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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.

Keywords

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).

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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 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, during ambulation, etc. The neuronal mechanisms underlying postural and motor components of the autonomic nervous system are in large part regulated through cortical and sub-cortical regions. One 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 fore-brain 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]. Stimulation of the motor cortex however 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 may 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. One review by Sequeira, et al summarizes efforts to further characterize how the cortical regions and the brainstem cooperate in regulation of cardiovascular autonomic reflexes [23].

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 (Figure 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 cardio-respiratory 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 one 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 horns of the upper thoracic spinal cord, which results in inhibition of preganglionic sympathetic neurons and, thus, decrease in sympathetic outflow. The NTS also directly modulates activity in the nucleus ambiguus, which receives both direct and indirect excitatory inputs from the NTS. The nucleus ambiguus contains preganglionic parasympathetic neurons that provide cardioinhibitory input to the heart and helps regulate blood pressure as well as cardiac rate and function [27, 28].

The dorsal motor nucleus, in turn, provides direct parasympathetic input to the heart. In turn, the dorsal motor nucleus' activity is modulated by the NTS through which it receives afferent input from the heart.

The interplay between the NTS, nucleus ambiguus, and dorsal motor nucleus, in concert with the peripheral components of the ANS at the level of the spinal cord, ultimately play a large role in the net balance of parasympathetic and sympathetic input to the heart [24-28]. This balance is in turn be affected by stimuli from other chemo-, thermo-, and mechano-sensitive areas elsewhere in the body as discussed later.

Non-central components of the ANS: Sympathetic chain

Much of the complex interactions that occur within the cardiac nervous system are regulated entirely outside the brainstem. In fact, the spinal cord composes a significant portion of the ANS, particularly in how data from distal organs, such as the kidneys, is received and fed back to both central and cardiac components of the sympathetic and parasympathetic nervous systems. Signals processed within the thoracic portions of the spinal cord feedback information via the paravertebral ganglia to the cervical sympathetic chain which, in turn, directly sends sympathetic stimulation to the heart (Figures 1-2). These signals are initially processed within the lateral aspect of the spinal column. Various studies have supported stimulation anywhere from the T1-2 to T5-6 regions of the spinal cord to exert direct effects on blood pressure and heart rate via the sympathetic chain ganglia.

The sympathetic chain ganglia generally consist of several ganglia arising from preganglionic sympathetic fibers that arise from the spinal cord. These ganglia include three cervical ganglia and three to four thoracic ganglia. These ganglia, receiving signals from sympathetic feedback from multiple spinal cord levels, process these signals prior to direct delivery to the heart, which in turn offers feedback to the central components of the ANS at the level of the brainstem. There is significant internal feedback both from direct inhibitory feedback from the NTS on preganglionic sympathetic neurons and the caudal ventrolateral medulla (CVLM) and stimulatory feedback from the rostral ventrolateral medulla (RVLM). These interactions have been well described in prior reviews [29-31].

Peripheral components of the ANS: Vagal components of autonomic innervation of the heart and the prevertebral ganglia

While the parasympathetic components seem simple in their distribution compared with the sympathetic components, they play a critical role in the afferent limbs mediated through the brainstem that offer direct inhibitory input to sympathetic tone. It is this interplay that allows maintenance of specific set points in blood pressure and other physiologic parameters such as perspiration and heart rate.

Another portion of the ANS that may be relevant in certain cardiac disease states but may otherwise be easily ignored is the prevertebral ganglia [32-34]. The prevertebral ganglia are related to the pelvic viscera. When nerves exit the spinal cord, they continue through the ventral rami and then go through the white rami communicans of the paravertebral body. However, while in the thoracic and cervical spinal cord they will then continue to their target organs, in the pelvic region they continue through splanchnic nerves to a prevertebral ganglion located proximal to the target organ where they synapse on a postganglionic neuron and then finally send postganglionic fibers to the organ. These ganglia provide both efferent and afferent information which, in turn, can provide feedback back to the cervical and thoracic sympathetic chain and, in turn, directly affect cardiac and vascular responsiveness. These ganglia play a major role in normal responsiveness to physiologic stimuli, including micturition, decrease or increase in renal blood flow, and digestion, and thus correlate with the typical physiologic responses associated with any of these situations [35, 36]. Diminishing neuronal responsiveness to these organs may attenuate normal sympathetic responses while increasing responsiveness may increase sympathetic tone.

