Ablation strategies to treat atrial fibrillation (AF) have evolved from the initial focal pulmonary vein ablation approach of Haïssaguerre et al.1 to new technical developments aimed at simplifying the procedure and increasing its safety.2 However, ablation procedures are still associated with unsatisfactory rates of long-term success, particularly in persistent and long-term AF.3 We submit that such disappointing outcomes are the result of the intrinsic limitations of a strategy that has relied mainly on anatomic landmarks during the past 2 decades, and paid scant attention to the underlying mechanisms of the arrhythmia.

Recently, approaches aimed at localizing and targeting AF sources based on careful analysis of the fibrillatory patterns often obtained via multiple electrode mapping systems (basket-catheter mapping, body surface mapping, and electrocardiographic imaging [ECGI]) have resulted in an increased specificity of ablation procedures, and long-term freedom from AF.4,5 Such mechanistically based ablation techniques have the potential to enable translational insights from experimental animal models into further improved AF ablation therapy. Indeed, they are a direct result of insights into the dynamic behavior of AF drivers, obtained from experimental optical mapping studies and computer simulations of AF dynamics.

The purpose of this article is to briefly review the following: (1) competing theories attempting to explain mechanisms underlying AF maintenance, (2) different methodologies to map electric activity during AF, (3) the most recent mechanistic ablation approaches aimed at targeting AF drivers and their outcomes, and (4) the controversies and near-future directions in the quest to increase the understanding of AF mechanisms and improve ablation outcomes.

Mechanisms Underlying AF Maintenance

Historical Perspective: Reentry, Ectopic Foci, Random Waves, Complex Fractionated Atrial Electrograms, and Endo-Epicardial Breakthroughs

AF mechanisms have a long history of controversy.6 During the first half of the 20th century, 2 theories were prevalent: the concept of reentry around an anatomic obstacle (circus movement reentry),9 and the ectopic focus theory.10 Focus isolation in the latter terminated the arrhythmia.10 In 1959, Moe and Abildskov11 postulated that fibrillation was sustained by multiple independent, electric wavelets propagating randomly throughout the atria. Clinical support for this hypothesis seemed to come from the Maze procedure, a surgical procedure that effectively creates an electric maze in the atrium, allowing sinus impulses to activate the entire atrial myocardium and AV node, but disallowing maintenance of the randomly propagating wavelets that, allegedly, would sustain AF.12 Importantly, this procedure isolated the pulmonary veins that were later recognized as important triggers of AF.1

In 1977, Allessie et al13 described the concept of functional reentry via the leading-circle hypothesis. Years later, leading-circle reentry was observed during pacing-induced AF in humans,14 and both foci and reentrant mechanisms were found during cardiac surgery in patients with permanent AF and mitral valve disease.15

A decade ago, Nademanee et al16 proposed that areas with complex fractionated atrial electrograms (CFAEs) may be critical for maintaining AF and their ablation might result in better clinical outcomes. CFAEs were described as fractionated or continuous electric activity at short cycle lengths.16 CFAEs may colocalize with potential drivers of AF (rotor cores).17 However, most CFAEs are passive, consequence of fibrillatory conduction, wavefront collision, drifting/acceleration of rotors,18 fibrosis,19 or might be even considered an artifact of the bipolar recording methodology because they are a function of the interelectrode distance.20

More recently, the so-called double-layer hypothesis based on high-density atrial data has been put forth,23 suggesting that persistent AF is maintained by endo-epicardial breakthroughs acting as randomly distributed multiplication sites of fibrillation waves. Such breakthroughs are envisioned to continuously generate new breakthroughs emerging at the contralateral layer, sometimes annihilating other preexistent waves in the new layer.21 A double-layer mechanism of persistent AF would have important practical consequences because it would make
it impossible for a limited ablation to successfully restore sinus rhythm.\textsuperscript{21} However, it has been reported that acute termination of AF can be achieved after ablation at specific target sites in most patients with paroxysmal and persistent AF;\textsuperscript{4–7,22} which supports the idea of driving sources underlying AF.

