Driver Domains in Persistent Atrial Fibrillation

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Background—Specific noninvasive signal processing was applied to identify drivers in distinct categories of persistent atrial fibrillation (AF).

Methods and Results—In 103 consecutive patients with persistent AF, accurate biatrial geometry relative to an array of 252 body surface electrodes was obtained from a noncontrast computed tomography scan. The reconstructed unipolar AF electrograms acquired at bedside from multiple windows (duration, 9±1 s) were signal processed to identify the drivers (focal or reentrant activity) and their cumulative density map. The driver domains were catheter ablated by using AF termination as the procedural end point in comparison with the stepwise-aborlation control group. The maps showed incessantly changing beat-to-beat wave fronts and varying spatiotemporal behavior of driver activities. Reentries were not sustained (median, 2.6 rotations lasting 449±89 ms), meandered substantially but recurred repetitively in the same region. In total, 4720 drivers were identified in 103 patients: 3802 (80.5%) reentries and 918 (19.5%) focal breakthroughs; most of them colocalized. Of these, 69% reentries and 71% foci were in the left atrium. Driver ablation alone terminated 75% and 15% of persistent and long-lasting AF, respectively. The number of targeted driver regions increased with the duration of continuous AF: 2 in patients presenting in sinus rhythm, 3 in AF lasting 1 to 3 months, 4 in AF lasting 4 to 6 months, and 6 in AF lasting longer. The termination rate sharply declined after 6 months. The mean radiofrequency delivery to AF termination was 28±17 minutes versus 65±33 minutes in the control group (P<0.0001). At 12 months, 85% patients with AF termination were free from AF, similar to the control population (87%); P=not significant.

Conclusions—Persistent AF in early months is maintained predominantly by drivers clustered in a few regions, most of them being unstable reentries. (Circulation. 2014;130:530-538.)

Key Words: atrial fibrillation ■ mapping

Treating atrial fibrillation (AF) through surgical or catheter ablation is based on the elimination of the AF-initiating triggers and the AF-maintaining substrate. In paroxysmal AF, ablation successfully targets triggers that are mainly located in the pulmonary veins (PVs), whereas the results in persistent AF are less satisfactory, presumably because of the influence of wider atrial substrate in its determinism.1-2 Multiple atrial wavelets, macroneurenties, and localized (focal or reentrant) sources have been reported to contribute to the substrate of persistent AF.3-6 For determining a therapeutic strategy in persistent AF (localized target versus global intervention), the key question is whether the multitude of activation waves that characterize persistent AF individually emanate from few, stable, periodic drivers or whether the waves are transitory, widely distributed, and self-perpetuating. Localized drivers are difficult to detect in persistent AF with conventional techniques because of sequential temporospatial mapping, lack of specificity of complex atrial electrograms, intermittent firing, and spatial meandering.7-9 Wide-field mapping tools have been used to capture these sources with the use of balloon, multispline probes6,10-14 or electrode arrays enveloping the torso.15-18 Recent developments have allowed biatrial AF mapping using activation or phase-based analysis of body surface potentials. The objective of this study was to evaluate the ability of noninvasive mapping to identify driver domains and to characterize them in distinct categories of persistent human AF. The secondary objective was to evaluate the relevance of this approach for catheter ablation and compare the amount of radiofrequency (RF) energy delivery to achieve acute AF termination versus a matched group of patients treated previously by the use of the conventional ablation technique. Editorial see p 525

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Methods

Study Population
This is a hospital-based study of patients with persistent AF. All consecutive patients referred for ablation of persistent AF were enrolled between May 2012 and June 2013. Persistent AF was defined as continuous AF from 7 days to 12 months and long-lasting AF beyond 12 months. There were no exclusion criteria based on the left atrial size, ventricular ejection fraction, or structural heart disease.

All patients gave written informed consent to participate in the study, which involved the use of an investigational system for mapping. The study protocol was approved by the institutional Clinical Research and Ethics Committee.

Noninvasive Mapping
If patients presented in ongoing AF, mapping was performed bedside, within 24 hours preceding the invasive procedure. For those presenting in sinus rhythm, AF was induced in the electrophysiological laboratory by rapid atrial pacing decrementing up to 200-ms cycle length at the beginning of the invasive procedure and before transseptal puncture. Induced AF was analyzed after >30 minutes of sustenance (during this time, intracardiac catheter placement and invasive mapping were undertaken). Isoproterenol was not used to facilitate induction.

