

The Brain–Heart Connection Martin A. Samuels

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The Brain–Heart Connection

Martin A. Samuels, MD

Neurocardiology has many dimensions, but it may be conceptualized as divided into 3 major categories: the heart's effects on the brain (eg, cardiac source embolic stroke), the brain's effects on the heart (eg, neurogenic heart disease), and neurocardiac syndromes (eg, Friedreich disease). The present review deals with the nervous system's capacity to injure the heart. This subject is inherently important but also represents an example of a much more widespread and conceptually fascinating area of neurovisceral damage in general.

History of Learning the Nature of the Brain–Heart Connection

In 1942, at the culmination of his distinguished career as Professor of Physiology at Harvard Medical School, Walter B. Cannon published a remarkable paper entitled “‘Voodoo’ Death,”¹ in which he recounted anecdotal experiences, largely from the anthropology literature, of death from fright. These often remote events, drawn from widely disparate parts of the world, had several features in common. They were all induced by an absolute belief that an external force, such as a wizard or medicine man, could, at will, cause demise and that the victim himself had no power to alter this course. This perceived lack of control over a powerful external force is the sine qua non for all the cases recounted by Cannon, who postulated that death was caused “by a lasting and intense action of the sympathico-adrenal system.” Cannon believed that this phenomenon was limited to societies in which the people were “so superstitious, so ignorant, that they feel themselves bewildered strangers in a hostile world. Instead of knowledge, they have fertile and unrestricted imaginations which fill their environment with all manner of evil spirits capable of affecting their lives disastrously.” Over the years since Cannon's observations, evidence has accumulated to support his concept that “voodoo” death is, in fact, a real phenomenon but, far from being limited to ancient peoples, may be a basic biological principle that provides an important clue to understanding the phenomenon of sudden death in modern society as well as providing a window into the world of neurovisceral disease (also known as psychosomatic illness).

George Engel collected 160 accounts from the lay press of sudden death that were attributed to disruptive life events.² He found that such events could be divided into 8 categories:

(1) the impact of the collapse or death of a close person; (2) during acute grief; (3) on threat of loss of a close person; (4) during mourning or on an anniversary; (5) on loss of status or self-esteem; (6) personal danger or threat of injury; (7) after danger is over; (8) reunion, triumph, or happy ending. Common to all is that they involve events impossible for the victim to ignore and to which the response is overwhelming excitation, giving up, or both.

In 1957, Curt Richter reported on a series of experiments aimed to elucidate the mechanism of Cannon's “voodoo” death.³ Richter, a former student of Cannon, pursued an incidental discovery of an epidemic of sudden death in a colony of rodents, which was induced when a colleague, Gordon Kennedy, had clipped the whiskers of the animals to prevent contamination of the urine collection. Richter studied the length of time that domesticated rats could swim at various water temperatures and found that at a water temperature of 93°C these rats could swim for 60 to 80 minutes. However, if the animal's whiskers were trimmed, it would invariably drown within a few minutes. When carrying out similar experiments with fierce wild rats, he noted that a number of factors contributed to the tendency for sudden death, the most important of which was restraint, which involved holding the animals and confinement in a glass swimming jar with no chance of escape. By trimming the rats' whiskers, a procedure that destroys possibly their most important proprioceptive mechanism, the tendency for early demise was exacerbated. In the case of the calm domesticated animals in which restraint and confinement were apparently not significant stressors, removal of whiskers rendered these animals as fearful as wild rats with a corresponding tendency for sudden death. ECGs taken during the process showed development of a bradycardia prior to death, and adrenalectomy did not protect the animals. Furthermore, atropine protected some of the animals, and cholinergic drugs led to an even more rapid demise. All this was taken as evidence that overactivity of the sympathetic nervous system was not the cause of the death but rather it was caused by increased vagal tone.

We now believe that the apparently opposite conclusions of Cannon and Richter are not mutually exclusive, but rather that a generalized autonomic storm, which occurs as a result of a life-threatening stressor, will have both sympathetic and parasympathetic effects. The apparent predominance of one

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over the other depends on the parameter measured (eg, heart rate, blood pressure) and the timing of the observations in relation to the stressor (eg, early events tend to be dominated by sympathetic effects, whereas late events tend to be dominated by parasympathetic effects). Cerebral hemispherical dominance with regard to autonomic control (right predominantly sympathetic and left predominantly parasympathetic) probably also contributes to the dominant mechanism of sudden death (ie, sympathetic versus vagal) in a given person.⁴

