CLEVELAND CLINIC JOURNAL OF MEDICINE

PROCEEDINGS OF THE HEART-BRAIN SUMMIT

Hosted by the Earl and Doris Bakken Heart-Brain Institute at Cleveland Clinic

JUNE 15–17, 2006

SUPPLEMENT EDITOR:
MARC PENN, MD, PHD
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Supplement 1 to Volume 74, February 2007

Supplement Editor

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Introduction: Heart-brain medicine: Where we go from here and why S4
Marc S. Penn, MD, PhD, *Cleveland Clinic, Cleveland, Ohio*, and Earl E. Bakken, DSc (hon), *Medtronic, Inc., Minneapolis, Minnesota, and North Hawaii Community Hospital, Kamuela, Hawaii*

Opening remarks: The dream behind the summit S7
Earl E. Bakken, DSc (hon), *Medtronic, Inc., Minneapolis, Minnesota, and North Hawaii Community Hospital, Kamuela, Hawaii*

Keynote address: 'Voodoo' death revisited: The modern lessons of neurocardiology S8
Martin A. Samuels, MD, DSc (hon), *Brigham and Women's Hospital, Boston, Massachusetts*

The broken heart syndrome S17
Ilan S. Wittstein, MD, *Johns Hopkins University School of Medicine, Baltimore, Maryland*

Brain imaging in cardiovascular disease: State of the art S23
Michael Phillips, MD, *Cleveland Clinic, Cleveland, Ohio*

Cortical control of the heart S27
Stephen Oppenheimer, MD, PhD, *Sentient Medical Systems, Cockeysville, Maryland*

Neurological mechanisms of chest pain and cardiac disease S30
Robert D. Foreman, PhD, *University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma*

Hypertension in sleep apnea: The role of the sympathetic pathway S34
Diana L. Kunze, PhD; David Kline, PhD; and Angelina Ramirez-Navarro, PhD,
MetroHealth Medical Center and Case Western Reserve University, Cleveland, Ohio

(continued on next page)

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CONTENTS

Inflammation: Implications for understanding the heart-brain connection S37
Mehdi H. Shishehbor, DO; Carlos Alves, MD; and Vivek Rajagopal, MD, *Cleveland Clinic, Cleveland, Ohio*

The anti-ischemic effects of electrical neurostimulation in the heart S42
Jessica de Vries, MD, *University of Groningen, The Netherlands*; Robert D. Foreman, PhD, *University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma*; and Mike J.L. DeJongste, MD, PhD, *University of Groningen, The Netherlands*

The little brain on the heart S48
J. Andrew Armour, MD, PhD, *Hôpital du Sacré-Coeur and Université de Montréal, Montréal, Québec, Canada*

Open heart surgery and cognitive decline S52
Mark F. Newman, MD, *Duke University Medical Center, Durham, North Carolina*

The heart and the brain within the broader context of wellness S56
Michael O'Donnell, PhD, MBA, MPH, *Cleveland Clinic, Cleveland, Ohio*

The heart-brain interaction during emotionally provoked myocardial ischemia: Implications of cortical hyperactivation in CAD and gender interactions S59
Robert Soufer, MD, *Yale University, New Haven, Connecticut*; and Matthew M. Burg, PhD, *Yale University, New Haven, Connecticut, and Columbia University, New York, New York*

Depression and heart disease S63
François Lespérance, MD, *Montréal Heart Institute*, and Nancy Frasure-Smith, PhD, *McGill University and Montréal Heart Institute, Montréal, Québec, Canada*

Sick at heart: The pathophysiology of negative emotions S67
Laura D. Kubzansky, PhD, MPH, *Harvard School of Public Health, Boston, Massachusetts*

Role of the brain in ventricular fibrillation and hypertension: From animal models to early human studies S73
James E. Skinner, PhD, *Vicor Technologies, Inc., Boca Raton, Florida*

New paradigms in heart-brain medicine: Nonlinear physiology, state-dependent proteomics S79
James E. Skinner, PhD, *Vicor Technologies, Inc., Boca Raton, Florida*

Subarachnoid hemorrhage: A model for heart-brain interactions S86
J. Javier Provencio, MD, *Cleveland Clinic, Cleveland, Ohio*

Cardiac denervation in patients with Parkinson disease S91
David S. Goldstein, MD, PhD, *National Institutes of Health, Bethesda, Maryland*

Aging and the brain renin-angiotensin system: Insights from studies in transgenic rats S95
Debra I. Diz, PhD; Sherry O. Kasper, PhD; Atsushi Sakima, MD; and Carlos M. Ferrario, MD, *Wake Forest University School of Medicine, Winston-Salem, North Carolina*

Contextual cardiology: What modern medicine can learn from ancient Hawaiian wisdom S99
Paul Pearsall, PhD, *University of Hawaii at Manoa and Hawaii State Consortium for Integrative Medicine, Honolulu, Hawaii*

Cardiocerebral resuscitation: The optimal approach to cardiac arrest S105
Gordon A. Ewy, MD, *University of Arizona College of Medicine, Tucson, Arizona*

CONTENTS

Heart transplantation: A magnified model of heart-brain interactions **S110**
Mohamad H. Yamani, MD, and Randall C. Starling, MD, MPH, *Cleveland Clinic, Cleveland, Ohio*

Patent foramen ovale and migraine **S114**
Gian Paolo Anzola, MD, *S. Orsola Hospital FBF, Brescia, Italy*

Patent foramen ovale and stroke: To close or not to close? **S118**
Anthony J. Furlan, MD, *Cleveland Clinic, Cleveland, Ohio*

Sudden unexplained death in epilepsy: The role of the heart **S121**
Stephan U. Schuele, MD, *Cleveland Clinic, Cleveland, Ohio, and Northwestern University, Chicago, Illinois*;
Peter Widdess-Walsh, MD, Adriana Bermeo, MD, and Hans O. Lüders, MD, PhD, *Cleveland Clinic, Cleveland, Ohio*

Hydrocephalus and the heart: Interactions of the first and third circulations **S128**
Mark Luciano, MD, PhD, and Stephen Dombrowski, PhD, *Cleveland Clinic, Cleveland, Ohio*

Cognitive impairment in chronic heart failure **S132**
Cathy A. Sila, MD, *Cleveland Clinic, Cleveland, Ohio*

Cardiac events and brain injury: Ethical implications **S138**
Paul J. Ford, PhD, *Cleveland Clinic, Cleveland, Ohio*

Articles in these proceedings were either submitted as manuscripts by the Summit faculty or developed by the *Cleveland Clinic Journal of Medicine* staff from transcripts of audiotaped Summit presentations and then reviewed and revised by the Summit faculty.

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Heart-brain medicine: Where we go from here and why

This past June, the Earl and Doris Bakken Heart-Brain Institute (BHBI) held the first annual Heart-Brain Summit at the Cleveland Clinic. The BHBI's goal is to investigate physiological and molecular relationships between the heart and the brain and to translate these findings into strategies to improve patient outcomes.

The need for this type of innovative approach for the development of novel therapies has never been greater. Modern medicine, through the development of early diagnostic imaging and endovascular approaches, has significantly reduced the morbidity and mortality of previously devastating acute conditions such as acute myocardial infarction and subarachnoid hemorrhage. In the case of acute myocardial infarction, 30-day mortality rates have declined from nearly 20% two decades ago to less than 5% in recent clinical trials using primary percutaneous intervention **(Figure 1)**.[1] This amazing achievement has unfortunately fostered a population of patients with chronic heart failure, which has a prevalence of greater than 5 million in the United States and affects more than 10% of the US population older than 65 years. While significant efforts have been put forth to improve outcomes in patients with chronic heart failure, mortality rates in clinical trials have not decreased significantly over the same span of time **(Figure 2)**.[1]

THE GOAL: THERAPIES BASED ON HOW THE ORGANS INTERRELATE

Thus, in an attempt to improve patient outcomes beyond the acute event, the BHBI aims to "put the body back together," or understand how different organ systems interrelate and, with this information in hand, develop therapeutic strategies to reduce morbidity and mortality.

Several lines of evidence suggest that in-depth investigation in the area of heart-brain medicine will yield significant results. Recent examples of the importance of heart-brain interactions in physiology and patient populations with chronic disease include the following:

- Studies showing that angina pectoris can be controlled by carotid stimulation
- Multiple studies that have demonstrated the link between depression and poor outcomes in patients with coronary artery disease
- Findings that cardiac arrhythmias and sudden cardiac death are frequent causes of death over the long term in patients who survive subarachnoid hemorrhage
- The observation that vagal stimulation is mechanistically linked to leukocyte activation and inflammation at the molecular level
- Evidence that chronic hypertension can be controlled by carotid body stimulation.

Each of these conditions represents a significant patient population, many of which are underserved by current strategies and techniques.

Beyond these examples there is a large literature, often discounted by modern science, that suggests that integrative lifestyle approaches improve patients' well-being and outcomes. The least controversial and best supported of these approaches is exercise. However, other approaches—including yoga, biofeedback, and mind-body stress-relieving techniques—have their supporters, and they warrant study to further determine their clinical benefit and what might be the mechanism responsible for such benefit.

