Atrial Fibrillation: Focal or Reentrant or Both?

A New Autonomic Lens to Examine an Old Riddle

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Ablation for atrial fibrillation (AF) is a genuinely viable and increasingly used option for improving quality of life in patients with symptomatic drug-refractory AF. What is remarkable about the limited success achieved with these procedures is that progress has occurred despite a near complete lack of knowledge about what causes or maintains AF. Focal origins for AF were first demonstrated decades ago1–4 with topical application of acetylcholine to junctional tissues and atrial sites triggering AF. More recently, there has been convincing documentation of rapid tachycardia arising from the pulmonary veins inciting AF, thus supporting the concept of “trigger elimination” contributing to the success of pulmonary vein isolation. However, studies also support the presence of multiple reentrant circuits maintaining and possibly initiating AF.5, 6 The ablation era has taught us7–9 that in persistent and chronic AF, trigger elimination alone is not enough and that substrate modification is probably necessary to decrease the likelihood of reentrant wavelet continuance and thereby increase success rates. Even the most ardent supporter of either hypothesis recognizes the limitations of each. How can a focal source exist in this milieu indefinitely, producing and maintaining chronic AF, and how do multiple reentrant wavelets arise spontaneously?

In this issue of Circulation: Arrhythmia and Electrophysiology, Niu et al10 provide important, interesting, and novel insights into solving this age-old riddle using a previously unexplored angle-autonomic manipulation. Acetylcholine was used to induce AF in 31 canines. In 12 of the animal studies, propafenone was administered. They then ablated the ganglionated plexi (GP). Before ablation, AF could still be induced despite administration of propafenone. After ablation, there was a consistent pattern of electrogram organization and atrial synchronization. In addition, subsequent administration of propafenone resulted in the inability to induce atrial tachyarrhythmia. There are several important insights that we glean from the authors’ findings. Although one would expect propafenone to prevent acetylcholine-induced AF, it clearly does not unless the ganglia are ablated. Ablating the ganglia alone, however, does not always work, and induction of regular reentrant tachycardias may still be possible. The remaining organized atrial tachycardia (AT), however, is effectively terminated by propafenone. Further, when the GP was ablated, regularization of atrial activity at proximal and distal sites was consistently seen as was the loss of complex fractionated atrial electrograms (CFAE). Inherent to their findings and well brought out by the authors is that both reentrant and focal origins are operative in causing AF. The way they have validated this assertion, by using an autonomic manipulation model, is novel and nuanced at several levels. First, acetylcholine was used as a trigger for initiating AF with or without standard atrial stimulation. Second, stimulation of the ganglia to document ablation was done so as to not stimulate or affect atrial myocardium. Finally, they integrated observations with regard to where electrogram characteristics change after ganglion ablation with the known complexity of the autonomic neuroanatomic networks. These findings allow us to appreciate the coexistence of both focal and reentrant mechanisms underlying AF.

A careful study of their experimental results and discussion is needed to better appreciate the impact of their findings on our understanding of AF pathogenesis and specifically concepts that may allow interventional electrophysiologists to better appreciate what it is that we ablate with limited success. A few observations are discussed below.

Complexity

The reader of the report by Niu et al may be struck by its complexity. This is not a reflection of their study design or writing but rather reflects the necessary complexity when trying to analyze evidence supporting the role of the autonomic nervous system in arrhythmogenesis. Unlike the conduction system and the primary cardiac chambers, the anatomy of the neural input traced from the brain stem or the lateral horn of the spinal cord to the actual sites of myocardial interface is extremely complex and careful anatomic—physiological correlation is required to identify meaningful patterns. This is further complicated by the need to interpret electric effects of autonomic modulation. Although stimulatory maneuvers looking for hemodynamic consequences may be more straightforward, modifying the ganglia may simultaneously alter myocardium and thereby make interpretation of electric effects more difficult. Importantly, ablation of the GP using present technology invariably involves ablation of atrial myocardium, which will also affect activation pattern, and, depending on the amount of ablation, directly modify the substrate. Thus, care must be taken when interpreting results stemming from ganglia ablation. Future studies involving
atrial myocardial control sites or epicardially targeted neural structures as part of the protocol may help to more clearly delineate the effects of autonomic modulation per se.

