablation as an adjunct to pulmonary vein isolation (PVI) in reducing AF recurrence.

METHODS We randomized 80 patients with high-burden paroxysmal or persistent AF (age 61 ± 10 years; 75% male) to PVI alone (n = 41) or PVI+FaST mapping/ablation (n = 39). The primary endpoint was time to AF recurrence >30 seconds between 3 and 12 months after 1 procedure.

RESULTS FaST sites were identified in all but 1 patient and were localized to pulmonary vein (PV) (2.1 ± 1.1 per patient) and extra-PV regions (2.8 ± 1.4 per patient). FaST mapping and ablation times were 27 ± 9 minutes and 8.5 ± 5 minutes, respectively. Patients with AF termination during ablation had greater AF cycle length prolongation with PVI+FaST than PVI (Δ20 ± 14 ms vs Δ5 ± 17 ms; $P = .046$). Freedom from AF recurrence at 12 months was higher in PVI+FaST vs PVI for patients off antiarrhythmic drugs (74% vs 51%; hazard ratio 0.48; 95% confidence interval 0.21–1.08; $P = .064$) but did not quite reach statistical significance. Major adverse events were similar between the 2 groups.

CONCLUSION In this randomized controlled pilot, real-time FaST mapping provided an intuitive, automated approach for localizing focal AF sources. FaST ablation as an adjunct to PVI may reduce AF recurrence, which requires verification with a larger multicenter trial.

KEYWORDS Atrial fibrillation; Catheter ablation; Focal sources; Pulmonary veins; Signal processing

(Heart Rhythm 2020;■:1–9)

Introduction

Focal sources have been shown to drive atrial fibrillation (AF) in animals with structurally normal atria,[1] but their role in sustaining human AF is less clear. Targeting focal AF sources may improve AF ablation outcomes. However, their identification remains challenging because of nonstationary, complex AF signal features and the low spatiotemporal resolution of catheter-based mapping approaches,[2] which has yielded inconsistent findings using a variety of analytical techniques. In contrast to catheter-based mapping, Lee et al[3] performed high-resolution, intraoperative biatrial activation mapping and demonstrated focal activations during human AF. At their epicenter, bipolar electrograms (EGMs) appeared periodic and manifested a unipolar QS EGM morphology.[3] Using retrospective analysis of similar EGM features, we reported focal activations in patients with high-burden paroxysmal/persistent

This work was supported by an operating grant from MaRS Innovation, Biosense Webster Inc, Peter Munk Cardiac Center Innovation Fund, and the Pennycook Arrhythmia Research Fund to Dr Chauhan. Dr Chauhan is a Career Scholar of the Heart and Stroke Foundation of Ontario (MC 7577). Dr Andreu Porta-Sanchez was supported by the Miriam Burnett Fellowship and la Caixa Banking Foundation grant. Dr Nayyar was supported by a fellowship award from the Lewar-Heart and Stroke Foundation of Canada. Drs Chauhan and Gizurarson are authors of FaST intellectual property (US 10,111,598 B2) owned by University Health Network, Toronto, Canada. The study sponsors were not responsible for the FaST algorithm development, trial design/conduct, data collection/analysis or manuscript preparation. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Clinicaltrials.gov Identifier: NCT02271152. **Address reprint requests and correspondence:** Dr Vijay S. Chauhan, Gerrard Wing, 3-522, Toronto General Hospital, University Health Network, 150 Gerrard St W, Toronto, ON M5G 2C4 Canada. E-mail address: vijay.chauhan@uhn.ca.

