Epicardial wave mapping in human long-lasting persistent atrial fibrillation: transient rotational circuits, complex wavefronts, and disorganized activity

Geoffrey Lee1,2, Saurabh Kumar1,2, Andrew Teh1,2, Andrew Madry1,2, Steven Spence1,2, Marco Larobina3, John Goldblatt3, Robin Brown3, Victoria Atkinson3, Simon Moten3, Joseph B. Morton1,2, Prashanthan Sanders6, Peter M. Kistler1,2,4,5, and Jonathan M. Kalman1,2*

1The Department of Cardiology, The Royal Melbourne Hospital, Melbourne, Australia; 2The Department of Medicine, University of Melbourne, Melbourne 3050, Australia; 3The Department of Cardiothoracic Surgery, The Royal Melbourne Hospital, Melbourne, Australia; 4The Department of Cardiology, The Alfred Hospital, Melbourne, Australia; 5The Baker IDI Diabetes and Heart Research Institute, Melbourne, Australia; and 6Centre for Heart Rhythm Disorders, University of Adelaide, the Royal Adelaide Hospital, Adelaide, Australia

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Objectives
To characterize the nature of atrial fibrillation (AF) activation in human persistent AF (PerAF) using modern tools including activation, directionality analyses, complex-fractionated electrogram, and spectral information.

Background
The mechanism of PerAF in humans is uncertain.

Methods and results
High-density epicardial mapping (128 electrodes/6.75 cm²) of the posterior LA wall (PLAW), LA and RA appendage (LAA, RAA), and RSPV-LA junction was performed in 18 patients with PerAF undergoing open heart surgery. Continuous 10 s recordings were analysed offline. Activation patterns were characterized into four subtypes (i) wavefronts (broad or multiple), (ii) rotational circuits (≥ 2 rotations of 360°), (iii) focal sources with centrifugal activation of the entire mapping area, or (iv) disorganized activity [isolated chaotic activation(s) that propagate ≤ 3 bipoles or activation(s) that occur as isolated beats dissociated from the activation of adjacent bipoles sites].

Activation at a total of 36 regions were analysed (14 PLAW, 3 RSPV-LA, 12 LAA, and 7 RAA) creating a database of 2904 activation patterns. In the majority of maps, activation patterns were highly heterogeneous with multiple unstable activation patterns transitioning from one to another during each recording. A mean of 3.8 ± 1.6 activation subtypes was seen per map. The most common patterns seen were multiple wavefronts (56.2 ± 32%) and disorganized activity (24.2 ± 30.3%). Only 2 of 36 maps (5.5%) showed a single stable activation pattern throughout the 10-s period. These were stable planar wavefronts. Three transient rotational circuits were observed. Two of the transient circuits were located in the posterior left atrium, while the third was located on the anterior surface of the LAA. Focal activations accounted for 11.3 ± 14.2% of activations and were all short-lived (≤ 2 beats), with no site demonstrating sustained focal activity.

Conclusion
Human long-lasting PerAF is characterized by heterogeneous and unstable patterns of activation including wavefronts, transient rotational circuits, and disorganized activity.

Keywords
Atrial fibrillation

* Corresponding author. Tel: +61 3 9342 7133, Fax: +61 3 9347 2808, Email: jon.kalman@mh.org.au
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Introduction

