Temporal Stability of Rotors and Atrial Activation Patterns in Persistent Human Atrial Fibrillation

A High-Density Epicardial Mapping Study of Prolonged Recordings


ABSTRACT

OBJECTIVES This study aimed to determine the spatiotemporal stability of rotors and other atrial activation patterns over 10 min in longstanding, persistent AF, along with the relationship of rotors to short cycle-length (CL) activity.

BACKGROUND The prevalence, stability, and mechanistic importance of rotors in human atrial fibrillation (AF) remain unclear.

METHODS Epicardial mapping was performed in 10 patients undergoing cardiac surgery, with bipolar electrograms recorded over 10 min using a triangular plaque (area: 6.75 cm²; 117 bipoles; spacing: 2.5 mm) applied to the left atrial posterior wall (n = 9) and the right atrial free wall (n = 4). Activations were identified throughout 6 discrete 10-s segments of AF spanning 10 min, and dynamic activation mapping was performed. The distributions of 4,557 generated activation patterns within each mapped region were compared between the 6 segments.

RESULTS The dominant activation pattern was the simultaneous presence of multiple narrow wave fronts (26%). Twelve percent of activations represented transient rotors, seen in 85% of mapped regions with a median duration of 3 rotations. A total of 87% were centered on an area of short CL activity (<100 ms), although such activity had a positive predictive value for rotors of only 0.12. The distribution of activation patterns and wave-front directionality were highly stable over time, with a single dominant pattern within a 10-s AF segment recurring across all 6 segments in 62% of mapped regions.

CONCLUSIONS In patients with longstanding, persistent AF, activation patterns are spatiotemporally stable over 10 min. Transient rotors can be demonstrated in the majority of mapped regions, are spatiotemporally associated with short CL activity, and, when recurrent, demonstrate anatomical determinism. (J Am Coll Cardiol EP 2015;1-2:14–24) © 2015 by the American College of Cardiology Foundation
The mechanisms by which human atrial fibrillation (AF) is perpetuated remain unclear, with considerable ongoing debate as to the prevalence, nature, and importance of rotors as AF drivers (1,2).

Previous high-density epicardial mapping studies, with activation mapping and detailed analysis of electrogram (EGM) progression, have not observed rotors (3,4) or have reported only infrequent transient rotational activity (5). Such studies have evaluated short segments of AF lasting only seconds, potentially a significant limitation when considering the presence of transient rotors. These studies have suggested that AF is maintained by multiple wavelet propagation, with multiple dissociated wave fronts (WFs) in the remodelled atrium separated by regions of fibrosis and poor tissue coupling (3). Observations in these studies have also suggested that dissociation between epicardial and endocardial layers allows “endo-epi” WF breakthrough, which may aid perpetuation of fibrillation (4).

An alternative hypothesis invokes focal drivers of fibrillation. Experiments in vitro and in animals have demonstrated the presence of high-frequency rotors involved in driving fibrillation (6–8). Findings from studies in humans using low-density endocardial mapping and phase analysis (9,10) suggest that AF in humans may be driven by a small number of rotors that are highly stable over prolonged time periods (11). Ablating these circuits has been reported to be effective in acutely terminating AF and in maintaining sinus rhythm in the intermediate term (10,12–14). In contrast, “panoramic” atrial mapping through phase analysis of body surface potentials has demonstrated a very different type of rotor activity, these rotors appearing unstable and persisting for only 2 to 3 rotations (15). These disparate results remain unexplained. The paucity of regular monomorphic EGMs or repetitive sequential activation around the presumed path of the rotor within existing reports, and observations such as the strong dependence of rotor demonstration on the band pass filter applied to body surface potentials, have raised important methodological questions (16).

In the present study, we used high-density epicardial mapping over 10-min periods to identify the presence of rotors and to characterize their spatiotemporal stability and relationship to short cycle-length (CL) activity in patients with longstanding, persistent AF.

METHODS

Ten patients with longstanding, persistent AF undergoing a first elective cardiac surgical procedure were studied (Table 1). Participants were undergoing coronary artery bypass graft surgery (CABGS) (n = 3), aortic valve implantation (AVI) (n = 2), mitral valve replacement (MVR) (n = 2), CABGS/AVI (n = 2), or CABGS/MVR/AVI (n = 1). Antiarrhythmic medications were ceased ≥5 half-lives prior to surgery. All participants gave written informed consent, with the protocol approved by the Melbourne Health Human Research and Ethics Committee.

