*Behavioral Aspects of Heart Disease*

# Brain–Heart Interactions

## The Neurocardiology of Arrhythmia and Sudden Cardiac Death

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*Neuroanatomic connections between the brain and the heart provide links that allow cardiac arrhythmias to occur in response to brain activation. Recognition and analysis of such links in the pathogenesis of malignant cardiac arrhythmia are emphasized in this review. Neurocardiac links have been shown to produce arrhythmia both experimentally and clinically; specific examples, including stroke, epilepsy, and environmental stress are presented. We hypothesize that the individual with a diseased heart has a greater likelihood of experiencing cardiac arrhythmia and sudden cardiac death when the neurocardiac axis is activated. Reviewing possible mechanisms of brain-related arrhythmias, we suggest that the nervous system directs the events leading to cardiac damage by raising catecholamine levels and potentially inducing arrhythmia.* ***(Texas Heart Institute Journal 1993;20:158-69)***

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Neurocardiology investigates the interactions between the brain and the heart that are not generally taught during specialty training within either neurology or cardiology. Cardiology primarily evaluates the end-organ; neurology traditionally evaluates the nervous system. A case study of a neurologist's wife who had migraines and palpitations illustrates how neglecting brain–heart interactions can lead to delayed diagnosis and treatment.[1] In this case, an otherwise healthy young woman experienced sudden onset of palpitations, shakiness, tremor, sweating, lightheadedness, and feelings of dread. She had episodes of palpitations while falling asleep and awakening. These symptoms suggested epilepsy, which her husband, the neurologist, evaluated by electroencephalography. Finding the results to be normal, he requested a cardiac evaluation. Consultations by 3 cardiologists and an internist revealed mitral valve prolapse and the possibility of a psychiatric disorder. Holter monitor electrocardiography revealed frequent runs of sinus tachycardia and one 15-beat series of unifocal ventricular beats. The patient was treated with quinidine, digoxin, and verapamil, propranolol, and nadolol; only the latter 2—the β-blockers—suppressed the tremor, sweating, and the magnitude of the tachycardia. Although diminished, the bursts of tachycardia and the feelings of dread continued, prompting treatment for suspected visceral epilepsy. Her symptoms initially abated with clonazepam administration; when the efficiency of the benzodiazepine waned, her symptoms abated with carbamazepine. Finally, a computed tomographic scan was ordered, which documented a large, partially calcified, right frontal mass lesion despite the patient's normal results on neurological examination. At surgery, a large glioma was found and removed.

This case report epitomizes the deficiency of our nonintegrated specialty training process. The individual physicians responded to the patient's symptoms with treatment from their specific system of interest without considering the ways in which the central nervous system interacts with the heart to produce arrhythmia; consequently, correct diagnosis and treatment were delayed.

A 1985 neurocardiology review from our laboratory[2] examined the neuroanatomy of brain–heart interactions, presented animal models demonstrating these interactions, and cited clinical studies showing brain–heart interactions occurring within patient populations frequently seen in medical practice. The present review includes additional neuroanatomic findings that have appeared in the literature more recently. We review the anatomy of the connections between the brain and the heart and discuss how activation of this neurocardiologic axis can produce arrhythmia. We hypothesize that the heart, particularly when diseased, is more likely to develop arrhythmia when central nervous system structures are

activated. We show how the neuroanatomic brain–heart links that produce arrhythmia can be activated experimentally by diseases commonly seen in practice, such as stroke and epilepsy, as well as by environmental stress.

## Sudden Cardiac Death

Sudden cardiac death epitomizes the most devastating arrhythmia and is responsible for nearly one-half million deaths annually in the United States. Smith[3] defines arrhythmia as any disturbance in the cardiac activation sequence or any deviation from accepted limits of rate or regularity of the normal impulse, which is formed in the sinus node and conducted through a specialized system to the endocardial Purkinje network and the myocardium. The main types of arrhythmia leading to sudden cardiac death are tachyarrhythmias and bradyarrhythmias. The tachyarrhythmias associated with sudden cardiac death include ventricular fibrillation, ventricular tachycardia, and torsade de pointes. The bradyarrhythmias include sinus bradycardia, complete atrioventricular block, and sudden asystole. Holter monitor recordings in patients with cardiac disease frequently demonstrate ventricular tachycardia leading to ventricular fibrillation and, less frequently, bradyarrhythmic heart block leading to asystole.[4-9] Elevation of the ST segment often precedes bradyarrhythmic asystole,[4,5,8] although 1 series[10] has documented an equal frequency of ST segment abnormalities in both the tachyarrhythmias and the bradyarrhythmias that lead to sudden cardiac death.

