Heart–Brain Axis
Effects of Neurologic Injury on Cardiovascular Function

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Abstract: **A complex interaction exists between the nervous and cardiovascular systems. A large network of cortical and subcortical brain regions control cardiovascular function via the sympathetic and parasympathetic outflow. A dysfunction in one system may lead to changes in the function of the other. The effects of cardiovascular disease on the nervous system have been widely studied; however, our understanding of the effects of neurological disorders on the cardiovascular system has only expanded in the past 2 decades. Various pathologies of the nervous system can lead to a wide range of alterations in function and structure of the cardiovascular system ranging from transient and benign electrographic changes to myocardial injury, cardiomyopathy, and even cardiac death. In this article, we first review the anatomy and physiology of the central and autonomic nervous systems in regard to control of the cardiovascular function. The effects of neurological injury on cardiac function and structure will be summarized, and finally, we review neurological disorders commonly associated with cardiovascular manifestations. (*Circ Res*. 2017;120:559-572. DOI: 10.1161/CIRCRESAHA.116.308446.)**

Key Words: arrhythmias ■ autonomic nervous system ■ cardiomyopathy ■ cerebrovascular disease ■ stroke ■ sudden cardiac death

The link between the heart and the brain has been known for several centuries by examples such as syncope or death from extreme emotions and stressors.[1] Earlier studies by Gaskell and Langley at the end of 19th century established the basic structure of the autonomic nervous system (ANS), its divisions, and its role in regulation of the visceral and cardiovascular function. In the 1930s, Cannon developed the concept of homeostasis as an active process to maintain and regulate the physiological variables within a narrow range based on the idea of the internal environment introduced by Claude Bernard in the middle of the previous century.

The homeostatic processes are mediated by the ANS and the endocrine system and coordinated by the central nervous system (CNS). Cannon also noted that the cases of death from extreme emotions are likely because of hyperactivity of the sympathetic nervous system.[2] Since then, a large number of clinical observations, electrocardiographic (ECG) studies, and pathological assessments in patients having various neurological disorders

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Nonstandard Abbreviations and Acronyms

ANS	autonomic nervous system
CaMKII	calmodulin-dependent protein kinase II
CGRP	calcitonin gene–related peptide
CNS	central nervous system
CSD	cardiac sympathetic denervation
ECG	electrocardiography
PSH	paroxysmal sympathetic hyperactivity
RVLM	rostral ventrolateral medulla
SAH	subarachnoid hemorrhage
SCD	sudden cardiac death
SIC	stress-induced cardiomyopathy
TBI	traumatic brain injury

expanded our understanding of the neural regulation of the cardiovascular function.[3] In addition, surgical interventions to modulate the neuronal control of the cardiac function initiated over a century ago. In 1916, a patient with refractory angina and arrhythmia underwent surgical section of the left stellate ganglion with favorable results. The cardiac sympathetic denervation (CSD) procedures with some modifications (such as bilateral of more extensive denervation) were continued for several decades until they were replaced by newer pharmacotherapies. In 1970s, left CSD was reintroduced for treatment of a child with long-QT syndrome.[4] A recent interest in application of the surgical neuromodulation in treatment of heart failure and arrhythmias has reemerged and will be discussed later.

From a clinical perspective, the heart–brain axis can be approached as (a) the effects of cardiovascular disease on the nervous system (such as cardioembolic strokes in atrial fibrillation) or (b) the effects of neurological disorders on the cardiovascular system (such as stress cardiomyopathy after aneurysmal subarachnoid hemorrhage [SAH]). The neurological consequences of cardiac diseases, including cerebral ischemia and cognitive disorders, have been well studied (and will be described in another section of this publication). However, only in the past few decades, we started to learn about the basic pathophysiology underlying the heart–brain axis and, hence, provided implications for future treatments. In this article, we review the anatomy and physiology of the CNS and ANS in regard to control of the cardiovascular function in physiological and pathological states and the effects of different nervous system disorders on cardiovascular function.

Neural Control of Cardiovascular Function

CNS Control of Cardiovascular System

Experimental and clinical studies of both animals and humans have illustrated a complex network of cortical and subcortical regions involved in processing and control of the cardiovascular function (Figure 1).[5] This network involves several highly interconnected cortices, subcortical forebrain structures (including the amygdala and the hippocampus), and brain stem areas (including the hypothalamus, the bed nucleus of the stria terminalis, the periaqueductal gray, the parabrachial region, and the ventrolateral medulla). Higher cortical areas, including the orbitofrontal cortex and the dorsal cingulate cortex, process the afferent information ascending from the periphery and other brain areas and modulate the efferent autonomic outflow to adjust the cardiovascular function.

Within this network, the insular cortex seems to play a central role in the regulation of the heart–brain axis.[6,7] The cardiac afferent input is relayed to the posterior insula via the thalamus and integrated with the information received from the higher cortical centers in the rostroventral insula.[8] Stimulation of the caudal and rostral posterior insula in rats results in decreased and increased heart rate, respectively, and both effects are reversible by administration of β-blocker medication atenolol but not anticholinergic medication atropine, suggesting an underlying sympathetic mechanism.[9] Stimulation of the posterior insula in rats can also cause atrioventricular block that can progress to complete heart block, QT prolongation, myocardial injury, and ultimately asystole, similar to arrhythmias observed after stroke or seizure activity.[10] Occlusion of the left middle cerebral artery in rats has been shown to be associated with increased sympathetic outflow and plasma catecholamine levels along with QT prolongation and histopathologic evidence of myocytolysis only when the infract involved the insula.[11] Stimulation of the right and left insula lead to increased sympathetic and parasympathetic tone, respectively (laterality hypothesis).[12] This phenomenon can be attributed to the lateralized distribution of the baroreceptor units and processing of the emotions.[13,14] Although similar findings have been observed in human subjects, the laterality in humans is still controversial, and conflicting results have been reported in different clinical settings. For instance, although some observations had emphasized the prominent role of the right insula in sympathetic regulation of the cardiac function, emergence of electrographic changes, and even mortality,[12,15–17] other prospective studies showed a similar role for the left insula.[18–20]