The noninvasive mapping technique with an array of body surface electrodes and computed tomography–based cardiac geometry has been used to map and locate the origin of cardiac arrhythmias with a reported localization accuracy of 6 mm.\textsuperscript{17} We used a commercially available noninvasive mapping system (ECVUE, CardiolInsight Technologies Inc, Cleveland, OH), which works on the same principle. In brief, a 252-electrode vest was applied to the patient’s torso and connected to the system to record unipolar surface potentials. This was followed by a noncontrast thoracic computed tomography scan (1.2–2 mSv irradiation) to obtain high-resolution 3-dimensional images of the individual biatrial geometry and the relative electrode positions via segmentation.

The system reconstructed biatrial unipolar electrograms from torso potentials by using mathematical computation. Activation maps were computed by using the traditional unipolar electrogram intrinsic deflection-based (\(\pm dV/dT\text{max}\)) method. The windows with long (≥1 s) ventricular pauses (spontaneous or diltiazem-provoked) were randomly selected for AF electrogram analysis. QRST subtraction was not considered, for fear that it could impact the underlying low-voltage atrial electrogram patterns and modify the maps. Maps of AF were generated by using specific algorithms combining signal filtering and phase mapping.\textsuperscript{16–18} The movies (animation) of each AF window showing multiple simultaneous wave propagation patterns, and their beat-to-beat changes were displayed on individualized 3-dimensional biatrial geometry of every patient. The phases of wave propagation were color coded. Surrogates of the depolarization and repolarization wave fronts were computed from the isophase values equal, respectively, to \(\pi/2\) and \(-\pi/2\).

All accumulated movies were analyzed in every patient, to identify active driver regions and passive wave propagation and create a spatiotemporal density map. The AF driver was classified into asynchronous electrograms and expressing the sum as the percentage of AF electrogram activity.

The noninvasive data were acquired before ablation. Oral anticoagulation was administered with target international normalized ratio: 2 to 3 for at least 1 month before the procedure, and transesophageal echocardiography was performed within 5 days of the procedure to exclude left atrial thrombus. Surface ECG and bipolar endocardial electrograms were continuously monitored and stored on a computer-based digital amplifier/recorder system (Labsystem Pro, Bard Electrophysiology). Intracardiac electrograms were filtered from 30 to 500 Hz.

The following catheters were introduced via the right femoral vein for the electrophysiological study: (1) A steerable decapolar catheter (5-mm interelectrode spacing, Xirem, Sorin Medical, Montrouge, France) was positioned in the coronary sinus; (2) an irrigated-tip quadripolar catheter with a distal 3.5-mm tip and three 1-mm proximal electrodes separated by interelectrode distance of 2.5, 2, and 2 mm (Thermocool, Biosense-Webster) was used for ablation; and (3) a 20-pole steerable mapping catheter arranged in 5 soft radiating splines (1-mm electrodes separated by 4-mm interelectrode spacing) laid out flat to cover an area with a diameter of 3.5 cm (PentaRay, Biosense-Webster) in the left or right atrium (LA or RA). It allowed the recording of sharp electrograms and better assessment of their fractionation. After transseptal puncture, intravenous heparin was infused to achieve an activated clotting time of 250 to 300 s.

Endocardial Electrograms at the Reentrant Activity Sites
In a subset of 12 patients presenting in persistent AF, high-density biatrial mapping was performed invasively to define the characteristics of intracardiac electrograms during AF at the sites harboring reentrant activity versus those without such activity on noninvasive maps. Reentrant activity was consistently present in 1 to 3 regions of every window of noninvasive maps of these patients. The multispline catheter was moved sequentially to all regions of LA and RA to record AF. All the regions where all the splines could be applied to the endocardial tissue simultaneously for 5 s were analyzed by an observer (Y.K.) blinded to the noninvasive mapping data. This analysis was limited by the inability to get synchronous recordings because the noninvasive data were acquired before ablation.