A NEED FOR INTERDISCIPLINARY COLLABORATION

Whether the goal is to evaluate clinically based strategies like those listed above or integrative approaches, it is clear that collaboration among disciplines is required before any significant improvements in patient outcomes can be achieved.

For example, clearly the development of implantable cardiac pacemakers was one of the great advances of the 20th century. This innovation not only treated patients with bradycardia, it led the way to the development of internal cardiac defibrillators[2] and, more recently, biventricular cardiac resynchro-

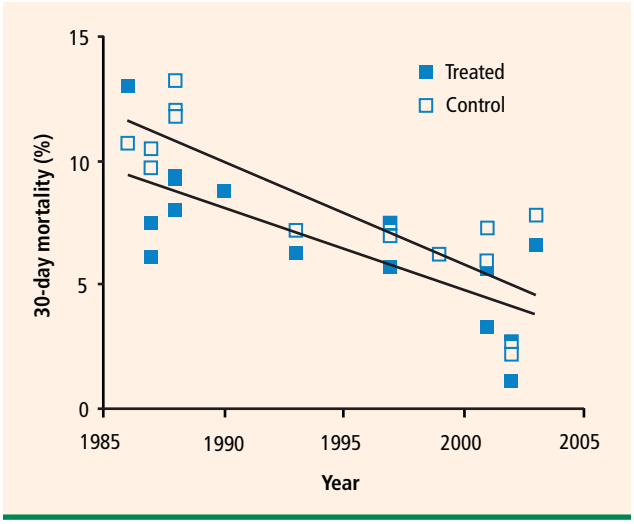

FIGURE 1. Reported mortality in treatment and control groups in studies of patients with acute myocardial infarction with ST elevation, including the GISSI, ISIS, GUSTO (I, IIb, III, and V), ASSENT-2, ADMIRAL, CADILLAC, and DANAMI-2 investigations. Adapted from Penn and Topol[1] with permission; copyright © 2007 Humana Press.

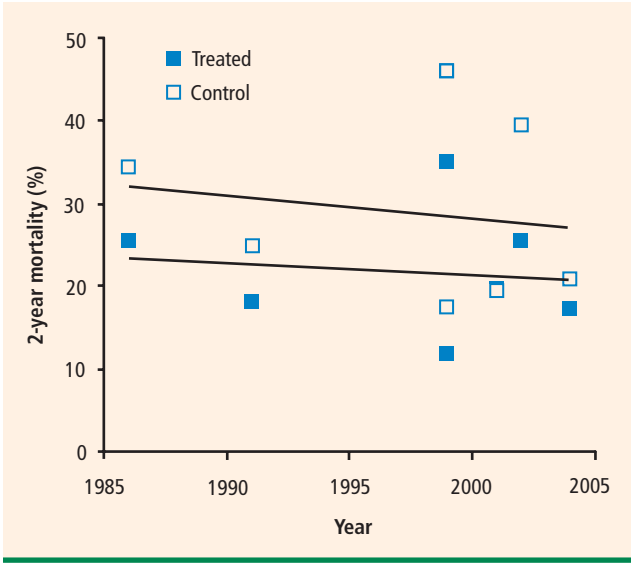

FIGURE 2. Reported mortality in treatment and control groups in chronic heart failure trials, including the V-HeFT, V-HeFT-2, Val-HeFT, RALES, CHARM, COPERNICUS, and CIBIS II investigations. Adapted from Penn and Topol[1] with permission; copyright © 2007 Humana Press.

nization therapy,[3] techniques that improve patients' well-being and reduce mortality.

Unfortunately, it took more than 40 years for similar technology to be applied to the other electrically active organ of the body, the brain. Just as cardiac pacing has revolutionized the cardiologist's approach to patients with rhythm abnormalities, deep brain stimulation is on the verge of revolutionizing the treatment of patients with depression, Parkinson disease, and many other psychiatric and movement disorders. However, before we can learn how to improve cardiac function through neurostimulation, improve the outcomes of patients with coronary artery disease by treating their depression, or improve outcomes in stroke and subarachnoid hemorrhage through rhythm management, we must be able to cross the often wide chasms between medical disciplines.

In reality, there are many similarities between the heart and the brain:

- As already mentioned, they are both electrically active organ systems.
- Each has its own form of electrical instability—seizures in the brain, and ventricular tachycardia and fibrillation in the heart. Interestingly, patients with either condition are at risk of dying of sudden cardiac death.[4,5] Electrical stimulation or conversion is a treatment in both organs.
- Chronic changes within each organ system lead to organ dysfunction—specifically, atherosclerosis in the heart and amyloid plaques in the brain. Studies have suggested that these two processes are linked at the molecular level.[6]
- Ischemic disease is the greatest cause of organ dysfunction in both systems—obviously, stroke in the brain and myocardial infarction in the heart. Restoration of blood flow is the optimal treatment of both, and improving organ-specific cell function is critical.
- A process known as ischemic preconditioning can significantly reduce the area of ischemic damage in both organs. Yet little focus has been directed at understanding the commonalities of the molecular pathways in the two systems.[7,8]

There have been previous and ongoing attempts at fostering heart-brain research. The ongoing collaborative network led by J. Andrew Armour, MD, PhD, Mike J.L. DeJongste, MD, PhD, and Robert D. Foreman, PhD, has performed important studies on the role of spinal cord stimulation for the control of myocardial ischemia.[9] The National Institute of Neurological Disorders and Stroke has its Clinical Neurocardiology Section, headed by David S. Goldstein, MD, PhD, which has similarly done revolutionary work in the field of neurological control of cardiac function.[10] We are thrilled that each of these investigators has joined us this year for the first Heart-Brain Summit.

A GATHERING PLACE FOR HEART-BRAIN MEDICINE

Where have previous programs failed? In fact, it is not clear that they have. Rather, what has hindered

growth of this field has been the lack of a gathering place that inherently believes in the potential of heart-brain medicine, fosters collaboration among investigators and industry, encourages young investigators to enter the field, and works to obtain seed funding for interesting areas of research.

The acceleration of medical knowledge is staggering. Over the past 20 years, our colleagues have dramatically improved the outcomes of patients with acute neurological and cardiac events. Industry has miniaturized devices and has developed the technology to enable endovascular therapy. At the bench, the genome has been unraveled so that we now stand at the threshold of an abundance of insights and treatments to be derived from stem cells.

We could clearly continue in our organ-based silos and undoubtedly advance science and improve patient outcomes. However, so many disciplines—including neurology, cardiology, neurosurgery, neuroscience, psychiatry, cardiothoracic surgery, molecular cardiology, physiology, biomedical engineering, and psychology—have very real input and unique insights into our understanding and measurement of heart-brain interactions. For this reason, we believe that coming out of our silos will make possible significantly greater advances and that those advances will be more rapidly translated into improved patient outcomes.

We are deeply grateful to all of our colleagues who joined us in Cleveland this past June. What follows are brief summaries and transcripts of many of the lectures presented at this inaugural Heart-Brain Summit. It was an extraordinary collection of speakers and attendees from multiple disciplines, and the result was a stimulating and rewarding experience. We look forward to a similarly rewarding and enjoyable summit in Cleveland this June and for many Junes to come, and we hope you all can join us.

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The dream behind the summit

Aloha kakou. I am known as a dream weaver, and I have had a dream since the mid-1960s about heart-brain medicine. From 1965 to 1969 I worked with Drs. Seymour Schwartz and Eugene Braunwald on stimulating the carotid sinus nerve for various cardiac problems and on stimulating the brain for different heart reactions. From that point forward my dream was to start an in-depth study of heart and brain interactions. I hoped we could get results easily.

I tried in the "Medical Alley" in Minnesota to get some groups interested, but each group wanted to start a heart center or a brain center, not to have them combined.

In 1978, Medtronic was able to put together a convention on heart-brain interactions in Miami. Dr. Douglas P. Zipes and Dr. Michael Bilitch attended. "That was the start of something of great importance," said Dr. Zipes and other leading physicians. Yet after the convention was over, nothing really happened—not for the next quarter century.

Then, in July 2004, a meeting was held at my condo at the Mauna Lani Hotel in Hawaii with two doctors from Cleveland Clinic who wanted to see our hospital (North Hawaii Community Hospital). The topic of heart-brain medicine came up, and the doctors thought it was interesting and went back to Cleveland with the idea. From that idea came the development of the institute that has convened this summit.

Since then much has happened, and we now have a great team of people that form the Bakken Heart-Brain Institute.

PUTTING THE BODY BACK TOGETHER

Our language tricks us into thinking that we have "organs" that operate alone. So we end up in silos where we study and specialize in a single "organ." But this approach doesn't really compute.

The body operates as one whole; everything impacts everything else. The cause of a problem that seems to manifest in the heart could actually lie in some other part of the body, or in the brain, or even outside the body.

Let's put the body back together and look for these things that affect the whole body but manifest as a problem in a single "organ." This is not "new medicine" but rather a return to old medicine of 5,000 years ago.

