Advances in Arrhythmia and Electrophysiology

Maintenance of Atrial Fibrillation
Are Reentrant Drivers With Spatial Stability the Key?

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Presented in the following review are the insights on atrial fibrillation (AF) gained from our recent simultaneous endo-epicardial transmural and panoramic optical mapping studies of the human atria that may begin to resolve the controversy about AF maintenance mechanisms.1–3 It is still hotly debated whether the sustaining mechanism of AF involves multiwavelets self-replicating across the entire atrial myocardium4 or if fibrillatory conduction in the atria is maintained by localized AF drivers.1 Even the term “AF driver,” which is widely used in the current literature,1–3,5–15 is not well defined. In this review, AF drivers are defined as one or several patient-specific localized sources of fast, repetitive activity from which activation propagates and breaks down into fibrillatory conduction in the rest of the atria, targeted ablation of drivers would slow AF, organize AF to atrial tachycardia, or terminate AF (Figure 1).

Even if one is convinced that AF drivers exist, there is no clear consensus on the specific electrophysiological mechanism of AF drivers. AF drivers have been hypothesized to represent reentry circuits, rotors, focal sources, or a complex mixture of all these mechanisms. We hypothesize that human AF is maintained by a limited number of spatially stable but temporally competing, patient-specific intramural microanatomic reentries, the true nature of which may remain hidden to clinical surface electrode mapping, which instead visualizes the activity as stable/unstable rotors, focal activity, or breakthroughs because of the transmural complexity of the atrial wall (Figure 2). We propose a theory for AF maintenance that incorporates nearly all observations made by different clinical mapping studies based on direct evidence from transmural and panoramic optical mapping of the human heart.

Intramural Microanatomic Reentry as AF Driver Mechanism

Almost 100 years ago, Lewis et al16 hypothesized that reentry, where electric circus movement can occur around a site of anatomic or functional unexcitable core/block, could drive AF with fibrillatory conduction propagating from it. This hypothesis was supported by surface electrode mapping by Schuessler group17 and optical mapping studies by Jalife group2 ex vivo in animal models of acetylcholine-induced sustained AF and later by simultaneous endo-epicardial (dual-sided) mapping.18 However, the above studies were performed in animal models, and the spatiotemporal stability and electrophysiological characteristics of these reentrant drivers may differ in the diseased human heart.

Early studies of the aged, diseased human heart, such as the microelectrode study by Spach et al19 showed that myofiber orientations and microfibrosis in right atrial pectinate bundles act as substrates for microanatomic reentry, which represents a possible driver of AF. Indeed, the complex human atrial anatomy, consisting of a web of small fibrotically insulated myobundle tunnels, creates an ideal substrate for intramural reentry,1 which would require transmural mapping to determine the activation patterns within the 3-dimensional (3D) atrial wall (≈1–7 mm). To accomplish this, we recently studied diseased human right atria (RA) with simultaneous endo-epicardial optical mapping (330-µm spatial resolution).1

The utilization of nontoxic near-infrared voltage-sensitive dye20,21 allowed us to record optical action potentials ≤4 mm deep simultaneously from subendocardial and subepicardial layers (Figure 3A). Rapid pacing led to endo-epicardial activation dissociation because of transmural conduction blocks along fibrotically insulted pectinate bundles (Figure 3B). These conduction blocks allowed the induction of sustained intramural reentry that appeared to drive AF.1 These reentrant AF drivers were spatially and temporally stable (>90 minutes) sources of electric activity correlating with the highest dominant frequency during fibrillatory conduction. The AF drivers were confirmed by targeted radiofrequency ablation that eventually terminated AF.

Importantly, integration of transmural optical mapping with high resolution contrast-enhanced magnetic resonance imaging (CE-MRI) allowed us to study region-specific structural substrates of reentrant AF drivers1 (Figure 3C). This revealed that the combination of increased intramural fibrotic strands (≈200 µm thick), greater endo-epicardial myofiber misalignment, and atrial thickness variation created microanatomic tracks for stable reentrant AF drivers. Specifically, the 3D microanatomic tracks consisted of 2 limbs of either subendocardial or subepicardial pectinate muscle bundles, which...
were connected by small myobundles that created conduction pivot points (Figure 3C).