Autopsy studies performed after sudden cardiac death usually lack evidence of new myocardial infarction.[11,12] Whether an acute arterial lesion forms during the period just before sudden cardiac death remains controversial. In an autopsy study of 100 individuals after sudden cardiac death, Davies and Thomas[13] defined major luminal occlusion as ≥50% of the cross-sectional area, and found that 44% of the individuals with ischemic heart disease had a recent thrombosis of that magnitude. When all cases of intraluminal thrombosis were included (1% to 100% luminal occlusion), 74 of 100 hearts tested had thrombosis. Davies[14] performed pathologic evaluation on the hearts of 168 individuals who died of ambulatory sudden cardiac death. Of these, 73.3% showed a recent coronary thrombotic lesion, and the remainder showed chronic high-grade coronary stenosis. Study of the cardiac neural elements has yielded results suggesting that autonomic damage is associated with sudden death. James[15] demonstrated that a variety of inflammatory and degenerative lesions can affect the intracardiac nerves and ganglia, as well as the coronary chemoreceptor. Another group[16] documented catecholamine depletion in adrenergic elements of the cardiac nerve plexi.

The underlying cause of sudden cardiac death remains unclear despite several proposed mechanisms. Early research emphasized heart disease as the cause of the arrhythmias that produce sudden cardiac death. Indeed, the patient who has cardiac disease does have a higher risk of sudden cardiac death; congestive heart failure[17] and complex ventricular activity[18] both increase the risk. In 25% to 30% of individuals who have multiple-vessel atherosclerotic coronary artery disease, no recognized symptoms of heart disease precede sudden cardiac death.

Alternative hypotheses focus on the compromised heart as fertile ground for the development of arrhythmia. One such hypothesis proposes that the premature ventricular beat may trigger ventricular fibrillation, particularly in the presence of myocardial ischemia. Within this framework, individuals who have ischemic heart disease would be considered at greater risk for sudden cardiac death due to an increased frequency of premature ventricular beats.[19] The hypothesis of autonomic balance[20,21] suggests that the heart maintains normal activity when sympathetic and parasympathetic activities are in balance; cardiac arrhythmias result from the loss of autonomic balance. In studies using the balanced autonomic animal model,[21] parasympathetic blockade has resulted in tachyarrhythmias, and sinoatrial node removal has produced brady-tachyarrhythmia similar to that which accompanies the sick sinus syndrome seen in clinical practice. Lown[22] described the heart as a target and the brain as the trigger. Sudden cardiac death in this context is triggered by an "electrical accident,"[23] which can be treated with ventricular defibrillation; in such cases, patients generally return to their prior state of health.

## Neuroanatomy

Review of neuroanatomy facilitates recognition and analysis of the neurocardiologic links in the pathogenesis of malignant cardiac arrhythmia. Since our 1985 article on neurocardiology,[2] more recent literature has described influences on the heart from additional brainstem nuclei, the amygdaloid complex, and the cortex.[24-33] Figure 1 depicts a complex of higher nervous influences that descend to the heart in cascade fashion, innervating key autonomic structures affecting heart rate and rhythm within the brainstem and modifying the efferent information relayed to the heart. The heart receives neural input through parasympathetic ganglia and the intermediolateral gray column of the spinal cord, both of which are influenced by multiple medullary nuclei.

With few exceptions, most of the higher centers provide descending efferent connections with medullary nuclei. The cortex and amygdaloid complexes have many connections with all of the lower levels.