To set the stage for the summit, let me list a few ways of thinking that came out of this heart-brain idea:

1. Heart problems can often be caused by other parts of the body or by things outside of the body.
2. The mind is not in the brain. The mind is throughout the whole body and external to the body.
3. We must consider the impact of chronobiology on the functioning together of the heart and brain. The sun and the moon have great impact on the function of parts of our body, including the heart and brain.
4. We must treat people with "blended medicine"—high tech, high touch, and a healing environment. All three are integral parts of healing.
5. We must treat people completely as a whole—body, mind, spirit, nature, and community. Organs cannot exist alone. There are important roles for *Ho`oponopono* and naturopathic, homeopathic, chiropractic, and blended medicine.
6. The heart is a sensor organ and tells much of the body how to operate. We have memory tissue in the brain, heart, and gut. Major decisions need to be made in the gut.
7. Multiple connections exist between the brain and the heart, with at least six kinds of signals: electrical, chemical, hormonal, muscular, ballistic, and energy.
8. The power of the spiritual component cannot be ignored. High tech is 20%; high touch and a healing environment are 80%. Most treatment centers leave out this 80%.
9. Mind-related medicine is of great importance: relationships, stress, compassion, caring, love, attitude, hate, depression, belief.
10. Energy medicine has an important role: reiki, chi gong, guided imagery, massage, tai chi, yoga, healing touch, prayer, aloha.

This Summit is very exciting for me. Let's fulfill my dream. *Mahalo nui loa*, or "thank you from the heart."

I now start the summit.

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'Voodoo' death revisited: The modern lessons of neurocardiology†

In 1942, Walter Bradford 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 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 soct, 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 biologic 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. 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 eight 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; and (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, Carl Richter reported on a series of experiments aimed at elucidating the mechanism of Cannon's "voodoo" death.[3] Richter studied the length of time domesticated rats could swim at various water temperatures and found that at a water temperature of 93° 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, Richter noted that a number of factors contributed to the tendency for sudden death, the most important of which were the restraint involved in holding the animals and confinement in the glass swimming jar with no chance of escape. Trimming the rats' whiskers, which destroys possibly their most important proprioceptive mechanism, contributed to the tendency for early demise. In the case of the calm domesticated animals in which restraint and confinement were apparently not significant stressors, shaving the whiskers rendered these animals as fearful as wild rats with a corresponding tendency for sudden death. Electrocardiograms taken during the process showed a bradycardia developing 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 that death was caused by increased vagal tone.

We now know that the apparently opposite conclusions of Cannon and Richter are not mutually exclusive but rather that a generalized autonomic storm, occurring as a result of a life-threatening stressor, will have both sympathetic and parasympathetic effects. The apparent predominance of one over the other depends on the parameter measured (eg, heart rate,

* Dr. Samuels reported that he has no financial relationships that pose a potential conflict of interest with this article.

† This article is adapted from "Introduction to Neurocardiology" by Martin A. Samuels, chapter 43 in: Mathias CJ, Bannister R, eds. *Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System, 4th ed;* 1999:421–427, by permission of Oxford University Press (www.oup.co.uk).

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).

In human beings, one of the easily accessible windows into autonomic activity is the electrocardiogram (ECG). Edwin Byer and colleagues reported six patients whose ECGs showed large upright T waves and long QT intervals.[4] Two of these patients had hypertensive encephalopathy, one had a brainstem stroke with neurogenic pulmonary edema, one had an intracerebral hemorrhage, one had a postpartum ischemic stroke possibly related to toxemia, and one had no history except a blood pressure of 210/110 mm Hg. Based on experimental results of cooling or warming the endocardial surface of the dog's left ventricle, Byer et al concluded that these ECG changes were due to subendocardial ischemia.

Levine reported on several disorders other than ischemic heart disease that could produce ECG changes reminiscent of coronary disease.[5] Among the reported cases was that of 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. An ECG 2 days later 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 injecting caffeine into the cerebral ventricle.

Burch et al reported on 17 patients who were said to have "cerebrovascular accidents" (ie, strokes).[6] 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
(3) U waves in 11 of the 17 patients.

Cropp and Manning reported on the details of the ECG abnormalities in 29 patients with subarachnoid hemorrhage.[7] Twenty-two of these patients survived. Two of those who died had no postmortem examination, leaving five in whom autopsies confirmed the presence of a ruptured cerebral aneurysm. In three of these five, the heart and coronary arteries were said to be normal, but the details of the pathological examination are not revealed. The point is made that ECG changes seen in the context of neurologic disease do not represent ischemic heart disease but are merely a manifestation of autonomic dysregulation, possibly emanating from a lesion affecting 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.

In contrast to this rather inconclusive clinical data, there is clear evidence that cardiac lesions can be produced as the result of nervous system disease. The concept of visceral organ dysfunction occurring as a result of neurologic stimuli can be traced to Pavlov, who may have introduced the concept of a neurogenic dystrophy. Selye, a student of Pavlov, described an electrolyte–steroid cardiopathy with necroses, referred to as ESCN.[8] His view was that this cardiac lesion was common and often described using different names in the world's literature. He argued that this lesion was distinct from the coagulation necrosis that occurred as a result of ischemic disease, but could exist in the same heart. Selye felt 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-alpha-methyl-9-alpha-chlorocortisol. Among the factors that led to ESCN in steroid-sensitized animals were certain electrolytes (eg, NaH_2PO_4), 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 with adrenalectomy, suggesting that the process, if related to autonomic 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 pretreating with either 2-alpha-methyl-9-alpha-fluorohydrocortisone (fluorocortisol), dihydrotachysterol (calciferol), or thyroxine and then restraining the animals on a board for 15 hours or by using cold stress.[9] 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 in protecting 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 pharmacologic data support the concept that the cardiac necrosis is due to catecholamine toxicity and that catecholamines released directly into the heart via neural connections are much more toxic than those reaching the heart via the bloodstream, though clearly the two routes could be additive in the intact, nonadrenalectomized animal. Intracoronary infusions of epinephrine reproduce the characteristic ECG pattern of neurocardiac disease that is reminiscent of subendocardial ischemia, though no ischemic lesion can be found in the hearts of dogs sacrificed after several months of infusions.[10] In the years that followed, numerous reports emanated from around the world documenting the production of cardiac repolarization abnormalities in the context of various neurologic catastrophes and proposing that this was due to 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 al produced ECG changes and myocardial necrosis by stimulating the hypothalamus of cats.[11] With anterior hypothalamic stimulation, parasympathetic responses occurred, with bradycardia predominating. 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 et al referred to this lesion as "infarction," it is probably best to reserve that term for coagulative 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, demonstrating that sympathetic innervation arises from a more rostral part of the posterior insula than does parasympathetic innervation.[12]

Despite the fact that myocardial damage could definitely be produced in animals, there was little recognition that this actually occurred in human beings with acute neurologic or psychiatric illness until the mid-1960s, when Koskelo et al reported on three patients with ECG changes due to subarachnoid hemorrhage who were noted on postmortem examination to have several small subendocardial petechial hemorrhages.[13] Connor reported focal myocytolysis in 8% of 231 autopsies, with the highest incidence seen in patients dying of intracranial hemorrhages.[14] 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 pathologic reports probably overlooked the lesion because it was multifocal, with each individual focus being quite small, requiring 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 Reichenbach reported on three new patients with subarachnoid hemorrhage and a review of six prior patients from the same medical center.[15] All nine of these patients had cardiac lesions of varying degrees of severity, ranging 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, supporting the contention that the ECG changes and cardiac lesion are due to direct intracardiac release of catecholamines.

Hawkins and Clower injected blood intracranially into mice, thereby producing the characteristic myocardial lesions.[16] 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 lesions were attributable in part to sympathetic overactivity (humorally reaching the myocardium from the adrenal and by direct release into the muscle by intracardiac nerves) and in part to parasympathetic overactivity. This supports the concept that the cause is an autonomic storm with both divisions contributing to the pathogenesis.

Jacob et al experimentally produced subarachnoid hemorrhage in dogs and carefully studied the sequential hemodynamic and ultrastructural changes that occurred.[17] The hemodynamic changes occurred in four 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

(4) Up to twofold increase in coronary blood flow.

Ultrastructurally, a series of three stereotyped events occurred that could be imitated exactly with norepinephrine injections. These were:

(1) Migration of intramitochondrial granules containing Ca^{2+} to the periphery of the mitochondria

(2) Disappearance of these granules

(3) Myofilament disintegration at the I bands while the density of the I band was increased in the intact sarcomeres.[17]

Partially successful efforts to modify the development of neurocardiac lesions were made by using reserpine pretreatment in mice subjected to simulated intracranial hemorrhage[18] and by Hunt and Gore, who pretreated a group of rats with propranolol and then attempted to produce cardiac lesions with intracranial blood injections.[19] Lesions were found in none of the control animals, in 21 of the 46 untreated rats, and in only 4 of the 22 treated rats.[19] This suggested that neurologic influences via catecholamines may be partly responsible for cardiac cell death due to ischemic causes.

The phenomenology of the various types of myocardial cell death was finally clarified by Baroldi, who pointed out that there were three 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 the 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

(3) Coagulative myocytolysis, in which the cell dies in a hypercontracted state, with early myofibrillar damage and anomolous irregular cross-band formations.[20]

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 clearly the lesion seen in animals and people suffering acute neurologic 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)**.

