Mechanisms of Atrial Fibrillation – Reentry, Rotors and Reality

Jonathan W Waks[1] and Mark E Josephson[2]

1. Clinical Fellow in Cardiac Electrophysiology, Harvard Medical School, Harvard-Thorndike Electrophysiology Institute and Arrhythmia Service, Beth Israel Deaconess Medical Center, Boston, US; 2. Herman C. Dana Professor of Medicine, Harvard Medical School, Chief of the Cardiovascular Division, Beth Israel Deaconess Medical Center and Director, Harvard-Thorndike Electrophysiology Institute and Arrhythmia Service, Beth Israel Deaconess Medical Center, Boston, US

Abstract

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice, yet our understanding of the mechanisms that initiate and sustain this arrhythmia remains quite poor. Over the last 50 years, various mechanisms of AF have been proposed, yet none has been consistently observed in both experimental studies and in humans. Recently, there has been increasing interest in understanding how spiral waves or rotors – which are specific, organised forms of functional reentry – sustain human AF and how they might be therapeutic targets for catheter-based ablation. The following review describes the historical understanding of reentry and AF mechanisms from earlier in the 20th century, advances in our understanding of mechanisms that are able to sustain AF with a focus on rotors and complex fractionated atrial electrograms (CFAEs), and how the study of AF mechanisms has resulted in new strategies for treating AF with novel forms of catheter ablation.

Keywords

Atrial fibrillation, rotor, reentry, arrhythmia mechanisms, complex fractionated atrial electrograms, pulmonary vein isolation

Disclosure: The authors have no conflicts of interest to declare.
Received: 6 August 2014 **Accepted:** 8 August 2014 **Citation:** *Arrhythmia & Electrophysiology Review* 2014;**3**(2):90–100 **Access at:** www.AERjournal.com
Correspondence: Mark E Josephson, Harvard-Thorndike Electrophysiology Institute, Beth Israel Deaconess Medical Center, Harvard Medical School, 185 Pilgrim Road, Baker 4, Boston, MA 02215. E: mjoseph2@bidmc.harvard.edu

Atrial fibrillation (AF), the most common sustained arrhythmia, is a leading cause of stroke, and is associated with significant morbidity and mortality worldwide. Despite its frequency, clinical importance, and advances in technology and our knowledge of the molecular, ionic and physiological fundamentals of cardiac electrophysiology, our limited understanding of the mechanisms that initiate and sustain AF has prevented us from being able to truly cure this arrhythmia with antiarrhythmic drugs and/or ablation. This contrasts with other arrhythmias, such as AV nodal tachycardia or circus movement tachycardia using an accessory pathway, which have well-defined mechanisms and circuits that can be safely targeted with high rates of cure. The observations that AF may have different mechanisms in different patients, and that paroxysmal, persistent and permanent forms of AF may differ in how they are initiated and sustained, only serves to reinforce our lack of understanding of this ubiquitous arrhythmia.

Historical Mechanisms of Atrial Fibrillation and the Multiple Wavelet Hypothesis

Interest and understanding of the mechanism of AF began to take form in the early 1900s. Given the chaotic and irregular nature of AF on the surface electrocardiogram, rapid firing of automatic atrial foci was considered a potential mechanism. However, after the seminal work of Mayer[1], Mines[2] and Garrey[3] in laying the foundation for describing and understanding reentrant arrhythmias, atrial reentrant circuits emerged as the likely drivers of AF.[4–7] Although these theories were conceptually sound, it was impossible to prove a specific mechanism with the technology of the time. In 1959, Moe et al. described the 'multiple wavelet hypothesis' of AF which extended the concept of reentry to include multiple simultaneous atrial reentrant circuits with separate initiating and sustaining factors. According to this theory, if a critical number of reentrant wavefronts existed in an appropriate atrial substrate (a combination of atrial size and mass, conduction velocity and tissue refractory period) these wavefronts could continually re-excite the atria resulting in chaotic, fibrillatory conduction.[8] The multiple wavelet hypothesis was further supported by an early computer model of AF in which propagation of multiple atrial impulses demonstrated self-perpetuating activity with many similarities to clinical AF in humans.[9] Moe et al. demonstrated that it was probabilistically unlikely that a large number of simultaneous wavefronts would all die out simultaneously, and AF would therefore perpetuate. However, if the number of simultaneous wavelets were small and/or below a critical value (between 15 and 30 in Moe's computer model),[9] at some point all reentrant wavefronts would be simultaneously extinguished, and AF would therefore terminate.[8,9]

Allessie et al. provided experimental evidence supporting this mechanism in a canine heart model of AF where four to six simultaneous reentrant wavelets were needed to sustain arrhythmia.[10] Further evidence supporting multiple wavelets in AF was demonstrated in a separate model, which evaluated the effect of various antiarrhythmic drugs on canine myocardium. This model demonstrated that termination of AF was associated with a reduction

in the number of simultaneous atrial reentrant wavelets.[11,12] Cox et al. subsequently mapped multiple reentrant atrial wavefronts during human AF, and this formed the basis for the surgical maze procedure in which multiple, small, electrically-isolated atrial compartments were created to prevent sustained reentry.[13]

More recently it has become accepted that separate mechanisms may be responsible for triggering and sustaining AF. Focal discharges (especially from within the pulmonary veins, as described by Haissaguerre et al)[14] can initiate AF. However, AF maintenance probably involves some form of reentrant activity, with the observed irregular fibrillatory activity caused by 'wavebreak' of the main reentrant wavefront into multiple chaotic daughter wavelets as a consequence of inhomogeneity in atrial structure, refractoriness and conduction velocity.[15] Additionally, the mechanisms that sustain AF may evolve over time as the atria electrically and structurally remodel and AF progresses from paroxysmal, to persistent and then permanent forms. This concept has been supported by multiple studies which have demonstrated more frequent reentrant drivers of AF in patients with longstanding arrhythmia.

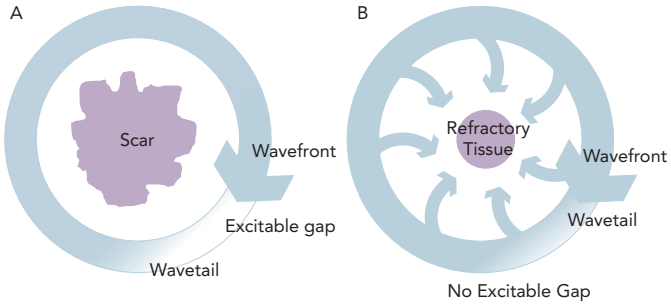
Functional Reentry and the Leading Circle Model

Functional reentry in its simplest form can be described by the 'leading circle model', first described by Allessie et al. in 1977.[16] In this model, circus movement of a unidirectional wavefront results in constant centripetal activation of the centre of the circuit which renders it continuously refractory. This refractory area then forms a functional barrier which can sustain reentry in a way similar to a fixed anatomic barrier such as a scar (see *Figure 1*). In the leading circle model, unidirectional block in tissue allows an impulse to initiate circus movement in one direction, with the impulse simultaneously spreading radially outwards to activate the adjacent myocardium and radially inwards towards the centroid of the circuit.