The mechanism of persistent atrial fibrillation (AF) remains elusive. Although the multiple wavelet hypothesis\(^1\) has long been the dominant theory governing AF wave dynamics, more recent experimental and animal models suggest focal sources or drivers may be critical in maintaining the fibrillatory process.\(^2\)\(^,\)\(^3\) These may be either high frequency focal sources with radial activation and fibrillatory conduction to the rest of the atria or a rotational wave of excitation (rotor).\(^2\)\(^,\)\(^3\) There are relatively limited data characterizing wavefront patterns in human persistent AF (PerAF) due to the spatial-temporal complexities and technical challenges. Existing epicardial mapping studies have generally involved isochronal maps of 1–2 s duration. Konings et al. performed epicardial mapping of pacing-induced AF in patients without a history of AF and reported the presence of one or multiple wavelets with varying degrees of complexity. More recently, Allessie and coworkers\(^5\) mapped patients with long-standing PerAF and hypothesized that AF was maintained by focal fibrillation waves from epicardial breakthrough of sources propagating in deeper layers of the atrial wall. Sahadevan et al.,\(^6\) in an epicardial mapping study of nine patients with chronic AF observed regional short-cycle length activity in seven of these and speculated that this may represent the presence of a driver as one mechanism of AF. However to date, all epicardial mapping studies during human AF have failed to confirm the existence of rotors. In contrast, the recent study by Narayan et al.\(^7\) used a 64-electrode basket catheter and customized software to map the atria endocardially. Preliminary work has shown that rotors were present in the majority (98%) of patients with AF. In the present study, we analysed prolonged AF recordings obtained from large, high-density epicardial mapping plaques in patients with long-lasting persistent atrial fibrillation. Our aim was to characterize the nature of AF activation in human PerAF using modern tools including activation, directionality analyses, complex-fractionated electrogram, and spectral information.

Methods

This study included 20 patients with PerAF (defined in accordance with HRS Expert Consensus Statement) undergoing elective cardiac surgery for mitral regurgitation (12), aortic stenosis (2), aortic regurgitation (1), hypertrophic obstructive cardiomyopathy (1), mitral stenosis (1), and ischaemic heart disease (3). All the patients gave written and informed consent prior to the surgery and the study protocol was approved by the research and ethics committee of Melbourne Health.

Data acquisition

Following median sternotomy and prior to cardiopulmonary bypass, high-density atrial epicardial mapping was performed. A custom-made high-density triangular epicardial plaque comprising 128 silver-plated copper electrodes with an inter-electrode distance of 2.5 mm (effective mapping area 6.75 cm\(^2\)) was positioned sequentially at four regions (i) oblique sinus on the posterior left atrium (PLAW) between the pulmonary veins, (ii) most anterior surface (surface which is in direct contact with the visceral pericardium) of the left atrial appendage (LAA), (iii) most anterior surface (surface which is in direct contact with the visceral pericardium) of the right atrial appendage (RAA), (iv) the anterior surface of the right superior RSPV-LA junction (RSPV-LA). Electrograms were sampled at 1000 Hz with a band pass filter of 0.05 to 400 Hz employed. Continuous bipolar atrial electrograms were recorded using a computerized mapping system (Unemap, Uniservices, Auckland, New Zealand) for offline analysis. Ten second recordings were obtained after plaque stability and signal quality had been confirmed.

Data analysis

Beat-to-beat activation time

The entire recording was scanned to ensure overall signal quality. Unemap signals were imported into the customized computer software Cardiac ElectroPhysiology Analysis System (CEPAS, Cuoretech Pty Ltd, Sydney, Australia) that was used to determine beat-to-beat activation times from each bipolar on the epicardial mapping plaque.\(^7\) CEPAS has specific user-defined characteristics to identify electrogram activations. These include (i) a baseline noise threshold; (ii) electrogram width criterion to avoid detection of broad far-field activations; (iii) electrogram slope; and (iv) electrogram ‘refractory’ periods to avoid multiple detections within the same activation. Based on the previous work by Aizer et al.,\(^8\) a noise threshold of 0.1 mV, width criterion of 10 ms, and refractory period of 50 ms were utilized for the analysis. All automated electrogram analysis was visually verified to ensure accurate annotation of activation times. Activations were manually corrected if automated annotation was incorrect (Figure 1).

The first step in our analysis was to determine the beat-to-beat activation time from each bipolar recording site. Thus for the purposes of this analysis each bipolar site was defined by two specific variables (i) the Cartesian co-ordinates for the bipolar; (ii) a time series of activation times (t) referenced to the onset of the 10 s recording (time zero) for each atrial depolarization. This data set was then exported in the matrix form for wavefront animation and analysis.

Complex-fractionated atrial electrograms

Complex-fractionated atrial electrograms (CFAEs) were defined as electrograms displaying continuous electrical activity (CEA) over the entire 10 s recording period consistent with the original description\(^9\). The location of CFAE sites was recorded for spatial analysis. Given the ambiguity of assigning activation times at sites of CEA, these sites were excluded from the animation and atrial fibrillation cycle length (AFLC) analysis.