How Intramural Microanatomic Reentry Can be Visualized From Atrial Surfaces

Here, we discuss how the visualization of microanatomic reentrant AF drivers becomes much more complex when intramural conduction and the 3D atrial structure are considered. The 3D size of microanatomic reentrant tracks observed in our integrated optical mapping and 3D CE-MRI study,1 and more recently with 3D micro-CT,2,3 were on average of ≈15×6 mm, with a 3 mm depth, supporting microanatomic reentry as opposed to macroanatomic reentry around anatomic obstacles, such as the tricuspid valve or the intercaval region. The size of microanatomic substrates suggests that these AF drivers could be seen not only by optical mapping but also by contact electrode mapping with adequate resolution when the track is located only in the subepicardial or subendocardial surface, which is usually not the case.

Importantly, subendocardial optical mapping visualized ≈80% of the intramural reentry circuit versus ≈40% by simultaneous subepicardial mapping because the complex subendocardial myobundle network is more suitable for reentry than the smoother subepicardial myocardial layer.1 Interestingly, the stable breakthrough visualized by subepicardial mapping frequently represented a transmural pivot point of the reentry circuit seen from the subendocardium (Figure 3A). In general, transmural optical mapping revealed 4 distinct patterns of intramural driver visualization from a single atrial surface: (1) complete reentry circuits, (2) incomplete reentry circuits, (3) stable breakthrough, and (4) unstable, variable breakthroughs. Thus, transmural optical mapping1 demonstrated that alternative mechanisms of AF maintenance could be hypothesized based on the visualization by single surface electrode mapping (Figure 3D).

One of the visualization patterns of intramural reentrant AF drivers may appear as rotors,10 which are functional reentries with an excitable but unexcited core. A continuum may exist with a variety of mechanistic explanations of reentrant AF drivers having varying degrees of experimental support. However, we observed, with our high-resolution transmural optical mapping and 3D CE-MRI, activation conducting unidirectionally through microanatomic reentry tracks, which are composed of distinct fibrotically insulated myobundles (tunnels) 0.5 to 2 mm thick.1 Therefore, reentrant AF drivers observed directly in the human heart1 and discussed in this review refer only to microanatomic reentry19 that lack in their structural track/tunnels, a functional rotor core seen in animals and computer models, but they create similar rotational activation patterns observed in clinical AF mapping.

The Number of Reentrant AF Drivers Present in the Heart May Affect Visualization and Treatment

Temporal Stability

The temporal stability of an AF driver is defined as the percent of AF cycle lengths that are generated by the AF driver. Our transmural optical mapping study on the isolated human lateral RA showed a single driver that was 100% temporally stable. However, recent panoramic biatrial optical mapping studies2,3 revealed that sustained AF in explanted human hearts may be maintained by two or more spatially stable, but temporally competing, reentrant drivers in both left and right atria (Figure 4). In cases when two or more localized AF drivers are present, the temporal stability of each driver may be <100%. In our experience, the presence of two or more spatially stable reentrant drivers within the human atria may allow these drivers to be temporally unstable or intermittent while permitting AF to be constantly maintained by at least 1 active driver. We consider these drivers to be spatially stable because activation returns to the same location with the same pattern when the driver is not 100% temporally stable. A localized AF driver lacking complete temporal stability directly correlates with some clinical mapping observations8,9 that may only show driver activity at one location for a limited number of beats.

