Drivers of Atrial Fibrillation: Theoretical Considerations and Practical Concerns

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Abstract
Understanding the mechanisms responsible for driving AF is key to improving the procedural success for AF ablation. In this review, we look at some of the proposed drivers of AF, the disagreement between experts and the challenges confronted in attempting to map AF. Defining a ‘driver’ is also controversial, but for the purposes of this review we will consider an AF driver to be either a focal or localised source demonstrating fast, repetitive activity that propagates outward from this source, breaking down in to disorganisation further away from its origin.

Keywords
Arrhythmia, atrial fibrillation, mechanisms

The discovery of focal ectopy in the pulmonary veins (PVs) initiating AF has resulted in electrical isolation of the PVs forming the mainstay of current treatment strategies. Success rates from PV isolation (PVI) for patients with paroxysmal AF (PAF) are approximately 70–75%. However, PVI is significantly less effective for those with persistent AF, in whom many studies quote single-procedure success rates of about 50%. The suboptimal outcomes from catheter ablation have resulted in significant research efforts to identify the underlying mechanisms driving AF in the hope of identifying targets for catheter ablation therapy.

Re-entry as a Mechanism Underlying AF
While watching the exposed fibrillating atrium of an animal heart, in 1914, Garrey described chaotic activity, with contractions that did not appear to be independent of one another. He was also able to induce circus movement with a single stimulus in ring preparations. From these observations, he cut fibrillating tissue into four equal parts and found that fibrillation continued, providing evidence against a focal source, as "only one of the pieces can contain the original hypothetical tachysystolic pacemaker". By cutting tissue into smaller pieces, he also concluded that a critical mass was required to sustain fibrillation.

In 1921, Lewis et al. hypothesised that re-entry around anatomical structures, or functional re-entry around an unexcitable core due to functional block, could be potential drivers of AF. This model was based on a meandering central or mother wave moving in multiple directions and giving rise to daughter waves.

While AF could be induced with high-rate pacing in animal models, these episodes would not persist beyond a few seconds. Moe and Abildskov, therefore, developed a canine model of AF, which enabled AF to be sustained for much longer periods of time. During AF, the appendage was excluded with a clamp. Upon discontinuation of atrial appendage pacing, the appendage was no longer in AF, however the rest of the atrium continued to fibrillate, suggesting the original focus was not required to sustain AF. The authors concluded that re-entry was the most likely mechanism for AF, with grossly irregular wavefronts becoming fractionated and producing independent, randomly wandering daughter wavelets as offspring (the multiple wavelet hypothesis). To further challenge this potential mechanism, Moe et al. undertook computational modelling. An estimate of 23 to 40 electrical wavelets re-entering random regions of the substrate was determined to be required to sustain fibrillation. This model also illustrated that re-entrant circuits could be generated without an anatomical obstacle, adding support for the multiple wavelet hypothesis. Interestingly, Lee et al. restudied Moe’s canine vagal nerve stimulation model of AF some 50 years later, proposing that multiple foci are responsible for driving AF, rejecting the multiple wavelet hypothesis.

With the advent of mapping technology, Allessie et al. corroborated Moe’s findings in a series of elegant studies by placing micro-electrodes on rabbit atria, and demonstrated that re-entrant circuits could be independent of an anatomical substrate. From this, the ‘leading-circle’ concept of re-entry was proposed, in which functional circuits could operate anywhere in the heart under the right local conditions. Initiation of re-entry was found to be dependent on the inhomogeneity of refractoriness of atrial fibres in close proximity to one another, and the activation wavefront continually emitting wavefronts centrally to produce and sustain a refractory core.