Multi-component electrograms were defined by \(\geq 3\) deflections over \(\geq 50\) ms duration separated by a discrete iso-electric baseline. These were manually annotated at the onset of electrogram activation. Figure 1 shows representative examples of annotation of non-fractionated, multi-component, and CFAE electrograms from the data set.

AF mapping

Within the 10 s recording, each bipolar site was sampled at 1 ms intervals (sampling rate of mapping system of 1000 Hz). Using commercially available software (DataTank, Visual Data Tools, Inc., Chapel Hill, NC, USA), individual activations at each fixed bipolar site on the epicardial plaque were animated independently.

Definition of timing intervals

Activation time window

When activation occurred at a given site, this was animated ‘on’ for a duration of 20 ms being the activation time window. Atrial slow conduction has been defined as a local conduction velocity of 10–20 cm/s and conduction block as \(< 10\) cm/s.\(^10\) Given the 2.5 mm inter-bipole spacing between adjacent bipoles, a difference in local activation times of 25 and 35 ms (horizontal and oblique trajectories) between adjacent bipoles would represent conduction block. It is unlikely that two adjacent bipoles are activated by the leading edge of the same wavefront if the difference in local activation times were \(> 25\) ms in the horizontal direction or 35 ms in the oblique direction. These values set the physiological limits of normal wavefront propagation and were used for the animation.
process. Using heuristic principles, Activation Time Windows from 1 to 35 ms were analysed and an activation time window of 20 ms resulted in the best discrimination of wavefront patterns. However, the evaluation of activation time windows over a range of 15–35 ms did not result in differences in map interpretation. The activation time window determined whether activations at adjacent bipole were displayed either (i) simultaneously and as part of the leading edge of the same depolarizing wavefront; (ii) sequentially as propagation of the leading edge of an existing wavefront or (iii) discontinuously and activated as part of a new wavefront.

In a recent epicardial mapping study, de Groot et al. used similar values (15–40 ms) when defining discontinuous conduction as fibrillation waves starting from the boundary of another wave. All maps were analysed at a speed of 20 ms/s. When interpretation needed further clarification, the play back speed was reduced to 5 ms/s.

**Refractory period**

The refractory period of a given bipole was defined at 50 ms. Repeated activations occurring within this interval were either part of a multi-component signal or CFAE or represented far-field activity.

**Dominant frequency**

Dominant frequency (DF) analysis was performed using CEPAS on the raw electrogram signals exported from the Unemap data. Within the
same 10-s recording window, spectral analysis for determination of DF was analysed. For the specific purposes of DF analysis, exported signals were rectified, filtered using a Butterworth filter and edge-tapered with a Hanning window. Dominant frequency was determined by Fast Fourier Transform using zero-padding with a spectral resolution of 0.1 Hz. The DF of each individual bipole-recording site was defined as the frequency demonstrating the highest power within the 3–15-Hz frequency domain. For the purposes of the spatial analysis in this study, a high-dominant frequency (HDF) site within the recording plaque was identified if the local bipole DF was 20% greater than the DF of its adjacent bipoles.11

Classification of activation pattern morphologies
Based on prior studies,2,5,12 activation patterns were classified into four morphologies; wavefronts, focal activations, rotational circuits, and disorganized activity (Supplementary material online, Movies S1–4).

Wavefronts
The number, size, and direction of wavefront propagation were noted for each activation. We measured the size of wavefronts that were visible within the mapping field. Wavefronts that only appear at the edges of the mapping field or activate the entire mapping area could not be determined. Wavefront directionality was determined using visual inspection. Wavefronts were subclassified according to the following definitions:

1. Broad wavefronts: where the width of the activation wave front spans the entire plaque, activating it in a linear fashion.
2. One narrow Wf: the width of the propagating wavefront is only 2–6 bipoles wide.
3. Two narrow Wfs: two narrow wavefronts occupy the mapping area at the same time.
4. Three narrow Wfs: ≥3 narrow wavefronts occupy the mapping area at the same time.

Focal activation
Earliest activation occurs at a discrete bipole site located inside the mapping area with centrifugal wavefront activation that spreads radially to the periphery.