Figure 1. Defining atrial fibrillation (AF) drivers. AF drivers are defined as localized sources of fast, repetitive activity from which activation propagates and breaks down into fibrillatory conduction in the rest of the atria. One or few patient-specific AF drivers may exist simultaneously or sequentially, and targeted ablation (orange stars) of AF drivers would slow, organize to atrial tachycardia (AT), or terminate AF. Light purple ovals, black arrows, and gray arrows represent the AF driver region, path of reentry, and fibrillatory conduction, respectively. IVC indicates inferior vena cava; LA, left atria; RA, right atria; SVC, superior vena cava.
Driver Hierarchy

Furthermore, during our ex vivo experiments where radio-frequency ablation successfully disrupted the microanatomic reentry track of the sole AF driver, a secondary reentrant AF driver with a longer cycle length was unmasked in some hearts. These secondary reentrant drivers were in unique locations and not present when the original primary driver was active. The presence of several temporally competing drivers and secondary drivers may have an impact on the lack of acute AF termination seen clinically after ablation treatments. These findings suggest that repeated mapping of AF may be necessary to identify all patient-specific drivers.

Translational Application of Ex Vivo Optical Mapping of Human Atria

As we have discussed in our recent review, optical mapping, while it provides the opportunity to detect intramural activation within the 3D atrial wall, has inherent limitations. Previous concerns with optical mapping such as tissue absorbing and scattering light as well as the phototoxicity of fluorescent dye have been mitigated by new near-infrared voltage-sensitive dye, di-4-ANBDQBS. Importantly, our ex vivo electrophysiological parameters, including action potential duration, conduction velocity, and AF dominant frequency are within clinical ranges for patients with AF, even after the addition of autonomic or metabolic pharmacological stimulation. Therefore, with functional parameters within clinical ranges, it is highly likely that the mechanism we have observed in the diseased human atrial structure is representative of clinical phenomena. Finally, and most importantly, optical mapping cannot be performed in patients. Thus, this review looks to clinical studies that use surface electrodes, with their own sets of limitations, for evidence that may suggest the presence of intramural microanatomic reentrant AF drivers in patients. Our optical mapping observations of intramural microanatomic reentrant AF drivers...
corroborate, as well as bridge, the results from all major clinical epicardial and endocardial mapping studies.

**Clinical Surface Electrode AF Mapping: 2 Sides of the Same Coin**

Endocardial Contact Electrode Mapping

In concordance with our optical mapping studies, clinical studies that mapped AF from the endocardial surface were more likely to visualize a reentry circuit, which may be visualized as rotor activity by phase mapping. Local endocardial mapping using a PentaRay catheter (35 mm mapped area diameter, 20 electrodes, 4 mm interelectrode distance) found reentry circuits and discrete centrifugal activation. Recently, several clinical groups have identified both localized reentrant drivers/rotors and focal impulses in paroxysmal and persistent AF patients by using panoramic endocardial basket (FIRM) catheters (64 electrodes, 9 mm interelectrode distance). In general, FIRM mapping found a limited number (≈2–3 per patient) of spatially and temporally stable (>10 minutes), primarily reentrant drivers in both atria that become more prevalent with progression/duration of AF. Furthermore, these studies demonstrated that targeted ablation could successfully alter or...
terminate AF in the majority of patients, which supports a localized driving mechanism for AF maintenance, rather than multiple random wavelets.

However, two other studies, including the recent OASIS study (Outcome of Different Ablation Strategies in Persistent and Long-Standing Persistent Atrial Fibrillation), show relatively poor outcomes for ablations relying on FIRM maps alone. The OASIS trial compared FIRM only ablation to FIRM plus pulmonary vein isolation or pulmonary vein isolation plus trigger elimination. Of the 3 available studies that have investigated FIRM only ablation, 2 report 14% and 22% success rates in a total of 56 patients, whereas 1 study in 31 patients reports 81% success. With contradicting results from FIRM only ablation, some attribute the lack of success as evidence against the presence of AF drivers; however, it may be because of the fact that FIRM did not identify all AF drivers, especially drivers at the ostium of a PV that are hidden by poor basket catheter contact with these regions. Other possible reasons why some studies only achieved marginal success with FIRM only ablation procedures could be operator learning curve, map interpretation, and choice of comparator group, emphasizing the opportunity for improvement/validation of FIRM.

