

EDITORIAL

## Atrial Fibrillation and the Autonomic Nervous System

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**KEY WORDS:** atrial fibrillation; radiofrequency catheter ablation; pulmonary vein isolation; autonomic nervous system; ganglionated plexi; autonomic denervation

**ABBREVIATIONS**

AF = atrial fibrillation  
CFAE = complex fractionated atrial electrograms  
GP = ganglionated plexi  
LLVNS = low level vagal nerve stimulation

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**ABSTRACT**

Catheter ablation of atrial fibrillation (AF) has been increasingly employed as a therapeutic modality to maintain sinus rhythm. However, the procedure is potentially associated with major complications and its long-term efficacy is relatively poor. Thus, the quest for additional non-pharmacological, non-ablative therapies for the management of patients with AF continues. Present methodology for catheter ablation of AF includes pulmonary vein isolation by applying radiofrequency current around the pulmonary vein ostia, in order to prevent the ectopic activity arising from the pulmonary veins from reaching the atria and thereby inducing AF. However, this approach failed to answer the fundamental question of how the generally short episodes of focal firing in the pulmonary veins are converted into AF. Experimental work has provided many lines of evidence linking the intrinsic cardiac autonomic nervous system with focal firing from the pulmonary veins via activation of the ganglionated plexi (GP) adjacent to these veins. Autonomic denervation is common following pulmonary vein isolation and has been associated with decreased risk of AF recurrence. Recent clinical studies where GP ablation was performed either in addition to the standard procedure of pulmonary vein isolation, or as a stand-alone procedure support these experimental data. These intriguing new concepts and data linking the autonomic nervous system to AF will herein be briefly reviewed.

**ATRIAL FIBRILLATION: EPIDEMIOLOGY AND CURRENT TREATMENT OPTIONS**

Atrial fibrillation (AF) is the most common clinically significant cardiac arrhythmia and is associated with increased cardiovascular morbidity and mortality.<sup>1,2</sup> Although a rhythm control strategy may offer no survival benefit over a rate control strategy for older individuals,<sup>3,4</sup> current guidelines acknowledge that for younger individuals, especially those with paroxysmal AF, rhythm control may be a better initial approach.<sup>5</sup> The currently available treatment options for maintenance of sinus rhythm in patients with AF include anti-arrhythmic drugs and surgical or catheter ablation.<sup>5</sup> Anti-arrhythmic drug therapy is recommended as first line for maintenance of sinus rhythm, whereas catheter ablation, previously recommended as second line therapy, after anti-arrhythmic drugs have failed,<sup>5</sup> may be appropriate as first line therapy for some patients.<sup>6</sup> However, anti-arrhythmic drug therapy is associated with inconsistent efficacy

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and potential toxicity, including proarrhythmia.<sup>5</sup> On the other hand, catheter ablation, despite being more efficacious than anti-arrhythmic drugs, is still suboptimal in maintaining sinus rhythm in the long term. Specifically, the long-term efficacy of catheter ablation for AF, as reported recently by 2 very experienced centers, is relatively poor, ranging from 29% to 46% at 5 years after a single procedure.<sup>7,8</sup> Moreover, catheter ablation is associated with a major complication rate of about 5-6%, including cardiac tamponade, pulmonary vein stenosis, phrenic nerve injury, esophageal injury/ left atrial fistula and thromboembolism.<sup>5,9</sup> The number of patients with AF in the US is expected to increase to more than 5.6 million by the year 2050 as the population ages.<sup>2</sup> Considering the current long-term success rate of catheter ablation, the development of additional non-pharmacological, non-ablative therapies could play a significant role in the management of patients with AF.

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**ATRIAL FIBRILLATION: THE ROLE OF  
THE INTRINSIC CARDIAC AUTONOMIC  
NERVOUS SYSTEM**

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The intrinsic cardiac autonomic nervous system consists of an extensive epicardial neural network forming numerous ganglionated plexi (GP) not only on the atria, but also on both ventricles. These GP, most of which are embedded within epicardial fat pads, vary in size, from those that contain just a few neurons, to those that contain over 200 neurons.<sup>10,11</sup> Several studies have demonstrated that the GP are composed of efferent, afferent and interconnecting neurons, which contain both sympathetic and parasympathetic elements, in addition to a variety of neuropeptides and neuromodulators.<sup>12,13</sup> Of interest, the four largest GP lie adjacent to the four pulmonary veins.<sup>10,11</sup> A seminal observation by Haissaguerre and co-workers established the role of the pulmonary veins in the pathogenesis of AF. These investigators found that the majority of their patients with drug-resistant paroxysmal AF manifested rapid focal firing arising from the myocardial sleeves of the pulmonary veins.<sup>14,15</sup> This focal firing was responsible for initiating and often maintaining episodes of AF. This breakthrough observation laid the foundation for the present methodology for catheter ablation of AF, which includes pulmonary vein isolation by applying radiofrequency current around the pulmonary vein ostia, in order to prevent the ectopic activity arising from the pulmonary veins from reaching the atria and thereby inducing AF.<sup>16,17</sup> However, this approach failed to answer the fundamental question of how the generally short episodes of focal firing in the pulmonary veins are converted into AF, nor did it answer why pulmonary veins rather than other atrial regions become the sites of focal firing in those patients with drug-resistant AF. Recently, a series of basic experiments provided many lines of evidence linking the intrinsic cardiac autonomic nervous system with focal firing from the