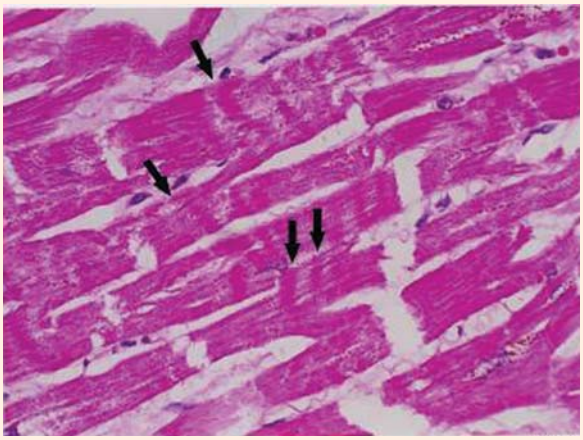

FIGURE 1. The neurocardiac lesion: contraction band necrosis (arrows), also known as myofibrillar degeneration or coagulative myocytolysis.

It is likely that the subcellular mechanisms underlying the development of coagulative myocytolysis involve calcium entry. Zimmerman and Hulsmann reported that the perfusion of rat hearts with calcium-free media for short periods of time creates a situation such that upon readmission of calcium, there is a massive contracture followed by necrosis and enzyme release.[21] This phenomenon, known as the calcium paradox, can be imitated almost exactly with reoxygenation followed by hypoxemia and reperfusion following ischemia. The latter, called the oxygen paradox, has been linked to the calcium paradox by pathologic calcium entry.[22] This major ionic shift is probably the cause of the dramatic ECG changes seen in the context of neurologic catastrophe, a fact that could explain the phenomenon of sudden unexpected death (SUD) in multiple contexts.

Although SUD is now recognized as a medical problem of major epidemiologic importance, it has generally been assumed that neurologic disease rarely results in SUD. In fact, it has been traditionally taught that neurologic illnesses almost never cause sudden demise, with the only exceptions being the occasional patient who dies during an epileptic convulsion or rapidly in the context of a subarachnoid hemorrhage. Further, it has been assumed that the various SUD syndromes (eg, sudden death in middle-aged men; sudden infant death syndrome [SIDS]; sudden unexpected nocturnal death

syndrome; being frightened to death ["voodoo" death]; sudden death during a seizure; sudden death during natural catastrophe; sudden death associated with 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) that results in functional cardiac arrest, while most work on SIDS focuses on respiratory failure.

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 SUD. Powerful evidence from multiple disparate disciplines allows for a neurologic explanation for SUD.[23]

NEUROGENIC HEART DISEASE

Definition of neurogenic ECG changes

A wide variety of changes in the ECG is seen in the context of neurologic disease. Two major categories of change are regularly noted: (1) arrhythmias and (2) repolarization changes. It is likely that the increased tendency for life-threatening arrhythmias found in patients with acute neurologic disease is due to 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 that are known to change in the context of neurologic disease are the ST segment and T wave, reflecting 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 present subendocardial infarction or anterolateral ischemia. The ECG abnormalities usually improve, often dramatically, with death by brain criteria.

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.[24] 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 production of neurogenic heart disease

Catecholamine infusion. Josué first showed that epinephrine infusions could cause cardiac hypertophy.[25] This observation has been reproduced on many occasions, documenting that systemically administered catecholamines are associated not only with ECG changes reminiscent of widespread ischemia but with a characteristic pathologic 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 is seen with pheochromocytoma. Patients with stroke often have elevated systemic catecholamine levels, which 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 on light microscopy. Nearly every muscle cell shows some pathologic alteration, ranging 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, 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 pathologic changes in the cardiac muscle are usually less at a distance from the nerve, often returning completely to normal by a distance of 2 to 4 μm away from the nerve ending.[17]

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, the major lesion of myocardial infarction.[20,26] 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 occurs only late and the lesion elicits a polymorphonuclear cell response. In stark contrast, in myofibrillary degeneration, the cells die in a hypercontracted state with prominent contraction bands

(Figure 1). The lesion is visible early, perhaps within minutes of its onset. It elicits a mononuclear cell response and may calcify almost immediately.[26,27]

Stress plus or minus steroids. A similar, if not identical, cardiac lesion can be produced using various models of "stress." This concept was applied to the heart when Selye published his monograph, *The Chemical Prevention of Cardiac Necrosis*, in 1958.[8] 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-alpha-methyl-9-alpha-fluorohydrocortisone (fluorocortisol), and then subjected to various types of stress. Other hormones, such as dihydrotachysterol (calciferol) and thyroxine, could also sensitize animals for stress-induced myocardial lesions, but less potently than fluorocortisol. This so-called stress could be of multiple types, including restraint, surgery, bacteremia, vagotomy, toxins, and others. He believed that the "first mediator" in translating these widely disparate stimuli into a sterotyped 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 operable 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 Hirsch 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.[28] Eleven of the 15 individuals showed myofibrillar degeneration. Age-matched and cardiac disease-matched controls showed little or no evidence of this change. This appears to represent a human stress cardiomyopathy.[28] Whether or not such assaults can be considered murder has become an interesting legal correlate of the problem.

Since the myofibrillar degeneration is predominantly subendocardial, it may involve the cardiac conducting system, thus predisposing 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 neurologic 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 the stress-induced myocardial lesions can be prevented by sympathetic blockade using many different classes of antiadrenergic agents, most notably ganglionic blockers such as mecamylamine and catecholamine-depleting agents such as reserpine.[9] This suggests that catecholamines, either released directly into the heart by sympathetic nerve terminals or reaching the heart through the bloodstream after release from the adrenal medulla, may be excitotoxic to myocardial cells.

Reversible left ventricular dysfunction affecting the apex out of proportion to the base is known to occur in human beings (predominantly older women) after emotional stress.[29] This so-called myocardial stunning may present with chest pain, ECG abnormalities, or frank heart failure (pulmonary edema) and is usually associated with a modest myocardial enzyme (troponin) leak. Endocardial biopsies show contraction bands, and plasma catecholamines are usually found to be elevated.[30] The four-chamber view of the echocardiogram or the ventriculogram characteristically shows a dilated apex and relatively uninvolved base, producing an appearance that is reminiscent of the Japanese octopus trapping pot (takotsubo), which has led this phenomenon to be named takotsubo-like cardiomyopathy.[31] Takotsubo-like cardiomyopathy is known to increase in frequency around the time of large-scale stressors, such as earthquakes.[32] It is likely that takotsubo-like cardiomyopathy represents the tip of an iceberg, below which lurks a much larger problem of neurally induced visceral organ damage, of which severe left ventricular apical ballooning is only one small, albeit dramatic, component.

Nervous system stimulation. Nervous system stimulation produces cardiac lesions histologically indistinguishable from those just described for stress- and catecholamine-induced cardiac damage. It has been known for a long while that stimulation of the hypothalamus can lead to autonomic cardiovascular disturbances, and many years ago, lesions in the heart and gastrointestinal tract had been produced using hypothalamic stimulation. It has been clearly demonstrated that stimula-

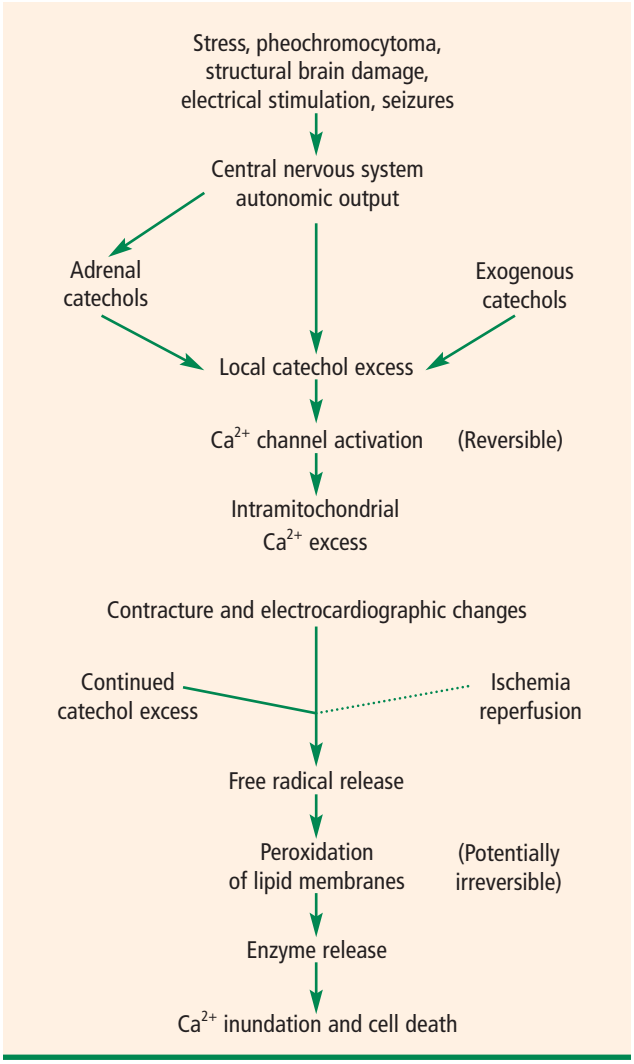

FIGURE 2. Cascade of events leading to neurocardiac damage.

tion of the lateral hypothalamus produces hypertension or ECG 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, suggesting 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 histologic 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.[11]

Other methods of producing 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 hemorrages 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.[16] This evidence argues strongly against an exclusively humoral mechanism in the intact organism. High levels of circulating catecholamines exaggerate the ECG findings and myocardial lesions, but high circulating catecholamine levels are not required for the production of pathologic changes. These ECG 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.