The amygdala, particularly its central part, receives inhibitory projections from the prefrontal and orbitofrontal areas[21] and is connected with the hypothalamus and the brain stem nuclei involved in control of the cardiac function[22] and, thereby, seems to modulate the effects of emotional stimuli (especially negative emotions) on the heart.[23] Several nuclei of the hypothalamus (such as the lateral, dorsomedial, and paraventricular[24,25]) play an important role in the transition of autonomic information from the higher cortical areas to the brain stem by their projections, the nucleus tractus solitaries, periaqueductal gray, parabrachial region, rostral ventrolateral medulla (RVLM), and dorsal motor nucleus of the vagus.[26] In animals, the cardiac effects of stimulation of the lateral and anterior hypothalamus are preventable by sympathectomy and vagotomy, respectively.[27]The nucleus tractus solitarius located in the posterior medulla receives hemodynamic input from the afferent neurons and sends efferent inhibitory and excitatory outputs to the RVLM and dorsal motor nucleus of the vagus, which in turn increases the sympathetic and parasympathetic outflow, respectively.[3]

Autonomic and Neurohumoral Control of the Cardiovascular System

The CNS regulates cardiovascular function through the cardiomotor sympathetic and parasympathetic outflow of the ANS to the cardiac conduction system and myocardium.

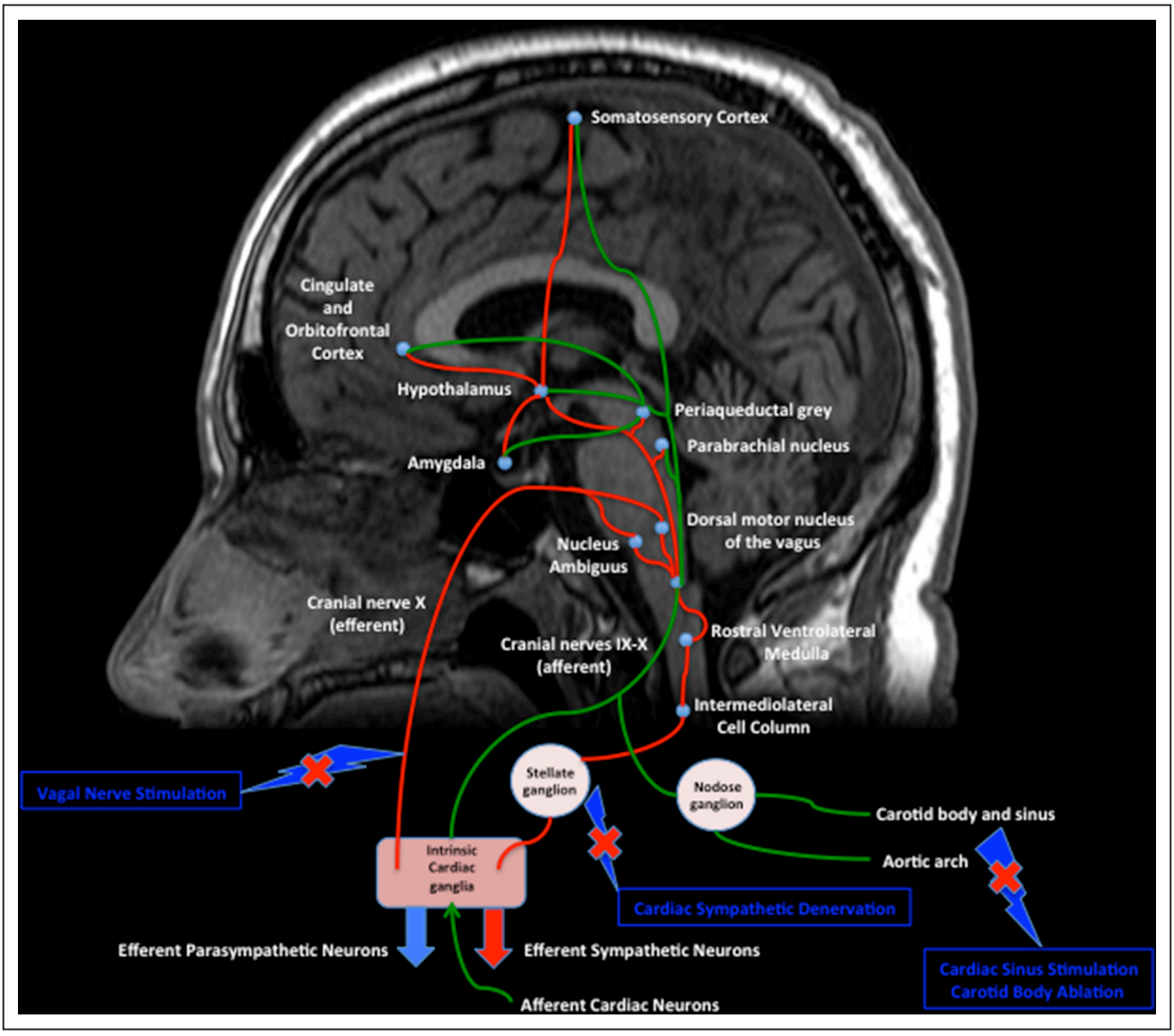

Figure 1. Neural control of the cardiovascular system. Afferent and efferent pathways are shown in green and red lines, respectively. Some potential sites for therapeutic interventions are illustrated in the blue text boxes. The figure has been simplified to illustrate the major cortical, subcortical, and brain stem areas involved in control of the cardiovascular function. Most of the shown areas are interconnected. For anatomic details and physiological effects of the illustrated pathways, please refer to the text.