**Rotors and Scroll Waves**

The use of voltage-sensitive probes and high-resolution video imaging in isolated animal hearts has provided support for the hypothesis that AF may be driven by one or a small number of high-frequency rotors.\textsuperscript{23–29} Rotors are 3-dimensional (3D) electric objects (scroll waves) but current technical limitations restrict their detection to 2 dimensions (Figure 1A) either from the epicardial or from the endocardial surface. In theory, a typical scroll wave rotates around a linear {\textregistered}shaped filament (Figure 1B) that spans the atrial wall, although filaments may also acquire more complex shapes (L shape, U shape, and O shape).\textsuperscript{30} Often, one can only observe indirect footprints of scroll waves in the form of breakthrough patterns resembling focal activation.\textsuperscript{21} In addition, the true drivers that maintain AF are those with the highest rotation frequency, and whose domain of 1:1 activation is the narrowest, which makes it extremely difficult to find them even at the highest spatiotemporal resolution provided by optical mapping. The waves generated by such rotors propagate through the cardiac muscle and interact with anatomic and functional obstacles leading to fibrillatory conduction, fragmentation, and new wavelet formation.\textsuperscript{31} Narayan et al\textsuperscript{7} have recently reported evidence of stable rotors in human patients with either paroxysmal, persistent, or long-lasting AF. Haissaguerre et al\textsuperscript{6} have also recently reported that 80% of the drivers during persistent AF were reentrant. Most rotors and focal breakthroughs colocalized and \textgtrtext{}70% of them were in the left atrium (Figure 1C). Therefore, not only experimental but also growing clinical evidence indicates that rotors can be key players in AF maintenance.

**Mapping Methods to Localize Sources and Understand AF Dynamics**

**Spectral Analysis and Phase Mapping**

Both spectral analysis and phase mapping of cardiac potentials can be applied to any of the approaches described in the next subsections. Both algorithms derive originally from optical mapping experiments conducted in isolated hearts.\textsuperscript{23,32}

Spectral analysis is used to map the distribution of AF frequencies and localize the areas with the highest activation frequencies (ie, the shortest cycle lengths),\textsuperscript{23} which usually coincide with the location of AF sources (foci or rotors) that maintain AF.\textsuperscript{5,55} A good tutorial for clinicians on spectral analysis of AF electrograms may be found elsewhere.\textsuperscript{33} Briefly, the spectrum of a signal displays its energy/power distribution in the frequency domain. The frequency of the highest peak in the spectrum at 1 location is called dominant frequency (DF), which is often used as a surrogate for the average activation rate (ie, the inverse of the cycle length) at that location (Figure 2A).\textsuperscript{33} Spectral analysis becomes particularly useful when the activation rate is difficult to measure in the time domain, as may happen during AF. Figure 2B and 2C illustrates examples of DF maps obtained during optically mapped AF, where areas of maximum DF (DF\textsubscript{max}) thought to drive the fibrillation process are displayed. These areas are surrounded by others that are incapable of activating at such exceedingly high frequencies and depict fibrillatory conduction.\textsuperscript{31}

Phase mapping is a complementary approach that enables visualization of the spatiotemporally distributed patterns of propagation during cardiac fibrillation by determining the local phase of the activation/recovery cycle at each time point. It makes it possible to detect the phase singularities (ie, the rotor pivots) that organize reentry and fibrillation (Figure 3). It can also be used to analyze electrograms,\textsuperscript{34} although optical mapping (the gold standard) provides much higher resolution and accuracy in space and time when tracking rotor formation and maintenance.\textsuperscript{35} A tutorial on phase mapping during cardiac fibrillation can be found elsewhere.\textsuperscript{34}

**Simultaneous Epicardial and Endocardial Optical Mapping**

The introduction of optical mapping more than 2 decades ago enabled the characterization of wave propagation with submillimeter resolution and postulated rotors as potential drivers of cardiac fibrillation in animal models.\textsuperscript{23,26,29,32,36–38} More recently, recording voltage-sensitive dye fluorescence simultaneously from the endocardial and epicardial surfaces (Figure 4A)\textsuperscript{24,25,27,28} enabled interpretation of the
Ablating the Drivers of Atrial Fibrillation