In human beings, one of the easily accessible windows into autonomic activity is the ECG. Edwin Byer and colleagues reported 6 patients whose ECGs showed large upright T waves and long QT intervals.⁵ Two of these patients had hypertensive encephalopathy, 1 patient had a brain stem stroke with neurogenic pulmonary edema, 1 patient had an intracerebral hemorrhage, 1 patient had a postpartum ischemic stroke possibly related to toxemia of pregnancy, and 1 patient had no medical history except a blood pressure of 210/110 mm Hg. On the basis of experimental results of cooling or warming the endocardial surface of a dog's left ventricle, Byer and colleagues concluded that these ECG changes were caused by subendocardial ischemia. Harold Levine reported on several disorders other than ischemic heart disease that could produce ECG changes reminiscent of coronary disease.⁶ Among these was a 69-year-old woman who was admitted and remained in coma. Her admission ECG showed deeply inverted T waves in the anterior and lateral precordial leads. Two days later, it showed ST segment elevation with less deeply inverted T waves, a pattern suggestive of myocardial infarction. However, at autopsy a ruptured berry aneurysm was found and no evidence of myocardial infarction or pericarditis was noted. Levine did not propose a specific mechanism but referred to experimental work on the production of cardiac arrhythmias by basal ganglia stimulation and ST and T-wave changes induced by injection of caffeine into the cerebral ventricle.

George Burch and colleagues⁷ reported on 17 patients who were said to have "cerebrovascular accidents" (ie, strokes). In 14 of the 17, hemorrhage was demonstrated by lumbar puncture. It is not possible to determine which of these patients had hemorrhagic infarction, intracerebral hemorrhage, and subarachnoid hemorrhage, and no data about the territory of the strokes are available. The essential features of the ECG abnormalities were: (1) long QT intervals in all patients; (2) large, usually inverted, T waves in all patients; and (3) U waves in 11 of the 17 patients.⁷

Cropp and Manning⁸ reported on the details of ECG abnormalities in 29 patients with subarachnoid hemorrhage. Twenty-two of these patients survived. Two of those who died had no postmortem examination, which left 5 patients in whom autopsies confirmed the presence of a ruptured cerebral aneurysm. In 3 of these 5 patients, the heart and coronary arteries were said to be normal, but the details of the pathological examination were not revealed. The point is made that ECG changes seen in the context of neurological disease do not represent ischemic heart disease but are merely a manifestation of autonomic dysregulation, possibly caused by a lesion that affected the cortical representation of the

autonomic nervous system. The authors argued that Brodmann area 13 on the orbital surface of the frontal lobe and area 24 on the anterior cingulate gyrus were the cortical centers for cardiovascular control.

There is clear evidence that cardiac lesions can be produced as the result of nervous system disease. The concept of visceral organ dysfunction that occurs as a result of neurological stimuli can be traced to Ivan Pavlov. Hans Selye, a student of Pavlov, described electrolyte-steroid-cardiopathy with necroses (ESCN).⁹ Selye's view was that this cardiac lesion was common and often described by different names in the literature. He argued that this lesion was distinct from the coagulation necrosis that occurred as a result of ischemic disease, but that it could exist in the same heart. Selye demonstrated that certain steroids and other hormones created a predisposition for the development of ESCN, but that other factors were required for ESCN to develop. The most effective conditioning steroid was 2- α -methyl-9- α -fluorocortisol. Among the factors that led to ESCN in steroid-sensitized animals were certain electrolytes (eg, NaH₂PO₄), various hormones (eg, vasopressin, adrenaline, insulin, thyroxine), certain vitamins (eg, dihydrotachysterol), cardiac glycosides, surgical interventions (eg, cardiac reperfusion after ischemia), and psychic or nervous stimuli (eg, restraint, fright). The cardiac lesions could not be prevented by adrenalectomy, which suggests that the process, if related to sympathetic hyperactivity, must exert its influence by direct neural connection to the heart rather than by a blood-borne route.

Cardiac lesions may be produced in rats by pretreatment with either 2- α -methyl-9- α -fluorohydrocortisone (fluorocortisol), dihydrotachysterol (calciferol), or thyroxine and then restraint of the animals on a board for 15 hours or with cold stress.¹⁰ Agents that act by inhibition of the catecholamine-mobilizing reflex arc at the hypothalamic level (eg, chlorpromazine) or by blockade of only the circulating but not the neurogenic intramyocardial catecholamines (eg, dibenamine) were the least effective for protection of cardiac muscle, whereas those drugs that act by ganglionic blockade (eg, mecamylamine) or by direct intramyocardial catecholamine-depletion (eg, reserpine) were the most effective. Furthermore, it is clear that blood catecholamine levels are often normal but that identical ECG findings are seen with high systemic catecholamines. These clinical and pharmacological data support the concept that the cardiac necrosis is caused by catecholamine toxicity and that catecholamines released directly into the heart via neural connections are much more toxic than those that reach the heart via the bloodstream, though clearly the 2 routes could be additive in the intact, nonadrenalectomized animal. Intracoronary infusions of epinephrine reproduce the characteristic ECG pattern of neurocardiac disease, which is reminiscent of subendocardial ischemia, though no ischemic lesion can be found in the hearts of dogs euthanized after several months of infusions.¹¹ In the years that followed, numerous reports emanated from around the world that documented the production of cardiac repolarization abnormalities in the context of various neurological catastrophes and that proposed that this was caused by an autonomic storm. It seemed likely that the connection

between neuropsychiatric illness and the visceral organs would be provided by the autonomic nervous system.

