

Neurocardiology: Structure-Based Function

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ABSTRACT

Cardiac control is mediated via a series of reflex control networks involving somata in the (i) intrinsic cardiac ganglia (heart), (ii) intrathoracic extracardiac ganglia (stellate, middle cervical), (iii) superior cervical ganglia, (iv) spinal cord, (v) brainstem, and (vi) higher centers. Each of these processing centers contains afferent, efferent, and local circuit neurons, which interact locally and in an interdependent fashion with the other levels to coordinate regional cardiac electrical and mechanical indices on a beat-to-beat basis. This control system is optimized to respond to normal physiological stressors (standing, exercise, and temperature); however, it can be catastrophically disrupted by pathological events such as myocardial ischemia. In fact, it is now recognized that autonomic dysregulation is central to the evolution of heart failure and arrhythmias. Autonomic regulation therapy is an emerging modality in the management of acute and chronic cardiac pathologies. Neuromodulation-based approaches that target select nexus points of this hierarchy for cardiac control offer unique opportunities to positively affect therapeutic outcomes via improved efficacy of cardiovascular reflex control. As such, understanding the anatomical and physiological basis for such control is necessary to implement effectively novel neuromodulation therapies.

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Overview

It is now evident that neuronal elements distributed throughout the cardiac neuraxis, from the level of the insular cortex to the intrinsic cardiac nervous (ICN) system, are in constant communication with one another to assure that cardiac output matches an ever-changing demand for regional blood flow. As such, the various neural elements/levels of this hierarchy become differentially recruited to optimize coordination of regional cardiac function (9, 26). The anatomical basis for its varied functional interactions is relevant to understanding hierarchical control in both normal and pathological states. The overriding hypothesis presented in this paper is that the coordination of regional cardiac indices is dependent upon the target organ's local coordinating nervous system—*the intrinsic cardiac nervous system*—that is under dynamic modulation by (i) intrathoracic extracardiac ganglia (21, 30, 207, 208) and (ii) central (medullary and spinal cord) neural networks (79, 81, 171, 267).

Underlying the evolution of our understanding of integrated cardiac neuronal control (158, 229) has been the concept of central neuronal command (141, 175, 201, 252). In this thesis, cardiac control resides primarily within central neuronal projections that target peripheral postganglionic adrenergic and cholinergic motor neurons acting in a reciprocating fashion (161). The two major central autonomic outputs include: (i) parasympathetic efferent preganglionic neurons located in the medulla oblongata primarily in the ventrolateral component of the nucleus ambiguus (79, 113, 131) and (ii) sympathetic efferent preganglionic neurons located in caudal cervical and cranial thoracic spinal cord segments (intermediolateral cell column) (63, 93, 162). In such a

scenario, these central (medullary and spinal cord) motor outputs are under the tonic influence of central inputs derived primarily from cardiovascular sensory neuronal somata located in nodose and thoracic dorsal root ganglia (37, 61, 191). These, in turn, influence medullary (7, 79) and spinal cord neurons (93) respectively that, in turn, influence forebrain neurons (74). These also affect cortical neurons—particularly those in the insular cortex (122, 187, 188). This view of centrally determined neuronal command has been recently enlarged upon, given the fact that it is now recognized that additional processing of the intrathoracic cardiovascular milieu occurs within peripheral ganglia (25, 26). As depicted in Figure 1, these interconnected intrathoracic neural networks, both intrinsic cardiac and extracardiac, allow for shorter-loop dynamic reflex control over regional cardiac function (29). Moreover, they can function independent of central influences (10, 178, 179, 245).

In this review, the anatomical basis for cardiac control is focused on peripheral aspects of this hierarchy. We first discuss what is currently known about the locations of cardiac afferent neurons in dorsal root, nodose, intrathoracic

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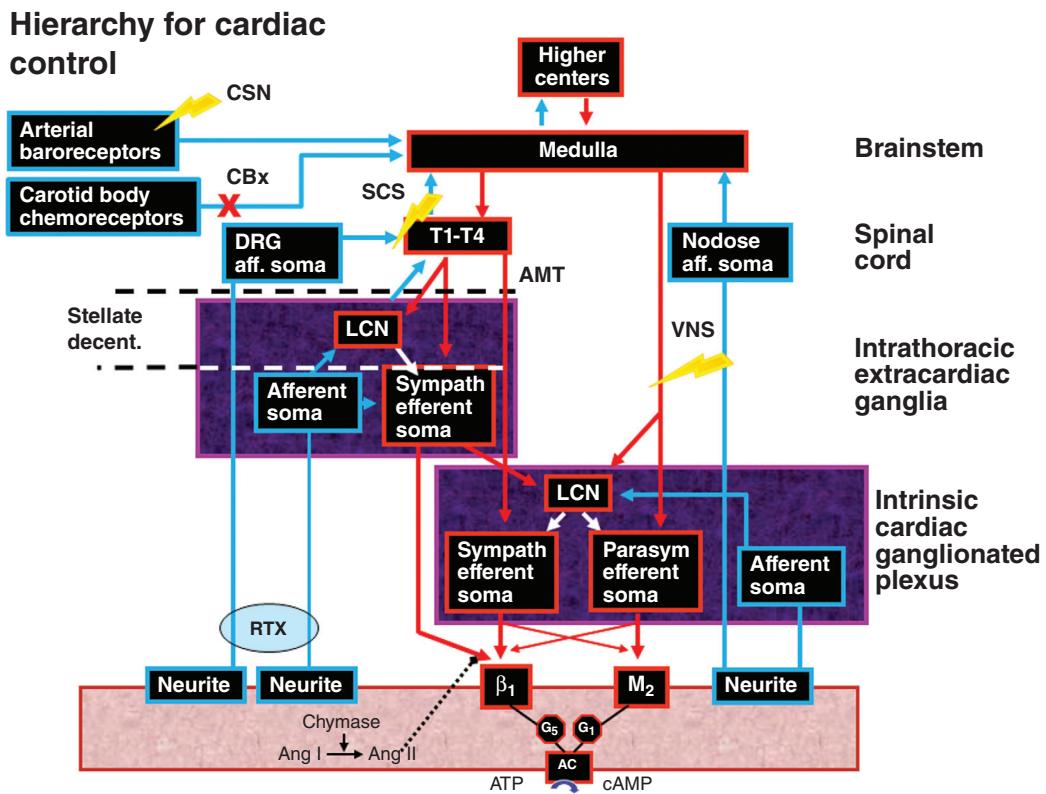


Figure 1 Network interactions occurring within and between peripheral ganglia and the central nervous system for control of the heart. The intrinsic cardiac nervous system (ICNS) possesses sympathetic (Sympath) and parasympathetic (Parasymp) efferent postganglionic neurons, LCN's and afferent neurons. Extracardiac intrathoracic ganglia contain afferent neurons, LCN's and sympathetic efferent postganglionic neurons. Neurons in intrinsic cardiac and extracardiac networks form nested feedback loops that act in concert with CNS feedback loops (spinal cord, brainstem, hypothalamus, and forebrain) to coordinate cardiac function on a beat-to-beat basis. Primary nexus points for neuromodulation of the neural hierarchy are indicated: these include carotid sinus nerve (CSN) stimulation; spinal cord stimulation (SCS); vagus nerve stimulation (VNS); axonal modulation therapy (AMT); surgical ablation of the carotid body chemoreceptors (CBx); surgical decentralization (decent) of the stellate ganglia from the central nervous system; and an example of selective pharmacological interruption of cardiac afferent inputs with resiniferatoxin (RTX). Adapted, with permission, from (62).

extracardiac and intrinsic cardiac ganglia, along with their varied transduction capabilities. This is followed by a summary of the roles that cardiac (adrenergic and cholinergic) efferent neurons play in motor control. Thereafter, the key role that peripheral interactive local circuit neurons (LCNs) play in reflex control of regional cardiac indices will be discussed. Finally, we will consider structure/function characteristics of the hierarchy for cardiac control in relationship to mechanistic-based autonomic regulation therapy for cardiac pathology.

Structural Determinants of Cardiac Control—Peripheral Neuronal Hierarchy

Cardiac control is achieved through a hierachal network that may be considered in three levels. Level 1: CNS neurons (medullary and spinal cord neurons modulated by higher centers); Level 2: Peripheral: extracardiac-intrathoracic neuronal pool; and Level 3: Peripheral: the ICN system. These levels

are schematically illustrated in Figure 1. The peripheral ones (Levels 2 and 3) form cardio-centric reflex control loops, while the CNS (Level 1) engages central neural mechanisms for cardiac and peripheral vasculature regulation (25, 149). Acting together, these hierarchical populations coordinate and regulate regional cardiac electrical and mechanical indices throughout each cardiac cycle to assure that cardiac output matches blood flow demands. To understand network interactions within and between levels 1 and 3, one must first understand the characteristics of its constituent parts.

The corner stone for cardiac control is the ICN system (ICNS). It possesses all the essential neural elements to function as the “little brain” on the heart, including afferent, local circuit, and efferent neurons (sympathetic and parasympathetic) (9, 26). It has the capability to manifest integrated cardiac control, even when functioning disconnected from all higher neural elements of the cardiac nervous system (10, 42, 178, 179, 246). This includes the capacity to increase and decrease regional cardiac function via modulation of the contained sympathetic and parasympathetic motor neurons

(69,259). While, the ICNS itself is comprised of a distributed aggregates of ganglionated plexi (45, 197, 260), each with a preferential sphere of influence (14, 69, 85, 259), common shared inputs (afferent and efferent), inter- and intraganglionic interconnections mediated by LCN's subserve beat-by-beat coordination of regional cardiac (electrical and mechanical) function (16, 46, 235, 248).