3D behavior of scroll waves. Generation of phase movies identified several patterns of activation, including rotors (Figure 3A) and breakthroughs (Figure 3B). Interestingly, these experiments identified I-shaped scroll waves in the left atrium spanning from epicardium to endocardium.28 As expected, each mapped surface showed synchronized 2D rotors (Figure 4B). Other recorded patterns also suggested the presence of L- or U-shaped intramural scroll waves by the presence of differing activation patterns at each surface (Figure 4B).27 Recently, simultaneous subendo-subepicardial optical mapping of ex vivo diseased human right atria has shown that pinacidil-induced fibrillatory activity was driven by spatially and temporally stable intramural reentry anchored to fibrosis-insulated and twisted atrial bundles. Radiofrequency ablation of these localized microreentrant tracks terminated the fibrillatory activity.39 However, current optical mapping strategies do not allow panoramic endocardial mapping and require the use of potentially toxic voltage-sensitive dyes that preclude their use for human in vivo studies.

Figure 2. A, Bipolar electrogram obtained from the left atrial appendage of a patient with atrial fibrillation (AF). Red circles display activation times. Note that the fundamental peak of the spectrum is located at a frequency (DF) that matches the average activation rate (AAR). The peaks located at the frequencies multiple of the DF are called harmonics. A harmonic peak should not be selected as DF because this would lead to wrong conclusions. B, Top, DF maps in a normal sheep heart during stretch-induced AF showing fibrillatory conduction from the highest frequency domain (DF_max, 16 Hz, in red) located at the PLA, specifically at the left superior pulmonary vein (LSPV) and left inferior pulmonary vein (LIPV). Colors in each map indicate atrial areas (domains) with different DFs. The color bar on the right indicates frequency in Hz. A large frequency gradient between the fastest (red) and the slowest (blue) domains is usually found in acute episodes of AF. Bottom, Aggregated data from normal sheep hearts during stretch-induced AF showed that rotors were mainly located at the PLA and left atrial appendage (LAA). C, Top, DF maps of atria from sheep with persistent AF where a more homogeneous distribution of DFs (lower gradient) was found. The DF_max domain was located at the LAA (in red, 7.4 Hz). Colors in each map indicate atrial areas (domains) with different DFs. The color bar on the right indicates frequency in Hz. As shown, in persistent AF, the frequency gradient between the fastest and the slowest domains is usually smaller than in paroxysmal episodes. Bottom, Aggregated data from hearts showed that, in persistent AF, the role of the pulmonary veins becomes less prevalent in terms of harboring rotors. AAR indicates average activation rate; CL, cycle length; DF, dominant frequency; Endo, endocardial view; Epi, epicardial view; FT, Fourier transform; IVC, inferior vena cava; PLA, posterior left atrium; RAA, right atrial appendage; RIPV, right inferior pulmonary vein; RPV, right pulmonary vein; and SVC, superior vena cava. B and C, Adapted from Yamazaki et al.28
Multielectrode Plaque Epicardial Electric Mapping

Over the years, many studies have used high-density multielectrode plaques to record local epicardial electric activity from patients undergoing cardiac surgery.14,15,21,40 These approaches have the advantage of not requiring the use of voltage-sensitive dyes, which makes the technique suitable for in vivo mapping in humans. However, placing multielectrode plaques on the epicardium requires open chest surgery and is limited to small areas with limited spatial resolution when compared with optical mapping, although

![Figure 3](image-url)

**Figure 3.** Varying activation patterns identified in phase movies from the left atrium of the sheep heart. **A**, Sequential snapshots show a rotor pivoting around a phase singularity (point where all phases converge). **B**, Breakthrough activation pattern. The wave seems on the center of the field of view and propagates outward. **Right**, Key for the different phases of the action potential is color-coded. Reproduced from Filgueiras-Rama et al.24

