Unravelling the Paradoxical Effects of Ganglia Ablation

Benjamin J. Scherlag, PhD; Warren M. Jackman, MD

In 1973, Lazzara et al.1 described 2 clusters of nerve bodies called ganglionic plexi (GP) adjacent to the sinus node and AV junction; high-frequency electric stimulation, which did not excite the underlying atrium, induced heart rate or AV conduction slowing, respectively. We are indebted to Randall et al.2 who spent the next several decades delineating the anatomy and physiology of the intrinsic cardiac autonomic nervous system consisting of GP located at several sites in the atria and ventricles. Carrying on the legacy of Dr. Randall,2 Armour and Ardell3,4 produced numerous publications and books, providing a hierarchical construct of the neural innervation of the heart, starting at the nuclei and axonal fields in the brain (extrinsic autonomic nervous system) followed by the spinal cord (intrathoracic) ganglia and axons and their connections to the intrinsic cardiac autonomic system with its GP and their axons of passage. The last part of this interconnected chain (the atrial neural network) was delineated anatomically by Armour et al.5 and Pauza et al.6 and functionally by Hou et al.7

The overall function of the intrinsic autonomic nervous system consisting of the GP and the atrial neural network was summarized by Ardell,8 “...the intrinsic cardiac nerve plexus (GP and neural network) acts as more than a simple relay station for extrinsic autonomic projections to the heart...modulating...extrinsic and local cardio-cardiac reflexes. The intrinsic cardiac nerve plexus contains a heterogeneous population of cell types, including parasympathetic and sympathetic efferent neurons as well as afferent neurons.” Furthermore, as pointed out by Ardell,8 these afferent neurons participate in reflex loops between and within the various levels of the extrinsic, intrathoracic, and intrinsic systems, yet each level when disconnected from the other would retain independent functionality.

From 1997 to 1998, the seminal studies by Jais et al.9 and Haïssaguerre et al.10 showed that the myocardium of the pulmonary veins (PVs) manifested ectopic firing in patients, and this ectopy was directly associated with the initiation and maintenance of atrial fibrillation (AF). As a result, the accepted catheter ablation procedure for AF became isolation of the PVs. This finding engendered basic experimental studies demonstrating that chemical stimulation11 of the GP at the atrial PV entrances or electric stimulation of the nerves within the PV could induce PV firing and AF.12 Moreover, these studies specifically implicated the excessive release of both the cholinergic (marked shortening of the refractory period) and the adrenergic (induction of triggered firing) neurotransmitters as the mechanism for PV firing and ensuing AF. Clinical studies,13,14 including surgical approaches,15,16 have provided evidence that ablation of GP is an important adjunctive procedure to PV isolation in the treatment of AF.

These clinical and recent experimental studies have provided enlightening insights into how the autonomic nervous system interacts in the normal and pathological heart to induce and or suppress AF. For example, high-level electric stimulation via the vagal trunks (which markedly slows the heart rate) has been used for >100 years to induce AF acutely in experimental animals. Schauerte et al.17 showed that ablating the GP located on the main right pulmonary artery running underneath the aorta and the superior vena cava to the right lung (GP) could suppress the AF induced by vagal stimulation. In regard to chronic forms of AF, Allessie and his associates found that pacing induced AF for weeks provided a chronic model of sustained AF in goats.18 In a series of studies from our laboratory, we found that low level vagal nerve stimulation (at a voltage 50% lower than that which slows the heart rate) paradoxically suppresses or even prevents pacing induced AF19,20 by diminishing both the frequency and amplitude of GP firing.21 Another recent paradoxical finding was a study by Lo et al.22 in which they ablated the superior vena cava-aorta GP, which has been described as the head stage or nexus point GP,22 connecting the extrinsic and the intrinsic autonomic nervous systems. During a period of 10 weeks, the operated animals progressively developed atrial tachycardia/AF, whereas the sham controls did not. This unexpected paradoxical finding was explained based on the inhibitory control normally imposed by the extrinsic on the intrinsic autonomic nervous system. With the disconnect the intrinsic system is now freer to act independently (as alluded to by Ardell8) and achieve a hyperactive state of the intrinsic GP leading to atrial tachycardia/AF.