The Cardiac Plexus

One important feature of how all of the afore-mentioned components exert control on the heart lies in how they directly innervate the heart. Generally, parasympathetic input to the heart largely arises from the vagus nerve and sympathetic components arise from several extrathoracic nerves including at least 4 right-sided (stellate cardiac (sometimes also referred to as the right interganglionic nerve), craniovagal, caudovagal, and recurrent cardiac) and 3-left sided (innominate, ventromedial, and ventrolateral) nerves. Nomenclature may vary but the route of innervation to the heart tends to be fairly consistent and is defined by the cardiac plexus which is found at the base of the heart and comprises how these various sources of neuronal input get to the heart [37, 38]. The cardiac plexus is generally divided into a superficial and deep portion. The superficial portion lies beneath the aortic arch, just in front of the right pulmonary artery, and is formed by the superior branches of the left sympathetic nerves and the lower superior cervical branches of the left vagus nerve. The superficial portion, in most patients, has a ganglion located at the junction of these nerves termed the cardiac ganglion of Wrisberg which is generally located just below the aortic arch, just right of the ligamentum arteriosum. The critical importance of this ganglion lies in that it reflects a junction point from which several major branches arise, including: 1) a branch that passes behind the pulmonary artery to the back of the heart and follows the left coronary artery; 2) a branch to the anterior pulmonary plexus; and 3) a branch which passes behind the aorta just anterior to the pulmonary artery and runs with the right coronary artery to the anterior portion of the heart. This ganglion may not reflect a true ganglion but rather a swelling

point / junction point prior to the division of the superficial plexus into several branches. Its importance may lie in offering a fixed anatomical point for targeted therapy in patients [39].

The deep cardiac plexus lies in front of the tracheal bifurcation behind the aortic arch and is formed by cardiac nerves arising from the cervical ganglia of the sympathetic trunk and cardiac branches off the vagus and recurrent laryngeal nerves. Thus, this plexus tends to have both left and right sided input. Essentially, the deep cardiac plexus receives all neuronal input not contained within the superficial plexus. The deep plexus then divides into a right and a left half. Branches from the right half run both anterior and posterior to the right pulmonary artery and form most of the anterior coronary plexus, with some fibers also going to the right atrium and posterior coronary plexus. The left half, in turn, connects back with the superficial cardiac plexus and gives branches to the left atrium and portions of the anterior pulmonary plexus, but generally forms most of the posterior coronary plexus [39]. In terms of nomenclature, the coronary plexus refers to portions of the intrinsic cardiac nervous system that supplies a region that runs in line with the course of the left and right coronary arteries and the pulmonary plexus supplies the region of the pulmonary artery and right ventricular outflow tract. It needs to be noted, however that the cardiac plexus and its divisions tend to be more complex with a lot of potential diversity between patients [40].

From an electrophysiologic perspective, the right sided nerves tend to supply the sinoatrial node while the left sided nerves tend to supply the atrioventricular node. In addition, there can be a marked difference in effect on ventricular refractoriness depending on stimulation of the left versus right sided system, with stimulation of the left shortening refractoriness of the posterior ventricle while that of the right shortening refractoriness of the anterior ventricle [41, 42]. However, due to the extensive cross-over as well and studies have shown that this functional distribution is not so simple or clear-cut [43]. Also, there is additional cross-over that exists at the level of the epicardial cardiac ganglia (discussed below).

Direct cardiac innervation: Pericardiac ganglia and their anatomic relationships

At the level of the heart, extrinsic neuronal inputs either directly innervate myocardium (in the case of postganglionic nerves) or interface at the level of the cardiac ganglia (in the case of preganglionic nerves). Generally, parasympathetic and sympathetic nerve endings that are preganglionic need to first synapse in a cardiac ganglion. These ganglia then act as nerve centers that respond to both parasympathetic and sympathetic feedback when controlling net neuronal output and also provide feedback to one another. They are capable of even creating their own local stimuli independent of the extrinsic cardiac nervous system and thus altering cardiac function independent of the rest of the ANS [44].

The ganglia are largely distributed around the epicardial aspect of the atrium but also occur at major branch points of the coronary arteries on the ventricular side (Figure 3). Not only do these ganglia provide direct inputs to myocytes but also link between one another, offering a complex system within which the heart has some intrinsic feedback control. Despite being under active study for over a century, the exact anatomic and physiologic relevance of the cardiac ganglia remains under active study. The cross-linking and distribution of the cardiac ganglia have been well described in prior reviews [45-47]. The total estimate of the number of neurons ranges from 14,000 to 94,000 with the total number

of epicardial ganglia ranging from 700 to 1500 [45, 46, 48]. Interestingly, the total number of neurons has been suggested to decrease by as much as 50% with age and can similarly be affected by regional ischemia [49, 50]. These neurons do generate spontaneous activity that can be recorded using extracellular electrode. As a result, electrophysiologic methods for locating epicardial ganglia during endocardial mapping have been proposed though the accuracy of these methods is not clear [51, 52].