1547-5271/$-see front matter https://doi.org/10.1016/j.hrthm.2019.12.011

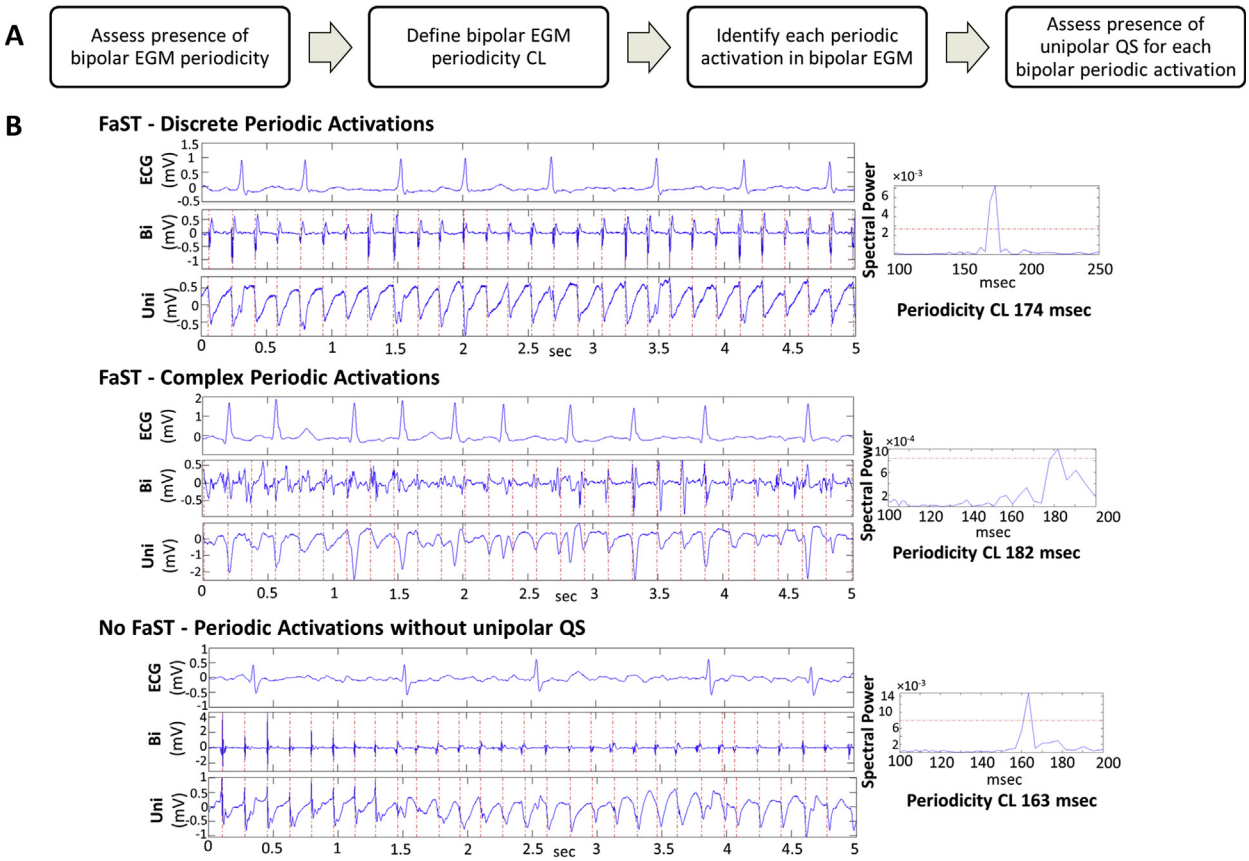

Figure 1 **A:** Outline of FaST hierarchical analysis. **B:** Example of FaST with discrete periodic bipolar EGMs **(top)** and complex periodic bipolar EGMs **(middle).** Example of no FaST where near-periodic activations are not associated with sustained unipolar QS **(bottom).** The periodicity CL is indicated to the right of each example, which is based on the spectral peak above threshold *(red line).* Bi = bipolar electrogram; CL = cycle length; ECG = electrocardiogram; EGM = electrogram; FaST = Focal Source and Trigger; Uni = unipolar electrogram.

AF undergoing pulmonary vein isolation (PVI) ablation.[4,5] When these focal activations were present exclusively in the pulmonary veins (PVs), patients had reduced AF recurrence after PVI compared to those with extra-PV focal activations.[4,5]

Further to this report, we have developed a real-time computational algorithm, referred to as Focal Source and Trigger (FaST) mapping, which automatically evaluates the presence of sustained bipolar EGM periodicity and unipolar QS morphology in periodic activations. We hypothesized that catheter ablation of FaST sites would decrease the number of focal sources and triggers potentially sustaining and initiating AF, thereby together reducing AF recurrence. Our objective was to evaluate the feasibility of real-time FaST mapping using long-duration EGM recordings to define FaST sites and their spatiotemporal stability. We also sought to determine the efficacy of FaST site ablation, as an adjunct to PVI, in reducing AF recurrence among patients with high-burden paroxysmal/persistent AF, in whom both AF sources and triggers may be arrhythmogenic.

Methods

Study design and population

In this single-center, randomized controlled pilot trial, consecutive patients were randomized in a 1:1 single-blinded fashion to either PVI alone, or PVI and FaST ablation (PVI+FaST). Patients were included if they were undergoing first-time ablation for high-burden paroxysmal AF (ie, >4 self-terminating episodes of AF within the last 6 months with 2 episodes lasting >6 hours within the last year)[6] or persistent AF (ie, lasting >7 days and still responsive to cardioversion), and had failure of, or intolerance to, ≥1 antiarrhythmic drug, including β-blockers. Major exclusion criteria were long-standing persistent AF and left atrial (LA) diameter >55 mm. All patients provided written informed consent, and the study was approved by the research ethics board of University Health Network.

FaST mapping

Preprocedural details are provided in the Supplemental Methods. In both patient arms, FaST mapping was performed during either spontaneous or induced AF using burst atrial pacing at a cycle length (CL) of 200–300 ms and Isuprel 0.5–3 μg/min, as needed. After 5 minutes of sustained AF, the LA was mapped using a roving 20-pole, variable curve, circular catheter (LassoNav, Biosense Webster Inc, Diamond Bar, CA). Adequate catheter–tissue contact was ensured using firm contact force and cardiac computed tomographic imaging of the LA. After catheter stability was achieved, 10 bipolar (bandwidth 30–400 Hz) and 20-unipolar (bandwidth 0.05–400 Hz) EGMs

Table 1 Patient demographics

	All patients (N = 80)	PVI (n = 41)	PVI+FaST (n = 39)
Age (y)	61 ± 10	62 ± 9	60 ± 10
Male	60 (75)	32 (78)	28 (72)
BMI (kg/m^2)	29.4 ± 5.2	29.6 ± 4.4	29.2 ± 6.0
LVEF (%)	59 ± 8	58 ± 8	59 ± 8
LA dimensions			
LA diameter (mm)	42 ± 7	41 ± 7	42 ± 7
LA volume (mL)	90 ± 34	89 ± 38	90 ± 30
LA volume index (mL/m^2)	43 ± 16	43 ± 17	44 ± 14
AF characteristics			
High-burden paroxysmal	42 (52)	21 (51)	21 (54)
Persistent	38 (48)	20 (49)	18 (46)
Duration of AF (y)	5.6 ± 5.0	4.8 ± 5.0	6.6 ± 5.0
LA appendage CL (ms)	188 ± 29	186 ± 29	189 ± 30
Comorbidities			
Diabetes	4 (5)	2 (5)	2 (5)
Hypertension	38 (47)	23 (56)	15 (38)
Sleep apnea	26 (32)	14 (34)	12 (31)
Obesity (BMI >30 kg/m^2)	30 (37)	13 (32)	17 (44)
Coronary artery disease	2 (2)	1 (2)	1 (3)
Cerebrovascular accident	2 (2)	0	2 (5)
Hyperlipidemia	8 (10)	2 (5)	6 (15)
Valvular heart disease	6 (7)	3 (7)	3 (8)
Thyroid dysfunction	3 (4)	1 (2)	2 (5)
Renal dysfunction (eGFR <50 mL/min/1.72 m^2)	0	0	0
Current antiarrhythmic drugs			
Flecainide or propafenone	29 (36)	16 (39)	13 (33)
Sotalol	6 (8)	5 (12)	1 (3)
Amiodarone	23 (29)	8 (20)	15 (38)
β-blocker	38 (48)	16 (39)	22 (56)
Calcium channel blocker	15 (19)	9 (22)	6 (15)
No. of failed AADs	1.7 ± 0.9	1.7 ± 1.0	1.6 ± 0.9

Values are given as mean ± SD or n (%).

AAD = antiarrhythmic drug; AF = atrial fibrillation; BMI = body mass index; CL = cycle length; eGFR = estimated glomerular filtration rate; FaST = Focal Source and Trigger; LA = left atrium; LVEF = left ventricular ejection fraction; PVI = pulmonary vein isolation.

were simultaneously acquired for 5 seconds at a sampling rate of 1000 Hz. The unipolar EGMs were referenced to a quadripolar catheter in the inferior vena cava. EGMs were streamed to a proprietary computer workstation for real-time FaST analysis. After mapping, the anatomic coordinates of each electrode were exported from the electroanatomic workstation (CARTO3, Biosense Webster Inc) and paired with FaST analysis to provide the location of FaST sites in the LA. AF CL in the LA appendage and coronary sinus (CS) was evaluated from the average CL of 10 consecutive bipolar EGM recordings.