pulmonary veins. Scherlag et al<sup>18</sup> demonstrated that stimuli applied to pulmonary veins would not induce AF unless there was simultaneous activation of the GP adjacent to that pulmonary vein. Importantly, the GP stimulation was achieved with high frequency (20 Hz) and very short duration (0.1 ms) pulses at a voltage which did not excite the atrial muscle but did activate the neurons found in the GP. In another series of experiments, Po et al<sup>19</sup> showed that injection of the neurotransmitter acetylcholine into the GP induced, within minutes, premature beats and sustained AF arising from adjacent pulmonary veins. Additional *in vitro* studies by Patterson et al<sup>20,21</sup> demonstrated that pulmonary vein myocytes have cellular electrophysiological properties distinctive from adjacent atrium, particularly, a shorter action potential duration and greater sensitivity to autonomic stimulation, which facilitates the initiation of AF. Under conditions of local stimulation of both parasympathetic and sympathetic nerve endings,<sup>21</sup> or simultaneous administration of acetylcholine plus norepinephrine (or isoproterenol),<sup>20</sup> early afterdepolarizations were induced, giving rise to rapid, non-sustained triggered firing from canine pulmonary veins, similar to the focal firing observed in patients with paroxysmal AF. In pulmonary vein myocytes, early afterdepolarizations are facilitated because of the temporal discrepancy between the abbreviated action potential duration and the longer calcium transient. Under autonomic stimulation (parasympathetic and sympathetic) these differences are further exacerbated so the sodium-calcium exchanger extrudes  $Ca^{++}$ , bringing in 3  $Na^{+}$  and a net positive charge into the pulmonary vein myocytes, thereby leading to early afterdepolarizations and triggered firing.<sup>20</sup> Triggered firing from the pulmonary veins is suppressed by muscarinic cholinergic receptor blockade, beta-adrenoceptor antagonism, inhibition of calcium transients, or sodium-calcium exchange blockade.<sup>21</sup> Therefore, parasympathetic activation which causes action potential shortening, and sympathetic activation which enhances the calcium transient are important and necessary components for such triggered firing.

Autonomic denervation is common following pulmonary vein isolation<sup>22-24</sup> and has been associated with decreased risk of AF recurrence.<sup>22,25,26</sup> In a recent elegant study, Lemola et al<sup>27</sup> investigated the role of pulmonary veins versus the GP in maintenance of experimental vagal AF. These investigators performed pulmonary vein isolation in dogs while preserving the GP and in others ablated the GP while leaving the pulmonary veins intact. They demonstrated that intact pulmonary veins are not needed to maintain experimental vagal AF, whereas ablation of GP prevented AF. The same group of investigators expanded these results in a different experimental model of AF showing that pulmonary veins play a minor role in AF induced by chronic rapid atrial pacing, whereas intact GP play an important role in AF maintenance in the presence of rapid atrial pacing-induced remodeling.<sup>28</sup> It should be noted, however, that the specific neural elements within the

GP (efferent, afferent or interconnecting neurons) which are responsible for the beneficial results of GP ablation remain unclear. Clinical studies showing that complete electrical isolation of the pulmonary veins is not necessary for maintenance of sinus rhythm support these experimental data.<sup>29,30</sup> These investigations suggest that it is the GP associated with the pulmonary veins and not the pulmonary veins themselves that are important in the pathogenesis of AF and that the interruption of axons from these hyperactive GP to pulmonary veins may have also contributed to procedural success. Interruption of the axons may explain the usual elimination of pulmonary vein firing by pulmonary vein isolation. Recent animal data have provided evidence that GP hyperactivity manifests clinically as complex fractionated atrial electrograms (CFAE).<sup>31</sup> In this canine model, the distribution of the CFAE correlated well with the locations of the GP, consistent with the original clinical report by Nademanee et al,<sup>32</sup> and the CFAE were eliminated by ablating the GP at a distance.<sup>31</sup> In the clinical electrophysiological laboratory, we have shown that the degree of fractionation was markedly reduced by GP ablation.<sup>33</sup> Although the response of CFAE to atropine administered intravenously in patients with AF has not been consistent among different studies,<sup>34,35</sup> the overall evidence suggests that the autonomic nervous system plays an important role in the formation of CFAE.<sup>36</sup>