The cardiac ganglia are mostly encased by epicardial fat within the pericardial space and tend to coalesce in specific locations as demonstrated in Figure 2. Interestingly, different groups of ganglia have different courses of innervation throughout the heart. Thus, one can choose to define these ganglia by either their functional significance or anatomic location. In anatomic terms, the ganglia can be divided into the retro-atrial (along the posterior portion of the left and right atria), annular-ventricular (around the junction between the atria and ventricles in the area of the mitral and tricuspid annulus), and peri-great vessel (around the LVOT/aorta and RVOT/pulmonary trunks). Anatomic location of these different groups is important when considering how to access them for epicardial modulation, e.g. the oblique sinus offers access to the retro-atrial ganglia while the transverse sinus offers access to the peri-great vessel ganglia [53].

The functional distribution of atrial ganglia has generally been done by dividing their preferential input to the sinoatrial versus atrioventricular nodes, with the sinoatrial ganglia mainly consisting of those inferior and posterior to the sinoatrial node, extending from the right pulmonary veins to the sulcus terminalis, and the atrioventricular ganglia mainly consisting of those in and near the interatrial groove and at the coronary sulcus junction. However, there is crosslinking between ganglia such that ganglia that preferentially affect the sinus node may also have innervation to the atrioventricular node, and vice versa. This cross-modulation from unidirectional and bidirectional feedback makes study difficult due to the multiple levels of complexity [54]. Prior reviews have focused on how the intrinsic cardiac nervous system is integrated and is beyond the scope of this review but well summarized elsewhere [55, 56]. In addition it is important to understand the cardio-cardiac and vascular-cardiac reflexes which reflect dynamic ways by which mechanical activation of the heart and major vessels exert influence on cardiac nerves. These reflexes have been recognized since the 1970s and were well-described previously [57, 58].

While most modern work has focused on the atrial ganglia, much less is understood about the ventricular ganglia and their function in controlling cardiac electrical and physiologic function. There is a possibility these ganglia play a role in nerve sprouting which in turn correlates with ventricular arrhythmogenesis after prior myocardial infarction. However, their anatomic and physiologic relevance is still less well understood.

Direct cardiac innervation: Cardiac sensory afferents and related ganglia

Cardiac sensory afferent fibers have been long recognized to play a critical role in the regulation of cardiac function [59-61]. These afferent fibers generally run along with the sympathetic nerves supplying the heart. These fibers have been implicated in cardiac pain and reactions during myocardial ischemia which, in turn, result in activation of autonomic pathways (e.g. the Bezold-Jarisch reflex) [62]. The interplay between the dorsal root ganglia

and cardiac sensory afferents, and how these interplay to exert reflex feedback upon the heart and blood vessels is beyond the scope of this review and well described elsewhere [59-62].

Clinical Correlates

Arrhythmogenesis

The role of the autonomic nervous system in arrhythmogenesis has been well described. Specific disease states in which advances in understanding of the autonomic nervous system have contributed to novel therapeutic targets include atrial fibrillation, ventricular arrhythmias, and inappropriate sinus tachycardia (we will focus on the first of these two in this review). Part of the reason for the increased tendency towards arrhythmias in certain patients may relate to remodeling of the autonomic nervous system (including nerve sprouting into border zones around areas of infarction, increases in synaptic density within the stellate ganglia, and neuronal hypertrophy leading to both increased and heterogeneous sympathetic activation) that may occur secondary to various cardiac disease states (e.g. heart failure, infarction, etc) [63-67]. These principles that the autonomic nervous system may not be a “fixed” structure is lent credence by the concept of reinnervation seen in patients after heart transplant. Further study is required to better understand how autonomic remodeling contributes to arrhythmogenesis, and more relevantly how this remodeling may be targeted to either reduce risk of or target arrhythmias.