Melville et al¹² produced ECG changes and myocardial necrosis by stimulation of the hypothalamus of cats. With anterior hypothalamic stimulation, parasympathetic responses occurred, predominantly in the form of bradycardia. Lateral hypothalamic stimulation produced tachycardia and ST segment depressions. With intense bilateral and repeated lateral stimulation, persistent irreversible ECG changes occurred and postmortem examination revealed a stereotyped cardiac lesion characterized by intense cytoplasmic eosinophilia with loss of cross-striations and some hemorrhage. The coronary arteries were normal without occlusion. Although Melville referred to this lesion as “infarction,” it is probably best to reserve that term for coagulation necrosis caused by ischemia. This lesion is probably identical to Selye’s ESCN and would now be called coagulative myocytolysis, myofibrillar degeneration, or contraction band necrosis. More recently, Oppenheimer and Cechetto have mapped the chronotropic organizational structure in the rat insular cortex, which demonstrates that sympathetic innervation arises from a more rostral part of the posterior insula then causes parasympathetic innervation.¹³ The insula and thalamus had already been shown to have a sensory viscerotropic representation that included the termination of cardiopulmonary afferents.¹⁴ The central role of the insula in the control of cardiovascular function has been supported by a robust experimental and clinical literature.^{15,16}

Despite the fact that myocardial damage could definitely be produced in animals, until the mid-1960s there was little recognition that this actually occurred in human beings with acute neurological or psychiatric illness until Koskelo and colleagues¹⁷ reported on 3 patients with ECG changes caused by subarachnoid hemorrhage who were noted on postmortem examination to have several small subendocardial petechial hemorrhages. Connor¹⁸ reported focal myocytolysis in 8% of 231 autopsies, with the highest incidence seen in patients who suffered fatal intracranial hemorrhages. The lesion reported by Connor conforms to the descriptions of Selye’s ESCN or what might now be called myofibrillar degeneration, coagulative myocytolysis, or contraction band necrosis. Connor pointed out that previous pathology reports probably overlooked the lesion because of the fact that it was multifocal, with each individual focus being quite small, which would require extensive tissue sampling. It is clear now that even Connor underestimated the prevalence of the lesion and that serial sections are required to rigorously exclude its presence.

Greenshoot and Reichenbach¹⁹ reported on 3 new patients with subarachnoid hemorrhage and a review of 6 previous patients from the same medical center. All 9 of these patients had cardiac lesions of varying degrees of severity that ranged from eosinophilia with preservation of cross-striations to transformation of the myocardial cell cytoplasm into dense eosinophilic transverse bands with intervening granularity, sometimes with endocardial hemorrhages. Both the ECG abnormalities and the cardiac pathology could be reproduced in cats given mesencephalic reticular formation stimulation. Adrenalectomy did not protect the hearts, which supports the

contention that the ECG changes and cardiac lesions are due to direct intracardiac release of catecholamines.

Hawkins and Clower²⁰ injected blood intracranially into mice, which thereby produced the characteristic myocardial lesions. The number of lesions could be reduced but not obliterated by pretreatment with adrenalectomy and the use of either atropine or reserpine, which suggested that the cause of the lesions was in part caused by sympathetic overactivity (humoral arrival at the myocardium from the adrenal and by direct release into the muscle by intracardiac nerves) and in part caused by parasympathetic overactivity. This supports the concept that the cause is an autonomic storm with a contribution from both divisions to the pathogenesis.

Jacob et al²¹ produced subarachnoid hemorrhage experimentally in dogs and carefully studied the sequential hemodynamic and ultrastructural changes that occurred. The hemodynamic changes occurred in 4 stages and directly paralleled the effects seen with intravenous norepinephrine injections. These stages were: (1) dramatic rise in systemic blood pressure; (2) extreme sinus tachycardia with various arrhythmias (eg, nodal or ventricular tachycardia, bradycardia, atrioventricular block, ventricular premature beats, ventricular tachycardia, ventricular fibrillation with sudden death), all of which could be suppressed by bilateral vagotomy or orbital frontal resection; (3) rise in left ventricular pressure parallel to rise in systemic pressure; and (4) up to 2-fold increase in coronary blood flow.