Rotational circuit
A rotational wave (≥2 rotations of 360°) of excitation centred on a central area located inside the mapping area.

Disorganized activity
Activations that do not fulfil the criteria for a wavefront and are composed of early activation at >2 adjacent bipoles inside the mapping area that propagate ≤3 bipoles or activations that occur as isolated beats dissociated from the activation of adjacent bipole sites. ‘Disorganized’ activations are characterized by multiple simultaneous ‘epicardial breakthroughs’ within the mapping field with collision of wavefronts so that there is no obvious organized pattern of activation.

Preferential conduction pathway
Preferential conduction pathway was defined by the presence of a stereotypical repeated pattern (>2) and trajectory of wavefront activation within the mapping area during the recording period. Preferential conduction was determined by the visual analysis of the AF maps.

Statistical analysis
All statistical analysis was performed using SPSS software version 17.0 (SPSS, Chicago, IL, USA) Normality of all quantitative data variables was checked using the Kolmogorov–Smirnov test. Continuous variables are reported as means ± standard deviation and median and interquartile range (IQR), as appropriate. Categorical variables are reported as numbers and percentages. Comparisons of continuous variables between different anatomic regions were performed using a one-way analysis of variance, with post hoc analysis using Bonferroni correction for multiple comparisons.

To determine the degree of intra- and inter-observer variability in activation pattern classification, the principal investigator and a second observer (S.K.) were asked to classify a blinded sample of 100 patterns from the data set using the above study criteria. For the principal investigator, there was a 98% INTRA-observer agreement in the classification of activation patterns, kappa = 0.95, P < 0.001. For the second observer (S.K.), there was 97% INTER-observer agreement with the principal investigator in the classification of activation patterns, kappa = 0.86, P < 0.05. In cases where there was disagreement between the principal and the second observer, activation patterns were decided after review and mutual consensus. All tests were two-sided and a P-value < 0.05 was considered statistically significant.

Results
The mean total AF duration was 8.4 ± 7.5 years. All the patients had PerAF for > 1 year. The mean LA diameter was 5.0 ± 0.6 cm. The percentage of patients with an EF > 59, EF40–59, and EF20–39% were 70, 20, and 10%, respectively. Only one patient was taking anti-arrhythmic medications at the time of the mapping procedure. A total of 20 patients were mapped, with two patient’s data excluded due to a poor signal noise ratio. From the remaining 18 patients, a total of 36 regions were mapped (14 PLAW, 3 RSPV-LA, 12 LAA, and 7 RAA) creating a database of 2904 activation patterns. Half of the mapped regions could not be analysed due to poor quality electrograms. Of the available high-quality recordings, an average of 2.1 ± 0.9 sites was analysed in each patient. There was an average of 6630 ± 2345 individual electrogram activations per map.

Heterogeneous activation patterns
The vast majority of AF recordings showed highly dynamic patterns of activations comprising multiple combinations of broad and narrow wavefronts, transient focal activations, and periods of disorganized activity. Three patients demonstrated transient rotational circuits. Figure 2 shows the regional analysis of the types of activations seen in each patient at the PLAW and LAA. There was marked heterogeneity in the types of activation patterns seen, both between patients and also between regions within the same patient. In the vast majority (91%) of maps, activation patterns during PerAF were characterized by multiple unstable activations, consisting of predominantly multiple wavefronts, focal activations and disorganized activity. These dynamic patterns transitioned from one to the next without a discernable order in the 10-s period. The most common activations seen were multiple wavefronts (56.2 ± 32%) and disorganized activity (24.2 ± 30.3%). Focal activations accounted for 11.3 ± 14.2% of all activations. Rotational circuits were only seen in 3 of 18 patients. The mean wavefront size was 20.9 ± 15 mm. The median and IQR of wavefronts sizes seen were 15 mm and 15.0–35.0 mm. Only two recordings showed a single consistent pattern of activation throughout the 10-s period. Both of these consisted of broad wavefronts passing through the LAA.
Figure 2  Regional characterization of AF activation patterns. This figure shows the regional analysis of activation wavefront patterns for each patient at each anatomical site. For each location, the coloured bars represent the proportion of activation types seen during that AF recording. As can be seen, there was marked heterogeneity in both activation patterns between patients and within the same patient.
Figure 3 Dynamic activation patterns. This diagram shows an example of the dynamic activation patterns seen in the PLAW of Patient 5. See text for description. Mapping key is displayed at the bottom of the panel. The colours denote the order of activation: black, first; blue, second; orange, third.
Dynamic activity
The majority of maps showed highly dynamic patterns of wavefront and on average 3.8 ± 1.6 activation pattern morphologies were observed per map. Figure 3 (Supplementary material online, Movie S5) illustrates the dynamic nature of the activation patterns seen in the majority of the AF maps. In just 3 s of AF, there are 24 activation pattern transitions, which are made up of various morphologies of activations including broad wavefronts, one to three narrow wavefronts, disorganized activity and focal activations. Focal activations although frequent were never sustained and were present for only one to two beats at each site of origin. Periods of disorganized activity in this patient were stereotypically brief. There is marked heterogeneity in the complexity of wavefront activations ranging from simple broad wavefronts or focal activations to multiple wavefronts within the same mapping area.