Sympathetic System

The presympathetic neurons arise from the RVLM and synapse, with the preganglionic cholinergic sympathetic neurons of the heart located in the intermediolateral cell column of the upper thoracic spinal cord, which in turn make synapses in the cervicothoracic stellate ganglia. The heart is innervated by asymmetrically distributed superior, middle, and inferior cardiac nerves. The noradrenergic postganglionic sympathetic axons innervate the cardiac conduction system, atria, and ventricles. Sympathetic innervation, however, is heterogeneous and less dense in the cardiac apex. The sympathetic effects on cardiovascular function are mediated by activation of β_1 receptors in myocytes. The coupling of the adrenoceptor to the G_s protein increases intracellular cAMP levels, which in turn activates protein kinase A and induces phosphorylation of various intracellular targets, such as L-type calcium channels and delayed rectifier potassium channels, with the net effect of shortening of the action potential duration required for increased heart rate and conduction velocity.[28,29] The phosphorylation of phospholamban and type 2 ryanodine receptors (via CaMKII [calmodulin-dependent protein kinase II]) augments calcium reuptake in the sarcoplasmic reticulum, and intracellular calcium release enhances cardiac contractility and performance in physiological stress.[30,31]

Parasympathetic System

The parasympathetic innervation of the heart originates from the nucleus ambiguus and dorsal motor nucleus of the vagus in the medulla (preganglionic neurons), travels along the vagus nerve, and makes synapses with postganglionic neurons within the intrinsic cardiac ganglia. Parasympathetic fibers not only innervate the atrial conduction system and myocardium but also project to the ventricles.[32]The mechanisms of transmission and regulation of the neural activity in these ganglia is

not well understood and seems to be more complex than a simple relay site. For instance, the activation of the preganglionic parasympathetic fibers does not alter the activity of more than half of the parasympathetic neurons within the ganglia or can stimulate the sensory afferents.[33] Acetylcholine released from axon terminals of the postganglionic parasympathetic fibers primarily binds to M_2 muscarinic receptors, opens potassium channels, and thereby decreases heart rate and contractility.

The balance between sympathetic and parasympathetic activity is also under the influence of various neuromodulators released from the myocardium and coronary vessels (such as natriuretic peptides and angiotensin II), as well as cotransmitters between the sympathetic and parasympathetic nerve endings (such as neuropeptide Y and vasoactive intestinal peptide) and the intrinsic neuromodulators (such as the nitric oxide). Brain-derived and C-type natriuretic peptides shift the balance toward parasympathetic pathway via production of cyclic GMP, although in conditions such as heart failure, their effect may be limited by upregulation of phosphodiesterase 2A.[34] Ventricular myocardium can also augment the parasympathetic tone by expression of choline acetyltransferase and vesicular acetylcholine transporter.[35] Angiotensin II is locally produced in the heart and enhances sympathetic activity.[36] Nitric oxide is produced within both postganglionic sympathetic and parasympathetic neurons by neuronal nitric oxide synthase and its activator protein, CAPON, and results in increased release of cyclic GMP. In parasympathetic neurons, this will lead to release of acetylcholine by inhibition of phosphodiesterase-3 and phosphorylation of N-type calcium channels via cAMP–protein kinase A pathway,[37] whereas in sympathetic neurons, the inhibition of calcium influx via stimulation of phosphodiesterase-2 and protein kinase G results in release of norepinephrine.[38] The role of sympathetic and parasympathetic cotransmitters, especially in cardiovascular diseases, is still unclear.

Intrinsic Cardiac Nervous System and Cardiac Afferent Neurons

In addition to the extrinsic autonomic efferent fibers, the cardiovascular function is influenced by the intrinsic cardiac nervous system, as well as the cardiac afferent neurons. The intrinsic cardiac nervous system consists of an extensive and complex network of interconnected ganglionated plexi located within the epicardial fat tissue and innervates sinoatrial (by the right atrial ganglionated plexi) and atrioventricular (by the inferior vana cava–inferior atrial ganglionated plexi) nodes, as well as the pulmonary vein–left atrial junction that also contains closely located sympathetic and parasympathetic neurons.[39,40] A significant number of the neurons within the intrinsic cardiac nervous system are interneurons that synapse with local neurons within the ganglia; many are affected by both sympathetic and parasympathetic neurons and modulate the autonomic efferent fibers through the feedback loops.[33]

The afferent neurons carry the chemical and mechanical sensory information from the atria, ventricles, and large intrathoracic vessels. The cell bodies of these neurons reside within the spinal dorsal root ganglia, as well as extracardiac intrathoracic and intrinsic cardiac ganglia, and can also affect the efferent fibers. The afferent fibers release various peptides, including substance P and CGRP (calcitonin gene–related peptide).[41] Release of substance P into the spinal cord dorsal horn during cardiac ischemia is partially mediated by transient receptor potential vanilloid 1 receptors and coveys cardiac pain to the CNS.[42] Substance P also seems to reverse cardiac remodeling,[43] whereas CGRP has cardioprotective properties in cardiovascular diseases by promoting angiogenesis and inhibiting apoptosis induced by oxidative stress.[44–46] Downregulation of CGRP seen in autonomic neuropathy impairs angiogenesis and induces vasoconstriction, inflammation, and ultimately myocardial apoptosis and fibrosis that can result in arrhythmia and ischemia. The ascending fibers project via cranial nerves IX and X to the autonomic nuclei within the brain stem (including the paraventricular nucleus, parabrachial nucleus, and nucleus tractus solitaries), hypothalamus, amygdala, thalamus, and the cerebral cortex.[47,48] The sensory information undergoes processing throughout this pathway.

