Recurrent Post-Ablation Paroxysmal Atrial Fibrillation Shares Substrates With Persistent Atrial Fibrillation
An 11-Center Study

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ABSTRACT

OBJECTIVES The purpose of this study was to determine the mechanistic overlap between paroxysmal and persistent forms of atrial fibrillation (AF), focusing on AF sources as a classification approach.

BACKGROUND The role of AF substrates is unclear in patients with paroxysmal AF (PAF) that recurs after pulmonary vein isolation (PVI). We hypothesized that patients with recurrent post-ablation (redo) PAF despite PVI have electrical substrates marked by rotors and focal sources and structural substrates that resemble persistent AF more than patients with (de novo) PAF at first ablation.

METHODS In 175 patients at 11 centers, we compared AF substrates in both atria using 64-pole basket catheters and phase mapping, and indices of anatomical remodeling between patients with de novo or redo PAF and first ablation for persistent AF.

RESULTS Sources were seen in all patients. More patients with de novo PAF (78.0%) had sources near pulmonary veins (PVs) than patients with redo PAF (47.4%; p = 0.005) or persistent AF (46.9%; p = 0.001). The total number of sources per patient (p = 0.444), and number of non-PV sources (p = 0.701) were similar between groups, indicating that redo PAF patients had residual non-PV sources after elimination of PV sources by prior PVI. Structurally, left atrial size did not separate de novo from redo PAF (49.5 ± 9.5 mm vs. 49.0 ± 7.1 mm; p = 0.956) but was larger in patients with persistent AF (55.2 ± 8.4 mm; p = 0.001).

CONCLUSIONS Patients with PAF despite prior PVI show electrical substrates that resemble persistent AF more closely than patients with PAF at first ablation. Notably, these subgroups of PAF are indistinguishable by structural indices. These data motivate studies of trigger versus substrate mechanisms for patients with recurrent PAF after PVI.

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Pulmonary vein isolation (PVI) is central to the ablation of paroxysmal atrial fibrillation (PAF) and persistent atrial fibrillation (AF), yet its results remain suboptimal even in recent clinical trials (1-4). An increasingly recognized fact is that PAF patients may do well after PVI even when the pulmonary veins (PVs) have reconnected (5,6), suggesting that PVI lesion sets interrupt other mechanisms. Indeed, studies suggest that PAF is a heterogeneous population that may overlap with persistent AF (7), which may have substrate mechanisms remote from the PVs. However, these mechanisms are yet unidentified in PAF.

We hypothesized that patients with recurrent PAF after prior PVI are more likely to have substrates remote from the PVs, and more closely resemble patients with persistent AF than patients with PAF at their first PVI procedure. This may follow for several reasons. First, patients with recurrent PAF may have peri-PV mechanisms not eliminated at initial ablation. Second, it may be artificial to “dichotomize” populations with PAF and persistent AF given their overlap in true AF burden (7), left atrial (LA) size, and atrial structural abnormalities (8). Third, recent mapping of PAF shows substrates in the form of rotors and focal sources remote from the PVs where targeted ablation can eliminate AF acutely and long-term in many centers (9-12) with different techniques (13). Moreover, AF sources have now been demonstrated in human optical mapping studies (14) with many similarities to these clinical studies.

We tested our hypothesis by examining electrical substrates of rotors or focal sources, and structural substrates by echocardiography, in patients with PAF at first ablation, recurrent PAF despite prior PVI, and first-time persistent AF ablation in an 11-center prospective observational study.

METHODS

ENROLLMENT AT CONTRIBUTING CENTERS. Between 2012 and 2014, we enrolled 175 patients undergoing AF ablation for routine indications at 11 centers in the United States (Table 1). All studies and data analyses were performed with local institutional review board approval and patients provided written consent for data collection.

