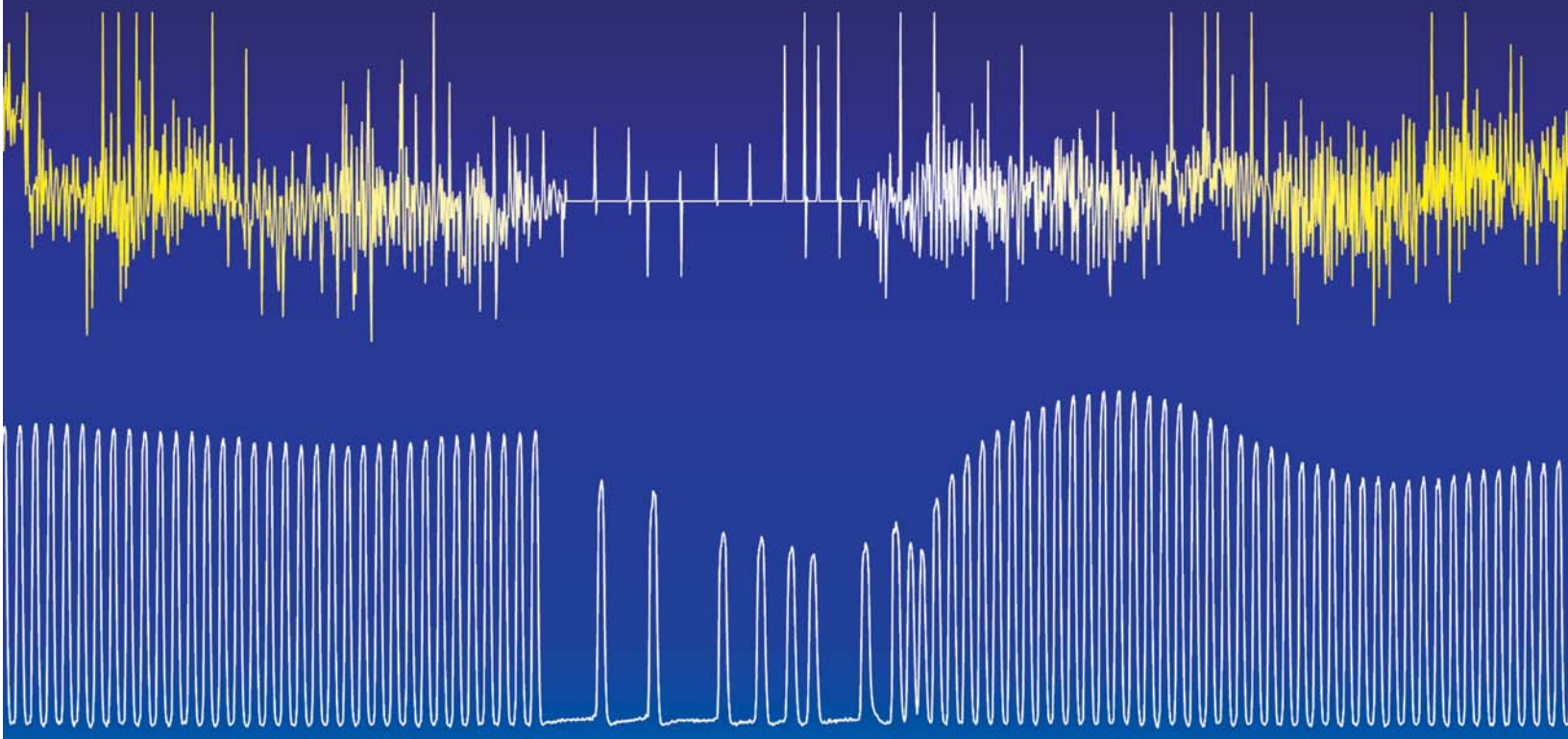
Neurocardiology

Anatomical and Functional Principles



J. Andrew Armour, M.D., Ph.D.
University of Montreal

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14700 West Park Ave., Boulder Creek, California 95006
831-338-8500
info@heartmath.org
http://www.heartmath.org

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Cover design by Sandy Royall

Cover graphic shows the activity of an afferent neuron within the intrinsic cardiac nervous sytem (top) and left ventricular pressure (bottom) simultaneously recorded from a canine heart *in situ.*

Neurocardiology—Anatomical and Functional Principles

J. Andrew Armour, M.D., Ph.D.

The dominant force in the whole body is that guiding principle which we term mind or intellect. This is firmly lodged in the midregion of the breast. Here is the place where fear and alarm pulsate. Here is felt the caressing touch of joy. Here, then, is the seat of the intellect and the mind.

—Lucretius, *On the Nature of Things, Book III* (circa 55 B.C.)

THE ISSUE AT HAND

People's ability to maintain their mental, emotional, and physical well-being is under constant stress. Our dependency on health providers, particularly formal health care practitioners, is placing an increasingly heavy burden on health care budgets. The enormous financial implications of this dependence come not only from the direct burden of health care costs, but also the massive loss of revenue to industry due to work absence and poor performance.[1]

The main reason this burden is increasing is that the ability of many people to cope with daily stressors is being overwhelmed. Exposure to stress for relatively long periods of time results in prolonged activation of the sympathetic nervous system, which, in turn, can lead to a variety of pathologies.[2-7] One frequently encountered pathological state is altered cardiac function, which can culminate in events such as sudden cardiac death.[8] In fact, a recent United Nations World Bank study identified heart disease as the leading cause of death throughout the world, even in financially underdeveloped regions.[9] The incidence of ischemic heart disease is especially high among lower socioeconomic groups.[10]

One of the earliest documented reports relating stress to heart disease was published in 1798 by Dr. Everard Holm, describing the medical condition of his brother-in-law, Dr. John Hunter. Holm reported that Hunter's pain, arising as a consequence of his heart disease, was usually initiated when his mind was "irritated." Holm described how during an upsetting discussion at a medical board meeting Dr. Hunter withheld "his sentiments" and, as a consequence, fell into a "state of restraint" from which he did not recover as he dropped down dead.[11] The autopsy that Dr. Holm performed on Dr. Hunter's body indicated that his coronary arteries were "bony tubes," hardened by local calcification. This first informed opinion of the neuronal origin of cardiac pain (angina) and its association with coronary artery disease has stood the test of time.[12] However, most physicians have tended to focus on the plumbing aspect of cardiovascular disease. Neuronal mechanisms involved in heart disease have received scant attention.

It is only recently that the neurocardiological aspects of heart disease have been considered anew.[2, 4, 13, 14] The reemergence of ***neurocardiology***, as the field is now called, has been driven by an increased amount of evidence demonstrating that complex and synergistic interactions occur between neurons in the heart and those in the brain. For example, there has been a tendency to assume that the brain is the primary source of neuronal input controlling the rhythmic activity of the heart. Although brain (central) neurons certainly are involved in cardiac rhythmicity, equally important are afferent neuronal signals arising from the heart that affect neurons not only in the central nervous system, but also in ganglia located in the thorax and in the heart itself.

The fact that the heart effectively possesses its own "***little brain***" has major implications with respect to neuronal interactions involved in regulating cardiac function. It has become clear in recent years that a

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Address for correspondence: HeartMath Research Center, Institute of HeartMath, 14700 West Park Avenue, Boulder Creek, CA 95006. Phone: 831.338.8500, Fax: 831.338.1182, Email: info@heartmath.org. Institute of HeartMath web site: www.heartmath.org.