This hierarchical concept for cardiac control represents a nervous system intrinsic to the heart that is under the tonic influence of (i) extracardiac intrathoracic and (ii) central reflex control neural networks. Each of these processing centers contains afferent, efferent and LCNs which interact locally and in an interdependent fashion with neurons in other levels of the neuraxis to coordinate regional cardiac indices on a beat-to-beat basis (9,26). As such, this system is optimized to respond to normal physiological stressors (standing, exercise, and temperature). However, it can be catastrophically disrupted by pathological events such as myocardial ischemia (MI) (151,225). In fact, it is now recognized that autonomic dysregulation is central to the evolution of heart failure and arrhythmias (26, 77, 122, 267). The challenge remains to understand all of its putative multihierarchical interactions that occur in the coordination of cardiac electrical and mechanical function. To tease out the various peripheral and central reflexes attending the cardiac neuraxis hierarchy, below we discuss how (i) its various populations of afferent neurons transduce the cardiac milieu to (ii) cardiac motor neurons via (iii) interposed central neurons and intrathoracic LCNs.

Cardiac Afferent Neurons

Overview

Cardiocardiac and major vascular-cardiac reflexes depend on cardiovascular sensory transduction by populations of afferent neurons in nodose, dorsal root, and various intrathoracic ganglia. Normally, they initiate complex and interactive reflexes in both the CNS and peripheral autonomic nervous system (29, 90, 267). With respect to pathology, nociceptive sensory inputs arising from the ischemic heart represent a stimulus that can evoke discord within and among neurons throughout the various levels of this hierarchy (5, 66, 89, 98, 101, 151). In fact, one can assume that this neural control hierarchy has not evolved to deal with MI (151). Abnormal sensory information arising from an ischemic ventricle can reflexly (151,203) disrupt autonomic motor outputs contributing to an increased potential for sudden cardiac death (24, 54, 98). As a corollary, targeting these multilevel reflex pathways represents an emerging therapeutic option for managing the arrhythmia potential and/or the progression of heart failure (see **Emergent Neuromodulation Therapies**).

Functional anatomy

Anatomical evidence indicates that afferent neuronal somata associated with sensory neurites in atrial, ventricular and

intrathoracic major intravascular tissues are located not only in nodose and dorsal root ganglia (35, 129, 244), but also in intrathoracic extracardiac (17, 19) and intrinsic cardiac (10, 46) ganglia. Sensory neurites embedded in cardiac tissues are concentrated in the sinoatrial nodal region, dorsal aspects of either atrium, endocardium of either ventricular outflow tract and in the papillary muscles of both ventricles (15, 189-192). Other mechanosensory neurons are associated with neurites embedded in the fibrous coating of the major vessels adjacent to the heart (37, 169, 170, 199, 241) and within the carotid sinus (7, 72, 156, 222, 265).

The somata of cardiac and vascular sensory neurons associated with these sensory neurites are distributed among (i) nodose (129, 132) and (ii) dorsal root (129, 132, 244) ganglia as well as (iii) intrathoracic extra-cardiac (17, 19, 37), and (iv) intrinsic cardiac ganglia (10, 46, 260). The sensory neurites associated with somata in nodose, dorsal root, intrathoracic extracardiac, and intrinsic cardiac ganglia transduce their local mechanical and/or chemical milieu in a differential manner, depending on the cardiac region in which their neurites are located and the ganglion in which their various somata reside (37). This is particularly the case with regard to significant populations of dorsal root (143) and nodose (238) ganglion cardiac sensory neurons that transduce both modalities (demonstrate multimodal properties) (37). Table 1 summarizes the primary functional characteristics of such cardiac afferent neurons.

While bipolar cardiac afferent neurons in nodose ganglia project to neurons in the nucleus tractus solitarius of the medulla oblongata (7), those in dorsal root ganglia project first to spinal cord neurons (93). Both populations, acting via central interneurons, exert reflex control over cardiac parasympathetic efferent preganglionic neurons in the medulla and spinal cord sympathetic efferent preganglionic neurons, respectively, in the control of intrathoracic cardiac adrenergic and cholinergic motor control (79, 81, 104, 166, 252, 267).

Table 1 Summary of Functional Characteristics of Cardiac Afferent Neurons; Taken from (37) With Permission

Fast responding, mechanotransduction	Slow responding, chemotransduction
Sensory-specific (mechanosensory)	Frequently multimodal
Transducing constantly varying local mechanics	Transducing multiple, nonuniform events
High fidelity	Noisy signal that limits resolution
Produces phasic activity	Tonic (nonphasic), relatively low frequencies
Limited memory	Memory, affected by past events
Noise-free transduction	Requires noise for transduction
Primary inputs to short control loops	Inputs to intermediate and longer-latency control loops

Functional data indicate that clusters of mechanosensory neurites associated with these afferent neurons are localized in select atrial and ventricular regions, in particular in the region of the sinoatrial node, the dorsal atria and the outflow tracts of either ventricle (15). These cardiac afferent neurons have been classed as being (i) mechanosensory, (ii) chemosensory, or (iii) multimodal (transducing both modalities) in nature (25, 61, 90, 97, 143, 152, 169, 238, 240, 241). Subsets of dorsal root ganglia neurons can concurrently transduce both modalities, each being transduced within different time domains as assessed by power spectral analysis of their respective activities (143). This confers the capacity of individual afferent neurons to transduce differing stimuli at a particular time depending on the strength of the local milieu (90, 91, 143). It is presumed that such multiple coding allows for limited populations of sensory neurons to transduce to second order neurons the status of regional cardiac mechanical and/or chemical milieus concomitantly (37).

The transduction capabilities of ventricular sensory neurites associated with somata in nodose, dorsal root, and intrinsic cardiac ganglia are known to transduce a number of ion species (215), along with ischemic events (24, 37, 90). Although a variety of chemical stimuli can be so transduced by these varied afferent neuronal populations, purinergic receptor agonists appear to be important in transducing ventricular ischemic events (143, 239), as has been made evident in a clinical setting (233).

Nodose ganglion cardiac afferent neurons

Many atrial sensory neurites that project axons centrally to nodose ganglion primarily transduce regional mechanic events, as do many ventricular sensory neurites associated with other nodose ganglion afferent neuronal somata (35). Only a relatively small proportion of cardiac afferent neurons in nodose ganglia (about 10%) appear to transduce the local mechanical milieu of the atria or ventricles to nucleus tractus solitarius' neurons (37). Many of the latter can also concomitantly transduce the chemical milieu when their associated sensory neurites are exposed to ischemic events, thereby displaying multimodal transduction capabilities (142, 238).

Local cardiac chemical stimuli induce an order of magnitude greater enhancement of their activity than do local cardiac mechanical stimuli (37). Furthermore, their capacity to transduce enhancement of the chemical milieu—for instance, in the presence of ischemia around their sensory neurites—can persist for up to an hour after removal of the chemical stimulus (37). Perhaps their capacity to do so accounts, in part, for the observation that nodose ganglion ventricular sensory neurons frequently display persistent enhanced activity during the reperfusion phase post-MI (37). Taken together, these data indicate that most nodose ganglion cardiac afferent somata generate stochastic activity in control states, enhancing such activity when transducing regional ventricular ischemia. The association of purinergic receptors with their sensory neurites may be critical to such sensitization (239).

A number of intrathoracic afferent neuronal somata transduce aortic wall dynamics, doing so with considerable fidelity (37). Transduction of aortic arch wall length, as well as stretch of the carotid sinus, are transmitted to the nucleus tractus solitarius (7, 71, 127, 156, 171, 267). It is their mechanosensory neurites, embedded in the outer walls of the aorta or carotid artery that transduce with local wall mechanics. Their grouped firing yields activity patterns that track local arterial wall dynamics as reflective of arterial pressures waves (7, 71, 156). Such afferent neuronal mechanoreceptor function affects not only nucleus tractus solitarius neurons in the medulla via their nodose ganglion somata inputs, but also many LCNs in adjacent intrathoracic extracardiac ganglia (17, 19, 20).

Dorsal root ganglion cardiac afferent neurons

Limited populations of cardiac related afferent neurons are found in dorsal root ganglia, primarily from the C6 to the T6 levels of the spinal column (87, 128, 132). Their associated sensory neurites are found in all four cardiac chambers of the heart, with a propensity to be located in cranial ventricular regions (143). They transduce the cardiac milieu quite differently than do nodose ganglion cardiac afferent neurons (37). Firstly, in control states dorsal root ganglion cardiac afferent neurons generate higher frequency activity (~10 Hz) than do nodose ganglion cardiac afferent neurons (~0.1 Hz) (144). Secondly, most (~95%) display multimodal transduction characteristics (143). Furthermore, they display different activity characteristics when their associated cardiac sensory neurites transduce maximal mechanical (activity enhancement range of about +225%) versus chemical (activity enhancement range of about +500%) stimuli (37, 152). Their activity is greater than that generated by nodose ganglion cardiac afferent neurons (maximum activity enhancement of about 75%) when transducing the cardiac mechanical or chemical milieu (37). Perhaps their multiple transduction capabilities account for the fact that individual dorsal root ganglion cardiac afferent neurons display varied activity patterns when transducing local mechanical versus chemical stimuli, including when transducing multiple chemical stimuli simultaneously (37). This transduction capacity/plasticity of individual dorsal root ganglion neurons acts to minimize the number of cardiac afferent neurons required to transduce a constantly varying cardiac milieu to spinal neurons. It may be of interest that purinergic receptors associated with their cardiac sensory neurites appear to be involved in their capacity to transduce ventricular ischemia (239). Such data support the clinical observation that administering low doses of purinergic agents locally via close coronary arterial injection can mimic angina symptoms in patients exhibiting symptomatology associated with ventricular ischemia (233). These sensory neurites likewise transduce a variety of chemicals, including neuropeptides, that can contribute to vascular reactivity as well as signaling to higher centers of the cardiac neuraxis (37, 90, 96, 251, 258).