Real-time FaST analysis

Using custom software written in MATLAB (MathWorks, Natick, MA), FaST analysis was performed as previously described[4,5,7] and is outlined in Figure 1A. In brief, the algorithm uses a hierarchical analysis of bipolar and unipolar EGMs to identify periodic focal activations. First, bipolar EGMs with periodicity are identified using fast Fourier transformation–based spectral analysis of each preprocessed 5-second signal and the presence of a spectral peak >10% of the total spectral power. Second, the dominant periodicity CL in the range from 100 to 250 ms is determined from this spectral peak. All individual activations during the 5-second bipolar EGM recording that have the same dominant periodicity CL are then annotated using a proprietary graph-search function.[7] Third, the periodic annotations on the bipolar EGM are transposed to the corresponding unipolar EGM to define unipolar onset, thereby allowing unipolar morphology features to be assessed semi-quantitatively. A FaST site was defined as a unipolar QS or R/S ratio <0.1 for >90% of the periodic activations in the 5-second window. Figure 1B illustrates examples of FaST sites with varying bipolar EGM complexity. FaST sites located >5 mm from the LA anatomic shell were excluded to minimize far-field signal. FaST sites were classified as either PV ostial/antral or extra-PV, and they were grouped as one if within 7 mm of each other.[4] Long-duration FaST sites were defined as ≥3 FaST sites acquired from separate circular catheter recordings that were within 7 mm of each other (ie, cumulative duration ≥15 seconds).

PVI and FaST ablation

In all patients, catheter ablation was performed after FaST mapping using a saline-irrigated contact force-sensing catheter (Smart-Touch SF, Biosense Webster), as detailed in the Supplemental Methods. In a random sample of 5

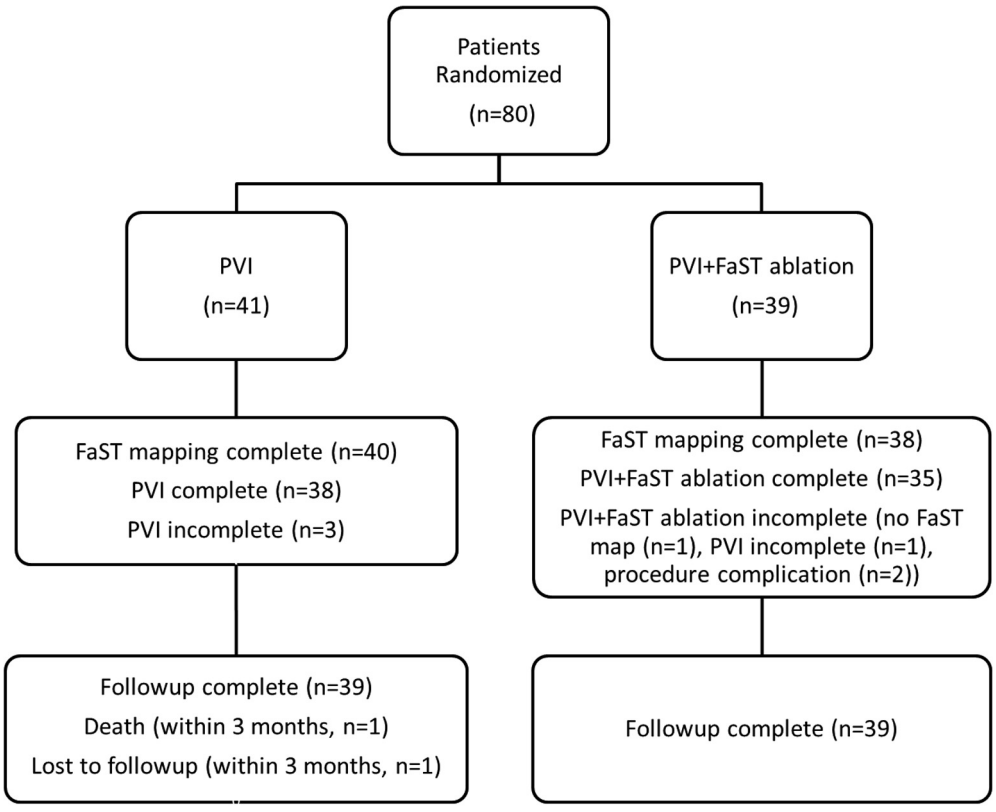

Figure 2 Enrollment and randomization flowchart of study patients. FaST = Focal Source and Trigger; PVI = pulmonary vein isolation.

PVI+FaST patients who remained in AF after ablation was completed, FaST remapping was performed in the LA during AF before electrical cardioversion to determine whether any FAST sites remained or new FaST sites developed.

Postablation care and follow-up

After ablation, antiarrhythmic drugs were resumed for 3 months and then discontinued. Oral anticoagulation therapy was also resumed for 3 months and then continued further in patients with CHA_2DS_2 score $\geq$1. Patients were followed prospectively for 12 months, and AF recurrence was assessed from 48-hour Holter and ECG recordings every 3 months, or sooner if patients experienced symptoms suggesting arrhythmia recurrence. Repeat PVI ablation was performed after 3 months for AF recurrence at the discretion of the physician. The primary endpoint was time to AF recurrence >30 seconds on and off antiarrhythmic drugs between 3- and 12-month follow-up after 1 procedure. The secondary endpoint also included time to atrial tachycardia or flutter >30 seconds. All atrial arrhythmia episodes were adjudicated blinded to the study assignment.

Statistical analysis

Continuous variables are reported as mean ± SD unless otherwise stated. Continuous variables were compared between groups using the Student *t* test or Mann-Whitney U test where appropriate. Categorical variables were compared using the Fisher exact test. Correlation was assessed using the Pearson correlation coefficient. Time-to-event outcomes were displayed by the Kaplan–Meier method, and the rates of AF recurrence starting 3 months after the intervention were compared between PVI+FaST and PVI using Cox proportional hazards models with censoring at 12 months from the time of the procedure. The sample size calculation is provided in the Supplemental Methods. All analyses were intention to treat, and a 2-tailed $P < .05$ was considered significant. Statistical analysis was performed using SPSS Version 20 (IBM, Armonk, NY).

Results

Patient characteristics

Table 1 summarizes the patient characteristics for the 80 patients randomized to PVI (n = 41) or PVI+FaST (n = 39) who were enrolled between July 2015 and December 2017. Mean LA volume index was 43 ± 16 mL/m^2, and 48% of patients had persistent AF. Randomization resulted in good balance in baseline characteristics between PVI and PVI+FaST. Figure 2 outlines the patient flow through the study.