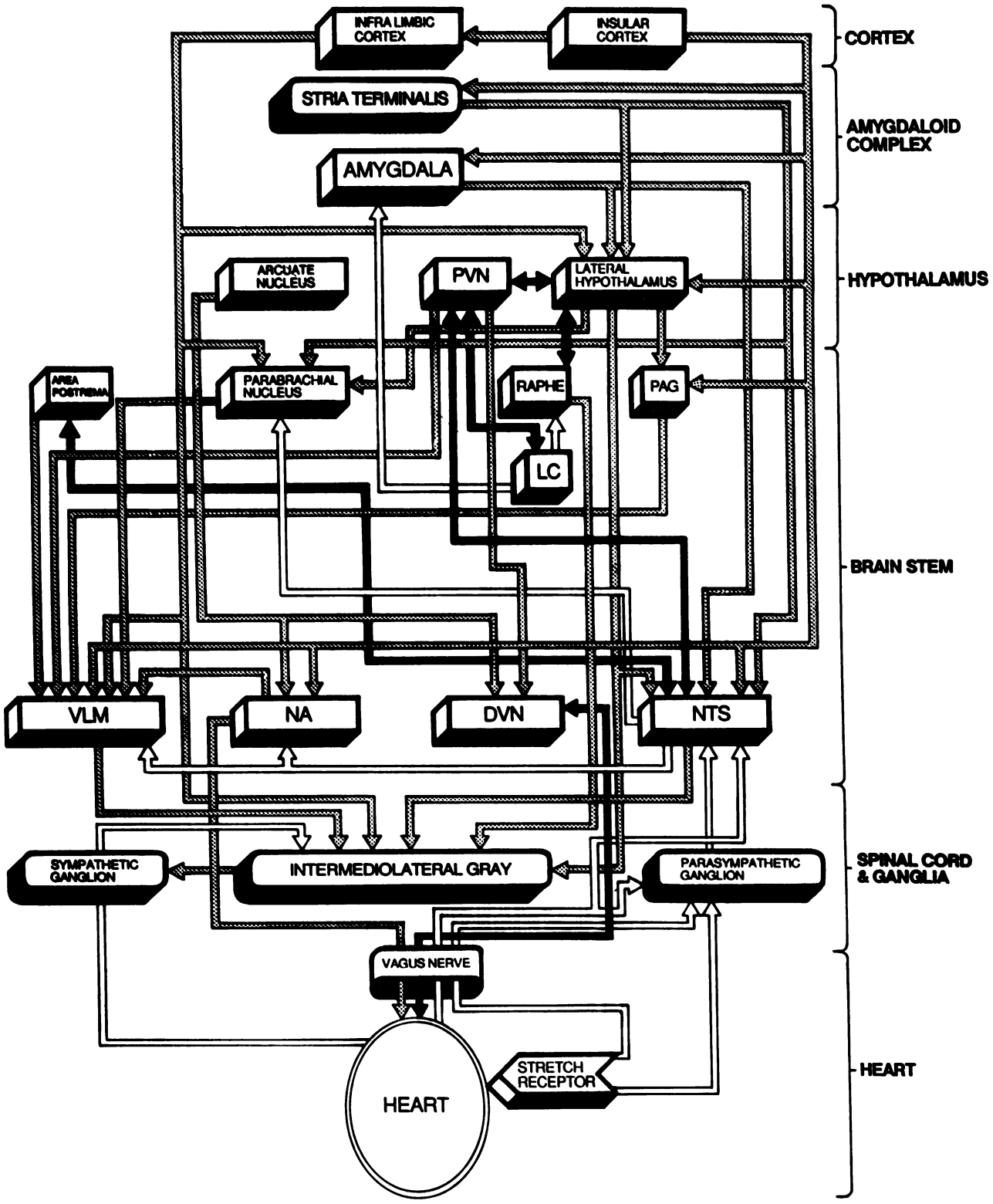


***Fig. 1*** *Neuroanatomic links producing arrythmia.*

*DVN = dorsal vagal nucleus; LC = locus coeruleus; NA = nucleus ambiguus; NTS = nucleus tractus solitarius; PAG = periaqueductal gray matter; PVN = paraventricular nucleus; VLM = ventrolateral medulla*

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Hypothalamic nuclei send descending connections to brainstem, spinal cord, and ganglia. The nucleus tractus solitarius (NTS) connects reciprocally with both the paraventricular nucleus (PVN) and the area

postrema. As part of the parasympathetic efferent motor system, the NTS provides afferent information to the parabrachial nucleus, which sends fibers to the ventrolateral medulla (VLM). Depending on the species studied, vagal and sympathetic nerves leading to the heart may be confluent rather than discrete. Afferent nerves from the heart stretch, and chemoreceptors ascend via the spinal cord or the 9th or 10th cranial nerve to terminate in the NTS and the dorsal vagal nucleus (DVN).

## Peripheral Nerve Activity and Arrhythmia

*Animals with Normal Hearts.* We now examine the conditions that contribute to malignant arrhythmias, or "electrical accidents" in the case of sudden cardiac death. Studies of neurocardiac axis activation in animals have documented that stimulating the peripheral nervous system can produce both arrhythmia and pathologic changes within the heart. Stimulating either the ventrolateral[34] or the ventromedian[35] sympathetic cardiac nerve in dogs elicits nodal arrhythmias and, less often, ventricular arrhythmias. Randall and co-authors[20] developed a canine model of autonomic imbalance leading to cardiac arrhythmias; they surgically denervated the heart, sparing only the ventrolateral nerve. During strenuous exercise, the dogs manifested multiple abnormal rhythms, including ventricular tachycardia and premature ventricular beats.