The following electrogram characteristics were evaluated in every region: (1) the presence of prolonged (>100 ms) fractionated electrograms; (2) the percentage of AF cycle length covered by electric activity in the mapped region, determined by adding the duration of all asynchronous electrograms and expressing the sum as the percentage...
of the AF cycle length in the given window (continuous electric activity would be 100%); (3) mean amplitude of electrograms; and (4) mean local cycle length calculated on the bipolar showing the most discrete electrograms.

**RF Ablation**

The procedural end point was AF termination, because it had been associated with better outcome in our and others' experience.12,13 The ablation was started in the region with highest driver activity and sequentially performed in the decreasing order of arrhythmogenic density (see Results) until AF terminated. RF lesions were delivered point-by-point at the area covering the focal and reentrant drivers with the use of serial applications.10,20 When drivers were seen in the PVs, circumferential ablation of ipsilateral PVs was undertaken. The point end of regional ablation was the slowing of local electric activity. If AF still persisted after the ablation of all driver regions, linear lesions were undertaken on the LA roof and mitral isthmus, with the end point of linear block (assessed in sinus rhythm).

RF energy was delivered with a power of 30 to 40 W (lower power in the posterior left atrial wall along the trajectory of esophagus as determined from computed tomography scan) by using irrigation rates of 5 to 60 mL/min (0.9% saline via Cool Flow; Biosense-Webster). Therefore, regional RF duration varied from 3 to 12 minutes depending on the surface targeted and the achievement of the local end point. The temperature was limited to 45°C. Until AF termination, the AF cycle length was determined simultaneously in the RA with the multispline catheter left in situ and in the LA appendage by using the ablation catheter, before and after ablation of each driver region by averaging 30 consecutive cycles with the use of automated cycle length–monitoring software (Bard Electrophysiology). The automated annotation was manually verified and corrected with online calipers at a screen speed of 100 mm/s, if required.

When AF terminated into atrial tachycardia, ablation was pursued to eliminate ≥1 sequential atrial tachycardias until sinus rhythm was restored. PV isolation was completed in sinus rhythm, if required, at the end of the procedure. If AF persisted after completion of the ablation protocol, the procedure concluded with cardioversion.

**Control Group**

To evaluate the acute benefit of ablation targeting driver regions, we compared the amount of RF delivery to achieve acute AF termination versus a matched group of patients whose AF terminated with our conventional ablation strategy (involving PV isolation-electrogram–based ablation lines) until AF termination. From a database of 482 patients ablated conventionally in a period of 2 years before starting this study, 82 controls were selected based on certain characteristics at the time of the procedure. These patients were matched 1:1 according to age, sex, the presence of structural heart disease, and the duration of continuous AF (categorized similarly to the study group: persistent presenting in sinus rhythm, persistent 1–6 months, 7–12 months, and >12 months).

**Follow-Up**

After ablation, the patients received subcutaneous heparin in-hospital until the target internal normalized ratio was achieved on oral anticoagulation. Antiarrhythmic drugs were continued for 3 to 6 months (amiodarone in patients with heart disease, flecainide/b–blocker in others). After discharge from the hospital, the patients were admitted for clinical interrogation and 24-hour (continuous), in-hospital telemetry at 3, 6, 9, and 12 months serially. The outcome was categorized as persistent or paroxysmal arrhythmia (AF or atrial tachycardia), or stable sinus rhythm beyond the third month. If patients maintained sinus rhythm for 6 months, the cessation of anticoagulation was considered based on their risk profile. Reablation was considered after 6 months of follow-up.

**Statistical Analysis**

Continuous variables were reported as mean±standard deviation or median (interquartile range, first to third quartiles) as appropriate. Continuous variables were compared by using the Student t test or Mann-Whitney test and analysis of variance for multiple group comparisons. Endocardial electrogram characteristics were compared by using the mixed-effect regression model to take into account intrapatient correlation. Categorical data were expressed as numbers and percentages and were compared by using the Pearson χ² test.

Statistical significance was established at P<0.05. All statistical analyses were performed by using SPSS version 21.0 (SPSS Inc, Chicago, IL) and SAS 9.1 (SAS Institute, Inc, Cary, NC) and Prism version 6.00 (GraphPad Software, LA Jolla, CA).

**Results**

**Clinical Characteristics**

One hundred eleven consecutive patients were included. Eight patients were excluded, because left appendage thrombus was detected in 6 patients and AF could not be induced in 2. The clinical parameters of the remaining 103 patients are provided in Table 1. This group was remarkable owing to the high prevalence of structural heart disease.