FaST characteristics

FaST mapping was completed during AF in 78 patients (98%), and the LA maps included 340 ± 60 points per patient after exclusion of points >5 mm from the endocardial surface. FaST mapping was performed during spontaneous AF in 36 patients (45%), while the remaining had induced

Table 2 Characteristics of FaST sites

	All patients (N = 78)	PVI (n = 40)	PVI+FaST (n = 38)	*P* value
Patients with FaST mapping				
Spontaneous AF	36 (46)	21 (53)	15 (39)	.266
Induced AF	42 (54)	19 (47)	23 (61)	
Isuprel for AF induction	16 (21)	7 (18)	9 (24)	.580
Isuprel dose (μg/min)	1.1 ± 0.7	1.3 ± 0.8	0.9 ± 0.5	.384
No. of LA mapping points	340 ± 60	347 ± 69	330 ± 53	.231
No. of periodic points	162 ± 61	169 ± 62	158 ± 59	.337
Patients with ≥1 FaST site				
Any sites	77 (99)	40 (100)	37 (97)	.487
PV	71 (91)	36 (90)	35 (92)	1
Extra-PV	73 (94)	38 (95)	35 (92)	.671
FaST sites per patient				
All sites	4.9 ± 1.9	4.9 ± 1.7	4.8 ± 2.0	.800
PV	2.1 ± 1.1	2.2 ± 1.2	2.1 ± 1.1	.638
Extra-PV	2.8 ± 1.4	2.8 ± 1.4	2.8 ± 1.5	.968
Long-duration FaST sites per patient				
PV	0.9 ± 1.0	0.9 ± 0.9	1.0 ± 1.1	.446
Extra-PV	1.2 ± 0.9	1.1 ± 0.7	1.2 ± 1.0	.672

Values are given as n (%) or mean ± SD unless otherwise indicated.
PV = pulmonary vein; other abbreviations as in Table 1.

AF (Table 2). FaST mapping times were similar between PVI+FaST and PVI (26.8 ± 9.5 minutes vs 24.8 ± 5.4 minutes; $P = .26$).

All but 1 patient manifested at least 1 FaST site in the LA. The number of patients with FaST sites in the PV and extra-PV regions was 71 (91%) and 73 (94%), respectively. The number of FaST sites in the PV and extra-PV regions was 2.1 ± 1.1 and 2.8 ± 1.4 per patient, respectively, whereas the number of long-duration FaST sites in the PV and extra-PV regions was lower at 0.9 ± 1.0 and 1.2 ± 0.9, respectively (Table 2). PV and extra-PV FaST sites are illustrated for 2 patients in Figures 3 and 4, respectively. The location of FaST sites and their periodicity CL are shown in Supplemental Table S1. The left-sided PV FaST sites had the shortest periodicity CL in the LA at 160 ± 20 ms. The most common extra-PV FaST site was located at the LA appendage base (75%), where the periodicity CL was 175 ± 28 ms. The periodicity CL of extra-PV FaST sites ranged from 165 ± 23 ms on the anterior wall to 181 ± 30 ms on the inferior wall. LA mapping and FaST site characteristics were similar in PVI and PVI+FaST (Table 2).

Ablation characteristics and AF termination

PVI was performed in all 80 patients, but 3 PVI and 3 PVI+FaST patients had incomplete PVI. PVI ablation time was similar between PVI+FaST and PVI (63 ± 18 minutes vs 69 ± 23 minutes; $P = .22$). During PVI in all patients, AF terminated to sinus rhythm in 22 patients (28%), and the conversion rate was similar between PVI alone and the PVI portion of PVI+FaST (29% vs 26%; $P = .804$). Patients with FaST mapping (n =78) and AF termination (n = 22) after PVI or the PVI portion of PVI+FaST ablation had a similar number of PV FaST sites as those without AF termination (2.2 ± 1.1 vs 2.1 ± 1.2; $P = .744$). However, the number of extra-PV FaST sites was fewer in these patients with AF termination post PVI compared to those without (2.2 ± 1.3 vs 3.0 ± 1.4; $P = .034$), suggesting that AF maintenance after PVI may be dependent on a greater number of extra-PV FaST sites. Supplemental Figure S1 illustrates 1 patient with a FaST site deep in the right inferior PV. Upon completion of right PVI, the AF terminated to sinus rhythm, but a regular PV tachycardia continued in the right inferior PV potentially driven by the FaST site.

Among the 39 PVI+FaST patients, extra-PV FaST ablation was incomplete in 3 patients. In the remaining 36 patients, extra-PV FaST ablation covered an area of 8.5 ± 4.8 mm^2 and was performed in 8.5 ± 5.1 minutes. The total procedure time, including mapping and ablation, was longer by an average of 15 minutes for PVI+FaST compared to PVI (282 ± 35 minutes vs 267 ± 39 minutes; $P = .075$). Among the 29 PVI+FaST patients (74%) who remained in AF after PVI was performed, AF terminated to sinus rhythm in 2 patients during extra-PV FaST ablation, 1 at the base of the LA appendage and the other on the anterior wall (Supplemental Figure S2).

Relationship of AF CL, FaST periodicity CL, and AF termination with ablation

In order to characterize the acute effect of FaST ablation, AF CL was measured from the CS preablation and postablation before the last radiofrequency application that terminated AF. Preablation, there was no difference in AF CL between PVI vs PVI+FaST (192 ± 28 ms vs 203 ± 40 ms; $P = .240$). Among patients with AF termination during ablation, AF CL prolonged in both PVI (216 ± 28 ms) and PVI+FaST (235 ± 55 ms), but the prolongation was greater in PVI+FaST than PVI (20 ± 14 ms vs 5 ± 17 ms; $P = .0461$) (Figure 5). Among patients without AF termination during ablation, AF CL did not change in both PVI (190 ± 28 ms) and PVI+FaST (203 ± 38 ms). Furthermore, the change in AF CL was similar between PVI and PVI+FaST (8 ± 16 vs 8 ± 18 ms: $P = .739$) (Figure 5). Further analysis of AF CL and FaST periodicity CL among patients with and without AF termination during ablation is provided in the Supplemental Results.

FaST remapping

In a subset of 5 PVI+FaST patients who remained in AF after isolation of all PVs and completion of extra-PV FaST ablation, FaST remapping during AF was performed. Details are provided in the Supplemental Results and Supplemental Figures S3 and S4.