Programmed ventricular stimulation is a method of testing for sensitivity to the development of ventricular arrhythmias. The ventricle is stimulated for a short series of beats, and additional stimulation is administered in an attempt to elicit ventricular ectopy. One group of investigators[36] used programmed ventricular stimulation combined with either bilateral ansa subclaviae stimulation or norepinephrine infusion, which produced ventricular arrhythmias after regional sympathetic denervation in dogs. Pathologic changes due to arrhythmia after peripheral nerve stimulation include subendocardial hemorrhage with myofibrillar degeneration and necrosis, which have been noted after stellate ganglion stimulation in healthy dogs,[37] after peripheral stimulation and aortic arch stimulation,[38] and after norepinephrine infusion.[36]

*Animals with Abnormal Hearts.* Arrhythmias may develop in an ischemic or infarcted heart during peripheral nervous system stimulation. Sympathetic hyperactivity due to ischemia[39] and dyshomogeneity of sympathetic innervation due to infarction[40] are associated with malignant ventricular arrhythmia. Inoue and Zipes[41] developed a canine model of myocardial infarction with sympathetic or parasympathetic denervation, or both. Using programmed ventricular stimulation, they measured the incidence of ventricular fibrillation and found that it occurred most frequently in the nontransmural infarction group with sympathetic fiber interruption. The group that had transmural myocardial infarction and interrupted sympathetic fibers showed denervation supersensitivity; however, programmed stimulation did not increase their vulnerability to ventricular fibrillation. These researchers suggested that the dyshomogenous nontransmural myocardial infarction might produce nonuniform depression of excitability and conduction. The incidence of ventricular fibrillation increased most in those dogs with sympathetic denervation, and during norepinephrine infusion. Propranolol attenuated both the shortening of the effective refractory period and the induction of ventricular fibrillation.

In a similar cat model, Schwartz and colleagues[42] evaluated the effectiveness of antiarrhythmic agents. Class I antiarrhythmics (lidocaine, mexiletine, and propafenone) did not protect the animals from lethal arrhythmias, and in some cases were proarrhythmogenic. Prazosin and propranolol (Class II antiarrhythmics), however, were 60% and 80% effective, respectively. The calcium channel blocker verapamil (Class III) protected completely against induced ventricular tachycardia and ventricular fibrillation, as did amiodarone (Class IV). Effectiveness seemed related to the ability of the drug to decrease both sympathetic outflow and coronary ischemia through vasodilation. Using left ansae stimulation and right ansae transection in an ischemic canine model, Euler and associates[43] demonstrated that the sympathetic nervous system has a direct arrhythmogenic effect (on ventricular fibrillation) independent of heart rate.

In contrast to sympathetic stimulation, parasympathetic stimulation appears to protect the heart against arrhythmia. In studies of previously infarcted dogs, direct stimulation of the right vagus nerve provided 90% protection against ventricular fibrillation during exercise.[44] Decreasing vagal activity with atropine increased the incidence of arrhythmias, including ventricular fibrillation, in approximately 75% of exercising dogs tested.[45] Low levels of intravenous acetylcholine were found to augment the duration of ventricular fibrillation in rats; higher doses produced the opposite effect.[46]

Risk of exercise-induced ventricular fibrillation can also be assessed by measuring baroreceptor reflex sensitivity, which is the change in heart rate that occurs as blood pressure is manipulated pharmacologically. Integrating sympathetic and parasympathetic reflexes, Schwartz and coworkers[47] measured baroreceptor reflex sensitivity in previously infarcted dogs to evaluate susceptibility to ventricular fibrillation during the sympathetic stimulation caused by ischemia and strenuous exercise. Dogs with a lower baroreceptor reflex sensitivity had a significantly higher risk of exercise-induced ventricular fibrilla-

tion. These studies support the hypothesis that there is a critical autonomic balance that prevents cardiac arrhythmia. Ischemia and myocardial infarction appear to upset this balance, which predisposes the diseased animal heart to a higher risk of arrhythmia.

## Central Nervous System Activity and Cardiac Dysfunction

*Animals with Normal Hearts.* Animal models of human central nervous system disease demonstrate that electrocardiographic changes, cardiac arrhythmias, and sudden death may arise from the effects of central nervous system activation. Spinal cord compression and head trauma have both produced cardiac arrhythmias in monkeys.[48,49] In a study by McNair and coworkers,[50] subarachnoid blood in mice produced myocardial necrosis in 48% of the animals. This cardiac damage was prevented by pretreatment with reserpine and attenuated by atropine.[50,51] Raising intracranial pressure in rats resulted in increased plasma catecholamine levels and myocardial damage.[52] Uchida and associates[53] injected rabbits with prostaglandin $PGF_{2\alpha}$ intracisternally and recorded electrocardiographic changes, including bradycardia, premature beats, ventricular tachycardia, and ventricular fibrillation. Middle cerebral artery stroke in the rat resulted in subendocardial damage, increased pulse and arterial pressures, and increased plasma catecholamines.[54] Smith's group[55] measured plasma levels of norepinephrine, epinephrine, and dopamine in cats during occlusion of the left middle cerebral artery; these plasma levels were elevated significantly when the stroke involved the insular cortex, but not when sham-operated or cerebral infarction spared the insula. This finding suggests that the sympathetic stimulation occurring after stroke may be specific to the insula.

