Driver Domains in Persistent Atrial Fibrillation

Running title: Haissaguerre et al.; Driver domains in persistent atrial fibrillation

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Abstract

Background—A specific non-invasive signal processing was applied to identify drivers in distinct categories of persistent atrial fibrillation (PsAF).

Methods and Results—In 103 consecutive PsAF patients, accurate biatrial geometry relative to an array of 252-body-surface-electrodes was obtained from non-contrast CT-scan. The reconstructed unipolar AF-electrograms acquired bedside from multiple windows (duration:9±1seconds) were signal-processed to identify the drivers (focal or re-entrant activity) and their cumulative density-map. The driver domains were catheter ablated using AF termination as procedural endpoint in comparison with stepwise-ablation control group. The maps showed incessantly changing beat-to-beat wavefronts and varying spatio-temporal behaviour of driver activities. Re-entries were not sustained (median 2.6 rotations lasting 449±89ms), meandered substantially but recurred repetitively in the same region. Totally, 4720 drivers were identified in 103 patients: 3802(80.5%) re-entries and 918(19.5%) focal breakthroughs; most of them co-localized. Of these, 69% re-entries and 71% foci were in 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 1-3months, 4 in AF 4-6months and 6 in AF lasting longer. Termination rate sharply declined after 6 months. Mean RF delivery to AF termination was 28±17min vs. 65±33min in control group (p<0.0001). At 12 months, 85% patients with AF-termination were free from AF, similar to control population(87%); p-NS.

Conclusions—Persistent AF in early months is maintained predominantly by drivers clustered in few regions, most of them being unstable reentries.

Key words: persistent atrial fibrillation, driver domain, non-invasive mapping, phase mapping, rotor activity, noninvasive imaging, atrial fibrillation arrhythmia, phase analysis, rotor
Treating atrial fibrillation (AF) through surgical or catheter ablation is based on the elimination of the AF-initiating triggers and/or the AF-maintaining substrate. In paroxysmal atrial fibrillation, ablation successfully targets triggers which are mainly located in the pulmonary veins (PVs) while the results in persistent AF are less satisfactory, presumably because of the influence of wider atrial substrate in its determinism.\textsuperscript{1,2} Multiple atrial wavelets, macro-reentries and localized (focal or re-entrant) sources have been reported to contribute to the substrate of persistent AF\textsuperscript{3-6}. For determining a therapeutic strategy in persistent AF (localized target vs. global intervention), the key question is whether the multitude of activation waves that characterize persistent AF individually emanates 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.\textsuperscript{7-9} Wide-field mapping tools have been used to capture these sources using balloon, multispline probes\textsuperscript{10-14} or electrode arrays enveloping the torso.\textsuperscript{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 non-invasive mapping to identify driver-domains and characterize them indistinct categories of persistent human AF. The secondary objective was to evaluate this approach as an individualized guide 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 using conventional ablation technique.

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.

**Non-invasive 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 non-invasive mapping technique with an array of body surface electrodes and CT-based cardiac geometry has been used to map and locate the origin of cardiac arrhythmias with a reported localization-accuracy of 6 mm\(^17\). We used a commercially available non-invasive mapping system (ECVue\(^\text{TM}\), CardioInsight Technologies Inc., Cleveland, OH), which works on the same principle. Briefly, 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 non-contrast thoracic CT scan (1.2 to 2 mSv irradiation) to obtain high-resolution three-dimensional images of the individual bialtrial geometry and the relative electrode positions via segmentation.

The system reconstructed bialtrial unipolar electrograms from torso potentials using
mathematical computation. Activation maps were computed using traditional unipolar electrogram intrinsic deflection-based (-dV/dTmax) method. The windows with long (≥1second) 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 using specific algorithms combining filtering to eliminate artefacts in signal morphology and phase mapping.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 3D biatrial geometry of every patient. The phases of wave propagation were color-coded. Surrogates of the depolarization and repolarization wavefronts were computed from the isophase values equal respectively to π/2 and −π/2.