![Figure 4](image-url)

**Figure 4.** **A**, Optical mapping setup for simultaneous endo-epicardial mapping. An endoscope is focused on the endocardial surface of the posterior left atrium (PLA) or left atrial appendage (LAA). A CCD camera is coupled to the endoscope and laser illumination is provided. Epicardial mapping of PLA or LAA is simultaneously performed. **B**, From left to right: examples of simultaneous endo-epicardial breakthrough activation and potential intramural I-, L-, and U-shaped scroll waves. LIPV indicates left inferior pulmonary vein; LSPV, left superior pulmonary vein; LV, left ventricle; MV, mitral valve; RA, right atrium; RAA, right atrial appendage; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; and RV, right ventricle. **A**, Reproduced from Yamazaki et al.28 **B**, Adapted from Yamazaki et al.27
occasionally it is possible to identify rotational activation sequences, which might be compatible with rotors (Figure 5).40

**Basket-Catheter Endocardial Electric Mapping**

Recently, Narayan et al7 used two 64-pole basket-catheters to obtain simultaneous unipolar endocardial electrograms from 128 locations in both atria of patients undergoing AF ablation (Figure 6A). A computational mapping system (Rhythm-View, Topera, Inc) processed these electrograms to generate activation movies of the atrial electric activity after considerable processing and interpolation.41 Local activation times were calculated as the times when each unipolar electrogram crosses a certain voltage threshold. Monophasic action potentials were used to establish the minimum repolarization interval and obtain physiologically feasible sequential activation paths. Movies of activation patterns and isochronal maps from individual cycles were obtained after using bilinear interpolation of the “phase state” between each electrode and its nearest neighbors (Figure 6B).41 Rotational activities (early-meets-late, ie, red-meets-blue) around a center of rotation were identified as rotors. Focal (centrifugal) activations were also identified. Both were considered drivers only if they sustained for ≥50 rotations or focal discharges (arbitrary limit).7 The main advantages of this approach are that, in contrast to the ECGI method described below, (1) it does not use estimated but real cardiac potentials and (2) enables real-time assessment of changes in driver activity during the ablation procedure. More arguments in favor of this mapping approach can be found elsewhere in a recent theoretical study.41

However, there are many limitations that need to be considered: (1) the system uses a proprietary algorithm that makes the methodology difficult to evaluate because the electrograms from which the color maps are obtained are not usually shown; (2) like any other electrode recording system, extracellular signals are subject to artifacts,35 and ventricular

---

**Figure 5.**

A. Activation map of a clockwise revolution of a rotational circuit at the posterior left atrial wall. Electrodes registering complex fractionated atrial electrograms (CFAEs) at the core are shown in gray (no local activation times were assigned given their ambiguity). B. Frequency domain (left, 3–15 Hz) and time domain (right) electrograms from sites just outside the core (1–12). The numbers in the frequency domain signals display dominant frequencies. The white arrow in the time domain displays the clockwise sequence of activation. C. Frequency domain (left, 3–15 Hz) and time domain (right) CFAEs from sites inside the core. DF indicates dominant frequency. Reproduced from Lee et al40 with permission of the publisher. Copyright © 2013, The Authors.
activity often contaminates atrial recordings; thus an appropriate QRS-T complex subtraction technique is critical; (3) basket-catheters often offer suboptimal electrode-tissue contact at many poles; (4) the splines are sometimes not equidistantly separated once they are deployed in the atria and the raw interspline spatial resolution offered by basket-catheters is poor; (5) in the presence of scarce or poor quality data, the amount of extrapolation is difficult to determine; and (6) interpolation of phases is inherently biased toward detection of rotors as the algorithm is devised to demonstrate rotational activity. Thus, focal activation might be displayed as rotational activity if the wavefront reaches the surrounding electrodes sequentially.35 Although the approach is not universally accepted, it is one of the first mechanistically based approaches to AF ablation that has reported promising results in the long-term42 and during its first multicenter validation.22