Arrhythmic outcomes

One-year prospective follow-up was completed in 78 patients (98%). At this time, 90% of PVI patients and 88% of

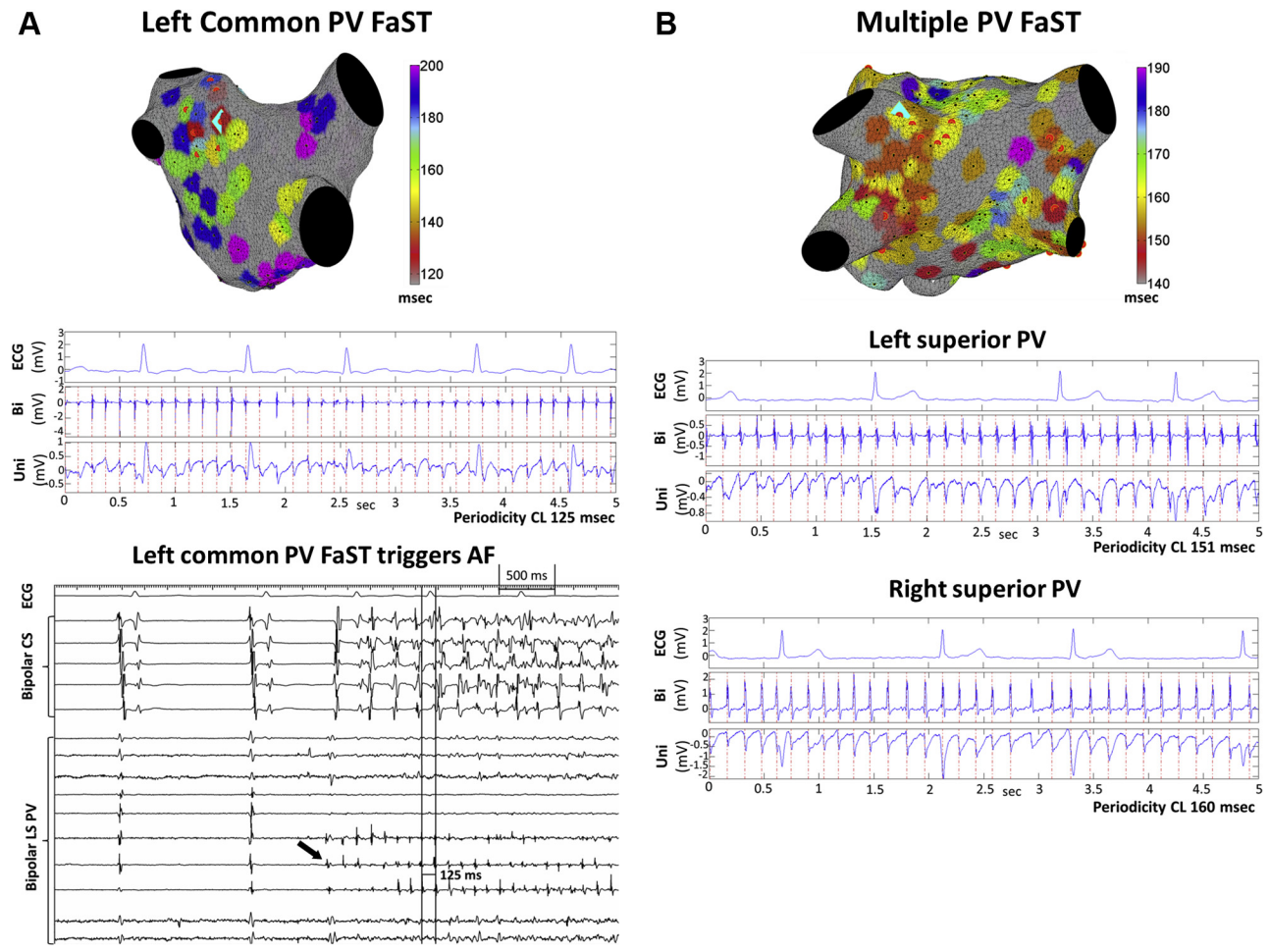

Figure 3 PV FaST sites in 2 patients. **Top:** LA periodicity CL maps. *Red tags* indicate FaST sites. *Blue tag* highlights the FaST site with EGMs shown in the panel below. **A:** FaST mapping during spontaneous AF in a patient with persistent AF revealed a left common PV FaST site (periodicity CL 125 ms) **(top).** A periodicity CL gradient with longer CL is present around the PV FaST site. **Middle:** EGMs of the FaST site. **Bottom:** After FaST mapping but before ablation, the AF spontaneously terminated and then repetitive AF salvos were triggered by premature atrial contractions from the same FaST site *(arrow).* The AF CL of these salvos was 125 ms, similar to the periodicity CL of the FaST site during sustained AF. **B:** FaST mapping during spontaneous AF in patient with persistent AF revealed FaST sites in all 4 PVs with periodicity CLs shorter than the rest of the LA **(top). Middle, bottom:** EGMs of the FaST site in the left superior PV and right superior PV are shown. AF = atrial fibrillation; CS = coronary sinus; LA = left atrium; LS = left superior; PV = pulmonary vein; other abbreviations as in Figure 1.

PVI+FAST patients were off antiarrhythmic drugs. Event-free survival for the primary endpoint after 1 procedure for all patients is shown in Figure 6A and for those off antiarrhythmic drugs in Figure 6B. Freedom from AF recurrence was higher in PVI+FaST vs PVI for all patients (72% vs 51%; hazard ratio [HR] 0.52; 95% confidence interval [CI] 0.25–1.10; $P = .077$) and for those off antiarrhythmic drugs (74% vs 51%; HR 0.48; 95% CI 0.21–1.08; $P = .064$) but did not quite reach statistical significance. Event-free survival for the secondary endpoint after 1 procedure for all patients is shown in Figure 6C and for those off antiarrhythmic drugs in Figure 6D. Freedom from atrial arrhythmia recurrence for all PVI+FaST and PVI patients was 61% and 46%, respectively (HR 0.61; 95% CI 0.32–1.19; $P = .139$), whereas for those off antiarrhythmic drugs it was 65% and 46%, respectively (HR 0.54; 95% CI 0.26–1.11; $P = .086$). During 12-month follow-up, the prevalence of atrial flutter or tachycardia for PVI+FaST and PVI was 10% and 2.4%, respectively ($P = .195$).

Repeat PVI ablation

Repeat PVI ablation was performed in 19 patients (24%) (7 PVI+FaST; 12 PVI) 14.7 ± 6.9 months after the index procedure due to AF recurrence. Electrical reconnection in ≥1 PV was demonstrated in 15 of these patients (79%), and all reconnected PVs manifested FaST sites at the index ablation. Further details are provided in the Supplemental Results and Supplemental Figures S4 and S5.