The wavelength of the circuit – defined as the product of the impulse conduction velocity and the tissue refractory period – describes the distance traveled by the wavefront during the refractory period. Wavelength is critical to understanding how reentry is established in this model. Consider a prototypical circular reentrant circuit with a circumference or path-length equal to the wavelength of the circuit (see *Figure 2A*). This circuit will have no excitable gap and will rotate continuously with the leading edge of the impulse (the wavefront) encroaching on tissue which has just recovered excitability (the wavetail). This will therefore define the smallest circuit which can sustain reentry. A smaller circuit, with path length less than wavelength, would occur in areas located closer towards the centroid of the circuit (see *Figure 2C*). This smaller circuit will not be able to sustain reentry because the circulating wavefront will encounter refractory tissue and will therefore block and terminate. A larger circuit, with path length greater than wavelength, would occur in areas located radially further away from the centroid of the circle (see *Figure 2B*) and can sustain reentry with an excitable gap. However, if conduction velocity throughout the atria remains relatively fixed, this larger reentrant circuit will rotate and activate the surrounding myocardium at a slower frequency.

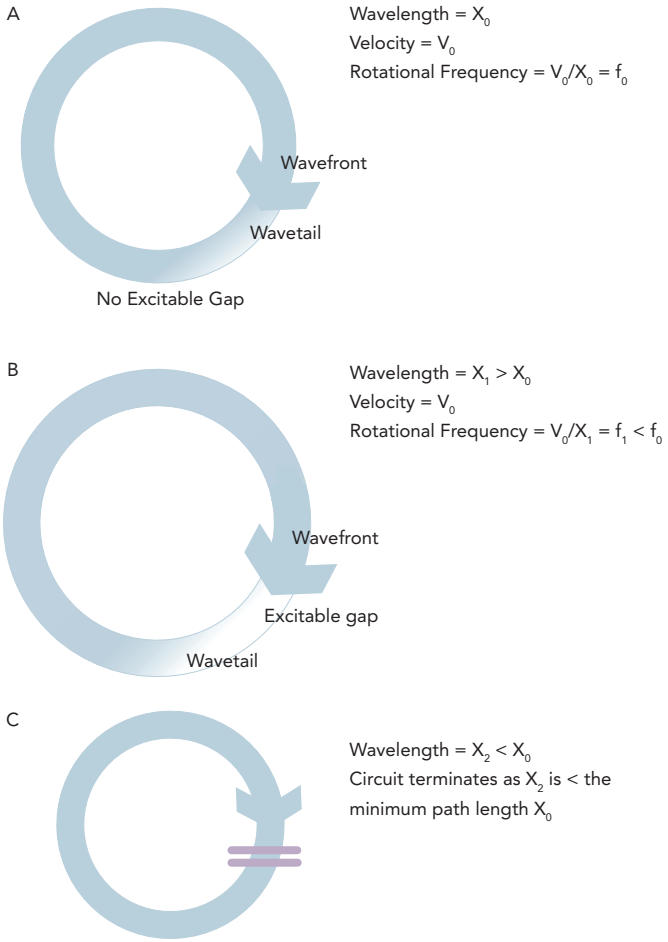
The 'leading circle' reentrant circuit with its path length/circumference equal to its wavelength (see *Figure 2A*) is thus the smallest circuit that can sustain reentry. By virtue of its smallest size it also rotates with the highest frequency, and so will 'overdrive' and suppress all larger circuits while maintaining a core of refractory tissue towards

Figure 1: Schematics of Anatomic and Functional Reentrant Circuits



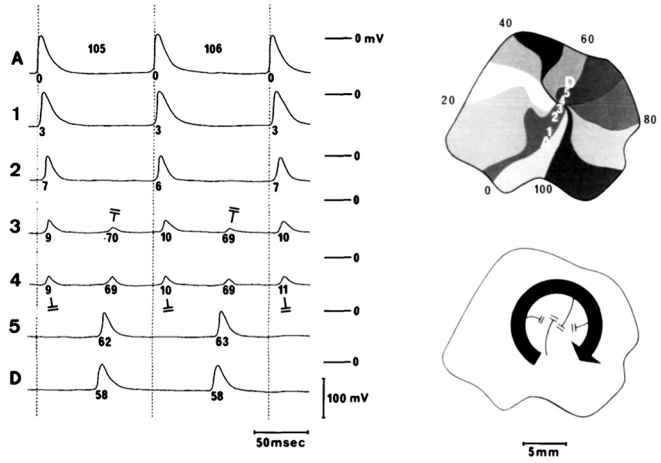
A. A simple reentrant circuit around an anatomic barrier (scar). The wavefront is represented by the blue arrow, and the wavetail is represented by the end of blue shading. The size of the circuit's excitable gap is shown between the wavefront and wavetail in white.
B: Leading circle reentry. There is no excitable gap as the wavefront continuously encroaching on the wavetail. Because of constant centripetal activation of the center of the circuit, this area becomes refractory and unexcitable which allows reentry to sustain itself in the absence of an anatomic barrier.

Figure 2: Leading Circle Reentry



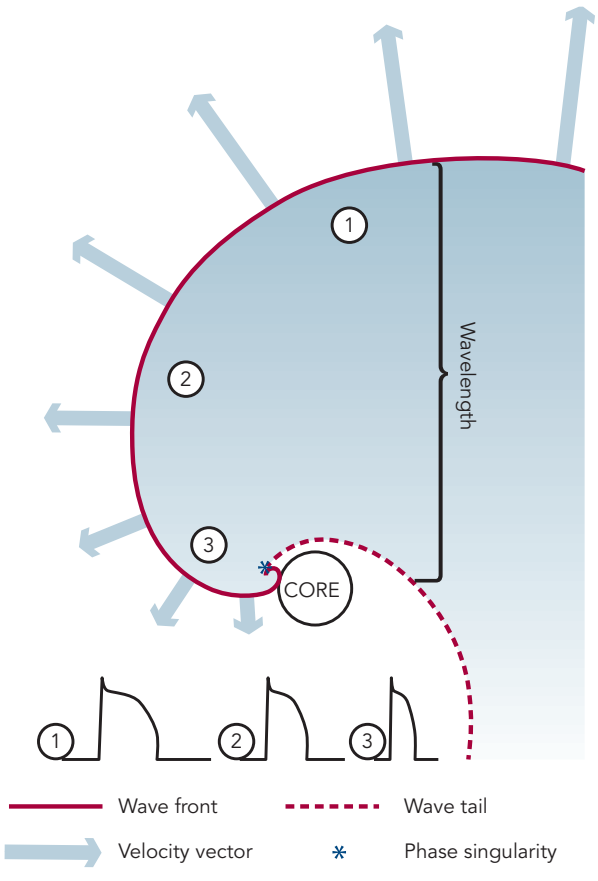
A: Leading circle reentry. No excitable gap is present, and the circuit rotates with a frequency of f_0. This is the smallest circuit which can sustain functional reentry.
B: Functional reentrant circuit larger than the leading circle. An excitable gap is present and the circuit rotates with a frequency of f_1 which is slower than f_0.
C: Functional reentrant circuit smaller than the leading circle. This circuit cannot sustain reentry as the circulating wavefront encounteres refractory tissue and will therefore block and terminate. See text for additional details.