Animal models of epilepsy also demonstrate that central nervous system dysfunction may result in cardiac arrhythmias and sudden death. Using a cat model of epilepsy induced by pentylenetetrazol, Lathers and co-authors[56] observed that preganglionic sympathetic and vagal discharges were correlated in time with both ictal and interictal spikes on the concurrent electroencephalogram. This synchronization of electroencephalographic activity with cardiac neural discharge occurred more frequently with sympathetic than with vagal neural discharge. The authors suggested this synchronization of epileptiform spikes with cardiac sympathetic neural discharge as a possible explanation of sudden unexplained epileptic death without overt seizure activity. Various doses of pentylenetetrazol[56,57] produced differential autonomic imbalance without overt epileptiform activity. Moderate doses (50 mg/kg) resulted in more parasympathetic variability in discharge, whereas higher doses (100 mg/kg) resulted in increased sympathetic nerve discharge.[57] Kindled seizures in rats[58] generated by subthreshold electrical stimulation of the amygdala induced cardiac arrhythmias, including premature ventricular complexes, profound bradycardia, and increased PR interval during seizure activity. Hypothalamic chemical stimulation producing focal epilepsy in hemispherectomized rats[59] resulted in bradyarrhythmias, sinus arrest, and ventricular bigeminy. These results show that epilepsy also activates the neurocardiac axis and disrupts autonomic balance, leading to potentially fatal cardiac arrhythmias.

Stimulation of specific brain areas activates the brain–heart links and results in cardiac arrhythmia and morphologic cardiac changes. Administering lateral hypothalamic stimulation in cats[60] has produced subendocardial damage. In a study by Evans and Gillis,[61] sinoatrial node denervation prior to hypothalamic stimulation consistently allowed the occurrence of stimulus-bound nodal arrhythmias, presumably due to unmasking of the subatrial pacemakers. Propranolol and phenytoin each prevented these arrhythmias and the concomitant sympathetic hyperactivity. Oppenheimer and associates[62] used phasic electrical stimulation of the insula locked to specific times in the cardiac cycle of rats, producing electrocardiographic changes and progressive heart block leading to ventricular ectopy and death in asystole. Plasma norepinephrine levels were raised markedly and myocardial damage was documented.

*Animals with Abnormal Hearts.* Similarly, experimental studies demonstrate that central nervous system stimulation of the abnormal heart through anatomic links can also affect the production of malignant arrhythmias. Digitalis toxicity, a commonly seen cardiac problem, may cause ventricular arrhythmias. Sympathetic blockade prevents these arrhythmias in guinea pigs.[63] The brain site for digitalis-related cardiac arrhythmias has not been clearly identified. In their work with rabbits, Markgraf and Kapp[64] administered digitalis and then electrically stimulated the amygdaloid central nucleus, which elicited bradycardia followed by ventricular ectopy, premature ventricular beats, and bundle-branch block. These investigators then used Pavlovian conditioning to reproduce the arrhythmias with an aversive conditioned stimulus in the rabbits[64] as had been done previously in guinea pigs.[65] Experimentally-induced bilateral lesions in the amygdaloid central nuclei attenuated the conditioned-stimulus arrhythmias.[64] In cats, the anterior hypothalamus[66] and the midbrain[67] are other sites that have been shown to attenuate the production of digitalis-related arrhythmias. The area postrema has been disproved as a facilitating area for these arrhythmias.[68]

Using the infarcted animal heart enables investigators to examine the ways in which the central

nervous system contributes to arrhythmogenesis. In such studies, a coronary artery is usually ligated to predispose the heart to arrhythmia before specific areas of the central nervous system are stimulated or ablated. Somberg and colleagues[69] ligated the left coronary artery and recorded a lower incidence of arrhythmias in cats after brainstem transection at the obex. Skinner's group functionally blocked the frontal lobes[70] and the amygdaloid central nucleus[71] in pigs, which decreased the incidence of ventricular fibrillation.

Recently, investigators using animal models of arrhythmia caused by drugs or infarction have modified arrhythmias with a variety of drugs administered by intracerebroventricular injection. In 1 study involving guinea pigs,[72] both morphine and dynorphin were found to increase the dose at which digoxin-induced arrhythmias occurred; this attenuation was reversed by atropine sulfate, which crosses the blood–brain barrier. These results support evidence that central cholinergic parasympathetic mechanisms influence the production of arrhythmias. Central nervous system activation, superimposed upon the compromised heart, provides a fertile setting for arrhythmogenesis.