PATIENT CLASSIFICATION. We classified the 175 patients prospectively into de novo PAF, redo PAF, and persistent AF groups. PAF was defined as AF that terminates spontaneously or with intervention within 7 days of onset, whereas persistent AF was defined as continuous AF that is sustained >7 days (15). The de novo PAF group consisted of patients presenting for their first catheter ablation of AF (n = 48). Redo

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PAF patients had recurrent PAF despite 1 prior PVI (n = 31) and persistent AF patients were presenting for their first ablation for persistent AF (n = 96). We excluded those presenting for repeat persistent AF ablation.

**Electrophysiological Study.** Patients discontinued antiarrhythmic medications for >5 half-lives except amiodarone, which was stopped as early as possible prior to the procedure. During the procedure, heparin was used to maintain activated clotting time >350 s. A 64-pole basket catheter was advanced to the right atrium (RA), then transseptally to the LA (Figure 1A), with attention paid to basket location to prevent errors such as inadvertent ventricular placement as noted in some recent studies (16). Our practice is to move the basket during successive focal impulse and rotor mapping (FIRM) map epochs to ensure basket coverage of the majority of the atrial surface (Figure 1B). Electrodes were referenced to electroanatomic shells (NavX, St. Jude Medical, St Paul, Minnesota, Minnesota, or Carto, Biosense-Webster, Inc., Diamond Bar, California). In both NavX and Carto shells, distances were estimated based on the fixed distance between electrodes along basket splines, and cartographic rulers on the atrial shell when available.

**FIRM Mapping of AF Substrate.** FIRM maps identify electrical rotors as phase singularities with surrounding disorganization. Rotors were considered AF sources if stable within <1 electrode for multiple recording epochs over 2 min to 5 min. Focal AF sources were defined as origins with centrifugal activation and breakdown into meandering wavelets.

FIRM mapping uses algorithms to map propagation sequences from observed AF activations. For unipolar deflections that are noncomplex, mapping can be straightforward. Figure 2A depicts activation mapping from a basket catheter where points of maximum negative dV/dt (green line) indicate each AF activation cycle. These activations identify a counterclockwise rotational circuit in the inferior LA (shown in iso-chrones in Figure 2B and on electroanatomic map in Figure 2D) where ablation terminated AF to atrial tachycardia (AT) (Figure 2C). Conversely, in cases where multiple AF deflections are seen for any cycle, classical rules often misidentify signals within repolarization which are by definition far-field (17). In such cases, FIRM determines local activation by analyzing variations in signal morphology between each basket electrode and neighboring channels. A sawtooth-shaped wave of normalized amplitude is obtained from action potential duration (18), conduction restitution data (19), and rate adapted to estimate phase to identify rotors. If no signal is detected, that region of the atria remains black on FIRM maps. FIRM-identified rotors show many similarities to micro-re-entrant AF drivers found in optical mapping of AF in human atria (14), with early data showing concordance between FIRM-mapped and optically mapped AF sources in human hearts (20).

**Characterizing Substrate by Functional Mapping.** We described functional substrate in each patient prospectively using the following criteria: source number, the total number of sources reported by FIRM mapping, whether or not ablated; and source location, which was further subcategorized into PV versus non-PV location (those within 1 cm of a PV where considered PV, all others being remote from the PVs) and RA versus LA. These were identified prospectively at each case. Reproducibility of this assignment by individual operators has recently been reported to be good with kappa = 0.89 (21). These data were collected prospectively by each investigator during each case, then collated and retrospectively blinded to patient group.

**Characterizing the Anatomical Substrate.** We measured LA size on 2-dimensional echo, a well-validated index of LA structural remodeling, in all patients pre-ablation. Additional imaging tests such as late-gadolinium enhanced cardiac magnetic resonance (CMR) were not in widespread use at the time of the study.