EPICARDIAL MAPPING PROTOCOL. High-density atrial epicardial mapping was performed after median sternotomy and pericardial division and prior to cardioplegia and cardiopulmonary bypass. Mapping involved a triangular plaque comprising 128 silver-plated copper electrodes (117 bipoles), with inter-electrode spacing of 2.5 mm and a mapping area of 6.75 cm². The plaque was positioned by the operating surgeon (M.L., V.A., P.A., J.G., A.R., M.O.K.), and bipolar signals were recorded for a minimum of 10 min. Nine prolonged recordings from the left atrial posterior wall (LAPW) were made, with 4 from the right atrial free wall. Bipolar EGMs, with a sampling frequency of 1,000 Hz and a band pass filter of 0.05 to 400 Hz, were recorded using the UnEmap mapping system (UniServices, Auckland, New Zealand). After the entire recording was visually scanned, 6 discrete 10-s AF segments with high-quality signal across the entire plaque were analyzed. These 6 segments

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spanned the entire 10 min, with a mean intersegment interval of 109 ± 19 ms.

**Signal Analysis.** UnEmap recordings were exported into customized software (Cardiac ElectroPhysiology Analysis System, Cuoretech, Sydney, Australia) for further analysis. An automated algorithm was used for identifying discrete atrial EGMs by peak negative dV/dT events in the voltage signal. Consistent with a previous report (5), a noise threshold of 0.1 mV, a maximal width criterion of 10 ms, and a refractory period of 50 ms were applied to avoid the detection of broad far-field activations and multiple detections of the same activation complex. All automated annotations were visually verified and manually adjusted as required.

**AF Wave Front Mapping.** The output data from the Cardiac ElectroPhysiology Analysis System were a series of activation times for each bipolar referenced to time zero, corresponding beat-to-beat CLs and Cartesian coordinates precisely locating each bipolar. These data were exported for WF animation using commercially available software (DataTank, Visual Data Tools, Chapel Hill, North Carolina). At each activation event, electrodes were animated on for a defined duration before returning to the off state, and the sequences of on-off activations at each bipolar location combined to produce dynamic activation maps. An activation duration of 20 ms was selected for consistency with that utilized by Lee et al. (5) to display activation at adjacent bipole sites either by a single propagating WF or discontinuously by different WFs, on the basis of the characterization of atrial slow conduction as a local velocity of 10 to 20 cm/s and conduction block as a velocity of <10 cm/s (17). With 2.5 mm of spacing, differences in local activation times of 25 and 35 ms between adjacent bipole sites in the horizontal and oblique directions, respectively, would represent conduction block. Activation durations ranging between 15 and 35 ms have previously been demonstrated not to result in differences in interpretation of the dynamic WF maps (5). Activation patterns were analyzed at an animation speed of 20 ms/s.

**Activation Pattern Classification.** Consistent with findings from prior studies (3–5,18), activation patterns were classified as WFs, focal activations, rotors, and disorganized activity. Broad WFs activated the entire width of the plaque. Multiple broad or narrow WFs could exist simultaneously, or as a combination of broad and narrow WFs. WFs were subclassified by the direction of propagation on the triangular plaque.

A rotor was defined as a WF rotating at least twice within the mapped area and governing overall regional activation, with differences in activation times at adjacent electrodes around the pathway of activation of <25 and <35 ms in the horizontal and oblique directions, respectively. Focal activations were represented by activation emanating from within the mapped region and subsequently spreading radially a distance of more than 3 bipole sites. Disorganized activity failed to fulfill criteria for the patterns detailed above. It was composed of early activation inside the mapping area that failed to propagate more than 3 bipole sites, or activations that occurred as isolated beats dissociated from activation of adjacent bipolar sites.

**Determination of the Mechanism of Rotor Initiation.** All rotors were reviewed for the determination of their mechanism of onset. They were classified as being initiated by a WF moving perpendicularly across the refractory tail of the preceding WF, as has been described in animal (19) and computation (20) models, or by spontaneous wave break of a planar WF.

**AF Cycle-Length Mapping.** For each 10-s segment, a mean AF CL was determined at each bipolar location.
from its series of beat-to-beat CLs, and a color-encoded mean AF CL map was constructed. Short DL activity was defined as a CL <100 ms. The CL distribution was also visualized within the dynamic WF maps by the on color being color-coded according to the current CL at that location. The relationship of activation patterns to local CLs across the mapping plaque was thus determined.

**STATISTICAL ANALYSIS.** Statistical analysis was performed using Stata software version 12.1 (StataCorp, College Station, Texas). Continuous variables are expressed as mean ± SD if normally distributed and otherwise as median (interquartile range [IQR]), and categorical variables, as n (%). Normality was tested with the Shapiro-Wilk method. Statistical significance was assessed at the 0.05 level.

