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Commentary: The cardiac neuronal hierarchy and susceptibility to arrhythmias

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Anatomical and functional data collected over the past two decades have led our group and others to propose the presence of a complex neuronal hierarchy that controls regional cardiac function ¹. The maintenance of adequate cardiac function during basal conditions, as well as in the presence of stressors, ultimately depends upon the transduction characteristics of cardiac afferent neurons located in various levels of the cardiac neuronal hierarchy. It is the interdependent reflex processing of that sensory information at the peripheral and central aspects of the hierarchy for cardiac control that ultimately determines the efferent neuronal outflows that modulate regional cardiac function ¹.

With regards to neural control of cardiac electrical stability, numerous lines of investigation have indicated that heterogeneous activation of select neuronal populations within the cardiac nervous system predisposes the heart to arrhythmias ²⁻⁵. Furthermore, other studies have shown there are inherent differences between animals with respect to reflexes evoked in response to acute cardiac stress such that i) reflex-induced changes in efferent neuronal output (sympathetic and parasympathetic) that remain coordinated, especially within and between intrathoracic processing networks, represent “electrically” stable states vs ii) those in which such reflex processing is heterogeneous - thereby leading to disruption of normal efferent neuronal outputs to the heart to induce cardiac electrical instability ^{1, 4}. With the onset and progression of chronic cardiac disease, interactions between cardiac efferent nerves and cardiomyocytes remodel and the characteristics of these adjustments are fundamental to the etiology of disease progression. More importantly, recent studies have indicated that targeted modification of select elements within the cardiac nervous system provides novel opportunities for effective management of arrhythmias.

The paper by Shen et.al. ⁶ “Patterns of baseline autonomic nerve activity and the development of pacing-induced sustained atrial fibrillation” evaluates the potential differential contribution of the cardiac nervous system to induction of atrial arrhythmias using a rapid-pacing induced animal model of atrial fibrillation. Extracellular neural activity was continuously and simultaneously recorded from the left stellate ganglia, left vagus nerve, and from the left superior intrinsic cardiac ganglionated plexus. The characteristics of that neural activity were related to the spontaneous generation of paradoxical atrial tachycardia (PAT) and the time to onset of sustained atrial fibrillation (AF). The primary conclusions for the study were: 1) that ambulatory dogs with higher levels of symphovagal correlation and higher vagal tone exhibited faster induction of sustained AF by rapid pacing;

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and 2) the majority (75%) of animals, which did not demonstrate these activity patterns, exhibited increased vagal activity in the week preceding the pacing-induced induction of sustained AF in association with a progressive reduction in indices of sympathetic activity.

The coordination of cardiac efferent neuronal activities in the regulation of regional cardiac indices is critically dependent upon the stochastic nature of cardiovascular sensory information processed by peripheral (intrinsic cardiac ganglia, intrathoracic extracardiac ganglia) as well as central (spinal cord and brainstem) components of the cardiac neuronal hierarchy¹. While the interactions within this system usually act to compensate for normal cardiovascular perturbations, this neuroaxis can be catastrophically disrupted by stresses that induce highly localized and excessive input signals to specific nexus points within the hierarchy^{2, 4, 7}. Recording of extracellular activity from specific nexus points in the cardiac nervous system has provided important insights into the neurocardiological interactions subserving cardiac control. First and foremost, has been the characterization of the complex functional and neurochemical diversity evident within these peripheral ganglia, including multiple cell types (afferent, efferent and local circuit neurons) which utilize a variety of putative neurotransmitters to affect cardiac control^{1, 8}. Rather than being obligatory relays for descending projections, the majority of intrinsic cardiac neurons recorded using such recording techniques are likely to be local circuit ones that are involved in the coordination of intra- and interganglionic neuronal reflex activities with resultant modulation of regional cardiac function^{9, 10}. Moreover, in conjunction with end-organ effects, interactions between sympathetic and parasympathetic efferents can occur within intrinsic cardiac ganglia, with major effects on the control of cardiac electrical function¹¹. Stellate/middle cervical ganglia neuroanatomy exhibits a similar network complexity, including the capacity for interganglionic interactions with the intrinsic cardiac nervous system independent of higher center influences¹⁰ and with only a subset of these neurons projecting directly to the heart¹². Vagal fiber recordings likewise represent a heterogeneous population of efferent and afferent projections to cardiac and non-cardiac structures. These factors should be considered and controlled for when possible when interrupting neural activity from various levels of the cardiac nervous system.

That being said, the current study from Shen et. al.⁶ does provide important new information with respect to the potential contributions of different patterns of autonomic activities as related to cardiac electrical stability. In animals with strong left-sided sympathovagal coordination, there is an increased incidence of sympathovagal co-activations with increased incidence of PAT, yet the incidence of PAT is 20% of co-activation episodes. Future studies should consider if there are unique characteristics of unit and/or population discharge that predispose to arrhythmia formation. When considering nerve-end effector interactions, the direct relationship between stellate ganglion neuronal activity and heart rate is expected, yet a similar direct relationship between recorded vagal activity and heart rate is reported. While indeed this may reflect a potential for co-activation as the authors propose, it is counter to classical concepts of reciprocal innervation¹³ with parasympathetic predominance. Indeed, this study supports the emerging concept of differential control of regional cardiac function as manifest by interdependent and nested feedback networks that comprise the cardiac nervous system. This study further substantiates the neural remodeling that accompanies end-effector remodeling associated with the cardiac stress of rapid-pace. Future studies should expand on this concept, especially as related to the cardiac stress-induced changes in functional and neurochemical/neurohumoral alterations in the cardiac nervous system and the cardiac tissues they innervate.

Recent studies have indicated that targeting the cardiac nervous system provides new and novel opportunities for effective management of cardiac arrhythmias. Methodologies

employed include pharmacological¹⁴, physical^{15, 16} and/or electrical^{17, 18} means to target specific nexus points within its associated neural networks. While ablation therapy has demonstrated efficacy in AF management^{16, 19, 20}, such procedures destroy critical elements of the cardiac nervous system that are essential for coordinating regional cardiac function. Recent studies have indicated that local circuit neurons in the cardiac nervous system may be regarded as a potential therapeutic target in arrhythmia suppression. Stabilization of such neurons, either pharmacologically^{2, 14} or with electrical neuromodulation¹⁷, has the potential to stabilize the multiple components within the intrinsic cardiac nervous system, reduce the arrhythmogenic potential to nerve imbalances, while at the same time preserving regulatory networks.

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