Published in final edited form as:

Heart Rhythm. 2015 November ; 12(11): 2294–2295. doi:10.1016/j.hrthm.2015.07.008.

It's not the heart: autonomic nervous system predisposition to lethal ventricular arrhythmias

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For the better part of the last century, it has been recognized that the heart, and the cardiovascular system as a whole, can respond to a number of noncardiac extrinsic factors. Chief among these is the autonomic nervous system, which mediates signals from physiologic “sensors” in the heart and great vessels, such as baroreceptors, stress receptors, and various chemoreceptors. Input from this myriad of physiologic sensors integrates to create a complex, yet elegantly precise, autonomic regulatory mechanism. Just as the physiologic role of the autonomic nervous system has been delineated, so has the pathophysiologic role that this system can play in the predisposition to, and genesis of, arrhythmias. In this issue of *HeartRhythm*, Machhada *et al*¹ explored the role of vagal tone in ventricular arrhythmia by functional inhibition of the dorsal vagal motor nucleus (DVMN). This study offers new insights into the role of parasympathetic control of the heart and its relationship to fatal ventricular tachycardias.

Autonomic control of the heart is complex and is generally divided into extrinsic and intrinsic components. The extrinsic autonomic nervous system is composed of sympathetic fibers and parasympathetic fibers. The sympathetic innervation of the heart is carried through ganglia consisting of cervical, stellate (cervicothoracic), and thoracic ganglia, while the parasympathetic preganglionic innervation is carried by the vagus nerve, which innervates the sinus and atrioventricular nodes. Central to this study is the DVMN, which projects vagal preganglionic neurons that ultimately exert parasympathetic influence on the heart. Through this functionally parallel cardiac innervation, the sympathetic and parasympathetic systems antagonize each other in a balancing act that confers exquisite regulatory control of the heart.

As the physiologic extrinsic control of the heart has been explored, the consequence of perturbed regulation and the pathologic neuronal signaling that predisposes to arrhythmias has emerged. Atrial arrhythmias, such as atrial fibrillation, have a long-established relationship with the autonomic nervous system, including associations with both sympathetic and parasympathetic signaling.² This association has been extended to primary ventricular arrhythmias, which predispose to sudden death as well as to the modulation of arrhythmia risk in the setting of inherited dysfunction of cardiac ion channels—the so-called cardiac channelopathies. These studies have mainly focused on the role of the sympathetic nervous system, specifically evaluating the effect of increased sympathetic activity. It has been well documented that heart rate variability is diminished, and heart rate increases, before ventricular tachycardia in humans, which is likely reflective of increased sympathetic tone.³ Furthermore, stimulating left stellate sympathetic ganglia in dogs, which increases left ganglia sympathetic tone, induced QT prolongation and preceded ventricular arrhythmia and sudden death.⁴ More recently, the role of the parasympathetic nervous system in ventricular arrhythmias, particularly in specific channelopathies such as idiopathic ventricular fibrillation (VF), has become appreciated. For example, in patients with idiopathic VF with the so-called J-wave syndrome, the presence of J waves was associated with high vagal tone. This manifested as increased J-wave elevation during bradycardia and increased propensity to nighttime VF events, each associated with increased vagal tone.⁵ Yet despite this progress, the predisposition of ostensibly normal hearts to potentially fatal ventricular tachycardias with loss of parasympathetic regulation has remained unexplored.

In the article, Machhada et al¹ functionally silence the DVMN to examine the electrophysiological effects on the ventricles. To accomplish this, the *Drosophila melanogaster* neuropeptide allatostatin was delivered via cannulation to the rat DVMN, where previous viral injections were used to express the ligand's receptor *AlstR* under a *Phox2* synthetic promoter. Administration of allatostatin triggers *AlstR* and a subsequent intracellular G_i-mediated signaling cascade that activates endogenously expressed *Kir* channels to produce an inward-rectifying potassium current that hyperpolarizes DVMN neurons, inhibiting action potentials and thus perturbing DVMN functional output. In addition, triple synuclein null mice, which demonstrate a loss of DVMN activity and a Parkinson disease (PD)-type phenotype, were used as a corroborating model. The authors report a proarrhythmic reduction in the ventricular effective refractory period, an elevation in the corrected QT interval, and reduction in the ventricular tachycardia threshold in rats expressing the allatostatin receptor compared to green fluorescent protein-expressing controls. Similarly, aged triple synuclein null mice demonstrated a reduction in the ventricular effective refractory period and an elevation in the corrected QT interval as compared with age-matched controls. All the experimental animals survived without apparent sudden death. Overall, these findings are considered to be indicative of a proarrhythmic phenotype imparted by reduced parasympathetic vagal tone.

While this study offers some of the first insights into the interplay between the parasympathetic nervous system and ventricular tachycardias, additional questions arise. The use of a general anesthetic can alter ventricular excitability and predisposition to arrhythmia. In addition, arrhythmia was observed only during electrical stimulation designed to evoke arrhythmia. Replication of these findings in conscious nonsedated mice with

cardiac telemetry monitoring to evaluate the native cardiac rhythm would enhance the clinical applicability. As allatostatin does not cross the blood-brain barrier, cannulation is required for brainstem access, making chronic inhibition and *in vivo* conscious studies difficult. The use of the G-protein coupled receptor–based Designer Receptors Exclusively Activated by Designer Drugs (DREADD) receptors in transgenic rodents should obviate some of the complications in the current experiments, including the need to cannulate the brainstem for ligand application since DREADD ligands clozapine *N*-oxide and salvinorin B can be administered via intraperitoneal injection or the drinking water.^{6, 7} DREADDs further open the possibility of combinatorial experiments by using inhibitory and excitatory receptors that have been differentially targeted to subsets of sympathetic and parasympathetic neurons through combinations of viral and transgenic approaches. Thus, truly *in vivo* analysis of models with selective functional silencing and excitation of autonomic neurons as well as expanded mapping of key central neural circuits influencing autonomic output becomes possible. In addition, while aged synuclein null mice replicated the findings, recent studies have demonstrated no clinically significant physiologic modulation of the parasympathetic innervation of the heart in humans with PD in the setting of degeneration of the dorsal motor nucleus of the vagus nerve.⁸ More extensive studies in the aged synuclein null and other animal models of PD are needed to clarify whether DVMN degeneration contributes to autonomic function in PD or is a by-product of some other central or peripheral mechanism.

Should future studies confirm and clarify these findings, the interplay between the parasympathetic autonomic system and inherited channelopathy may yield novel insight into disease prognosis and sudden death risk stratification. Further studies to fully map the preganglionic vagal innervation of the ventricles while examining transmitter type for the projecting fibers and their sites of innervation and activity will be key in elucidating the role of nitrous oxide, acetylcholine, and other transmitters of the vagus in heart rate stability. It will also be exciting to see how cardiac function is mapped across other vagal efferents, including the nucleus ambiguus and other areas of the ventral medulla that have been identified through retrograde labeling. Indeed, this work will undoubtedly serve as a substrate from which additional genetic, molecular, and anatomical studies will clarify the role of the parasympathetic nervous system in ventricular arrhythmias and may open the door to targeted therapeutics for a number of deadly diseases.

Acknowledgments

This work was in part funded by the National Institutes of Health (grant nos. HL089598, HL091947, and HL117641) and the American Heart Association established investigator award (grant no. 13EIA14560061, to X.H.T.W.).

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