Neurohumoral Control of Cardiovascular Function in Heart Disease

The neuronal control of the cardiovascular system undergoes significant alterations and may contribute to progression of the underlying heart disease. In the CNS, oxidative stress, decreased nitric oxide, and abnormal baroreceptor and chemoreceptor signals conveyed by cardiac afferent fibers to the nucleus tractus solitaries, paraventricular nucleus, and RVLM lead to a maladaptive increase in sympathetic tone that can result in fatal arrhythmias or worsening of heart failure and ischemia[49–51] (see Effect of Neurological Disorders on Cardiovascular Function). Some of these effects can be abolished by CSD procedures. In the cardiovascular system, enhanced sympathetic activity with increased release of catecholamines, aldosterone, and angiotensin II will increase intracellular release of Ca^{2+}, as well as oxidative stress and generation of reactive oxygen species. Binding of calcium to calmodulin in this oxidative environment leads to sustained activation of CaMKII, which further facilitate progression of an underlying heart failure.[52–54] Therefore, administration of β-blockers, angiotensin-converter enzyme inhibitors, or angiotensin receptor blockers can decrease oxidative stress and counteract the effects of extended CaMKII activation.[55] Sympathetic activity also changes by increased or decreased innervation mediated by alterations in cardiac nerve growth factor.[56] Prolonged sympathetic activation and hyperinnervation decreases β-adrenoceptor responsiveness and prolongs the action potential duration mediated by downregulation and internalization of the adrenoceptors and the rectifier potassium channels, respectively.[57,58] It can also result in increased myocardial apoptosis and fibrosis. On the contrary, decreased sympathetic innervation increases the sensitivity of adrenoceptors. Distribution of altered sympathetic innervation is heterogeneous[59] and can increase the risk of conduction blocks, arrhythmias, and even sudden cardiac death (SCD).[60] The transdifferentiation of adrenergic to cholinergic neurons mediated by increased secretion of interleukin-6 family cytokines from damaged myocardium, on the other hand, may have cardioprotective properties, although this is still controversial.[61,62] The intrinsic cardiac ganglia also undergo significant changes in pathological states, such as ischemic heart disease and heart failure.[63,64]

Effect of Neurologic Disorders on Cardiovascular Function

Neurological disorders are frequently associated with ECG and structural cardiac changes, with various clinical manifestations ranging from benign, mild, or even asymptomatic and transient alterations in cardiovascular function to severe, irreversible, and potentially life-threatening injury. In addition, both the underlying neurological disorder and the cardiovascular dysfunction may impose limitations in optimal treatment of the other; therefore, high clinical suspicion and closed cardiac monitoring—at least in the acute phase—may assist in prevention, early identification, and, hence, prompt treatment of cardiovascular dysfunction. It is important to note that given high prevalence of cardiovascular disorders and shared risk factors in these patients, at times it can be difficult to establish the neurological injury as the cause or the consequence of cardiovascular dysfunction.

Electrocardiographic Changes

Electrocardiographic alterations, both benign and fatal, are commonly seen after brain injury even without a preexisting heart disease. Calcium influx associated with sympathetic activity after CNS injury releases degrading enzymes that can damage the subendocardial conductive network and alter cardiac automaticity, refractoriness, and repolarization.[65,66] The ECG findings are frequently encountered in the context of elevated catecholamine release, and some are preventable with antisympathetic medications.

Electrographic changes are usually transient and are better seen in the precordial and lateral leads. Typically, these changes are more frequent and pronounced in the first 24 hours after catastrophic neurological injuries (such as SAH) and are expected to resolve within a few days after the neurological injury. The commonly seen ECG changes include diffuse inversion of tall T waves (also known as cerebral T waves; Figure 2), emergence of prominent U waves in the absence of any electrolyte abnormalities, and prolongation of ST and QT segments. Repolarization changes are also common after neurological injury. Various arrhythmias, including fatal ventricular tachycardia, may also emerge and will be discussed below.[67,68]

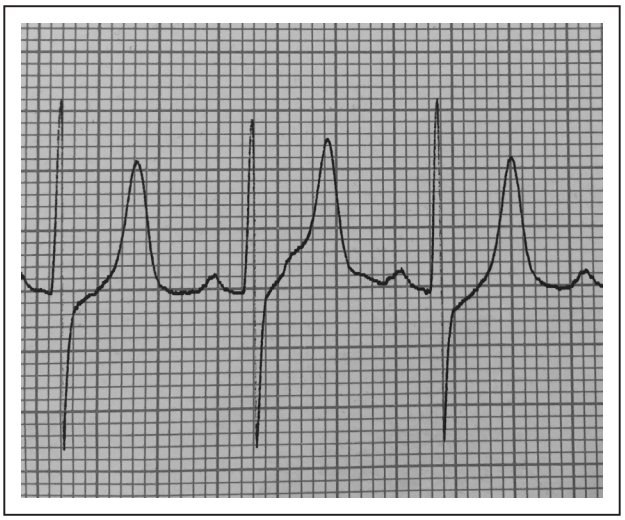

Figure 2. Cerebral T waves in a 59-year-old man presented with aneurysmal subarachnoid hemorrhage.

Clinical Considerations

It is important to rule out primary or contributory cardiovascular causes for ECG changes particularly in high-risk individuals by evaluation of serum cardiac enzymes, echocardiography, and even coronary angiography. Although majority of electrographic changes are benign and do not require treatment, prevention, continuous monitoring, and early treatment of malignant rhythms and conduction abnormalities are essential. Electrolyte abnormalities (specifically hypokalemia and hypomagnesemia) and medications inducing or worsening QT prolongation (such as antipsychotics) should be avoided or used with caution in a monitored setting. Treatment of electrographic changes in the setting of brain injury has not been well studied; however, attention to brain protection measures, such as maintenance of adequate cerebral perfusion or controlling secondary brain injury, is advised.