**FIRM-Guided Ablation.** Ablation commenced with FIRM-guided radiofrequency ablation for AF, using 3.5-mm (Biosense-Webster, Inc.) or 4-mm (St. Jude Medical) tipped irrigated catheters or a non-irrigated catheter (Boston Scientific, Inc., Marlborough, Massachusetts) in some patients with heart failure. Ablation was delivered to the organized domain of rotors (areas of 2 cm² to 3 cm², similar to AF driver areas in human optical mapping) (14). Ablation typically commenced in the RA then proceeded to the LA sites and was repeated to eliminate rotors on remapping (Figure 1A). Rotors and focal sources were not ablated if near sensitive structures such as the phrenic nerve.

**Pulmonary Vein Isolation.** Ablation was performed to isolate left and right PVs in pairs, with verification of PV entrance block using a circular mapping catheter. Ablation was avoided near sensitive structures such as the esophagus or phrenic nerve. The ablation protocol was FIRM first, until no more sources, then PVI. If AF sources (identified prospectively) fell within the operator’s planned PVI lesion set, this sequence could be changed. At redo-ablation, if veins were reconnected they were re-isolated.
FIGURE 1 Technique for FIRM-Guided Ablation

(A) Typical workflow for FIRM mapping, with basket placement by fluoroscopic images. Sequential atrial basket recordings were taken with source elimination prior to PVI. (B) Multiple basket positions used per FIRM-mapping epoch to minimize unmapped atrial regions. Positions 1-2 are in the RA; positions 3-4 are in the LA. AF = atrial fibrillation; AT = atrial tachycardia; FIRM = focal impulse and rotor mapping; LA = left arterial; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; PV = pulmonary vein; PVI = pulmonary vein isolation; RA = right atrium; RSPV = right superior pulmonary vein; SVC = superior vena cava.
STATISTICAL ANALYSIS. Continuous variables with a normal distribution are presented as mean ± SD unless otherwise noted and evaluated with 1-way analysis of variance (ANOVA), Bonferroni and Tukey post hoc tests where indicated. Counts of sources and congestive heart failure, hypertension, age, diabetes, stroke, vascular risk factors, age, sex (CHADS2_VASC) scores are reported with medians and quartiles and compared among groups with Kruskal-Wallis tests. Nominal variables are reported as counts and percentages and evaluated with chi-square tests. Logistic regression was used to evaluate the group difference in the presence of PV sources controlling for site differences. Probabilities below 0.05 were considered significant.

RESULTS

A total of 175 patients were included in the present study; Table 2 summarizes patient characteristics.

NUMBER OF SOURCES. There were 144 total FIRM identified rotors/sources in the de novo PAF group compared to 129 in the redo PAF and 304 in the persistent AF group. This corresponded to roughly equal numbers of sources per patient of 3 (range 2 to 5) in the de novo PAF group, 3 (range 2 to 4) in the redo PAF group, and 3 (range 2 to 4) in the persistent group (p = 0.444). Overall, 91% were rotors and 9% focal sources.

SOURCE LOCATIONS. Only 54.3% of patients had any sources within 1 cm of PVs. The presence of any PV-localized sources differed by group (p = 0.002). More patients with PAF at first ablation (78.0%) showed 1 or more PV sources than patients with redo PAF (47.4%; p = 0.005) and persistent AF (46.9%; p = 0.001). Group difference in the presence of any PV sources remained significant (p = 0.008) in a logistic regression model controlling for study-site differences. When analyzed as a count, the number of PV-localized sources per patient showed a similar pattern of differences (p = 0.002). By contrast, there was no difference among the groups in the number of non-PV sources (p = 0.701).

The distributions of PV and non-PV sources by group are illustrated in Figure 3. In patients with redo PAF, sources near PVs lay near gaps in prior PV isolation lesion sets or just outside prior lesion sets.
such that electrograms were detected to yield sources (e.g., see case in Figure 2). Figure 4 illustrates rotor sites near and remote from PVs with direct termination to sinus rhythm during ablation.

