Creating Order From Chaos
Practical Interventional Targets for the Multiple Wavelets of Atrial Fibrillation

Krishna Kancharla, MD; Suraj Kapa, MD; Samuel J. Asirvatham, MD

It’s always seemed like a big mystery how nature, seemingly so effortlessly, manages to produce so much that seems to us so complex. Well, I think we found its secret. It’s just sampling what’s out there in the computational universe.

—Stephen Wolfram, 2010

Pathogenesis of nearly all arrhythmia relies on a fundamental premise—that there exists within the cellular milieu regions of unexpected or unwanted heterogeneous conduction that may allow for initiation and propagation of wave fronts along a nonstandard pattern. The simplest paradigm for this may be atrioventricular reentrant tachycardias wherein 2 paths exist, both capable of propagating signals in either the antegrade or retrograde direction, but with fundamentally different conductive properties that ultimately allow for development of reentry with an appropriately timed stimulus. This appropriately timed stimulus, or trigger, has for the past 3 decades been the focus of electrophysiologists in the treatment of more complex arrhythmias that exist outside the ability of our modern day understanding and technology to map and ablate. Where a single circuit or reentry comes straight forward, and we must prove it exists and that it participates in the tachycardia, identify its location, and then determine the best means by which to ablate it. However, in the case of atrial fibrillation, understanding, identifying, and determining an ideal ablative solution for the substrate is eminently more difficult. This is because the propagation and continuation of atrial fibrillation is fundamentally dependent on the continuous activity of many sites simultaneously. Thus, we have often referred to atrial fibrillation almost as chaos, throwing up arms at the seemingly inexplicable and indescribable complexity and focused instead on the elimination of triggers, whether by pulmonary vein isolation or targeting other sites, rather than the myocardial substrate responsible for arrhythmia maintenance as we would with any other simpler arrhythmia, such as atrial flutter or ativoventricular nodal reentrant tachycardia.

See Article by Carrick et al

Ablation of these triggers, although a reasonably effective therapy for certain individuals with atrial fibrillation, has proven not nearly as effective for individuals with more persistent forms of atrial fibrillation.1 In theory, this is because of the larger quantity of substrate in patients with persistent atrial fibrillation. However, it is likely unreasonable to expect that we can eliminate all potential triggers (eg, a retrogradely conducted premature ventricular stimulus, atrial ectopics from other nonpulmonary vein sites, etc.) For cavotricuspid isthmus-dependent flutter, efforts to treat the arrhythmia by targeting presumptive triggers (eg, via pulmonary vein isolation) would seem unreasonable given that there is a discrete circuit that can be targeted instead. This then begs the question of why we are unable to do the same in atrial fibrillation—namely why we are left to target triggers rather than the substrate. To address this, recent advances in the mapping and treatment of atrial fibrillation have focused on a long-assumed but heretofore unmappable theory about how atrial fibrillation is sustained—the multiple wavelet reentry (MWR) hypothesis.

In this issue of Circulation: Arrhythmia & Electrophysiology, Carrick et al report results of a computational tissue model with varying functional heterogeneity and structural dimensions to offer evidence of the role of MWR in the genesis of atrial fibrillation.2 Although this builds on experimental and computational models done over the course of 50 years, of further interest is their focus on the methods of ablation that may be best used to treat these reentrant regions—whether branch lesions, box lesions, or linear lesions crossing through the tissue’s functional center is best. They note that, in their model, a linear ablation approach could be prospectively defined based on the calculated tissue fibrillogenicity and, in turn, reduce or eliminate fibrillatory potential. These findings serve to further our understanding of how to practically approach these functionally reentrant circuits when identified, though clinical application needs to be considered carefully, especially when considering whether currently available imaging and mapping techniques are sufficient to define and successfully target these MWR circuits.