Cardiac afferent neurons in intrathoracic extracardiac ganglia

Unipolar neurons have been identified in ganglia located within the thoracic cavity (17, 20, 57). Many cardiac afferent neurons identified in stellate and middle cervical ganglia transduce aortic arch wall dynamics, doing so in a manner such that their collective active patterns reflect the pressure waves that occur during each cardiac cycle (12, 17, 19, 20). On the other hand, a considerable fraction of these cardiac sensory neurons are multimodal in nature, transducing both mechanical and chemical stimuli (37). The latter include adenosine, ATP, bradykinin, substance P, and various other peptides (37). It is also known that the transduction properties of their cardiac sensory neurites involve a number of ion species *in situ* (37).

Intrinsic cardiac afferent neurons

Afferent (unipolar) neurons have also been identified in each major intrinsic cardiac ganglionated plexus by anatomical means, to date, in canines and humans (38, 100). They have also been identified by physiological means (Figs. 2 and 3). The population of primary afferent neurons in intrinsic cardiac ganglia that transduce regional cardiac and major intrathoracic vascular sensory information has been estimated to represent less than 10% of the total population of neuronal somata therein (10, 46). With respect to canines, their presence in major atrial and ventricular ganglionated plexuses has been confirmed by physiological data that demonstrate their capacities to transduce the chemical milieu of the heart along with regional dynamics (10, 33, 100, 235, 236), even when chronically decentralized from all higher centers of the cardiac neuronal hierarchy (10, 178, 179). Afferents inputs directly or indirectly alter short-term firing patterns in ~50% of IC neurons (Fig. 3, top right panel).

Cardiac Motor Neurons

Cardiac myocytes and coronary vessels are modulated by sympathetic and parasympathetic motor neurons (207, 209) along with circulating hormones (84, 267). Efferent neuronal outflows from the autonomic nervous system to the heart depend on both central (preganglionic) and peripheral neuronal mediated (postganglionic) reflexes (29, 79, 207, 265). Within each nexus points of the neuronal hierarchy for cardiac control, from the CNS to intrinsic cardiac ganglia, network interactions occurring within and between its levels are fundamental to network output control of cardiac motor neurons (9, 26, 127).

Starting in the early seventies, the predominant regulatory concept put forth had the two representative limbs of the efferent autonomic nervous system (sympathetic vs. parasympathetic) controlled in a reciprocal fashion by primarily central mediated medullary and spinal cord reflexes (54, 81, 161, 162, 252). The concept that the two efferent limbs of the cardiac nervous system function in a “reciprocal” fashion wholly under central neuronal command has been revised of late given the fact that: (i) it is now known that some neurons in either of these motor limbs can be activated or suppressed concurrently (25, 79); (ii) that there is cardiocentric control by neurons on the target organ—those of the ICNS—that receive concurrent inputs from both efferent limbs of those central neurons (46); and (iii) intrathoracic reflexes maintain bidirectional control of regional cardiac function even when operating totally disconnected from the central nervous system (10, 178, 179, 245).

Cardiac sympathetic efferent neurons

Cardiac sympathetic efferent preganglionic neurons located in the caudal cervical and cranial thoracic spinal cord project axons via the right- and left-sided spinal nerves to

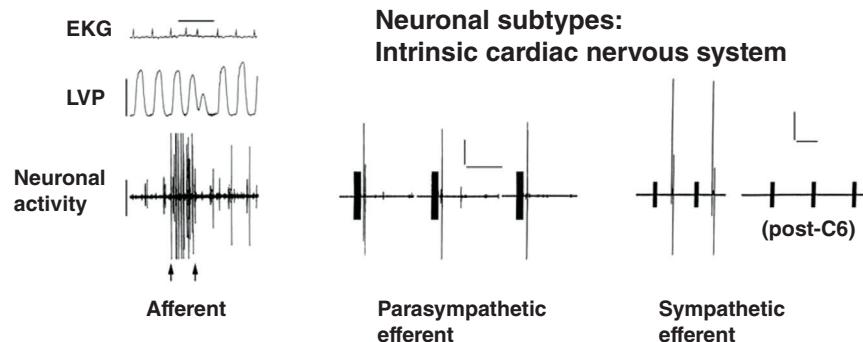


Figure 2 Neural recordings from intrinsic cardiac ganglia. Left panel: An afferent neuron in the right atrial ganglionated plexus was activated by a discrete mechanical stimulus applied to the LV epicardium. In this animal, all connections to and from the ICNS to higher centers were interrupted chronically. Middle panel: Intrinsic cardiac parasympathetic efferent postganglionic neurons in an atrial ganglion respond with fix latency to low-frequency stimuli delivered to a cervical vagus. Right panel: Intrinsic cardiac neurons responded after a fixed latency to low-frequency stimuli delivered to a subclavia ansae—thereby being classified as sympathetic efferent postganglionic neurons. The latter was no longer activated following hexamethonium. Adapted from (10, 33, 34) with permission.

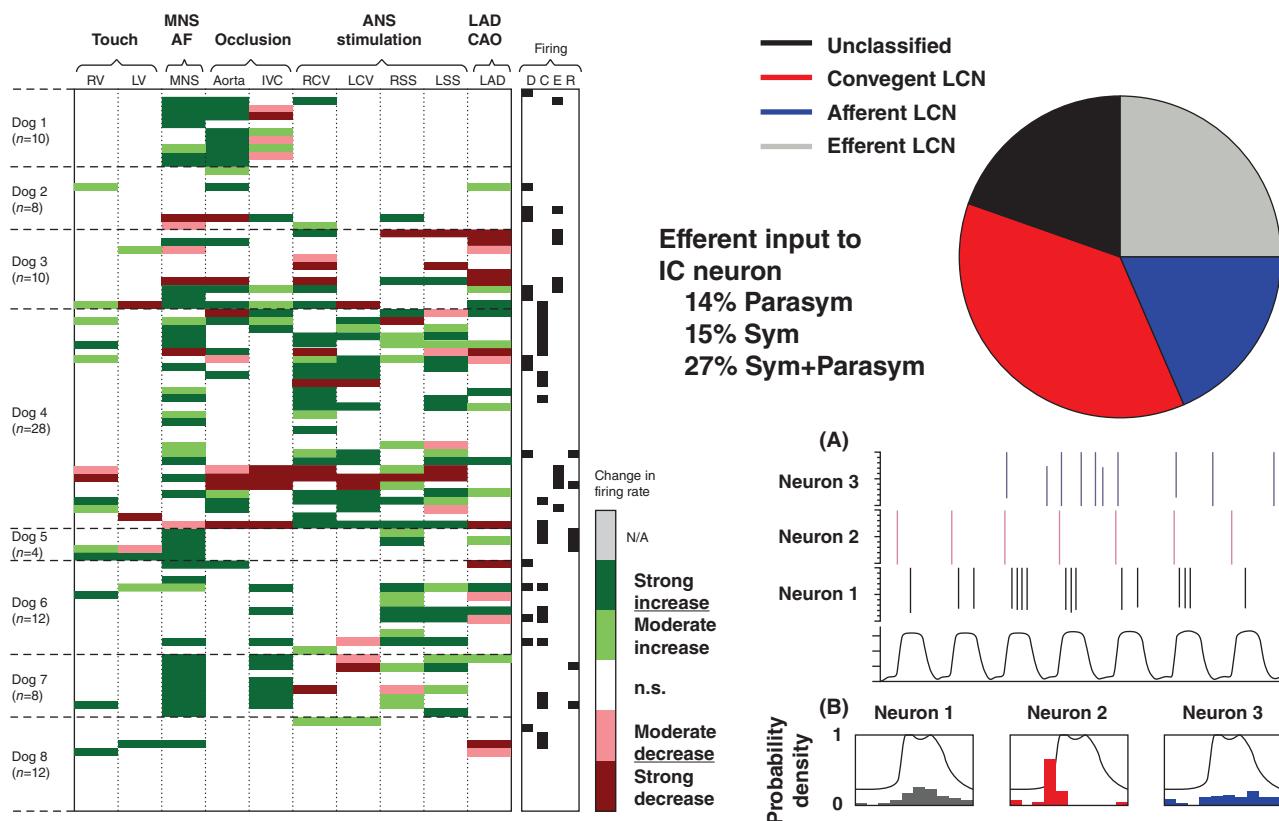


Figure 3 Functional classification of intrinsic cardiac neurons. Left panel: Neural responses evoked from intrinsic cardiac neurons in response to: (i) discrete cardiac mechanoreceptor stimuli (right or left ventricular touch: RV; LV); (ii) global activation of cardiac mechanoreceptors via transient occlusion of the (iii) inferior vena cava (IVC) or (iv) descending aorta; (v) activation of cardiac nociceptors via transient MI (LAD CAO); or (vi) low-level cervical vagal (right or left, RCV; LCV), or (vii) stellate ganglion (right or left, RSS; LSS) stimulation. Significance for each intervention was based on a Skellam distribution and was subdivided based on induced increases (green) or decreases (red) in evoked activity. IC LCN populations can be functionally subdivided into: (1) afferent LCNs, which transduce cardiac sensory information; (2) efferent LCNs or (3) convergent LCNs, which transduce both afferent and efferent inputs (pie chart, upper right). Bottom right panel illustrates the different functional characteristics of cardiac-related neuronal activity including that related to isovolumetric contraction (neuron 2), the left ventricular ejection phase (neuron 1), or neurons with activity unrelated to the cardiac cycle (neuron 3). Adapted from (46) with permission.