There was a nonsignificant trend towards a difference among the groups in the number of LA sources ($p = 0.070$) with medians of 3 (range 2 to 3) for de novo PAF and 2 (range 1 to 3) for both redo PAF and persistent AF (Figure 5).

**STRUCTURAL REMODELING.** There was a significant difference among groups in LA size ($p < 0.001$). LA size did not separate de novo from redo PAF ($49.5 \pm 9.5$ mm vs. $49.0 \pm 7.1$ mm, respectively; $p = 0.956$) but was significantly larger in patients with persistent AF ($55.2 \pm 8.4$ mm; $p = 0.001$ vs. each using 3-group ANOVA with post hoc pairwise comparisons).

Thus, despite the electrical similarities between redo PAF and persistent AF, they were structurally distinct using traditional indices (Figure 6). The CHADS$_2$VASc score did not differentiate among the 3 groups ($p = 0.681$) with a median of 1 (range 0 to 2) in each group. Likewise, left ventricular ejection fraction did not differentiate among the 3 groups ($p = 0.777$, using 3-group ANOVA with post hoc pairwise comparisons) (Table 2).

**ACUTE IMPACT OF ABLATION.** The acute impact of ablation is summarized in Table 3. Acute termination was seen in 83 patients, of which 41% were to AT and 59% to sinus rhythm directly. Figure 2 shows an example of a phase-identified AF rotor, in which good unipolar signal quality enabled confirmation of FIRM-mapped rotors by showing rotational activation using traditional analysis of minimum $dV/dt$ (green line), in a patient with persistent AF. Targeted ablation of this rotor in the inferior LA (Figure 2D) terminated AF prior to PVI. Figure 4 shows another patient with abrupt

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**TABLE 2 Population Demographics**

<table>
<thead>
<tr>
<th></th>
<th>De Novo Paroxysmal AF</th>
<th>Redo Paroxysmal AF</th>
<th>Persistent AF</th>
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<tbody>
<tr>
<td>(n = 41)</td>
<td>(n = 38)</td>
<td>(n = 96)</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>58.8 ± 12.5$^*$</td>
<td>61.3 ± 9.5</td>
<td>63.5 ± 10.1</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>49.5 ± 9.5</td>
<td>49.0 ± 7.1</td>
<td>56.1 ± 8.0$^*$</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>57.6 ± 9.7</td>
<td>56.9 ± 7.9</td>
<td>56.4 ± 10.3</td>
</tr>
<tr>
<td>CHADS$_2$VASc</td>
<td>1 (0-2)</td>
<td>1 (0-2)</td>
<td>1 (0-2)</td>
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</table>

Values are mean ± SD or n (range). $^*$p < 0.05 vs. persistent AF, $p = 0.001$ using three-group analysis of variance with post hoc pairwise comparisons.

AF = arterial fibrillation; CHADS$_2$VASc = congestive heart failure, hypertension, age, diabetes, stroke, vascular risk factors, age, sex score; LA = left arterial; LVEF = left ventricular ejection fraction.

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**FIGURE 3 Higher Number of PV Sources in De Novo PAF**

(Left) The bar chart shows a higher percentage of patients with PV rotors/sources in de novo PAF compared to redo PAF and persistent AF ($p = 0.002$). Differences in the number of non-PV sources (right) were not significant ($p = 0.701$). PAF = paroxysmal atrial fibrillation; PV = pulmonary vein.
**FIGURE 4** Ablation of AF Sources Adjacent and Remote to PVs Causing Acute Termination to Sinus Rhythm

(A) Antero-posterior bi-atrial NavX map with RA, non-PV, and PV LA sources labelled in a patient at redo ablation for PAF. (B) AF signals on ablation catheter at FIRM-mapped rotor adjacent to prior left superior PVI lesion set, where AF was terminated by FIRM-guided ablation. Black bar represents 1,000 ms. ABL = ablation catheter; other abbreviations as in Figures 1 and 2.