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sophisticated two-way communication occurs between the heart and brain, with each influencing the other's function. Interestingly, immunologists and gastroenterologists have come to the same conclusion about the immune system and the gut.[15, 16] This paper focuses on the communication between heart and brain in the maintenance of adequate cardiac function.

General Principles Regarding the Autonomic Nervous System

Everyone understands the importance of the central nervous system because it regulates our interactions with our external environment. Neurons located centrally in the brain and spinal column process information arising from our external environment via our eyes, ears, skin touch receptors, temperature sensors, proprioceptive organs (joint changes), etc. The result of central processing of this type of sensory (afferent) information is the execution of body motion by motor (efferent) neurons that regulate the muscles of our limbs, face, etc. Since much of the information that flows in this sensory-motor nervous system ***can*** be under the control of our conscious awareness, it is amenable to memory. Much of what we experience in "life" is dependent on our conscious experience and memory of the external environment as perceived by our sensory system and interacted with by our motor system, all controlled by our central nervous system (CNS).

The nervous system devoted to regulating our internal environment is the autonomic nervous system (ANS). This nervous system has been assumed to be independent of reason, beneath consciousness, functioning in an ***autonomous*** fashion. It acts to maintain our internal environment by coordinating the functions of various internal organs, including the cardiovascular system, the immune system, the digestive tract, and the urogenital tract (including urinary bladder function and reproduction). The fact that our ANS rarely impinges on our consciousness, however, should not be interpreted as indicating that it is "primitive" or that we can exert no conscious influence on it.

The ANS controls internal organs as well as our protective outer coat (skin) via effector (motor) neurons and circulating chemicals. Two major branches of the ANS, the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS), are recognized. The SNS is generally believed to predominate during "fight-or-flight." When major external stressors arise (***e.g.***, chased by a tiger), activation of the efferent SNS enhances cardiovascular function, increasing blood flow to limb muscles and allowing us to run away. In contrast, while relaxing after supper and digesting a meal, the PNS predominates (gastric juices flow and limb motion is at a minimum) so that blood flow is directed to digestive organs and away from other body regions, such as skeletal muscles. However, this simplistic "accelerator and brake" thesis, although applicable in some situations, does not hold true most of the time.

The ANS is, in fact, more sophisticated than merely a simple accelerator and brake. It is made up of anatomically distinct components, each of which regulates the function of one or more internal (visceral) organs. The clusters of neurons that regulate the gastrointestinal tract, heart, lungs, kidneys, and urinary bladder lie near each organ they subserve. However, functional interconnections exist between these clusters of neurons such that they form distributive networks for information exchange. For instance, neurons that control the respiratory tract communicate with neurons that control the heart. Furthermore, peripheral autonomic neurons regulate the internal environment in concert with neurons in the CNS that sense the external environment.

When all is well, the various components of the ANS associated with each major internal organ do not transfer much information to central neurons; hence, the lack of awareness of our normally functioning inner world. What else would you expect of an efficient nervous system organized to maintain your internal environment? It is when the breakdown of internal organ function occurs that we become aware of our internal environment, presumably because of the fact that neuronal information arising from a diseased organ increases to such a degree that it impinges on our consciousness.

Past Views of Our Autonomic Nervous System

Much of what we know about the ANS is based on the pioneering research of J. N. Langley, who in 1921 published his book ***The Autonomic Nervous System***, so called because he conceived of this nervous

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system as functioning outside the control of conscious will.[17] Building on the concepts developed by Gaskell,[18] he divided the ANS into major components based primarily on its anatomy. Langley identified three distinct clusterings of neurons located in the cranial (upper), thoracolumbar (middle), and sacral (lower) portions of the CNS. These project nerves to internal organs.[17] The middle component of this nervous system (thoracolumbar) makes up the bulk of what is now called the ***sympathetic*** nervous system, as it was thought to provide "sympathy" (or coordination) among the various body organs. The cranial (head) and caudal (sacral) components of this nervous system he called the ***para*sympathetic** nervous system, since its neurons project axons in nerves arising from either extreme ("para") of the sympathetic nervous system.

Remarkably, the concept of ***sympathy*** between bodily organs was first proposed by Galen of Pergamum (130–200 A.D.). He suggested that sympathy between various bodily components was made possible by an internal, ***autonomously functioning*** nervous system. Building on concepts developed by ancient philosopher scientists, Galen proposed that body sympathies are coordinated via the rows of interconnecting ganglia strung along either side of the thoracic and abdominal spine—the pre and paravertebral sympathetic chains.

Langley developed the concept of the ANS based on the anatomical differences between autonomic nerves and nerves that innervate skeletal muscles from central neurons. He noted that autonomic nerves are always interrupted by a synapse, whereas the nerves that run to skeletal muscles are direct and thus are uninterrupted. The effect of this anatomic arrangement is quite profound because it means that nerve signals to skeletal muscle arrive intact, unchanged; they perform their functions in an all-or-nothing manner. In contrast, autonomic signals to target tissues are interrupted, and therefore can be modified en route.

Langley also described two types of ganglia, or sites where neuronal interactions occurred, which he distinguished according to their anatomical locations. Ganglia of one type were located in or close to the organs they innervated, while the others were located in the thoracic and abdominal regions adjacent to the spine. The ganglia located close to the organs they innervate were supplied predominantly by parasympathetic efferent nerves from the upper (cranial) and lower (caudal) axes of the spinal cord. Sympathetic thoracolumbar nerves supplied the ganglia lying adjacent to thoracic and abdominal vertebrae.

Autonomic efferent axons are also present in cranial nerves that arise from the midbrain (***i.e.***, to the ciliary ganglion) and the brain stem (***i.e.***, the seventh, ninth, and tenth cranial nerves). The tenth cranial nerve, the ***vagus***, contains the largest autonomic (parasympathetic efferent) neuronal outflow from the brain as well as a sizable population of afferent neurons, which are connected to sensory neurites (sensors) associated with internal organs.[18] This "great wanderer" (***vaga***bond) nerve courses through the thorax into the abdomen, its axons carrying afferent information from and efferent information to various intrathoracic and abdominal organs. Through the vagus and other smaller nerves, the ANS innervates many tissues throughout the body, including muscles of piloerection (hair mobility), sweat glands, and the pupillary muscles of your eyes.

Walter B. Cannon, attempting to classify the functions of our ANS, developed six major postulates:[19]

i) The functional state of mammals is unstable and constantly subject to disturbances. Such disturbances are counteracted by bodily acts that are directed at maintaining the stability of the organism, what Cannon called ***homeostasis***.

ii) Any tendency to alter that homeostatic state is normally met with alterations in neurohumoral factors acting to maintain stability.

iii) One homeostatic agent (such as a hormone) affects a target organ in one manner, thus exerting consistent actions on its different targets (***i.e.***, displays uniformity of function).

iv) Different homeostatic agents that act in opposition to regulate the function of one organ may act in a synergistic manner (together) in the regulation of another organ.

v) The overall system that regulates the internal state of our body is made up of a number of cooperative factors, such as chemicals that reach a target organ via the circulation versus those released from local nerve endings.

vi) When one chemical alters the homeostatic state of an individual in one direction, other factors

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become operational (other chemicals are liberated) that exert opposing effects. In that manner, overall stability of the interior milieu of the individual is maintained.