Atrial fibrillation—The mechanism by which the ANS contributes to the pathogenesis of atrial fibrillation has been a major focus of study in the past decade. Part of the basis for this focus is the observation that in denervated hearts (such as after orthotopic heart transplant) there tends to be much less atrial fibrillation [68]. In turn, part of the theory behind which pulmonary vein isolation is an effective ablation technique for atrial fibrillation lies in that the act of isolating the pulmonary veins also leads to partial autonomic denervation. This may be due in part to the relatively high density of nerve endings occurring at the junction of the pulmonary veins and left atrium [69]. Trials have also focused on the potential role of targeted autonomic ganglia ablation on the incidence of atrial fibrillation, with data suggesting that there can be some benefit in this approach [70]. However, data is continuing to evolve about what exact role the ganglia play and which ones may play the most significant roles [71-73].

Part of the theory behind which autonomic ganglia may play a role in atrial fibrillation has to do with the known effects of ganglion stimulation on the local cardiac action potential that may allow for net electrical dispersion and a resultant greater tendency to fibrillate. However, whether this reflects a primary imbalance within the ANS supply to the heart or the underlying tendency of the atria to fibrillate is unclear. Both “sympathetic” and “vagal” types of atrial fibrillation have been postulated over the years, and it is possible that ganglia modulation/ablation may prove of utility in only certain subtypes of atrial fibrillation. Thus, further study is required to understand the direct effects of targeted ganglia modification/ablation.

Part of the limitation in our understanding has been the difficulty in identifying ways to primarily target the ganglia without also injuring the underlying myocardium. Even identification of the ganglia in a minimally invasive way has proven difficult, with mostly surrogate markers used to correlate with proximity to a ganglion. For example, authors have suggested using complex fractionated electrograms or looking for an autonomic response to high frequency stimulation as a marker of being close to a ganglion. However, given these ganglia are epicardial and often encased in fat, these can at best be thought of as surrogate markers. Newer data from our lab suggests that it may be possible to directly affect ganglia via an epicardial approach using different energy sources and avoid affecting the underlying myocardium, but the clinical and pathologic relevance of this approach remains to be determined [74]. Furthermore, data on endocardial approaches to ganglia ablation have suggested an increased risk of developing arrhythmias including other macroreentrant atrial arrhythmias (likely secondary to need for more extensive myocardial ablation to achieve ganglia ablation with currently available technology) [75]. The value of study in this area lies in the evidence to support a potential role for ganglia modulation in treating electrophysiologic diseases such as atrial fibrillation, though definitive evidence will require means of selectively affecting the ganglia and then studying the clinical effects.

Another promising area of study in atrial fibrillation is that of modulation of extracardiac nerves without direct ablation of the ganglionated plexi. Methods of achieving this have included renal denervation, spinal cord stimulation, and vagal nerve stimulation (whether direct via invasive stimulation or non-invasively via stimulation of the auricular branch of the vagus located in the tragus) [76-80]. Much of the published work in these areas to date is limited to animal studies, though human work in renal denervation has been provocative.

Ventricular arrhythmias—Ventricular arrhythmias are often difficult to treat, particularly in patients with extensive substrate from prior infarction or other non-ischemic cause. The role of autonomic modulation in ventricular arrhythmias has been well described. Stellate ganglion block, both temporarily via injection or permanent via thoracoscopic sympathectomy, have been shown to have significant anti-arrhythmic effects in certain disease states (e.g. long QT syndrome) [81-83]. However, whether such interventions may be used for all ventricular arrhythmias or only a subset is unclear [84-86].

Interestingly, studies suggest that anti-arrhythmic effects may be achieved not just by sympathectomy at the level of the stellate but also by either renal denervation or direct spinal cord stimulation [87, 88]. This possibility is supported by the afore-mentioned complex cross-linking between peripheral, central, and cardiac components of the ANS. Thus, it is possible that a variety of treatment options may exist to achieve similar effect, with some (e.g. spinal cord stimulation) avoiding the permanent, irreversible effects of thoracic sympathectomy or renal denervation.

One as of yet little explored area, however, is what role the intrinsic cardiac nervous system plays in arrhythmogenesis. Several studies have shown that there tends to be nerve sprouting and hyperinnervation in border zones around areas of prior infarct in patients more prone to ventricular arrhythmias [89, 90]. Similarly, performing I-131 MIBG scans in these patients suggests that heterogeneity of sympathetic innervation correlates with ventricular arrhythmia

risk [91]. Animal studies have also shown that targeted ablation of these innervated areas around scar may lead to either a decrease in the rate of or inability to induce ventricular arrhythmias [92]. A better understanding of the anatomy of the intrinsic cardiac nervous system at the ventricular level, the mechanisms by which nerve sprouting and hyperinnervation occur, why they only occur in certain patients, and targeted treatment options require further study.