## Environmental Stress and Cardiac Dysfunction

*Animals with Normal Hearts.* Stress alone does not produce potentially lethal arrhythmias in studies of animals with normal hearts.[2] However, stress does appear to cause cardiac damage that may lead to arrhythmia. A study in which monkeys were given a high-cholesterol diet and then subjected to social disruption[73] revealed development of microscopic endothelial damage, the precursor of coronary artery disease. To test whether sympathetic arousal and the resulting increase in heart rate led to these changes, the researchers administered the $\beta_1$-adrenergic blocking agent metoprolol and noted inhibition of the endothelial injury.[73] When pharmacologically paralyzed pigs were subjected to occasional electric shocks[74] over a 15- to 20-minute period, malignant arrhythmias developed in 16 of 23. Two days later the 20 surviving animals were killed, and pathologic heart changes were noted in all.

*Animals with Abnormal Hearts.* Researchers have formulated 3 basic animal paradigms to evaluate the contribution of stress to arrhythmogenesis in the compromised heart: drug administration, coronary infarction, and genetic predisposition to heart disease. Drug administration may increase the susceptibility of the normal heart to arrhythmia. In our laboratory,[75,76] psychological stress sensitized guinea pigs to digitalis-induced arrhythmias due to changes in peripheral cholinergic function. In a learned fear model using rabbits,[77] arrhythmias due to digitalis toxicity occurred earlier and more frequently in the rabbits conditioned to expect a shock after hearing a tone than in those that were given randomly administered shocks and tones.

The 2nd model uses a coronary infarct to sensitize the heart to arrhythmia. Randall and Hasson[78] applied classical aversive conditioning in monkeys after left anterior descending coronary artery occlusion. Although the aversive situations did not necessarily cause more arrhythmia, the investigators noted that ventricular arrhythmias occurred most frequently when the heart rate of an animal was within a specific range. This finding was attributed to the underlying sympathetic and parasympathetic balance. In dogs with healed, experimentally-induced myocardial infarction, stress caused a re-emergence of the early ventricular arrhythmias seen in the acute infarction period.[79,80] In a study of pigs[70] having temporary occlusion of the left anterior descending coronary artery, ventricular fibrillation occurred when the animals were stressed by having their feet taped together. Bilateral cryoblockade of the amygdala blocked this lethal effect in 5 of 8 animals. Kirby's group[81] used a porcine model with previous myocardial infarction and noted that increased behavioral arousal or social stress enhanced the inducibility and rate of ventricular tachycardia; metoprolol blocked this enhancement. In another study[82] using pigs with recent experimentally-induced myocardial infarction, researchers noted a decreased extrasystole threshold during repetitive stimulation in comparison with normal controls. Ninety minutes after administration of the catecholamine precursor tyrosine, the threshold increased to near-control levels.

The 3rd method uses animals with genetic predisposition to heart disease. Cardiomyopathic hamsters, for example, develop congestive cardiomyopathy with focal sites of micronecrosis and die early. When cold and immobilization[83] were used as stressors to activate the sympathetic nervous system, healthy hamsters were not affected by the stress, but cardiomyopathic hamsters died. Alprazolam significantly reduced the stress-induced mortality.[83] Verapamil sensitized the hamsters to stress,[84] causing arrhythmic death, presumably due to verapamil's inhibition of atrioventricular nodal conduction. As opposed to those with normal hearts, animals with abnormal hearts frequently died of arrhythmia when subjected to environmental stress.

## Laterality of Function

*Animal Hearts.* Both the sympathetic and the parasympathetic branches of the central nervous system that influence cardiac rhythms demonstrate laterality of function. In our earlier review,[2] we noted a right-sided predominance for the control of heart

rate and a left-sided predominance in the genesis of arrhythmias. The work with animals[85] showed that stimulating the left stellate ganglion lowered the threshold for ventricular fibrillation; in contrast, stimulating the right stellate ganglion raised the threshold.[85] The left stellate ganglion was ablated in experiments designed to reduce the risk of arrhythmogenesis. Because animal studies showed that stimulation of the left stellate ganglion produced ventricular fibrillation and its ablation protected the animal from this arrhythmia,[63,86] similar studies were developed for application in human beings.

*Human Hearts.* Individuals with idiopathic long Q-T syndrome[87] have prolonged Q-T interval and syncopal episodes due to ventricular fibrillation; these usually result in sudden death during the first 2 decades of life. Death often occurs under conditions that increase sympathetic activity, such as strong emotions or physical exertion. β-Adrenergic blocking agents markedly decrease the syncopal episodes; however, a subgroup of individuals with long Q-T syndrome continue to experience syncope. Fifty-seven patients who did not respond to β-blockers underwent neurosurgical treatment with high left thoracic stellectomy, a surgical approach that removes the first 4 to 5 thoracic ganglia. This approach markedly decreased the mortality rate of this high-risk subgroup from 70% in the first 5 years to less than 7% after 7 years of this ongoing study.[87] In a clinical trial[88] enrolling patients with anterior myocardial infarction complicated by ventricular fibrillation, high thoracic left sympathectomy decreased the mortality rate from 21.3% to 3.6%.