Subsequent detailed studies by Allessie et al. were conducted on Langendorff-perfused canine hearts using epicardial multi-electrode arrays. Continuous beat-to-beat variations in activation pattern, including functional turning, collision, fractionation and extinction, in functional lines of block were described. Rather than the 23 to 40 wavelets required to maintain AF as proposed by Moe et al., the critical number of wavelets suggested by Allessie et al. was just three to six.
The potential benefit of multi-electrode mapping during cardiac surgery in humans was first described by Canavan et al.\textsuperscript{15} Atrial activation patterns were recorded from 156 epicardial electrodes during sinus rhythm, atrial pacing and reciprocating tachycardia. This group went on to study electrically induced AF in patients undergoing surgery for Wolf-Parkinson-White syndrome.\textsuperscript{16} Although re-entrant circuits involving anatomical obstacles were present, there was further confirmation of circuits existing in the absence of structural obstacles. Further work in a similar patient population by Konings et al. showed different degrees of disorganised activation patterns, ranging from predominantly planar activation to those with completely disorganised activation.\textsuperscript{16} In addition, the authors described a small number of new wavelets appearing to originate from the free wall of the right atrium. These focal activations were thought to be the result of epicardial breakthrough due to the frequent presence of a small R wave on the unipolar signal at the earliest site of activation, rather than a true focal source. These events were infrequent, and the dominant mechanism for sustaining AF was concluded to be multiple re-entry wavelets.

Around the same time, Schuessler et al. described activation patterns in a canine model of induced AF.\textsuperscript{16} With increasing concentrations of acetylcholine, they observed a decrease in atrial refractory period, with eventual sustained fibrillation induced. Based on the multiple wavelet hypothesis, as the refractory period decreased, the number and instability of re-entrant circuits should have increased. As predicted, this was observed for non-sustained rapid repetitive responses, with activation sequence maps revealing multiple re-entrant circuits. However, with further shortening of the refractory period at higher acetylcholine concentrations, the trend did not continue. Instead, the re-entry "stabilized to a small, single, relatively stable re-entrant circuit", independent of anatomic obstacles. The same group further challenged Moe's hypothesis by demonstrating that re-entry is able to occur in a three-dimensional manner because of the connecting transmural muscle fibres between epi- and endocardium during epicardial electrode mapping in canine atra.\textsuperscript{17}

Initiation and Maintenance of AF by Focal Drivers

Rothberger and Winterberg first hypothesised that AF was the result of a single electrical focus in 1909. In a series of experiments, Scherf et al. suggested that AF was the result of an ectopic focus.\textsuperscript{18} In one study, they injected aconitine into canine atria, which led to rapid excitation with the appearance of AF. When they undertook local cooling of the area the arrhythmia terminated but restarted on discontinuation of cooling. Crucially in their observations, they stated that the wavefront interacted with islands of refractory tissue, causing the weaving and interweaving contraction characteristic of fibrillation as it entered the larger mass of auricular muscle. They concluded that AF was caused by a rapid stimulus rather than re-entry. Consequently, the re-entry waves of excitation are a concomitant feature of AF rather than its cause.

While some groups have failed to demonstrate a repetitive focal activation as the mechanism driving AF,\textsuperscript{14,15} Harada et al. demonstrated regular and repetitive activation originating in the left atrium in 10 patients with chronic AF undergoing isolated mitral valve surgery.\textsuperscript{19} Interestingly, they found activation in the right atrium to be chaotic, suggesting that the left atrium was driving the AF. Jais et al. described a small series of nine patients with paroxysmal AF in which the surface ECG pattern of AF was the result of focal, rapidly firing activity, exhibiting a consistent and centrifugal pattern of activation.\textsuperscript{20} All patients underwent limited focal radiofrequency ablation with elimination of the foci and subsequent non-inducibility of AF. The following year, in 1998, Haïssaguerre et al. made the important discovery of focal ectopy from PVs initiating AF.\textsuperscript{21} This has been important in both advancing our understanding of AF and identifying a treatment target, with PV forming the mainstay of conventional ablation procedures.

