The recent explosion of literature on rotors in human atrial fibrillation (AF) is no surprise to followers of the history of science in which return to an old paradigm paradoxically heralds incremental progress based on the emergence of new evidence. Although the rotor paradigm is neither confirmed nor universal, it does revitalize a more mechanistic approach to addressing persistence in human AF. Although determining the relevance of rotors is the current obsession, we must reach beyond this existential debate and focus on the underpinning mechanisms. Critical to this is understanding how the underlying tissue architecture governs conduction and is manifest in electrograms and their spatiotemporal distribution and how therefore the hierarchical rotor paradigm can be unified with the anarchical paradigm of diffuse, widely distributed complex microreentry. It is the challenge of unifying these apparently irreconcilable bodies of evidence that is the stimulus for reviewing the areas of mechanistic importance common to the relationship between myocardial architecture and conduction that lies at the heart of understanding persistence in human AF.

Rotors: From Macroscopic to Microscopic

The rotor revolution has focussed attention on conduction characteristics that promote drivers as the underlying mechanism of persistence and increasing refractoriness to treatment of AF. This has shifted thinking away from a purely anatomic ablation strategy to a mechanistic one based on propagation mapping. Regardless of the discussion surrounding how rotors are detected and whether therefore they exist at all, mechanisms are now in fashion again. Although rotors are the paradigm of the moment, the debate with proponents of multiple mechanisms are now in fashion again. Although rotors are the para-

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empirical adjunct. Attractive electrograms were indiscriminately ablated as the empirical—like when pulmonary vein encirclement only, and tissue level. But this would once again make us slaves to considerations to obviate the need to understand causation at the cell and spatial gradients in AF, such as dominant frequency, organizational index, and Shannon entropy, have proven unstable and of no significant clinical utility. That results in panoramically detectable localized sources. The inability to combine low- and high-resolution mapping in the intact human heart may also explain why measures of organization and spatial gradients in AF, such as dominant frequency, organizational index, and Shannon entropy, have proven unstable and of no significant clinical utility. That the hierarchical nature of AF organization is only revealed at the most global level using complex algorithms may be considered to obviate the need to understand causation at the cell and tissue level. But this would once again make us slaves to the empirical—like when pulmonary vein encirclement only, with or without the aim of isolation was uniformly applied for all clinical presentations of AF, or when variably defined attractive electrograms were indiscriminately ablated as the empirical adjunct.

The solution must come from staying close to the translational/reverse-translational interface, ensuring that we seek to provide mechanistic explanations for clinical observations and then testing these clinically. We must consider this interface tripartite by incorporating expertise in the fields of mathematical and computer modeling, image, and signal processing. Mathematics is the lingua franca of science, and we clinical and basic scientists have a tendency to consider ourselves relatively expert in maths. However, our largely intuitive efforts have borne little fruit, and we must engage with experts as part of truly multidisciplinary collaborative efforts anchored around the patient.

In this review, we address the following factors that are known to affect myocardial conduction, to change with myocardial remodeling in AF, to do both or, although not currently known to do either are worth considering, by dividing them according to an appropriate epipheth.

**Known Unknowns**

**Electrograms**

The electrogram represents the raw data from which all clinical electrophysiology is derived. It is the principal source of information about both the local and the global; the electro-architecture and the panorama. This makes it all the more extraordinary that we still simply binarize electrograms using qualitative terms, such as simple, complex, fractionated, and largely ignore their rich content. The result is what has proven to be a largely counterproductive pursuit of a quantitative science drawn from an excessively simplistic visually driven binary classification. Whatever the mechanistic theories and classifications of AF, variation in electrograms exists and requires a coherent cell/tissue level mechanistic understanding if we are ever to answer the question of whether electrogram features are traceable and predictive of underlying substrate remodeling and tissue characteristics.

Surmounting this challenge offers one route to a unifying explanation. Better understanding of the roles of bipole wavefront orientation and local coupling interval on electrogram content, together with development of novel catheters, such as orthogonal bipolar electrodes, may help tackle this problem, and industry needs to continue to match the drive for mechanistic insight with novel tools. It may be that areas of complex fractionation or low voltages can be completely ignored, but the future of electrophysiology will surely include the interpretation of electrograms as the raw data from which we work. If we are to avoid the pursuit of an excessively simplistic invocation of the signal processing toolkits of Matlab, Labview and so on, then a higher order understanding of the electroarchitectural derivation of the electrogram is required.