Figure 3: Experimental Exidence of Leading Circle Reentry



Membrane potentials located in a straight line (A through D) through a clockwise reentrant circuit in atrial tissue with a cycle length of 105 milliseconds. Fibres 3 and 4, which are located in the centre of the circle, are activated twice as often, but they do not reach normal amplitude and cannot propagate out of the centre of the circuit, rendering it functionally unexcitable because the tissue is continually depolarised. Reproduced with permission from Allessie et al.[16]

Figure 4: Schematic of a Rotor



Points 1–3 represent a gradient of action potential duration along the curvature of the rotor. See text for additional details. Reproduced with permission from Pandit et al.[22]

its centre.[6] Reentry compatible with the leading circle model was elegantly demonstrated by Allessie et al. in experiments on rabbit myocardium. Here, rapid activation by a circular reentrant wavefront maintained a reduced membrane potential and therefore tissue refractoriness in the centre of the circuit (see *Figure 3*).[16]

The multiple wavelet hypothesis of AF and the leading circle model of reentry complement each other, as the number of reentrant circuits that can be sustained is dependent on wavelength and atrial size. Large atria and small reentrant circuits (short wavelength due to a short atrial refractory period and/or slow conduction velocity) allow multiple reentrant circuits to form and increase the probability of sustaining AF, while small atria (or surgically partitioned atria as in the maze procedure) and large reentrant circuits (long wavelengths) are unlikely to be able to sustain reentry and AF.[4] These observations also complement experimental human studies which have demonstrated increased rates of AF in patients with enlarged left atria[17], intra-atrial conduction defects,[18–20] or abnormal atrial refractory periods.[18,20,21] Recent experimental data have suggested, however, that although functional reentry may be of critical importance in initiating and sustaining AF, it is significantly more complex than can be accounted for by only leading circle reentry with multiple simultaneous wavelets.

Functional Reentry Due to Rotors/Spiral Waves

Recent computational and experimental data have suggested that special types of functional reentry may be of critical importance in sustaining AF. Rotors, or spiral waves, describe a specific type of functional reentry where, instead of being circular, the wavefront has a curved or spiral form, and the wavefront and wavetail meet at a focal point called a phase singularity (PS). Unlike the leading circle model, however, the wavefront velocity in a rotor is not constant, depending instead on wavefront curvature due to current source–sink mismatch associated with the propagation of non-planar wavefronts. The wavefront in close proximity to the PS is the region of highest curvature, and therefore is also the area of slowest wavefront conduction velocity (see *Figure 4*). In fact, at the PS, the wavefront curvature is so high and conduction velocity is so slow, that the propagating wavefront is unable to invade a core of tissue in the centre of the rotor. This tissue core is therefore effectively unexcitable, thus forming an area of functional block similar to the centre of a leading circle reentrant circuit. Unlike the leading circle model, tissue at the core of a rotor is not truly refractory. Because conduction velocity at the PS is so slow, tissue in the core is simply extremely difficult to penetrate and excite.

This fundamental difference has important implications for the behaviour of reentrant circuits driven by rotors as compared with leading circles. A reentrant circuit in the leading circle model must remain fixed in space because the centre of the circuit is completely unexcitable. A rotor, however, is able to move through space and, due to constant source–sink current mismatch at the PS and core, under certain circumstances the rotor can meander in various complex forms which in turn have important effects on rotor behaviour and sustainability.[6,22] The variable curvature of a rotor establishes a gradient of conduction velocity, and because the core constantly acts as a current sink from cells in close proximity to the core, this in turn also establishes gradients of action potential duration (APD) and wavelength which rise with increasing distance from the PS.[6,22] As a result of these gradients, rotors establish a gradient of excitable gap and heterogeneous conduction properties that also follow the spiral shape of the rotor and influence its behaviour.[22]

Rotors can theoretically and experimentally form when a wavefront interacts with some form of barrier, either due to a structural obstacle such as a scar or functional myocardial electrical inhomogeneity or

anisotropy. As a wavefront passes through a barrier it can, under certain conditions, bend and break into two daughter wavelets by a process called vortex shedding. This is somewhat analogous to the flow of turbulent water around an obstacle in a river.[22] Due to variations in wavefront curvature and velocity caused by the barrier, these daughter wavelets can, under the proper conditions, form and rotate around a PS. In certain instances they will anchor in place (often to areas around the pulmonary veins and in areas of heterogeneous atrial tissue) and form stable rotors.[23] As the rotating wavefronts spread away from the PS and core, they interact with other areas of anatomic or functional inhomogeneity in myocardium and fragment. They can then induce multiple disorganised 'fibrillatory' waves which then induce the chaotic atrial activation associated with AF.[24]

Tissue anisotropy, which is likely to be a critical determinant of rotor formation, can also allow the formation of rotors without the requirement of a fixed structural barrier or tissue inhomogeneity. Consider a homogenous medium being uniformly and continuously depolarised from a fixed site. If a premature extrastimulus is delivered from a distant site during phase three repolarisation, the extrastimulus will conduct into the area which has fully repolarised while blocking in the area which remains refractory. The excitation wavefront of the premature stimulus will therefore bend and, under favourable circumstances, can initiate spiral wave reentry around a functionally unexcitable core (see *Figure 5*).[25,26] Thus, rotor formation requires areas of non-uniform repolarisation, either due to fixed tissue inhomogeneity, or transient repolarisation non-uniformities due to the delivery of premature stimuli from multiple sites.[25]

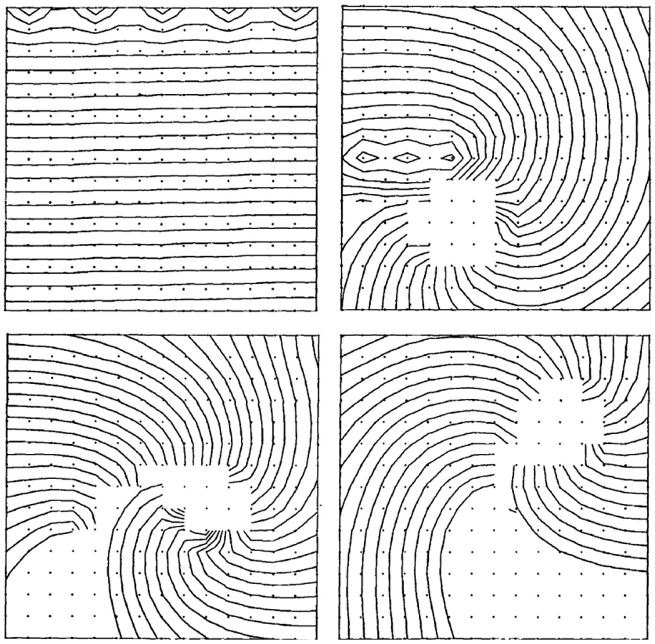
Evidence for Rotors and Other High Frequency Sources as Drivers of AF