It is important to recognise that mapping either the epicardial or endocardial surface will present two-dimensional data, ignoring the transmural conduction, which might be interpreted as focal activation. Biatrial high-density unipolar mapping of the epicardium has revealed frequent epicardial breakthrough of waves propagating in deeper layers in the so-called “double-layer hypothesis”. De Groot et al. describe the observation of small R waves in unipolar electrogram recordings, suggesting that this supports breakthrough rather than a true focal mechanism resulting from automatic cellular discharge.\textsuperscript{22} Although this alone is not proof of breakthrough, they used a number of other metrics to support the concept. A wave-mapping approach was used to identify individual fibrillation waves. This approach defines the starting point of the first fibrillation wave as the earliest activated site in the mapping area. The shortest time difference with the neighbouring eight electrodes is then calculated. If the time difference was ≤12 ms, the electrode activation was attributed to the surrounding wave. In case of a time difference >12 ms, the electrode was annotated as the starting point of a new wave. Four criteria were required for the classification of epicardial breakthrough. The epicardial breakthrough site had to be activated earlier than all surrounding electrodes, located at least two electrodes from the mapping array border and not obscured by large QRS complexes or artefacts. Lastly, a time delay of >40 ms between the site of epicardial breakthrough and the lateral border of another wave was required; otherwise, the wave was attributed to discontinuous conduction from the lateral boundary of that wave.

This elegant mapping study does suggest some compelling evidence for the double-layer hypothesis. However, it remains challenging to understand how a small R wave from a unipolar electrogram can definitively be assigned to that of transmural activity. The complexities of interpreting electrogram morphology during AF means that this deflection may merely be the result of wavefront collision or far-field signal. Furthermore, the measurement of the smallest time delay between epicardial and endocardial signal may be difficult to interpret without the use of a reliable fiducial signal because of myocardial anisotropy. Lastly, a wavefront was deemed to reflect transmural conduction if it was present within a 4 mm distance and <15 ms before the origin of the focal wave based on normal atrial conduction properties. It is rare that patients with AF have normal atra, and therefore the likelihood of having normal conduction properties would seem doubtful in this patient population. Simultaneous mapping of the
endocardial surface has suggested asynchronous activation between the two layers, promoting maintenance of AF by replacing fibrillation waves that die out with breakthrough from the opposite side. This has important implications as limited and focal ablation is unlikely to result in termination of AF owing to the multiple potential breakthrough sites, and may explain the high recurrence rates of AF after ablation of focal and rotational drivers.

The Rotor Revolution

Despite recent popularity in this field of research, rotors are not a new concept. Seminal work by Winfree in canine ventricular myocardium demonstrated spiral waves rotating around a phase singularity. In 1992, with the use of optical mapping in animal myocardium, Davidenko et al. demonstrated cardiac fibrillation where spiral waves could be non-stationary, shifting the position of the phase singularity, as well as stationary by anchoring to anatomical structures. The idea that one or a number of localised rotors may drive AF holds important therapeutic implications as they may be targets for catheter ablation. Complex computational algorithms have been developed that afford investigators important insight in to the patterns of activation in human AF.

The group led by José Jalife have published extensively on their optical mapping studies in the Langendorff-perfused ovine model of acetylcholine-induced AF. They demonstrated sustained rotors during AF, predominantly on the posterior left atrial wall, but also on the anterior wall of the left atrial appendage.

Biatrial endocardial mapping using multispline basket catheters and a proprietary computational algorithm have been undertaken in focal impulse and rotor mapping (FIRM) by Narayan et al. In this approach, phase analysis has shown the presence of a small number of rotors in more or less fixed locations. Employing a completely different mapping modality, which applies a complex algorithm of inverse-solution-based analysis of body surface electrogram data, Haïssaguerre et al. have also identified rotors, but instead observed them to be transient and migratory with a tendency to cluster around fibrotic zones.

Furthermore, the median rotor duration was 2.6 rotations, in contrast to minutes or hours as observed by Narayan et al.