Adverse events

Major adverse events related to the first ablation procedure occurred in 3 PVI+FaST patients (7.6%) and 1 PVI patient (2.4%) ($P = .353$). There were no complications related to

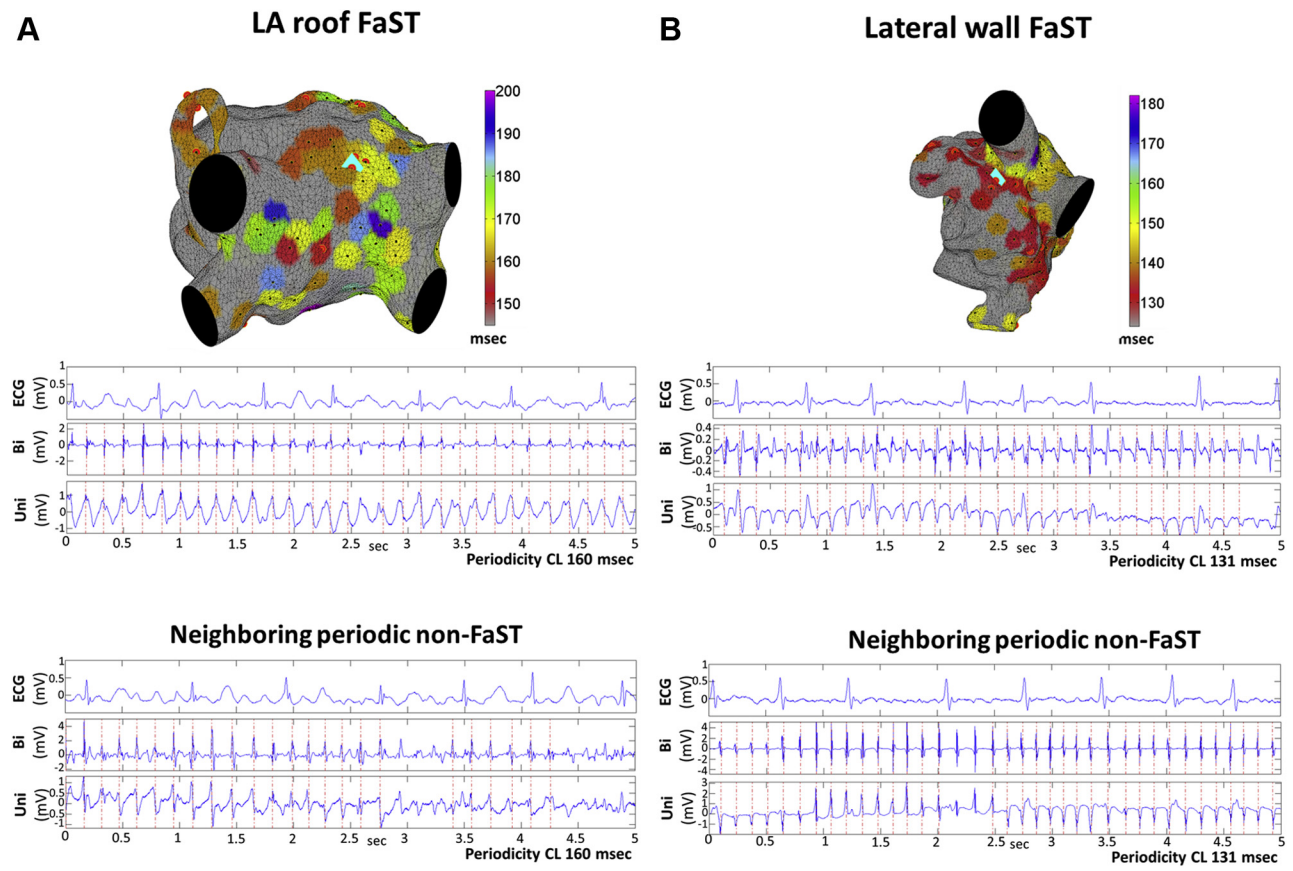

Figure 4 Extra-PV FaST sites in 2 patients. **A:** FaST mapping during spontaneous AF in patient with persistent AF revealed FaST site on the LA roof (periodicity CL 163 ms) **(top). Middle:** EGMs of the FaST site in the LA roof. **Bottom:** The adjacent site is also periodic with similar periodicity CL of 160 ms, but not a FaST site due to nonsustained periodicity and RS unipolar EGMs. **B:** FaST mapping during spontaneous AF in patient with persistent AF revealed FaST site on the LA lateral wall (periodicity CL 131 ms) **(top)**. **Middle:** EGMs of the FaST site on the LA lateral wall. **Bottom:** The adjacent site is also periodic with similar periodicity CL of 131 ms, but not a FaST site due to the transient RS unipolar EGMs. Abbreviations as in Figures 1 and 3.

FaST mapping or extra-PV FaST ablation. Further details are provided in the Supplemental Results.

Discussion

Our FaST computational algorithm represents a novel, hierarchical schema to identify sustained periodic bipolar and unipolar QS EGMs during AF, which are features of putative focal sources. In this randomized controlled pilot, we demonstrated that automated, real-time FaST mapping is feasible and only a few FaST sites are identified, half of which demonstrated spatiotemporal stability. PVI+FaST ablation decreased AF recurrence compared to PVI alone in patients with high-burden paroxysmal/persistent AF, but this did not quite reach statistical significance.

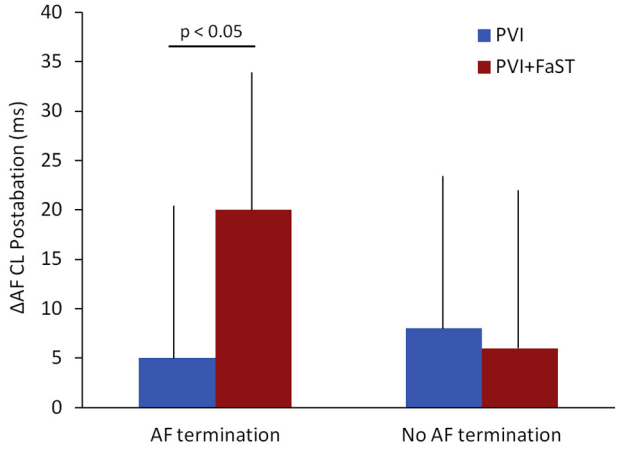

Figure 5 Prolongation in AF CL with PVI vs PVI+FaST in relation to AF termination. AF CL was measured from the coronary sinus preablation and postablation. Abbreviations as in previous figures.