E.H. Starling introduced the term ***hormone*** in his 1905 Croonian lecture to account for the fact that bloodborne (circulating) chemicals (hormones) can affect the function of internal organs. Some of the chemicals that circulate in the bloodstream affect the behavior of autonomic neurons and thereby influence the interior milieu. One of the best known of these circulating hormones is ***epinephrine***, or ***adrenaline*** if you are from England. It was so named because this hormone is produced by a gland located on top of (***epinephros***) or beside (***ad-renal***) the kidneys, depending whether you are considering animals that stand upright or walk on all four limbs.

Hans Selye, enlarging upon this thesis, elaborated a concept of general bodily adaptation in response to externally applied noxious stimuli.[20] He emphasized the importance of our neurohumoral axis when overcoming stressors.

Relevance of the Autonomic Nervous System to Disease

In recent years, a large amount of data from the field of neurocardiology has provided excellent reasons why we should revise our opinions about the relevance of the entire cardiac nervous system in mediating the effects of stress, both physical and mental, on the cardiovascular system.[13] Compelling reviews of the factors involved in the stress-induced breakdown of the human organism have been provided by the European Union Commission.[9] Epidemiological data demonstrate the accrual of escalating health costs as more and more of the population develops such stress-related illnesses.

Stresses arising from alterations in our external environment, including emotional stress derived from interpersonal relationships, have been shown to be involved in the genesis of internal organ disease. For example, there is ample evidence to suggest that stress plays an important role in the pathogenesis of gastroduodenal ulcers, high blood pressure, and sudden cardiac death.[9] The identification of "little brains" in the heart[21] and gut,[22] which are dedicated to internal self-regulation of these organs, suggests that local autonomic networks may be involved in the effects that stress exerts on these tissues.

These little brains have the capacity to process sensory information arising from an organ and to influence the efferent neuronal input to that organ. Thus, these little brains play a key role in maintaining normal organ function. Moreover, they communicate on an ongoing basis with each other while relying only minimally on input from central neurons. These local nervous systems process sensory information arising from their organs and send this information, via local circuit neurons, to other neuronal networks regulating other organs' function. In other words, these local nervous systems are capable of processing information to perform tasks relative to the demands of organ homeostasis.

The idea that peripheral autonomic ganglia function as "little brains" dates from the time of Joacque Benigne Winslow, a Swedish anatomist who worked in Paris during the eighteenth century.[23] These neuronal networks perform most of the routine tasks required to maintain organ function, thereby ensuring that the CNS is not flooded with afferent information arising from each internal organ in a normal state. Autonomic neurons interact via a virtual soup of chemicals to perform these tasks.

It is well established that external stressors, both physical and psychological, can overwhelm the ANS and compromise organ function through excessive central input. Similarly, the CNS may be overloaded when excessive (unusually high) input arises from autonomic afferent neurons associated with a diseased organ. A person's ability to perform the simplest of mental (***e.g.***, arithmetic) or physical tasks may become impaired when the CNS is flooded with afferent information (perceived as pain) arising from a diseased internal organ. This occurs, for example, when passing a kidney stone. Consciousness then becomes fixated on survival, being flooded with information about the function of that organ.

When our ANS is overwhelmed and becomes maladaptive, one organ may become the target of repeated exposure to stress.[13] Thus, repeated emotional/behavioral stress may lead to patterns of neural behavior that promote instability within the ANS, which then manifests in a specific organ. The specific diseases so induced reflect each individual's experiences

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and the response characteristics of one's ANS to repeated stimuli (stressors).

For example, once you have had pneumonia you are more susceptible to a recurrence of that disease when reexposed to the pathogen involved. The same thing may happen when considering the responsiveness of our ANS to our environment. Thus, repeated exposure to emotional or physical stress may result in repeated dysfunction of one organ through a deranged autonomic input to that organ, thereby eventually leading to pathology (*e.g.*, skin disease, gastric ulcers, or cardiac disease).

The patients whom I was fortunate enough to look after during the time that I was a general practitioner taught me that breakdown of major organ function frequently occurs secondary to repeated exposure to seemingly innocuous daily events. External environmental stressors, both physical and emotional, may bring more people to the doctor than most people realize. That the clinical presentation of a disease induced in response to repeated stressors differs among individuals, depending on the individual's response to stress, is to be expected given the fact that the capacity to train our nervous system varies among individuals. Therefore, comprehending the makeup of the internal nervous system may lead to an understanding of how to exert some degree of control over the responses provoked by external stressors.

Contrary to the views held by many investigators of the ANS, most people can exert more control over their internal environment than they imagine, particularly when confronted with significant unwanted external stressors. Our lack of confidence in such ability may be responsible, in part, for the fact that our ANS has been thought to function totally independent of conscious will.

Life-threatening diseases, such as a heart attack, heighten our awareness of information arising from internal organs, making people keenly attentive to their inner environment. At a time when humankind is expending enormous resources to understand our external environment (outer space), a coterie of scientists scattered throughout the globe is exploring communications within our internal environment. This paper reviews recent insights concerning how the ANS regulates one organ—the heart. This information is reviewed on the basis that the knowledge so generated may provide some degree of empowerment in staving off the negative consequences of maladaptation syndromes induced by exposure to repeated stressors.

NEUROCARDIOLOGY: BASIC ANATOMY AND FUNCTION

In the last ten years, evidence has accumulated for the presence of a functional ***heart brain***—first described as the "little brain on the heart."[21] From a neuroscience perspective, the nervous system within the heart, that is intrinsic to the heart, is made up of populations of neurons capable of processing information independent of extracardiac neurons (including those in the CNS).

This collection of neurons can sense alterations in the mechanical and chemical milieu of various regions throughout the heart. With every beat of the heart, changes in heart rate and regional dynamic changes are detected and transduced into neuronal impulses that are processed internally. Such information is also sent to neurons in the base of the brain via afferent axons in the vagus nerve and to the spinal column neurons via afferent axons in sympathetic nerves. This information is returned via efferent neurons controlling the heart. Furthermore, circulating hormones influence the behavior of the little brain on the heart (see figure).

One of the unique features displayed by this little brain is that it processes neuronal information arising from the rest of the body. Intrinsic cardiac local circuit neurons (interconnecting neurons) process information in order to make continuous adjustments to the neuronal outflow of the heart. Thus, this nervous system is capable of integrating information arising extrinsic to the heart via sympathetic and parasympathetic neurons and responding to input arising from sensory neurites in tissues throughout the body.[21] In addition, its neurons respond rapidly to alterations in the local milieu of the heart. The local neuronal circuitry of this "heart brain" displays short-term memory capabilities, as do collections of similar neurons in intrathoracic extracardiac ganglia.[21, 24]

Although neurons are distributed throughout the heart, they are mainly found in ganglionated plexuses