All accumulated movies were analysed in every patient and the maps displaying the active driver regions and passive wave propagation were obtained to create a spatiotemporal probabilistic map. The AF driver was classified into focal, when centrifugal activation originated from a point or an area (for example, a PV) or re-entrant when at least one wave fully rotated around a center on phase progression and confirmed by sequential activation of raw unipolar local electrograms. An activity (focal or re-entrant) appearing more than once consecutively was considered ‘repetitive’.

The CT-based biatrial geometry was divided into 7 regions to provide distinct anatomical classification to display aggregated driver-density map. Although the septum could not be directly visualized from the torso, septal origin/sources could be inferred from their exit from the interatrial groove on the right and left surfaces. Four regions were defined in the left atrium, 2 in the right atrium and 1 in the anterior interatrial groove (Figure 1). Because of their proximity,
left PVs were grouped with the left appendage into one region en bloc. Similarly, the right atrial appendage was grouped with the upper right atrium. When the drivers were observed simultaneously in the right PV and the anterior interatrial groove, the latter was considered as anterior projection of right PV drivers through the septum and the drivers were considered belonging to the right PV region alone. The drivers observed in the anterior interatrial groove but not the right PVs were considered to belong to the anterior interatrial groove region.

Electrophysiological Study

All antiarrhythmic drugs, except for amiodarone (n = 44), were ceased >5 half-lives before ablation. Oral anticoagulation was administered with target international normalized ratio: 2-3 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, USA). 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 inter-electrode spacing, Xtrem, 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 inter-electrode distance of 2, 5 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 inter-electrode spacing) laid out flat to cover an area with diameter of 3.5 cm (PentaRay, Biosense-Webster, USA) in the left or right atrium (LA or RA). It allowed recording of sharp electrograms and better assessment of their fractionation. After
transseptal puncture, intravenous heparin was infused to achieve activated clotting time of 250 – 300 seconds.

**Endocardial Electrograms at the Re-entrant 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 re-entrant activity versus those without such activity on non-invasive maps. Re-entrant activity was consistently present in 1 to 3 regions of every window of non-invasive 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 seconds were analyzed by an observer (YK) blinded to the noninvasive mapping data. This analysis was limited by the inability to get synchronous recordings since non-invasive data were acquired before ablation.

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

**Radiofrequency Ablation**

The procedural endpoint was AF termination, since it has been associated with better outcome in our and others’ experience. 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. Radiofrequency lesions were delivered point-by-point at the area covering the focal and/or re-entrant drivers using serial applications.\textsuperscript{10,20} When drivers were seen in the PVs, circumferential ablation of ipsilateral PVs was undertaken. The endpoint of regional ablation was slowing of local electrical 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 endpoint of linear block (assessed in sinus rhythm).

RF energy was delivered with a power of 30-40W (lower power in the posterior left atrial wall along the trajectory of esophagus as determined from CT-scan) using irrigation rates of 5 to 60mL/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 achievement of local endpoint. 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 using the ablation catheter, before and after ablation of each driver region by averaging 30 consecutive cycles using automated cycle length monitoring software (Bard Electrophysiology, USA). The automated annotation was manually verified and corrected with online calipers at a screen speed of 100mm/s, if required.

When AF terminated into atrial tachycardia (AT), ablation was pursued to eliminate one or more sequential ATs until sinus rhythm was restored. Pulmonary vein 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.

\textbf{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 pulmonary vein 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, presence of structural heart disease and duration of continuous AF (categorized similar 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 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/beta-blocker in others). Post-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, cessation of anticoagulation was considered based on their risk-profile. Re-ablation was considered after 6 months of follow-up.

**Statistical Analysis**

Continuous variables were reported as mean ± standard deviation (SD) or median (interquartile range (IQR): 1st-3rd quartiles) as appropriate. Continuous variables were compared using Student’s t test or Mann-Whitney test and ANOVA for multiple group comparisons. Endocardial electrogram characteristics were compared using mixed-effect regression model to take into account intra-patient correlation. Categorical data were expressed as numbers and percentages.
and were compared using the Pearson’s chi-squared test ($\chi^2$).