Consistent with previous findings regarding lateralization of rhythm control, a review of the Holter monitor recordings of patients with lateralized stroke[89] documented sinus tachyarrhythmias only in patients with right-sided strokes. These results demonstrate a loss of right-sided predominance of parasympathetic control in addition to the increased sympathetic tone associated with stroke.

## Noninvasive Assessment of Nerves to the Heart and Risk of Sudden Death

Parasympathetic activity generally provides an antiarrhythmic effect by slowing heart rate, antagonizing sympathetic activity, and effecting electrophysiologic changes in the myocardium.[90] Vagal overstimulation rarely causes arrhythmias.[91] Measuring the level of parasympathetic activity may therefore provide a rational basis for assessing risk of sudden cardiac death. Heart rate variability results from the coupling of respiration to the duration of time between heart beats, which produces the commonly observed respiratory sinus arrhythmia seen during electrocardiographic evaluation of young healthy individuals. This coupling, which results in heart rate variability, is mediated by the parasympathetic nervous system through the vagus nerve and can be diminished by atropine.[92] Because this variability can be measured electrocardiographically, investigators have a noninvasive method to determine the level of cardiac parasympathetic activity.

This approach has been used by Kleiger and coworkers[93] to calculate the relative risk of cardiac mortality after myocardial infarction. They found that patients with reduced heart rate variability (<50 msec) had 5 times the mortality of individuals whose heart rate variability was more than 100 msec. Rich and co-authors[94] extended the study of heart rate variability to include 100 individuals without recent myocardial infarction who were undergoing coronary angiography. Using baseline Holter monitor recordings and observing these individuals for 1 year, the investigators noted a markedly higher mortality rate in those with reduced heart rate variability (<50 msec, 36%; >50 msec, 2%).

Recently, more sophisticated methods of measuring interbeat interval change during respiration have led to clearer insights into the factors contributing to heart rate variability. Power spectrum analysis of heart rate variability serves as a very sensitive tool for understanding cardiac control. This statistical technique allows greater precision in finding sources of interbeat variability, breaking them down into specific frequencies. A peak on the frequency spectrum occurring at about 0.2 cycles/sec represents the variability due to respiration and has been shown to be purely parasympathetic.[92,95] Other sources of cardiac rhythm control such as sympathetic activity, parasympathetic–sympathetic interaction, and hormonal release can also be analyzed with power spectrum analysis. In addition, this method has been used to demonstrate a circadian rhythm in heart rate variability,[96] to show abnormal autonomic heart rate influences in patients with Alzheimer's disease,[97] to provide a marker of vulnerability to stress,[98] and to calculate the likelihood of surviving sudden cardiac arrest.[99] Spectrum analysis has also enabled investigators to measure reproducible differences in the heart rate variability of individuals who have congestive heart failure compared with those who have normal heart function.[100] The heart rate spectrum has been correlated with mortality to determine the prognosis of patients with end-stage heart failure.[101]

Baroreceptor reflex sensitivity measurement evaluates vagal reflexes and has also been used to assess the risk of sudden death. Baroreceptor reflex sensitivity (BRS) represents the change in heart rate that occurs as blood pressure is manipulated pharmacologically. Low BRS indicates that heart rate changes minimally in response to such changes; high BRS indicates that the heart rate responds readily to changes in blood pressure. In a prospective clinical

study of patients enrolled 1 month after myocardial infarction, Schwartz and colleagues[102] assessed the correlation between BRS and cardiac mortality. During the course of the study, mortality was 50% in the group having absent or low BRS compared with 3% in the group having higher BRS.

## Human Studies Implicating the Nervous System in the Pathogenesis of Arrhythmias

After reviewing neuroanatomy and animal studies that show the existence and function of brain–heart links leading to cardiac arrhythmias, we examine whether commonly encountered neurologic syndromes also lead to arrhythmia. Stroke, epilepsy, and environmental stress all provide clinical examples of how the neurocardiac axis may be activated.

*Stroke.* Stroke activates the neurocardiac axis, producing arrhythmia, cardiac damage, and sudden death. Electrocardiographic abnormalities and cardiac arrhythmias following stroke have been reported. Andreoli and associates[103] systematically evaluated 70 patients during the 1st acute phase of subarachnoid hemorrhage using continuous Holter monitoring. They found that 41% of the individuals studied had severe cardiac arrhythmias, including ventricular fibrillation, successive ventricular premature complexes, supraventricular tachycardia, and bradyarrhythmias. They noted no correlation between age and the occurrence or severity of heart disease. Continuous electrocardiographic monitoring after subarachnoid hemorrhage[104] documented more cardiac arrhythmias (except for sinus bradycardias and asystole) in a subgroup of patients with midbrain symptoms, which may provide clinical evidence of lost hypothalamic–medullary integration at a midbrain synapse. Overactivity of the parasympathetic nervous system may also cause sudden death with asystole after stroke.[105] Oppenheimer and Hachinski[106] have suggested that an increase in catecholamines is 1 possible mediator of electrocardiographic changes and heart damage.