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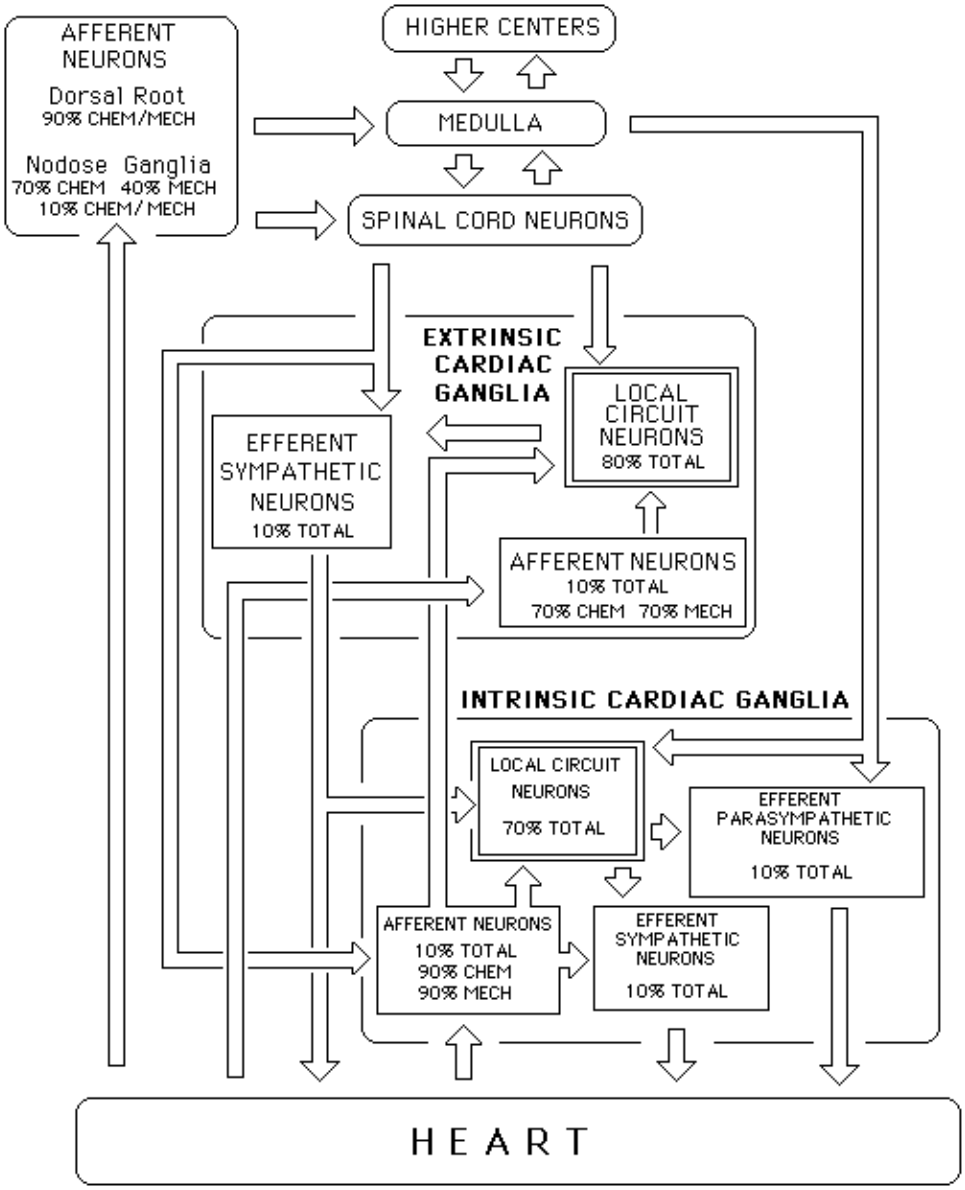
located in the fatty tissues at its base. Some of these neurons interconnect with neurons located external to the heart in intrathoracic extracardiac ganglia, as well as with central neurons. As neurons on the heart are uniquely connected to other intrathoracic neurons and central neurons (see figure), the autonomic nervous system regulating the heart is made up of a complex hierarchy of feedback loops.[21]



Schematic representation of various postulated populations of neurons in the peripheral autonomic nervous system, as well as their connectivity. Cardiac sensory (afferent) neurons are located not only in dorsal root and nodose ganglia (upper left), but also in intrinsic cardiac and other intrathoracic ganglia. These regulate sympathetic efferent neurons via the local circuit neurons. The multiple populations of autonomic neurons in various intrathoracic ganglia are in constant communication via a host of neurochemicals to maintain cardiovascular stability. Intrinsic cardiac neurons are capable of generating spontaneous activity independent of inputs from central neurons and other intrathoracic neurons. Activity generated by these neurons can be modified by both intracardiac and extracardiac afferent neuronal information. Cardiac efficiency is maximized by this complex regulatory hierarchy of nested feedback control loops that is organized in three levels of the nervous system: the intrinsic cardiac nervous system, the intrathoracic extrinsic cardiac nervous system, and the central nervous system.

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Overview of the Cardiac Nervous System

During the last decade, cardiac research has been fueled, in part, by an appreciation of the fact that neurohumoral mechanisms play an important role in the genesis of cardiac dysrhythmias (electrical disturbances of the heart) as well in the maintenance of adequate cardiac output by the failing heart. Anecdotal evidence abounds which suggests that neurohumoral mechanisms are important in the evolution of heart disease.

Much of our misunderstanding of the role that the cardiac nervous system plays arises because it has been characterized using the simplistic "brake and accelerator" model mentioned earlier: parasympathetic efferent neurons acting to suppress cardiac function and sympathetic efferent neurons enhancing cardiac function in a reciprocal fashion.

Another ill-conceived concept about the cardiac sympathetic efferent nervous system has been the proposal that neurons in the right side of your chest exert cardioprotective effects whereas left-sided ones exert deleterious effects on the heart's electrical behavior.[25, 26] This assumption has led to the removal of left stellate ganglia in patients with cardiac electrical disturbances, therapy that proved to be of questionable value since it was based on faulty anatomical and physiological logic.

A further misleading concept was the division of all humans into two groups with respect to the likelihood of developing heart disease: the so-called "Type A" versus "Type B" personalities. Suffice it to say that human responses to stressors, including psychological ones, defy simplistic categorization.

Current evidence points to a much more sophisticated picture. The complexity and redundancy of autonomic neurons involved in cardiac regulation ensures that if part of the peripheral ANS becomes compromised, limited alterations in cardiac control ensue.[21] In order to overcome previous simplistic stereotypes, the complexity of the cardiac nervous system is discussed in this overview, first in terms of its anatomy and then in terms of how its various populations of neurons interact to maintain adequate cardiac output.

The Peripheral Cardiac Nervous System

Intrathoracic ganglia have long been thought to act as simple relay stations of efferent information to intrathoracic organs.[27] That is, information flow between the CNS and an internal organ has been thought to involve one synapse between preganglionic (central) and postganglionic (peripheral) motor (efferent) neurons in both the sympathetic[28] and parasympathetic[29] nervous systems. Furthermore, cardiac parasympathetic and sympathetic efferent neurons have been thought to act in a reciprocal fashion. That is, when one population is activated the other becomes suppressed. Recently, these concepts have been challenged in view of the fact that:

i) activity generated by neurons in either efferent limb of the intrathoracic nervous system can increase or decrease together, depending on the populations of neurons studied and the circumstances when they are studied;[24, 28-31]

ii) a small population of intrinsic cardiac neurons receives inputs from both limbs of the efferent ANS;[21]

iii) sensory information arising from the heart and lungs can be processed within the intrinsic cardiac nervous system;[21, 31]

iv) intrinsic cardiac local circuit neurons synapse with other neurons on the heart as well as those located in intrathoracic extracardiac ganglia;[21]

v) the intrinsic cardiac nervous system possesses not only parasympathetic efferent postganglionic neurons, but also sympathetic efferent postganglionic neurons.[32, 33]

These concepts are based on the fact that mammalian intrathoracic ganglia, including those on the heart, possess four classes of neurons: i) afferent neurons, ii) interconnecting local circuit neurons, as well as iii) sympathetic efferent neurons, and iv) parasympathetic efferent neurons.