Defining focal sources during AF to improve AF ablation outcomes remains challenging due to complex, nonstationary local EGMs and the low spatiotemporal resolution of clinical mapping.[2] Under these conditions, traditional activation mapping and even phase mapping can be unreliable,[8] which may account for reporting discrepancies. A unique aspect of FaST analysis is the graph search function, which annotates individual periodic, bipolar EGMs once the periodicity CL is known.[7] Based on these annotations, the unipolar morphology can be classified without the need to remove far-field ventricular EGMs. As such, nonperiodic, complex EGMs are excluded from analysis, which improves reliability and allows visual verification.

The majority of patients had at least 1 PV and extra-PV FaST site, and half of these sites demonstrated temporal stability $\geq$15 seconds in spatially conserved regions. FaST

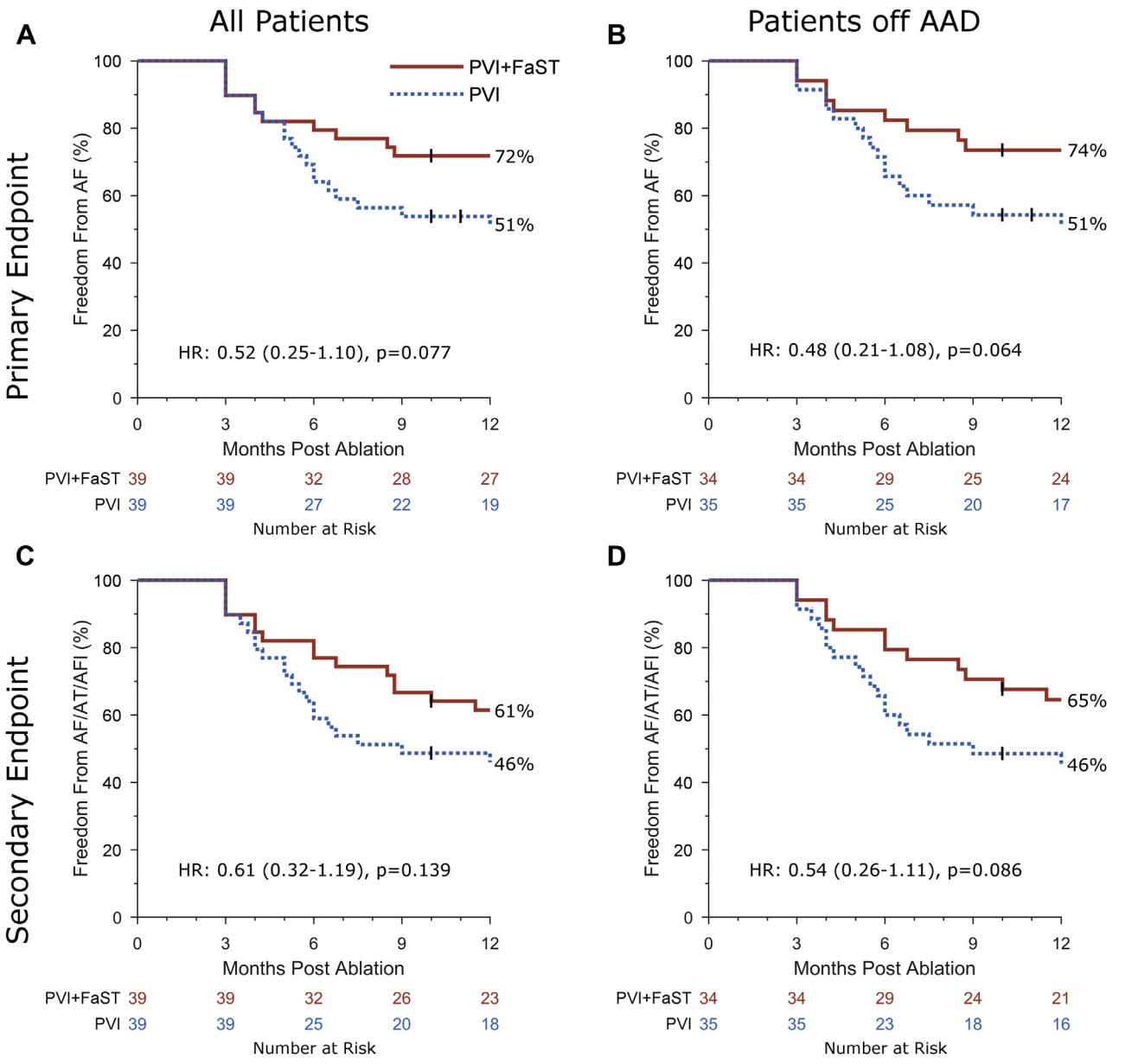

Figure 6 Kaplan–Meier survival curves for the primary endpoint of AF recurrence in all patients (**A**) and those off AADs (**B**). Kaplan–Meier survival curves for secondary endpoint of atrial arrhythmia recurrence in all patients (**C**) and those off AADs (**D**). AAD = antiarrhythmic drug; AFl = atrial flutter; AT = atrial tachycardia; HR = hazard ratio; other abbreviations as in previous figures.

periodicity CL was typically shorter in the PVs than in the extra-PV regions, suggesting that PV focal sources represent a prevalent AF sustaining mechanism. In patients with ≥1 FaST site with different periodicity CL, entrance block around the slower FaST sites may have prevented overdrive (ie, parasystole).

In addition to the aforementioned signal features of FaST sites, their ablation and arrhythmia outcomes provided further support for AF source activity. Foremost, freedom from AF recurrence was trending higher in PVI+FaST compared to PVI alone. Second, among patients with AF recurrence who underwent redo PVI, all patients with PV electrical reconnection harbored PV FaST sites at their index ablation. In those patients with no PV reconnection at redo PVI, unablated or incompletely ablated extra-PV FaST (based on FaST remapping) was associated with AF recurrence. Third, the periodicity CL of FaST sites influenced AF CL and AF termination during ablation. Patients with AF termination had greater AF CL prolongation with PVI+-FaST ablation than PVI alone.[9] Finally, based on the posta-blation FaST remap, PVI+FaST ablation reduced the LA surface area with organized periodic activity and prolonged AF CL, which would be anticipated if our FaST sites were driving AF.

