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Innervation of the heart: An invisible grid within a black box

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ABSTRACT

Autonomic control of cardiovascular function is mediated by a complex interplay between central, peripheral, and innate cardiac components. This interplay is what mediates the normal cardiovascular response to physiologic and pathologic stressors, including blood pressure, cardiac contractile function, and arrhythmias. However, in order to understand how modern therapies directly affecting autonomic function may be harnessed to treat various cardiovascular disease states requires an intimate understanding of anatomic and physiologic features of the innervation of the heart. Thus, in this review, we focus on defining features of the central, peripheral, and cardiac components of cardiac innervation, how each component may contribute to dysregulation of normal cardiac function in various disease states, and how modulation of these components may offer therapeutic options for these diseases.

Key words: Autonomic innervation, Cardiac, Heart, Vascular, Arrhythmias, Nervous system, Cardiovascular system.

The autonomic nervous system (ANS) comprises an elegant framework by which the human body regulates everything from heart rate to blood pressure via complex feedback loops. At the level of the heart, sympathetic and parasympathetic inputs integrate together to directly affect cardiac function, down to the level of the local cardiac action potential. Abnormalities in autonomic function have been implicated in everything from atrial fibrillation to ventricular arrhythmias to hypertension. In turn, feedback loops also modulate the body's response to primary cardiac pathology such as myocardial infarction (e.g., when bradycardia and hypotension occur during an inferior myocardial infarction, also known as the Bezold–Jarisch reaction).

Much study has been done in the fields of cardiology and, in particular, cardiac electrophysiology related to the impact of autonomic function on cardiac pathology and on methods of modulating autonomic input to treat a variety of cardiac diseases. In order to understand these interactions, their clinical impact, and future research potential, knowledge of the fundamentals of the anatomy of the innervation of the heart, the central integration centers responsible for the processing of information, and the cross-linking that occurs between the different components of the ANS is necessary. In this review, we focus on the innervation of the heart in terms of the linking between central, peripheral, and cardiac components, how each component may contribute to dysregulation of normal cardiac function, and ongoing studies into modulating the autonomic nervous system to treat a variety of cardiac diseases. While a comprehensive review of each of these individual points is well beyond the scope of this review, we have sought to offer a general overview of these

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anatomic and clinical considerations and to reference resources the reader may refer to in order to obtain a detailed understanding of specific components.

Anatomic considerations

The anatomy and physiology of cardiac components of the autonomic nervous system has been well described in multiple reviews [1–4]. Here, we offer a brief overview of the critical portions of the autonomic nervous system, including central and peripheral components in addition to the intrinsic cardiac nervous system. Via a basic understanding of these aspects, the reader may better understand current clinical studies into modulating the autonomic nervous system to treat a variety of cardiac diseases.

Central components of the ANS: the role of the cortex

Much of the cardiac control exerted by the autonomic nervous system is seen through normal every day activities, e.g., when standing from a supine or seated position and during ambulation. The neuronal mechanisms underlying postural and motor components of the autonomic nervous system are in large part regulated through cortical and subcortical regions. A simple way of understanding this is that many cardiovascular variations (e.g., heart rate or blood pressure) actually precede movement and thus can only be accounted for by some element of cortical control rather than through afferent input from peripheral muscles and organs alone. This higher level of "central command" in autonomic function was first proposed by Krogh and Lindhard in the early 1900s and understanding of its role has been validated through a variety of animal and human studies over the ensuing century [5–8]. These concepts highlighting the importance of the forebrain in normal autonomic control are further validated by studies of differences in sympathetic/parasympathetic balance in states such as depression or anxiety, as well as in studies of the potential impact of yoga or meditation on net autonomic tone [9–12].

Several cortical areas are critical in regulation of autonomic control of the heart. In addition to the sensorimotor cortex, the medial prefrontal and insular cortices have been implicated in regulating autonomic control of the heart [2,5–8]. In turn, stimulation or inhibition of these cortical regions may directly impact sympatho-vagal balance. For example, stimulation of the medial prefrontal cortex has been demonstrated to decrease blood pressure and sympathetic nerve activity (potentially via effects on spinal circuitry) [13,14]. In turn, manipulations which typically increase sympathetic activity have been shown by functional MRI studies to increase activity within the medial prefrontal cortex, likely as a reflex response to restore appropriate levels of sympathetic activity [15]. However, stimulation of the motor cortex has been shown to result in increased sympathetic activity [15,16]. It is also possible to harness the cortical contribution to sympatho-vagal balance, such as via anodal transcranial stimulation, which has been suggested to increase sympathetic nerve activity, likely via inhibition of the medial prefrontal cortex and/or stimulation of the motor cortex [17].

Functional MRI studies of the brain have suggested that multiple areas of the brain may be associated with changes in sympathetic nerve activity. For example, spontaneous increases in muscle sympathetic nerve activity versus skin sympathetic nerve activity have been correlated with different regions of cerebral activation [18]. This concept that sympathetic nerve activity control may be heterogeneous is in part borne out by studies on lateralization of normal autonomic control [19]. This is best seen within the insular cortices, with right insular cortex stimulation being associated with increases in sympathetic activity and left insular cortex stimulation being associated with increases in parasympathetic activity [20,21]. This complex interplay between multiple cortical centers has been well reviewed elsewhere and highlights the importance of understanding the importance of "central command" functions in normal autonomic control and that the sympathetic/parasympathetic balance extends beyond simple "reflexes" that occur at un- or subconscious levels [2].

Specific regions of the brainstem, which might be affected by impulses from cortical regions, include the nucleus tractus solitarius (NTS), dorsal nucleus of the vagus (DMV), and rostral ventrolateral medulla (RVLM), as has been validated by studies of c-fos protein expression upon stimulation of the motor cortex [22]. The NTS is the primary integration center for the baroreflex, while the DMV helps in modulation of heart rate and the RVLM helps regulate tonic and phasic sympathetic control of blood pressure. A review by Sequeira et al. [23] summarizes efforts to further characterize how the cortical regions and the brainstem cooperate in regulation of cardiovascular autonomic reflexes.

Central components of the ANS: nucleus ambiguus versus nucleus tractus solitarius

The central component of the ANS is also heavily regulated within the brainstem, with cardiac sympathetic and parasympathetic control coordinated principally through the NTS and nucleus ambiguus, though the DMV and RVLM also play important roles (Fig. 1). The NTS is a series of nuclei in the medulla oblongata and receives afferent input from bundles of nerve fibers arising from the facial, glossopharyngeal, and vagus nerves. In turn, projections from the NTS extend to parasympathetic preganglionic neurons, the hypothalamus, thalamus, and the reticular formation, all of which are involved in regulating the ANS. The caudal portion of the NTS is specifically involved in regulating cardiorespiratory function, including cardiovascular responses to baroreceptor, chemoreceptor, and cardiopulmonary receptor activation [24–26].

Cardiopulmonary vagal afferents make their first synapse in the NTS, but such is also true for some sympathetic afferents arising from the spinal cord thus regulating NTS outflow. The nodose ganglion is a component within this feedback loop and chiefly manages visceral afferent fibers arising from the heart and other structures, which eventually synapse back in the NTS. This ganglion chiefly is traversed by parasympathetic fibers, though some sympathetic fibers may pass through as well. The feedback supplied to the heart from the NTS is also mediated in part via NTS input to the lateral