Body Surface Mapping

The noninvasive body surface mapping (BSM) methodology has recently gained visibility for the analysis of activation patterns during AF.43,44 Guillem et al43 used a custom-made 67-electrode vest that covered the whole torso of the patient (Figure 7A and 7B); intracardiac signals at several locations were simultaneously recorded. They selected either segments without ventricular activity after adenosine infusion or applied QRS-T subtraction if such intervals were not found. After computing and performing comparisons between intracardiac and surface DF maps, they demonstrated that high-frequency sources could be reflected on a small area of the body surface close to the atrium harboring the highest DF (Figure 7C).43 More recently, Rodrigo et al44 used phase mapping and filtered the unipolar signals with a narrow 2-Hz band-pass around the highest DF filtering to improve the detection of stable rotors (8.3% of the time before filtering and 73% after filtering, Figure 7D and 7E). Before highest DF band-pass filtering, phase maps displayed unstable reentries, probably as a result of superposition of the disorganized electric activity coming from the rest of atrial tissue. Highest DF band-pass filtering accentuated the organized activity of scroll waves, after which...
Figure 8. A, Block diagram of the electrocardiographic imaging (ECGI) procedure. B, Phase mapping of ECGI data in a patient with persistent AF. A full rotation of a rotor in the inferior left atrium is displayed. Electrograms around its core are also shown (1–12). C, Example of a driver density map used to guide the ablation process in a patient with drivers clustered in 3 regions: inferoposterior left atrium (ILA) and right and left pulmonary veins. CT indicates computed tomography; LAA, left atrial appendage; LIPV, left inferior pulmonary vein; MV, mitral valve; RAA, right atrial appendage; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; and TV, tricuspid valve. A, Reprinted from Ramanathan et al.45 with permission of the publisher. Copyright © 2004, Nature Publishing Group. B and C, Reproduced from Haissaguerre et al.6
rotors were the main pattern of activation during AF (median of 2.8 rotations, present 73% of the time). Also, computer simulations showed that epicardial propagation is spatially smoothened when projected on the torso. For example, nearby epicardial rotors with opposing chirality may not be detected on the torso. This fact and the possibility of temporal intervals in which AF activity may be affected by ectopic foci, could explain the lack of detected rotors during the remaining 27% of the time.44

**Electrocardiographic Imaging**

The output of BSM is potentials on the body surface, not on the heart. In contrast, the ECGI mapping system developed by the Rudy laboratory (Figure 8A) provides estimated epicardial electrograms in relation to the heart’s anatomy. The approach uses >250 electrodes distributed throughout the patient’s torso, which in combination with computed tomographic imaging enables the positioning of the heart’s epicardial geometry in relation with the electrode positions. The body surface potentials recorded by the electrodes and the geometric information provided by computed tomography are combined by complex mathematical algorithms that solve the electrocardiographic inverse problem to noninvasively obtain estimated epicardial electrograms.45,46

The main advantage of this approach is that it is noninvasive and it does not require surgery or sedation, and could be used to provide detailed data on follow-ups and AF recurrence.45,46 However, limitations similar to the BSM approach apply because AF body surface potentials often have low voltages and are smoothed by the torso volume conductor.45,46

These include poor sensitivity for detecting low amplitude signals (eg, from scarred or previously ablated areas) or highly localized sources.45,46 Indeed, ECGI does not discern among epicardial breakthroughs, spontaneous depolarizations and microreentry (subcentimeter), which are seen as focal activity.46 Also, ECGI is limited to providing virtual electrograms of the atrial epicardium. Therefore, activity on the interatrial septum, pulmonary vein-left atrial appendage ridge, etc, is not recorded. Importantly, computed tomographic imaging is required to obtain the torso geometry, so the patient is exposed to a considerable dose of radiation.45,46

Haissaguerre et al45,46 have recently used the ECGI approach,45,46 combined with phase mapping to detect AF drivers during persistent AF and guide the ablation procedure. Intervals (≥1 s) free from ventricular activity were selected for analysis to avoid QRS-T complex subtraction.6 Phase mapping movies were displayed over the biatrial geometry. AF sources were classified as either focal or reentrant. In the latter, raw local electrograms were visualized to confirm their truly reentrant nature (sequential activation around the core, Figure 8B). The authors reported that these rotors moved over wide regions of the atria, but recurred periodically in the same region. The median and maximum number of rotations per rotor was 2.6 and 8, respectively.