Initiation of AF
The Niu et al report highlights an inherent problem in interpreting clinical and experimental protocols looking at end points of modulatory therapy for AF. Most patients can be induced into AF with rapid single- or dual-site atrial pacing, and this inducibility probably is physiologically normal. Although some centers use inducibility as an end point for ablation procedures, it is likely that aggressive stimulation will result in AF regardless of eventual clinical outcome. For example, after a surgical Maze procedure, postoperative AF is common and probably secondary to inflammatory nidi; after ablation of atrial arrhythmias, AF during the first few weeks after ablation (“blanking period”) does not necessarily portend long-term failure to control AF.

Thus, spontaneous initiators of AF may be quite different from pacing-induced AF. Autonomic induction (for example, ganglia stimulation or acetylcholine administration, as used in this study) further nuances the issue of AF induction. Do autonomic modulation and electrophysiological ablations specifically help us in getting rid of autonomically mediated AF, or can we extrapolate these results to spontaneously triggered AF as well?

AF Termination
Although much has been learned in this last decade on what initiates AF, perhaps a more mysterious issue is what causes AF to stop. Multilayer neural networks\(^{11,12}\) for identifying approximate entropy in the time frequency domain predict as “integration centers.”\(^{15,16}\) For example, direct connections between the superior left and anterior right GPs may mediate how ablation of either of these GPs may lead to effects on sinoatrial and atrioventricular nodal function. This may be by bidirectional feedback between the GPs themselves or cross-innervation. Why is there such handedness? Cross-innervation in the central nervous system is the rule more than the exception.\(^{17,18}\) Although not generally appreciated, local sensory and autonomic nerve input in the gastrointestinal tract may also exhibit such handedness.\(^{19}\) The intervention of electrophysiology, however, needs to be aware of these possibilities when encountering, for example, high-grade atrioventricular block when ablating in the posterior free wall left atrium near the ostia of the left-sided pulmonary vein.\(^{20}\)

Focal Versus Reentrant Origin?
Clearly, it is nearly impossible to account for all known observations with regard to AF using a solely focal or reentrant hypothesis for AF pathogenesis.\(^{3,4,6,21}\) Niu et al demonstrate clearly that both mechanisms coexist. However, when considering interactions and the type of arrhythmia mechanism, coexistence itself may exhibit heterogeneity. Before deciding whether focal or reentrant mechanisms predominate, we must know which mechanism is present at a given point during a clinical ablation or experimental study. These determinations themselves, however, are far from straightforward. First, there may be fairly regular atrial electrograms at some locations during AF. However, when a focal driver for AF induces fibrillation but the driver still exists, fragmented signals may be seen during a regular AT. How do we tell the difference? Niu et al point out the limitations in prior studies in which the diagnosis of AT as entrainable, because AF cannot be universally applied to distinguish AF and AT because local, as well as fairly regional entrainment of AF may occur, especially after ganglion ablation. Niu et al point out the limitations in a prior study in which the diagnosis of AT was based on entrainment characteristics. This is because entrainment cannot be universally applied to distinguish AF and AT because local, as well as fairly regional, entrainment of AF may occur, especially after ganglion ablation. These difficulties in simply defining the arrhythmia mechanisms both locally and globally for the atria are a source of difficulty in identifying which arrhythmogenic mechanism is operative, though there are other complicating factors as well.

Clinical ablation studies show numerous examples (Figure) in which an automatic tachycardia is the primary driver but a macroreentrant AT may be induced by the focus followed by termination of the focus itself. The clinical arrhythmia is then diagnosed as reentrant though the “cause” is focal. Even more complex are scenarios in which the automatic focus may continue to exist and continually resets a macroreentrant
Ablation experience has highlighted the importance of distinguishing between CFAE and electrograms with a distinct isoelectric period. Similar dynamic maneuvers during entrainment mapping, for example, have to be carefully analyzed not only to define the mechanism of arrhythmia but to define the true nature of the signals being recorded.

