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 ago 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. The ablation era has taught us 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 al 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 for identifying approximate entropy in the time frequency domain predict a nonrandom pattern of organization of the atrial electrograms (loss of CFAE, etc.) before spontaneous termination. This suggests that ablation of the GP may not only affect induction of AF but may create a prerequisite for termination. The authors also report simultaneous increase in the cycle length of the atrial electrograms along with regularization. Do these necessarily need to go together? If there is a disjoint in these parameters (shorter cycle length but increased regularity), which finding is more likely to predict termination? What is the significance of the variable effects seen on action potential duration based on the exact location and type of autonomic nerve being stimulated and the dose of systemic autonomic modulators used? The answers to these questions may be relevant when seeking specific sites in the autonomic system for stimulation, blocking, or ablation.

**Does One Hand Know What the Other One Is Doing?**
At first glance, it may seem surprising that in the Niu et al study, the right atrial appendage recording, which was closer to the ganglia being ablated, continued to show electrograms with very short cycle lengths. It was only after the left-sided ganglia were ablated, which are significantly further from the right atrial appendage, that these electrograms became organized. However, understanding the complex cross-innervation and integration of information between the ganglia would actually predict that such apparently counterintuitive findings should occur. These authors have previously explained these complex interactions between the right and left ganglia and the concept of handedness in atrial autonomic innervation and have proposed that the GP serve as “integration centers.” 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. Although not generally appreciated, local sensory and autonomic nerve input in the gastrointestinal tract may also exhibit such handedness. The interventionist electrophysiologist, 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.

**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. 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
tachycardia, which in turn would overdrive suppress the automatic focus or induce yet another reentrant circuit. This interaction between mechanisms is highlighted by the unexplained but clinically useful observation that spontaneous triggers for AF are more likely to be seen after cardioversion of artificially induced AF (ie, early recurrence of AF).

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 antihypertrophic agents or perhaps antitachycardia pacing algorithms probably affects another.

**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 of slow conduction observed at the pulmonary vein ostia. Niu et al and other studies add another layer of possible relationships between these structures noting that a dynamic transition between CFAE and electrogroms with a distinct isoelectric period may occur at the same site after GP ablation. Second, the overlapping anatomic structures (septa, pulmonary veins, atria, vein of Marshall, left atrium, and so forth) allow multiple electrogroms to be detected from a single location.2324 Ablation experience has highlighted the importance of distinguishing such signals with pacing maneuvers to know what truly represents a contact electrogram. During AF, undoubtedly there are contaminant far-field signals that are more likely to be observed at certain catheter locations, making it difficult to know whether true CFAE are present or simply superimposed electrogroms at a site where local activation does in fact have an isoelectric period. Similar dynamic maneuvers during entrainment mapping, for example, will 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 autonomics 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 cells25 in the pulmonary veins, and the phenomics 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.26 Further evidence has strongly supported a role for a calcium-activated chloride current in modulating both ventricular and atrial tachyarrhythmias.2728 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.

**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.
Disclosures

None.

References


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