**Fibrosis**

The mechanistic role of fibrosis and any causal relationship with conduction remodeling is surprisingly unclear in human AF. Although some studies have failed to detect an excess of myocardial fibrosis in AF, some authors continue to suggest that AF is merely one manifestation of a fibrotic atrial cardiomyopathy, drawing parallels with ventricular tachycardia in dilated cardiomyopathy. In clinical studies, despite
improvements in MRI quantification of fibrosis, spatial and temporal correlation with known electrophysiological measures are weak. Despite work correlating the extent of late gadolinium enhancement MRI with AF recurrence and our recent point-by-point correlation of enhancement and voltage (Figure 3), identifying the late gadolinium enhancement MRI signature of areas critical to AF stability remains elusive. It is striking that concurrent MRI or any other structural data from any of the groups advocating the hierarchical model demonstrating rotors in persistent human AF has not been presented but must be addressed if this paradigm is to be strengthened.

Fibrosis certainly plays a role in many animal models of AF, with detailed quantitative relationships linking it to development of the atrial substrate via effects on conduction velocity. However, the lack of consistency between models and in particular in human studies leads ultimately to a fundamental concern for which the question of fibrosis acts as an ideal example: If fibrillation of animal atria can be provoked ubiquitously and variably, how can all such models be representative of human AF and how can we discover in which respects any of them are representative?

Although fixed structural factors are no doubt important, they cannot explain why AF is paroxysmal in some patients, why the tendency to persistence may change with time, or why many older patients with extensive fibrosis do not have AF. This suggests a role for dynamic factors in AF pathophysiology.

Connexins

A further example of how observations derived from clinically remote animal models may not help progress in understanding human disease is the concept of massive redundancy of myocardial gap junction (GJ) coupling. This was based on studies in connexin-knockout mice that created a dogma rendering quantitative changes in connexin levels of questionable functional significance.

However, our recent work challenges this concept. First, naturally occurring variations in connexin expression correlate with conduction velocity (CV) with a direct relationship linking GJ resistivity and CV in humans and animals (Figure 4). Second, studies in human myocardium indicate a direct role for GJ remodeling in the electrophysiological changes in heart failure. Observations such as these challenge the concept of overwhelming GJ redundancy in intact myocardium and indicate that naturally occurring variation in health and disease affects conduction velocity and arrhythmogenesis. In an era of increasing focus on the role of conduction and repolarization in complex arrhythmogenesis, it is essential to clarify the role of connexin remodeling and GJ modulation in the dynamics of human atrial conduction and the unique effects that this may have on myocardial predisposition to the initiation or stabilization of AF. The heterogeneous nature of GJs may provide gradients of distribution throughout the atria that create a hierarchy of the apparently anarchical remodeling at the tissue level.

In AF, although connexin levels do not correlate with fibrillatory wavefront propagation velocity, they correlate with the complexity of activation (the number of wave fronts per unit area). Hence, it has long been hypothesized that reduction in gap junctional coupling is central to arrhythmogenesis both as the cause of slow conduction and by limiting the passage of current between adjacent cells. This mechanism would unmask differences in action potential duration, increasing heterogeneity and nonuniformity of anisotropy, and be of particular importance in conditions of only partially excitable gaps and incomplete excitability that are characteristic of AF.

Calcium

Calcium handling is abnormal in atrial myocytes and underpins the APD alternans that precedes AF initiation. The role of calcium modulation will be indirectly investigated by the CUPID2 trial, which is using SERCA2a gene therapy in heart failure and will measure AF as a study outcome. What is certain from the vast calcium literature is that AF in all its forms is accompanied by significantly altered cellular calcium handling—what is less clear is whether these are causative or sequelae of remodeling. Also unclear is the precise magnitude of focal source activity required to depolarize well-coupled atrial myocardium acting as a sink.

The effects of abnormal calcium handling on CV restitution dynamics and on dispersion of refractoriness prove that calcium can also play a key role in affecting tissue conduction properties by promoting the conductive heterogeneity required for AF persistence. Calcium-dependent modulation of connexin subunits demonstrate the interplay between factors and require sophisticated experimental design and the correct disease models to tease apart.

Autonomic Nervous System

There is convincing clinical and animal model evidence for the role of autonomic modulation of triggers and substrate in AF. It has been suggested that ablation of the ganglionated autonomic plexi located epicardially near each of the PVs is the principal reason for success of left atrial ablation. Our recent work on ablation of persistent AF has identified novel end points based on autonomic modulation (Figure 5). and previous work has shown the effect of high frequency stimulation of ganglionated plexi on increasing heterogeneity of AF cycle length potentially promoting PV drivers. However,
Further studies are required to determine the extent to which the effectiveness of PV isolation is via ablating ganglionated plexi and whether these sites coincide with areas of rotor formation. Furthermore, any ex vivo model of AF, however elegant, will necessarily omit this important autonomic modulation and hence have limited applicability to in vivo findings.

Sites of atrial electrogram fractionation and high dominant frequency have been shown often to overlie ganglionated plexi. These areas are at or adjacent to the PV antra and therefore ablation of ganglionated plexi and antral PV isolation cannot easily be investigated separately, and evaluating why strategies targeting high frequency fractionation are effective is difficult because of the overlap in potential mechanisms. Vagal responses which are present before ablation can be absent when AF recurs. However, evidence from cholinergic studies in canine AF and from the well recognized clinical phenomena of postprandial or postexertional AF are supportive of an important role for the autonomic nervous system in the genesis of AF. Nevertheless, the specific role of the autonomic nervous system in either the multiple wavelet or the rotor paradigms requires further clarification.

