Several lines of evidence suggest that autonomic innervation plays a role in the generation of atrial fibrillation (AF). Ganglionated plexi (GPs) that modulate autonomic innervation have been identified over both atria, particularly the pulmonary vein (PV) antral regions. Stimulation of GPs results in the local release of parasympathetic and sympathetic neurotransmitters, which may lead to increased automaticity, shortening of the action potential duration and the effective refractory period, and/or triggered activity (1). Stimulation of GPs has been demonstrated to promote PV arrhythmogenicity and facilitate induction of sustained AF by premature atrial depolarizations (2,3). It is possible that GPs function as an upstream regulator of both PV- and non-PV-dependent mechanisms of AF.

The role of parasympathetic innervation in generating AF is most obvious in patients with the vagotonic variety of AF, in which episodes of AF occur exclusively during states of increased vagal tone, such as sleep. The prominent role of autonomic innervation in vagotonic AF, and its possible role in all types of AF, has suggested an important question: can AF be eliminated by ablation of GPs?

One of the first studies indicating that autonomic denervation might prevent AF was performed in the operating room. The fat pads that surround the superior vena cava, aorta, and pulmonary artery contain autonomic ganglia. Melo et al. (4) demonstrated that dissection of these fat pads was associated with a marked reduction in the incidence of AF after open heart surgery. However, that was not a randomized study and the findings were not definitive. In fact, a more recent study that was randomized demonstrated that dissection of the anterior fat pad actually increased the incidence of AF after open heart surgery (5).

A small number of catheter ablation studies have looked into the role of GPs in elimination of AF, and the results of those studies also have been conflicting. In one study, a bradycardia response to radiofrequency ablation during circumferential pulmonary vein ablation was used as an indicator of sites of parasympathetic innervation (6). In a series of 297 patients with paroxysmal AF, approximately one-third of the patients displayed a bradycardia response that was eliminated by catheter ablation. The clinical efficacy of circumferential PV ablation was found to be significantly higher in those patients than in the patients who did not display bradycardia in response to radiofrequency ablation. However, in a more recent study, high-frequency endocardial and epicardial stimulation was used to identify GPs in a series of 10 patients with vagotonic AF (7). The GPs were identified in 7 of the 10 patients and were specifically targeted for ablation. However, AF recurred in 5 of those 7 patients. It is noteworthy that ablation of GPs was the primary ablation strategy in that study, whereas circumferential PV ablation was the primary ablation strategy in the study by Pappone et al. (6). Therefore, the results are not necessarily conflicting. It may be that parasympathetic denervation has a therapeutic effect, but only as an adjunct to PV isolation.

Nademane et al. (8) proposed that complex fractionated atrial electrograms (CFAEs) be targeted to eliminate AF. The CFAEs are characterized by a short cycle length, fractionation, and/or continuous electrical activity. The CFAEs have been considered to represent sites that may facilitate classic reentry due to slow conduction, conduction block, or wavefront collision or sites of high-frequency sources such as rotors. Of note is that CFAEs also may be recorded at sites of GPs. Local autonomic innervation presumably shortens the atrial refractory period, resulting in CFAEs during AF (9).

The CFAEs typically have been characterized during AF. There have been limited data on the characteristics of electrograms during sinus rhythm. In a study based on fast Fourier transformation (FFT) analysis of atrial electrograms, myocardium was described as compact or fibrillar (10). Fibrillar myocardium displayed out-of-phase anisotropic conduction, shorter refractoriness, and higher frequencies during AF. These sites, also referred to as AF nests, were thought to be indicative of neural inputs. In a similar study, spectral analysis was used to identify sites of parasympathetic innervation, characterized by fractionated electrograms and a rightward shift of the FFT envelope (11). In 21 patients with vasovagal syncope, vagotonic atrioventricular block, or sinus node dysfunction, all symptoms were eliminated by ablation of these sites.