sympathetic efferent postganglionic neurons in ganglia located in the neck and thorax (63, 184, 185). The latter neurons are located in the superior and middle cervical ganglia, stellate ganglia, and mediastinal ganglia (19, 20, 34, 36, 131). Figure 5, left-hand panel, illustrates one such neuron which was functionally characterized within the middle cervical ganglia. Lesser numbers synapse with sympathetic efferent postganglionic neurons located throughout the major atrial and ventricular ganglionated plexuses (46, 100, 235, 248). Figure 4, bottom panels, illustrate this subpopulation of intrinsic cardiac neurons using immuno-histochemical methodologies and Figure 2, right panel, using electrophysiological techniques. In that regard, mRNA and protein enzymes involved in catecholamine biosynthesis have been associated with populations of intrinsic cardiac neurons (108, 128, 136, 195, 252). Moreover, these neural populations retain the capability to augment cardiac function even when disconnected from higher centers of the cardiac nervous system (10, 30, 178, 179). The ability to isolate and study individual intrathoracic neurons (e.g., in terms of their calcium handling and

neuromodulating pathways), as well as to dissect these ganglia and isolated heart with their connections still intact, allows for more detailed study of cardiac sympathetic (and parasympathetic) efferent regulation of the heart (167, 195). These data indicate quite clearly that peripheral ganglia are capable of complex reflex processing (10-12, 19, 20).

Sympathetic efferent postganglionic neurons in each major atrial and ventricular ganglionated plexus influence cardiac indices throughout the heart (33, 34, 64, 69, 259). Thus, when select populations of intrinsic cardiac neurons in one are activated by microliter quantities of exogenously applied chemicals like alpha- or beta-adrenoceptor agonists, heart rate as well as regional electrical and mechanical indices can be affected (25, 26). Furthermore, sympathetic efferent postganglionic neurons in each major ganglionated plexus exert control over electrical and mechanical indices throughout the atria and ventricles (64, 65, 69). That sympathetic efferent postganglionic neurons in each intrinsic cardiac ganglionated plexus regulate tissues throughout the heart assures redundancy of adrenergic control such that sufficient cardiac control persists

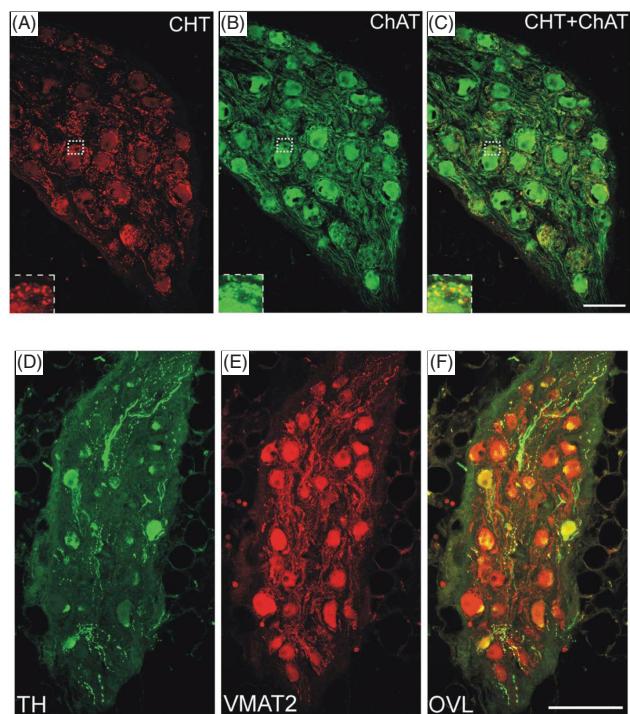


Figure 4 Neurochemical diversity in human intrinsic cardiac ganglia. Top panels: Intrinsic cardiac neurons that demonstrate the cholinergic phenotype and receive cholinergic input. (A-C) Confocal images of a ganglion that was double labeled to show high affinity choline transporter (CHT) (A) and choline acetyltransferase (ChAT) (B). Staining for CHT (A, red) was prominent in varicose nerve fibers around intrinsic cardiac neurons and faint or absent in the neuronal cell bodies. ChAT immunoreactivity (B, green) was associated with neuronal somata with less intensity in surrounding nerve processes. (C) Colocalization of CHT and ChAT was evident from the yellow color of some cell bodies and nerve processes in an overlay image (CHT+ChAT). Scale bar = 100 μ m in A-C. Bottom panels: Most intrinsic cardiac neurons stained for vesicular monoamine transporter type 2 (VMAT2), but only a subpopulation of these neurons were also tyrosine hydroxylase (TH)-positive (D-F). Confocal images of a section that was double labeled to show TH and VMAT2. (D) A few neurons and nerve fibers show TH immunoreactivity. (E) Prominent staining for VMAT2 occurred in most somata and many nerve fibers. VMAT2-positive nerve varicosities are evident around several neurons. (F) OVL of TH and VMAT2 images shows that much of the TH is colocalized (yellow) with VMAT2. Adapted from (128) with permission.

even when the function of one ganglionated plexus is compromised. The same holds true with respect to cholinergic efferent postganglionic neurons located in the various atrial and ventricular cardiac ganglionated plexi (25-27).

Cardiac parasympathetic efferent neurons

Parasympathetic efferent preganglionic soma originate within the medulla oblongata, primarily with the nucleus ambiguus with some additional contributions from somata distributed in the dorsal motor nucleus and the intermediate zone between them (105, 106, 113, 130, 133, 147, 148, 172). Although there has been the suggestion that parasympathetic efferent pre-ganglionic neurons in one medullary region (namely, NA or DMV) target efferent postganglionic neurons in select atrial

versus ventricular ganglionated plexuses that control select cardiac indices (e.g., rate vs. conduction) (85, 102, 103, 113), functionally that has not proven to be the case. That is in part because of the bilateral projections of vagal preganglionic neurons to multiple ganglionated plexi (divergence) supplemented by interganglionic connections between the aggregates of intrinsic cardiac neurons (33, 34, 46, 108, 112, 171). Thus, parasympathetic efferent preganglionic cholinergic neurons in select medullary regions or parasympathetic efferent postganglionic neurons located in each major intrinsic cardiac ganglion do not solely control select cardiac indices. Rather they exert widespread control over the various regions of the heart (10, 33, 34, 78, 100). For example, autonomic control of chronotropic function involves coordinated activities of the right atrial, posterior atrial, and dorsal atrial intrinsic cardiac ganglionated plexi (14, 99, 173, 204, 205). Moreover, even following discrete ablation of one element of the ICNS, the network adapts and functional control is restored (159). This functional anatomy has been emphasized to dispel the concept that one may ablate select neuronal populations with the presupposition that select cardiac modalities can be chronically targeted (213).

Cholinergic neurons are located throughout the various intrinsic cardiac ganglionated plexuses and project to all regions of the heart (103, 112, 171, 181, 198, 200, 223, 228, 256, 259). Figure 4, top panels, illustrates one such subpopulation of intrinsic cardiac neurons evaluated from a human (128). When these neurons are activated from their preganglionic inputs, reductions occur in atrial rate, atrial contractility, atrioventricular nodal conduction, and ventricular contractile force (13, 79, 161, 162, 257). Divergent and overlapping cardiac regional functions are controlled by neurons located in each major atrial and ventricular ganglionated plexus (26, 27). Since the first demonstration of functional parasympathetic efferent postganglionic projections to the ventricles (210), it is now well recognized that cholinergic efferent postganglionic neurons preferentially suppress ventricular endocardial contractile function, in particular that of the papillary muscles (39, 40, 209). Taken together, these data demonstrate that neurons located in atrial or ventricular ganglionated plexus (38, 45, 260) target widely distributed regions throughout the heart (64, 65, 69, 85, 259), supporting the thesis that the ICNS as a collective acts as a distributive center (9, 26, 27).

Local Circuit Neurons

LCNs subserve major processing functions within and between peripheral autonomic ganglia (9, 25, 26). By LCNs we mean neurons that are not directly transducing cardiac indices (cardiac afferent neurons) or having direct motor function. These neurons play a principal role in integrating sensory inputs from the heart and major intrathoracic vessels with descending inputs from central autonomic motor neurons (22). These neurons are located throughout all intrathoracic ganglia, including those distributed on the heart (22, 26, 46).

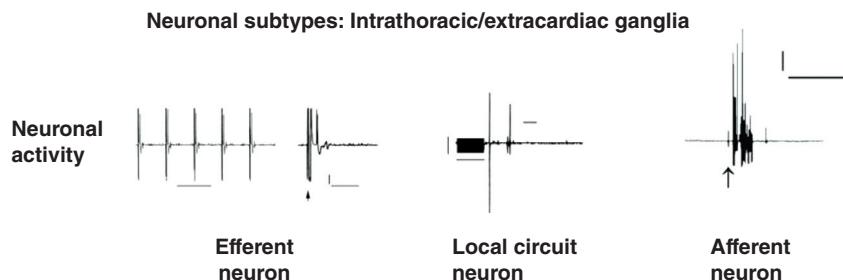


Figure 5 Neuronal recordings obtained from canine middle cervical ganglia. Efferent neurons respond with fixed latency to stimuli delivered to preganglionic axons (left panel). LCNs were only activated by trains of stimuli delivered to axons in nerves connected to their ganglia and then with variable latency (middle panel). Middle cervical ganglia afferent neurons can be activated when discrete mechanical stimuli are applied to the heart, even when disconnected from the central nervous system right panel. Adapted from (18, 20, 36) with permission.

