Cardiac Innervation and the Autonomic Nervous System in Sudden Cardiac Death

William A. Huang, MD, Noel G. Boyle, MD, PhD,
Marmar Vaseghi, MD, PhD, FHRS*

KEYWORDS

• Autonomic • Innervation • Sympathetic • Parasympathetic • Sudden death
• Ventricular tachycardia • Ventricular fibrillation

KEY POINTS

- Cardiac neural control occurs at multiple levels, and each level has the capability to receive afferent neurotransmission and control efferent outflow to the heart.
- Sympathetic nervous system activation in myocardial infarction increases ventricular fibrillation/ventricular tachycardia (VT/VF) by providing both of the ingredients required for arrhythmogenesis: increased myocardial excitability and heterogeneous repolarization predisposing to reentry.
- Myocardial infarction remodels the sympathetic nervous system such that sympathetic activity is amplified, promoting VT/VF.
- Strategies for neuraxial modulation have aimed at decreasing sympathetic activity and augmenting parasympathetic tone, at various levels of cardiac neural control.
- Autonomic modulation has progressed from basic science to animal studies and human studies, although in clinical trials, some therapies have had mixed results.

INTRODUCTION

The autonomic nervous system controls every aspect of cardiac physiology. Autonomic imbalances, whether from central nervous system disorders such as in epilepsy[1] or from cardiac pathologic remodeling of the peripheral nervous system, can cause significant atrial and ventricular tachyarrhythmias and bradyarrhythmias. In this article, the role of the autonomic nervous system in sudden cardiac death (SCD) is reviewed with a particular focus on the levels at which neuromodulatory therapies may have proven benefit.

ANATOMY

The autonomic nervous system consists of sympathetic and parasympathetic branches. Neural processing occurs at several levels (**Fig. 1**). The intrinsic cardiac ganglia reside on the epicardium and receive postganglionic sympathetic and preganglionic parasympathetic connections. In the thorax, the extracardiac but intrathoracic ganglia, such as the stellate ganglia, the middle cervical ganglia, and the thoracic ganglia of T2-T4, also process neural information, controlling sympathetic outflow to the heart. Finally, sympathetic afferent information passes through the dorsal

Disclosure Statement: The authors have nothing to disclose.
UCLA Cardiac Arrhythmia Center, David Geffen School of Medicine at UCLA, 100 MP, Suite 660, Los Angeles, CA 90095, USA
* Corresponding author.
E-mail address: mvaseghi@mednet.ucla.edu

Card Electrophysiol Clin 9 (2017) 665–679
http://dx.doi.org/10.1016/j.ccep.2017.08.002

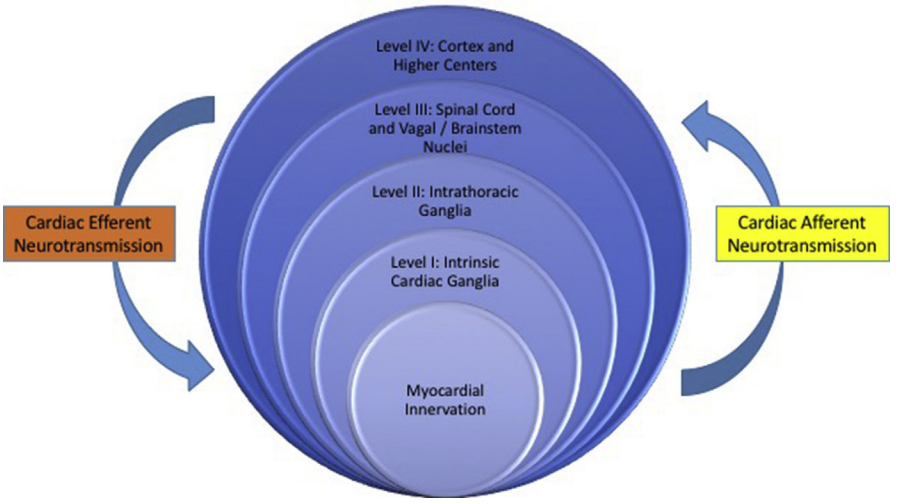

Fig. 1. Cardiac neural control occurs at multiple levels, and each level has the capability to receive afferent neurotransmission and control efferent outflow to the heart (directly or indirectly). Level I represents the intrinsic cardiac ganglia, located in the fat pads of the epicardium. Level II includes the stellate, middle cervical, and thoracic ganglia. Level III includes the spinal cord, vagal nerve, and brainstem nuclei. Level IV represents cortex and higher centers. Each level also demonstrates parallel processing of neural information.

root ganglia and reaches the spinal cord, where additional neural processing can take place. Some of this information is then sent to the brainstem and higher centers. At each level, afferent neurotransmission feeds back information to neurons that in turn affect efferent control of the heart, completing an independent neural circuit that modulates cardiac function. In addition, direct vagal afferent fibers originate from the myocardium and synapse via pseudounipolar neurons of the nodose ganglia in the nucleus tractus solitarius of the brainstem. Finally, although sympathetic efferent fibers originate in the thoracic ganglia and parasympathetic preganglionic fibers travel in the vagal trunk, it is important to note that there is significant intermixing of these fibers in the thorax so that most nerves reaching the heart in the mediastinum have mixed (sympathetic and parasympathetic) fibers.[2,3]

Sympathetic Efferent Neurotransmission

The journey of cardiac sympathetic preganglionic fibers originates in the central nervous system primarily in the brainstem, with modulation by higher centers such as the subthalamic and periaqueductal gray as well as rostral ventrolateral medulla.[4] These preganglionic fibers leave the spinal cord at the level of T1 to T4 and synapse in the right and left stellate ganglia, T2-T4 thoracic, and middle cervical ganglia. Postganglionic fibers then originate from these ganglia and travel along epicardial vascular structures as dictated by embryologic growth cues of endothelin-1 and nerve growth factor (NGF) released by vascular smooth muscle cells, particularly along coronary veins and then arteries.[5,6] Therefore, sympathetic innervation is particularly dense around the sinus node and coronary sinus, with decreasing density from the base of the ventricle to the apex.[7] In addition, these fibers provide input to the numerous ganglionated subplexuses interspersed throughout bilateral atria and ventricles.[4,8] Most postganglionic sympathetic fibers, however, synapse directly onto the myocardium. The major neurotransmitter of the sympathetic nervous system is norepinephrine, which stimulates myocardial beta-receptors. Roles for additional neurotransmitters such as neuropeptide Y are currently under investigation.[9]

Parasympathetic Efferent Neurotransmission

Preganglionic cardiac parasympathetic efferent fibers begin in the nucleus ambiguus and dorsal motor nucleus of the brainstem and travel in the vagosympathetic trunk bilaterally.[10] These preganglionic fibers synapse within the intrinsic cardiac ganglia residing in fat pads on the heart.[11] Postganglionic neurons then provide direct innervation to the sinus node, atrioventricular node, and bilateral atria and ventricles.[12–15] Acetylcholine is the major neurotransmitter of the heart, stimulating muscarinic (predominantly