There is a great need for mechanistic and clinical studies to better understand the relationship between atrial electrogram morphology and autonomic innervation, and the study
by Lellouche et al. (12) in this issue of the Journal is a timely contribution. The authors examined the characteristics of atrial electrograms recorded in sinus rhythm at sites typically targeted during circumferential PV ablation and correlated their morphology with the presence or absence of a parasympathetic response during ablation. The study was an exhaustive retrospective analysis of 1,662 electrograms from 30 patients with paroxysmal AF. A parasympathetic response was identified by an increase in cycle length of at least 20% or in the AH interval of at least 10 ms during an application of radiofrequency energy. Electrogram characteristics that were most predictive of a parasympathetic response were identified by using a rigorous decision-tree analysis (CART model). Electrograms characterized by ≥4 deflections, amplitude ≥0.7 mV, and duration ≥40 ms were found to be strongly associated with a parasympathetic response during ablation. This type of electrogram had a sensitivity of 72% and specificity of 91% for predicting a parasympathetic response.

To provide further evidence that fractionated atrial electrograms were related to parasympathetic innervation, the authors prospectively tested the effects of adenosine on atrial electrogram characteristics in 8 patients. Adenosine resulted in a significant increase in the mean number of deflections but not in electrogram amplitude or duration. In an additional component of the study, the effects of acetylcholine and the outward potassium current (I\textsubscript{K,ACH}) on electrogram morphology were simulated in a mathematic model. The authors concluded that sites of parasympathetic activation during ablation are more likely to display high-amplitude fractionated electrograms during sinus rhythm. Local release of acetylcholine was proposed to explain these electrogram characteristics.

The study was meticulously conducted, and rigorous statistical analyses were performed to identify the electrogram criteria that were associated with a parasympathetic response. The results suggest that sites of parasympathetic innervation can be identified during sinus rhythm simply by identifying fractionated large-amplitude electrograms. This would provide a major advantage over high-frequency stimulation to identify GPs. The GPs are epicardial, and high-frequency stimulation usually is performed endocardially, often requiring large currents to evoke a vagal response. Anecdotal observations indicate that high-output stimulation may result in hydrolysis of blood (13).

Although the study is a useful contribution, it does have some limitations that should be considered in interpreting the findings. First, because this was a retrospective analysis in patients who were undergoing circumferential PV ablation, the analysis of electrograms was limited to sites that were ablated. It would have been helpful to perform detailed mapping of the PVs, antral areas, and left atrium to determine whether the sites at which the fractionated large-amplitude electrograms are recorded correlate with the sites where GPs are located. In this type of study, GPs would have to be identified either by ablation or by high-frequency stimulation. Another limitation is that prior applications of energy in the vicinity of a recording site may have affected the electrogram characteristics and the ability to provoke a vagal response. Furthermore, an 8-mm-tip catheter, which has limited spatial resolution, was used to record the electrograms. Although adenosine resulted in fractionation of electrograms, it still is not clear whether fractionation observed at sites where a parasympathetic response was provoked was entirely functional and due to a high local concentration of acetylcholine or fixed and simply due to an overlapping layer of neurofibrils (11). Last, it would have been helpful to validate the criteria identified in this retrospective analysis in a prospective set of patients.

The issues raised by Lellouche et al. (12) point out the need for additional studies. For example, the fractionated large-amplitude electrograms were stable and present during sinus rhythm in the absence of an overt vagal response, implying that there was tonic release of acetylcholine at the recording sites. If so, pharmacologic autonomic blockade with atropine and propranolol would be expected to reduce or eliminate the complexity of the atrial electrograms. Furthermore, it would be interesting to determine whether or not pharmacologic autonomic blockade modulates the response of atrial electrograms to adenosine. Another interesting study would be to determine whether fractionation of electrograms provoked by adenosine is limited to atrial sites near the GPs. Ultimately, the efficacy of an AF ablation strategy that targets fractionated, large-amplitude atrial electrograms during sinus rhythm, either by itself or as an adjunct to some other strategy, will require evaluation in a randomized study.

Many questions remain to be answered regarding the relationships between autonomic innervation, AF, and atrial electrogram morphology, be it during AF or during sinus rhythm. The study by Lellouche et al. (12) is a step in the right direction, but it also reminds us of how much further we have to go.

Reprint requests and correspondence: Dr. Hakan Oral, Cardiovascular Medicine, Cardiovascular Center, 1500 East Medical Center Drive, Ann Arbor, Michigan 48109-5853. E-mail: oralh@umich.edu.

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