In this issue of the journal, Mao et al.23 have reported another example of the apparently paradoxical interaction between the cardiac autonomic nervous system and AF. In a group of dogs, the major 4 GP and ligament of Marshall were ablated, whereas a comparably sized second group served as sham controls (no GP ablation). In the ablated group, the acute studies showed a significant prolongation of effective refractory period (ERP) (atrial refractoriness) and a significant decrease in AF inducibility when compared with baseline values. Eight weeks after ablation the ERP was significantly shorter and AF inducibility was significantly greater than the Sham control group.

The authors offer several explanations for their findings, including incomplete denervation and neural GP bypasses both parasympathetic, which would shorten ERP, and sympathetic,
which would enhance triggered firing by programmed stimulation. As support for this hypothesis of increased sympathetic and parasympathetic innervation, several ancillary findings are cited by the authors, specifically, the heart rate at 8 weeks was significantly higher in the experimental group when compared with that in the sham group. Furthermore, immunohistochemical studies showed a higher cholinergic and sympathetic nerve density in the experimental but not in the sham group. Moreover, they recognized that the third tier of the cardiac autonomic innervation, the atrial neural network (see above) could serve as the substrate for these proarrhythmic effects. It is interesting to note that in a previous acute study, after inducing the same GP and ligament of Marshall ablation, it was shown that the atrial neural network was easily made proarrhythmic by the application of acetylcholine. Indeed, the same concentrations of acetylcholine applied over a small area of the atrial neural network resulted in a significantly shorter induced AF duration than when applied over a larger area of the atrial free wall and appendages.

However, what remains to be addressed is the mechanism(s), during the 8-week period, which provided the changes in atrial refractoriness and AF inducibility. The authors refer to their finding that atrial natriuretic peptide levels were increased, which could be a potential contributor for the 8-week findings in the experimental group.

An intriguing clue for a neural mechanism to explain the paradox may be from the recent and past studies about blood pressure, a commonly found comorbidity with AF. Renal artery denervation has recently been touted as an effective means for reducing resistant hypertension in patients. Of interest, the suggested mechanism is that the ablation of the hyperactive afferent nerves from the renal arteries reduce the abnormal neural input to the medullary centers that control blood pressure in the brain. During a period of time (like the blanking period in AF ablation), there is a reverse remodeling of medullary activity allowing a reduction of the sympathetic outflow, thereby reducing the abnormal vasoconstriction of the renal vessels. Could the same medullary centers play a role, albeit in inducing paradoxical hypertension, when normal neural inputs, providing homeostatic control of blood pressure, are ablated? In this regard, Pardo and Vidrio showed that daily dosing of mecamylamine, a ganglionic blocker, in normal dogs, for a period of several months paradoxically induced a sympathetic form of hypertension. Indeed, the same concentrations of acetylcholine applied over a small area of the atrial neural network resulted in a significantly shorter induced AF duration than when applied over a larger area of the atrial free wall and appendages.

The present authors clearly recognize that differences exist between their findings on the GP ablation in the experimental setting and when GP ablation is performed in patients particularly when combined with PV isolation as stated in the Limitations section. It seems possible that circumferential ablation of the PV can act to dissect the afferent and efferent portions of the reflex loop described above and thereby further increase the success rate for catheter ablation combining PV isolation and GP ablation when compared with GP ablation alone.

We think that Mao et al by presenting the apparently conflicting findings between the acute and the chronic effects of GP ablation have helped us understand the intricate and interconnected nature of the autonomic nervous system as it applies to the normal heart and to the hearts afflicted with the most common form of clinical arrhythmia, AF.

Disclosures

Dr Jackman: Consultant for Biosense Webster, Boston Scientific, VytronUS, and ACT; and Lecture Honoraria from Biosense Webster, Boston Scientific, Biotronik, and AtriCure Dr Scherlag reports no conflicts.

References


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