Statistical significance was established at $P \leq 0.05$. All statistical analyses were performed 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

1. Clinical Characteristics

111 consecutive patients were included. Eight patients were excluded because left appendage thrombus was detected in 6 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 higher 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 5±2 months. 2) 57 persistent AF patients had continuous AF for ≤ 12 months: 20 patients with AF ≤ 3 months, 11 patients with AF 4-6 months, 12 patients with AF 7-9 months and 14 patients with AF 10-12 months and 3) 20 patients had persistent AF lasting > 12 months.

2. 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 seconds 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 time-interval.

3. Spatiotemporal Distribution of AF Drivers
Continuously varying wavefronts were observed on biatrial maps due to varying and simultaneous occurrence of active drivers and passive waves. The percentage of time without any driver activity was $38 \pm 22\%$. The spectrum of driver activities varied temporally from single occurrence of focal breakthrough/re-entry to several repetitive or periodically recurring activity. Per patient, repetitive re-entrant activities and single rotation were mean $73\pm11\%$ and $27\pm11\%$, 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 mean duration of $449 \pm 89\text{ms}$, the maximum being 8, observed in 3 patients. Single versus recurrent focal breakthroughs were observed in 14\% vs 86\% respectively. A focal site fired mean 6 times over the cumulative mapping time. Totally, 4720 driver activities were mapped in 103 pts: 3802 (80.5\%) re-entries and 918 (19.5\%) focal breakthroughs. Of these, 69\% re-entrant events and 71\% focal breakthroughs were in the LA and the remainder were in the RA.

Spatially re-entries were meandering with their core travelling variably over a mean area of $7 \pm 2\text{cm}^2$. The episodes of re-entrant 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. Re-entrant drivers were mainly located in right pulmonary veins/septum region, left pulmonary veins/appendage, left inferior wall/coronary sinus and upper right atrium, 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 re-entrant 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 vs. PsAF/long-lasting PsAF: p-NS for PsAF vs. long-lasting PsAF). Figure 3 shows a repetitive focal discharge which initiated re-entrant wave in its vicinity and Figure 4 shows intermittent re-entrant drivers involving 23 different parts of both atria.

4. Endocardial Electrogram Characteristics at Driver and Non-driver regions

In 12 patients we compared bipolar electrogram characteristics at 21 driver regions harbouring re-entrant activities versus 85 without any driver activity. Prolonged fractionated electrograms were more frequently recorded at the re-entrant driver regions (62% vs. 40%, OR 3.41, IC95% (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% vs. 47%, beta=17.17 IC95% (7.74; 36.61), p<0.001). There was no significant difference in mean local cycle lengths (185ms vs. 189ms), and mean electrogram amplitude (0.84 vs 0.83 mV).

5. Results of RF Ablation

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

Out of 103 patients, AF terminated in 82 (80%). AF terminated directly into sinus rhythm in 28 and into atrial tachycardia in 54 (focal: 22, macro-reentry: 32), which required further ablation to achieve sinus rhythm.

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±36ms to 198±28ms until AF termination. The AF termination rate declined as continuous AF got longer: 85% (17/20) for ≤ 3-month-long AF, 82% (9/11) for 4-6-month-long AF, 67% (8/12) for 7-9-month-long AF, 36% (5/14) for 10-12-month-long AF and 15% (3/20) for >12-month-long AF (83% for AF ≤ 6 months vs. 50% for AF 6-12 months, p= 0.0096). AF termination rate was 88% (23/26) in those presenting in sinus rhythm.

Seventeen patients required additional linear lesions to terminate AF after driver ablation. Their baseline AFCL was shorter than above patients (153±32ms vs. 179±36ms, p=0.008) suggesting a greater degree of electrical remodeling in accordance with their longer median AF duration (10(11-13) months vs. 6(2-8) months; p<.0001). Finally, the total termination rate was 88%(23/26) in those presenting in sinus rhythm, 90%(28/31) in 1-6-month-long AF, 85%(22/26) in 7-12-month-long AF and 45%(9/20) in >12-month-long AF.