Mapping studies have demonstrated the existence of localised, organised and high frequency drivers in AF, some of which are thought to represent rotor-like activity. The rotor model of AF maintains that although AF appears to be a chaotic and disorganised rhythm, it is actually being continually driven by the highly organised activity of a limited number of high frequency reentrant circuits. These produce wavefronts that eventually degenerate into chaotic and fibrillatory atrial activity at a distance.[23]

Early evidence of organised, high frequency drivers of AF was demonstrated by Schuessler et al. using isolated, perfused canine right atria (RA) with induction of AF using extrastimuli in the setting of various concentrations of acetylcholine (ACh). At lower concentrations of ACh, non-sustained, rapid, repetitive responses were induced and activation mapping demonstrated multiple reentrant wavelets and circuits. With higher doses of ACh the number of wavelets increased until a critical point at which sustained AF was induced, and the multiple reentrant circuits collapsed into one stable, high-frequency circuit that drove the resulting fibrillatory conduction.[27]

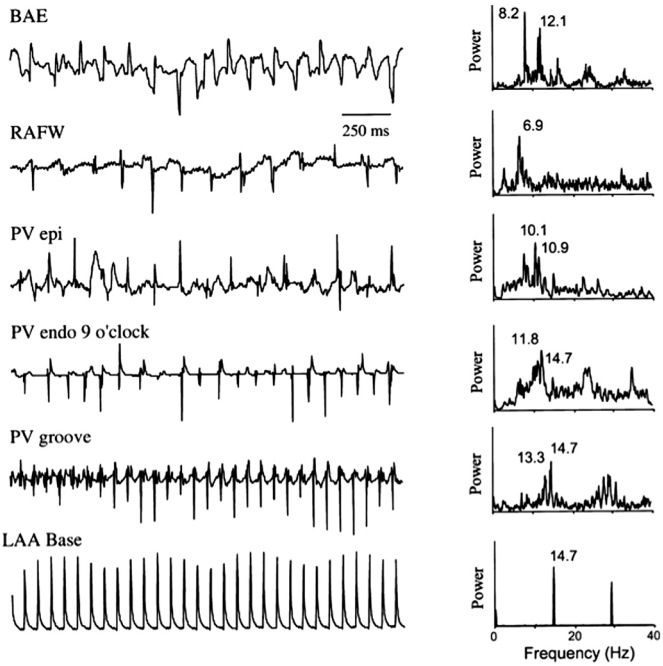
Evidence of high-frequency reentrant activity was demonstrated in a Langendorff-perfused sheep heart model in which AF was again induced with rapid atrial pacing in the presence of ACh. A bipolar mapping electrode and optical fluorescence recordings were used to sample atrial electrical activity at various left atrial (LA) and RA sites, and fast Fourier transformation was used to define the dominant frequency (DF) of local activation at each site. Despite the apparently chaotic atrial activation during AF, Fourier frequency analysis revealed an ordered gradient of stable DFs between the LA and RA (see *Figure 6*). The sites with the highest DF were mostly located in the posterior LA near the pulmonary vein ostia, and with optical mapping these sites corresponded to rotor-like reentry with a very rapid cycle length at the maximum DF (mean frequency 14.7 Hz).[28] Similar LA to RA DF

Figure 5: Initiation of Spiral Reentry in a Continuous, Uniform Sheet Model



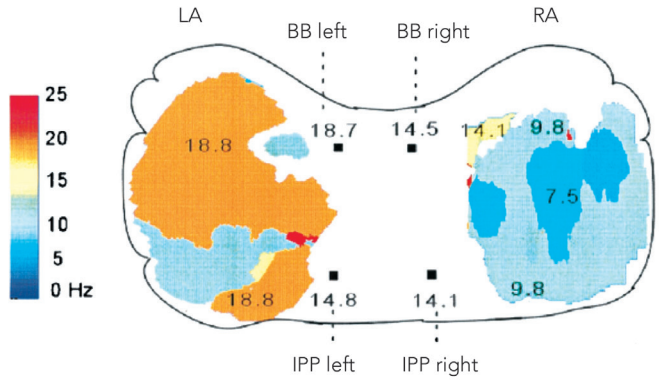
Upper left panel: A uniform conditioning stimulus is applied. Upper right panel: A premature stimulus applied at a site distant from the conditioning stimulus initiates clockwise circus movement tachycardia (reentry). Lower panels: The spiral reentry wave continues to rotate around an inexcitable core and is able to meander in space. See text for additional details. Reproduced with permission from van Capelle and Durrer.[26]

Figure 6: Simultaneously Recorded Electrograms, Pseudoelectrograms and Corresponding Fast Fourier Transformations During an AF Episode



The highest frequency (14.7 Hz) and greatest amount of organisation (single, narrow frequency peak) is seen in the LAA base. There is a gradient of frequency and disorganisation between the LA and RA. RAFW = right atrial free wall; LAA = left atrial appendage; PV = pulmonary vein; Endo = endocardial; LA = left atrium; RA = right atrium. Reproduced with permission from Mandapati et al.[28]

Figure 7: Left to Right Dominant Frequency Gradients in the Sheep Left and Right Atria



Numbers represent measured dominant frequencies at various atrial sites. BB = Bachmann's bundle; IPP = inferoposterior pathway; LA = left atrium, RA: right atrium; Reproduced with permission from Mansour et al.[29]

gradients were reproduced in a subsequent study by the same group (see *Figure 7*).[29] Because the frequency of rotational activity was so high, only tissue in close proximity to the rotor could activate in a 1:1 fashion, and at distant sites the wavefronts underwent wavebrake and initiated chaotic and fibrillatory conduction.[29]

Lazar et al. extended the concept of DF mapping to humans and demonstrated LA to RA DF gradients in patients with paroxysmal AF, with the highest DFs at the junction between the pulmonary veins and the LA. This gradient, however, was not present among patients with persistent AF, again suggesting a different mechanism for sustaining AF of longer duration.[30] The correlation between sites of high DF and rotor-like activity was not assessed in this study. In a later study by the same group, atrial DF gradients were assessed before and after pulmonary vein isolation (PVI). Although all patients did not have a pre-procedure DF gradient, LA to RA DF gradients in patients with paroxysmal AF were abolished with successful ablation. The presence of a pre-ablation LA to RA DF gradient was correlated with improved freedom from recurrence of AF after conventional PVI, and patients with recurrence of AF after PVI also had recurrence of LA to RA DF gradients at the time of repeat ablation.[31]

Studies that have explored a strategy of real-time DF mapping and ablation at the site of maximal DF have resulted in improved freedom from AF recurrence.[32] It is important to realise, however, that although animal studies have correlated sites of maximal DF with rotor-like activity, it remains unclear if all sites of maximal DF represent areas of rotor-like reentry or other types of localised reentry, especially in humans. Further studies with high-resolution mapping systems will be needed to further define the local activation in areas of high DF, and to determine if these sites are truly caused by functional reentry due to rotors.