Preferential conduction of wavefronts
Although the order in which the activation patterns occurred appeared to be random, the directionality of wavefront activation appeared to be constrained to certain paths of preferential conduction. Evidence of preferential conduction patterns was seen in 15/36 (41%) regions mapped. They were typically seen in maps where the dominant pattern of activations was made up of broad and narrow wavefronts, with minimal disorganized activity. Figure 4 (Supplementary material online, Movie S6) shows example of preferential conduction from the PLAW of Patient 7. During this short-time segment, the PLAW is passively activated by a series of broad and narrow wavefronts that originate from outside the mapping area. Intermingled with the travelling wavefronts, there are brief periods of disorganized activity originating from within the mapping area. Despite the random order in which wavefronts appear at the mapping field, the wavefronts travel along preferential conduction pathways. Activation wavefront patterns are repeated despite multiple intervening activations of different morphology.

Transient rotational circuits
Evidence of transient rotational circuits was seen in three patients. The first of these circuits was located in the PLAW of Patient 4 (Figure 5, Supplementary material online, Movie S7). This circuit consisted of an unstable circuit (rotational frequency of ≏ 5.1 Hz) around a small area of consistent CFAE located at the centre of the rotational core. The size of the region of CFAE at the centre of the rotational circuit’s core measured 87.5 mm². Sites of high DF (DF: 11–14 Hz) were also located at the centre of this rotational circuit. Rotational activity involved a wavefront propagating clockwise around the mapping area, a scale consistent with macro-re-entry. As can be seen from the activation map and representative electrograms from the first beat (Figure 5A and B, respectively), we were not able to map the entire rotational circuit and only 78% of the total cycle length could be accounted for. As can be seen from Supplementary material online, Movie S7, this rotational circuit was not stable but broke up during the recording. Figure 6 shows the difference in the activation map and electrogram sequence between the first (Figure 6A) and last beat (Figure 6B) of the recording. As can be appreciated from this figure, there has a marked change in activation between the two beats, confirming that this circuit was not stable. In addition, only 50–60% of the cycle length of this final beat could be recorded on the mapping plaque.

Evidence of transient rotational circuit activity was also found in a further two patients (LAA of Patient 6 and PLAW of Patient 7). The diameter of both transient rotational circuits spanned the entire mapping plaque. For Patient 6, a transient rotational circuit activity appeared three separate times during the recording, with each episode lasting for five to seven revolutions (5.3–6.2 Hz) before disappearing (Supplementary material online, Movie S8). On all occasions, the rotational circuit’s activity occurred in the same counter clockwise direction with the rotational circuit’s core (diameter 62.5 mm²) appearing stationary. In between rotational circuit activity, several broad wavefronts can be seen passing directly through the location of the rotational circuit’s core on the mapping area without any evidence of slowed conduction or conduction block. Sites of HDF or CFAE did not localize to the centre of the rotational core in this rotational circuit. For Patient 7, a rotational circuit was seen once and consisted of six counter clockwise revolutions with a rotational frequency of 11.1 Hz (Supplementary material online, Movie S3). The rotational circuit’s core measured 31 mm² with sites of CFAE located within this region. In contrast, sites of HDF were not found at the centre of this circuit.