For each 10-s AF segment, all activation patterns were classified. By systematic analysis of all regional activation patterns during the segment, the most frequently observed pattern was defined as the dominant pattern for that AF segment. To further analyze temporal stability of activation patterns, 2-way tables of AF segment (1-6) and activation pattern frequency for the 3 most common activation patterns were constructed for each mapped region. The relationship of activation patterns to local CLs across the mapping region was thus determined.

**RESULTS**

All participants had preserved left ventricular systolic function (Table 1). The mean age was 69 ± 17 years, 60% were male, and 90% were hypertensive. The median AF duration was 4.5 (IQR: 2 to 6) years. The mean left atrial diameter was 5.1 ± 0.7 cm.

**ACTIVATION PATTERNS.** Reproducibility of activation pattern classification was high. Cohen’s kappa statistics were 0.94 (p < 0.001) for intraobserver agreement and 0.81 (p < 0.001) for interobserver agreement.

Within each 10-s AF segment over the 10-min recording period, a mean of 6,521 ± 1,443 discrete atrial EMGs were annotated and 58 ± 7 activation patterns were classified. Across all 78 segments, there was a total of 4,557 activation patterns. Within each 10-s AF segment, atrial activation was highly dynamic, with transitions between WF activation, focal activation, rotors, and disorganized activity (Figure 1). The overall distribution of classified activation patterns observed was: 1) transient rotors, 12%; 2) disorganized activity, 10%; 3) focal activation, 7%; and 4) WFs, 71% (multiple narrow WFs, 26%; single broad WF, 22%; single narrow WF, 13%; multiple simultaneous broad WFs, 6%; and simultaneous broad and narrow WFs, 4%).

**FOCAL ACTIVATIONS.** Seven percent of activations satisfied criteria for focal activation. Focal activation of 2 or more consecutive cycles represented 4% of all activation patterns and was seen in all participants, in 12 of 13 regions (92%), and 36 of 78 patients’ 10-s segments (46%). The median number of consecutive focal activations was 2 (IQR: 2 to 3), and the longest consecutive sequence was 5, occurring on 3 occasions. There was no association between focal activation and local short CL activity.

**TRANSIENT ROTORS.** Twelve percent of all observed atrial activations appeared as rotors of more than 2 complete cycles. Transient rotors were seen in total on 78 occasions in 9 of 10 participants, 11 of 13 mapped regions (85%) (7 LAPW and 4 right atrial free wall), and 46 of 78 of patients’ (59%) 10-s segments. The mean duration of 7 ± 15 rotations was influenced by more prolonged periods of rotational activation in a single LAPW map, in which an uninterrupted clockwise rotor was observed throughout 4 of the 6 discrete 10-s segments. The median number of rotations was 3 (IQR: 2 to 3), and the mean CL of rotation was 187 ± 20 ms.

Within all 10-s AF segments spanning the 10-min recording period, the anatomical location within the mapped region at which the core of a recurring transient rotor was identified was preserved. The direction of rotation, however, was variable, with both clockwise and counterclockwise rotation observed in 8 of the 11 mapped regions with occurrences of repetitive reentry (73%).

In a single LAPW map, a transient clockwise rotor was relatively more stable. In one 10-s segment, clockwise rotation was broken by a single occurrence of a counter-clockwise rotor lasting 3 rotations, and in a second 10-s segment, it was broken by a single sequence of 4 consecutive focal activations. Mean rotational CL was 155 ± 3 ms. Color-encoded CL maps showed short CL activity, with a CL of 78 ± 4 ms, to consistently co-locate to the core of rotation (Figures 2 and 3, Online Videos 1, 2, 3, 4, 5, 6, 7, and 8).
**MODE OF ROTOR INITIATION.** In 49%, rotors were established by perpendicular WF–wave tail interaction, with rotation established as the leading edge of a WF interacted with the repolarizing tail of the preceding WF (Online Videos 9 and 10). In 51%, rotation appeared to be initiated by spontaneous wave breaks. There was, however, no evidence of anatomical block at the pivot point of rotation, with this location also activated by linear WFs, without evidence of wave break, in all mapped regions manifesting rotors, in total during 65% of activations.

**RELATIONSHIP BETWEEN ROTORS AND SHORT CL ACTIVITY.** A total of 87% of rotors were anchored on...
an area of short CL activity, with a CL of <100 ms. This area occupied 4 ± 3 bipoles, with organized rotation around this core being consistent with spiral wave arms emanating from a small high-frequency rotor. In all cases, the area at the center of rotation represented the area on the mapping plaque with the shortest CL over the time period during which the rotor was seen. The occurrence of short CL activity, however, was not specific for rotors. Although overall 11.9 ± 26.4% of occurrences of confluent short CL activity were located at a rotor core, 53.8 ± 21.5% were associated with WF collision, 19.8 ± 13.1% were associated with slowed conduction of linear WFs, 13.9 ± 12.0% were associated with disorganized activation, and 0.6 ± 1.2% were associated with focal activation (Table 2).