Recent clinical studies where GP ablation was performed, either in addition to the standard procedure of pulmonary vein isolation,<sup>37,38</sup> or as a stand-alone procedure,<sup>39-41</sup> support these experimental data. In these studies, the overall success rate of the procedure in eliminating AF was significantly increased with the addition of GP ablation by approximately 25%,<sup>37,38</sup> whereas GP ablation alone was successful in 71% to 86% of the patients.<sup>39-41</sup> However, these additional lesions create large areas of scarring in the left atrium that might promote iatrogenic arrhythmia formation, i.e. macro-reentrant atrial tachycardia (left atrial flutter).<sup>42</sup> In these cases, second and third ablation procedures may be required to close gaps which allow reentry. In addition, GP ablation alone is not sufficient to treat longstanding persistent AF, as indicated by the poor success rate of the procedure in this group of patients.<sup>43</sup> Therefore, although GP ablation is a promising modality for the treatment of paroxysmal AF, it is limited by certain caveats, as described above, which make it a less than an ideal treatment option. Surgical techniques have also used the combination of pulmonary vein isolation with GP ablation.<sup>44</sup> Minimally invasive, thoracoscopic surgical ablation procedures, combining epicardial pulmonary vein isolation with GP ablation, have been shown to achieve freedom from atrial tachyarrhythmias of approximately 80%, without major adverse cardiac events at 1 year of follow-up.<sup>45-47</sup> However, despite the promising results of surgical pulmonary vein isolation and GP ablation, data from randomized clinical trials are scarce.

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**LOW LEVEL VAGUS NERVE  
STIMULATION: A NON-ABLATIVE NON-  
PHARMACOLOGIC TREATMENT FOR AF**

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Autonomic neuromodulation is a novel therapeutic approach that takes advantage of the plasticity of the neural tissue to shape it to our advantage without injuring it and has been successfully used in some diseases. Vagus nerve stimulation delivered through an implantable device is being frequently used for the treatment of drug-refractory epilepsy.<sup>49,50</sup> Preliminary studies of the use of vagus nerve stimulation in patients with heart failure showed promising results, including improvement in heart failure functional class, quality of life, left ventricular ejection fraction and left ventricular end-systolic volume.<sup>51,52</sup> In experimental models, vagal activation protects the heart from ventricular arrhythmia during myocardial infarction<sup>53</sup> and limits infarct size.<sup>54</sup> Importantly, recent evidence supports the emergence of low level vagal nerve stimulation (LLVNS) as a novel non-pharmacological, non-ablative treatment modality for AF. We have recently shown that LLVNS, at voltages substantially below that which slows the sinus rate or atrio-ventricular conduction, significantly increases the effective refractory period (ERP) in the atria as well as the pulmonary vein myocardium, suppresses AF inducibility and decreases AF duration, induced by strong cholinergic stimulation.<sup>55-59</sup> In those experiments, LLVNS was applied to both vagal trunks dissected in the neck or to the vagal pre-ganglionics at the posterior wall of the superior vena cava.<sup>58</sup> We have also provided evidence that the effects of LLVNS were mediated by inhibition of GP activity.<sup>56-58</sup> Ganglionated plexi inhibition was indicated by LLVNS-mediated suppression of the ability of the anterior right GP stimulation to slow the heart rate. In addition, there was marked suppression of the frequency and amplitude of the neural activity recorded from the anterior right GP or superior left GP.<sup>56-58</sup> Furthermore, LLVNS of the right vagus nerve alone was sufficient to exert a strong anti-arrhythmic action by suppressing the neural activity of both the adrenergic and the cholinergic component of the intrinsic cardiac autonomic nervous system.<sup>59</sup> The anti-arrhythmic effects of LLVNS were also observed in ambulatory dogs. In this experimental model, left-sided LLVNS suppressed left stellate ganglion neural activity, especially in the morning and decreased tyrosine-hydroxylase positive cells in the left stellate ganglion 1 week after cessation of LLVNS.<sup>60</sup> Moreover, in the same study, LLVNS prevented paroxysmal atrial tachycardia and paroxysmal AF induced by rapid atrial pacing.<sup>60</sup> Based on the observation that transcutaneous electrical stimulation of the tragus, the anterior protuberance of the outer ear, where the auricular branch of the vagus nerve is located, elicits evoked potentials in the brainstem in humans,<sup>61</sup> we recently demonstrated that AF inducibility can be suppressed by stimulation of the tragus in dogs.<sup>62</sup> A promising clinical implication of

these results is that intermittent transcatheter LLVNS can be used as a non-invasive approach to terminate or prevent paroxysmal AF. Further studies are required to test the utility of this treatment modality in humans.

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