Myocardial Injury

Neurological injury and even psychological stressors can affect cardiac structure characterized by rapid (within minutes) development of subendocardial microinfarcts, early calcification, and formation of contraction bands (myofibrillar degeneration or myocytolysis).[69,70] These changes are likely because of excessive exposure to catecholamines, and similar microscopical changes are seen after infusion of external catecholamines and stimulation of the dorsal medulla and hypothalamus.[71,72] Myocytolysis is concentrated around nerve endings along with a predominantly monocytic infiltration and are pathologically distinct from coagulative necrosis seen in myocardial ischemia induced by coronary artery disease that presents with delayed myocardial necrosis confined to a vascular territory and associated with a predominantly polymorphonuclear infiltration.[73]

Deregulation in the function and structure of either central or peripheral components of the ANS (presenting as hyperactivity or failure) is associated with prominent cardiovascular manifestations.[74] Below we briefly review some of the most severe cardiac complications seen after neurological damage because of various etiologies. Autonomic failure mostly manifests as decreased sympathetic outflow, whereas paroxysmal sympathetic hyperactivity (PSH) and stress-induced cardiomyopathy (SIC) are typically associated with increased sympathetic tone. Both increased and decreased sympathetic innervation, as well as impairment of cardiac afferent neurons, can increase the risk of SCD.

Autonomic failure may develop in several nervous and systemic diseases affecting various components of the ANS. Patients may remain asymptomatic or have lightheadedness, falls, and even syncope typically because of orthostatic hypotension, although symptoms can be secondary to other mechanisms such as arrhythmia with sudden reduction of cardiac output and global cerebral perfusion.[75]Other neurological disorders that can induce syncope include vasovagal syncope, (bilateral) carotid disease, vertebrobasilar insufficiency, and cerebral vasospasm. Some patients may present with postural tachycardia without a significant drop in the blood

pressure (postural tachycardia syndrome).[76,77] CNS diseases associated with autonomic failure include strokes (involving the insular lobe), spinal cord diseases (myelopathy), and neurodegenerative diseases (particularly synucleinopathies, such as Parkinson's disease and multiple system atrophy). Some well-recognized peripheral etiologies include pure autonomic failure, primary autonomic neuropathy and ganglionopathy, and small fiber neuropathies affecting autonomic fibers (secondary to diabetes mellitus and other metabolic disorders, mitochondrial and genetic diseases, as well as autoimmune and inflammatory processes) and diseases affecting afferent fibers (baroreflex failure and familial dysautonomia). In addition, multiple medications can affect autonomic function and fibers.

Clinical Considerations

Orthostatic hypotension mostly presents with a subacute to chronic course and is associated with worsened outcomes.[78] It can be managed by nonpharmacological measures, such as support stockings, increased dietary salt (for instance, 2 g two times a day), and water intake, and avoidance of activities after meals (especially foods rich in carbohydrates). Water exercises and orthostatic training can enhance physical conditioning, improve cerebral perfusion, and prevent falls. Severe or refractory symptoms may require pharmacotherapy with mineralocorticoids (fludrocortisone), sympathomimetics (midodrine), acetylcholinesterase inhibitors (pyridostigmine), somatostatin analogs (octreotide), or droxidopa.

Paroxysmal Sympathetic Hyperactivity

PSH, sometimes referred to as sympathetic storms or surges, can develop in primary pathologies of the ANS (such as inflammation, ischemia, or trauma of the ANS) or as a consequence of the CNS or systemic disorders. Characteristic brain disorders associated with PSH include (aneurysmal) SAH, focal and global (postcardiac arrest) cerebral ischemia, severe traumatic brain injury (TBI), and less frequently in brain neoplasms. Clinical presentations include tachypnea, hypertension, fever, profound diaphoresis, shivering, mydriasis, dystonia or extensor posturing, and elevated intracranial pressure.[79] Typical ECG changes include sinus tachycardia, T wave inversion, and even fatal ventricular tachycardia. Neurogenic pulmonary edema and elevated troponin levels—with or without heart failure—may also pursue. Episodes may be provoked by otherwise minor stimulations, such as body turning. Although typically paroxysmal and short-lasting, the storms may continue to recur up to months and interfere with patient care. Important differential diagnoses for PSH include neuroleptic malignant syndrome, serotonin syndrome, seizure, and Cushing response.[79]

Clinical Considerations

In contrast to autonomic failure, PSH is usually seen acutely after catastrophic neurological injuries. Treatment of PSH after brain injury primarily consists of prevention of known triggers and pharmacotherapy with opioids (eg, morphine or fentanyl) and β-blockers (usually nonspecific medications that cross the blood–brain barrier, such as propranolol). In more severe cases, dopamine agonists (such as bromocriptine), central α-2 agonists (clonidine), benzodiazepines, baclofen, gabapentin, and dantrolene can be administered.[80]