Focal activations
Focal activations accounted for 11.3 ± 14.2% of all activations and were seen in all areas mapped. Focal activations were all short lived lasting for less than two consecutive beats at each bipole site before becoming quiescent. None of the maps had sustained discrete focal activation from a single bipole or bipolar region that would be consistent with a focal driver. For one patient (Patient 9), focal activations accounted for 45% of total activations seen in the LAA map. Sites of earliest activation were mapped to a diffuse area (~ 2.19 cm²) on the anterior epicardial surface of the LAA rather than to a single bipole.

Disorganized activity
Disorganized activity accounted for 28.6 ± 33.9% of all activations seen per map. During disorganized activity, activations of individual bipoles appear dissociated from adjacent bipoles (Supplementary material online, Movie S4). Intermittently, small contiguous areas (one to two bipoles) of the adjacent epicardium are activated together; however, they fail to form wavefronts as ongoing propagation is blocked by refractory tissue caused by the disorganized activation of other sites. The mean number of bipoles activated at a focal site was 2.1 ± 1.3. The duration of disorganized activity was quite heterogeneous, with an average of 3.2 ± 3.6 s seen per recording. In some instances, it only appeared transiently (100–200 ms), while in others disorganized activity was present for the entire recording.

Complex-fractionated atrial electrogram
The percentage of CFAE per epicardial map was 13.3 ± 10.4%. The percentage of CFAE in each of the four anatomical regions mapped was PLAW 12.9 ± 11.0%, LA appendage 11.3 ± 9.6%, RA appendage 17.2 ± 12.9%, and RSPV-LA junction 13.3 ± 10.4%. There was no difference in the prevalence of CFAE in each of these anatomical regions (P = 0.711).
Discussion

The main findings of this study are as follows:

1. Human PerAF was characterized by highly dynamic and heterogeneous patterns of atrial activation consisting predominantly of multiple unstable wavefronts (56.2 ± 32%) and disorganized activity (24.2 ± 30.3%). In these 10 s recordings, transient rotational circuits were seen in 3 of 18 patients but repetitive focal activity was not observed.

2. Unstable wavefronts were made up of a combination of broad (31.5%) and one to three narrow wavefronts (68.5%). In 41%
of maps, wavefronts showed repetitive patterns of preferential activation.

3. Periods of disorganized activity were seen in all mapping regions with a trend to be more commonly seen in the PLAW compared with other regions.

4. Transient rotational circuits were observed in 3 of 36 (8.3%) atrial regions mapped and in 3 of 18 (16.7%) patients. In each of these patients rotational activity was transient, extinguishing and reforming. The rotational circuits involved the activation of the entire mapping plaque, a size consistent with macro re-entry.

5. Focal activations were commonly seen (11.3 ± 14.2%), but generally occurred as one to two isolated beats with no regions demonstrating sustained focal activity.

Theoretical and animal models of AF

While the pulmonary veins are known to be the source of triggers for the initiation of AF, the mechanisms that sustain PerAF in humans are not well understood. Existing hypotheses propose that AF may be maintained either by (i) ‘multiple unstable wavelets’ or (ii) single or multiple sources within the atria. Well-known computer models and animal studies exist, which support these differing mechanisms. Recently, Allessie and coworkers have proposed an alternate mechanism termed the double layer hypothesis.

Human mapping studies

Several epicardial mapping studies in patients with PerAF and structural heart disease have found evidence for multiple unstable wavefronts within the LA, while another observed regional regular short-cycle length activity potentially indicative of focal sources. To date, no high-density epicardial mapping study has confirmed the existence of rotors in human PerAF. Recently, Allessie and coworkers analysed AF wavefronts in patients with long-standing PerAF. By breaking down the complex activations in AF into individual fibrillatory waves, they found that the vast majority (90.5%) of focal fibrillatory waves were due to epicardial breakthrough from waves.