Ultrastructurally, a series of 3 stereotyped events occurred that could be imitated exactly with norepinephrine injections. These were: (1) migration of intramitochondrial granules that contained Ca^{2+} to the periphery of the mitochondria; (2) disappearance of these granules; and (3) myofilament disintegration at the I bands while the density of the I band was increased in the intact sarcomeres.²¹

Partially successful efforts to modify the developments of neurocardiac lesions were made with reserpine pretreatment in mice subjected to simulated intracranial hemorrhage²² and by Hunt and Gore,²³ who pretreated a group of rats with propranolol and then attempted to produce cardiac lesions with intracranial blood injections. No lesions were found in the control animals, but they were found in 21 of the 46 untreated rats and in only 4 of the 22 treated rats. This suggested that neurological influences via catecholamines may be at least partly responsible for cardiac cell death. More modern studies have confirmed the fact that myocardial injury occurs in the context of subarachnoid hemorrhage and that the likelihood of myocardial necrosis was correlated with the severity of the clinical neurological state as judged by the standard Hunt-Hess grading system for subarachnoid hemorrhage.²⁴

The phenomenology of the various types of myocardial cell death was articulated most clearly by Baroldi,²⁵ who pointed out that there were 3 main patterns of myocardial necrosis: (1) coagulation necrosis, the fundamental lesion of infarction, in which the cell loses its capacity to contract and dies in an atonic state with no myofibrillar damage; (2) colliquative myocytolysis, in which edematous vacuolization with dissolution of myofibrils without hypercontraction occurs in the low-output syndromes; and (3) coagulative myo-

30 Year Old Man who Jumped to His Death after 20 Minutes on Roof

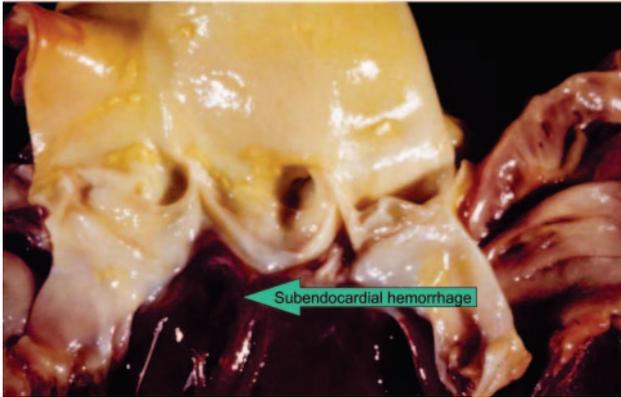


Figure 1. The neurocardiac lesion: Gross specimen of a patient who died during an acute psychological stress shows fresh endocardial hemorrhages (1 of many is shown by the arrow).

cytolysis, in which the cell dies in a hypercontracted state with early myofibrillar damage and anomalous irregular cross-band formations.

Coagulative myocytolysis is seen in reperfused areas around regions of coagulation necrosis in transplanted hearts, in "stone hearts," in sudden unexpected and accidental death, and in hearts exposed to toxic levels of catecholamines, such as in patients with pheochromocytoma. This is probably the major lesion described by Selye as ESCN and is likely to be the major lesion seen in animals and people who suffer acute neurological or psychiatric catastrophes. Although coagulative myocytolysis is probably the preferred term, the terms myofibrillar degeneration and contraction band necrosis are commonly used in the literature. This lesion tends to calcify early and to have a multifocal subendocardial predisposition (Figure 1, 2, and 3).

Intense rapid calcification makes it likely that the subcellular mechanisms that underlie the development of coagulative myocytolysis involve calcium entry. Zimmerman and Hulsmann²⁶ reported that the perfusion of rat hearts with calcium-free media for short periods of time creates a situation such that on readmission of calcium there is a

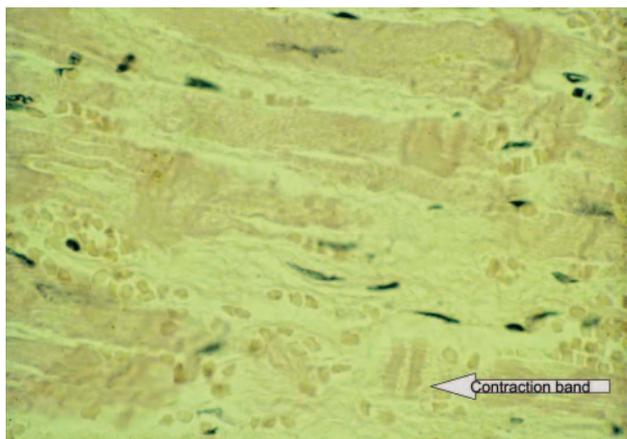


Figure 2. Cardiac contraction band necrosis (also known as coagulative myocytolysis, myofibrillar degeneration). The arrow shows 2 of the contraction bands.