**Outcomes of New Mapping and Mechanistic Approaches for AF Ablation**

Pulmonary vein isolation (PVI) remains the “gold standard” approach to treat drug-refractory AF. However, its success rate remains suboptimal especially in patients with persistent AF in whom more extensive ablation techniques have been proposed.3 Targeting CFAEs or linear ablation are some of the complementary strategies after PVI.3 Recent results from the Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II (STAR AF II) trial have shown that the addition of further ablation (lines or CFAEs) to PVI increased ablation time but did not reduce the recurrence of AF in 589 patients with persistent AF.3 At 18 months, the percentage of patients who were free from AF recurrence after 1 procedure without antiarrhythmic medication did not significantly differ among groups (PVI alone, 48%; PVI+CFAEs, 37%; and PVI+lines, 33%).3 This confirms that CFAE and extensive ablation has clearly lost momentum in favor of more specific and mechanistically based approaches for AF ablation.

**Ablation of High DF Sites**

Because atrial regions with the highest activation frequencies (DF max) may host the drivers that maintain AF,4,5,22 targeting DF max areas may effectively terminate AF. Atienza et al4 first used such a strategy in patients with AF.4 They used an electroanatomical mapping system with embedded real-time spectral analysis capabilities to generate DF maps during sequential acquisition of bipolar signals.5 PVI was complemented with ablation of DF max sites. This protocol achieved 88% and 56% long-term freedom of AF in patients with paroxysmal and persistent AF, respectively, in all cases a DF gradient was abolished by the ablation.4 Even though sequential point-by-point acquisition of bipolar signals is limited in its ability to identify high-frequency sources that are often dynamic, and may drift or change over time, the recent multicenter Radiofrequency Ablation of Drivers of Atrial Fibrillation (RADAR-AF) trial conducted in 232 patients demonstrated that targeting DF max sites in paroxysmal AF was not inferior to, and was associated with a lower incidence of severe adverse events than conventional PVI at 1-year follow-up.5 Although a pure DF max mapping strategy has not been compared with PVI in persistent AF cases, DF max ablation after PVI did not improve ablation outcomes and significantly increased the risk of adverse events.5 These results have been interpreted by some as “more evidence favoring antral PVI in patients with either paroxysmal or persistent AF”.47 However, an alternative interpretation is that (1) PVI is not the “cure” for all AF, (2) extensive ablation procedures that include PVI predict a poor long-term outcome,3 and (3) there is an urgent need for more mechanistically based mapping to guide limited ablation strategies.

**FIRM Ablation**

The novel computational mapping approach described in a previous section (Basket-Catheter Endocardial Electrical Mapping) has recently shown localized sources (long-standing rotors or foci) sustaining the arrhythmia in 98% of patients with AF.7 The patients (71% with persistent AF) were prospectively treated by focal impulse and rotor modulation (FIRM)–guided ablation followed by PVI versus PVI alone. In each case, a median of 2 sources were classified as reentrant. The number of sources was significantly higher in patients with persistent AF than in patients with paroxysmal AF. Interestingly, AF acutely terminated in 56% of cases after brief ablation of the primary source without performing PVI. Conversely,
AF termination was only achieved in 20% of cases who underwent conventional PVI. Recently, an extended 3-year follow-up results of the trial have been reported. Patients in the FIRM-guided ablation group maintained higher rates of freedom from AF (78% versus 36%) after a single procedure. However, it is important to note that FIRM-guided ablation protocol included not just the ablation of potential drivers, but also, PVI and other standard procedures. The initial independent outcomes for FIRM ablation at 10 experienced centers have been also reported. Each patient exhibited a similar mean of rotors/focal sources (≈2.3) as previously reported (25% in the right atrium). After a single procedure and 1-year follow-up freedom from AF was 87.5%.22