Their importance in arrhythmia maintenance has been suggested by limited ablation of these localised regions resulting in termination of AF. In the Conventional Ablation for AF With or Without Focal Impulse and Rotor Modulation (CONFIRM) trial, the acute efficacy endpoint of AF termination or >10% consistent slowing of AF cycle length was achieved in 85% of cases, with AF termination in 56%, after a mean of 4.3 ± 6.3 minutes of FIRM ablation at the primary source. This limited ablation success was not the case in the AFACART study, in which the mean radiofrequency time for driver-only ablation resulting in AF termination was 46 ± 28 minutes despite a mean of only 4.9 ± 1.0 driver sites mapped per patient. It, therefore, seems surprising that radiofrequency ablation times are so long despite rotors being localised sources. One possible explanation may be that the proposed source areas are on the order of cm², and the choice of ablation area is wider and operator dependent. The authors did, however, report AF termination in 64% of patients undergoing ‘driver-only’ ablation. Despite this, evidence suggesting that rotors are transient and migratory does not explain why focal ablation should result in termination of AF.

Initial high success rates were achieved with FIRM-guided catheter ablation, but several other groups were unable to achieve comparable success rates. If focal drivers such as rotors were spatiotemporally stable, it would be expected that a focal ablation would result in successful treatment of AF. Furthermore, evidence that focal sources are stable is also challenged by the recent double-layer hypothesis demonstrating endocardial–epicardial dissociation, where multiple different breakthrough locations are possible. With this hypothesis, it is understandable why a focal ablative strategy would fail, and may in part contribute to the low procedural success rates.

In the largest series of focal source ablation, Miller et al. undertook FIRM-guided ablation in 170 consecutive patients, including patients with paroxysmal AF (37%), persistent AF (31%) and long-standing persistent AF (32%). Overall, 43% of these patients had undergone at least one prior ablation for AF. In combination with PVI, a single FIRM procedure achieved freedom from AF at 1 year in 87% of participants. The authors concluded that higher rates of procedural success could be obtained with FIRM-guided ablation than with PVI alone, supporting localised sources as a mechanism for AF, and corroborating the findings of CONFIRM.

If the maintenance of AF is related to a hierarchical (focal sources) rather than non-hierarchical (multiple wavelet) mechanism, it may be possible to explain why persistent AF has been terminated with relatively localised ablation. Narayan’s group has undertaken computational modelling, suggesting a possible explanation. They simulated spiral wave re-entry in monodomain two-dimensional myocyte sheets. Ablation lesions were applied, with models confirming that localised ablation may anchor re-entry, resulting in organised tachycardias. The ablation results in an excitable gap, which can be invaded by fibrillatory waves, which collide and rapidly terminate spiral re-entry. Targeted ablation may also terminate spiral waves by connecting lesions to large, non-conducting obstacles, such as large areas of scar or an anatomic orifice.

There is disagreement as to whether rotors are stable or migratory. If rotors primarily localise at borders of fibrotic regions, it may be more appropriate to target these regions of scar rather than the rotors themselves. However, the extent of delayed-enhancement MRI abnormalities has been frequently shown to far exceed driver domains, and the microfibrosis that anchored drivers in optical studies was beyond the resolution of clinical scanners. Distinction between ‘culprit’ and ‘bystander’ regions would likely be required if this approach was to be successful.

Autonomic Function Initiating AF

Animal models have often needed autonomic stimulation to maintain induced AF. In patients, the role for the autonomic nervous system has been assumed to occur on this background. The description of vagal symptoms and changes in heart rate variability prior to AF initiation has been presented as circumstantial evidence. Richly innervated areas on the epicardial surface of the left atrium have been identified around the PVs, known as ganglionated plexi (GP). The GP sites are located at the four PV atrial junctions and are highly innervated with both adrenergic and cholinergic nerve fibres. These sites form part of the epicardial neural network, which compromises multiple ganglia with interconnected neurons and axons, including sensory fibres and sympathetic and parasympathetic efferents. During the delivery of radiofrequency energy at catheter ablation for AF, an increase in dispersion of AF cycle length has been observed with vagal responses. The increase in dispersion may promote wavefront formation in other areas of the heart.
Clinical Arrhythmias

Fragmentation into multiple, smaller wavelets – a potential mechanism that sustains AF.