It seems clear that the insula is the region of the cerebral cortex that most directly affects cardiac structure and function. There is a great deal of clinical evidence that insular diseases are the most likely to produce neurally induced cardiac changes, though the issue of lateral dominance of one insula over the other has not yet been completely settled.[33–37]

The histologic changes in the myocardium range from normal muscle on light microscopy to severely necrotic (but not ischemic) lesions with secondary mononuclear cell infiltration. The findings on ultrastructural examination are invariably more widespread, often involving nearly every muscle cell, even when the light microscopic appearance is unimpressive. The ECG findings undoubtedly reflect the total amount of muscle membrane affected by the pathophysiologic 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 ECG 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 dying after a period of time on a left ventricular assist pump for cardiac surgery. Similar lesions are seen in hearts that were reper-

fused using angioplasty or fibrinolytic therapy. The mechanism by which reperfusion of ischemic cardiac muscle produces myofibrillar degeneration involves entry of calcium after a period of relative deprivation.[38]

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 norepinephine) may be the final common pathway by which the irreversible contractures occur, leading 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 wherein excitotoxicity with glutamate results in a similar, if not identical, series of events.[39]

The precise cellular mechanism for the ECG change and the histologic lesion may well reflect the effects of large volumes of norephinephrine released into the myocardium from sympathetic nerve terminals.[40] The fact that the cardiac necrosis is greatest near the nerve terminals in the endocardium and is progressively less severe as one samples muscle approaching the epicardium provides further evidence that catecholamine toxicity produces the lesion.[15] 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 ECG changes.[17] The actin and myosin filaments interact under the influence of calcium but do not relax unless the calcium channel closes. Continuously high levels of norephinephrine in the region may result in failure of the calcium channel to close, leading to cell death, and finally to leakage of enzymes out of the myocardial cell. Free radicals 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, leading to leakage of cardiac enzymes into the blood.[41,42] Thus, the cardiac toxicity of locally released norepinephrine would represent a continuum ranging from a brief reversible burst of ECG abnormalities to a pattern resembling 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 Q waves seen on the ECG.

Histologic changes would also represent a continuum ranging from complete reversibility in a normal heart through mild changes seen best with electron microscopy to severe myocardial cell necrosis with mononuclear cell infiltration and even hemorrhages. The level of cardiac enzymes released and the ECG changes would roughly correlate with the severity and extent of the pathologic process. This explanation, summarized in **Figure 2**, would tie together all the observations in the models discussed here (catecholamine infusion, stress plus or minus steroids, nervous system stimulation, and reperfusion).

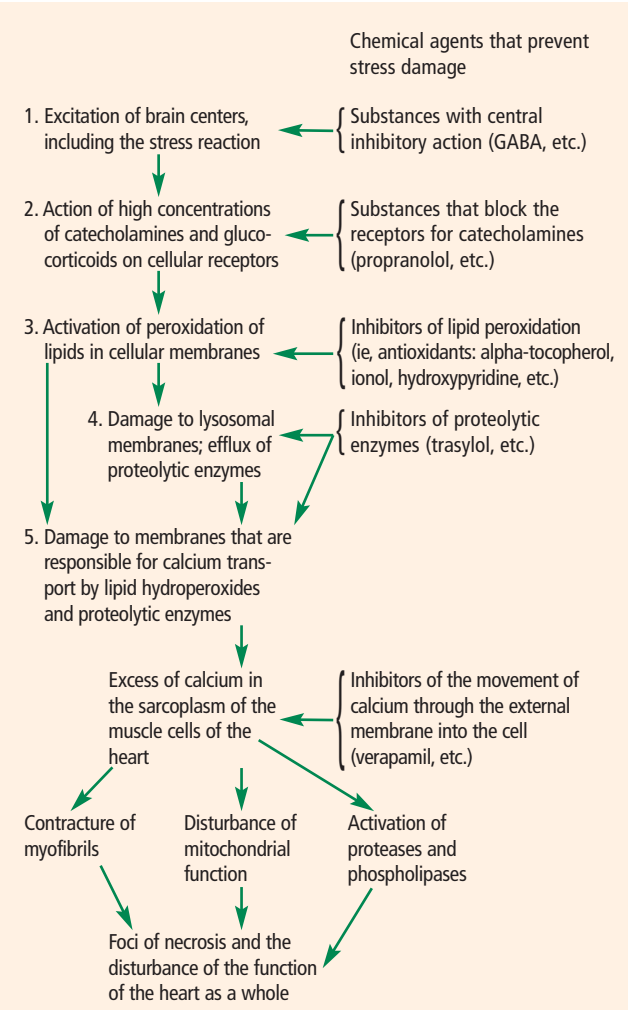

FIGURE 3. Therapeutic approaches aimed at preventing neurocardiac damage. GABA = gamma-aminobutyric acid.

CONCLUSION

There is powerful evidence suggesting that overactivity of the sympathetic limb of the autonomic nervous system is the common phenomenon that links the

major cardiac and pulmonary pathologies seen in neurologic catastrophes. These profound effects on the heart and lungs may contribute in a major way to the mortality rates of many primarily neurologic conditions such as subarachnoid hemorrhage, 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 altering the natural history of these events using catecholamine receptor blockade, calcium channel blockers, free radical scavengers, and antioxidants are ongoing in many centers around the world and are summarized in **Figure 3**.

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The broken heart syndrome

Throughout history, mankind has had an intuitive understanding of the connection between emotional stress and the heart. Descriptions of "heartache" and "dying from a broken heart" have appeared in the literary works of diverse cultures for centuries. Similarly, the medical literature is replete with descriptions of sudden death and myocardial infarction (MI) in the setting of fear, anxiety, and bereavement.[1,2] In the modern era, reports of sudden death and MI have been well documented in populations subjected to emotionally traumatic events such as natural disasters[3] and acts of war,[4] but the direct effect of acute emotional stress on cardiac contractile function has remained obscure.

Recently, a novel syndrome of transient left ventricular (LV) systolic dysfunction precipitated by acute emotional or physical stress has appeared in the medical literature.[5–7] For years this syndrome has been underrecognized and misdiagnosed, and only now are physicians beginning to appreciate the constellation of clinical features that characterize it.

This brief review will highlight those distinguishing features, provide some historical background of this relatively new syndrome, and review what is known about its possible pathophysiologic mechanisms.

A SYNDROME WITH SEVERAL NAMES

In 1980, Cebelin and Hirsch reported a series of murder victims who had been emotionally and physically traumatized prior to their deaths. At autopsy, no internal injuries were identified, but most of the victims had extensive myocardial contraction band necrosis.[8] This histologic finding, frequently observed in high catecholamine states, suggested to the authors that these victims may have died from the deleterious effects of catecholamines on their hearts, and they referred to the condition as "human stress cardiomyopathy." This term reappeared in the medical literature in 1997 when Pavin et al reported two cases of reversible LV dysfunction precipitated by acute emotional stress.[9] Stress cardiomyopathy was an obscure and almost unheard of condition in Western medical literature at the time of Pavin's publication. In the Japanese literature, however, reversible LV dysfunction precipitated by acute emotional or physical stress had already been well described. In 1990, Satoh et al were the first to refer to this syndrome as takotsubo cardiomyopathy,[10] named after the octopus trapping pot with a wide base and narrow neck that they believed resembled the unusual shape of the left ventricle in patients with this syndrome.

Throughout the 1990s, takotsubo cardiomyopathy appeared in Japanese journals in the form of case reports and small case series. Ironically, when Japanese authors finally introduced this syndrome to a Western audience in 2001,[5] they referred to it as transient LV apical ballooning, a name they perhaps felt would be more descriptive to and more easily remembered by Western physicians.

In February 2005, the clinical and neurohumoral features of myocardial stunning due to emotional stress were presented in the *New England Journal of Medicine*.[6] This study referred to the syndrome as stress cardiomyopathy, but because several of the patients had presented following the death of a loved one, the name "broken heart syndrome" was also introduced. The article received a great deal of media coverage (perhaps in part due to it being released just before Valentine's Day) and brought international attention to a syndrome that just a few years earlier had been almost unheard of. In the year and a half since that publication, the number of journal articles regarding this syndrome has increased considerably, and at the present time the names *stress cardiomyopathy*, *takotsubo cardiomyopathy*, *LV apical ballooning syndrome*, and *broken heart syndrome* are used interchangeably to refer to this condition.