Figure 3. Intense mineralization within minutes of the onset of contraction band necrosis.

massive contracture followed by necrosis and enzyme release. This phenomenon, known as the calcium paradox, can be imitated almost exactly with reoxygenation after hypoxemia. The latter, called the oxygen paradox, has been linked to the calcium paradox by pathological calcium entry.²⁷ This major ionic shift is probably the cause of the dramatic ECG changes seen in the context of neurological catastrophe, a fact that could explain the phenomenon of sudden unexpected death (SUD) in many contexts.

Although SUD is now recognized as a medical problem of major epidemiological importance, it has generally been assumed that neurological disease rarely results in SUD. In fact, it has been traditionally held that neurological illnesses almost never cause sudden demise, with the occasional patient who dies during an epileptic convulsion or rapidly in the context of a subarachnoid hemorrhage as the exception. Further, it has been assumed that the various SUD syndromes (eg, sudden death in middle-aged men, sudden infant death syndrome, sudden unexpected nocturnal death syndrome, frightened to death ("voodoo" death), sudden death during an epileptic seizure, sudden death during natural catastrophe, sudden death associated with recreational drug abuse, sudden death in wild and domestic animals, sudden death during asthma attacks, sudden death during the alcohol withdrawal syndrome, sudden death during grief after a major loss, sudden death during panic attacks, sudden death from mental stress, and sudden death during war) are entirely separate and have no unifying mechanism. For example, it is generally accepted that sudden death in middle-aged men is usually caused by a cardiac arrhythmia (ie, ventricular fibrillation), which results in functional cardiac arrest, whereas most work on sudden infant death syndrome focuses on immaturity of the respiratory control systems in the brain stem.

However, the connection between the nervous system and the cardiopulmonary system provides the unifying link that allows a coherent explanation for most, if not all, of the forms of neurocardiac damage. Powerful evidence from multiple disparate disciplines allows for a neurological explanation for many forms of SUD.²⁸

Neurogenic Heart Disease

Definition of Neurogenic Electrocardiographic Changes

A wide variety of changes in the ECG is seen in the context of neurological disease. Two major categories of change are regularly noted: arrhythmias and repolarization changes. It is likely that the increased tendency for life-threatening arrhythmias found in patients with acute neurological disease is a result of the repolarization change, which increases the vulnerable period during which an extrasystole would be likely to result in ventricular tachycardia and/or ventricular fibrillation. Thus, the essential and potentially most lethal features of the ECG, which are known to change in the context of neurological disease, are the ST segment and T wave, which reflect abnormalities in repolarization. Most often, the changes are seen best in the anterolateral or inferolateral leads. If the ECG is read by pattern recognition by someone who is not aware of the clinical history, it will often be said to represent subendocardial infarction or anterolateral ischemia. The electrocardiographic abnormalities usually improve, often dramatically, with death by brain criteria. In fact, any circumstance that disconnects the brain from the heart (eg, cardiac transplantation, severe autonomic neuropathies caused by amyloidosis or diabetes, stellate ganglionectomy for treatment of the long QT syndrome) blunts neurocardiac damage of any cause.

The phenomenon is not rare. In a series of 100 consecutive stroke patients, 90% showed abnormalities on the ECG compared with 50% of a control population of 100 patients admitted for carcinoma of the colon.²⁹ This of course does not mean that 90% of stroke patients have neurogenic ECG changes. Obviously, stroke and coronary artery disease have common risk factors, so that many ECG abnormalities in stroke patients represent concomitant atherosclerotic coronary disease. Nonetheless, a significant number of stroke patients have authentic neurogenic ECG changes.

Mechanism of the Production of Neurogenic Heart Disease

Catecholamine Infusion

Josué³⁰ first demonstrated that epinephrine infusions could cause cardiac hypertrophy. This observation has been reproduced on many occasions, which documents the fact that systemically administered catecholamines are not only associated with ECG changes reminiscent of widespread ischemia but with a characteristic pathological picture in the cardiac muscle that is distinct from myocardial infarction. An identical picture may be found in human beings with chronically elevated catecholamines, as seen with pheochromocytoma. Patients with stroke often have elevated systemic catecholamine levels, a fact that may in part account for the high incidence of cardiac arrhythmias and ECG changes seen in these patients. On light microscopy, these changes range from increased eosinophilic staining with preservation of cross-striations to total transformation of the myocardial cell cytoplasm into dense eosinophilic transverse bands with intervening granularity. In severely injured areas, infiltration

of the necrotic debris by mononuclear cells is often noted, sometimes with hemorrhage.