It is worth mentioning that 2 studies in roughly 100 patients that report only a 37% to 52% success rate of FIRM-guided ablation plus pulmonary vein isolation may represent a minor proportion of the field. In contrast, 8 studies from multiple groups with a total of roughly 500 patients show a collective success rate of 75% to 88%, which suggest that localized AF drivers may exist in the majority of paroxysmal and persistent AF patients, and appropriate ablation of these drivers could treat AF. Overall, the findings from the majority of studies attest to the ability of endocardial mapping to locate and guide ablation of localized AF drivers.

**Figure 4.** Atrial fibrillation (AF) maintained by competing drivers during sustained AF in the ex vivo human heart. **A,** Schematic representation of 2 spatially stable AF drivers competing in the right atria (RA). Pink oval, black arrows, and gray arrows represent the AF driver region, path of reentry, and fibrillatory conduction, respectively. **B,** Activation maps showing AF driven first by a superior and then by an inferior spatially stable AF driver. Arrows indicate the location and direction of AF reentrant drivers. **C,** Optical action potentials (OAPs) from superior driver, inferior driver, and the middle right atrial free wall. Reprinted from Li et al with permission of the publisher. Copyright © 2016, Wolters Kluwer Health, Inc. CT indicates crista terminalis; Inf, inferior; IVC, inferior vena cava; LA, left atria; RAA, right atrial appendage; and SVC, superior vena cava.
Epicardial Contact Electrode Mapping

Epicardial mapping during open-chest surgery also revealed reentry circuits in several clinical studies. However, these studies had a lower probability of visualizing reentrant drivers, and the reentrant drivers that were identified had lower stability, compared with endocardial mapping, which may be explained by the differences in structural organization between the endocardium and the epicardium of the human atria (Figure 3C). Cox et al35 epicardially mapped both atria during acute AF and showed a single stable reentrant circuit in the RA could maintain AF in 6 patients with Wolf–Parkinson–White Syndrome syndrome. Moreover, local RA epicardial mapping (36 mm diameter, 244 electrodes, 2.25 mm inter-electrode distance) by Allessie group36 showed random reentry and a shifting leading circle in patients with acute AF. Another local epicardial mapping (6.75 cm² or ≈10% of the atria, 128 electrodes, 2.5 mm inter-electrode distance) study by Lee et al24 reported mostly multiple wavefronts, disorganized activation, and focal activation but also saw reentrant circuits in 3 of 18 patients (Figure 5B). Biatrial epicardial mapping (250 electrodes) by Schuessler et al37 identified a single discrete region of high frequency in the majority of persistent and paroxysmal AF patients, yet they were only able to visualize a reentrant circuit within this region in some patients.

However, other recent contact epicardial mapping studies9,24,38 observed only stable and unstable breakthroughs or focal discharges in patients with persistent AF that match how intramural reentrant drivers appear when recorded from the epicardial surface in our optical mapping studies. A study by de Groot et al38 used high-resolution local epicardial mapping (64–244 unipolar electrodes, 2.25–2.5 mm distance), which visualized a large proportion of fibrillatory waves originating from a focal origin, suggesting breakthroughs from endocardial waves.

Lee et al9 biatrial epicardial mapping study (92.85 cm², 512 bipolar electrodes, 5.2–7 mm inter-electrode distance) mapped
atrial activation of persistent AF and concluded that AF could be maintained by epicardial focal activity but lacked confirmation by intervention (Figure 5C). Notably, this study provided the longest whole atrial activation analysis (32 s). These focal drivers, present across both atria, were found to be temporally stable for 32 s in 6 of 12 patients, with most focal sources having intermittent activity but a recurring location. Our study showed intramural reentry circuits often travel between the subendocardium and the subepicardium through small intramural bundles, which causes both focal and breakthrough phenomena if mapped from a single surface (Figure 3).