Figure 5 Rotational circuit. (A) Activation map of one revolution of the rotational circuit with the central area of complex-fractionated atrial electrogram shaded in grey. Arrows represent clockwise rotation of the rotational circuit, which had a CL of ≏200 ms (≏5 Hz). Numbers (1–12) represent location of electrograms shown in (B). (B) Representative dominant frequency and electrograms from sites just outside the rotational core. (C). Representative dominant frequency and electrograms from the centre of the rotational core of this circuit.
travelling in deeper layers of atrial tissue and not due to a focal mechanism. They hypothesized that endocardial–epicardial dissociation allowed the breakthrough of these focal waves, which became the equivalent of multiple focal sources. In support of this concept, Eckstein et al.\textsuperscript{14} recently performed simultaneous endocardial–epicardial in vivo mapping data in a goat model of AF and showed that both the incidence and degree of endocardial–epicardial dissociation increased with increasing AF duration and complexity of AF substrate. In both of these mapping studies, rotors were not detected. Sahadevan et al.,\textsuperscript{4} in an epicardial mapping study of nine patients with chronic AF observed regional short-cycle length activity in seven of these and speculated that this may represent the presence

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{This figure shows a comparison of activation pattern and electrogram activation sequence between the first beat (A) and the last beat (B) of the recorded rotational circuit. As can be seen, there is a clear change in the activation between the two beats, confirming that the rotational circuit was not stable but broke up during the recording.}
\end{figure}
of a driver as one mechanism of AF. In contrast, Narayan et al.6 used a 64-electrode basket catheter and customized software to endocardially map and target focal sources (rotors and focal impulses) in patients with persistent and paroxysmal AF. Localized rotors (70%) or focal (30%) impulses were detected in the majority (98%) of patients with a mean of 2.1 ± 1.0 sources per patient. AF sources were conserved for at least 10 min during mapping and were found in a variety of left and right atrial regions. Targeted ablation at the centre of these focal sources resulted in AF termination in 86% of cases.

Using a high-density epicardial wave-mapping technique, which allowed analysis of 10 s recordings, we observed that in the majority (97%) of patients with PerAF, maps are characterized by the presence of multiple unstable activations. Although highly unstable, wavefronts showed repetitive patterns of activation and preferential conduction suggesting elements of deterministic behaviour possibly due to constraints of anatomic architecture or transient linking due to areas of functional conduction block created by previous wavefront activations.15 Additionally, the presence of preferential conduction pathways may be more consistent with the concept of fibrillatory conduction (mapped) from an upstream source (unmapped) than with the alternative hypothesis of self-regenerating disordered random wavelets.

The transient focal activations and disorganized activity seen in our study may represent epicardial breakthrough from fibrillation waves propagating in deeper layers of the atrial wall as proposed by Allessie et al. The disorganized activity seen in our study is consistent with the description of PerAF fibrillation waves seen by Allessie et al. In that study, epicardial activation during PerAF was predominately characterized by multiple narrow wavefronts bounded by conduction block, whereby inter-wave conduction block exhibited highly dynamic behaviour and shifted continuously in positions. The high incidence (~29% of activations per map) of disorganized activity seen in our study supports the concept of endo-epicardial dissociation and mutual endo-epicardial breakthroughs as a potential mechanism for perpetuation of AF in patients with long-standing AF and valvular disease.

The rotational circuits seen in our study are large and occupy the entire mapping area. Rotors observed in optical animal mapping studies also activate large areas of atria tissue.16,17 Although Mada- pati et al.16 reported rotor activation around minuscule cores in a sheep model of AF (mean perimeter 10.4 ± 2.8 mm and mean core area 3.9 ± 2.8 mm²), the authors also demonstrated 1:1 rotor activation occupying up to 20–50% of the mapping area.17 Whether or not rotor activation is conducted in a 1:1 manner to all areas of the atria or breaks down (i.e. fibrillatory conduction) may be dependent on a number of factors such as rotor cycle length, tissue heterogeneities, refractory periods, and the presence of scar. An area of CFAE obscured the centre of the stable rotation circuit and, therefore, we were unable to use our mapping algorithm to visualize wavefront dynamics in this location. In particular, we were unable to determine whether the leading edge of the depolarizing wavefront was convex and consistent with a rotor/spiral wave or planar and consistent with ‘leading-circle’ re-entry. Given that optical mapping studies in animals16,18 have suggested that the centre of rotors have submillimeter spatial resolutions, the epicardial mapping plaque used in this study probably does not have the spatial resolution to clearly define centre of a rotor or the so-called phase singularity.