Ultrastructurally, the changes in cardiac muscle are even more widespread than they appear to be in light microscopy. Nearly every muscle cell shows some pathological alteration, which range from a granular appearance of the myofibrils to profound disruption of the cell architecture with relative preservation of ribosomes and mitochondria. Intracardiac nerves can be seen and identified by their external lamina, microtubules, neurofibrils, and the presence of intracytoplasmic vesicles. These nerves can sometimes be seen immediately adjacent to an area of myocardial cell damage. The pathological changes in the cardiac muscle are usually less at a distance from the nerve, often with a complete return to normalcy by a distance of 2 to 4 μm away from the nerve ending.²¹

Myofibrillar degeneration (also known as coagulative myocytolysis and contraction band necrosis) is an easily recognizable form of cardiac injury, distinct in several major respects from coagulation necrosis, which is the major lesion of myocardial infarction.^{25,31} In coagulation necrosis, the cells die in a relaxed state without prominent contraction bands. This is not visible by any method for many hours or even days. Calcification only occurs late, and the lesion elicits a polymorphonuclear cell response. In stark contrast, in myofibrillar degeneration the cells die in a hypercontracted state with prominent contraction bands (Figures 2 and 3). The lesion is visible early, perhaps within minutes of its onset. It elicits a mononuclear cell response and may calcify almost immediately.^{31,32}

Stress Plus or Minus Steroids

A similar, if not identical, cardiac lesion can be produced with various models of stress. This concept was applied to the heart when Selye published his monograph *The Chemical Prevention of Cardiac Necrosis* in 1958.⁹ He found that cardiac lesions probably identical to those described above could be produced regularly in animals that were pretreated with certain steroids, particularly 2- α -methyl-9- α -fluorohydrocortisone (fluorocortisol) and then subjected to various types of stress. Other hormones, such as dihydrotestosterone (calciferol) and thyroxine, could also sensitize animals for stress-induced myocardial lesions, though less potently than fluorocortisol. This so-called stress could be of multiple types such as restraint, surgery, bacteremia, vagotomy, and toxins. He believed that the first mediator in the translation of these widely disparate stimuli into a stereotyped cardiac lesion was the hypothalamus and that it, by its control over the autonomic nervous system, caused the release of certain agents that were toxic to the myocardial cell. Since Selye's original work, similar experiments have been repeated in many different types of laboratory animals with comparable results. Although the administration of exogenous steroids facilitates the production of cardiac lesions, it is clear that stress alone can result in the production of morphologically identical lesions.

Whether a similar pathophysiology could ever be repeated in human beings is, of course, of great interest. Many investigators have speculated on the role of stress in the

pathogenesis of human cardiovascular disease and, in particular, on its relationship to the phenomenon of SUD. A few autopsies on patients who experienced sudden death have shown myofibrillar degeneration. Cebelin and Hirsch³³ reported on a careful retrospective analysis of the hearts of 15 victims of physical assault who died as a direct result of the assault, but without sustaining internal injuries. Eleven of the 15 individuals showed myofibrillar degeneration. Age- and cardiac disease-matched controls showed little or no evidence of this change. This appears to represent human stress cardiomyopathy. Whether such assaults can be considered murder has become an interesting legal correlate of the problem.

Because the myofibrillar degeneration is predominantly subendocardial, it may involve the cardiac conducting system, which thus predisposes to cardiac arrhythmias. This lesion, combined with the propensity of catecholamines to produce arrhythmias even in a normal heart, may well raise the risk of a serious arrhythmia. This may be the major immediate mechanism of sudden death in many neurological circumstances, such as subarachnoid hemorrhage, stroke, epilepsy, head trauma, psychological stress, and increased intracranial pressure. Even the arrhythmogenic nature of digitalis may be largely mediated by the central nervous system. Further evidence for this is the antiarrhythmic effect of sympathetic denervation of the heart for cardiac arrhythmias of many types.

Furthermore, it is known that stress-induced myocardial lesions may be prevented by sympathetic blockade with many different classes of antiadrenergic agents, most notably, ganglionic blockers such as mecamylamine and catecholamine-depleting agents such as reserpine.¹⁰ This suggests that catecholamines, which are either released directly into the heart by sympathetic nerve terminals or reach the heart through the bloodstream after release from the adrenal medulla, may be excitotoxic to myocardial cells.

Some people who are subjected to an extreme stress may develop an acute cardiomyopathy that presents with chest pain and/or symptoms of heart failure. This process is most commonly seen in older women, whose echocardiograms and ventriculograms show a typical pattern of left ventricular apical ballooning, which was named takotsubo-like cardiomyopathy³⁴ because of the similarity in the appearance the left ventricle to the Japanese octopus trapping pot, the takotsubo. If a lethal arrhythmia does not intervene, the process is potentially completely reversible. Some debate exists regarding whether this syndrome (variously described as myocardial stunning or myocardial hibernation) could be explained by ischemia, but it is striking that this pattern of dysfunction is most consistent with a neural rather than a vascular distribution.^{35,36} Wittstein and colleagues³⁷ reported a series of such patients and referred to the problem as myocardial stunning. In patients in whom endocardial biopsies were performed, contraction band lesions were found. The finding of contraction bands suggests either catecholamine effect and/or reperfusion. The 2 mechanisms are not mutually exclusive in that a neural stimulus could produce both catecholamine release and coronary vasospasm followed by vasodilation. There is no direct evidence that the nervous

system can cause coronary vasospasm, but the possibility remains. Regardless of the precise mechanism, the fact remains that takotsubo-like cardiomyopathy occurs after an acute psychological stress and thereby represents an example of a neurocardiac lesion. It seems likely that this dramatic condition may be the tip of an iceberg under which lurks a much larger, albeit less easily demonstrable, problem; namely neurocardiac lesions that are not sufficiently severe and widespread to produce gross heart failure but may predispose to serious cardiac arrhythmias.

