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STATE-OF-THE-ART REVIEW

The Role of the Autonomic Ganglia in Atrial Fibrillation

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CME Objective for This Article: Describe the role of the autonomic ganglia in the initiation and maintenance of atrial fibrillation; discuss the role of inadvertent ablation of the autonomic ganglia and their axons in the success of the pulmonary vein isolation procedure; discuss the benefit of adding ablation of the autonomic ganglia to the standard pulmonary vein isolation procedure for patients with paroxysmal atrial fibrillation; and describe the concept of neuromodulation and how it may be applied in atrial fibrillation.

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The Role of the Autonomic Ganglia in Atrial Fibrillation

ABSTRACT

Recent experimental and clinical studies have shown that the epicardial autonomic ganglia play an important role in the initiation and maintenance of atrial fibrillation (AF). In this review, the authors present the current data on the role of the autonomic ganglia in the pathogenesis of AF and discuss potential therapeutic implications. Experimental studies have demonstrated that acute autonomic remodeling may play a crucial role in AF maintenance in the very early stages. The benefit of adding ablation of the autonomic ganglia to the standard pulmonary vein isolation procedure for patients with paroxysmal AF is supported by both experimental and clinical data. The interruption of axons from these hyperactive autonomic ganglia to the pulmonary vein myocardial sleeves may be an important factor in the success of pulmonary vein isolation procedures. The vagus nerve exerts inhibitory control over the autonomic ganglia, and attenuation or loss of this control may allow these ganglia to become hyperactive. Autonomic neuromodulation using low-level vagus nerve stimulation inhibits the activity of the autonomic ganglia and reverses acute electrical atrial remodeling during rapid atrial pacing and may provide an alternative nonablative approach for the treatment of AF, especially in the early stages. This notion is supported by a preliminary human study. Further studies are warranted to confirm these findings. (J Am Coll Cardiol EP 2015;1-2:1–13) © 2015 by the American College of Cardiology Foundation.

Recent experimental and clinical studies have shown that the intrinsic cardiac autonomic nervous system (CANS), which is formed by interconnected clusters of autonomic ganglia, known as ganglionated plexi (GP), plays an important role in the initiation and maintenance of atrial fibrillation (AF) (1). Variations in autonomic tone in humans (2) and hyperactivity of the GP in ambulatory dogs (3) often precede episodes of paroxysmal AF. Four of the left atrial GP heavily innervate each of the myocardial sleeves of the 4 pulmonary veins (PVs) (4,5). Recent experimental evidence suggests that it is the GP activity to the PVs that is important in the pathogenesis of AF and that the interruption of axons from these hyperactive GP to the PV myocardial sleeves may be an important factor in the success of PV isolation procedures (6,7). In this review, we present the current data on the role of the autonomic ganglia in the pathogenesis of AF and discuss potential therapeutic implications.

ANATOMY OF THE AUTONOMIC GANGLIA

The heart receives innervation from both the extrinsic (central) and the intrinsic CANS. The extrinsic CANS includes the ganglia in the brain or along the spinal cord, where the cell bodies reside, as well as their axons (e.g., the vagosympathetic trunk) en route to the heart. The intrinsic CANS is essentially an extensive, highly interconnected epicardial neural network that consists of multiple GP, nerve axons, and interconnecting neurons (**Figure 1**). These GP, except the ligament of Marshall, are embedded within epicardial fat pads and vary in size, from those that contain just a few neurons to those that contain more than 400 neurons (4,5). It should be noted that although the epicardial surface of both atria is covered by a dense neural plexus, the highest density of neurons is found at the posterior wall of the left atrium (5). Several studies have demonstrated that the GP contain both sympathetic and parasympathetic elements, in addition to a variety of neuropeptides and neuromodulators (8,9). Four of the left atrial GP each innervate 1 of the 4 PVs, as well as the surrounding atrial myocardium (4,5). These 4 GP are located within areas of fractionated atrial potentials during AF and can be identified during electrophysiological study by applying high-frequency stimulation (20 Hz) at the respective anatomical locations (10,11). The high-frequency stimulation activates the GP, leading through interconnecting neurons to activation of the inferior right GP. The latter depresses atrioventricular (AV) nodal conduction, increasing the R-R interval by >50% during AF (**Figure 2**). Although the AV block is not mediated by the vagus nerve, this positive response is often referred to as "vagal response." This response is specific but not completely sensitive.

On the basis of the response to high-frequency stimulation, the anterior right GP is located