The Influence of Ion Channels and Antiarrhythmic Drugs on Rotors in AF

Rotor dynamics are fundamentally governed by the activity of ion channels, and experiments have demonstrated that potassium channels have an important role in defining rotor behaviour. In the previously described Langendorff perfused sheep heart model, AF and rotors were induced with rapid atrial pacing in the setting of ACh, which, among its multitude of biologic actions, potentiates the effects of a specific inward rectifying potassium channel I_{KACh}. The link between I_{KACh}, DF gradients, and rotor dynamics was explored by measuring the density of I_{KACh} in the sheep atria. The highest density of I_{KACh} was localised at LA sites with the highest DFs and the majority of observed rotors, and increased concentrations of ACh resulted in both an increased number of rotors and a higher frequency of rotor rotation.[33] In transgenic mouse models, overexpression of the inward rectifying potassium channel I_{K1} resulted in rotors which were two to three times as rapid (50–60 Hz vs. 20–25 Hz) and significantly longer lasting (one hour vs. 10 seconds) compared to rotors induced in wild-type mice.[34] Similar effects on rotor dynamics have been observed with overexpression of the rapid delayed rectifying potassium current I_{Kr} in tissue culture, and *in vitro* I_{Kr} gradients (and resulting APD gradients) have been shown to be critical in reducing rotor meander, increasing rotor frequency and stability and inducing wavebreak and fibrillatory conduction.[35] Jalife and colleagues performed *in vitro* experiments evaluating the effect of varying concentrations of I_{Kr} in neonatal rat ventricular myocytes and demonstrated higher DF and increased rotor activity with I_{Kr} overexpression. In addition, they found that wave break and fibrillatory conduction were most likely to occur at areas with an abrupt transition in I_{Kr} concentration.[36]

The importance of potassium channels in AF dynamics has also been extended to humans using patch clamp and Western blot analysis of atrial tissue from patients with chronic AF, paroxysmal AF and no history of AF undergoing cardiac surgery. Western blot analysis demonstrated increased expression of I_{K1} subunits in patients with chronic AF compared with patients with paroxysmal AF or no AF. Additionally, in patients with any AF, the basal LA I_{K1} current was up-regulated two-fold compared with patients without AF. Interestingly, a LA to RA gradient of potassium current (analogous to LA to RA DF gradients) was also only observed in patients with paroxysmal AF. *In vivo* human studies using DF and rotor mapping during electrophysiological studies have also demonstrated that administration of adenosine increases rotor frequency to a greater extent in patients with persistent AF compared with paroxysmal AF likely due to differential effects on I_{KACh}.[37]

Increased inward potassium current (through multiple potassium channels) causes shorter APD and resting membrane hyperpolarisation. Given the importance of I_{KACh}, I_{K1} and probably other similar inwardly rectifying potassium channels, it would make sense that drugs that block these channels would slow and/or destabilise rotors resulting in termination of AF and prevention of reinduction. These electrophysiological effects of potassium channel drugs on rotor dynamics have been observed in animal models,[22,35] although studies in humans are currently lacking.

Sodium channel blockade by antiarrhythmic drugs can terminate AF and prevent its re-induction, presumably by slowing conduction and making reentry unfavourable. Proposed mechanisms of AF rotor termination with sodium channel blockade include: an increase in rotor size so that the rotor extinguishes at tissue boundaries; reduced anchoring of the rotor which promotes meander of the core and eventual termination; reduced rotational frequency and a reduction in the number of daughter wavelets that can generate new rotors to sustain AF.[38]

Therapeutically Targeting High Frequency Drivers and Rotors in Human AF

The strongest clinical evidence for high-frequency rotors and focal drivers and their critical role in maintaining human AF comes from

work by Narayan et al. In the CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial, conventional PVI was compared with focal impulse and rotor modulation (FIRM) guided ablation followed by conventional PVI. In a non-randomised fashion, 92 patients with drug-refractory paroxysmal (29 %) or persistent (71 %) AF underwent ablation during which 64-pole basket catheters were used to map the right and left atria and construct AF activation maps using special computational protocols. Importantly, patients who presented in sinus rhythm (SR) had to have AF induced for mapping purposes. Using these AF activation maps, the operators looked for stable (defined as lasting more than 10 minutes), high frequency drivers of AF defined as rotors (areas of spiral or rotational activation) or focal impulses (repetitive focal activation without clear rotation). In the FIRM-guided group these areas were then targeted with focal ablation followed by conventional PVI. The primary endpoint was acute termination of AF or slowing of the AF cycle length by ≥10 %.

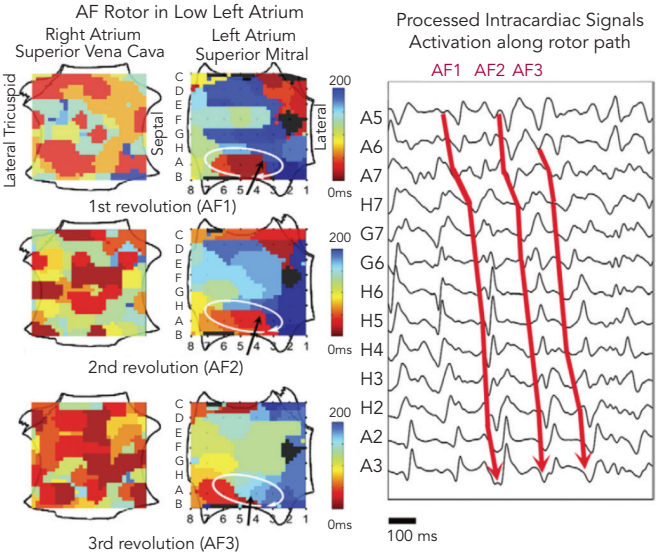
Computational AF mapping demonstrated the presence of rotors and focal impulses in 97 % of patients, and 70 % of stable drivers demonstrated rotational activity potentially consistent with rotors (see *Figure 8*). Patients with persistent AF had more rotors and focal impulses than patients with paroxysmal AF (median 2 vs. 1, p=0.03). Three quarters of rotors and focal impulses were located in the LA (including sites far removed from the pulmonary veins), and interestingly, one-quarter of sources were located in the RA, an area often neglected during conventional PVI.

FIRM ablation prior to conventional PVI achieved AF termination in 56 % of patients after a median of only 2.1 minutes of ablation. In comparison, the conventional PVI group achieved AF termination with ablation in only 9 % of patients (p<0.001). During median follow-up of 273 days, freedom from any AF after a 3-month blanking period was significantly higher in the FIRM-guided ablation group than in the conventional PVI group (82.4 % vs. 44.9 %, p<0.001).[39] Importantly, the rate of freedom from AF in the conventional PVI group was lower than would be expected based on other contemporary series.[40]

The authors then retrospectively analysed computational AF maps in the patients who underwent only conventional PVI to determine the location of rotors and focal impulses in these patients and to see if ablation lesions performed blindly as part of the conventional PVI procedure coincidently eliminated these sources. When conventional PVI coincidently eliminated a rotor or focal impulse, freedom from AF during follow-up was four-fold higher than in patients in whom AF drivers were not eliminated (80.3 % vs. 18.2 %, p<0.001). There was no difference in freedom from AF recurrence if all AF sources were ablated using FIRM-guided ablation or by coincidence in the conventional PVI group (p=0.551). Patients who had some but not all rotors or focal impulses ablated by coincidence had intermediate success.[41]

Narayan et al. have also presented preliminary results from the PRECISE-PAF (Precise Rotor Elimination Without Concomitant Pulmonary Vein Isolation For Subsequent Elimination Of Paroxysmal AF) trial, which evaluated FIRM-guided ablation without conventional PVI in 31 patients with paroxysmal AF and no prior ablation. After a mean follow-up of 223 days, 83 % of patients remained free of recurrent AF.[42] The results suggest that by eliminating the rotors that sustain AF, it is not necessary to eliminate the triggers for AF (which come predominantly from the pulmonary veins).This study has not yet been formally published, and given the very small sample size, lack of a control group and short follow-up, it is difficult to draw meaningful conclusions from the results.