**What Constitutes Autonomic Modulation?**

Part of the difficulty in appreciating the potential impact of autonomic modulation to treat AF is the multiple levels at which interventions may be used and the various methods that may be used to modulate autonomic input. The autonomic inputs may be ablated, stimulated, or blocked, and these maneuvers may be applied to the sympathetic trunks, vagus nerve, GP or local innervation sites. Add to this the fact that autonomic regulation may have differential effects on ion channel function, the discovery of interstitial Cajal-like cells in the pulmonary veins, and the phenoms of specific chloride channels in the heart, and one can see the complexity of understanding how autonomic modulation affects cardiac electrophysiology. For example, it has long been recognized that part of the β-adrenergic effect on myocardial cells may be mediated by a phenomically active chloride current. Further evidence has strongly supported a role for a calcium-activated chloride current in modulating both ventricular and atrial tachyarrhythmias. The fact that these calcium-activated chloride channels play a key role in cellular activation at the level of the interstitial cells of Cajal in the gastrointestinal tract and that these neurally mediated, stretch-activated “pacemaker” cells populate the pulmonary vein–atrial interface raises several questions. Are there other cells that are mediating the onset and propagation of AF, possibly the interstitial cells of Cajal or other electrophysiologically active structures? What other factors may mediate how and to what degree the autonomic nervous system at its various levels of innervation affects myocardial activation? These recent advances in the study of the heart suggest that there is a lot more to be appreciated if we are to fully comprehend the complexity of autonomic modulation of arrhythmias.

**CFAE, GP, Pulmonary Veins, and Nodal Remnants: Are They the Same, and What Are We Ablating?**

The anatomic proximity of the thoracic vein ostia, conduction tissue, GP sites, and sites where CFAE are found are striking (Figure). There are 2 considerations that stem from this observation. The first is whether CFAE may represent areas where the GP are present and whether the presence of GP, abnormal atrial myocardium, or CFAE represents the areas where the use of antiarrhythmic agents or perhaps antitachycardia pacing algorithms probably affects another.

Although this complexity in differentiating temporally and spatially overlapping arrhythmogenic mechanisms for AF continues to exist, an important advance from Niu et al is that ganglia ablation predominantly affects one mechanism whereas the use of antiarrhythmic agents or perhaps antitachycardia pacing algorithms probably affects another.

**Summary**

Niu et al have provided important insights in their study, which adds to their group’s groundbreaking prior reports on how we can understand the coexistence of focal and reentrant mechanisms for arrhythmia. An important clinical application of their data is for practitioners to appreciate that because more than 1 mechanism may be responsible at a given point in a patient’s clinical course, more than 1 type of therapy may be required (antitachycardia pacing, drugs, GP ablation, pulmonary vein isolation, etc). Thus, individualization of therapy not only to the patient but to the arrhythmia mechanism that may be present during an ablation procedure may be essential. Their further insights should propel investigation as to how we can manipulate or ablate the GP without affecting the atrial myocardium.

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**Figure. Issues to resolve in defining pathogenesis and best management of AF. A, Teasing out the exact role of the ganglionated plexuses, the finding of fragmented signals endocardially, and the pulmonary venous contribution to atrial fibrillation, initiation, and management is rendered complex by the anatomic juxtaposition of these tissues. B, The interaction between focal sources and reentrant circuits in patients with AF is complex. A focal driver may initiate atrial flutter and spontaneously terminate leaving a persistent flutter. In other instances the two may coexist with the focal driver, at times entraining the flutter or at other times the flutter having an intrinsically shortly cycle length override suppressing the focal source. Finally, an induced flutter may in turn induce either a second flutter or create the right milieu for a triggered automatic focus to initiate AF from within the vein. Ablation or modulation of the autonomic ganglia or may affect AF pathogenesis by affecting either mechanism.**

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In some ways, however, their work raises more questions than it answers and brings into sharp focus the complexity and enormity of the task facing interventionalists who wish to modulate cardiac autonamics to treat arrhythmias. This complexity, however, should be appreciated and in fact embraced and enormity of the task facing interventionalists who wish to stand the potential application for this type of intervention.

Disclosures

None.

References


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