Stress-Induced Cardiomyopathy

SIC is a distinct form of acquired acute heart failure. It is predominantly seen in postmenopausal women.[81] Acute clinical presentation consists of chest pain, dyspnea, and syncope, along with electrographic (such as ST segment changes and QT prolongation) and laboratory (such as elevated troponin and brain natriuretic peptide) findings.[68,82] These finding may be similar to those seen in the acute coronary syndrome, which may delay or obscure its diagnosis and delay treatment, and at times, coronary angiography may be required to distinguish between them, although the 2 conditions may coexist. The classic and most common type of echocardiographic change in SIC shows a heart that resembles an octopus trap (takotsubo in Japanese) because of the ballooning of the left ventricular apex. This can be attributed to higher sensitivity of apical myocytes to catecholamines.[83] However, other types of the left ventricular changes (midventricular, basal, and focal) can also be seen.[84] Depressed left ventricular ejection fraction is seen more commonly in SIC than in acute coronary syndrome. SIC is perceived as a disorder of the heart–brain axis. This is supported by high prevalence of neuropsychiatric disorders, including SAH, TBI, stroke, seizure, depression, and traumatic emotions such as loss of a beloved one (hence, the term broken heart syndrome).[84] The exact pathophysiology of SIC is still unclear, but some have proposed that catecholamine surge, as seen in catastrophic neurological disorders, may result in coronary artery spasm or cardiac microvascular dysfunction.[85] Accordingly, SIC can also be seen after exposure to exogenous catecholamines such as inhaled β-agonists or psychostimulants.[86,87] In animal models, exposure to high concentrations of catecholamines converted the net effect of β-receptor activation on cardiac function from excitatory to inhibitory outflow, mediated by G_s and G_i proteins, respectively.[88] Reperfusion injury with release of reactive oxygen species has also been proposed, although direct evidence in its support is lacking.[89,90]

Clinical Considerations

Although clinical and echocardiographic improvement is seen in majority of patients with SIC, this condition can be associated with other in-hospital complications, including cardiogenic shock, malignant arrhythmias, and death. This is noted especially in younger patients with physical triggers and neuropsychiatric diseases, high levels of troponin, and low ejection fraction. In addition, secondary brain injury may occur because of emergence of cardiogenic shock or arrhythmia with associated reduction in cerebral perfusion or new strokes because of mural thrombosis. A recent prospective study showed better outcomes associated with use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, but not of β-blockers.[84]

Sudden Cardiac Death

SCD consists of unexpected deaths because of cardiac arrest in temporal proximity (usually within 1 hour) to the triggering event without another known pathogenesis.[91] Although SCD occurs most frequently in patients with a preexisting coronary artery disease, a wide range of neuropsychiatric disorders may result in SCD without a preexisting cardiac disorder.[92,93] In

fact, death from emotional stressors has been known for centuries, reflected in expressions such as scared to death. Other conditions associated with SCD include strong emotions and stressors (such as anger, fear, grief, and natural disasters), exposure to endogenous or exogenous catecholamines (such as pheochromocytoma or psychostimulants), SAH and intracerebral bleeds, acute ischemic stroke (particularly infarcts involving the insular lobe), and seizures.[94–97] Neurological injury can result in SCD by inducing fatal arrhythmias or massive myocytolysis and cardiac infarction.[98] Neuromodulatory strategies (discussed below) may provide new therapeutic tools not only to treat cardiovascular diseases such as heart failure and refractory arrhythmias but also to prevent SCD.

Cardiac Manifestations of Specific Neurological Disorders

Cardiovascular events are frequently seen after several neurological disorders. Commonly seen cardiac presentations of selected neurological disorders are reviewed below.

Ischemic and Hemorrhagic Strokes

Cardiac changes after strokes are among the most commonly observed alterations in the heart–brain axis and are associated with increased mortality in the acute phase after stroke.[99] Electrocardiographic changes are seen in >90% of patients with ischemic stroke on prolonged cardiac monitoring and include ST segment changes, QT prolongation, tall and inverted T waves, and prominent U waves, as well as premature ventricular beats and decreased heart rate variability.[100–102] Strokes, particularly those involving the insular lobe, are frequently associated with both bradycardia and heart blocks (including third-degree block), as well as tachyarrhythmias with either atrial (supraventricular tachycardia, atrial flutter/fibrillation) or ventricular (ventricular tachycardia/fibrillation and torsade de pointes) origin.[103–105] The most commonly observed arrhythmia after stroke is atrial fibrillation (up to a fifth of patients), although at times it is not clear whether this arrhythmia is a cause or a consequence of the stroke.[106,107] Cardiac arrhythmias are associated with increased rates of SCD.[104,105]

Hemorrhagic stroke, both deep and lobar, are also associated with high rates of ECG changes similar to those seen after focal cerebral ischemia.[108–110] Although correlation between localization of the hemorrhage with the type of arrhythmia has been reported, there is not enough evidence to support this concept.

Effects of strokes on the heart also involve alterations in cardiac mechanical function and structure, although patients may remain asymptomatic.[99,111] Elevated serum level of troponin and brain natriuretic peptide is seen commonly after both ischemic and hemorrhagic strokes, especially in those with ECG changes.[112–114] Increased cardiac enzymes is associated with increased mortality in ischemic stroke; however, this is controversial in brain hemorrhage.[115–118] In contrast to myocardial infraction secondary to coronary artery disease, serum troponin levels rise slowly and typically to lower levels after neurological injury.[119] A recent prospective study showed significantly lower frequency of coronary culprit lesions in patients after ischemic stroke in comparison to patient presenting with non–ST-elevation acute coronary syndrome with similar baseline troponin levels, and half of the patients with ischemic stroke did not have an angiographic evidence of an underlying coronary artery disease.[120] SIC can also be seen after focal ischemia and hemorrhage, especially in women with left insular strokes.[84] Although cardiac changes also occur in younger patients without an underlying heart disease, preexisting cardiac diseases and electrolyte abnormalities predisposing to arrhythmias are not uncommon in patients with cerebrovascular diseases. Attribution of cardiac alterations to cerebral dysfunction must, therefore, be approached cautiously.