AF could not be terminated in 21(20%) patients after driver and linear ablation.

6. 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 vs. 65±33 minutes in 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).

7. Outcomes

Out of 103 patients, 90 attained follow up of 12 months, wherein 37 were off antiarrhythmic
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 AT 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-NS. The AF free outcome was more favorable in patients with acute AF termination than those who did not achieve AF termination (85% vs 63%, p=0.045). On the other hand, there was no difference (p=NS) 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 high rate of AF termination from limited catheter ablation.

**Progressive Remodeling of Atrial Tissue with AF Continuation**

Electrical and structural remodeling is fundamental to the AF disease process. A landmark study demonstrated that AF maintained by continuous pacing for 2–3 weeks led to spontaneous sustained AF in healthy goats. This electrical remodeling reversed completely within weeks of restoration of sinus rhythm. The AF persisting longer led to structural remodelling altering atrial cellular and tissue composition resulting in fibrosis, which increased AF complexity. The structural remodelling reverses slowly if at all. While 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 multiplication of randomly circulating waves associated with 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

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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. Single relatively stable source in canine right atrium using high concentration of acetylcholine by Schuessler et al as well as multifocal atrial fibrillation in the sterile pericarditis model by Waldo et al have been reported. Jalife et al 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 but 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 using multielectrode tools or noninvasive torso electrode arrays using activation, spectral or phase mapping. Recently, Narayan et al reported their experience of basket mapping where they predominantly observed 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 re-entries 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 behaviour 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 anatomical distribution of drivers confirmed the importance of
regions of pulmonary vein antra, adjacent septum and left appendage with wide inter-individual variations at other locations including the right atrium.\textsuperscript{14,28} An interesting finding was the proximity of foci and re-entrant events suggesting that they possibly share common underlying tissue-level pathology or a functional link whereby foci promote formation of re-entry in the vicinity. Recent data indicate that re-entrant drivers have affinity for the patchy zones bordering dense fibrosis shown by atrial magnetic resonance imaging.\textsuperscript{29} The latter may help to evaluate structural substrate, and combined with electrical mapping (drivers) may help to improve 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\textsuperscript{1}, 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 progression of the structural substrate during AF continuation.

\textbf{Clinical Implications}

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

In keeping with prior 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 prior observations showing fractionated activity at the wave pivot points\textsuperscript{31} or directly produced by meandering
rotors due 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 \textit{regions} to substitute \textit{discrete sites} as targets of ablation to address the spatial meandering of re-entries. The functional role of these regions was supported by prolongation of fibrillatory cycle length during their ablation, culminating in AF termination in most. Even if AF termination is a non-consensual endpoint, this robust and objective procedural endpoint allows comparison between techniques.\textsuperscript{19} The significant reduction in radiofrequency-energy-delivery targeting driver domains indicated that ablation focused on most critical regions may produce AF termination rate similar to more widespread anatomical energy delivery. A turning point appeared after 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 favourable outcome by targeting drivers alone, presumably due to limited structural substrate. These results strongly argue for early intervention.

\textbf{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 due to incomplete wave curvatures as the interpolation algorithm is devised to demonstrate mainly local phase progression/rotational activity.\textsuperscript{34} To ascertain the re-entries, the pre-phased (raw) local electrograms were analysed to demonstrate the sequential propagation of regional waves. (2) The recorded AF time may be considered short, and may not reflect all mapping scenarios happening over time in every
individual. In animal models, a prior study demonstrated that 12 consecutive windows of 100ms were representative of the entire period of AF.24 (3) The current resolution of body surface mapping cannot track small signals (<0.15mV) and far-field signals particularly in scar tissue may make calculations erroneous; 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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**References:**


Table 1. Baseline Population Characteristics.