Afferent Neurons

The heart has a variety of sensory neurites (nerve endings) that are associated with cell bodies in nodose,[29, 34] dorsal root,[34, 35] and intrathoracic[36, 37] ganglia. It is generally thought that most cardiac afferent neurons are found in left-sided dorsal root ganglia, thus accounting for the localization of symptoms arising from heart disease to the left arm and chest. However, anatomic evidence indicates that cardiac afferent neu-

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rons are distributed relatively evenly among right- and left-sided nodose and dorsal root ganglia,[28] as well as intrinsic cardiac and intrathoracic extracardiac ganglia.[34]

Nodose ganglion neurons

One population of cardiac sensory neurons is located in nodose ganglia associated with the vagus nerves in the neck. These neurons transfer information to central neurons located at the base of the brain (nucleus tractus solitarius of the medulla oblongata). The majority of these cardiac afferent neurons sense changes in the chemical milieu of the heart and communicate this information to central neurons, while fewer transduce local cardiac mechanical alterations.

Many of these neurons sense adenosine, a chemical known to be released by the myocardium in increased quantities in the presence of myocardial ischemia.[38, 39] The activity generated by these sensory neurites can increase up to 500-fold in the presence of a compromised cardiac blood supply. Other chemicals normally liberated by the myocardium (***i.e.***, peptides such as bradykinin or substance P) also influence the sensory neurites of nodose ganglion cardiac afferent neurons.[40] At the present time, it is not known how different chemicals liberated by the ischemic heart interact to cause symptoms and/or altered cardiac reflexes. But it is widely believed that adenosine-sensitive cardiac afferent neurons play a key role in such alterations.

Dorsal root ganglion neurons

Cardiac sensory neurites capable of transducing signals from an infarcted region of the heart to spinal cord neurons are associated with afferent neurons in right and left dorsal root ganglia located adjacent to the spinal column.[34, 35] The activity that these afferent neurons generate in control states is higher (~10 Hz) than that generated by their nodose ganglion counterparts (~0.1 Hz).[40, 41] This gives them a greater ability to exert ongoing influence on central neurons in that region of the neuroaxis.

These dorsal root ganglion cardiac afferent neurons sense mechanical and chemical stimuli simultaneously. Thus, the afferent information they transfer to spinal cord neurons is multimodal in nature, depending on alterations in the local mechanical and chemical milieu of the heart. Furthermore, during myocardial ischemia, the intensity of information that these afferent neurons deliver to spinal cord neurons is an order of magnitude greater than that delivered by nodose ganglion cardiac afferent neurons.[41]

Intrathoracic afferent neurons

Anatomical and functional evidence indicates that there is yet another population of cardiac afferent neurons that is located in intrathoracic extracardiac[36, 42] and intrinsic cardiac[37, 43, 44] ganglia. This population of afferent neurons, residing outside the central nervous system, is influenced by alterations in the local mechanical and chemical milieu of the heart. Such intrathoracic afferent neurons transduce not only adenosine and peptides, but also local ischemia.[31] They modify intrathoracic local circuit neurons that, in turn, exert local reflex control over autonomic efferent postganglionic neurons that regulate regional cardiac behavior.

Efferent Neurons

The efferent neurons that exert control over each region of the heart are made up of the two major motor components, one sympathetic and one parasympathetic in nature. The chemicals that are released from their nerve terminals influence cardiac myocytes tonically.

Sympathetic efferent neurons

Sympathetic efferent preganglionic neurons in the spinal cord that are involved in cardiac regulation project axons via cranial (upper) thoracic spinal nerves on either side of the body[45] to synapse with efferent sympathetic postganglionic neurons located in all intrathoracic ganglia,[46] including those on the heart.[32, 47-49]

The sympathetic efferent postganglionic neurons located in each ganglion project axons to divergent regions of the heart, whether their ganglia are located on the heart[50] or in the rest of the thorax.[32] This redundancy of efferent neuronal input to the heart permits adequate cardiac control to be maintained if the function of one part of the intrathoracic nervous system becomes compromised.

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Parasympathetic efferent neurons

The parasympathetic efferent preganglionic neurons that are involved in cardiac regulation are located in specific regions of the medulla oblongata at the base of the brain. These cardiac neurons project axons to parasympathetic efferent postganglionic neurons on the heart[51] that are located in widely divergent atrial and ventricular ganglionated plexuses.[28, 52]

Parasympathetic neurons in each region of the heart, in turn, project their axons to myocytes throughout the heart. In other words, such neurons in each region of the heart affect cardiomyocytes everywhere, thereby providing a redundancy of function similar to that of the sympathetic efferent nervous system.[50]

Intrathoracic Local Circuit Neurons

Intrathoracic extracardiac ganglia have long been considered to act as monosynaptic relay stations distributing efferent sympathetic centrifugal information to the heart.[27, 53] However, recent evidence indicates that the peripheral cardiac nervous system also contains neurons that connect afferent and efferent neurons, which process *afferent* information arising from the heart.[36, 54-56]

The term *local circuit neuron* has been used to describe a set of neurons in the hippocampus region of the brain that project axons to multiple neurons located some distance away.[57] A significant population of neurons in the thoracic ganglia similarly project to neurons in other intrathoracic ganglia as well as to neurons in the same ganglion.[31, 46] These neurons have also been termed local circuit neurons.[21] In the hippocampus, local circuit neurons are believed to be involved in long-term memory. Similarly, some local circuit neurons in intrathoracic ganglia are involved in feed-forward regulation of regional cardiac function, a form of short-term memory that affects subsequent cardiac beats for up to 20 seconds.[36, 44]

Interactions Among Populations of Cardiac Neurons

Interactions Among Peripheral Autonomic Neurons

Information processing within the intrathoracic autonomic nervous system involves, to a large extent, local circuit neurons.[58] Most intrathoracic local circuit neurons are inactive when systemic vascular pressure is either abnormally high or low.[47, 48, 54, 55] That most intrathoracic local circuit neurons involved in cardiac regulation become quiescent during hypotension (low blood pressure) or hypertension (high blood pressure) presumably is a result of either too little or excessive input, respectively, to them.

Thus, during systemic vascular hypotension the heart would rely primarily on central neurons, as there would be a generalized reduction of the activity generated by intrathoracic local circuit neurons controlling the heart.[21] Similarly, when systemic vascular pressure increases above about 150 mm Hg, cardiac sympathetic efferent neuronal input to cardiomyocytes becomes reduced as input from various populations of intrathoracic local circuit neurons is reduced. This may occur in order to further minimize cardiac augmentation induced by excessive sympathetic efferent neuronal input.[54] The interneuronal interactions required for such complex computation presumably rely to a large extent on the relatively large population of intrathoracic local circuit neurons.[58]

Neurons in different intrathoracic ganglia that are involved in cardiac regulation receive inputs from cardiac mechanosensory and chemosensory neurites, as well as from mechanosensory neurites located on major intrathoracic vessels and in the lungs. A small population of intrathoracic extracardiac neurons is influenced by sensory neurites located on the carotid arteries in the neck as well, these being mediated via spinal cord neurons.

That different populations of intrathoracic neurons respond differently to similar cardiac events suggests that selective feedback mechanisms exist at successive hierarchical levels of the intrathoracic nervous system.[31] That neurons in different ganglia display functional dissimilarities also implies a minimal reliance of the heart on any one population of peripheral autonomic neurons.