Aneurysmal SAH

Cardiovascular changes are extremely common in SAH and most commonly occur within the first few days after hemorrhage, especially in women with high-grade SAH.[121,122] These changes are mostly reversible and recover within days to weeks.[123,124] Electrocardiographic changes and cardiac arrhythmias are similar but more common in SAH than in focal cerebral ischemic or spontaneous intracerebral hemorrhage.[121,125–127] This can be because of severity and more intense monitoring of the disease. Prolongation of QT interval is the most common ECG abnormality seen both in the acute posticta phase and during the vasospasm window, is associated with angiographic vasospasm, and can predispose the patients to fatal ventricular arrhythmias, such as torsade de pointes.[128] Tachycardia and ST changes are associated with worse outcomes.[129] Myocytolysis and elevated serum levels of cardiac enzymes and brain natriuretic peptide are seen in about one third of patients (more common in those with ECG abnormalities and high-grade SAH and in the presence of SIC and cerebral vasospasm) and are associated with worse prognosis.[130–133] SIC is also seen in higher rates compared with ischemic stroke, despite relatively younger age of patients and lower risk of preexisting heart disease, and is associated with worse prognosis.[122,134–137] Importantly, these changes may limit the use of induced hypertension and administration of vasopressors and inotropic agents as part of the management of delayed cerebral ischemia in SAH and, at times, may necessitate other measures such as intra-aortic balloon pump counterpulsation to maintain adequate cerebral perfusion.[138,139] Pulmonary edema seen in SAH can be secondary to catecholamine surge or diastolic heart failure.[140]

Brain Stem and High Spinal Cord Injury

Multiple nuclei within the brain stem are involved in control of the cardiovascular function. The outflow of both divisions of the ANS is from the spinal cord: parasympathetic fibers from the cervicosacral (S2-S4) and sympathetic fibers from the thoracolumbar (T1-L2/L3) segments. Therefore, pathologies that involve the brain stem or spinal cord injury (especially at cervical and high thoracic levels above T5) can result in autonomic dysreflexia and impaired cardiac function.[141–143] Early after spinal cord injury, increased vagal tone along with bradycardia and (orthostatic) hypotension may evolve. However, after resolution of the initial spinal shock, sympathetic hyperactivity may develop and induce episodic and dramatic rises in blood pressure. The sympathetic hyperactivity can be triggered by minor stimulations below the level of injury, such as

bladder distension or catheterization. Of note, some manifestations of autonomic hyperactivity such as diaphoresis occur above the level of spinal injury.[144] The brain stem and spinal cord pathologies associated with cardiac changes include stroke,[145] tumors, chiari malformation,[146] syringobulbia and syringomyelia,[147,148] traumatic spinal cord injury,[149] and demyelinating diseases (such as multiple sclerosis,[150] neuromyelitis optica,[151] and transverse myelitis[152]).

Clinical Considerations

Patients with spinal cord injury are sensitive to the effects of sympathetic agonist and antagonist medications, and therefore, these medications need to be administered cautiously because the responses may be exaggerated.

Epilepsy

Focal seizures involving insular lobe or amygdala, such as temporal lobe epilepsy, are associated with marked dysautonomia and cardiac changes. Dysautonomia may also provoke a seizure in specific epileptic syndromes, such as nocturnal frontal lobe epilepsy.[153] Ictal hypertension and arrhythmias (including both tachycardia and less frequently bradycardia in temporal lobe seizures originating from the left) are commonly seen even in focal or nonconvulsive seizures.[154,155] Electrographic changes include ictal or postictal blocks and ischemic changes and interictal decrease in heart rate variability.[156–158] Benign rhythms, however, may infrequently evolve into potentially fatal rhythms, such as asystole, supraventricular tachycardia, atrial flutter/fibrillation, and ventricular tachycardia/fibrillation, that can partly explain the well-recognized sudden death in epilepsy in young patients with refractory epilepsy.[159–161] Sudden death in epilepsy can potentially develop in response to autonomic alterations during ictal (predominantly sympathetic) and postictal (predominantly parasympathetic) periods, although its underlying mechanisms are still unclear.[162–164] Besides electrographic and cardiac rhythm changes, SIC can also be seen in seizures and may increase risk of sudden death in epilepsy.[165] Other epileptic characteristics associated with sudden death in epilepsy include early onset and prolonged history of poorly controlled or refractory epilepsy and generalized seizures.[166]

Neurodegenerative Disorders

Cardiac changes are commonly seen in neurodegenerative diseases, particularly synucelinopathies such as Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy (formerly known as Shy-Drager syndrome).[167,168] Friedreich's ataxia, an autosomal recessive neurodegenerative disease, is associated with multiple cardiac abnormalities, including hypertrophic cardiomyopathy. Dementia, particularly vascular and to some extent Alzheimer type, share several risk factors for cardiovascular diseases; on the other hand, dysautonomia may correlate with severity of cognitive decline.[169] The most common cardiac abnormality is orthostatic hypotension. Orthostasis in multiple system atrophy is secondary to involvement of components of the central autonomic network, while in Parkinson's disease, it is because of loss of postganglionic sympathetic fibers.[170] Orthostatic hypotension is more severe, refractory, and of earlier onset in multiple system atrophy but is seen in several neurodegenerative diseases, including dementias of Alzheimer and vascular type. The most important electrographic change in neurodegenerative diseases is QT prolongation and is thought to be associated with SCD.[171]

Other Neurological Disorders

Traumatic Brain Injury

Cardiac changes after TBI are probably less common but similar to the site-specific damage caused by brain injuries described above, including electrographic changes (QT prolongation and T wave inversion) and SIC, especially when the areas involved in regulation of the cardiovascular function are affected.[172,173] On the other hand, PSH is more commonly and severely seen in severe TBI and is associated with worse prognosis.[174,175]

Primary Headaches

Autonomic alterations occur frequently in migraine and other headaches. These changes include diaphoresis, flushing, lacrimation, and Horner's syndrome, as well as ictal and interictal cardiac (orthostatic hypotension) and electrographic changes (such as repolarization and arrhythmia).[176,177] Cardiac structural variants such as atrial septal defect (including patent foramen ovale), right-to-left shunting, and mitral valve prolapse are more commonly seen in patients with migraine,[178] although closure of the defect has not been shown to reduce the frequency or severity of migraines.[179,180] In addition, triptans used to abort migraine headaches can lead to hypertension and coronary vasospasm and need to be used cautiously in patients with history of coronary artery or cerebrovascular disease.[181] Deep brain stimulation of the posterior hypothalamic area is a proven treatment for refractory cluster headache, and given the role of posterior hypothalamus in control of cardiovascular function, this treatment may be complicated by cardiac effects, such as tachycardia or elevated blood pressure, although the clinical experiences in humans have been inconsistent.[182,183]

