

STATE-OF-THE-ART REVIEW

Treatment of Atrial and Ventricular Arrhythmias Through Autonomic Modulation



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CME Objective for This Article: At the completion of this article the learner should be able to discuss: 1) the role of nuclear imaging in the identification of cardiac autonomic nervous system; 2) the benefit of intrinsic autonomic modulation through ganglionic plexi modulation or ablation in the treatment of atrial fibrillation; and 3) the developments in autonomic modulation of cardiac arrhythmias through targeting the extrinsic nervous system such as renal denervation and vagal stimulation.

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ABSTRACT

This paper reviews the contribution of autonomic nervous system (ANS) modulation in the treatment of arrhythmias. Both the atria and ventricles are innervated by an extensive network of nerve fibers of parasympathetic and sympathetic origin. Both the parasympathetic and sympathetic nervous system exert arrhythmogenic electrophysiological effects on atrial and pulmonary vein myocardium, while in the ventricle the sympathetic nervous system plays a more dominant role in arrhythmogenesis. Identification of ANS activity is possible with nuclear imaging. This technique may provide further insight in mechanisms and treatment targets. Additionally, the myocardial effects of the intrinsic ANS can be identified through stimulation of the ganglionic plexuses. These can be ablated for the treatment of atrial fibrillation. New (non-) invasive treatment options targeting the extrinsic cardiac ANS, such as low-level tragus stimulation and renal denervation, provide interesting future treatment possibilities both for atrial fibrillation and ventricular arrhythmias. However, the first randomized trials have yet to be performed. Future clinical studies on modifying the ANS may not only improve the outcome of ablation therapy but may also advance our understanding of the manner in which the ANS interacts with the myocardium to modify arrhythmogenic triggers and substrate. (J Am Coll Cardiol EP 2015;1:496-508)

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The atria and ventricles are innervated by an intricate network of autonomic nerves (1,2). The role of the sympathetic and parasympathetic nervous system in the pathophysiology of cardiac arrhythmias is complex. Parasympathetic and sympathetic activation influence atrial and ventricular electrophysiology and these changes can initiate, facilitate, or counteract cardiac arrhythmias depending on the presence of a suitable substrate (3,4). By selectively ablating or stimulating the different components of the autonomic nervous system (ANS), such as ganglionic plexuses (GPs) or the vagal nerve, the net activity of the ANS can be modulated and arrhythmias treated (5,6).

Here, we briefly review the role of the ANS as trigger and modulator of cardiac arrhythmias. Notably, we focus on novel methods to clinically identify the cardiac ANS and we discuss autonomic modulation as treatment for cardiac arrhythmias.

ANATOMY OF THE CARDIAC ANS

In the human heart, the extrinsic sympathetic innervation is mediated via the cervical, stellate (cervicothoracic), and thoracic ganglia. Parasympathetic extrinsic innervation is routed via the vagus nerve, although sympathetic fibers are found in vagal nerves and parasympathetic fibers in sympathetic nerves as well (7,8). The extrinsic nerves pass through the hilum of the heart along the great cardiac vessels and branch into 7 epicardial subplexuses, the intrinsic

neural pathways of the ANS (1). Small nerve fibers form an extensive neural network of small interconnecting efferent and afferent sympathetic, parasympathetic, and mixed nerve fibers, that contain the neurotransmitters noradrenaline and acetylcholine, respectively, but some also contain neuropeptide Y, somatostatin, vasoactive intestinal polypeptide, and substance P (2,9-12). The density of small fibers and ganglia is highest in the posterior part of the left atrium and around the antrum of the (left) pulmonary veins (PVs) (11,13). The atria are predominantly parasympathetically innervated, while in the ventricles (where only 16% of total cardiac ganglia reside) predominantly sympathetic nerve fibers are found (1,14,15). GPs are conglomerates of ganglia from different subplexuses and function as an integration center of the parasympathetic and sympathetic nerves and interconnect the intrinsic ANS (9,16,17). The atrial GPs are located near the sinus node and PVs and reside in epicardial fat pads as shown in [Figure 1](#). Ventricular GPs are located near the interventricular groove (9). The ligament of Marshall, the embryonic remnant of the left superior caval vein, near the left superior PV is densely innervated with parasympathetic and sympathetic nerves (18,19).

AUTONOMIC MODULATION IN ATRIAL FIBRILLATION

The atrial susceptibility to autonomic nervous modulation relates to the high density of autonomic

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