The population was divided into 3 distinct categories: (1) 26 persistent AF patients presented in sinus rhythm for at least 4 weeks as they underwent prior cardioversion for AF lasting for ≥2 months; (2) 57 persistent AF patients had continuous AF for ≤12 months: 20 patients with AF lasting ≤3 months; and (3) 19 patients ablated conventionally in a period of 2 years before starting our study.

<table>
<thead>
<tr>
<th>Table 1. Baseline Population Characteristics</th>
<th>n=103 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>18 (17.5)</td>
</tr>
<tr>
<td>Male</td>
<td>85 (82.5)</td>
</tr>
<tr>
<td><strong>Age, mean±SD, y</strong></td>
<td>59.2±11.2</td>
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<tr>
<td><strong>Hypertension, n (%)</strong></td>
<td>45 (43.7)</td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
<td>11 (10.7)</td>
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<td>Embolic events, n (%)</td>
<td>8 (7.8)</td>
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<tr>
<td>Structural heart disease, n (%)</td>
<td>63 (61.1)</td>
</tr>
<tr>
<td>Ischemic, n (%)</td>
<td>10 (9.7)</td>
</tr>
<tr>
<td>Valvular, n (%)</td>
<td>6 (5.8)</td>
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<tr>
<td>Idiopathic, n (%)</td>
<td>37 (35.9)</td>
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<tr>
<td>Hypertrophic, n (%)</td>
<td>8 (7.8)</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>2 (1.9)</td>
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<td><strong>Echocardiographic parameters</strong></td>
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<tr>
<td>Left atrial dimensions</td>
<td></td>
</tr>
<tr>
<td>Diameter, parasternal long axis, mm</td>
<td>48±7</td>
</tr>
<tr>
<td>Area, cm²</td>
<td>26±6</td>
</tr>
<tr>
<td><strong>Patients presenting in persistent AF, AF duration, mo</strong></td>
<td></td>
</tr>
<tr>
<td>≤6, n (%)</td>
<td>31 (30.1)</td>
</tr>
<tr>
<td>&gt;6, n (%)</td>
<td>20 (19.5)</td>
</tr>
<tr>
<td><strong>Patients presenting in sinus rhythm, n (%)</strong></td>
<td>26 (25.2)</td>
</tr>
<tr>
<td><strong>Patients with ≥1 DC cardioversion, n (%)</strong></td>
<td>82 (78.6)</td>
</tr>
<tr>
<td><strong>Number of AADs used before AF ablation, mean±SD</strong></td>
<td>2.5±0.7</td>
</tr>
<tr>
<td><strong>Patients on amiodarone before AF ablation, n(%)</strong></td>
<td>44 (42.7)</td>
</tr>
<tr>
<td><strong>Patients with prior pulmonary vein isolation, n (%)</strong></td>
<td>21 (20.3)</td>
</tr>
</tbody>
</table>

AAD indicates antiarrhythmic drug; AF, atrial fibrillation; DC, direct current; and SD, standard deviation.
months, 11 patients with AF lasting 4 to 6 months, 12 patients with AF lasting 7 to 9 months, and 14 patients with AF lasting 10 to 12 months; and (3) 20 patients had persistent AF lasting >12 months.

Cumulative Mapping Time
An increase in the number and spatial extent of driver activities was observed with increase in the cumulative duration of windows. A mean cumulative duration of the windows (cumulative map time) of 9±1 s was hence used to map drivers. In 10 patients, 6 hours later, another sequence of cumulative AF windows was analyzed, which confirmed the main AF driver regions over the time interval.

Spatiotemporal Distribution of AF Drivers
Continuously varying wave fronts were observed on biatrial maps owing to the varying and simultaneous occurrence of active drivers and passive waves. The percentage of time without any driver activity was 38±22%. The spectrum of driver activities varied temporally from a single occurrence of focal breakthrough/reentry to several repetitive or periodically recurring activity. Per patient, repetitive reentrant activities and single rotation were mean 73±11% and 27±11%, respectively. The distribution of mean number of rotations in 103 patients is shown in Figure 2, bottom. The median number of repetitive rotations was 2.6 (interquartile range, 2.3–3.3) lasting for a mean duration of 449±89 ms, the maximum being 8, observed in 3 patients. Single versus recurrent focal breakthroughs were observed in 14% versus 86%, respectively. A focal site fired a mean of 6 times over the cumulative mapping time. In total, 4720 driver activities were mapped in 103 patients: 3802 (80.5%) reentries and 918 (19.5%) focal breakthroughs. Of these, 69% reentrant events and 71% focal breakthroughs were in the LA, and the remainder were in the RA.