The MWR Hypothesis: A Half Century in the Making

It has been known since the mid 1700s that the pulmonary veins are capable of spontaneously firing independent of the
atria. However, it took nearly 250 years to recognize their role in arrhythmia pathogenesis and to identify a means of targeting this ectopic firing. Similarly, the MWR hypothesis has been described since Moe et al first postulated in the 1950s that atrial fibrillation was the result of the random propagation of multiple wavelets across the atria. Moe’s postulations were experimentally validated later on in animal models. These contrasted with other experimental models of the time that suggested that atrial fibrillation was a result of circus movement about an obstacle (Rosenblueth and Garcia-Ramos) or of multifocal ectopic pacemakers (Scherf et al). Over the ensuing 50 years, multiple investigators either through animal or computational methods have supported these initial hypotheses proposed by Moe and others in terms of the role of MWR in generation and maintenance of atrial fibrillation. In turn, experimental validation has led to the development of novel mapping systems aimed at identifying a subtype of reentrant wavelets (rotors) such that they may be targeted for ablation. However, the major limitations to date continue to be the following: (1) how to differentiate rotors, MWR, innocent bystander phenomena that simply appear by mapping to reflect functional reentry, or combinations thereof; (2) the best method of mapping and identifying these phenomena; and (3) a lack of understanding of how to actually target these regions for ablation without causing additional substrate that can lead to other complex arrhythmias (eg, atrial flutter).

Where Does MWR Fit in Rotor Theory?

It is critical to understand the differences between rotors and MWR when considering the implications of studies such as that by Carrick et al on clinical approaches to ablation of atrial fibrillation. In the case of both rotors and MWR, the clinical electrophysiologist is forced to reconsider the mechanism of reentry from one of anatomic reentry that typically underlies rhythms such as atrial flutter or scar-related ventricular tachycardia to that of functional reentry. If one views cardiac excitation as a wave, with the wave front being the action potential upstroke and the wave back being rapid repolarization, in normal rhythm there should never be a situation wherein the wave back (ie, the back end of the wave) confronts the wave front (ie, the front end). If the 2 collide, this constitutes a wave break or phase singularity. Once this occurs, one of 2 events may follow: (1) the electric wave extinguishes because of failure of propagation or (2) the wavebreak becomes spatially localized along the wavefront, resulting in reentry. It is the latter event that leads to rotation of the wave around the phase singularity (aka wave break), thus forming a rotor. In 2-dimensions, this rotor may be described as a spiral wave, whereas in 3-dimensions, it is described as a scroll wave. It is likely that multiple rotors, or so-called mother rotors, generate atrial fibrillation because of their relatively short cycle length and resulting capacity to rapidly activate surrounding cells. The MWR hypothesis suggests that after this initial phenomenon, there are ongoing wave breaks that occur to help maintain atrial fibrillation throughout the atria. In contrast, the theory of mother rotors suggests that the fibrillation is driven by the primary rotor(s), whereas other wave breaks are secondary events because of fibrillatory conduction block in other regions (eg, when colliding with nonconducting boundaries).

Though some suggest that these mother rotors are likely fixed, others have suggested that they may precess (ie, wobble), albeit in small fairly well-defined areas. In any case, it is the functional core (namely the wave break or the phase singularity) comprising the rotational activity that is thought to be the principal target of rotor-guided ablation. However, when considering this approach, it has been long recognized that these simplified models of fibrillation dynamics may not be sufficient, given the interactions of tissue heterogeneity and other dynamic factors in determining fibrillatory potential.

Limitation of Computational Methods

Advances in nonlinear dynamic modeling since Edward Lorenz first described the concept of chaotic modeling in the 1950s have led to significant advances in computational modeling, including the cellular automata methods that underlie much of the spatiotemporal dynamic modeling currently used to define the dynamics of excitable media, especially as related to fibrillatory potential of the heart. Several computational methods have been used to define spiral wave generation in heterogeneous excitable media. Gil Bub’s work defined much of the groundwork in this regard, which has been since advanced by several other authors, including the current work by Carrick et al. One of the fundamental precepts of spiral wave dynamics has been the incremental reduction of coupling between adjacent cells contributing to the tendency for fibrillation. Bub, in one of his original descriptions, demonstrated that spontaneous initiation and termination of spiral waves likely organize in distinct zones, leading to increased fibrillatory potential. However, study of this phenomenon primarily involved monolayers of chick embryonic heart cells and modeling with cellular automata computational methods.

