How the pulmonary veins ‘talk’ to the sinoatrial node: new insights into an old mystery

Rishi Arora*

Northwestern University - Feinberg School of Medicine, 251 E. Huron St., Feinberg 8-503, Chicago, IL 60611, USA

Online publish-ahead-of-print 28 June 2013

This editorial refers to ‘Nerves projecting from the intrinsic cardiac ganglia of the pulmonary veins modulate sinoatrial node pacemaker function’ by M. Zarzoso et al., pp. 566–575, this issue.

The role of the autonomic nervous system (ANS) in the genesis of atrial arrhythmias has been extensively studied in the past, with both the parasympathetic and the sympathetic nervous system having been implicated in the genesis of atrial fibrillation (AF). The discovery over a decade ago of the role of pulmonary veins (PVs) in the genesis of AF has renewed interest in understanding the autonomic profile of the atria, in order to understand the role of the ANS in the genesis of focal triggers in the PVs. Clinical and animal data suggest that these PV trigger and drivers appear to be at least partially modulated by the ANS, with different studies implicating either the sympathetic or the parasympathetic nervous system in the genesis and/or maintenance of focal AF. More recent studies postulate a dominant role for the parasympathetic nervous system (in focal AF), in part on account of the vagal or Bezold–Jarisch-like reflexes (e.g. sinus bradycardia, asystole, AV block, or hypotension) noted during radiofrequency ablation of the PV tissues in patients with paroxysmal focal AF. Indeed, some clinical studies have suggested that the attenuation of these ‘vagal’ reflexes at the time of AF ablation may increase success of ablation procedures for AF. However, other studies that attempt to target the PV ganglia (PVGs) by using this vagal reflex have not systematically shown an improvement in ablation success. This variability in ablation success is thought to be at least partially due to our poor understanding of the mechanisms underlying this bradycardia reflex (and more broadly speaking, of the autonomic profile of the atria and PVs). Indeed, the complete autonomic profile of the PVs and the precise role of the ANS in the genesis of focal AF are just beginning to be systematically investigated in clinical and animal models.

The study by Zarzoso et al. is therefore timely, as it sheds important light on how the PVG communicate with the sinus node. In this issue of the Journal, Zarzoso et al. demonstrate the presence of inter-connecting nerves between the PVG and the sinus node. They further demonstrate that these inter-connecting nerves contain both parasympathetic and sympathetic nerve fibres. The investigators also delve into the physiological function of these nerves by assessing the effect of PVG stimulation on the sinus node in the presence of sympathetic and parasympathetic blockade. These latter studies strongly suggest that the ‘vagal’ effect of PVG stimulation on sinus node function is in reality a mixture of both parasympathetic and sympathetic responses, with the dominant, initial effect of parasympathetic stimulation on the sinus rate effectively ‘concealing’ the sympathetic response. This demonstration of a combined parasympathetic and sympathetic response is consistent with prior observations that parasympathetic and sympathetic nerves in the atrium tend to be co-localized. Although the relative preponderance of sympathetic vs. parasympathetic nerves appears to be species specific (with sympathetic nerves appearing to predominate in humans, and vagal nerve fibres appearing to predominate in dogs), the relative functional dominance of the parasympathetic nervous system in contributing to atrial electrophysiology—and therefore the creation of AF substrate—is become clear from a variety of studies, with the sympathetic nervous system appearing to play more modulatory role in this regard.

The findings of Zarzoso et al. are also consistent with the demonstration by other groups of the presence of an inter-connecting neural network between the different ganglionated plexi (GPs) in the atria. Ablation of one or more of these GPs appears to result as a ‘remote’ effect at other sites in the atria. Indeed, Aistrup et al. showed that inhibition of M2/Gαi3 signalling in the PVG region in the study by Zarzoso et al. by using peptides targeting the C-terminus of Gαi3 proteins resulted in attenuation of vagal responsiveness not only at the site of peptide injection, but also in the rest of the left atrium. The effect of Gαi inhibition on sinus node responsiveness was not examined in that study.

Despite the importance of Zarzoso et al.’s findings in explaining the PV stimulation induced sinus bradycardia, it must be remembered that much of the bradycardia that is noted during AF ablation (or high-frequency stimulation) is noted during AF, with the bradycardia a consequence of AV nodal slowing. While the precise mechanisms underlying the effect of PVG stimulation on AV nodal function are not known, it is tempting to speculate, based on the findings by Zarzoso et al. that similar neural connections likely exist between the PVG and the AV node. Future studies are needed to systematically examine the presence of neural inter-connections between the PVG and the AV node.

An additional area of future investigation would be to examine how these PVG-SA nodal connections are affected by structural heart
disease, e.g. congestive heart failure. The effects of heart failure on sinus node function have been well described. More recent studies indicate that the autonomic innervation of the PVs is also significantly altered in heart failure, with significant parasympathetic and sympathetic remodelling occurring in the posterior left atrium. Autonomic remodelling also appears to contribute to AF substrate caused by atrial tachypacing.

How these changes in the innervation of the PVG and SA node influence PVG stimulation’s effects on the sinus rate is not known, and needs to be examined further.

As noted earlier, GP ablation has been shown in some studies to be correlated with improved PV ablation outcomes, with results being less promising in other studies. This may be at least in part because current clinical manoeuvres to localize the atrial GPs rely entirely on eliciting bradycardia during high-frequency stimulation or PV ablation. The current study illustrates that the connections between the PVG and the SA node—which are the likely cause of these reflexes—are complex and composed of both parasympathetic and sympathetic nerve fibres. Future studies are needed to examine whether the sensitivity of high-frequency PV stimulation in localizing the GPs can be improved by performing this manoeuvre in the presence of a variety of different autonomic conditions, e.g. in the absence and presence of sympathetic blockade (the latter to allow for uninterrupted vagal effect on the sinus node), as well as by examining for the effects of the sympathetic stimulation on the sinus node (e.g. in the presence of atropine).

**Conflict of interest:** none declared.

**References**