The recent publication by Narayan et al.6 using a multipolar basket catheter suggests that rotor activity involves depolarization of a significant portion of the atria and appear to be macrore-entrant in size as opposed to the small circuits seen in animal studies. In addition, they have also reported that rotors may process (wobble) within circumscribed spatial areas (~2.5 cm) and this phenomenon contributes to alter surrounding atrial activation over multiple rotor revolutions.19 Our mapping data are similar to observations by Narayan who reported that rotors seen during human AF may actually involve the activation of much larger areas of the atria than have been previously hypothesized. Unlike Narayan et al., we were not able to map the entire activation sequence of the transient rotational circuits seen in our study. This may be the result of rotor precession in and out of the mapping field of view or alternately represents rotational activity activated from outside the plaque accounting for the missing percentage of unmapped tachycardia cycle length. Additionally, in contrast to Narayan et al., we only observed the presence of rotational circuits in a minority of patients.

Recently, Ganesan et al.20 used Shannon entropy (ShEn) analysis to try and localize rotors in computer and animal models of AF. Unlike the ‘traditional’ method of directly visualizing rotors (as was used in the current study), ShEn is a statistical measure of the uncertainty in a random variable. They hypothesized that as a result of the constantly changing wavefront direction at the pivot point of a rotor, bipolar electrograms recorded close to the rotor’s core would have a higher calculated ShEn. Conversely, bipolar sites activated by ‘simpler’ wavefronts far away from chaotic central pivot point would have a lower calculated ShEn. In both their computer and animal models, Ganesan et al. found that maximum ShEn was consistently co-located at the pivot zone of rotors. At this stage, ShEn has only been validated in these animal models and their ability to localize rotors during human AF is yet to be determined.

In the presence of advanced structural heart disease, fibrosis, and a heterogeneous electrical substrate, rotors or spiral waves may interact with functional discontinuities, become anchored and exhibit properties of both unattached spiral waves and anatomic re-entry.21 As suggested by Comtois et al.,22 it may not be possible to characterize activation patterns in human AF as purely functional re-entry or pure rotor activity. To this end, the rotational circuits seen in our study may also represent ‘mother waves’ or stable re-entry circuits that are defined by the underlying atrial architecture that act to drive the AF process as described in previous mapping studies.23–25

Owing to the access constraints of high-density epicardial mapping in humans, coverage of the atrium was relatively limited. In the absence of global continuous mapping, we cannot confirm whether the rotational circuits or multiple wavefronts observed are critical to the persistence of human AF. Nevertheless, our data are consistent with a role both for rotational circuits and multiple wavefronts in the mechanism of this arrhythmia.

**Limitations**

The high-density epicardial mapping plaque used in this study provides coverage of ~10% of the atria and hence has a narrow field of view relative to the global bi-atrial surface area. Thus from a
segment of atria mapped, we could only determine whether a rotational
circuits or a focal source is present and not whether it was crit-
ical in driving wavefronts elsewhere in the atria. It is possible that
more rotational circuits could have been present if had we been
able to map more widely. In addition, we cannot exclude the possi-
biility that rotational circuits were quiescent during the recording
period. It is possible that drivers would be more frequently observed
in patients with PerAF of < 1 year in duration. There was heterogen-
ity in the types of structural heart disease present in the study popu-
lation. As such we were unable to determine the relative impact of
structural remodelling and differences in atrial fibrosis patterns on
the types of wavefront propagation patterns observed in this study.
The clustered samples used in this study are not as statistically ef-
icient as simple random samples and similarities among subject clus-
ters may reduce the variability of responses from a cluster compared
with those expected from a simple random sample. As a result, mul-
tiple measurements from the same patients tend to be positively cor-
related and hence are more alike than observations between
individuals.

Conclusion

Human long-lasting PerAF is characterized by heterogeneous and un-
stable patterns of activation including wavefronts, transient rotational
circuits, and disorganized activity.

Supplementary material

Supplementary material is available at European Heart Journal online.

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