### Ablation of Driver Domains in Persistent AF

Recently, Haissaguerre et al6 reported the results of their mechanistic approach in persistent AF ablation. They used ECGI combined with phase mapping to identify the drivers of persistent AF in 103 patients undergoing AF ablation. They observed incessantly changing wavefronts and a varying spatiotemporal behavior of drivers. Reentrant drivers were unsustained and meandered substantially, but recurred repetitively in the same region. Aggregated driver density maps (Figure 8C) were computed during a cumulative registering period to guide the ablation procedure (median, 4 driver domains per patient). Interestingly, the number of driver regions increased with the continuous duration of AF. Ablation of driver domains alone terminated AF in 63% of patients presenting in AF (75% persistent and 15% long-lasting persistent AF), which supports the presence of stable high-frequency sources at certain regions of the atria. The onset or extinction of drivers during ablation was not assessed, so there is room for improving the ablation results if real-time data are used. After a 12-month follow-up, 83% and 75% of patients with paroxysmal or persistent/long-lasting AF were free from AF, respectively.6

### Controversies and Future Directions

Multiple experimental and clinical studies using widely different technologies are creating a growing body of evidence in favor of organized sources underlying AF maintenance. It remains unresolved whether such sources are (1) one or a few stationary and stable rotors or microanatomic intramural reentries, (2) multiple short lived but iteratively created rotors at restricted locations, (3) stable ectopic foci, or (4) short lived but repetitively triggered focal bursts. Interestingly, some of these seemingly different underlying mechanisms might converge if one considers the different mapping, filtering, and interpolation approaches that are being used to display the atrial electric data, the 3D nature of the atrial tissue, and the imperfections of the recording systems being used. For example, although apparently different, rotors/intramural reentry and foci may be dynamic manifestations of the same mechanism within the 3D structure of the atria. Thus, so-called foci might actually represent breakthroughs generated by intramural scroll waves with nonlinear filament shapes (U shape, L shape, or even O shape, Figure 4B), or microanatomic intramural reentries.39

The noninvasive ECGI approach by Cuculich et al46 showed foci, but only rarely demonstrated reentry in AF. Rotors seemed short lived but their location was reproducible through several ECGI movies.46 However, ECGI lacks the ability to discern among epicardial breakthroughs, spontaneous depolarizations, and (subcentimeter) microreentry, which are seen as focal activity.46 In addition, in BSM (and likely in ECGI), appropriate filtering enables detection of more stable reentrant high-frequency sources by suppressing secondary influences from disorganized activity.44 Although not fully disclosed, the ECGI/phase mapping approach used by Haissaguerre et al6 might have included similar filtering because similar stabilities of rotors were reported in both studies (median, 2.8 rotations in Rodrigo et al44 and 2.6 rotations in Haissaguerre et al6). In both studies, rotors were detected most of the time.4,6,44 The presence of fast reentrant sources and the concept that targeting limited areas may be enough to terminate AF is supported by the outcomes of recent studies.4–7,10,42 In contrast, it is now clear that targeting CFAEs or performing additional linear ablation add unnecessary ablation because of lack of specificity.6

Even though low-density basket-catheter endocardial electric mapping3 and noninvasive BSM/ECGI approaches1,44 provide seemingly different descriptions of the drivers maintaining human AF, both coincide in their mostly reentrant nature. The former describe long-standing drivers.7 The latter observe substantial drifting and repetitive short-lived reentries requiring statistical driver density maps.6 Although the interaction of stable high-frequency sources (eg, intramural scroll waves) can produce the onset of repetitive drifting rotors,37 these differences most likely rely on the filtering methods in BSM/ECGI approaches and the extent of interpolation used in basket-catheter mapping. Thus, excessive interpolation/filtering or lack thereof may lead to differing conclusions about the actual stability of the sources driving AF.