Figures 2 and 5 (middle panels), illustrate some of their functional capabilities. Their sensory feedback, derived from the heart and intrathoracic veins and arteries, is 90% noisy and, as such, bears little correlation to cardiac indices (37, 46). Such afferent neural inputs are noisy since most sensory neurons transduce both the regional mechanical (mostly exponential transduction) and the chemical (noisy transduction) milieu (37, 149, 153). In fact, much of the information processing that occurs within intrinsic cardiac and intrathoracic extracardiac ganglia involves such local circuit neuronal populations. It is relevant to recall that intrathoracic LCNs are in constant communication with one another, even when chronically disconnected from the central nervous system (10, 17, 22, 179).

As one anatomical basis of such a concept, rosettes of relatively large diameter neuronal somata (i.e., about 30 μm) have been identified in intrathoracic extracardiac (134) and intrinsic cardiac (38, 129, 135, 179) ganglia. In such an anatomical arrangement, the majority of somata project axons centrally within the ganglion in which they are located interdigitating primarily with the axons of other neuronal somata within that ganglion. Such anatomical findings infer that many LCNs interact within one ganglion with adjacent somata (22), presumably accounting in part for the complex information processing that occurs within individual ganglionated plexuses at the level of the heart (46, 235, 248).

LCNs receive and process a variety of information. One subset of LCNs receive inputs from one or both of efferent limbs (sympathetic and parasympathetic) of the autonomic nervous system and, as such, have been defined as efferent-related LCNs (46). Others are involved in solely transducing regional cardiac, major intrathoracic vascular or the pulmonary milieus—as such these have been defined as afferent-related LCNs (10, 46). A third population integrates inputs from central sympathetic and/or parasympathetic efferent projections and afferent inputs and, as such, have been defined as convergent LCNs (46). There are other populations of intrinsic cardiac LCNs that do not receive direct or indirect inputs from central or cardiovascular afferent sensory source (22, 46), whose function to date remains unknown. Similar populations

of LCNs have been identified in intrathoracic extracardiac ganglia (22). These neural circuits, still under active investigation, are fundamental to coordinated neural control of regional cardiac function (26, 29).

Interactions among Autonomic Neurons in the Coordination of Regional Cardiac Indices

Overview

Intrathoracic ganglia have long been considered to act as centrifugal relays distributing efferent sympathetic (intrathoracic extracardiac ganglia) or parasympathetic (intrinsic cardiac ganglia) information to the heart (162). As depicted above, they also process centripetal information (26, 29). The complex functional interactions that occur among neurons within these various intrathoracic ganglia utilize excitatory and inhibitory synapses, particularly among their LCNs in the coordination of motor outflows to the heart (26, 28, 29). As schematically represented in Figure 1, afferent inputs are fundamental to the multilevel coordination of reflex action, from the intrinsic nervous system, extracardiac intrathoracic ganglia, spinal cord and brainstem, with higher centers modulating lower level cardiocentric processing (28, 29, 98).

While our understanding of such reflex processing remains incomplete, a tentative organization of the intrathoracic cardiac nervous system has been proposed in which cardiac afferent neurons influence LCNs therein which, in turn, modify autonomic efferent postganglionic neurons via multiple feedback loops—relatively short-loop reflex control (26, 29, 46, 149) (c.f., Figure 1). The varied intrathoracic reflexes transduce cardiodynamics on a beat-to-beat basis to cardiac motor neurons, even when disconnected from the CNS (10, 178, 179), employing both excitatory and inhibitory synapses (10, 17, 179). Given such varied interdependent reflex control circuits, there is a robust flexibility in meeting the constantly changing flow demands imposed by internal and external stressors.

Intrinsic cardiac neuronal interactions

Given the fact that the cardiac neuronal hierarchy acts as a distributive processor, final coordination of cardiac control resides among neurons contained within the various intrinsic cardiac ganglionated plexuses (28, 29, 150). Each major intrinsic cardiac ganglionated plexus contains a variety of neuronal somata (87, 94, 95, 128, 155, 177, 195, 228, 232, 255). Within the ICNS, anatomical and functional studies have identified subpopulations of afferent, efferent, and LCNs. There is a growing body of evidence, which indicates that intrinsic cardiac neurons utilize a variety of neurochemicals. The membrane properties of intrinsic cardiac neurons studied in tissue cultures or extirpated ganglia can be modified by nicotinic, β -adrenergic, or muscarinic agonists as well as by purine compounds or peptides (109, 136-139, 195). In accord with these findings, the *in situ* activity of intrinsic cardiac neurons can also be modified by locally applied nicotinic, muscarinic, β -adrenergic, amino acidergic, peptidergic, and purinergic agonists (16, 23, 56, 237, 259). For instance, when limited populations of intrinsic cardiac neurons are influenced by locally applied angiotensin, cardiac variables can be augmented (160). That angiotensin sensitive intrinsic cardiac neurons are involved in cardiac augmentation suggests that ACE inhibitor therapy may act, in part, to modify such neuronal function (84, 109, 119). As a corollary, β -adrenergic blockade may exert many of its beneficial effects in the setting of cardiovascular disease by targeting elements of the cardiac nervous system (116, 121, 154, 234).

Central neuronal inputs to the ICNS

The population of intrinsic cardiac neurons that receive obligatory pre- to postganglionic efferent projections is less than 15% of the total population (33, 34, 46, 100). There is a substantial population of the LCNs that responds with variable latency to such sympathetic and/or parasympathetic inputs (46). In the setting of chronic ischemic heart disease, the convergence of autonomic inputs onto LCNs may increase (203). Intrinsic cardiac neural interactions subserve critical roles in integrated autonomic control of cardiac function. The final end-organ response is dependent, in part, on: (i) end-effector pre- and postsynaptic interactions (161, 162); (ii) inter- and intraganglionic interactions within the ICNS (99, 173, 204-206); (iii) afferent-driven reflex loops (intrathoracic and central) (7, 29, 79); and (iv) and higher center inputs (74, 122-124).

Intrathoracic extracardiac reflexes

Cardiocentric reflexes depend in part upon neuronal somata located in superior cervical and intrathoracic (middle cervical, stellate, and mediastinal) sympathetic ganglia (9, 27). These intrathoracic extracardiac reflexes control, in part, adrenergic efferent neurons innervating the heart (27, 29). Such intrathoracic extracardiac reflexes receive both excitatory and

inhibitory inputs from spinal cord neurons (22) that, in particular, influence their LCNs to regulate of regional cardiac function (17, 82). The clinical relevance of these peripheral circuits are evidenced by the effective treatment of refractory ventricular tachycardia by bilateral partial stellate decentralization, a surgical procedure that leaves intrathoracic autonomic reflexes mostly intact (3, 58, 245, 247).

Central-peripheral reflex interactions in the coordination of cardiac indices

Hierarchy for cardiac control can, at its simplest, be thought of as nested feedback loops consisting of three major neuronal levels: (i) the ICNS, (ii) extracardiac intrathoracic (stellate, middle cervical, superior cervical, and mediastinal) ganglia, and (iii) the central nervous system (spinal cord, brainstem and higher centers) (6, 9, 26, 79, 93, 125, 127, 146, 171, 252). These three “functional” levels are capable of independent and interdependent reflex actions for control of cardiac motor neurons that target regional function (29).

Intrathoracic reflex circuits involve peripheral sensory, interactive, and motor neurons (16). These circuits impart a dynamic short-loop coordination of regional cardiac electrical and mechanical function (30, 235, 248). Superimposed upon these peripheral reflexes are those mediated by the central nervous system that involve spinal cord and medullary neurons, ones that are essential to coordinating cardiac function with whole body blood flow demands (29, 98, 146, 149, 265, 267). As such, in response to transducing normal physiological stressors (e.g., orthostatic stress and dynamic exercise) ongoing changes in cardiovascular afferent information engages both central and peripheral reflexes that control motor outputs to meet whole body blood flow/metabolic demands. This concept is predicated upon the fact that neuronal somata in the various intrathoracic extracardiac and intrinsic cardiac ganglia are in constant communication not only with each other, but also with neurons in the spinal cord, medulla oblongata, and higher centers in the initiation of interdependent feedback control of regional cardiac indices.