Most cellular automata models, including the present one by Carrick et al, have depended on the concept that individual cardiac myocytes, reflected as individual cells in automaton models, may develop action potentials when disturbed from rest, thereby transmitting current to adjacent members. However, there are several logical flaws to this paradigm.

First, computational models do not necessarily reflect the precise, complex 3-dimensional spatial variability of actual cardiac tissue. Although most mapping systems reflect the intracavitary chamber as a flat, continuous surface, the actual anatomy of the endocavitary atria and ventricles is characterized by significant trabeculation, with multiple potential sites of block, in- and out-pouching of cardiac tissue, and so on. Thus, we assume as clinical electrophysiologists that 2 points obtained close to one another by mapping are actually that close to one another. However, this conceptualization is inherently flawed. If, for example, one was to take a point on adjacent pectinates while spatially not accounting for a crevice between, they may appear spatially close though there is actually a fair bit of cardiac anatomy separating them. An analogy for this is that of the Grand Canyon. If a point is taken on either cliff side, the immediate bird’s eye distance in between is much closer than the actual distance accounted for by having to take a land-based route walking down the cliffside, across the canyon floor, and up the opposite cliffside. Thus, when trying to apply these 2-dimensional paradigms to highly complex 3-dimensional substrates, it must
be understood that no such model may truly offer a complete reflection of the cardiac surface.

Another limitation of cellular automata models is that of the assumption that end-to-end, cell-to-cell communication is equivalent at all ends. This is highlighted in a recent publication by Christensen et al. Their study reflects an incremental advance beyond the initial studies by Bub et al, in which isotropic tissue coupling was assumed. Specifically, the majority of automaton models assume the assignment of activity to each individual cell as a 0/1 sum—as either excited or quiescent. However, actual cell layers are not composed of a system wherein any cell may excite any adjacent cell equally. Rather, there is significant end-to-end interaction and less side-to-side interaction in these cylindrically oriented cells. Christensen et al assumed this anisotropic structural heterogeneity and demonstrated that the loss of lateral coupling between cells (ie, allowing for jumps of waves of activity to adjacent fibers) was what allows for development of reentrant wavelets. The fibrillatory potential was not dependent on introduction of an artificial obstruction (eg, fibrosis) into the model but rather solely on improved communication between adjacent, generally laterally oriented cell layers. This difference between end-to-end and side-to-side conduction is a well-recognized phenomenon because both the fastest and the slowest region of conduction in the human atria lies in Bachmann’s bundle, wherein conduction parallel to fiber orientation is rapid and conduction perpendicular is slow because of the vast majority of fibers lying parallel and thus having limited capacity for lateral communication with adjacent cell layers. There are 2 critical points that these findings evoke: (1) as we introduce levels of complexity that represent actual cellular mechanics, we can better understand clinical atrial fibrillation that occurs in the absence of apparent pathology and (2) we still clinically lack the ability to map or identify tissue heterogeneity in an end-to-end versus side-to-side configuration.

Finally, in all of these models, partly in an effort to simplify rules, investigators have assumed single or few cell layers in the atria. Similarly, at the time of endocardial mapping (eg, with rotor mapping), only the endocardial surface is mapped (and, as stated earlier, reflected as a flat 2-dimensional system with limited perturbations of the surface). These issues are compounded when considering that atrial tissue is not characterized by a single layer of myocytes but, in fact, has multiple layers with heterogeneous activation characteristics. Multiple investigators have demonstrated in animal models that there is a potential for not just side-to-side or end-to-end dissociation but also endo-epicardial dissociation of conduction leading toward transmural wavelet reentry. This has not been solved in the context of modern mapping techniques.

Multiple Wavelet Reentry: Is Prediction of Burden Feasible?
The propensity and burden of MWR in a tissue is dependent on several factors. Anatomic factors, including size of the tissue, length of boundaries, fibrosis from remodeling leading to heterogeneity, and functional factors, including cellular action potential duration and intercellular variation, conduction properties, electric remodeling, electrolyte balance affecting ion channel function, and autonomic factors all potentially affect the burden of MWR. The tissue burden of MWR can be imagined as a spectrum ranging from none to infinity depending on the above factors. The measure of MWR burden in a biological tissue can thus be challenging because it requires assessment of all of these factors, although several surrogates can be used—for example, magnetic resonance imaging to delineate fibrosis burden. However, even in using magnetic resonance–imaged fibrosis, we assume that it is only fibrosis that leads to delayed enhancement that can contribute to functional reentry, though it has never been demonstrated that regions of MWR are solely dependent on collagen deposition/fibrosis. One may postulate that, in fact, magnetic resonance–imaged delayed enhancement does not reflect all myocardial disarray and, thus, does not entirely reflect fibrillatory potential.