PREVALENCE

It is difficult at present to know the true prevalence of this syndrome. A few retrospective series have estimated the prevalence to be about 2% of patients pre-

* Dr. Wittstein reported that he has no financial relationships that pose a potential conflict of interest with this article.

senting with suspected acute coronary syndromes.[11–13] These series likely underestimate the true prevalence because they report only the patients who undergo coronary angiography and do not include patients in medical, surgical, and neurologic intensive care units, where the syndrome is common but often unrecognized. This notion is suggested by one prospective study that reported that of the 92 consecutive patients admitted to the medical intensive care unit for a noncardiac illness, 26 (28%) had echocardiographic evidence of LV apical ballooning.[14]

It will likely require several years and more widespread recognition of this syndrome by physicians in diverse subspecialties before its true prevalence is known.

PATIENT DEMOGRAPHICS AND PRESENTING SYMPTOMS

Although the initial reports of this syndrome were all from Japan, broken heart syndrome has now been reported in patients with diverse ethnic backgrounds from all over the world. As these reports have increased, it has become clear that this condition affects primarily postmenopausal women. In a recent systematic review of the literature, 88.8% of the reported cases were in women, with a mean age in the series reviewed ranging from 58 to 77 years.[15] This gender predisposition is similar to that at our center, where 80% of the cases have been women and the mean age is 60 years (unpublished data).

Patients can present with symptoms identical to those of an acute MI, with chest pain and shortness of breath being the most common.[15] In our experience, although the majority of patients are stable at the time of presentation, about one third have more serious clinical presentations including pulmonary edema, hypotension, cardiogenic shock, and ventricular arrhythmias (unpublished data).

DIAGNOSTIC CLUES

Although no single clinical feature is diagnostic of broken heart syndrome, a series of clinical clues can help solidify the diagnosis.

An acute event

Broken heart syndrome is typically precipitated by a sudden emotional or physical stressor. Patients with this condition do not present with chronic symptoms. Rather, they tend to be individuals without significant cardiac history who suddenly present with chest pain and/or shortness of breath after experiencing acute emotional or physical stress. In our experience, the most common emotional stressors include extreme grief, often due to the loss of a loved one, or extreme fear (eg, being held up at gunpoint, motor vehicle accident, public speaking). The most common physical stressors include neurologic insults, respiratory distress, and surgical procedures. The precipitating event may not always be obvious, but a thorough history will elucidate it in most cases.

Electrocardiographic features

Patients with broken heart syndrome can present with a variety of electrocardiographic (ECG) findings. At the time of admission, the ECG can look normal, can have nonspecific ST- and T-wave changes, or can demonstrate Q waves and ST-segment elevation. In the original descriptions from Japan, ST-segment elevation was considered an important feature of this syndrome. In the largest retrospective series of apical ballooning from Japan, 90% of the patients had ST-segment elevation,[5] but this finding appears to be less common in series reported from the United States.[6,7]

If ST-segment elevation is present, it is most commonly seen in precordial leads, and there is less inferior reciprocal ST-segment depression than is typically seen with an anterior ST-segment elevation MI.[16] Within 24 to 48 hours of the acute presentation, the ECG frequently develops some characteristic features that include a markedly prolonged QT interval and deep T-wave inversion in both precordial and limb leads.[6] The QT interval prolongation usually improves within a couple of days, but the T-wave abnormalities can take days, weeks, or even months to normalize.

Cardiac enzymes

Most patients with broken heart syndrome have elevated cardiac enzymes at the time of admission, but these elevations are usually quite mild. Though patients typically present with severe LV dysfunction, cardiac enzymes are much lower than those typically observed with an acute MI. In a study from our institution, despite a mean ejection fraction of 20% at the time of admission, the troponin I was only 0.18 ng/mL (interquartile range, 0.08 to 0.69 ng/mL; normal, < 0.06 ng/mL).[6]

Unique pattern of LV dysfunction

Perhaps the most distinguishing feature of this syndrome is the unusual LV contractile pattern at the time of admission. There is frequently akinesis or dense hypokinesis of the apical and midventricular segments, with sparing of the basal segments

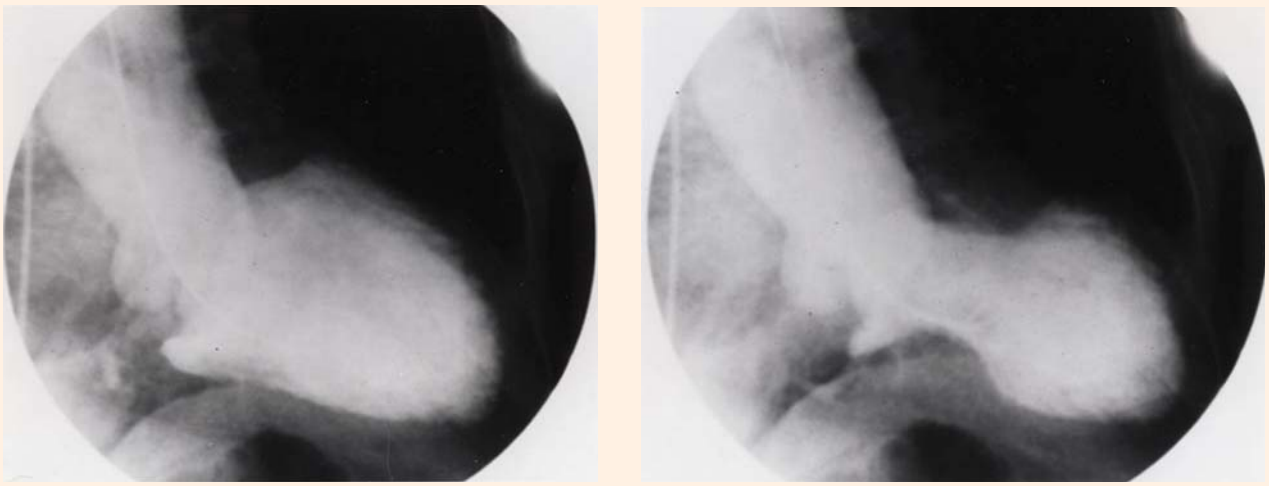

FIGURE 1. Contrast-enhanced ventriculography during diastole (A) and systole (B) in a patient with broken heart syndrome. Note the akinesis of the apex and midventricle with normal contractility of the base. Reprinted, with permission, from reference 6. Copyright © 2005 Massachusetts Medical Society. All rights reserved.

(Figure 1). As mentioned earlier, this contractile pattern has been referred to as both takotsubo cardiomyopathy and LV apical ballooning.

Absence of significant coronary disease

Because patients with broken heart syndrome frequently present with chest pain, dynamic ECG changes, troponin elevation, and focal wall motion abnormalities, coronary angiography is recommended unless there is an obvious contraindication. The vast majority of patients have either normal coronary arteries or mild luminal irregularities, and significant luminal stenoses have been rarely reported.[5–7]

Recovery of LV systolic function

Rapid and complete recovery of LV systolic function is one of the hallmarks of this syndrome. Despite the presence of extensive wall motion abnormalities at the time of admission, complete recovery of systolic function has been reported in all series to date.[15]

In our experience, significant improvement in systolic function frequently occurs during the first week following the initial presentation, and we recommend that patients hospitalized for several days have a repeat echocardiogram prior to discharge. The anterior wall frequently takes the longest to fully recover, but the majority of patients have completely normal LV systolic function by the end of the third week. As a general rule, if systolic function has not normalized after 4 to 6 weeks in a patient suspected of having the broken heart syndrome, the diagnosis should be reconsidered.

TREATMENT

The treatment of broken heart syndrome involves primarily supportive care. For hemodynamically stable patients, diuretics are used to treat congestion, and angiotensin-converting enzyme (ACE) inhibitors and beta-blockers are frequently used during the period of LV recovery.

There is no consensus on how long to continue these medications, but it is our practice to stop them once LV function has completely recovered. There are simply no data at this time to support that chronic use of ACE inhibitors and beta-blockers in these patients improves survival or helps to prevent recurrence. Unless there is a contraindication, anticoagulation should also be considered during the first few days until apical contractility begins to improve.

For hemodynamically unstable patients, reported treatment has included inotropic therapy, vasopressor support, and intra-aortic balloon counterpulsation. At our institution, because we believe that catecholamine excess may be responsible for the myocardial stunning seen with this syndrome, we prefer intra-aortic balloon counterpulsation for hemodynamically unstable patients, and we try to avoid the administration of exogenous catecholamines whenever possible. In addition, inotropes have been associ-

TABLE 1
Plasma catecholamine and neuropeptide levels at the time of admission in patients with broken heart syndrome and Killip class III myocardial infarction

	Broken heart syndrome (n = 13)	Killip class III MI (n = 7)	Normal value
Catecholamine precursor (pg/mL)			
Dihydroxyphenylalanine	2,859 (2,721–2,997)*	1,282 (1,124–1,656)	1,755†
Catecholamines (pg/mL)			
Epinephrine	1,264 (916–1,374)*	376 (275–476)	37†
Norepinephrine	2,284 (1,709–2,910)*	1,100 (914–1,320)	169†
Dopamine	111 (106–146)*	61 (46–77)	15†
Neuronal metabolites (pg/mL)			
Dihydroxyphenylglycol	2,706 (2,382–3,131)*	1,625 (1,412–1,702)	800†
Dihydoxyphenylacetic acid	2,758 (2,573–3,077)	1,513 (1,211–1,648)	1,497†
Extraneuronal metabolites (pg/mL)			
Metanephrine	178 (140–187)	106 (89–124)	59†
Normetanephrine	216 (130–319)	160 (145–170)	55†

MI = myocardial infarction
* $P < .01$ vs Killip class III MI.
† Data are from Goldstein et al.[26]
Adapted from reference 6.

ated with left ventricular outflow tract obstruction in some patients with this syndrome.[7] Whichever form of hemodynamic support is chosen, most patients only require it for a short time and typically demonstrate rapid clinical improvement.