Spatially, reentries were meandering with their core traveling variably over a mean area of 7±2 cm². The episodes of reentrant drivers could recur at the same or the adjacent spot. Thus, their locations could not be described as discrete sites but more broadly as regions.

The distribution of drivers in the patient population is shown in Figure 2, top. A median of 4 driver regions was observed per patient. Reentrant drivers were mainly located in right PVs/septum region, left PVs/appendage, left inferior wall/coronary sinus, and upper RA, but their individual distribution was variable. If 21 patients with prior PV isolation are excluded, the prevalence of reentrant drivers involving the left PV appendage and right PV regions is 97% and 94%, respectively. Focal breakthroughs originated more specifically from the PV ostia and the right and left appendages. Therefore, the main locations of foci were in contiguity with that of the reentrant drivers. The extent of biatrial surface covered by reentrant and focal drivers was 15±12% in AF presenting in sinus rhythm, 21±12% in persistent AF, and 24±11% in long-lasting AF (P<0.05 for sinus rhythm versus persistent AF (PsAF)/long-lasting PsAF; P=not significant for PsAF versus long-lasting PsAF). Figure 3 shows a repetitive focal discharge that initiated reentrant wave in its vicinity, and Figure 4 shows intermittent reentrant drivers involving 23 different parts of both atria.
Endocardial Electrogram Characteristics at Driver and Nondriver Regions

In 12 patients, we compared bipolar electrogram characteristics at 21 driver regions harboring reentrant activities versus 85 without any driver activity. Prolonged fractionated electrograms were more frequently recorded at the reentrant driver regions (62% versus 40%; odds ratio, 3.41; 95% confidence interval, 1.07–10.95; \( P = 0.04 \)). Electrograms recorded on the multispline catheter spanned across a greater part of AF cycle length in the driver regions than elsewhere (71% versus 47%, \( \beta = 17.17; 95\% \text{ confidence interval, 7.74–36.61; } P < 0.001 \)). There was no significant difference in mean local cycle lengths (185 versus 189 ms), and mean electrogram amplitude (0.84 versus 0.83 mV).

Results of RF Ablation

The median number of targeted regions increased with the duration of continuous AF (Figure 5): 3 in AF lasting \( \leq 3 \) months, 4 in AF lasting 4 to 6 months, and 6 in AF lasting > 6 months. Persistent AF presenting in sinus rhythm had a median of 2 driver regions targeted. The driver-density map of 3 representative patients is shown in Figure 6.

Of 103 patients, AF terminated in 82 (80%). AF terminated directly into sinus rhythm in 28 and into atrial tachycardia in 54 (focal, 22; macroreentry, 32), which required further ablation to achieve sinus rhythm.

The ablation of driver regions alone resulted in AF termination in 65 patients. In 6/65 patients, AF terminated at the first ablated driver region, not allowing the estimation of change in fibrillatory cycle length. In the remaining 59/65 patients, the AF cycle length prolonged from 179±36 ms to 198±28 ms until AF termination. The AF termination rate declined as continuous AF got longer: 85% (17/20) for \( \leq 3 \)-month-long AF; 82% (9/11) for 4- to 6-month-long AF; 67% (8/12) for 7- to 9-month-long AF, 36% (5/14) for 10- to 12-month-long AF; and 15% (3/20) for >12-month-long AF. AF could not be terminated in 21 (20%) patients after driver and linear ablation.