Unknown Unknowns

Genetics

Other than a few specific monogenic associations with AF, little was known about population-level susceptibility loci. This changed when an area of chromosome 4q25 was observed as an independent risk factor for recurrence of AF after pulmonary vein isolation, cardio-embolic strokes, and postoperative AF. Further mechanistic work is underway to investigate why these associations are present, and a recent study has confirmed these loci are present in non-white populations.

Obesity

Obesity has a well-recognized association with AF, but the molecular mechanisms and role of the hormonal axes that modulate this remain unknown. In a sheep model of AF, obesity has been shown to increase CV dispersion and reduce CV to promote inducible and spontaneous AF. These progressive tissue-level conduction effects are accompanied by cellular and anatomic remodeling, such as atrial liposis, inflammation, and fibrosis, and may underpin the complex electro-anatomic remodeling seen in obese patients. The finding that obese patients harbor more right atrial rotors, hence untreated during left atrial only ablation, requires further prospective study.

Inflammatory Mediators

Upstream inflammatory mediators, such as transforming growth factor B1 and galectin 3, are thought to regulate myofibroblast proliferation and contribute to the remodeled substrate. Effects of these mediators on conduction in the atria are emerging, with interplay with ion channels, connexins, and myofibroblasts explaining why inflammation seems integral to AF pathophysiology in many models. Whether there is a direct role in humans remains unproven. However, there...
is evidence principally from substudies of the large coronary risk outcome studies that targeting upstream factors associated with remodeling, such as using angiotensin-converting inhibitors, statins, and aldosterone antagonists, may reduce the incidence of AF. However, this has not translated into effective strategies for prevention and treatment of AF in large-scale randomized trials because remodeling may have progressed too far to be halted or reversed by the time AF becomes clinically manifest.54

**Stretch-Activated Ion Channels**

Structural and electric remodeling are often considered separately, yet the heart is the principal mecano-electric organ with feedback between these 2 defining characteristics. Stretch-activated channels, demonstrated to be of importance in acute rhythm disturbances, such as commotio cordis,55 will also have constitutive activity in chronic stretch. The intriguing finding that a tarantula venom peptide possesses antifibrillatory effects in rabbit hearts when mechanically loaded, mediated by its inhibition of stretch-activated channels,56 shows how these can be specifically targeted. This was unaccompanied by changes in the shape of the action potential, but was associated with shortening of effective refractory period with stretch, suggesting that greater uniformity of conduction, increased coherence of wavefront propagation, and less fragmentation may be the mechanism by which inhibition of stretch-activated channels prevent AF.

**Future Directions**

We are at a crossroads in AF research—once again. Reports of stable rotors in human AF and their targeted ablation have focussed attention on the methods used to map the atria and the processing of complex signals. There may never be a single unified mechanism for all forms of AF. Exploring the debated paradigms currently dominating the field will drive progress not only in enhancing mapping and ablation technologies but also in identifying the molecular mechanisms and functional sequelae of patient-specific myocardial architectural remodeling. The distribution of remodeling must determine the hierarchical distribution and macro-organization of fibrillatory conduction.

The ablation catheter is an effective investigational tool, providing extensive mechanistic insight from targeted intervention guided by phenomena detectable at this relatively low resolution, with interruption of fibrillatory conduction being the principal measure of effectiveness. In the absence of a molecular and cellular explanation for the criticality of these sites, however, by this approach alone we cannot hope to derive a unifying explanation for the apparently irreconcilable bodies of evidence. How would one ablate endo-epi dissociation or target complex wave maps when the electric signatures are equally obscure? Like learning-by-burning, we stand to learn from a retrospectively evaluated trial-and-improvement approach to the application of other emerging interventions that modify conduction—use of stem cells, over expression of gap junctions, pharmacological modulation of intercellular communication, and modulators of fibrosis.

**Conclusions**

As an electrophysiological community of clinical, basic, and mathematical scientists, we should be in a position of understanding those electroarchitectural processes that create the mechanistic hierarchy. We must be open and transparent to scrutiny by others and involve patients, industry, and scientific research in synergy to achieve real progress. Only then can we bridge the translational gap linking electroarchitectural remodeling, its hallmark signature, and therapeutic targets. We must continue our tradition of inference from intervention. But just as man did not move on from the Stone Age because he ran out of stones, it is time that we take the apparently irreconcilable paradigms of the moment to spark an age of true enlightenment—understand the relationship between rotors, fibrillatory conduction, their electroarchitectural determinants, and clinical manifestations.

**Disclosures**

None.

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R, Zaman and Peters Rotors and Conduction Review


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