Noninvasive Body Surface Epicardial Mapping
Cuculich et al noninvasive body surface mapping (256 electrodes) visualized the most common patterns of AF were multiple wavelets with focal sites across both atria but rotor/reentry activity was rarely seen. Later, Haissaguerre et al using a similar noninvasive body surface mapping approach, but with phase processing, found temporally unstable reentrant drivers (≈2.6 rotations; 80%) and focal breakthroughs (20%) that often localized in specific anatomic regions, ablation of which could terminate or organize AF (Figure 5D). Both studies saw that AF complexity (number of drivers or wavelets) increased with longer clinical history of AF. Further analysis by Rodrigo et al showed that reentrant activity seen on the body surface is significantly more stable when a narrow band-pass filter at the highest dominant frequency is applied. They suggest that the instability of AF drivers observed may stem from interference by atrial activation elsewhere and does not represent an inherent instability of the drivers themselves.
Although the body surface mapping benefits from being non-invasive, the inverse approach has relatively low spatial resolution, and it is inherently sensitive to noise and motion, which may also increase the instability of AF drivers.

**Dual-Sided Endocardial/Epicardial Contact Mapping**

Finally, the recent surgical study by de-Groot et al \(^\text{13}\) used local endo-epicardial electrode mapping of the lateral RA by dissecting the atrial appendage and inserting a clamp of 2 electrode plaques (1.5×3 cm², 128 electrodes, 2 mm interelectrode distance) during acute, paroxysmal, and persistent AF (Figure 6A). They demonstrated endo-epicardial dissociation and focal waves/breakthroughs in all patients, but they did not report reentrant activity. The majority (65%) of focal waves could be attributed to transmural excitation. In general, this in vivo study directly supports our ex vivo panoramic endo-epi-

**Clinical Electrode Mapping Limitations**

Electrogram Analysis and Interpretation

Importantly, for clinical electrode studies, no consensus has been reached not only on the resolution and coverage needed to resolve AF mechanisms, but there is no unifying approach to how electrograms should be analyzed and interpreted.\(^\text{10}\) Both unipolar and bipolar electrodes record extracellular activation with numerous problems, such as incomplete contact, mechanical movement, and far-field influence from surrounding tissue.\(^\text{18}\) Moreover, fibrotic layers and epicardial fat can diminish the already low amplitude, multicompontent electrogram signals. Phase signal processing may present another technical limitation because it is biased for rotor visualization.\(^\text{10}\) At the same time, it may provide an opportunity to visualize reentrant AF drivers as a core of rotational activity in the clinical setting limited by electrode resolution.

**Intramurality**

The specific path of intramural reentry through the atrial wall can be relatively tight, even a few millimeters when the circuit is viewed at an angle, as revealed in our study with 330 µm resolution.\(^\text{1}\) Thus, even dual-sided electrode mapping with >1 mm resolution may show only the AF driver location but not the mechanism. Therefore, clinical studies using surface electrograms may not see the whole picture and are destined to draw conclusions based on 1 of the 4 surface visualizations of intramural reentrant AF drivers. Surface electrograms may be complex or fractionated at AF driver locations, and studies of electrogram morphologies that define human AF drivers would benefit greatly from validation with transmural optical mapping that could distinguish electrogram deflections resulting from far-field versus local activation.\(^\text{41}\)

**Temporal Stability**

As discussed above, the temporal stability of an AF driver may be affected by the total number of AF drivers in the heart. Local mapping that may only see a driver for a fraction of the mapped arrhythmia might conclude that the AF episode did not rely on an AF driver for maintenance. Notably, panoramic clinical mapping studies have shown the presence of intermittent drivers that return to or stabilize in specific locations within the atria.\(^\text{8,9}\) Signal processing and far-field influence may further complicate the detection of AF drivers. Moreover, fibrillatory conduction outside the driver or through a surface layer overlaying the intramural driver may mask the small signal moving through intramural bundles. This may inappropriately cause the reentrant AF driver to appear and disappear from the surface maps, while in fact the reentry circuit may continuously drive the arrhythmia throughout this time.