Neuraxial Transduction of Cardiac Pathology

Overview

In the presence of cardiac pathology the “plastic capacity” of this network’s function, coupled with its memory capacity, elicit differing priorities among neurons at each level within the hierarchy in a reactive attempt to maintain adequate cardiac electrical and mechanical function (26, 98). While cardiac hierarchy control readily reorganizes in response to physiological perturbations (149), it may be incapable of responding adequately to the demands of deteriorating cardiac function over longer time scales such as occurs in slowly evolving heart failure or sudden shifts in demand initiated by events such as

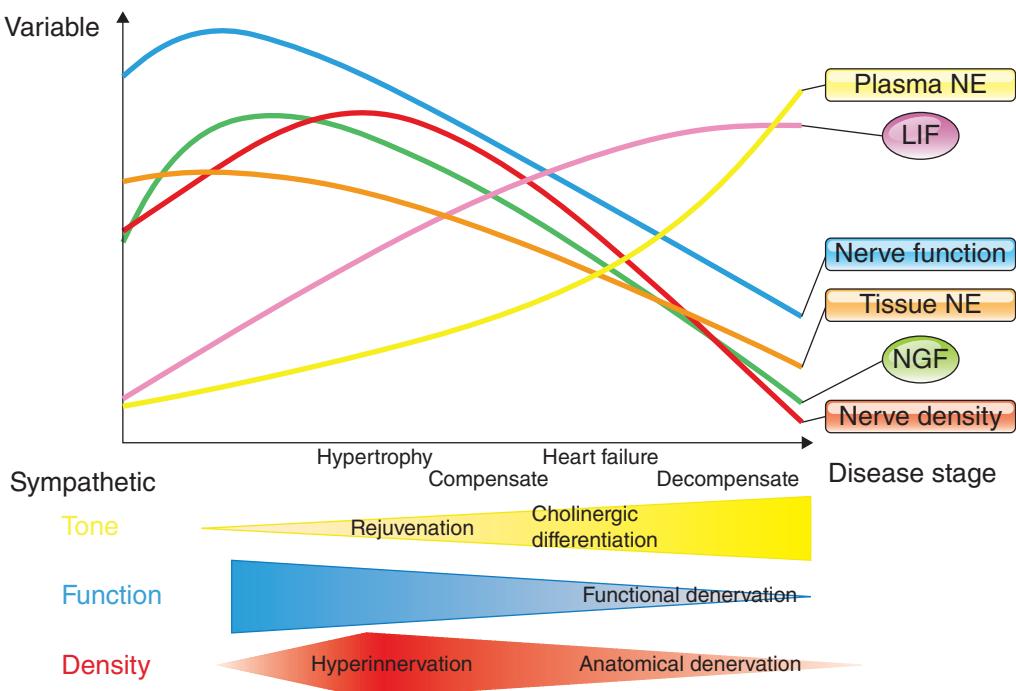


Figure 6 Temporal changes in cardiac innervation with disease progression: NE, norepinephrine; LIF, leukemia inhibitory factor; NGF, nerve growth factor. Taken from [98] with permission.

MI (89, 98, 151, 247). For instance, autonomic dysregulation can be reflective of the stochastic nature of intrinsic cardiac neuronal hyperactivity when transducing regional ventricular ischemia (43). Specifically, reactive and adaptive responses in response to sensory transduction of focal ischemia can lead to hyperexcitability in network interactions. Such dysfunction in neural processing may become manifest throughout the hierarchy—reaching from the level of the ICNS to populations in intrathoracic extracardiac ganglia, spinal cord, brainstem up to the level of the insular cortex (29). As such, autonomic dysregulation is now understood to be fundamental to the evolution of cardiac pathology (89, 98, 216, 262, 267).

Cardiac disease involves maladaptive interactions that occur not only at the level of the cardiomyocyte, but also among intrinsic cardiac and more remote extracardiac and central neurons regulating cardiac function (5, 140, 194, 227, 263). Figure 6 is a schematic of some of these principal adaptations with Figures 7-9 showing specific changes evoked in intrinsic and extracardiac intrathoracic ganglia. Alterations in leukemia inhibiting factor (LIF) and nerve growth factor (NGF) impact neuronal phenotype and innervation densities (98). Excessive sympathoexcitation coupled with withdrawal of central parasympathetic drive reorganizes pre- and postsynaptic mechanisms (5, 101, 117, 118, 167). Neuromodulators are likewise altered at multiple levels, contributing to network plasticity (5, 126, 203). Somata in the various “way stations” of the cardiac neuraxis, from level of the ICNS up to that of the insular cortex, can undergo obvious pathological changes as a consequence of their transduction of altered sensory inputs arising from cardiac pathologies

(4, 5, 44, 97, 118, 135, 157, 253, 254, 267). Such pathology alters transduction that ultimately leads to conflict among neurons located within each level of the hierarchy (151). This central-peripheral conflict is a cornerstone in the maladaptive neurohumoral response to cardiac pathology and to the evolution of cardiac disease (26, 54, 84, 98, 267).

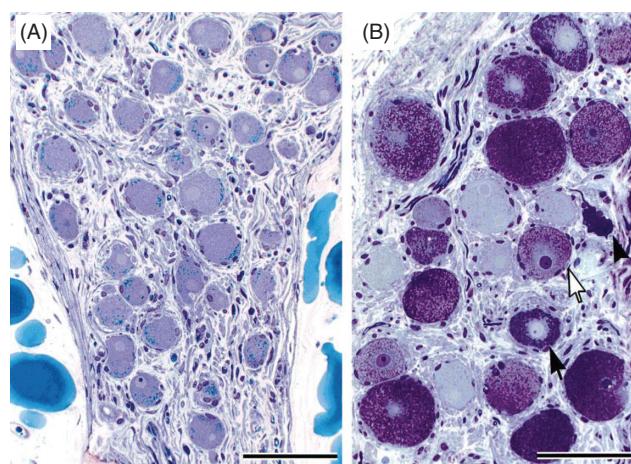


Figure 7 Photomicrographs of intrinsic cardiac ganglia obtained from the posterior right atrial ganglionated plexus from two patients with ischemic heart disease. (A) Neurons in this ganglion have a normal appearance, with many lipofuscin granules and a pale, eccentrically located nucleus. (B) In this ganglion, many neurons are enlarged and filled with dark (black arrow) or lucent (white arrow) inclusions. One neuron (arrowhead) that appears to be degenerating has very darkly stained cytoplasm and is misshapen. Scale bars: A,B = 100 μ m. Taken from (135) with permission.

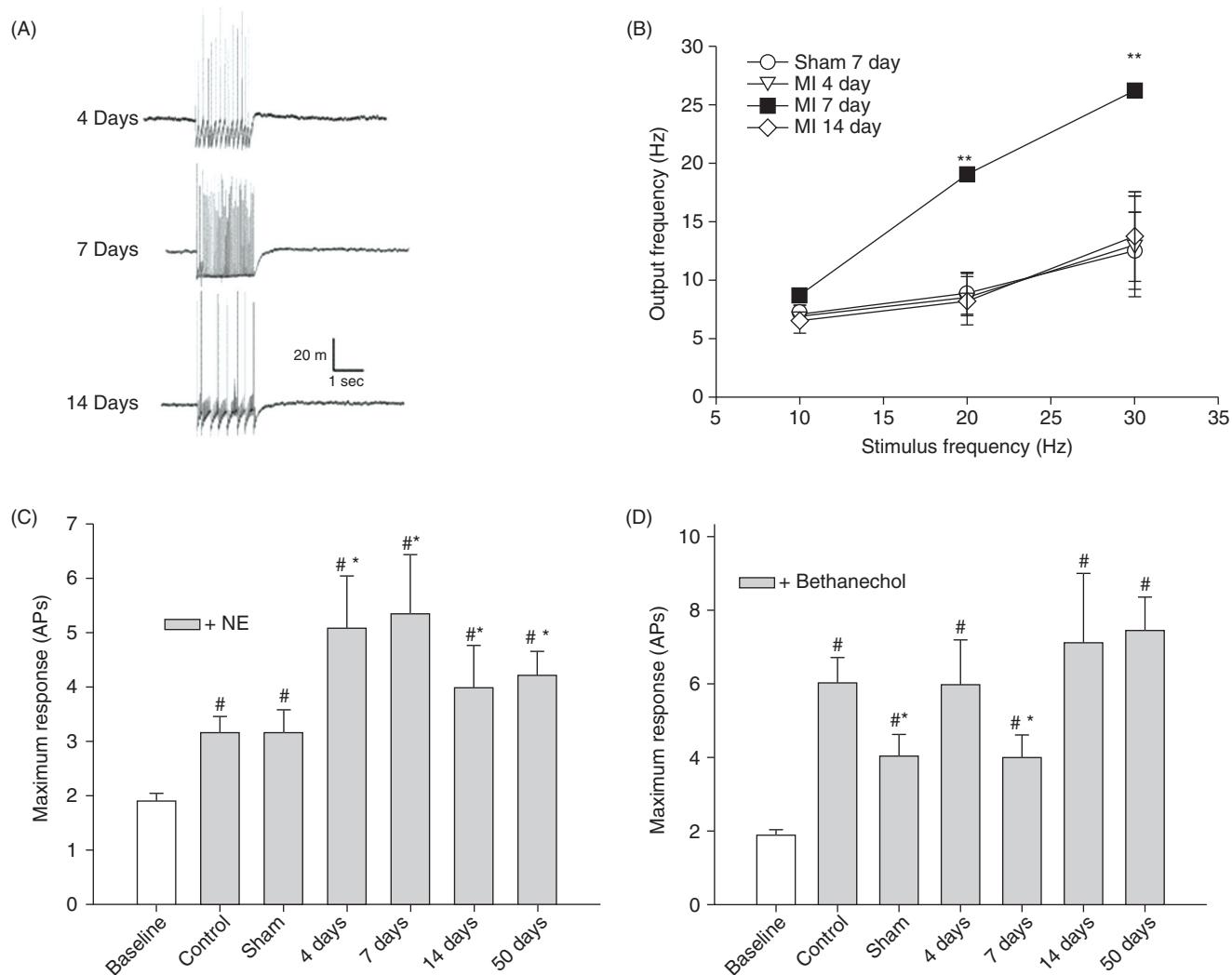


Figure 8 Chronic MI functionally remodels the ICNS. Panel A: From an *in vitro* whole mount preparation, fiber bundles synapsing with the intrinsic cardiac neurons were stimulated via an extracellular electrode. Panel B shows summary data from multiple cells, including shams. The output frequency with fiber tract stimulation was significantly greater in neurons from 7-day recovery preparations as compared with neurons from shams, 4 and 14 days recovery. Panel C: Adrenergic (norepinephrine: NE) modulation of IC neuronal excitability following MI. Excitability assessed by short-term (500 μ s) direct current intracellular injections into soma. The maximal responses (at 0.6 nA) shows a significant increase in evoked action potentials with NE application in control (NE), shams, and post-MI preparations. Panel D: Muscarinic modulation of IC neuronal excitability following MI. The maximal response (at 0.6 nA) shows significant increase in action potential generation versus baseline with bethanechol application under all conditions. The maximal responses with bethanechol application in sham preparations and at 7 days post-MI were significantly less than all other bethanechol application states. Adapted from (118) with permission.