From the foregoing, it can be surmised that rotors are an important mechanism for sustaining AF in humans, although other mechanisms might certainly be involved in initiation and specific cases of AF maintenance.48 Nowadays, experimental data and ablation outcomes are making it increasingly apparent that sequential acquisition of epicardial electric data over small areas of the atria during cardiac surgery21 may be insufficient as it might simply show epiphenomena, reflecting disorganized activity (fibrillatory conduction).

There is still substantial room for improvement in detecting AF drivers. New technological breakthroughs to obtain experimental and clinical panoramic data will certainly help in tracking drifting rotor trajectories over wide areas of the atria. In the clinic, a panoramic, direct-contact endocardial mapping system with higher density of electrodes than currently available would offer enhanced spatial resolution and help increase accuracy. This would provide more and better signals to compute, minimizing interpolation in the maps used to guide the ablation procedure. In this regard, new basket-catheters with more electrodes might be useful. In both experimental and clinical scenarios, robust algorithms to track drifting, meandering or stationary rotors during long periods of time would be of interest.37 We recently showed that beat phenomena and amplitude modulation patterns in cardiac potentials can be useful to track rotors.37 Potentially, this strategy might be used during AF even with a single mapping catheter. In addition, a
combined activation, phase, and frequency mapping approach might prove extremely useful. Areas allegedly hosting rotors or foci in endocardial basket-catheter or BSM/ECGI maps detected by any of these mapping approaches could be locally remapped with much higher spatial resolution using a novel 64-pole mini-basket catheter (IntellaMap Orion; Boston Scientific) to confirm or exclude the existence of a potential driver.

Concluding Remarks
Recent studies using differing novel mapping approaches specifically targeting potential AF sources have been reported with promising results. Such mechanistically based ablation techniques evolved thanks to insights into the dynamic patterns of AF provided by optical mapping studies and computer-based simulations of AF dynamics,23–29,32,36,38 which yielded algorithms that are now being used in point-by-point sequential mapping.6,7 basket-catheter mapping,7,23 BSM,33,41 and ECGI.6 Interestingly, all data generated to date are compatible with the concept that a small number of localized high-frequency sources can maintain AF for relatively long periods of time.

It is our expectation that, in the near future, (1) simultaneous panoramic endocardial and epicardial optical mapping in the experimental laboratory, (2) higher density electric mapping combined with activation, frequency, and phase mapping in the clinical laboratory, and (3) new algorithms to accurately detect and track rotors and foci in both scenarios will provide a more complete understanding of AF driver dynamics. Hopefully, the increase in knowledge will improve the acute and long-term success rates of AF ablation to the benefit of the patient.

Sources of Funding
This study was supported by grants from Fondo Europeo de Desarrollo Regional and Instituto de Salud Carlos III (RD12/0042/0036 [RIC], RD06/0003/0009 [REDINSCOR]). The Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) is supported by the Spanish Ministry of Economy and Competitiveness and the PRO-CNIC Foundation. Supported also by the Salud 2000 Foundation (Dr Filgueiras-Rama); the Leduq Foundation (Drs Jalife and Berenfeld), the University of Michigan Health System and Peking University Health Sciences Center Joint Institute for Translational and Clinical Research; grants R01-HL122352 (Dr Jalife) and R01-HL118304 (Dr Berenfeld) form the US National Institutes of Health.

Disclosures
Dr Jalife serves on the Scientific Advisory Board of Topera, Inc. Dr Berenfeld is a cofounder and scientific officer of Rhythm Solutions, Inc.

References


Mechanistic Approaches to Detect, Target, and Ablate the Drivers of Atrial Fibrillation
Jorge G. Quintanilla, Julián Pérez-Villacastín, Nicasio Pérez-Castellano, Sandeep V. Pandit, Omer Berenfeld, José Jalife and David Filgueiras-Rama

Circ Arrhythm Electrophysiol. 2016;9:
doi: 10.1161/CIRCEP.115.002481

Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/9/1/e002481

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Arrhythmia and Electrophysiology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Arrhythmia and Electrophysiology is online at:
http://circep.ahajournals.org/subscriptions/