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<th>Characteristic</th>
<th>n=103 (%)</th>
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<td>Gender, n (%)</td>
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<td>Female</td>
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<tr>
<td>Male</td>
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<td>&gt; 12, n (%)</td>
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<tr>
<td>Patients with ≥ 1 DC cardioversion, n (%)</td>
<td>82 (79.6)</td>
</tr>
<tr>
<td>Number of AADs used before AF ablation, mean±SD</td>
<td>2.5 ± 0.7</td>
</tr>
<tr>
<td>Patients on amiodarone before AF ablation, n(%)</td>
<td>44 (42.7)</td>
</tr>
<tr>
<td>Patients with prior pulmonary vein isolation, n (%)</td>
<td>21 (20.3)</td>
</tr>
</tbody>
</table>

AF: atrial fibrillation, AAD: antiarrhythmic drug, DC: direct current
Table 2. Characteristics of patients with AF termination (n=82) and their matched controls.

<table>
<thead>
<tr>
<th></th>
<th>Study population (n=82)</th>
<th>Control population (n=82)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±S.D, y</td>
<td>60.1±10.3</td>
<td>57.6±9.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Gender, 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 sinusrhythm</td>
<td>23 (28.1)</td>
<td>23 (28.1)</td>
<td>1</td>
</tr>
<tr>
<td>AF duration, months, 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>7 – 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: atrial fibrillation, RF: Radiofrequency
* Student’s t-test was used for continuous variables and Pearson’s chi-square test was used for categorical variables.
Table 3. RF duration for AF termination in the study population and the control group.

<table>
<thead>
<tr>
<th></th>
<th>AF termination in study population, n=82</th>
<th>Control group n=82</th>
<th>p*</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AF termination with drivers only n=65</td>
<td>AF termination with drivers and lines n=82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients in sinusrhythm, n</td>
<td>23</td>
<td>23</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>RF duration, mean±SD, min</td>
<td>22±17</td>
<td>22±17</td>
<td>50±28</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AF duration ≤ 6 months, n</td>
<td>26</td>
<td>28</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>RF duration, mean±SD, min</td>
<td>28±14</td>
<td>31±16</td>
<td>61±30</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AF duration 7-12 months, n</td>
<td>13</td>
<td>22</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>RF duration, mean±SD, min</td>
<td>38±20</td>
<td>46±21</td>
<td>78±32</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AF duration &gt; 12 months, n</td>
<td>3</td>
<td>9</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>RF duration, mean±SD, min</td>
<td>33±9</td>
<td>53±17</td>
<td>83±42</td>
<td>0.007</td>
</tr>
</tbody>
</table>

AF: atrial fibrillation, RF: radiofrequency.
P*: RF duration for AF termination with drivers only vs. control group
P†: RF duration for AF termination with drivers and lines vs. control group
*†: Student’s t-test was used to compare RF duration.
Table 4. Clinical Outcome at 12 months in 90(87%) patients of the study population

<table>
<thead>
<tr>
<th></th>
<th>Sinus Rhythm</th>
<th>Atrial Tachycardia</th>
<th>Atrial Fibrillation</th>
<th>AF-Free</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Paroxysmal</td>
<td>Persistent</td>
<td></td>
</tr>
<tr>
<td>Presenting in Sinus rhythm (n=23)</td>
<td>17 (74%)</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>AF ≤6 mon (n=25)</td>
<td>17 (68%)</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>AF 7-12 mon (n=22)</td>
<td>14 (64%)</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>AF &gt;12 mon (n=20)</td>
<td>10 (50%)</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>58</strong></td>
<td><strong>14</strong></td>
<td><strong>18</strong></td>
<td></td>
</tr>
</tbody>
</table>

|                                | Sinus Rhythm | Atrial Tachycardia | Atrial Fibrillation | AF-Free |
|                                |              | Paroxysmal         | Persistent          |         |
| **Based on AF-Termination**    |              |                    |                     |         |
| Termination (n=71)             | 47 (66%)     | 5                  | 8                   | 9       | 2       | 85%#   |
| Non-Termination (n=19)         | 11 (58%)     | 0                  | 1                   | 0       | 7       | 63%#   |
| **TOTAL**                      | **58**       | **14**             | **18**              |         |

*p=NS between subgroups;  # p =0.045
AF: Atrial Fibrillation
AF-Free patients include those in sinus rhythm or atrial tachycardia
Figure Legends

**Figure 1.** Biatrial schema is divided into 7 regions (1: Left pulmonary veins and left appendage, 2: Right pulmonary veins and posterior interatrial groove, 3: Inferior and posterior left atrium, 4: Upper half of right atrium and appendage; 5: Lower half of right atrium, 6: Anterior left atrium and roof, 7: Anterior interatrial groove).