The relevance of the cardiac neuronal hierarchy to cardiac arrhythmia induction

Autonomic dysfunction plays a significant role in the induction and maintenance of arrhythmias (31,77,98,107,213,262). Pathological stressors disrupt the cardiac neural hierarchy, sometimes with lethal consequences (5,54,76,98,101,214,217,218,225). Derangement of neural processing throughout the cardiac neuronal hierarchy in response to transducing pathologies can give rise to altered efferent neuronal outputs (24,151). Altered neural activities, coupled with changes in the cardiac electrophysiological substrate, are a primary determinant in the potential for sudden cardiac death (98).

Excessive activation of subpopulations of intrinsic cardiac neurons can initiate cardiac arrhythmias (11,41,46,54,76,108,168,221). Figure 10, panel A, illustrates this principal where focal activation of a small group of mediastinal projection fibers within the intrinsic cardiac ganglionated plexus reproducibly initiates atrial fibrillation (108). In fact, this propensity for atrial fibrillation appears to reside with excessive activation of its LCNs in both the initiation and maintenance of tachyarrhythmias (46,108). As discussed earlier, LCNs play a pivotal role in integrative control in the peripheral reflexes (26,30,171,248). As such, it has been suggested that targeting such populations therapeutically might act to stabilize information processing within the intrathoracic nervous

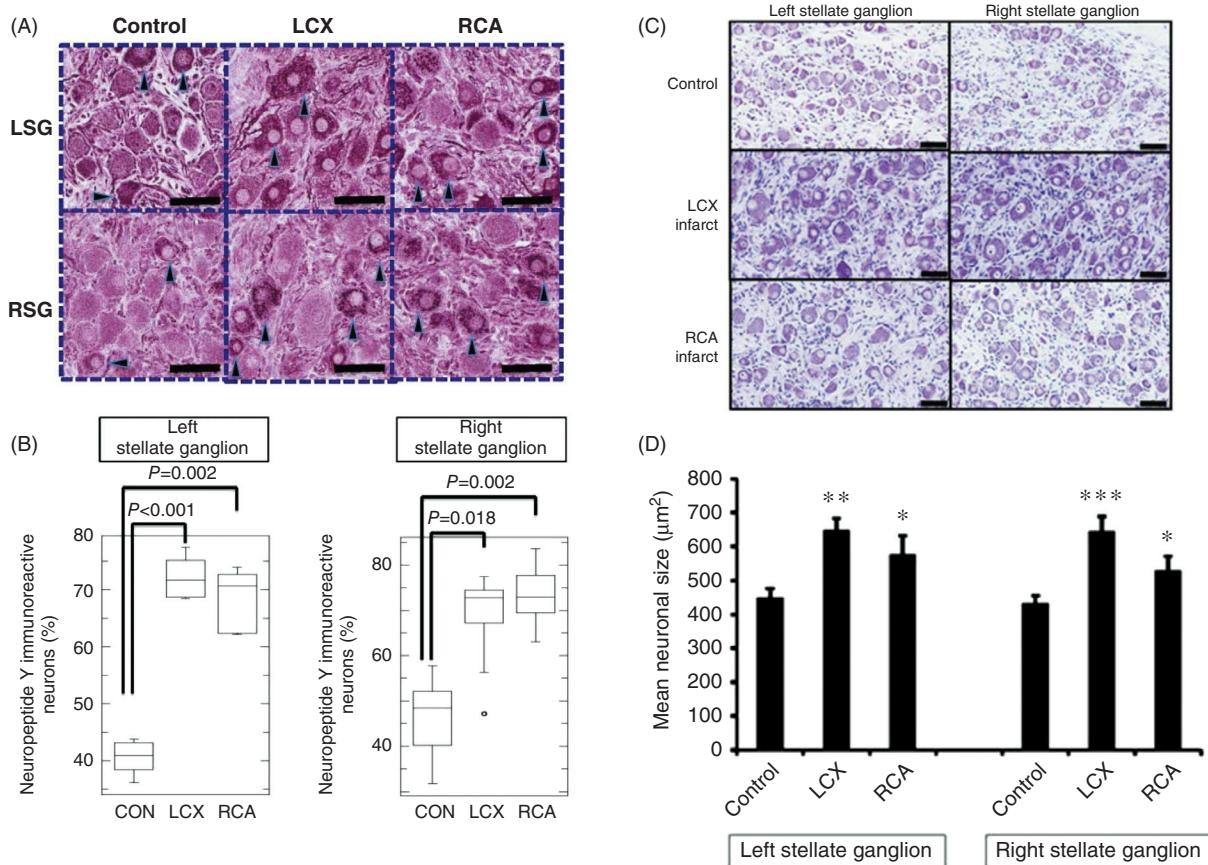


Figure 9 Chronic myocardial infarction (MI) induces bilateral changes in stellate ganglia. Panel A: Somata neuropeptide Y (NPY) immunoreactivity increased following MI in left and right stellate ganglia (LSG and RSG). Specimens obtained from control animals versus left circumflex (LCX) artery or right coronary artery (RCA) occlusions that created left and right-sided myocardial infarctions (Scale bar = 50 μm). Panel B: Quantification of NPY immunoreactivity in left and right stellate ganglia of control subjects compared to LCX and RCA infarcts. Panel C: Representative images of thionin-stained sections of right and left stellate ganglia from control animals, compared to animals with LCX or RCA induced chronic myocardial infarctions (Scale bar 50 μm). Panel D: Quantification of mean neuronal size in left and right stellate ganglia of control subjects compared to LCX and RCA infarcts are presented. Adapted from (5) with permission.

system to reduce excessive imbalance and thereby mitigate the arrhythmogenic substrate (108).

This concept of targeted neuromodulation of the cardiac nervous system has implications with respect to both atrial and ventricular arrhythmias (3, 67, 68, 164, 180, 213). With regard to autonomic regulation therapy, high thoracic spinal cord stimulation (SCS) exerts such antiarrhythmic effects (11, 67, 70, 108, 165). In Figure 10, note that SCS attenuated intrinsic cardiac neural reactivity in concert with a reduced potential for neurally induced atrial arrhythmias (108). This thesis of arrhythmia suppression is further supported by the finding that removal of the caudal portions of both stellate ganglia suppresses ventricular arrhythmia formation in humans (3, 220, 245). Correspondingly, heart transplant recipients rarely suffer ventricular tachycardia/ventricular fibrillation (VT/VF), but rather die from pulseless electrical activity or asystole (246). Taken together, such data indicate that differential targeting of select nexus points within the cardiac neuraxis may represent a novel manner with which to manage cardiac arrhythmias (77, 98, 262).

The cardiac neuronal hierarchy in heart failure

There is growing appreciation of the fact that the ICNS undergoes considerable remodeling during the evolution of heart failure (44, 117-119). In fact, in the failing heart, changes occur not only in the cardiac musculature, but also the neurohumoral control system that modulates its musculature (Fig. 6) (26, 174, 247, 263, 267). With respect to the cardiac neuronal hierarchy, in heart failure remodeling can occur at multiple levels from the ICNS (Figs. 7 and 8) (44, 51-53, 117, 118, 120, 227), to intrathoracic extracardiac neurons (Fig. 9) (5, 115, 116, 182, 234), extending up to central neural processing circuits associated with the arterial baroreflex (267). Alterations in neurohumoral control also include the renin-angiotensin-aldosterone system and circulating catecholamines (84, 174).