**FIGURE 5** Nonsignificant Differences in RA and LA Sources

There was a trend toward a difference among the groups in the number of LA sources ($p = 0.070$) which was somewhat higher in de novo PAF than in the other groups. There was no group difference in the number of RA sources ($p = 0.541$). Abbreviations as in Figures 1 and 3.
termination to sinus rhythm during ablation of a rotor adjacent to the PVs.

**DISCUSSION**

This study uses mapping of functional AF substrates in patients at 11 U.S. centers to show that patients with PAF despite prior PVI (redo PAF) are more similar electrophysiologically to patients with persistent AF than those with de novo PAF at first ablation. Compared to patients with de novo PAF, those with redo PAF had rotor distributions away from the PVs in the LA and in RA, more like persistent AF. Notably, this electrophysiological difference was not reflected in structural remodeling because patients with de novo and redo PAF had similar LA dimensions that were each lower than in patients with persistent AF. These data suggest the possibility of identifying a priori the 35% to 50% of patients with PAF who may not be arrhythmia-free after a single PVI. Mechanistically, these data motivate studies to examine the role of trigger versus substrate ablation in patients at repeat ablation procedures.

**ROLE OF ROTORS AND FOCAL SOURCES IN HUMAN AF.** Evidence continues to mount that human AF is sustained by localized rotors and focal sources. The characteristics of rotors on FIRM mapping are similar to those from optical mapping in human atria in that they show stable endocardial rotors in ~2-cm² areas where ablation can acutely terminate AF, yet are unstable and transient on the epicardium (14). These data may help reconcile differences between endocardial FIRM mapping and less stable rotors on epicardial electrocardiographic imaging (13). Early data show concordance between concurrent FIRM and optically mapped AF in human hearts (20).

FIRM-guided ablation (FIRM plus PVI) has been reported in many patients with many results in large series consistent with the original CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial (10–12,22). However, not all studies support the rotor mechanism. Some studies suggest that rotors do not exist, but typically used empirical rules with technical errors such as reported cycle lengths of 250 ms to 500 ms in AF (rates 2 to 4 Hz) that are less consistent with AF, and the use of Shannon entropy to unipolar signals although it is likely valid only for bipolar signals (16). The recent OASIS (Outcome of Different Ablation Strategies in Persistent and Long Standing Persistent Atrial Fibrillation) trial initially reported FIRM + PVI success of 52% in 40 patients (23) but has subsequently been retracted due to nonrandomization issues which may impact any comparisons between groups. Even despite this, those authors’ recently reported 20% 1-year success from PV antrum isolation alone in similar persistent AF patients (24) suggests that FIRM substantially improves the results of PV antrum isolation at that center. Direct comparisons of FIRM + PVI to PVI alone (akin to the STAR-AF2 [Substrate and Trigger Ablation for Reduction of Atrial Fibrillation] trial) are warranted and ongoing. Interestingly, other less impressive studies show a substantial acute termination rate of persistent AF to AT (>30%) with FIRM-guided ablation alone (25), supporting the mechanistic presence of sources. Large multicenter randomized trials are ongoing to test these questions.

**TABLE 3** Acute Impact of Ablation

<table>
<thead>
<tr>
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<th>Total Cases With Terminations During Ablation</th>
<th>Cases Terminating to SR</th>
<th>Cases Terminating to AT</th>
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<tbody>
<tr>
<td>De novo PAF (n = 41)</td>
<td>27 (65%)</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Redo PAF (n = 38)</td>
<td>24 (64%)</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Persistent AF (n = 96)</td>
<td>32 (33%)</td>
<td>16</td>
<td>16</td>
</tr>
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</table>

Values are n (%).

AT = atrial tachycardia; PAF = paroxysmal atrial fibrillation; SR = sinus rhythm.