PROGNOSIS AND RECURRENCE

In general, the prognosis of patients with this condition is quite favorable. The in-hospital mortality rate of cases reported in the literature is only 1.1%.[15] When discussing prognosis, it is important to distinguish the patients who present following emotional stress from those who present following a variety of physical stressors. In the 7 years that we have been following patients with this condition, none of the patients with emotional stress have died. We have observed a higher mortality among those who present following physical stress, but typically LV function fully recovers in these patients as well, and the ultimate cause of death is noncardiac.

Although patients can have recurrent symptoms of chest pain, recurrence of the full-blown syndrome appears to be relatively uncommon. Based on a review of the series published to date, the recurrence rate is only 3.5%,[15] which is similar to the rate at our institution.

POSSIBLE PATHOPHYSIOLOGIC MECHANISMS

Catecholamines appear to be central

Increased sympathetic tone may play an important role in the pathogenesis of myocardial stunning following emotional and physical stress. Patients with stress-induced cardiomyopathy have markedly elevated levels of plasma catecholamines and stress neuropeptides at the time of admission compared with patients with Killip class III MI **(Table 1)**.[6] The marked elevation in plasma norepinephrine and epinephrine in these patients reflects activation of both the sympathoneural and adrenomedullary hormonal systems, respectively. In addition, enhanced sympathetic activity in patients with takotsubo cardiomyopathy has been suggested by the increased washout rate of the norepinephrine analogue ^{123}I-metaiodobenzyl-guanidine (MIBG) using myocardial scintigraphy.[12]

Mechanism is elusive, but theories abound

Even if one accepts that catecholamines are central to the pathogenesis of broken heart syndrome, the precise mechanism in which enhanced sympathetic stimulation leads to myocardial stunning is unknown. Ischemia due to multivessel epicardial spasm has been suggested, but there are several compelling reasons to question this hypothesis.

• Spontaneous epicardial spasm during angiography has been rarely reported in the literature, and even the administration of provocative agents such as ergonovine and acetylcholine has failed to induce epicardial spasm in the majority of patients reported.[15]

• It is difficult to explain the LV apical ballooning pattern based on an epicardial vascular distribution, and even multivessel spasm would not account for selective sparing of the basilar segments.

• Most patients have only mild cardiac enzyme elevation, and many have no evidence of ST-segment elevation on admission ECG, findings that seem unlikely in the setting of diffuse epicardial spasm.

An alternative explanation is microcirculatory dysfunction. Using a Doppler flow wire at the time of coronary angiography, Kume et al demonstrated a significant reduction in coronary flow reserve and flow velocity in patients with takotsubo cardiomyopathy.[17] Bybee et al used the Thrombolysis in Myocardial Infarction (TIMI) frame count, a well-validated index of coronary blood flow, to assess coronary flow in patients with LV apical ballooning.[11] Patients with apical ballooning had significantly higher TIMI frame counts compared with controls, and the majority had evidence of abnormal flow in all three epicardial vessels.[11] Although these findings suggest the potential role of microvascular dysfunction in patients with this syndrome, it is unknown whether it is the primary cause of the myocardial stunning or simply a secondary phenomenon.

A third possible mechanism of sympathetically mediated myocardial stunning is the direct effect of catecholamines on cardiac myocytes. Catecholamines can decrease myocyte viability through cyclic adenosine monophosphate-mediated calcium overload,[18] which histologically can result in a unique form of myocyte injury called contraction band necrosis. Contraction band necrosis is characterized by hypercontracted sarcomeres, dense eosinophilic transverse bands, and an interstitial mononuclear inflammatory infiltrate. It has been described in clinical states of catecholamine excess such as pheochromocytoma[19] and subarachnoid hemorrhage,[20] and it has been observed in patients with stress cardiomyopathy as well.[6]

In a rat model of emotional stress, LV apical ballooning can be induced by immobilization stress and attenuated with the administration of alpha- and beta-receptor antagonists.[21] These observations suggest that stress-induced myocardial stunning is due to adrenergic receptor stimulation, though stunning due to ischemia cannot be definitively excluded. Further work with experimental animal models will be necessary to elucidate the precise mechanism.

REMAINING QUESTIONS

The increasing clinical awareness of the broken heart syndrome has raised several interesting questions that to date remain unanswered.

• Why does this syndrome affect primarily postmenopausal women? Sex hormones exert important influences on the sympathetic neurohormonal axis[22] as well as on coronary vasoreactivity,[23] but sex-related differences in catecholamine metabolism and responsiveness remain poorly understood.

• What accounts for the unusual LV contractile pattern seen with this syndrome? Proposed mechanisms include increased responsiveness of the apex to sympathetic stimulation,[24] and the development of apical subendocardial ischemia due to transient LV midcavity obstruction,[25] but a widely accepted explanation for the apical ballooning pattern remains elusive.

• Is the broken heart syndrome simply an exaggeration of the normal stress response, or do individuals with this condition have some pathologic defect, such as abnormal catecholamine production or metabolism, that renders them particularly susceptible to acute stress?

• What are the cellular and molecular mechanisms of stress-induced myocardial stunning?

The answers to these questions will undoubtedly be complex, but in time will provide tremendous insight into both the pathogenesis of broken heart syndrome and the intricacies of the heart-brain relationship.

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Brain imaging in cardiovascular disease: State of the art

Neuroimaging can be used to directly monitor the heart-brain interaction. Disruptions of the normal heart-brain interaction are common. Abnormalities can originate with cardiac or cardiovascular processes that have neurologic effects, such as embolic stroke and low perfusion states, or with neurologic processes that have direct cardiac effects, such as focal brain lesions caused by stroke or multiple sclerosis (MS).

Brain imaging techniques have advanced to the point where regions involved in changes in autonomic arousal during behavior can be located with precision. These regions can be localized by identifying lost function from specific lesions or by using functional brain imaging, such as positron emission tomography (PET) or magnetic resonance imaging (MRI). This article describes imaging of heart-brain interactions, focusing on functional imaging techniques that have enhanced our understanding of these interactions.

CARDIOVASCULAR DISEASE PRODUCING NEUROLOGIC DISEASE

Acute embolic stroke

At most institutions, computed tomography (CT) with perfusion is the imaging modality of choice in patients with acute embolic stroke because it is fast and readily available. CT techniques are limited by a lack of whole brain coverage. It could be argued that acute embolic stroke is best evaluated using MRI, which provides brain coverage and combines diffusion/perfusion imaging for a better assessment of brain at risk for infarction. Disadvantages of MRI, however, are its unfriendly (enclosed) environment for patients and the length of time required to obtain images. Several excellent reviews of the relative merits of CT and MRI for evaluation of acute stroke are available in the literature.[1–3]

Detecting diffusion/perfusion mismatch early is critical for institution of rapid therapy, as 1.9 million neurons are lost per minute during a middle cerebral artery stroke.[4]

NEUROLOGIC PROCESSES WITH CARDIAC EFFECTS

Neurologic processes have cardiac effects; this phenomenon has been reported extensively in the literature.[1–3, 5–8] Injury to the autonomic nervous system can occur with infarcts or MS lesions in specific regions of the brain. The brainstem, insular cortex, and anterior cingulate are the primary regions that have been described in this phenomenon.[9] Injury to the insular cortex, in particular, is associated with an increased incidence of heart rate variability and alterations in cardiac rhythm, placing patients at higher risk of sudden death.[10–12] Focal lesions produced by neurologic disease processes can be used to map autonomic function within the brain.

'Dysfunctional' imaging

Focal brain lesions result in specific functional loss. "Dysfunctional" imaging is the process of matching anatomic locations to specific functional loss. The advantages of dysfunctional imaging are that it requires little or no specialized imaging equipment and produces relatively good localization of functions.

Dysfunctional imaging has several important disadvantages. There is no control over the location of lesions in the brain, making a systematic evaluation of function difficult. Often, lesions will overlap several brain regions or multiple lesions will be present, making it difficult to map a single lesion to a single brain region. Most important, this technique does not allow for the study of normal subjects, either for understanding the normal heart-brain interaction or for developing potential screening tests for abnormal autonomic function.

Despite these shortcomings, dysfunctional imaging has provided a tremendous amount of data on autonomic brain function, and it specifically has provided a better understanding of cardiac abnormalities resulting from stroke and MS.

* Dr. Phillips reported that he has no financial relationships that pose a potential conflict of interest with this article.

