Ablation of Ganglionated Plexi in the Long Term
Is Half a Loaf as Good as None?

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In this issue of *Circulation: Arrhythmia and Electrophysiology*, Wang et al. demonstrated, in the dog heart, that ablation of the right-sided ganglionated plexi (GP) whose axons innervate the sinoatrial and atrioventricular nodes acutely induced significant prolongation of atrial effective refractory period (AERP) but in the long term these effects were reversed. Moreover, nerve density of parasympathetic and sympathetic nerves was markedly increased after GP ablation. These findings essentially confirm previous experimental studies by Oh et al., Sakamoto et al., and Mao et al. all of whom ablated GP, and found evidence of reinnervation providing a reversal of AERP shortening and restoration of atrial fibrillation (AF) inducibility.

We are indebted to Walter Randall and the cadre of neurophysiologists he mentored, who studied the intrinsic autonomic nervous system of the heart starting in the 1970s. His most prominent progeny, Andrew Armour and Jeffrey Ardell have and continue to contribute to our understanding of the important structural and functional aspects of the neural innervation in the normal heart and under pathological conditions. From a structural viewpoint, the neural innervation of the heart is a multitiered system of nerve bodies and axons starting at the brain and spinal cord proceeding through an intrathoracic station to reach the intrinsic autonomic nervous system on the heart itself. As delineated structurally by Yuan et al., the intrinsic cardiac autonomic nervous system consists of large GP associated with an extensive neural network of smaller groups of ganglia and their axons within the parenchymal musculature of the atria and ventricles. This system shows a high degree of interdependence between stations, which tend to maintain normal homeostatic function yet when, for example, the intrinsic cardiac nervous system is separated from extrinsic control, pathological results can readily occur.

In a recent experimental study, Lo et al. disconnected the intrinsic cardiac autonomic nervous system from the extrinsic autonomic nervous system. This was accomplished by ablating the head stage GP found on the right pulmonary artery as it traverses the space between the aorta and the superior vena cava. This GP serves as a nexus point between the 2 systems. After an initial increase of the AERP, by the fourth week there was a significant decrease in the AERP compared with the sham-operated group associated with a significant increase in the spontaneous occurrence of AF and atrial tachycardia during the a follow-up period of 10 weeks.

Just as the disconnect of the intrinsic cardiac autonomic nervous system from the extrinsic autonomic nervous system presumably led to the hyperactivity of the GP and the initiation of AF, the disconnection of the major GP at the pulmonary vein (PV)—atrial junctions and along the ligament of Marshal by Wang et al. and Mao et al. might also result in the hyperactivity of the ganglia of the atrial neural network. Initially, there would be an increase in AERP followed by a remodeling throughout the atrial neural network now manifesting a significant decrease in AERP and an associated propensity for AF inducibility. This hypothesis is supported by the recent acute experimental findings of Chang et al. who found significant increases in sympathetic nerve sprouting in dogs after pacing induced AF for >100 days. A similar sympathetic hyperinnervation was found in atrial appendages of patients with persistent AF. Gould et al. concluded that their findings suggest autonomic remodeling may be part of the atrial substrate for AF. Sympathetic hyperactivity has been shown to result in PV firing because of triggered activity when acetylcholine was injected into the GP at the PV—atrial junctions. Moreover, acetylcholine applied to the atrial neural network after GP ablation allowed inducible and sustained AF. It is of interest that long-term pacing induced AF and surgical disconnect of the intrinsic cardiac autonomic nervous system from the extrinsic autonomic nervous system both result in a significant increase of the AF burden in what was previously a normal heart. This remodeling has been shown to be related to electrophysiological, as well as structural changes, that is, development of fibrosis.

The potential of neural tissue for regeneration is exemplified by the distinct differences between muscle and nerves. Localized ablation of myocardial tissues leads to infarction and scar, whereas neural tissues have a different response to injury. The basis of this response is the property of neural tissue to exhibit plasticity. Assuming that there is no damage to nerve cell bodies, such as exist within the atrial neural network after major GP ablation, nerve sprouts can emerge from each parent axon, thereby increasing the total number of axons exceeding the number of parents.

The GP ablation studies of Wang et al. and the experimental and clinical studies of others have shown: (1) autonomic remodeling in the form of neural plasticity comes from...
within the atrial neural network in the form of nerve sprouting, reversal of AERP prolongation and rotor and focal source origins of AF initiation and maintenance.25 Indeed, a recent clinical report detailed previously unrecognized focal firing sources in the left atrial appendage found in 27% of patients having repeat procedures whose AF was successfully ablated by targeting these sites.26 (2) The unexpected increase in heart rate reported by Wang et al1 and others5 could be because of increased sympathetic innervation from the right stellate ganglion, which ordinarily connects to the sinus node via the anterior right GP. With the ablation of the latter, neural plasticity and nerve growth of the interganglionic nerve, which bypasses the GP27 can directly affect the sinus node to cause the persistent increased heart rate.

Overall, what have we learned, long term, from the clinical experience of catheter ablation for treating the various forms of AF? Single procedures, either with PV isolation alone or with extended lesion lines or PV isolation with GP ablation tend to beget more burning (repeat procedures) with diminishing returns.28,29 Long-term neural remodeling and iatrogenic scar production may contribute to the suboptimal success rates over the long term. Are there alternatives that could be added to the armamentarium of methodologies to treat the various forms of AF? Recent experimental30 and clinical31 studies have demonstrated that low-level nerve stimulation (that does not slow the heart rate and is nonsentient) applied at the auricular branch of the long term. Are there alternatives that could be added to the armamentarium of methodologies to treat the various forms of AF? Recent experimental30 and clinical31 studies have demonstrated that low-level nerve stimulation (that does not slow the heart rate and is nonsentient) applied at the auricular branch of the vagus nerve (the tragus of the outer ear) can consistently suppress AF. Other alternative therapies that have been proposed for the treatment of AF include acupuncture52 and Yoga.53

Disclosures
None.

References


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