Comparison of RF Energy With Matched Control Population

The characteristics of patients who achieved AF termination and their matched controls are shown in Table 2. The RF duration to terminate AF by driver ablation (65 patients) was 28±17 minutes versus 65±33 minutes in the control group (\( P < 0.0001 \)). This amount remained significantly less even after including the RF applied for the lines (17 additional patients; Table 3). RF delivery increased in direct relation to the AF duration in both study and control groups with a significant difference observed in all subgroups of persistent AF; there was no significant difference for long-lasting AF (Table 3).
Outcomes
Of 103 patients, 90 attained a follow-up of 12 months, wherein 37 were off antiarrhythmic drugs. Redo ablation was undertaken in 16 patients for atrial tachycardia (12 patients) or AF (4 patients). Table 4 shows that 58 (64%) patients were in stable sinus rhythm, 14 (22%) in atrial tachycardia, and 18 (20%) in AF. At the end of 1 year, 85% (60/71) patients with AF termination were free from AF, similar to the control population, 87% (71/82) patients; $P =$not significant. The AF-free outcome was more favorable in patients with acute AF termination (85%, 28/33) versus 63%, $P = 0.045$. On the other hand, there was no difference ($P =$not significant) in AF-free outcome when different subgroups based on AF duration were mutually compared.

Discussion
This study shows that persistent AF is mechanistically sustained by a few individual driving regions in the early months with a high rate of AF termination from limited catheter ablation.

Table 2. Characteristics of Patients With AF Termination (n=82) and Their Matched Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study Population (n=82)</th>
<th>Control Population (n=82)</th>
<th>$P$ Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>60.1±10.3</td>
<td>57.6±9.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>16 (19.5)</td>
<td>16 (19.5)</td>
<td>1</td>
</tr>
<tr>
<td>Male</td>
<td>66 (80.5)</td>
<td>66 (80.5)</td>
<td>1</td>
</tr>
<tr>
<td>Structural heart disease, n (%)</td>
<td>48 (58.5)</td>
<td>48 (58.5)</td>
<td>1</td>
</tr>
<tr>
<td>Persistent AF in sinus rhythm</td>
<td>23 (28.1)</td>
<td>23 (28.1)</td>
<td>1</td>
</tr>
<tr>
<td>AF duration, mo, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>28 (34.1)</td>
<td>28 (34.1)</td>
<td>1</td>
</tr>
<tr>
<td>&gt;6–12</td>
<td>22 (26.8)</td>
<td>22 (26.8)</td>
<td>1</td>
</tr>
<tr>
<td>&gt;12</td>
<td>9 (11)</td>
<td>9 (11)</td>
<td>1</td>
</tr>
<tr>
<td>RF duration, mean±SD, min</td>
<td>35±21</td>
<td>65±33</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; RF, radiofrequency; and SD, standard deviation.

*The Student $t$ test was used for continuous variables, and the Pearson $χ²$ test was used for categorical variables.

Progressive Remodeling of Atrial Tissue with AF Continuation
Electric and structural remodeling is fundamental to the AF disease process. A landmark study demonstrated that AF maintained by continuous pacing for 2 to 3 weeks led to spontaneous sustained AF in healthy goats. This electric remodeling reversed completely within weeks of restoration of sinus rhythm. The AF persisting longer led to structural remodeling altering atrial cellular and tissue composition resulting in fibrosis, which increased AF complexity. The structural remodeling reverses slowly if at all. Although AF could be terminated pharmacologically after few weeks, it could not be drug cardioverted after 6 months. Based on these works, the prevailing mechanism of AF remodeling in humans is thought to be the multiplication of randomly circulating waves associated with a decreased atrial refractory period and heterogeneous tissue structure. The current study suggests different time-critical mechanisms for persistent AF in humans. In the initial months, persistent AF is driven from a few regions generating a varying set of short-lasting periodic waves occupying part of the AF window span. With prolongation in the duration of AF, the substrate disseminates making AF a complex electrostructural disorder.

The determinant role of driver mechanism showing either discrete foci or reentries is supported by modeling and animal studies. A single relatively stable source in canine RA using a high concentration of acetylcholine by Schuessler et al, and multifocal AF in the sterile pericarditis model by Waldo and colleagues, as well, have been reported. Jalife and colleagues used phase-based optical signal processing to demonstrate rotor activities with a spectrum of scenarios from single meandering rotor to multiple, periodic rotors giving rise to fibrillatory activation. In all models, the apparition of fibrosis increased substrate dimension both in terms of rotor facilitation, and also in the complexity of propagation and multiplication of wavelets.
Characteristics of AF Drivers