Direct stimulation of GP sites has been shown to initiate PV ectopy and induce AF. Canine studies of PV sleeve preparations have shown action potential shortening and triggered firing in the adjacent PVs, but not the atrial myocardium, in response to GP stimulation. This indicates that PVs appear to be the main effectors of GP stimulation. A well-described method of functionally locating GP sites is to stimulate the left atrium with high-frequency stimulation (HFS) over a presumed GP site, if there is direct contact, a bradycardic atrioventricular (AV) nodal response can be elicited. Our group has used this technique to show autonomic modification of the AF substrate by demonstrating changes in atrial and PV AF cycle lengths both near and distant from the site of stimulation.

With evidence of PV ectopy being triggered by stimulation of GP sites, Katritsis et al. investigated the effect of anatomically guided ablation of GP sites in addition to PVI, and found outcomes to be superior to those of PVI alone. The same group went on to investigate the effect of GP ablation alone on AF, although they found this strategy to be less effective than either PVI alone or PVI in combination with GP ablation. However, formal evidence of autonomic modification was not presented, as the study did not use a functional method to confirm GP sites or a change after ablation.

There are methods described for locating GP sites that include continuous HFS, which locates GP sites with AV nodal effects, and stimulation delivered within the local refractory period (synchronised HFS), which identifies sites that trigger AF. These studies have used techniques that have been limited in capacity to demonstrate the autonomic network in the human left atrium and the feasibility to ablate these effects from the endocardium. Most studies have inferred a role for GP sites based on presumed anatomical colocalisation, with little direct evidence. In arrhythmias where there is a clear anatomical circuit, there is no need to target the autonomic stimuli, as there is a clear substrate to ablate. In AF, the stimuli and substrate appear to span a large part of the left atrial anatomy, and therefore the autonomic stimuli may actually represent a more targeted approach.

Left Atrial Substrate in AF

Fibrosis has been attributed with mechanistic importance in AF. Whether cause or effect, it has frequently been observed in this patient group. Lategadolinium-enhanced cardiac MRI (LGE-CMRI) has been utilised by several groups for the quantification of atrial fibrosis. Although a technically challenging technique, it has shown that the degree of atrial fibrosis is higher with AF persistence and the presence of more AF risk factors. Furthermore, atrial fibrosis demonstrated by LGE-CMRI has been independently associated with AF recurrence in patients undergoing catheter ablation for AF.

The electrical manifestations of fibrosis are sometimes, but not exclusively, seen during catheter ablation as regions of low voltage and slowed conduction. There are challenges when using voltage as a surrogate marker for fibrosis. While some areas are low-voltage during AF, they have been demonstrated to have increased voltage at the same site during sinus or paced rhythm. This is important as areas of low voltage measured during AF may not truly identify regions of abnormal atrial substrate.

High-resolution contrast-enhanced MRI has been integrated with transmural optical mapping. Conduction was found to occur in preferential microanatomic tracks via fibrotically insulated pectinate muscles and intramural myocardial bundles, such that re-entry was established. Radiofrequency ablation at primary re-entrant driver regions resulted in either termination of AF, continuation of AF with a new re-entrant driver established in a different location or macro-re-entry around the ablation lesion. This suggested the importance of the atrial microarchitecture in the maintenance of AF. The same group of investigators went on to hypothesise that human AF is maintained by a limited number of spatially stable, but temporally competing, microanatomic re-entrant sources. Haïssaguerre et al. reported a tendency for rotors to cluster around fibrotic zones. Some authors have raised the question of whether homogenisation of low-voltage regions from sinus rhythm maps to eradicate all potential channels and drivers supporting the arrhythmia is warranted. However, this risks damage to significant regions of atrial myocardium that may not even be implicated in arrhythmia maintenance.