Prescription of Amount of Ablation Based on MWR Burden: Biologically Applicable or Just a Mathematical Dream?
Carrick et al should be congratulated for the work to understand the effect of different strategically placed ablation lesions in altering MWR. Their results contrast with prior work on ablation of rotors in suggesting that linear ablation through the cores of sites of MWR may best limit fibrillatory potential. However, the amount of ablation needed to reduce MWR burden to a clinically meaningful level is still unknown. If we propose a titrated amount of ablation based on the MWR burden, it may range from minimal to extensive ablation just as we assume that the theoretical quantity of MWR may range from zero to infinity as noted previously. Thus, although the concept that linear ablation lesions can effectively reduce the burden of MWR and thereby reduce fibrillatory potential is attractive, it can also pose major challenges, especially when multiple lines/more extensive ablation is required:

1. Compartmentalization of the atrium may occur with significant ablation to the extent that conduction in sinus rhythm becomes impaired or clinically significant mechanical dysfunction is precipitated.
2. Assessment of block across multiple lines may be challenging to interpret and can be practically difficult with multiple linear lesions.
3. Ablations for pulmonary vein isolation or linear lesions are already complicated by incidence of gaps across the lines which can create additional substrate for micro- and macro-re-entrant flutters. The more lines created, the greater likelihood that some gaps may exist.

How Do We Integrate These Findings?
In modern electrophysiological practice, we are left with an almost impossible task: we have mother rotors, multiple-wavelet reentry, triggers, substrate as defined by fibrosis/scar, and cardiac ganglia. Each of these targets of ablation has proponents and opponents. In turn, mapping methods for all have been suggested, though all without exception are fundamentally flawed by their inability to account for the 3-dimensional anatomy, inadequate sampling, and inadequate temporal resolution. The latter 2 elements, spatial and temporal resolution, are particularly critical when considering MWR or mother rotors. Namely, an apparent rotor or region of functional
reentry in the setting of inadequate sampling may be inappropriately tagged and ablated, thus creating substrate on ablation of an otherwise innocent bystander.

Furthermore, the concept that “not all atrial fibrillation is created equal” should be considered. Gordon Moe, in his seminal 1959 paper proposing multiwavelet reentry as a mechanism for atrial fibrillation, stated “… it is unrealistic to propose that only one of these mechanisms can exist in patients.”4 It stands to reason that treating the mechanism of atrial fibrillation as identical in all patients, irrespective of their substrate, may not be a reasonable enterprise.

With the evolution of mapping systems with better dimensional, spatial, and temporal resolution, we may better understand atrial fibrillation and be able to hone our treatments better to the individual patient. Until then, similar debates regarding complex fractionated electrograms, lines, rotors, and pulmonary vein isolation/ablation of triggers will likely remain.

Conclusions

Descriptions of various putative mechanisms of atrial fibrillation, whether as multifocal ectopic pacemakers, reentry around electrically inert obstacles (eg, regions of scar), or MWR/mother rotors, are likely all relevant to the understanding of atrial fibrillation. Computational models, despite their limitations, hold particular interest in helping define animal models that may, in turn, inform clinical practice. The premise that linear ablation targeted through regions of MWR may reduce fibrillatory potential as suggested by Carrick et al holds promise, though whether that promise holds up to the scrutiny of rotors, complex fractionated electrograms, standardized linear lesion sets, or pulmonary vein isolation remains to be seen. Regardless, ongoing computational studies and advances in mapping and signal processing likely reflect an incremental advance in the likelihood of eventually realizing an individualized, more effective treatment for atrial fibrillation.

Disclosures

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References


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