Despite these features of AF source activity, extra-PV FaST ablation did not result in acute AF termination in the majority of patients. However, AF termination after PVI was seen in 25% of all patients, and this was associated

with fewer extra-PV FaST sites. These findings suggest that a critical number of FaST sites may be necessary to sustain AF after PVIs, but why extra-PV FaST ablation did not consistently terminate AF is unclear. A plausible hypothesis is that mechanisms independent of localized, stationary sources, such as epicardial–endocardial asynchrony[10] or meandering rotorlike sources.[11] continue to maintain AF in these patients after extra-PV FaST ablation. Alternatively, extra-PV FaST sites remained in unmapped regions, such as the right atrium or CS.

In addition to AF source activity, some FaST sites behaved as AF triggers. This was evident in a few patients in whom AF was initiated by premature atrial beats that colocalized to FaST sites defined during sustained AF. Thus, FaST ablation may reduce AF recurrence by decreasing the burden of localized impulses that potentially trigger and sustain AF.[12] The mechanistic basis for these impulses is unclear but likely involves a combination of triggered activity and microreentry, which can be spatially conserved in each patient.[13] We speculate that ganglionated plexuses may also give rise to some extra-PV FaST sites, especially those of long duration in proximity to the superior PVs, where these plexuses tend to cluster.[14]

Clinical implications

The success rate of maintaining sinus rhythm after PVI in patients with high-burden paroxysmal/persistent AF remains marginal at ~50%, and a variety of patient-tailored extra-PV AF source ablation strategies have not consistently improved this outcome.[6,15] Our study demonstrated that FaST ablation is a feasible, promising adjunct to PVI to reduce AF recurrence, which requires verification with a larger, multicenter, randomized trial. Real-time FaST mapping identified a select number of extra-PV FaST sites, thereby avoiding prolonged LA ablation (ie, extra-PV FaST ablation time 8.5 ± 5.1 minutes). The majority of patients had PV FaST, and most with redo PVI and PV reconnection had PV FaST sites. These findings highlight the relevance of the PVs in driving AF in our patients and the importance of creating enduring PVI using contemporary ablation strategies.[16] Finally, FaST mapping during AF identified triggers in some patients, which may reduce the need for additional trigger-based mapping in sinus rhythm with pharmacologic and programmed stimulation.[17] Other focal source mapping reports and potential limitations of FaST mapping are review in the Supplemental Discussion and Supplemental Figure S6.

Conclusion

In this randomized controlled pilot, our FaST computational algorithm provided an intuitive, hierarchical approach for identifying PV and extra-PV focal AF sources and triggers. Real-time, automated FaST mapping is feasible, and a limited number of ablation targets are identified. FaST ablation as an adjunct to PVI may reduce AF recurrence in patients with high-burden paroxysmal/persistent AF. These findings support proof of concept for a novel, patient-tailored ablation strategy after PVI and will inform future design of a larger, pivotal, multicenter, randomized trial.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2019.12.011

References

1. Lee S, Sahadevan J, Khrestian CM, Durand DM, Waldo AL. High density mapping of atrial fibrillation during vagal nerve stimulation in the canine heart: restudying the Moe hypothesis. J Cardiovasc Electrophysiol 2013;24:328–335.
2. Roney CH, Cantwell CD, Bayer JD, et al. Spatial resolution requirements for accurate identification of drivers of atrial fibrillation. Circ Arrhythm Electrophysiol 2017;10:e004899.
3. Lee S, Sahadevan J, Khrestian CM, Cakulev I, Markowitz A, Waldo AL. Simultaneous biatrial high-density (510-512 electrodes) epicardial mapping of persistent and long-standing persistent atrial fibrillation in patients: new insights into the mechanism of its maintenance. Circulation 2015;132:2108–2117.
4. Gizurarson S, Dalvi R, Das M, Ha ACT, Suszko A, Chauhan VS. Hierarchical schema for identifying focal electrical sources during human atrial fibrillation: implications for catheter-based atrial substrate ablation. JACC Clin Electrophysiol 2016;2:656–666.
5. Kochhauser S, Verma A, Dalvi R, et al. Spatial relationships of complex fractionated atrial electrograms and continuous electrical activity to focal electrical sources: implications for substrate ablation in human atrial fibrillation. JACC Clin Electrophysiol 2017;3:1220–1228.
6. Verma A, Sanders P, Champagne J, et al. Selective complex fractionated atrial electrograms targeting for atrial fibrillation study (SELECT AF): a multicenter, randomized trial. Circ Arrhythm Electrophysiol 2014;7:55–62.
7. Dalvi R, Suszko A, Chauhan VS. Graph search-based detection of periodic activations in complex periodic signals: application in atrial fibrillation electrograms. IEEE Can Conf Electr Comput Eng 2015;376–381.
8. Child N, Clayton RH, Roney CR, et al. Unraveling the underlying arrhythmia mechanism in persistent atrial fibrillation: results from the STARLIGHT Study. Circ Arrhythm Electrophysiol 2018;11:e005897.
9. Yoshida K, Chugh A, Good E, et al. A critical decrease in dominant frequency and clinical outcome after catheter ablation of persistent atrial fibrillation. Heart Rhythm 2010;7:295–302.
10. de Groot NM, van der Does L, Yaksh A, et al. Direct proof of endo-epicardial asynchrony of the atrial wall during atrial fibrillation in humans. Circ Arrhythm Electrophysiol 2016;9:e003648.
11. Zlochiver S, Yamazaki M, Kalifa J, Berenfeld O. Rotor meandering contributes to irregularity in electrograms during atrial fibrillation. Heart Rhythm 2008;5:846–854.
12. Santangeli P, Zado ES, Hutchinson MD, et al. Prevalence and distribution of focal triggers in persistent and long-standing persistent atrial fibrillation. Heart Rhythm 2016;13:374–382.
13. Schricker AA, Lalani GG, Krummen DE, Rappel WJ, Narayan SM. Human atrial fibrillation initiates via organized rather than disorganized mechanisms. Circ Arrhythm Electrophysiol 2014;7:816–824.
14. Katritsis DG, Pokushalov E, Romanov A, et al. Autonomic denervation added to pulmonary vein isolation for paroxysmal atrial fibrillation: a randomized clinical trial. J Am Coll Cardiol 2013;62:2318–2325.
15. Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med 2015;372:1812–1822.
16. Sandorfi G, Rodriguez-Manero M, Saenen J, et al. Less pulmonary vein reconnection at redo procedures following radiofrequency point-by-point antral pulmonary vein isolation with the use of contemporary catheter ablation technologies. JACC Clin Electrophysiol 2018;4:1556–1565.
17. Dixit S, Marchlinski FE, Lin D, et al. Randomized ablation strategies for the treatment of persistent atrial fibrillation: RASTA study. Circ Arrhythm Electrophysiol 2012;5:287–294.