In humans, AF drivers have been demonstrated during endocardial and epicardial mapping with the use of multielectrode tools or noninvasive torso electrode arrays by using activation, spectral, or phase mapping. Recently, Narayan et al reported their experience of basket mapping where they predominantly observed a discrete number of rotors temporally stable for hours in limited spatial domain. On the other hand, we observed more driver locations, substantial meandering, and periodic occurrence of unstable reentries requiring statistical density maps. Although the reasons for discrepancy are unclear, our results were corroborated with endocardial beat-to-beat electrogram variability and matched with the behavior of rotors evidenced by optical mapping. A lower incidence (16%) of rotors was reported by Cuculich et al, but these authors used noninvasive activation mapping; rotors were also short lived, mixed with other mechanistic patterns of activation, and arrhythmia complexity increased with longer-duration AF.

In the present study, the anatomic distribution of drivers confirmed the importance of regions of PV antra, adjacent septum, and left appendage with wide interindividual variations at other locations including the RA. An interesting finding was the proximity of foci and reentrant events suggesting that they possibly share common underlying tissue-level pathology or a functional link whereby foci promote formation of reentry in the vicinity. Recent data indicate that reentrant drivers have an affinity for the patchy zones bordering dense fibrosis shown by atrial MRI. The latter may help to evaluate structural substrate, and, combined with electric mapping, (drivers) may help to improve the stratification and therapeutic strategy of PsAF in individuals.

In our study, driver activity was not present throughout the cumulative AF mapping period, and passive waves were visible at times during ongoing AF, suggesting that such wave propagation may play a role to maintain AF. However, the mapping technique alone was unable to assign a contributing role to such propagating wave including macroreentry, an issue inherent to AF mapping, which may not be currently solved. Further studies are needed to characterize the respective contribution of drivers and wave propagation in human AF and the progression of the structural substrate during AF continuation.

Clinical Implications

The noninvasive system can map AF preprocedurally and help shorten invasive procedural time by performing an important task of identification of AF drivers.

Table 3. RF Duration for AF Termination in the Study Population and the Control Group

<table>
<thead>
<tr>
<th>AF Termination in Study Population, n=82</th>
<th>AF Termination With Drivers Only, n=65</th>
<th>AF Termination With Drivers and Lines, n=82</th>
<th>Control Group, n=82</th>
<th>P Value*</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients in sinus rhythm, n</td>
<td>23</td>
<td>23</td>
<td>23</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RF duration, mean±SD, min</td>
<td>22±17</td>
<td>22±17</td>
<td>50±28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF duration ≤ 6 mo, n</td>
<td>26</td>
<td>28</td>
<td>28</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RF duration, mean±SD, min</td>
<td>28±14</td>
<td>31±16</td>
<td>61±30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF duration 7–12 mo, n</td>
<td>13</td>
<td>22</td>
<td>22</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RF duration, mean±SD, min</td>
<td>38±20</td>
<td>46±21</td>
<td>78±32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF duration &gt;12 mo, n</td>
<td>3</td>
<td>9</td>
<td>9</td>
<td>0.007</td>
<td>0.07</td>
</tr>
<tr>
<td>RF duration, mean±SD, min</td>
<td>33±9</td>
<td>53±17</td>
<td>83±42</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; RF, radiofrequency; and SD, standard deviation.

Table 4. Clinical Outcome at 12 Months in 90 (87%) Patients of the Study Population

<table>
<thead>
<tr>
<th>Sinus Rhythm, n (%)</th>
<th>Atrial Tachycardia</th>
<th>Atrial Fibrillation</th>
<th>AF-Free,*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paroxysmal</td>
<td>Persistent</td>
<td>Paroxysmal</td>
</tr>
<tr>
<td>Presenting in sinus</td>
<td>17 (74)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>AF ≤6 mo (n=25)</td>
<td>17 (68)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>AF 7–12 mo (n=22)</td>
<td>14 (64)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>AF &gt;12 mo (n=20)</td>
<td>10 (50)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Termination (n=71)</td>
<td>47 (66)</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Nontermination (n=19)</td>
<td>11 (58)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td>14</td>
<td>18</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; and NS, not significant.