Heart failure

An overflow of sympathetic input to the heart in patients with heart failure has been associated with worse outcomes. In turn, there tends to be a reduced cardiac response to postganglionic sympathetic nerve stimulation in these patients [93]. The balance between these two has led to the recognition that beta-blockade is associated with improved outcomes in patients with heart failure. In turn, data has suggested that a variety of epiphenomena that may be related to an autonomic imbalance (e.g. beat to beat QT variability) may be more pronounced in patients with heart failure who are also at risk for ventricular arrhythmias [94]. Part of the reason for this altered autonomic control may be due to autonomic remodeling leading to a net increase in sympathetic outflow to the heart, via sympathetic nerve sprouting and hyperinnervation and neural hypertrophy at the level of the stellate ganglion [65-67]. Spinal cord stimulation and renal denervation has been studied to see if cardiac function can be improved by directly altering sympathetic output to the heart, though further data is still needed [95-97].

In turn, in order to counterbalance this “sympathetic overflow,” vagal stimulation has also been studied in heart failure. De Ferrari, et al. demonstrated in a multi-center, open label study on 32 patients that chronic vagal stimulation via an implantable stimulation system could result in significant improvements in NYHA class, 6-minute walk test, left ventricular ejection fraction, and left ventricular systolic volume that persisted for one year [98]. However, in this invasive study, there was a relatively high rate of serious adverse events (13/32 patients, 40.6%) with 3 deaths [98]. One small randomized clinical trial suggested that either left- or right-sided vagal nerve stimulation was both feasible and well tolerated in patients with reduced ejection fraction with similar improvements in NYHA class, 6-minute walking distance, and absolute ejection fraction [99]. However, larger trials have been inconsistent in terms of whether there is benefit in terms of cardiac remodeling or functional capacity, though quality of life measures such as NYHA class have been consistently been shown to improve with chronic vagus nerve stimulation [100]. Future technology may help improve the rate of adverse events from invasive methods of vagal nerve stimulation [101]. In turn, stimulation of the auricular branch of the vagus nerve may hold potential value as a non-invasive approach to vagal stimulation [102].

Whether or not and to what degree autonomic modulation plays a role in treatment of heart failure patients, and whether pathology at the level of the intrinsic cardiac nervous system makes outcomes worse in all heart failure patients, remains unclear and requires further study. While initial studies on spinal cord stimulation and vagal nerve stimulation appear promising, the small numbers of patients requires caution when interpreting the data. As

technology to make methods of autonomic modulation safer evolves, the opportunities for larger scale studies will likely similarly improve.

Hypertension

The story of hypertensive therapy has been the use of pharmacology to directly affect the ANS and/or the response of the vasculature to sympathetic stimuli. Medications, including beta-blockers, alpha-blockers, alpha-methyl-dopa, and others are purposed to directly alter responsiveness of vascular tone to sympathetic stimulation. However, more recently, study has been done into directly altering sympathetic tone to treat hypertension non-pharmacologically. Recently, much has been published about renal denervation as a treatment for refractory hypertension given the known role of the prevertebral ganglia in mediating net sympathetic tone [103-105]. However, data on efficacy has been mixed. Whether the variable data is a result of insufficient obliteration of the afferent components of the renal nerves versus a patient-specific aspect that has yet to be delineated is unclear.

Neurocardiogenic syncope

As a counter to treating hypertension, one recent study has evaluated the use of renal nerve stimulation to treat neurocardiogenic syncope [106, 107]. Neurocardiogenic syncope is associated with inappropriate drops in sympathetic tone in response to otherwise relative innocuous and/or unpredictable (and thus unavoidable) stimuli. Treatment, however, can be difficult. Patients may have either an excessive bradycardic or vasodilatory components from a mismatch in net parasympathetic-sympathetic tone. While the bradycardia component may be treatable with a pacemaker, excess vasodilation is more difficult to treat, particularly because medications used to raise blood pressure have limited efficacy. Madhavan, et al reported the ability to perform high frequency transvenous stimulation of the renal nerves to raise blood pressure in animals which could provide a therapy for patients with a significant vasodilatory component contributing to syncope [107]. Further work, however, is necessary to determine appropriate algorithms (e.g. whether a pacing system would be chronically active at some basal level or respond somehow to perceived changes in vascular pressure or efferent neuronal input), safety, and clinical efficacy in both the acute and chronic states before this can be assumed to be a promising treatment for neurocardiogenic syncope.