A number of chemicals—including nicotinic, muscarinic, and adrenergic agonists; nitric oxide; endothelin; excitatory and inhibitory amino acids; peptides; and purinergic agents—affect the intrathoracic neurons that are involved in cardiac regulation.[46] In addition to excitatory synapses, there are inhibitory ones that play an important role in the peripheral autonomic nervous system,[59] particularly during its pro-

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longed activation.[60, 61] For example, inhibitory synapses may suppress the function of cardiac efferent neurons when activated excessively for relatively long periods of time,[61] as would be the case during prolonged emotional stress.

Thus, neurons within intrathoracic ganglia process afferent information arising from the heart, major intrathoracic vessels, and lungs to influence cardiac efferent neurons via multiple synapses that utilize a soup of different information substances (*cf.* above). Short (latencies of 20–200 milliseconds) and longer (up to 2 seconds) latency feedback loops exist within the intrathoracic nervous system. In this manner, the afferent information generated during one cardiac cycle influences efferent cardiac neurons via local circuit neurons not only during the same cardiac cycle, but also for the next few cardiac cycles.[24, 36]

This facility represents a form of short-term memory that permits feed-forward information to influence upcoming cardiac behavior for the next few cardiac cycles. ***That such neuronal processing occurs in the intrinsic cardiac nervous system supports the thesis that the heart's little brain can process information to make decisions about its control independent of the central nervous system.*** This is an important concept since it places much of the routine control of regional cardiac function outside the CNS.

The nested feedback control loops within the thorax, made up of neurons in intrinsic and extracardiac ganglia, rely on multiple inputs. These control circuits receive not only direct inputs from cardiopulmonary and vascular mechanosensory neurites, but also indirect multisynaptic inputs via central neurons from sensory neurites located on carotid arteries as well as tissues in the neck, thoracic wall, upper limbs, and lower limbs.[31] These extensive connections allow the heart's nervous system to respond to indirect sensory inputs from various parts of the body.[48]

Most neurons in intrinsic cardiac and intrathoracic ganglia exhibit noncoupled behavior, even when they are mutually entrained to cardiac events by cardiovascular afferent feedback.[21] This implies a redundancy of cardioregulatory control among the different populations of intrathoracic neurons devoted to cardiac regulation (see figure).

That neurons in intrinsic cardiac and intrathoracic extracardiac ganglia display functional dissimilarities implies a minimal reliance of the heart at any one time on any one population of peripheral autonomic neurons. The selective influence of each population of intrathoracic neurons on the heart likely depends on the nature and content of their cardiac sensory inputs. In agreement with this, little coherence of activity occurs among neurons located in distinct intrathoracic extracardiac and intrinsic cardiac ganglia,[31] despite the fact that many of these neurons generate activity that is transiently phase-related to the cardiac cycle.[47, 48, 54, 55]

Because such cardiac phase-related activity is of short duration (a few cardiac cycles at a time), synchronization of the activity generated by intrathoracic extracardiac and intrinsic cardiac neurons to cardiovascular dynamics rarely occurs.[46] Such an arrangement ensures the maintenance of coordinated efferent autonomic outflow to cardiomyocytes. This provides the flexibility necessary for beat-to-beat regulation of efferent outflow to the heart involving short (intrinsic cardiac ganglia), medium (middle cervical and stellate ganglia), and long (spinal cord and brain) nested feedback loops. Rather than coupled oscillators functioning within the peripheral cardiac nervous system, the nested feedback system proposed here (see figure) represents a much more robust regulatory system, the redundancy of function among its components assuring adequate autonomic tone to the heart when major components malfunction.[58] In summary, the peripheral (intrathoracic) nervous system involved in cardiac regulation represents a highly complex parallel processor of information arising from many parts of the body, including cardiopulmonary tissues.

Interactions Among Peripheral and Central Autonomic Neurons

As mentioned above, sensory neurites (sensors) located in tissues throughout the body, including major extrathoracic vessels, interact via spinal cord neurons to modulate intrathoracic efferent neurons.[31, 36, 54, 56] The fact that a population of intrinsic cardiac neurons receives indirect information from sensory neurites in the arms may explain why individuals who experience angina of cardiac origin may find some

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symptomatic relief by rubbing the skin over their elbow. On the other hand, the reverse holds true in as much as central neurons that innervate limb muscles can become excited when dorsal root ganglion cardiac afferent neurons are activated, leading to anginal pain being felt in the arm.[62] Thus, there is two-way information transfer between the heart and peripheral tissues via communication occurring among peripheral and central (spinal cord) neurons.

Many, but not all neurons located in ganglia within the chest, including those in the heart, receive inputs from spinal cord sympathetic efferent preganglionic neurons.[46, 48, 54-56] In addition, the parasympathetic efferent postganglionic neurons on the heart receive inputs from medullary neurons that are somewhat under the influence of afferent neurons associated with sensory neurites on major arteries.[24, 63] Thus, contrary to the generally held opinion that the ANS functions in a global all-or-nothing fashion, discrete cardio-cardiac and vascular-cardiac reflexes exist within the ANS that influence various regions of the heart on a beat-to-beat basis.[24]

Furthermore, a relatively small population of intrinsic cardiac neurons receives inputs from parasympathetic efferent preganglionic neurons in the medulla as well as from sympathetic efferent preganglionic neurons in the spinal cord.[47, 48] That some intrinsic cardiac neurons receive inputs from both limbs of the efferent ANS indicates the fulsome and complex nature of the cardiac nervous system.[46]

THE RELEVANCE OF THE CARDIAC NERVOUS SYSTEM

The complex interactions occurring among the various neurons located in the intrathoracic ganglia described above generally occur with relatively little input from central neurons.[58] On the other hand, minor changes in the input from specific central neurons to this peripheral cardiac nervous system can exert devastating effects on its interactions.[64, 65] Furthermore, minor alterations in a relatively small population of neurons in its intrinsic cardiac component can have devastating effects on cardiac electrical behavior.[54, 55]

Alterations in autonomic neuronal activity can lead to the genesis of cardiac diseases,[66, 67] including coronary artery arteriosclerosis[68] or arrhythmias.[32, 46] The fact that daily stress affects the heart via autonomic neurons has been well documented.[1, 13, 69-71] Hostility has been widely recognized as a risk factor with respect to the development of coronary heart disease.[4] Such recognition, coupled with the knowledge that low-cholesterol diets are not sufficient to modify the onset of heart disease,[72, 73] has led to increasing attention being paid to the role that cardiac autonomic neurons play in heart disease.[5]

Autonomic Neurons in Normal Cardiac States

Cardiac myocytes are continuously bathed by chemicals not only arising from tonically active adjacent autonomic nerve terminals but also derived from the blood.[74] Adult mammalian cardiac myocytes cultured without autonomic neurons dedifferentiate (lose their cellular organization and thus contractile properties) within a matter of weeks. Conversely, cardiomyocytes cultured in the presence of intrinsic cardiac neurons retain their anatomical and functional integrity for months.[49] These data support the view that intrinsic cardiac neurons influence cardiomyocytes continuously, thereby sustaining their normal function.[32, 43, 75]

Autonomic Neurons Influence Cardiomyocytes Tonically

It has always been taught that cardiac contractility depends primarily upon alterations in the initial length of individual cardiomyocytes. During diastole, when the ventricles are relaxed but expanding with returning venous blood, cardiomyocytes are stretched. The greater the degree of their stretch, the greater the contractile force cardiomyocytes generate. This is known as the Frank-Starling hypothesis. This hypothesis proposed that increases in ventricular myocyte contractile force are secondary to increases in diastolic stretch and that this is the primary factor accounting for increases in cardiac output. Such a hypothesis suggests that the effects of circulating hormones on cardiomyocytes in "nonstressed" states are relatively minor. Although this view may be appropriate when studying the heart outside the body or in the laboratory as isolated segments, it may have little bearing on how the heart normally behaves ***in situ***.[74]