Figure 8: Example of a Left Atrial Rotor Visualised with FIRM Mapping



The rotor is rotating in a clockwise direction as noted by the arrow, and the colors represent activation time of each point in the atrium (see scale). Three rotations corresponding to the electrograms shown in AF1 through AF3 are shown. Reproduced with permission from Narayan et al.[39]

The results of the CONFIRM study are impressive, and other small studies using similar technology have demonstrated similar results.[43] However, given the non-randomised patient assignment, small numbers of patients and relatively short-term follow-up, these results will certainly have to be replicated in a large randomised trial with longer follow-up before FIRM-guided ablation can be incorporated into regular clinical practice.

Limitations of Targeting Rotors with Ablation for the Treatment of AF

The CONFIRM trial provides the best human evidence that rotor-like reentry is of key importance in sustaining AF.[39] This conclusion, however, has many caveats and limitations, and there remains uncertainty as to whether AF is truly the result or rotors or if it is secondary to other simpler reentrant mechanisms.

Observing rotors in human AF requires overcoming multiple technical obstacles, and the way in which presumed rotors were mapped in the CONFIRM trial reveals some critical limitations of this technology. Electrograms were obtained with a 64-pole basket catheter (Constellation® Catheter; Boston Scientific, MA, US)[39] which provides a relatively low resolution map of the atria. Given the irregular 3D structure of the atria, all catheter splines/electrodes will not be in contact with atrial tissue simultaneously, and far fewer than 64 points are likely being recorded at any given time. There is also the potential for far-field signals to be interpreted as local, especially since unipolar electrograms were used in the analysis. A related issue is that 'rotors' were observed after significant proprietary computational processing, averaging and interpolation of raw electrogram data.[44,45] With low resolution mapping, poor local tissue-electrode contact and heavy signal processing and interpolation, it is possible that

the observed 'rotor' activity is an artifactual representation of other forms of reentry. Additionally, with the resolution available with current generation FIRM mapping, it is only possible to observe rotational activity distant from the rotor core and not near or within the rotor core itself.

This does not mean that the 'rotors' targeted in the CONFIRM trial were not clinically important. Ablation of these areas did indeed correlate with both termination of AF and a significant reduction in rates of AF recurrence, but the technical aspects of the trial limit the ability to conclude that the observed reentry was truly rotor activity and not another form of reentry. The aetiology of focal impulses – seen in 30 % of patients in the CONFIRM trial – are also not necessarily explained by rotors. It remains unclear if these sites represent micro-rotors, which are simply too small to see with the current mapping catheter resolution, or if they represent other forms of local micro-reentry or even triggered activity.

Rotors Do Not Consistently Sustain AF

Although rotors were found in the majority of patients in the CONFIRM trial,[39] other mapping studies of human AF have not consistently demonstrated rotor-like reentry. This raises concerns about the trial's conclusions regarding mechanisms of AF. If rotors were truly present in over 90 % of patients with AF, and if they were critical to the maintenance of the rhythm, it would be expected that many other AF mapping studies would also find a similarly high prevalence of rotors. This, however, has not been consistently observed.

In a study of high-density mapping of persistent AF and pacing-induced AF during cardiac surgery, Allessie et al. found no evidence of stable rotors or other focal sources driving AF. Instead, they observed multiple wavelets constrained by lines of continuously-changing functional block. The main feature that differentiated persistent AF from AF induced in the operating room was an increase in the dissociation of atrial muscle bundles.[46] Data from our group, in which eight patients with chronic AF and 11 patients with electrically-induced AF had intraoperative RA mapping performed for up to 12 seconds with a 240 electrodes, reached similar conclusions. Patients with chronic AF tended to have more complex patterns of atrial activation, with multiple wavelets propagating around multiple arcs of functional conduction block, which were predominantly oriented perpendicular to the tricuspid annulus, and areas of random and complete reentry, suggesting a critical role for tissue anisotropy in the pathogenesis of AF.[47] These data also suggest that AF induced with rapid atrial pacing (such as prior to FIRM mapping and rotor ablation) may utilise different mechanisms than chronic AF. Studies or models that use pacing for the induction of AF to study mechanisms of the arrhythmia may therefore not be completely applicable to naturally occurring or long-lasting AF.

Kalman and colleagues performed intraoperative mapping using high density epicardial electrodes of multiple focal areas within the LA and RA in patients with persistent AF. They recorded activity over multiple 10-second periods and looked for multiple wavefronts, rotational circuits, focal sources and disorganised activity. Interestingly, in the majority of patients rapid transitions between multiple (mean 3.8 ± 1.6) unstable activation patterns were seen. Patients predominantly had multiple wavefronts or completely disorganised atrial activity during AF, and only 5.5 % of maps demonstrated stable activation patterns during the 10 seconds of data acquisition. No patients had sustained focal activity lasting more than two beats or sustained rotational circuits (rotors).[48] Rudy and colleagues utilised novel non-invasive electrocardiographic imaging (ECGI) to map activation in atrial fibrillation and found that 92 % of of patients demonstrated multiple wavelets driving AF, while only 15 % demonstrated circular reentry compatible with rotor activity.[49]

Complex Fractionated Atrial Electrograms as Potential Drivers in AF

Complex fractionated atrial electrograms (CFAEs) have recently attracted interest in terms of their relationship to the maintenance of AF and as potential ablation targets. Fractionated electrograms can be caused by multiple mechanisms, but in general represent areas of myocardium with separated or disorganised myocardial fibres that cause slowed, dyssynchronous, and/or anisotropic local conduction.[50,51] In human AF it has been proposed that fractionated electrograms may be caused by local collision of multiple wavelets, zones of slow conduction, local reentry, areas adjacent to high frequency sites where wavebreak and fibrillatory conduction occur or direct autonomic innervation.[51,52] Fractionated electrograms can be fixed and caused by anatomic barriers such as scar or inhomogeneous tissue, or they may be functional, dynamic and related to changes in wavefront propagation throughout the myocardium. It has been further proposed that these fractionated sites are important in sustaining AF,[53] and that targeting fractionated electrograms with ablation can terminate AF and prevent its re-induction or recurrence.[52,54–60] The data supporting these conclusions are rather weak overall, with only a few small, randomised clinical trials providing guidance, and different studies have arrived at disparate conclusions regarding the importance, or lack thereof, of fractionated electrograms in the pathogenesis of AF.