Future Research Considerations

Future research will need to focus on whether: a) specific negative effects may occur due to irreversible modulation of portions of the ANS; and b) what potential side effects may exist from active modulation of different parts of the ANS. For example, whether irreversible ablation of epicardial cardiac ganglia or renal sympathetic nerves may have long-term unexpected negative effects is unknown, especially because of how much remains to be discovered about the degree of cross-linking that occurs within the ANS. Removing a limb of that complex cross-talk may unpredictably affect other arms which may not be immediately recognized. Several ongoing clinical protocols for renal nerve denervation and spinal cord stimulation exist for treatment of everything from arrhythmias to hypertension. However, we also need better methods for studying ANS contribution to a disease process at

the level of the individual patient. It is quite possible that modulation of components of the ANS may not effectively treat hypertension, atrial fibrillation, or other conditions in all patients but only in certain patients, and thus population studies may not be sufficient to identify appropriate indications until we first determine how to properly specify the study population. Thus, any work on the innervation of the heart will require a marriage of understanding of the fundamental anatomic aspects, functional relationships throughout the ANS, and the nuances of clinical effects seen with novel therapies. It is likely that continued research will result in a fundamental evolution in our clinical definition of disease processes in terms of those that are principally autonomically mediated and those that result from other processes not as readily affected by ANS modulation.

Conclusion

The ANS comprises an elegant and complex series of interactions that directly impacts cardiovascular responses to physiologic stimuli and can play a large part in the pathogenesis of a variety of cardiac diseases. Understanding these interactions, however, may lend itself to an improved appreciation of the physiology underlying several different types of cardiac disease, ranging from arrhythmias to hypertension to syncope. In turn, recognizing at what levels one may directly affect input into the ANS may offer novel methods of regulating the ANS to treat a variety of cardiac diseases. Thus, basic, translational, and clinical research into the ANS is still needed in order to validate current and future innovations in treatment for cardiovascular diseases.

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Figure 1.

(A) Overview of critical components of the extrinsic cardiac nervous system. Shown are the prevertebral ganglia (g) at the level of the pelvic viscera, which is involved in relegating sympathetic stimuli to the lateral horns of the spinal cord. In turn, signals from the lateral horns of the spinal cord feedback via the paravertebral ganglia and back to both the right ventrolateral medulla (RVLM) and central ventrolateral medulla (CVLM) which are involved in increasing and decreasing sympathetic outflow, respectively. The dorsal motor nucleus (DMNX), nucleus tractus solitarius (NTS), and nucleus ambiguus (NA) are involved in regulating sympathetic outflow (via the NTS interfacing on the lateral horns of the spinal cord and CVLM) and parasympathetic outflow directly to the heart (via the vagus nerve). Afferent input from the heart feeds back to the NTS as well. (B) Shown are the differences in where the synaptic versus parasympathetic input to the heart synapses. Specifically, sympathetic fibers synapse within ganglia located in the spinal cord, sending post-synaptic fibers to the heart, while parasympathetic fibers synapse within ganglia located on the surface of the heart and around the great vessels.

Figure 2.

Shown is a general overview of how efferent and afferent innervation of the heart occurs. Please note afferent inputs that run back to the nucleus tractus solitarius (dotted blue line arising from the heart). Also shown are how afferent and efferent data interfaces between the lateral aspects of the spinal cord, the prevertebral ganglia, the paravertebral ganglia, the brainstem, and the heart.

Figure 3.

Diagram showing the complex course of cardiac innervation around the heart. Each abbreviation corresponds with a ganglionated plexus with the arrows delineating the direction of outflow of neuronal activity. DRA = dorsal right atrial. VRA = ventral right atrial. RC = right coronary. LC = left coronary. LD = left dorsal. VLA = ventral left atrial. MD = medial dorsal. Note how there is often flow in parallel between ganglia and directly between ganglia resulting in extensive cross-talk.

Figure 4.

Shown is an anatomical picture of the neural innervation of the left atrium. Note the dense nerve endings located at the junction of the pulmonary veins with the atrium. LSPV = left superior pulmonary vein. LIPV = left inferior pulmonary vein. RSPV = right superior pulmonary vein. RIPV = right inferior pulmonary vein. DRA = dorsal right atrium. Reproduced with permission from Vaitkevicius, et al. [30]