**Figure 2.** Top: Distribution of drivers (focal breakthroughs - asterisk and reentry events - curved arrows) in 7 regions is reported as %age of patients. For example, 82% of the 103 patients had repetitive reentries, and 58% had repetitive focal breakthroughs in left pulmonary vein-appendage region. Bottom: The bar-diagram shows the distribution of mean number of rotations in 103 patients.

**Figure 3.** The phase map shows a focal source which emanates an impulse from the RIPV and initiates a couple (“figure of 8”) of reentrant drivers. This phenomenon repeats consecutively for 5 beats (repetitive focal discharge and reentry events), the first of which is shown in the form of snapshots taken at successive time intervals. The blue colour represents depolarization. The pre-phase electrograms taken at the site of focal source (1 to 4) and at a distance (5 to 8) show characteristic QS and rS patterns respectively. The phases of wave propagation are color-coded using rainbow scale. The deep blue colour represents depolarizing wave. The phase map can be appreciated by following the blue colour. The time (ms) at the bottom of each snapshot represents the moment when the snapshot was taken. Abbreviations: SVC – Superior vena cava, RA – Right atrium, RIPV – Right inferior pulmonary vein, RSPV – Right superior pulmonary vein, LA – Left atrium, IVC – Inferior vena cava.
**Figure 4.** The phase maps of ≥1000ms-long AF window show reentry events visualized intermittently in the right and left atria with their pre-phase electrograms on the right. The time (ms) below each map is the instantaneous time of the snapshot in that AF-window. Panel A: One of the two consecutive rotations involving inferior left atrium and the pre-phase electrograms around its core (sites 1 to 12). Panel B: One of the two consecutive rotations involving posterior upper right atrium and the pre-phase electrograms around its core (sites 1 to 12). The colour code is explained in legend 3.

**Figure 5.** The median (1st and 3rd quartiles) number of driver regions ablated to terminate AF increases with the duration of persistent AF. Two regions were targeted in patients presenting in sinus rhythm (SR).

**Figure 6.** The arrhythmogenic driver density maps of three patients showing 2, 3 and 5 driver regions respectively. The red represents the cluster of drivers and blue is background colour of the biatrial geometry (Anterior views – A, C, E; Posterior views – B, D, F). Top: Drivers cluster at the base of RAA and LAA (A). No drivers found posteriorly (B). Middle: No drivers seen anteriorly (C), while they cluster in right and left pulmonary veins and ILA (D). Bottom: Drivers cluster in right atrium near the base of RAA, at the tip of LAA, anterior left atrium and inferior right atrium below the tricuspid valve (E). Posteriorly, drivers cluster in left pulmonary veins and posterior interatrial groove (F). Abbreviations: LAA – Left atrial appendage, RAA – Right atrial appendage, LIPV – Left inferior pulmonary vein, LSPV – Left superior pulmonary vein, RIPV – Right inferior pulmonary vein, RSPV – Right superior pulmonary vein, MV – Mitral valve, TV – Tricuspid valve, ILA – Infero-posterior left atrium, IVC – Inferior vena cava.
Figure 1
Figure 2
Figure 5

- Persistent in SR
- Persistent (1-6m)
- Persistent (7-12m)
- Long-Lasting

Number of targeted driver regions

- N.S.
- * 0.01 < p < 0.05
- ** 0.001 < p < 0.01
- N.S. p > 0.05
Figure 6
Driver Domains in Persistent Atrial Fibrillation
Michel Haïssaguerre, Mélèze 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, Frédéric Sacher, Olivier Bernus, Hubert Cochet, Pierre Jaïs and Remi Dubois

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