Altered afferent neuronal feedback to intrathoracic (ICN and stellate/middle cervical ganglion) neurons, induced by myocardial infarction, leads to remodeling of the intracardiac and intrathoracic networks of the cardiac nervous

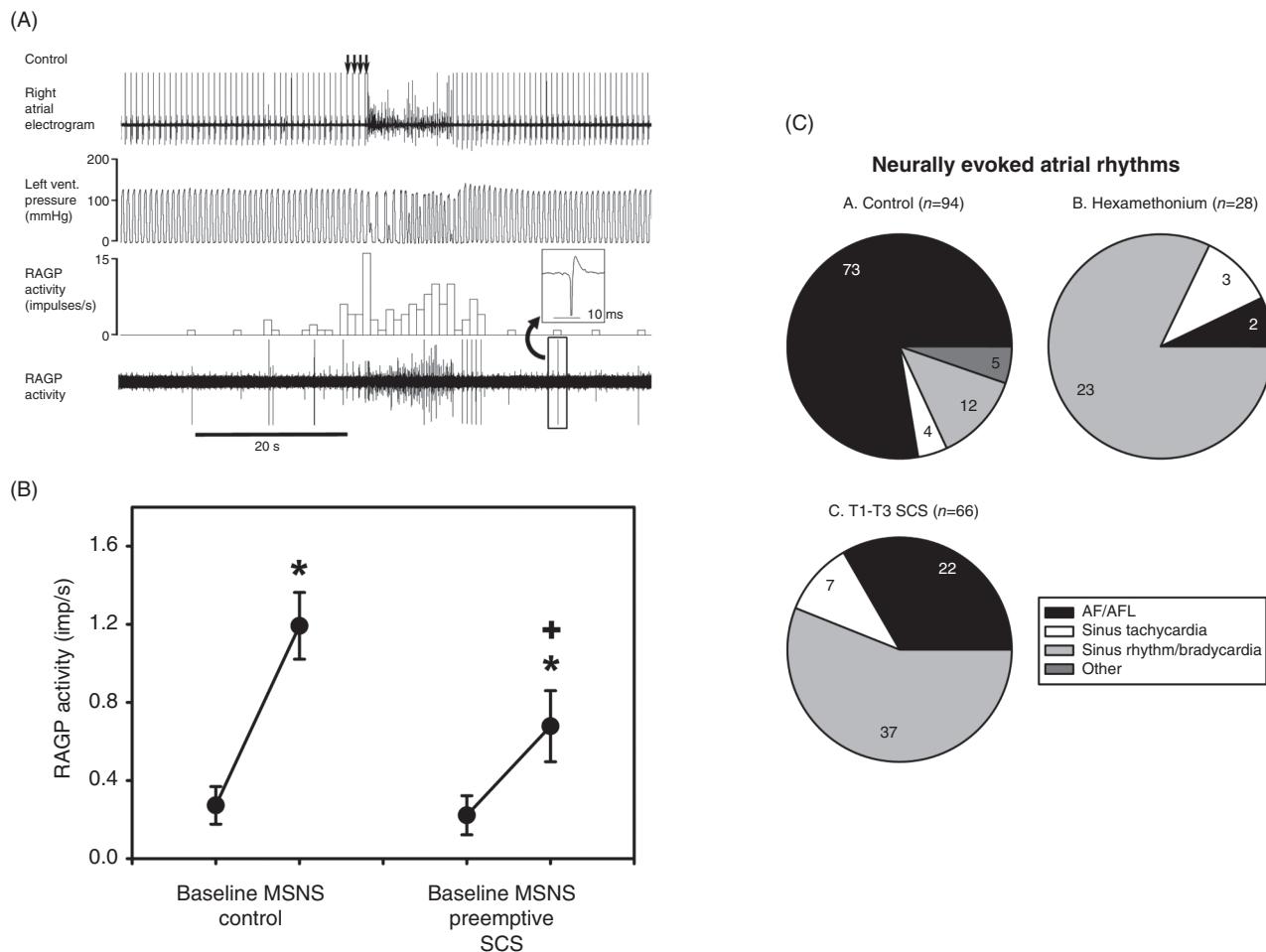


Figure 10 Bursts of electrical stimuli delivered to intracardiac mediastinal nerves (MSNS, panels A and B) reproducibly evoke transient periods of atrial fibrillation (1 s latency, duration of AF ~30 s). This methodology provides a reproducible stressor to evaluate cardiac network stability in the applications of various modes of autonomic regulation therapy (ART). Panel B: Preemptive ART with T1-T3 SCS blunted the MSNS-induced augmentation in IC neural activity, with a resultant decrease in the arrhythmogenic potential (panel C). Blockade of ganglionic nicotinic receptors with hexamethonium exerted similar suppression of neuronal activity concomitant with decreased atrial arrhythmia formation in response to MSNS. Adapted from (108) with permission.

system. Such altered afferent input involves an altered ventricular substrate produced by the infarct state (50, 80, 110, 111), efferent neural sprouting (66, 88, 101, 261), stress-induced changes in the collagen matrix (86, 243, 250), and disruptions in regional cardiac contraction (8, 176). Thus, it should be appreciated that, taken together, these lead to disruptions in central and peripheral nerve networks for cardiac control (2, 24, 26, 76, 89, 98, 267).

Emergent Neuromodulation Therapies

Therapeutic overview

The efficacy of neuromodulation therapies to reduce the potential for sudden cardiac death in response to acute MI, as well as to preserve myocyte viability in animal models in response to ischemic stress, has been demonstrated (24, 62, 98, 231, 262) (e.g., Figure 11). The efficacy of modi-

fying select populations within the cardiac neuronal hierarchy to suppress atrial (75, 108, 193, 224) or ventricular (3, 58, 145, 245, 249) arrhythmias is predicated upon the concept that the cardiac neuraxis adversely remodels in the presence of cardiac pathologies (5, 51, 53, 115, 116, 118, 135, 182, 227). It is further known that targeting the vatosympathetic complex with neuromodulation therapies retards progression into heart failure (47, 62, 73, 114, 163, 186, 212, 219, 220, 267).

From these studies, and others, it is becoming increasing evident that subsets of neurons in specific nexus points of this hierarchy can be targeted therapeutically to mitigate such pathologies. Figure 1 illustrates many of the emerging neuromodulation therapies including carotid sinus nerve stimulation (CSN) (1, 266), SCS (46, 108, 145, 165, 231, 242), vagus nerve stimulation (VNS) (47, 83, 163, 186, 202, 226), selective pharmacological modification of cardiac sensory fibers (e.g., resiniferatoxin; RTX) (249), and modulation of central-peripheral reflexes by axonal modulation therapies (AMT)

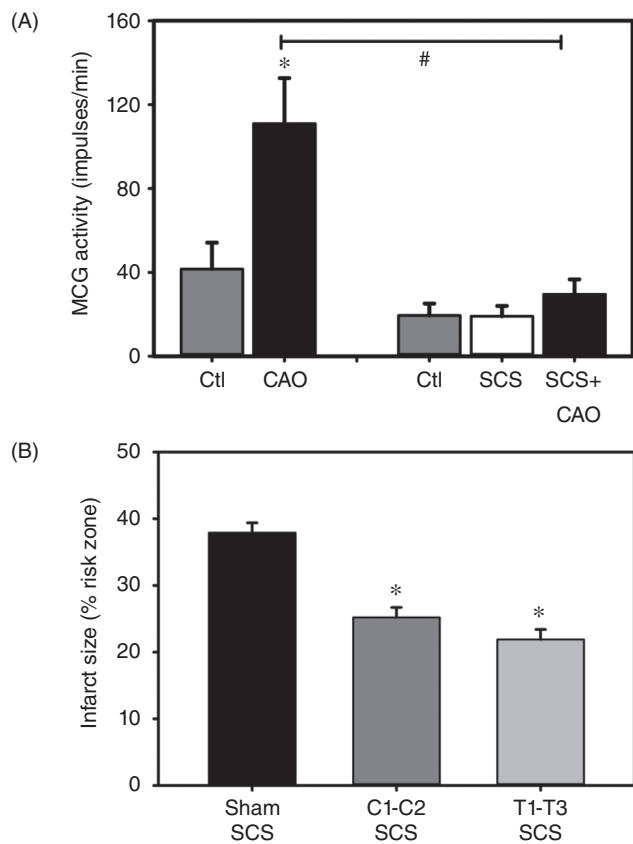


Figure 11 SCS alters peripheral autonomic reflex responses to acute ventricular ischemia, thereby exerting overall cardioprotective effects. Panel A. Coronary artery occlusion (CAO) increased middle cervical ganglia (MCG) neural activity, indicative of cardiac afferent neuron-mediated sympathoexcitation. Right columns: While SCS by itself did not change overall MCG activity, it blunted the neuronal response previously evoked by transient CAO. Adapted from (12) with permission. Panel B: Preemptive SCS delivered either to the high cervical or upper thoracic dorsal columns reduce infarct size in response to transient MI. Adapted from (230, 231) with permission.

or stellate decentralization (3, 58, 220, 245). Additional cardiovascular benefits, in the face of progressive cardiovascular pathologies, can be conferred by carotid body ablation (183, 196, 216) and renal denervation (59, 60, 211). Exercise regimens likewise can be considered as an endogenous form of autonomic regulation therapy (54), with documented efficacy to reduce mobility and mortality (48, 49).

While clinical efficacy has been demonstrated for several autonomic regulation therapies (see earlier), current bioelectric techniques for neuromodulation are relatively crude in the way in which they interact with the complex integrated hierarchical network as illustrated in Figure 1. Bioelectrical stimuli bidirectionally activate underlying efferent and afferent neuronal projections. As such, the long-term results that may be difficult to predict (1, 13, 55, 92, 257, 264). With increased understanding of neural hierarchy for cardiac control, there are substantial opportunities for refinement of site-specific autonomic regulation therapy for arrhythmia management and for treatment of heart failure.

Perspectives

This review has presented an overview of what is current in the literature with regard to the anatomic foundation of cardiac neuraxial function in normal and pathological states. What is clear is that the progression of cardiac disease involves adaptations in heart tissues and the neurohumoral systems that control them (77, 89, 98). Given the fact that many of the traditional therapies (implantable cardio-defibrillators, ablations, and drugs) have asymptoted in their efficacy (84, 89, 98, 262), neuromodulation-based approaches, that target select nexus points for cardiac control, offer unique opportunities to positively effect therapeutic outcomes via improved efficacy for cardiovascular reflex control. As such, understanding the anatomical and physiological basis for such control is necessary to effectively implement novel neuromodulation therapies.

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