**SHARED AND DISCORDANT MECHANISMS IN PAF AND PERSISTENT AF.** This study defines potential mechanisms that may separate PAF patients with and without AF recurrence after index PVI that may outline a spectrum for AF phenotypes, from de novo PAF to redo PAF then to persistent AF. Of particular
note is the electrical but not anatomical separation of de novo from redo PAF, which shared AF source distributions and characteristics with persistent AF.

Despite effective antral ablation at index ablation of PAF, up to 70% of patients may have reconnection at repeat electrophysiological study 3 months later (6), which could be due to gaps in radiofrequency ablation lines, or incomplete circumferential contact with balloon-based technologies. While PV reconnection may occur in patients with or without clinical AF recurrence, few studies have examined if substrates may differ between such groups. Other candidate differences in substrate between groups include fibrosis and CMR-identified scar that are the subject of intense investigation.

STRUCTURE-FUNCTION DISSOCIATION IN AF PROGRESSION. Structurally, there was no difference in LA size between de novo and redo PAF despite differences in atrial source numbers and atrial distributions. In contrast, persistent AF showed a significantly larger LA size. This structure-function dissociation is supported by recent data with a similar mix of AF phenotypes (26) and lone PAF patients compared to controls (27). Atrial CMR imaging using delayed enhancement CMR also reveals a wide spectrum of fibrotic substrates that do not conform to current classification schemes based on arbitrary time cut-offs. It is hoped such delineation of functional substrates will allow for patient-tailored risk stratification to improve outcomes (28).

FUTURE DIRECTIONS. These data contribute to the discussion on how to improve the results from PV antral isolation. This is timely. Recent trials show that empiric linear ablation or ablation of complex factionated electrogams may not improve the results of PV isolation in persistent AF patients (1,29,30). Success in PAF is limited to ~65% at 1 year and ~50% at 2 years with PVI by cryoballoon or radiofrequency energy using force-sensing catheters (1 or more procedures permitted in blanking period) (31). Although more durable PVI may further enhance outcomes, the present data demonstrate the presence of AF substrates that are often remote from the PVs or empirical line sites—such as in the RA—that could be targeted for ablation. In a retrospective analysis of the CONFIRM trial, the presence of rotors that were not directly or inadvertently targeted by ablation portended a worse arrhythmia-free prognosis (32).

STUDY LIMITATIONS. Ideally, it would have been useful to FIRM map all patients with PAF at first ablation, only perform PVI, and then assess what substrates were present on a repeat ablation. Such a trial is planned. More generally, the current study did not prospectively randomize substrates to ablation or nonablation; however, such a study is also underway. Echocardiographic indices of structure are increasingly being replaced by CMR, which is more widely available now, and neither LA volume data nor computerized tomographic data were universally available from all sites. Echocardiographic data were reported from clinical records at each site, not from a core lab. Further electrophysiological characterization with voltage or fractionation indices would be attenuated by prior ablation in redo PAF, and was not performed.

CONCLUSIONS

Across 11 U.S. centers, we found that PAF patients at repeat ablation are electrically more similar to patients with persistent AF with numerous extra-PV sources than to PAF patients at their first ablation, despite similar LA size. Our findings motivate studies to further define “functional substrates” and motivate trials to test the benefit of substrate ablation repeat PVI in patients at repeat procedures. These findings may also help improve knowledge of AF progression and improve clinical outcomes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This study advances the increasing literature highlighting heterogeneity within patients with PAF, suggesting that those with recurrent AF may overlap with persistent AF patients.

TRANSLATIONAL OUTLOOK: The scientific field continues to find growing evidence of organization within fibrillating atria, with a hierarchy of spatial sites identified by the methods in this study and corroborated by others that may guide ablation to improve outcomes in persistent AF. By showing similarities between patients with PAF who recurred despite prior PVI and those with persistent AF, these data start to define a functional spectrum of AF that may improve the current binary classification of AF based on detected duration. We believe this will allow for more tailored, patient specific therapies to help understand and treat this disease.
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KEY WORDS: atrial ablation, atrial fibrillation, sources