Ablation of CFAEs in the treatment of AF was initially proposed in a 2004 study of 121 patients with AF, 47 % of whom had paroxysmal AF. Ablating areas of CFAEs – defined as local bipolar electrograms with greater than two deflections, continuous activation or a cycle length ≤ 120 milliseconds – without conventional PVI resulted in acute termination of AF in 95 % of patients, with 76 % of patients remaining free of AF without repeat ablation at one year. Of note, many CFAE sites were located around the pulmonary veins, and it is unclear if CFAE ablation coincidently resulted in isolation of the pulmonary veins.[56] These results would support the conclusion that the areas of CFAEs were either drivers of AF or important to perpetuating AF, but follow-up studies of CFAE ablation without concomitant PVI have demonstrated disappointing results. In a subsequent study of 100 patients with chronic AF who underwent CFAE ablation alone, after an average follow-up of 14 months, only 33 % of patients remained free of arrhythmia without antiarrhythmic medications; 55 % of patients developed recurrence of AF; and 44 % of patients required a repeat ablation procedure.[61] In another study of 77 patients with persistent AF comparing CFAE ablation alone with CFAE ablation with PVI, over an average follow-up period of 13 months, 41 % of patients who had CFAE ablation alone had recurrence of AF compared with 9 % of patients who had CFAE ablation with PVI (p=0.008).[62] Di Biase et al. randomised 103 patients with paroxysmal AF to CFAE ablation, PVI, or the combination of CFAE ablation and PVI and found that freedom from atrial tachyarrhythmia at one year was present in only 23 % of patients who underwent CFAE ablation alone compared with 89 % in the PVI group, and 91 % in the CFAE plus PVI group (p<0.001 for a three-way comparison).[63]

Interest thus shifted to using CFAE ablation as an adjunctive procedure during standard PVI. Elayi et al. randomised 144 patients with long-standing permanent AF to circumferential pulmonary vein ablation, antral PVI or CFAE ablation followed by PVI. The study showed that at an average of 16 months of follow-up, freedom from AF recurrence was present in 61 % of the patients who received CFAE ablation and PVI, 40 % of patients who received PVI and only 11 % of patients who received circumferential pulmonary vein ablation (p<0.001 for a three-way comparison).[64] Similarly, in the STAR-AF (Substrate and Trigger Ablation for Reduction of AF) trial, 100 patients with high burden paroxysmal or persistent AF were randomised to CFAE ablation alone, PVI alone or the combination of PVI and CFAE ablation. After one year of follow-up, the combination of PVI and CFAE ablation had the highest freedom from recurrent AF (74 %) compared with PVI alone (48 %) and CFAE ablation alone (29 %) (p=0.004). However when paroxysmal and persistent patients were analysed separately, an improvement in freedom from recurrent AF with PVI plus CFAE ablation compared with PVI alone was only present among patients with persistent AF.[54] A 200-patient case-control study demonstrated that targeting CFAEs in addition to PVI had no effect on freedom from AF in patients with paroxysmal AF and only marginally improved the success rate of PVI in the subset of patients with persistent or permanent AF (success rate 82 % for PVI and CFAE ablation vs. 72 % for PVI alone, p=0.047).[65] Multiple other studies, however, have found that targeting CFAEs provided no additional freedom from AF over PVI alone even among patients with permanent AF.[57,59,60,63] A recent meta-analysis evaluated the outcomes in 622 patients across seven trials that compared PVI with PVI plus adjunctive CFAE ablation. It concluded that the addition of CFAE ablation to PVI resulted in only a modest increase in maintenance of sinus rhythm (SR) without antiarrhythmic drugs (relative risk [RR] 1.17, 95 % confidence interval [CR] 1.03-1.33, p=0.019) and in subgroup analyses only patients with non-paroxysmal AF derived any benefit (RR 1.35, 95 % CI 1.04-1.75, p=0.022).[66]

These studies of CFAE ablation support observations that patients with non-paroxysmal AF tend to have less success with conventional PVI alone, and they complement the previous data describing how patients with paroxysmal AF and non-paroxysmal AF appear to have variations in AF drivers. These results, however, must be interpreted with caution given the small sample sizes and the highly variable criteria for defining CFAEs which limits the ability to combine the results of such studies. Importantly, the majority of studies comparing PVI with either PVI and CFAE ablation or CFAE ablation alone did not require testing each isolated vein for entrance and exit block, and this may be one reason for the apparent benefit of CFAE ablation in some studies. A large scale randomised control trial of CFAE ablation in addition to standard PVI has not yet been performed.

Complex Fractionated Electrograms are Passive Bystanders in AF

Observations that CFAE ablation without PVI results in very high rates of AF recurrence[54,61–63,65] suggest that CFAEs are not drivers of AF. In fact, the vast majority of areas of observed fractionation are actually functional and passive electrophysiological manifestations. In a study of patients with AF and healthy controls who underwent mapping of fractionation during SR (in all patients) and AF (in AF patients only), there was no correlation between the location of fractionated electrograms during SR and during AF.[67] Additionally, the extent of electrogram fractionation in patients with and without AF was similar, and areas of fractionation did not correlate with abnormal voltage or atrial scarring in any patients, suggesting that fractionation was functional in nature.[67] Jadidi et al. mapped CFAEs – defined as an electrogram with at least four deflections or continuous activation – in AF, SR and with coronary sinus pacing in 18 patients with AF (nine persistent AF and nine paroxysmal AF). Although patients with persistent AF had more fractionation than did patients with paroxysmal AF, the distribution of fractionated electrograms was quite dynamic and variable, depending on the direction and rate of atrial activation during AF, sinus rhythm or atrial pacing, with minimal overlap between rhythms. In fact, less than 5 % of the LA area demonstrated fractionation in both SR and AF. In addition, areas of fractionation did not correlate with areas of abnormal voltage or scar, and electrogram fractionation was predominantly functional due to wavefront collision.[68] The vast majority of fractionated electrograms therefore played no role in the genesis or maintenance of AF, and targeting these areas during catheter ablation of AF would be time consuming, unnecessary and ineffective.

Although CFAEs appear to be predominantly functional and are thus unlikely to represent drivers of AF, it has been proposed that they might be spatially related to rotors or other high frequency AF drivers. This association could explain the success of some CFAE-guided ablation strategies. The local electrogram around presumed rotor activity is quite regular with very low levels of signal fractionation, but just beyond the local area of the rotor, at points where wavebreak and fibrillatory conduction occur, high levels of electrogram fractionation have been observed,[55] and fractionated electrograms have also been spatially correlated with areas of high DF during AF.[69] It has therefore been proposed that localising CFAEs may be an indirect way of localising rotor or high DF activity, and ablating CFAEs may therefore coincidently terminate AF or improve freedom from AF recurrences by coincidently destroying these other focal, organised AF drivers.[55] Given the predominantly functional nature of CFAEs, however, this explanation seems unlikely, and Narayan's group has demonstrated that CFAEs are largely spatially unrelated to sites of rotors or other focal AF drivers.[70]

Nevertheless, all CFAEs may not be equivalent,[71] and fractionation may evolve over time as AF transitions from paroxysmal to persistent.[72] Ablation of fractionated electrograms which demonstrate continuous activity or temporal activation gradients have been shown to be more strongly associated with AF slowing or termination,[73] and the subset of CFAEs that persist in AF, sinus rhythm or with atrial pacing might also be important in the pathophysiology of AF, with a potential role as an ablation target.[68] To evaluate this possibility, the SELECT AF (Selective Complex Fractionated Atrial Electrograms Targeting for AF) trial randomised 86 patients to PVI and either ablation of all CFAEs or ablation of only CFAE regions with continuous electric activity. Although both CFAE ablation strategies resulted in similar rates of AF termination (37 % and 28 %, p=0.42), at one year of follow-up, patients who underwent generalised CFAE ablation had a significantly higher rate of freedom from atrial tachycarrhythmias compared with those who had selective CFAE ablation (50 % vs. 28 %, p=0.03).[74] As of yet, there are no clinical trial data to suggest that specific types of CFAEs are especially critical to the pathogenesis or maintenance of AF, or that targeting specific types of CFAEs can improve outcomes after catheter ablation.