There is a relatively inelastic layer of fibrous tissue, the pericardium, which surrounds the mamma-

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lian heart. Because of this anatomical feature, the ventricles cannot expand very much ***in situ*** on a short-term basis to accommodate increasing venous return. As a matter of fact, when the pericardial sac surrounding the heart is opened in the operating theater, the heart expands. These data imply that ventricular diastolic dimensions are constrained normally within the pericardial sac. Thus, it is unlikely that, on a short-term basis, diastolic stretching of ventricular myocytes contributes significantly to increasing cardiac output in the presence of increasing venous return. Rather, during stress states, cardiac output increases primarily because heart rate increases secondary to increased sympathetic efferent neuronal tone to the heart.[76] Increased heart rate is accompanied by greater contraction and relaxation of the ventricles, the latter facilitating ventricular cavity emptying and filling in order to keep up with increasing heart rate.[77]

In fact, cardiac sympathetic efferent neurons enhance cardiac work while reducing the size of the left ventricle at the peak of contraction and during maximal relaxation (end-systolic and end-diastolic dimensions). Thus, when the sympathetic nervous system is activated during stress, the output of the normal heart increases at a time when ventricular dimensions remain the same or even decrease.[77] Taken together, these data emphasize the importance of sympathetic efferent neuronal tone on the heart to match cardiac output with the demands of the body.

There is considerable variability of heart rate in normal states; some of this variability is associated with the respiratory cycle. Thus, if you monitor your heart rate while taking a deep breath you will notice that breathing alters heart rate. Such heart rate variability (HRV) occurs over short time intervals and reflects short-term alterations in efferent neuronal tone to atrial pacemaker cells rather than fluctuations in circulating hormones.

These short-term fluctuations in HRV occur because respiratory mechanical events alter cardiopulmonary afferent neuronal activity[41] by influencing the activity of extracardiac parasympathetic efferent neurons.[31] This respiratory-related HRV virtually disappears after the heart is autotransplanted, a condition in which all efferent input to the heart becomes severed.[64] However, the heart brain displays plasticity after cardiac transplantation. In such a state, the activity its neurons generate depends not only on rhythmic sensory inputs from cardiac mechanosensors, but also on respiratory-related inputs, as reflected by respiratory-related alterations in atrial or right ventricular dynamics.[31] Thus, although much of the variability generated by the normal heart is due to the tonic input arising from extracardiac neurons, some is dependent upon sensory information arising from cardiac mechanoreceptors that are secondarily influenced by pulmonary mechanics.

Cardiac Efferent Neurons Fine-Tune Cardiac Performance

The various regions of each ventricle display unique anatomical and functional characteristics.[78] The outflow tracts of the two ventricles, the ventricular papillary muscles, the interventricular septum, and other ventricular regions have unique neuronal innervation patterns.[79, 80] The anatomical arrangement of the muscle fascicles in each ventricular region, as well as their separate neuronal inputs, account for the capacity of each cardiac region to function in a coordinated fashion to ensure efficient cardiac output.[79, 80]

Cardiac afferent neurons display unique activity profiles too, depending on the location of their associated sensory neurites.[63] The varied content of afferent information arising from various regions of the heart that project to different populations of intrathoracic local circuit neurons and central neurons ultimately determines the activity generated by individual cardiac efferent neurons.[24] This concept implies that each region of the heart generates specific sensory information secondary to regional dynamics that is fed into the computational processor represented by the cardiac nervous system. That computational capacity permits precise efferent neuronal control over each cardiac region, ensuring as efficient a cardiac output as possible given situational demands.[24, 31, 74]

The transplanted mammalian heart represents a unique opportunity to study the intrinsic cardiac nervous system, given the fact that many intrinsic cardiac neurons maintain their function following cardiac transplantation.[81] The intrinsic cardiac nervous system does receive some inputs from extracardiac neurons within the year following transplantation. Thus, if a population of donor intrinsic cardiac neurons survives cardiac transplantation and if recipient

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extracardiac neurons sprout axons to make contact with these donor neurons, the situation arises in which a patient's centrally located neurons may be capable of influencing intrinsic cardiac neurons originating from another individual. Conversely, if afferent neurons associated with a transplanted heart sprout axons to make contact with recipient intrathoracic and central neurons, then one has a possible explanation for behavioral changes that occur in some individuals following cardiac transplantation.[82] This raises the intriguing situation of sensory neurons associated with one person's heart influencing the CNS of another individual, that of the recipient.

Autonomic Neurons in Altered Cardiac States

The cardiac nervous system is intimately involved in a number of cardiac pathologies. For example, as mentioned earlier, when enhancement of sensory information derived from cardiac afferent neurons occurs, as in the presence of myocardial ischemia (heart attack), unusually high levels of sensory input may impinge on central neurons to influence our consciousness. This may account for the genesis of symptoms such as a feeling of impending doom and/or the perception of pain. Central neuronal behavior alterations induced as a consequence of such increased sensory input may result in the modification of cardiac efferent neuronal function.

This disruption of the cardiac nervous system during periods of ischemia is why some patients not only experience pain during a "heart attack," but may also experience bradycardia (slowing of the heart rate) or, if different reflexes are involved, tachycardia (fast heart rate).

Cardiac arrhythmias can also be initiated if insular cortical neurons are activated to a sufficient degree.[65, 67] Additionally, dangerous cardiac electrical events can occur when limited populations of neurons at the other end of the cardiac nervous system, those of the intrinsic cardiac nervous system, are activated excessively.[83-85]

Furthering our understanding of the role played by the cardiac nervous system in altered cardiac states may permit the development of improved therapies for the treatment of patients with various forms of heart disease. Below, we briefly discuss current understandings of autonomic neuronal regulation of the heart and attendant cardiovascular reflex alterations in myocardial ischemia, cardiac arrhythmias, and heart failure.

Myocardial Ischemia

Myocardial ischemia can occur in the presence of compromised local coronary arterial blood supply. Compromised cardiac blood supply may be secondary to fresh clot formation in a major coronary artery following damage to its intimal lining.[2, 73, 86] It may also involve local coronary arterial spasm,[14] which that presumably relates to autonomic neuronal malfunction. Myocardial ischemia alters the function of neurons throughout the hierarchy of the cardiac nervous system. Sensory information arising from cardiac afferent neurons during compromised ventricular blood supply can overwhelm the CNS and thus compromise clarity of thought.[13]

Intrinsic cardiac neurons

When the local arterial blood supply to a population of intrinsic cardiac neurons becomes compromised, the activity they generate changes.[87] A gradual loss of the capacity of some intrinsic cardiac neurons to generate activity may occur when their arterial blood supply becomes compromised due to a relative lack of energy substrates. Chemicals such as adenosine, hydroxyl radicals, and endothelin liberated locally as the result of myocardial ischemia can enter the downstream arterial blood perfusing a population of intrinsic cardiac neurons to modify their behavior too.[88] Upon restoration of local arterial blood flow, these locally accumulated chemicals can affect intrinsic cardiac neurons even further.[87] Thus, the cell bodies and dendrites of intrinsic cardiac neurons that receive their arterial blood supply from a diseased local coronary artery can be directly modified by that pathology. In other words, during a heart attack when the blood supply to your heart is compromised, the neurons in the little brain on your heart may be affected directly. This alters their capacity to regulate cardiac output in an efficient manner.