**Integration of CE-MRI to Overcome Clinical Electrode Mapping Limitations**

More importantly, a definitive answer on intramural AF driver mapping may not come from electrogram recordings alone, and instead may require integration with 3D structural imaging. The role of human atrial 3D myofiber anatomy is often overlooked in the functional studies that hunt for AF’s sustaining mechanisms.\(^\text{10,15,18,19,42}\) We showed in our ex vivo human heart study how the complexities of the 3D human atria, such as intramural fibrosis, transmural myofiber misalignment, and variations in atrial thickness affect atrial conduction, which is made worse by the fast activation rate during sustained AF. CE-MRI may be able to help bridge the gap between ex vivo and in vivo studies, and it may aid ablation strategies by placing in vivo functional, electrode-based maps in the context of the 3D human atrial anatomy. For now, clinical CE-MRI is limited by its resolution, and some atrial structural features identified by CE-MRI based on signal intensity differences, such as fibrosis, have yet to be definitively validated in vivo; therefore, the need for ex vivo studies directly on the human
Future Studies of AF Maintenance Mechanisms Ex Vivo and In Vivo

We propose that the focal, breakthrough, and rotor activity seen by the studies mentioned above represent different visualizations of intramural microanatomic reentrant AF drivers. Our theory of intramural microanatomic reentry appears to unify all clinical electrode mapping observations with this single unifying mechanism. However, we cannot rule out the possibility of other mechanisms responsible for sustaining AF present in a large, diverse cohort of AF patients. We suggest that the human heart experiments in which AF is mapped with high-resolution transmural optical mapping could be used to discern intramural drivers by optical mapping and then validate the electrogram by analyzing the contact electrogram morphologies from the AF driver region. These validated electrogram patterns, or intramural microanatomic reentrant AF driver fingerprints, could then be used as references when analyzing contact electrode mapping signals from ex vivo studies. Furthermore, a better understanding of the microanatomic reentry mechanism may be gained from detailed studies that use atrial pacing or local entrainment pacing near an AF driver, similar to the studies that have characterized reentry circuits in the human ventricle.43,44

On the basis of our integrated functional, structural, and molecular studies,1–3 we suggest that further study is needed on heterogeneous cellular refractoriness, complex myofiber twists, tissue dimension variations, and fibrotic remodeling because these pathological features may predispose some locations to serve as ideal substrates for microanatomic reentrant AF drivers in a patient-specific manner. This underlying structural substrate and its heart-specific progression may explain variations in driver locations, sizes, and plurality as patients progress from paroxysmal to long-standing persistent AF.7,8 Thus, it is important to study the diverse clinical histories and comorbidities of AF patients. Differences may exist in the type and extent of structural and molecular remodeling brought about by the various comorbidities, such as heart failure, myocardial infarction, hypertension, and even between paroxysmal and persistent AF. Additional attention should also be paid to how comorbidities may affect the right and left atria independently, as AF drivers have been shown to exist in both atria.7,9 Thus, structural information gained through CE-MRI mapping of human hearts during AF, which allowed us to reconstruct true fingerprints of AF driver characteristics, can be applied to AF driver identification in vivo. These heart-specific computer models would present the opportunity to test the multiple targeted ablation strategies for the same AF driver, as in silico ablation is uniquely reversible compared with ex vivo and in vivo studies.45

Conclusions

The interpretation of surface mapping techniques, especially without considering intramural conduction within the complex 3D human atria, will continue to fuel the debate of AF mechanisms. On the basis of our ex vivo experimental results and multiple clinical studies, we hypothesize that the primary mechanism of AF maintenance in diseased human hearts is localized intramural reentry anchored to patient-specific microanatomic tracks of varying number, size, and distribution. The intramural microanatomic reentry mechanism may unify the findings from many clinical electrode mapping studies. We are optimistic that better understanding of microanatomic reentrant AF driver fingerprints could lead to more reliable identification of these drivers in large cohorts of patients and targeted ablation strategies that will effectively treat AF.

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References


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