*Epilepsy.* Sudden unexplained death in patients with epilepsy occurs at a rate of about 2 per thousand.[107] According to their clinical histories, death occurs in young patients who have generalized seizures with subtherapeutic serum levels of anticonvulsant medication and have a history of alcohol or substance abuse.[108-110] Susceptibility to sudden cardiac death in a person having epilepsy might be due to a brain focus that is stimulating arrhythmia. Simultaneous recordings during seizures[111-113] have demonstrated an association between electrocardiographic abnormalities and electroencephalographic changes. Typical electrocardiographic changes include the onset of tachycardia just before the seizure with both atrial and ventricular ectopy. Sinus arrest [114-117] and ventricular tachycardia[111] have also been reported. Earnest and associates[109] retrospectively studied patients who died of epileptic sudden death in comparison with those who had epilepsy but were otherwise healthy. These investigators measured a significantly prolonged Q-Tc (corrected for rate) interval—a known risk for sudden death—in the group that died; their risk appears to be comparable with that of individuals who have idiopathic long Q-T syndrome. Prolonged Q-Tc interval may be a marker for electrical instability resulting from central nervous system stimulation or instability.[109] The tachycardia and elevated catecholamines[118] associated with sudden unexpected epileptic death may be a result of sympathetic activation or autonomic imbalance brought on by the same brain–heart links that lead to sudden cardiac death.

*Stress.* The lay community would not argue that emotional stress contributes to mortality. The expression that someone "died of a broken heart" does have epidemiologic support. In a prospective Finnish study of 95,647 widowed individuals,[119] the highest mortality occurred during the 1st week of bereavement with more than double the expected risk. The presence of ischemic heart disease further increased this rate to 2.3 times the risk for men and 3.5 for women.[119] The influence of psychosocial factors on mortality after myocardial infarction has been explored extensively.

Lown's group[120] suggested that stress is a precipitant of ventricular premature contractions with ventricular fibrillation, both in patients with normal hearts[120] and in those with heart disease.[19] In a group of patients with frequent ventricular premature beats but no previous myocardial infarction,[121] psychological profiles described higher hysteria scores and more anxiety, depression, and social isolation when compared with the profiles of general medical and surgical patients. In a study of 2,320 men enrolled in the β-Blocker Heart Attack Trial, Ruberman[122] noted that a high degree of life stress and social isolation occurred with greater frequency in the individuals with less education, and these factors correlated with a fivefold increased risk of sudden death for the 3 years following myocardial infarction. One study of arrhythmia after myocardial infarction[123] revealed that the level of self-reported psychological stress predicted an increased risk of ventricular ectopy and malignant arrhythmias. Frasure-Smith and Prince[124] monitored life stress intermittently in 453 male myocardial infarction patients and used stress reduction techniques when the stress score passed a critical level. During a 1-year period, fewer deaths occurred in the monitored group receiving treatment for stress than in the group not monitored. Tavazzi and associates[125] used programmed ventricular stimulation to study the stress of mental arithmetic in patients after myocardial infarction; their results suggested that this

stressor lowers the fibrillation threshold in such patients.

## Conclusions

This paper maps the nervous system anatomy affecting the genesis of cardiac arrhythmias, reviews experimental studies showing these interactions, and presents typical clinical examples of brain–heart interactions. The diseased heart is more sensitive to the development of arrhythmias than is the normal heart. Hypothetical mechanisms through which the neurocardiac links become activated include autonomic imbalance, premature ventricular beats leading to malignant arrhythmias, or heart disease itself. The role of catecholamines presents a unifying hypothesis involving such diverse entities as stroke, epilepsy, and environmental stress and how they result in arrhythmia and cardiac damage.[126-128] However, catecholamine release stems from neural activation; therefore, it is the nervous system that plays the crucial role in determining whether arrhythmias will occur in the compromised heart, and for this reason we place the nervous system at the top of a cascade of pathophysiologic events that can end in sudden cardiac death.

Clinicians evaluating patients who have been experiencing arrhythmia under conditions that stimulate the central nervous system should consider the neurocardiac links described. Medical training programs in the United States emphasize expertise in single systems at the expense of interdisciplinary skills. Growing recognition of this deficiency means that the physicians of the future are more likely to have a working knowledge of integrated systems, which will provide them with a broader perspective when evaluating and treating patients.

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