*AF-free patients include those in sinus rhythm or atrial tachycardia.
†P=NS between subgroups.
‡P=0.045.
In keeping with previous reports,\textsuperscript{5,30} the endocardial electrograms from reentry regions showed more fractionation and spanned wider across the fibrillatory cycle length. These characteristics indicated local tissue heterogeneity with slow conduction possibly anchoring the reentries but did not firmly predict the driver locations. They corroborate previous observations showing fractionated activity at the wave pivot points\textsuperscript{31} or directly produced by meandering rotors owing to beat-to-beat changes in directionality, using the same multispline catheter as in the current study.\textsuperscript{32,33}

We used the term of arrhythmogenic regions to substitute discrete sites as targets of ablation to address the spatial meandering of reentries. The functional role of these regions was supported by the prolongation of fibrillatory cycle length during their ablation, culminating in AF termination in most. Even if AF termination is a nonconsensual end point, this robust and objective procedural end point allows comparison between techniques.\textsuperscript{19}

The significant reduction in RF-energy delivery targeting driver domains indicated that ablation focused on most critical regions may produce an AF termination rate similar to more widespread anatomic energy delivery. A turning point appeared after a few months where a decrease in the acute efficacy of driver ablation was observed (even though it did not impact the final clinical outcome, because patients who did not terminate by driver ablation were resorted to lines to achieve AF termination). The patients presenting in sinus rhythm also have favorable outcomes by targeting drivers alone, presumably owing to limited structural substrate. These results strongly argue for early intervention.

**Limitations**

There were some limitations of this study. (1) The transformation of data to phase-based analysis has inherent limitations toward the detection of false rotors owing to incomplete wave curvatures because the interpolation algorithm is devised to demonstrate mainly local-phase progression/rotational activity.\textsuperscript{34} To ascertain the reentries, the prephase (raw) local electrograms were analyzed to demonstrate the sequential propagation of regional waves. (2) The recorded AF time may be considered short and may not reflect all mapping scenarios be considered short and may not reflect all mapping scenarios happening over time in every individual. In animal models, a previous study demonstrated that 12 consecutive windows of 100 ms were representative of the entire period of AF.\textsuperscript{24} (3) The current resolution of body surface mapping may have limited sensitivity in the case of highly localized sources, small signals (<0.15 mV) and far-field signals, particularly in scar tissue, the dynamic changes occurring during ablation (extinction or emergence of drivers) were not assessed, allowing room for improving the results. (4) Finally, this is a single-center experience, and prospective multicenter evaluation is required for confirmation.

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**Disclosures**

Drs Haissaguerre, Hocini, and Jais are stockowners and Drs Shah and Dubois are paid consultants to CardioInsight Inc, Cleveland, OH. The other authors report no conflicts.


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**CLINICAL PERSPECTIVE**

The ablation of persistent atrial fibrillation (AF) remains suboptimal mainly because of the complexity of the underlying mechanisms, including substrate remodeling. The present study evaluates a noninvasive phase-based signal processing capable of visualizing atrial waves propagating during AF; focal breakthroughs or reentrant sources at the origin of such waves were defined as AF drivers. The principal finding is that persistent AF is mechanistically sustained by a few individual driving regions in the early months of persistent AF. Drivers were mostly localized unstable reentries possibly anchored on to local tissue heterogeneity. The high rate of termination of AF was observed from limited catheter ablation. The patients presenting in sinus rhythm also have a favorable outcome of ablation targeting drivers alone, presumably because of the limited structural substrate. With prolongation in the duration of AF, the substrate disseminated, making AF a ubiquitous electrostructural disorder and its termination rate sharply declined. In the absence of perprocedural remapping, it is unknown whether the nontermination of AF was attributable to the emergence of new AF drivers or multiple wavelets. In summary, the study indicates that persistent AF in early months is maintained predominantly by drivers clustered in a few regions, most of them being unstable reentries.
Driver Domains in Persistent Atrial Fibrillation
Michel Haissaguerre, Meleze Hocini, Arnaud Denis, Ashok J. Shah, Yuki Komatsu, Seigo Yamashita, Matthew Daly, Sana Amraoui, Stephan Zellerhoff, Marie-Quitterie Picat, Adam Quotb, Laurence Jesel, Han Lim, Sylvain Ploux, Pierre Bordachar, Guillaume Attuel, Valentin Meillet, Philippe Ritter, Nicolas Derval, Frederic Sacher, Olivier Bernus, Hubert Cochet, Pierre Jais and Remi Dubois

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