Alternatively, chemicals that accumulate following local myocardial ischemia can affect myocardial sensory neurites associated with the intrathoracic and central cardiac afferent neurons depicted above. In that

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manner, ventricular ischemia indirectly affects the behavior of somata of intrinsic cardiac and intrathoracic afferent neurons[31] as well as cardiac afferent neurons in dorsal root and nodose ganglia.[41, 46] Ischemia-induced modification of cardiac afferent neuronal activity thereby generates varied cardiovascular reflexes, depending on the feedback loops involved.

Extracardiac afferent neurons

Central neuronal reflexes are initiated by cardiac sensory neurites associated with nodose and dorsal root ganglion cardiac afferent neurons exposed to ischemia.[89] Activation of dorsal root ganglion cardiac afferent neurons may reflexly excite populations of sympathetic efferent postganglionic neurons that innervate the heart and other regions of the body.[90] A heart attack can induce reflex activation of sympathetic efferent neurons that innervate the nonischemic region of the heart, while reducing sympathetic efferent neuronal input to the ischemic zone.[91] Such ischemia-induced adjustment of cardiac reflexes may help spare compromised regions of the ventricles. In contrast, activation of a sufficient population of nodose ganglion cardiovascular afferent neurons induces reflex activation of cardiac parasympathetic[24] and sympathetic[92] efferent neurons.

A variety of cardiovascular reflexes can thus be provoked, depending on the degree to which each population of cardiac afferent neurons is affected. All of these central feedback loops (see figure) need to be elucidated fully before we comprehend the various neurocardiological responses elicited during a heart attack.[31]

Adenosine, which is liberated by myocardial tissues in increased quantities during myocardial ischemia, activates the local sensory neurites associated with those populations of cardiac afferent neurons in nodose,[40] dorsal root,[93] and intrathoracic ganglia.[31] As mentioned above, functional data indicate that adenosine may be intimately involved in the genesis of cardiac symptoms (angina) that develop during myocardial ischemia.[94] Other neuropeptides such as substance P modify such sensory responses, but apparently do not initiate them.[95]

Arrhythmias

Activation of a sufficient population of intrinsic cardiac neurons can lead to the induction of ventricular arrhythmias, even in the presence of a normal coronary artery blood supply.[83] Ventricular fibrillation (which is incompatible with life) can also be induced when limited populations of intrinsic cardiac neurons are exposed to chemicals such as endothelin[84] or antihistamines.[85] Conversely, cardiac arrhythmias may arise if a sufficient number of higher center neurons that are involved in cardiac regulation, including those in the insular cortex, become activated excessively.[65] Thus, emotional stress may result in the activation of cardiac sympathetic efferent neurons that trigger cardiac arrhythmias (electrical disturbances) or even sudden cardiac death.

Heart Failure

Our understanding of the basic mechanisms involved in the development of heart failure has evolved in the past few decades such that the importance of neurocardiology in its etiology is now well recognized.[86] When the heart fails to generate sufficient output to match the needs of the body, cardiac neurohumoral support systems may become overwhelmed.

It has generally been assumed that the increased levels of norepinephrine circulating in the bloodstream of patients with heart failure reflect the fact that greater quantities of norepinephrine than normal are liberated by sympathetic efferent neurons throughout the body, including those that regulate the heart.[96] In heart failure patients, sympathetic efferent postganglionic neurons that innervate blood vessels do liberate more norepinephrine than the amount liberated in normal individuals.[96] However, this does not necessarily mean that cardiac sympathetic efferent neurons behave in a similar fashion, as they represent a distinct population of sympathetic efferent postganglionic neurons.

In fact, recent evidence suggests that the production of norepinephrine by human sympathetic efferent postganglionic neurons that innervate the heart becomes diminished during the evolution of heart failure.[97] This is supported by data from the tachycardia-induced animal model of heart failure.[98] Interestingly, cardiac myocyte cell surface beta-adrenoceptor function remains relatively normal in a genetically derived

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model of heart failure[99] as well as in the tachycardia-induced heart failure model.[98] However, cardiomyocyte second messenger function becomes impaired during the evolution of heart failure.[100] These data suggest that major alterations occur in the cardiac sympathetic efferent nervous system during the development of heart failure independent of alterations in cardiac myocyte function.

If these data are supported by further research, then it may be that progression into heart failure involves the suppression of cardiac sympathetic efferent neuronal function in addition to cardiac muscle cell malfunction. Of these two, the latter may not be readily amenable to therapy once cardiac muscle cell function has become deranged. However, it may be possible to modify the suppression of cardiac sympathetic efferent neuronal activity by pharmacological means.

If the depletion of the cardiac sympathetic efferent nervous system seen in heart failure in fact eventuates as a result of excessive sympathetic activation maintained over a prolonged period of time, pharmacological intervention at an earlier stage in this progression may be of therapeutic value. Drugs such as beta-adrenoceptor or angiotensin II receptor blocking agents, when administered in appropriate doses, act to reduce the capacity of cardiac sympathetic efferent neurons to release norepinephrine in sufficient quantities to exert deleterious effects on cardiomyocytes.[101] Thus, such therapy may act to reduce the pathogenic effects that excessive and prolonged activation of such neurons exerts on the heart.[102] The hypothesis that constant and excessive sympathetic efferent tone can impair cardiac myocyte function[60] warrants further investigation, and suggests the importance of regulating the cardiac nervous system in this syndrome.

CONCLUSION

The cardiac nervous system is intimately interconnected to whole body function. Multiple populations of autonomic neurons, in constant communication via a host of neurochemicals, function to maintain cardiovascular stability and maximize cardiac efficiency via a complex regulatory hierarchy of nested feedback control loops, organized in three levels of the nervous system: the intrinsic cardiac nervous system, the intrathoracic extrinsic cardiac nervous system, and the central nervous system. It is vital that these complex, redundant interactions be understood not only in order to develop novel therapeutic strategies for the management of various heart conditions, but also to apply psychological principles to such management.

Evidence presented here underscores the complexity of cardiac neuronal networks, in essence indicating that the heart possesses its own ***little brain***, capable of complex computational analysis on its own. Data clearly indicate that the intrinsic cardiac nervous system acts as much more than a simple relay station for extrinsic autonomic projections to the heart. It functions, rather, as a local integrative neural network, which processes inputs from multiple sources throughout the body as well as from the heart itself. As such, it is capable of modulating extrinsic autonomic projections to the heart as well as mediating local intracardiac reflexes.

An understanding of the complex anatomy and function of the heart's nervous system contributes an additional dimension to the newly emerging view of the heart as a sophisticated information processing center, functioning not only in concert with the brain but also independent of it. Further exploration of the part that neurocardiological interactions play in sustaining healthy functioning may permit a more comprehensive understanding of the heart's multidimensional role in facilitating successful adaptation to the challenges of daily living.

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J. Andrew Armour, M.D., Ph.D., is an acknowledged leader in the field of neurocardiology. A founding member of the International Neurocardiology Network, Dr. Armour is recognized in the field for his pioneering research on the anatomy and function of the heart's intrinsic nervous system. Following a distinguished research career at Dalhousie University in Nova Scotia, Dr. Armour currently continues his work at the Centre de recherche de l'Hôpital du Sacré-Coeur de Montréal at the University of Montreal.

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