Nervous System Stimulation

Nervous system stimulation produces cardiac lesions that are histologically indistinguishable from those described for stress and catecholamine-induced cardiac damage. It has been known for a long time that stimulation of the hypothalamus can lead to autonomic cardiovascular disturbances,³⁸ and many years ago lesions in the heart and gastrointestinal tract have been produced with hypothalamic stimulation.^{39,40} It has been clearly demonstrated that stimulation of the lateral hypothalamus produces hypertension and/or electrocardiographic changes reminiscent of those seen in patients with central nervous system damage of various types. Furthermore, this effect on the blood pressure and ECG can be completely prevented by C2 spinal section and stellate ganglionectomy, but not by vagotomy, which suggests that the mechanism of the electrocardiographic changes is sympathetic rather than parasympathetic or humoral. Stimulation of the anterior hypothalamus produces bradycardia, an effect that can be blocked by vagotomy. Unilateral hypothalamic stimulation does not result in histological evidence of myocardial damage by light microscopy, but bilateral prolonged stimulation regularly produces myofibrillar degeneration indistinguishable from that produced by catecholamine injections and stress, as previously described.⁴¹

Other methods to produce cardiac lesions of this type include stimulation of the limbic cortex, the mesencephalic reticular formation, the stellate ganglion, and regions known to elicit cardiac reflexes such as the aortic arch. Experimental intracerebral and subarachnoid hemorrhages can also result in cardiac contraction band lesions. These neurogenic cardiac lesions will occur even in an adrenalectomized animal, although they will be somewhat less pronounced.²⁰ This evidence argues strongly against an exclusively humoral mechanism in the intact organism. High levels of circulating catecholamines exaggerate the electrocardiographic findings and myocardial lesions, but high circulating catecholamine levels are not required for the production of pathological changes. These electrocardiographic abnormalities and cardiac lesions are stereotyped and identical to those found in the stress and catecholamine models already outlined. They are not affected by vagotomy and are blocked by maneuvers that interfere with the action of the sympathetic limb of the autonomic nervous system, such as C2 spinal section, stellate ganglion blockade, and administration of antiadrenergic drugs such as propranolol.

The histological changes in the myocardium range from normal muscle on light microscopy to severely necrotic (but not ischemic) lesions with secondary mononuclear cell infil-

tration. The findings on ultrastructural examination are invariably more widespread, often involving nearly every muscle cell, even when the light microscopic appearance is unimpressive. The electrocardiographic findings undoubtedly reflect the total amount of muscle membrane affected by the pathophysiological process. Thus, the ECG may be normal when the lesion is early and demonstrable only by electron microscopy. Conversely, the ECG may be grossly abnormal when only minimal findings are present by light microscopy, since the cardiac membrane abnormality responsible for the electrocardiographic changes may be reversible. Cardiac arrhythmias of many types may also be elicited by nervous system stimulation along the outflow of the sympathetic nervous system.

Reperfusion

The fourth and last model for the production of myofibrillar degeneration is reperfusion, as is commonly seen in patients who die after a period of time on a left ventricular assist pump or after they undergo extracorporeal circulation. Similar lesions are seen in hearts that were reperfused with angioplasty or fibrinolytic therapy. The mechanism by which reperfusion of ischemic cardiac muscle produces coagulative myocytolysis (also known as myofibrillar degeneration and contraction band necrosis) involves entry of calcium after a period of relative deprivation.⁴¹

Sudden calcium influx by one of several possible mechanisms (eg, a period of calcium deficiency with loss of intracellular calcium, a period of anoxia followed by reoxygenation of the electron transport system, a period of ischemia followed by reperfusion, or opening of the receptor-operated calcium channels by excessive amounts of locally released norepinephrine) may be the final common pathway by which the irreversible contractures occur, which leads to myofibrillar degeneration. Thus reperfusion-induced myocardial cell death may be a form of apoptosis (programmed cell death) analogous to that seen in the central nervous system, in which excitotoxicity with glutamate results in a similar, if not identical, series of events.⁴²