Autoimmune-Mediated Autonomic Neuropathies

Autoimmune-mediated autonomic neuropathies (such as Guillan–Barre syndrome) and encephalitis are associated with severe and even life-threatening dysautonomia and cardiac manifestations, including alterations in heart rate and blood pressure and cardiac arrhythmias.[184,185] Therefore, close monitoring in the intensive care units even in those who do not need mechanical ventilatory support is recommended. In addition, treatment of autonomic changes has to be approached cautiously given their rapid and extreme fluctuations.

Sleep Disorders

Apneic episodes during sleep are associated with transient hypertension and tachycardia. In obstructive sleep apnea syndrome, repeated apnea attacks driven by higher cortical and brain stem areas is associated with long-lasting sympathetic hyperactivity, which in turn increases risk of cardiovascular diseases and mortality.[186,187] On the other hand, sleep deprivation and sleep disorders such as narcolepsy are also associated with increased risk of cardiac diseases.[188,189]

Several other brain disorders such as brain tumors, infection, and inflammatory processes can present with ECG and

cardiac alterations discussed earlier, particularly when brain regions involved in control of cardiovascular function are involved. The common pathway in development of these cardiovascular changes is thought to be sympathetic hyperactivity and excessive catecholamine release.

Therapeutic Interventions

As discussed earlier, autonomic and neurohumoral control of the cardiovascular function is under the influence of the CNS. Therefore, although pharmacotherapy is currently the mainstay of treatment for heart failure, ischemia, and arrhythmia, neuromodulatory strategies targeting central control pathways hold promise in future treatment of these conditions. Endurance exercise training inhibits the NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells)-dependent inflammatory cascade, angiotensin II receptor expression, and oxidative stress in RVLM and paraventricular nucleus neurons.[190] CSD was first described over a century ago; however, there has been a recent interest in its application.[4] The surgical procedure involves resection of the lower half of the stellate ganglion (including the afferent fibers that pass through it) and the first 2 to 4 thoracic ganglia, preserving the sympathetic innervation through the upper half of the stellate ganglion and the middle cervical ganglia.[191,192] The procedure is typically performed on the left side, given that right CSD has been shown to increase ischemia-induced arrhythmias and lowers the threshold for ventricular fibrillation. The reduced sympathetic tone in the ventricles is thought to decrease the risk of ventricular arrhythmias,[193] especially in those with hereditary arrhythmias (such as long-QT syndrome and catecholaminergic polymorphic ventricular tachycardia[194]) that experience frequent syncopal episodes or implanted cardioverter defibrillator shocks and cannot take beta blockers. Similarly, local blockade of the cardiac sympathetic ganglia, by thoracic epidural anesthesia or stellate ganglion block, can prevent sympathetic-induced ventricular and supraventricular arrhythmias.[192,195,196] Vagal nerve stimulation has been shown to improve cardiac contractility and survival in heart failure[197–200] and protects against atrial and ventricular arrhythmias. These effects are mediated by not only augmented parasympathetic activity but also by reduction in the sympathetic tone mediated both centrally and peripherally (within the intrinsic cardiac ganglia).[201,202] In addition, vagal nerve stimulation inhibits the release of inflammatory cytokines (such as tumor necrosis factor-α and interleukin-6) and normalizing the expression of NOS isoforms. Spinal cord stimulation has been used to treat refractory angina for >2 decades, but also has cardioprotective properties by counteracting the sympathetic reflex in response to stressors.[203,204] The proposed mechanisms include inhibition of the preganglionic sympathetic activity and afferent sympathetic fibers (and thereby release of substance P) by secretion of dynorphin in extracardiac and intrinsic cardiac ganglia.[205–208] Other strategies for autonomic regulation include carotid body ablation, carotid sinus stimulation, renal denervation, as well as targeting the cardiac sympathetic afferents.

Current Perspectives and Future Directions

Our knowledge of the interaction of heart and brain has expanded and deepened significantly over the last few decades, thanks to the classical approach from molecular, to cellular, to organ, and to systems in individual and specific population of patients. From a clinical neurosciences perspective, it is time to harness the advances in research methodologies to better define the brain areas involved in control of the cardiovascular function. Our current knowledge has mostly been derived from studies that lesion specific brain regions resulting in the loss or alteration of function. However, recent laboratory techniques, such as optogenetics and CLARITY (a method of making brain tissue transparent), provide the opportunity to specifically modulate cells with high temporal and spatial resolution in vivo.[209] We have also made great advances in structural and functional neuroimaging. As we get better at understanding the underlying pathophysiological mechanisms, develop better diagnostic tools, and define the specific populations at risk, we also need to develop robust and more meaningful translational models to study relevant pathophysiological processes (such as SAH-induced cardiac injury). We also need to better understand how these systems interact while normal and in a diseased state. These approaches require not only focused work in specialized areas of research but also cross-collaboration across multiple disciplines and specialists, including neurologists, neurosurgeons, cardiologists, cardiac surgeons, intensivists, and trauma and emergency medicine specialists. Clinical settings such as intensive care and epilepsy monitoring units provide the optimal basis for prolonged, comprehensive, precise, and at times invasive, multimodal monitoring of both cardiac and nervous systems (clinical laboratories). At the moment, we are approaching a period of renewed opportunities, particularly in patients admitted for SAH, TBI, and even brain death cases.

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