**STABILITY OF ACTIVATION PATTERNS.** The distribution of activation patterns was highly consistent...
across the 6 AF segments for each mapped region (Figures 1 and 4). In the setting of WF activation, the directionality of propagation was highly conserved. In 8 of 13 regions (62%), there was a consistent, single, dominant pattern across all 6 AF segments. In 3 of 13 (23%), this was seen across 5 of the 6 segments and in 1 region (8%) across 4 of 6 segments. Using 2-way tables to relate the distribution of patterns to the 6 segments, no evidence of change in the relative distribution of activation patterns over time was seen in 9 of 13 mapped regions (69%).

**DISCUSSION**

In this study in a population of patients with long-standing, persistent AF, the major findings were: 1) transient rotors in 90% of participants and 85% of mapped regions, with a median of 3 rotations; 2) 49% of rotors were initiated by cross-field stimulation; 3) 87% of rotors were centered on an area of short CL activity (<100 ms); 4) areas of short CL activity were nonspecific for the identification of rotors (positive predictive value: 0.12); 5) there was no evidence of an anatomical discontinuity at the anchor point of rotation; 6) there were transient focal activations in all patients (92% of mapped regions), with a median of 2 consecutive activations and a longest sequence of 5, with only 0.6 ± 1.2% of short CL activity associated with focal activation; and 7) atrial activation patterns were highly dynamic within 10-s segments of AF, but over 10 min there was evidence of anatomical determinism, with a single dominant pattern across all 6 segments in 62% of mapped regions and the directionality of WF propagation highly conserved.
Based on these findings, it appears justified to conclude that it is adequate to analyze single, 10-s segments of AF, as has been done in prior studies.

**ROTORS IN HUMAN PERSISTENT AF.** There continues to be debate as to the importance of rotors in sustaining in-human persistent AF, with several studies suggesting that multiple wavelet reentry is primarily responsible for its maintenance (1,2). Furthermore, in studies that have demonstrated rotors, there have been fundamental differences in the reported prevalence and temporal stability of these possible AF drivers (9,10,15,16).

Narayan et al. (9) were the first to demonstrate rotors in human AF, in approximately 90% with persistent AF. Using low-density basket catheter mapping and phase analysis, they reported human AF to be driven by a small number (10) of macroscopic rotors that precess within small, patient-specific areas and to remain stable for thousands of cycles (11). In several reports, ablation at the core of the rotor resulted in a rate of acute AF termination and then maintenance of sinus rhythm of up to 82% (10,12-14). Patients in this series, even with very long-lasting, persistent AF, generally had 2 to 3 stable rotors the ablation of which led to AF termination. No relationship was observed between rotors and short CL activity (11).

In contrast, Haïssaguerre et al. (15), using phase analysis of body surface potentials, observed rotors for 62% of the mapped time. These were unstable and existed for a median of 2.6 rotations. Rotors frequently re-formed at the same anatomical location, although there was movement of the rotor core over an area of up to 7 ± 2 cm². Ablation of driver regions alone resulted in AF termination in 66%, but in contrast to the findings from the studies by Narayan et al. (9), termination of AF was not possible with driver region ablation alone in 85% of patients with an AF duration of >12 months. In a small study of body surface potential mapping, Rodrigo et al. (16) could identify phase singularities during 73% of the mapped time period, with a mean of 2.9 rotations. Without the application of narrow band pass filtering at the dominant frequency, however, phase singularities were observed during only 8.2% of the mapped time period, thus emphasizing the sensitivity of such techniques to methodological variation.

Prior epicardial mapping studies of persistent human AF using activation mapping have not reported such high rotor prevalence, but short-duration local mapping may underestimate the true prevalence. In a prior study using activation mapping of bipolar EGMs, we observed rotors in 17% of patients over 10 s (5).

In the present study, we extended the observation period to 10 min and observed transient rotors in 90% of patients and 85% of mapped regions, with a median of 3 rotations. The observation that transient rotors are seen relatively commonly in persistent AF concords particularly with the observations from body surface mapping studies (15,16). As epicardial mapping is spatially limited it is not possible to demonstrate rotor meandering, and we may have underestimated the duration of a transient rotor.