The precise cellular mechanism for the electrocardiographic change and the histological lesion may well reflect the effects of large volumes of norepinephrine released into the myocardium from sympathetic nerve terminals.⁴³ The fact that the cardiac necrosis is greatest near the nerve terminals in the endocardium and is progressively less severe as one samples muscle cells near the epicardium provides further evidence that catecholamine toxicity produces the lesion.¹⁹ This locally released norepinephrine is known to stimulate synthesis of adenosine 3',5'-cyclic phosphate, which in turn results in the opening of the calcium channel with influx of calcium and efflux of potassium. This efflux of potassium could explain the peaked T waves (a hyperkalemic pattern) often seen early in the evolution of neurogenic electrocardiographic changes.²¹ The actin and myosin filaments interact under the influence of calcium but do not relax unless the calcium channel closes. Continuously high levels of norepinephrine in the region may result in failure of the calcium channel to close, which leads to cell death, and finally to leakage of enzymes out of the myocardial cell. Free radicals

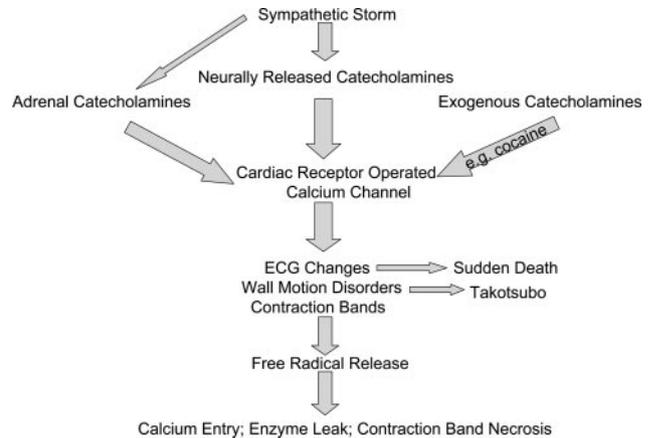


Figure 4. Cascade of events that lead to neurocardiac damage.

released as a result of reperfusion after ischemia or by the metabolism of catecholamines to the known toxic metabolite, adrenochrome, may contribute to cell membrane destruction, which leads to leakage of cardiac enzymes into the blood.^{44,45} Thus, the cardiac toxicity of locally released norepinephrine falls on a continuum that ranges from a brief reversible burst of electrocardiographic abnormalities to a pattern that resembles hyperkalemia and then finally to an irreversible failure of the muscle cell with permanent repolarization abnormalities, or even the occurrence of transmural cardiac necrosis with enzyme (eg, troponin, creatine kinase) release and Q waves seen on the ECG.

Histological changes would also represent a continuum that ranges from complete reversibility in a normal heart through mild changes seen only by electron microscopy to severe myocardial cell necrosis with mononuclear cell infiltration and even hemorrhages. The amount of cardiac enzymes released and the electrocardiographic changes would roughly correlate with the severity and extent of the pathological process. This explanation, summarized in Figure 4, rationalizes all the observations in the catecholamine infusion, stress plus or minus steroid, nervous system stimulation, and reperfusion models.

Concluding Remarks and Potential Treatments

In conclusion, there is powerful evidence to suggest that overactivity of the sympathetic limb of the autonomic nervous system is the common phenomenon that links the major cardiac pathologies seen in neurological catastrophes. These profound effects on the heart may contribute in a major way to the mortality rates of many primarily neurological conditions such as subarachnoid hemorrhage, cerebral infarction, status epilepticus, and head trauma. These phenomena may also be important in the pathogenesis of SUD in adults, sudden infant death, sudden death during asthma attacks, cocaine- and amphetamine-related deaths, and sudden death during the alcohol withdrawal syndrome, all of which may be linked by stress and catecholamine toxicity.

Investigations aimed at alteration of the natural history of these events with catecholamine receptor blockade, calcium-channel blockers, free-radical scavengers, and antioxidants

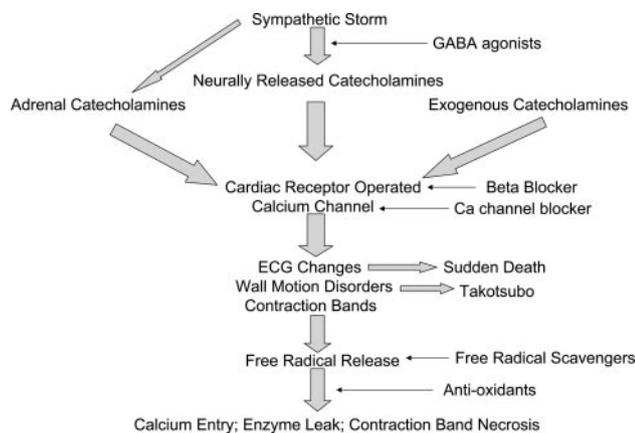


Figure 5. Possible therapeutic approaches aimed to prevent neurocardiac damage. GABA indicates gamma aminobutyric acid.

are in progress in many centers around the world and are summarized in Figure 5.

Disclosures

None.

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