Insights From Ablation Studies

CFAE ablation was based on the assumption that areas of myocardium with such electrical activity may be acting as drivers of persistent AF. Identifying which were true drivers of AF was challenging. Ablation of some CFAEs resulted in prolongation of the AF cycle length, indicating their importance in contributing as a driver, while others had no effect on cycle length at all.

Early studies by Konings et al. showed that CFAEs observed during intraoperative mapping in human AF were mainly in areas of slow conduction and/or regions of functional block where wavelets pivot. They were thought to represent either continuous re-entry of fibrillation or areas where multiple different wavelets enter the same area. In 121 patients, Nademanee et al. used electroanatomical mapping to tag and ablate CFAEs. They identified specific regions that were more likely to contain CFAEs, successfully ablasting 115 of the 121 patients to sinus rhythm, without the need for external cardioversion. However, other investigators have not been able to replicate these encouraging results. Oral et al. undertook solely CFAE ablation in 100 patients with persistent AF, reporting that only 33% of patients maintained sinus rhythm off medical therapy at a mean follow-up time of 14 months. Furthermore, the Benefit of Complex Ablation (BOCA) study showed that not only did adjunctive CFAE ablation confer no additional benefit in maintaining sinus rhythm, but it also significantly increased the incidence of both organised atrial tachycardia and gap-related macro-re-entrant flutter.

Most recently, the Substrate and Trigger Ablation for Reduction of AF II (STAR-AF II) trial reported no additional benefit of CFAE ablation in addition to PVI for patients with persistent AF. The variability in definition of CFAE may in part be responsible for the large disparity in results from catheter ablation, or the variability of operator experience with CFAE ablation. While some have defined CFAEs based on only simple visual descriptions, others have produced a more comprehensive visual classification system, or characterisation using automated algorithms. There are certainly observations that support CFAE ablation resulting in acute organisation of AF, and in some cases termination. However, there are no consistently reproducible data that prove long-term adjunctive benefit.

A recent meta-analysis of the efficacy of driver-guided catheter ablation for AF has demonstrated mixed results. A variety of
different strategies were used, including CFAE, FIRM and high-frequency source ablation. Four studies within the meta-analysis suggested increased single-procedure freedom from AF/Atrial tachyarrhythmia (AT) at ≥1 year (RR 1.34, 95% CI [1.05–1.70], p=0.02).23,24,42-44 However, after excluding cases of driver-guided ablation without PVI, this was no longer significant (RR 1.41, 95% CI [0.96–2.08], p=0.08).

Four studies also reported a higher proportion of acute AF termination with driver-guided ablation compared with controls (pooled RR 2.08, 95% CI [1.29–3.05], p=0.001).

This increased an RR of 2.90 (95% CI [1.15–5.53], p=0.001) after excluding patients undergoing driver-guided ablation without concomitant PVI.42-44 Although this is promising, the meta-analysis included primarily non-randomised studies of moderate quality, making results difficult to interpret. Interestingly, the only two fully randomised controlled trials in the meta-analysis did show greater acute AF termination with driver-guided ablation.42-44 Aserie et al.42,44 found that driver-guided ablation was non-inferior to PVI in achieving freedom from AF/AT at 12 months in patients with paroxysmal AF, however, there was no benefit when combined with PVI in patients with persistent AF. In contrast, Lin et al. reported greater freedom from AF/AT at 17.7 ± 8.2 months in patients who had undergone PVI with driver-guided ablation rather than with CFAE ablation.43

Conclusion

The demonstration of PV ectopy triggering AF led to 20 years of technological development to optimise PV ablation techniques. It has become clear that a purely PV-based approach can resolve AF in 50-70% of patients, implying the other drivers of AF have yet to be determined. At present there are many candidates for this role, yet conclusive proof of an alternative driver has remained elusive.
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