The concordance of the findings from this study with the data reported by Haïssaguerre et al. (15) is particularly interesting in the context of the discrepancy between the results of previous studies that used more panoramic techniques and those that recorded epicardial unipolar (3,4) or bipolar (5) EGMs. The former have used phase mapping of body surface potentials (15) or endocardial unipolar EGMs (9) to demonstrate a high prevalence of stable or transient rotors, whereas the latter, using timing-based activation mapping, have reported a much lower prevalence. It has been observed that, with phase analysis initially developed for the analysis of action potentials derived from optical mapping of ex vivo specimens, the artifact and far-field contamination often seen in extracellular EGM recordings and the relatively lower spatial resolution of such recordings might lead to overestimation of rotational activity by phase mapping (21). The present data suggest that transient rotors may be demonstrated by either technique.

One of the crucial questions raised by the observation of transient rotors is whether they are active

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<th>Mapped Region</th>
<th>Rotational Circuit</th>
<th>Focal Activation</th>
<th>Wave-Front Collision</th>
<th>Slow Conduction</th>
<th>Disorganized Activity</th>
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Values are %. Atrial activation patterns associated with short cycle length (CL) activity (atrial fibrillation: CL < 220 ms), expressed as a percentage of such periods observed in each mapped region. Wave-front collision accounts for 54% ± 22% of atrial short CL activity.
drivers of fibrillation or simply represent a passive phenomenon. In the present study, we observed that 87% of rotors were centered on an area of short CL activity representing the shortest CL on the plaque at that time. Although short CL activity was not specific for rotors and there was no evidence of anatomical discontinuity at the core of rotation, this finding provides indirect evidence that these rotors may be active drivers. In the study by Haïssaguerre et al. (15), ablation at the sites of transient drivers, which were more frequently associated with prolonged fractionated EGMs than were no-driver regions, resulted in AF termination in many patients, again implicating a possible role in the maintenance of persistent AF. An enduring limitation of mapping studies performed in the surgical department is that confirmation of the mechanistic importance of observed activation patterns by targeted ablation is unrealistic.

**FOCAL ACTIVATION.** In the current study, there were 7% of focal activations, but most persisted for only 2 consecutive activations, and there was no spatial relationship with short CL activity. These observations seem more consistent with endocardial-epicardial breakthroughs, as previously described (4), than with a true focal source.

**SPATIOTEMPORAL ORGANIZATION IN AF IN HUMANS.** Prior mapping studies of both induced (18,22) and persistent (3-5,23-25) AF in humans have emphasized that AF is characterized by complex patterns of WF propagation, with complexity related to the duration of AF and the extent of remodeling of the atrial substrate (3,4,18). Lee et al. (5) highlighted short-term AF instability, with the majority of 10-s maps demonstrating marked heterogeneity in activation pattern.

Nonetheless, spatiotemporal organization has previously been demonstrated in human AF by an analysis of directionality information encoded within EGM morphology (26,27). In the current mapping study, we observed that, although short-term activation is unstable, patterns of atrial activation consistently repeat over a 10-min period. This spatiotemporal stability is consistent with an anatomical determinism on the basis of atrial structural change but also might indicate the presence of recurring drivers existing outside the mapped area. The observations that the location of transient rotors within a mapped region is stable when they recur within 10-s AF segments over a 10-min period, but that there is no evidence of anatomical block at the core of rotation, suggest that heterogeneities in electrical...
remodeling may be more important than anatomical remodeling.

**STUDY LIMITATIONS.** Epicardial mapping of the atrium in the surgical department is, by necessity, confined to a limited region rather than being able to provide global coverage. In contrast, studies using a basket mapping catheter provide broader, although not universal, coverage and at low density. Patients in the present study had significant structural heart disease with atrial remodeling, and it is not clear whether its results are relevant to a population with only minor structural abnormalities.

In basic studies, rotors have been defined on the basis of the WF dynamics at a point of phase singularity. In clinical studies, the spatial resolution has not been adequate for demonstrating such WF dynamics, and the definition of a rotor has by necessity been broader, on the basis of the appearance of rotational activation. It remains conceivable that the patterns of rotational activation demonstrated by studies such as this represent a mechanism different from that demonstrated by optical mapping in animal models.

**CONCLUSIONS**

High-density epicardial mapping in patients with persistent AF demonstrates that atrial activation patterns are spatiotemporally stable over 10 minutes. Transient rotors can be demonstrated in the great majority of mapped regions and are associated with short CL activity, providing some support for a role as active drivers, and when recurrent, they demonstrate anatomical determinism.

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KEY WORDS cycle length, epicardial mapping, rotor

APPENDIX For supplemental videos and their legends, please see the online version of this article.