Another significant limitation in applying results from studies evaluating CFAE ablation is that there is no consensus on what defines a CFAE. Criteria used in studies are subjective and variable, including electrograms with various numbers of deflections, continuous atrial activation or electrograms with very short mean cycle lengths.[66] Automatic computer algorithms have been developed to remove some of the subjectivity in distinguishing important areas of fractionation, but in one study using such a method, 86 % of LA sites were classified as having CFAEs.[75]

Despite the initial excitement surrounding the relation of CFAEs to AF, CFAEs are non-specific electrophysiological manifestations which are unlikely to be drivers of AF, and coincidental ablation of reentrant circuits and AF drivers likely explains the occasional success when CFAEs are targeted with ablation. CFAE ablation has minimal effect on patient outcomes, and can result in increased procedure times and an increased potential for complications.

The Influence of the Autonomic Nervous System and Ganglionated Plexi on AF

The autonomic nervous system is likely to have a role in clinical AF.[76,77] Both sympathetic and parasympathetic stimuli may be involved,[76] although in humans, the extent and importance of autonomic influences vary based on patient characteristics and comorbidities.[78] Ganglionated plexi (GP) are epicardial networks of autonomic nervous tissue present near the junctions between the pulmonary veins and LA.[79,80] GP connect the extrinsic autonomic nervous system (brain, spinal cord, and ganglia/nerves outside of the heart) to the intrinsic autonomic nervous system within the heart, and are important mediators by which autonomic stimuli influence AF and other arrhythmias.[81] Autonomic signals to the heart via GP exert important electrophysiological effects including altering atrial refractory periods,[81,82] increasing the frequency of triggered atrial premature beats that can subsequently initiate AF,[83] and increasing the vulnerability of atrial tissue to the induction of AF.[81,84,85] Animal studies have demonstrated that stimulation of GP located around the pulmonary veins can reduce the number of atrial extrastimuli required to initiate AF, and that neuronal/autonomic blockade with drugs or GP ablation can prevent AF induction.[86,87]

Because GP are located near the pulmonary veins, conventional PVI can often coincidently eliminate these areas, and it has been suggested that ablation of GP may help explain the success of PVI. In an early study, Pappone and colleagues assessed for vagal responses (bradycardia, hypotension, heart block or asystole) which occurred within a few seconds after the onset of ablation. If such a response occurred, ablation was continued until the vagal response terminated and could not be re-induced with repeat ablation. The most common sites of vagal responses were located at the junctions between the pulmonary veins and LA where GP are located. Patients who had complete vagal denervation, as defined by elimination of all vagal responses at completion of PVI, had reduced rates of AF recurrence at one year (85% vs. 99%, p=0.0002).[88] Other studies have localised GP by use of high-frequency simulation, although data have suggested that an anatomic approach is preferred over high-frequency stimulation or identification of areas with vagal responses, which are both insensitive methods to identify GP.[89]

Katritsis and colleagues studied the benefit of GP ablation by randomising 242 patients with paroxysmal AF to standard PVI alone, GP ablation alone or PVI with additional GP ablation. GP were anatomically targeted by ablating at their expected locations around the pulmonary veins. At two years post-ablation, 56% of patients who had conventional PVI alone, 48% of patients who had GP ablation alone and 74% of patients who had a combination of PVI and GP ablation were free of recurrent AF or atrial tachycardias. Patients who had PVI with GP ablation had a HR for recurrence of arrhythmia of 0.53 (p=0.022) and 0.42 (p=0.001) compared with patients who had PVI alone and patients who had GP ablation alone, respectively. Surprisingly, over the entire two years of follow-up there was no statistically significant difference in recurrence of atrial tachyarrhythmias between patients who had PVI alone or GP ablation alone (p=0.31), although after one year patients who had GP ablation alone began to experience more arrhythmia recurrences than patients who had PVI alone. The similar and then divergent results for the PVI-alone and GP ablation-alone groups could be explained by the fact that conventional PVI lesions are likely to coincidently eliminate at least some GP located near the pulmonary veins, but PVI covers a larger area of the LA and completely isolates the pulmonary veins so that pulmonary vein triggers unrelated to GP activity cannot initiate AF.[90] It is also possible that targeting GP had a minimal effect on cardiac autonomic innervation, but the additional lesions performed to target GP may have resulted in a longer-lasting isolation of the pulmonary veins.[91]

Although GP may have a role in initiating AF by increasing both the frequency of pulmonary vein triggers and atrial vulnerability to these triggers, the relationship between GP and the mechanisms which sustain AF is much less clear. As previously discussed, autonomic tone can influence ion channel function which may subsequently influence the behavior of rotors or other AF drivers, but a definitive and direct link between GP and AF drivers has not been demonstrated. GP have also been correlated with areas of CFAEs,[52,92] but as discussed above, CFAEs are passive manifestations of inter-atrial conduction and are unlikely to be drivers of AF. In animal models, radiofrequency ablation can actually induce new nerve growth,[93] and in humans, ablation has been shown to result in elevations in nerve growth factor,[94] which may counteract the beneficial effects of GP ablation. Incomplete GP denervation may also be ineffective[95] or even proarrhythmic.[96] Overall, GP ablation has only been evaluated in a few small studies, and further trials will be required before it can be safely and effectively adopted into standard practice.

Conclusions and Future Directions

The totality of data suggests that there is highly organised reentrant activity underlying the seemingly chaotic and random atrial activity in AF. However, confirming whether or not these AF drivers are rotors or other forms of reentry will require carefully executed high-resolution human mapping and ablation studies. The goal of discovering a single mechanism for triggering and/or sustaining AF may also be impossible, as it is likely that variations in pathology will at least partially influence the way in which AF is initiated and sustained. In fact, AF may have multiple, disparate mechanisms in different patients or even in the same patient at different times. This may at least partially explain why targeting one specific mechanism, such as isolating the pulmonary veins, is often initially is successful but then fails over time. The best therapy for AF ultimately may involve discerning an individual patient's 'type' or mechanism of AF and

specifically targeting that, rather than relying on a one-size-fits-all approach. Understanding the electrophysiological mechanisms by which AF is initiated and sustained will be critical for developing safer and more effective therapies in the treatment of AF. ■

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