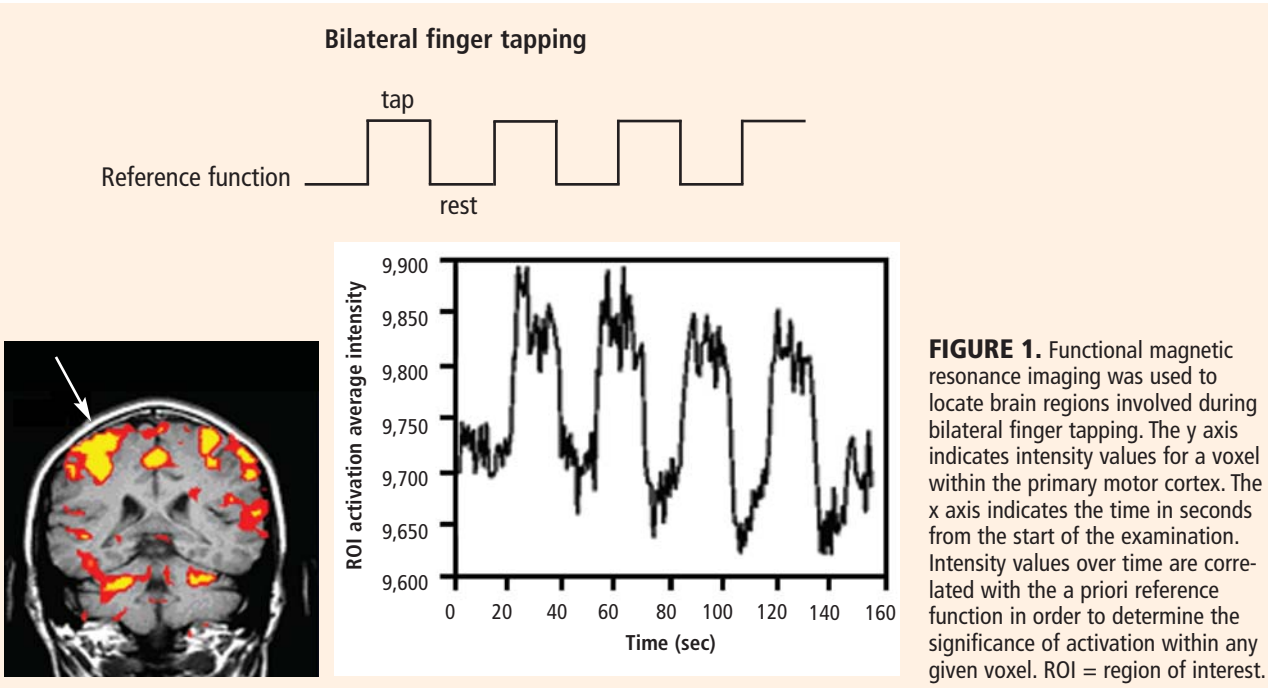

FIGURE 1. Functional magnetic resonance imaging was used to locate brain regions involved during bilateral finger tapping. The y axis indicates intensity values for a voxel within the primary motor cortex. The x axis indicates the time in seconds from the start of the examination. Intensity values over time are correlated with the a priori reference function in order to determine the significance of activation within any given voxel. ROI = region of interest.

Stroke. For instance, we have learned from dysfunctional imaging that right-sided middle cerebral artery/right insular strokes are associated with an increased incidence of arrhythmias, cardiac death, and catecholamine production.[10–12] Left insular strokes have been implicated in these processes as well.[13] Brainstem (medullary) strokes can also produce significant autonomic dysfunction.[14–16]

MS. Autonomic dysfunction has also been reported in as many as 45% to 50% of patients with MS.[5–8] Orthostatic intolerance is also reported commonly.[8] In MS, cardiac autonomic dysfunction may be linked to lesions in the brainstem and medulla. The variability and quantity of brain lesions in patients with MS, however, underscore the difficulties involved in using dysfunctional imaging to identify specific culprit lesions.

Functional brain imaging

Functional brain imaging can directly visualize brain control of autonomic function and can thus overcome the limitations of dysfunctional imaging.[17] Functional brain imaging can be accomplished with either PET or functional MRI. The latter has superior spatial and temporal resolutions compared with PET, allowing visualization of small objects over a smaller timeframe. The disadvantage to functional MRI is that it is not a quantitative but a qualitative methodology.

Functional MRI brain activation. Increased neuronal activity increases local cerebral blood flow, which decreases the amount of deoxyhemoglobin and magnetic susceptibility, resulting in a net enhancement of the MRI signal.[18–20] For this enhancement to occur, blood flow must be adequate, neuronal activity must be coupled with blood flow, and oxygen extraction must be relatively stable.

Functional MRI can be used to locate brain regions involved in simple tasks. Bilateral finger tapping with periods of rest in between has been used to locate brain pixels that demonstrate a similar pattern of activity, permitting mapping of the brain regions involved **(Figure 1)**.

Challenges in autonomic functional MRI. One challenge posed by autonomic functional MRI is that untrained individuals have little or no volitional control over autonomic functions. Therefore, the tasks chosen must elicit autonomic responses. In the case of sympathetic arousal, example stimuli would include maximal handgrip, pain, fear, anticipation, and anxiety. An example of a parasympathetic stimulus would be a Valsalva maneuver. The response to stimuli must then be monitored to compare the data obtained from functional MRI. This presents a problem, as the MRI scanner is a relatively unfriendly environment for most of the standard monitoring equipment used to evaluate autonomic responses. Until recently this required special modification of existing equipment. Fortunately, MRI-compatible equipment for measuring heart rate, blood pressure, galvanic skin response, and pupillary response is now becoming available.

Obtaining the desired signal. The most difficult task in functional imaging of the autonomic system is to carefully design stimuli and tasks to isolate autonomic effects. A good example from the literature is a paper by Cheng et al that assessed activity in the amygdala with anticipation of pain (Pavlovian fear condition-

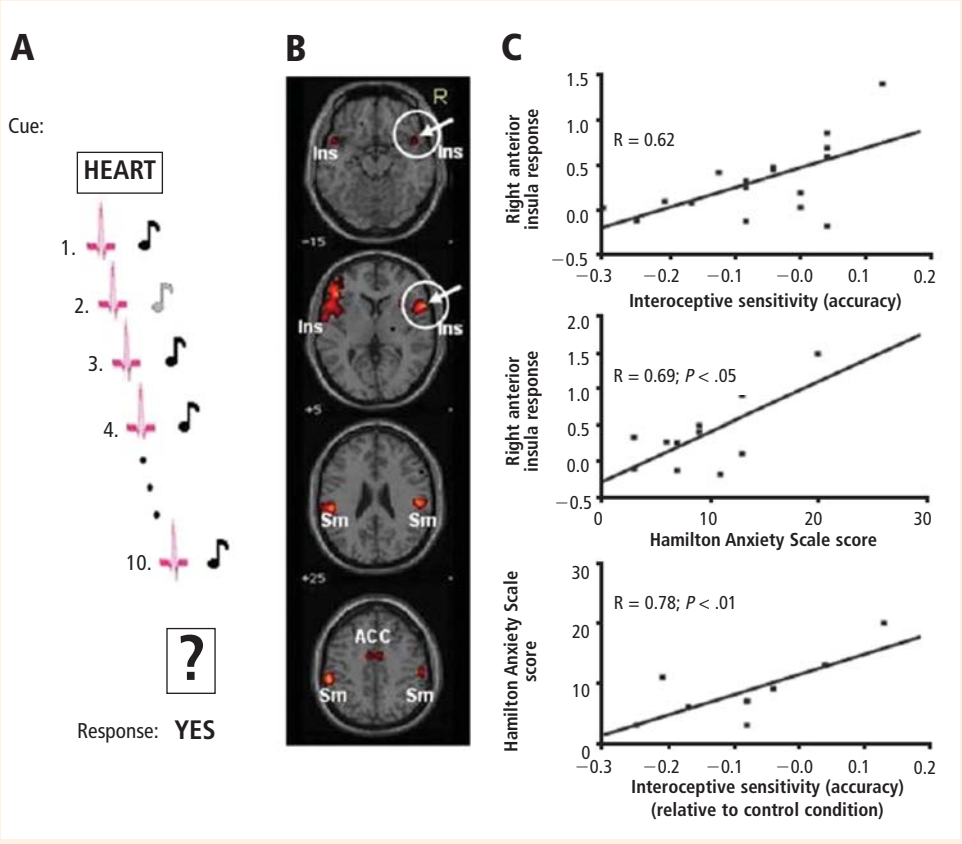

FIGURE 2. Interoceptive awareness was assessed in healthy subjects who performed a heartbeat detection task. Subjects were first exposed to a series of tones either synchronized to their heartbeat or delayed by 500 msec (A). While attending to heartbeat timing, activity was enhanced in the bilateral insula, bilateral somatomotor cortex, and anterior cingulate (B). Conscious awareness of the timing of the heartbeats (interoceptive awareness) was associated with activity in the right insular cortex, and scores indicative of anxiety on the Hamilton Anxiety Scale correlated with interoceptive sensitivity (C). Reprinted, with permission, from reference 17.

ing).[21] The researchers exposed 20 healthy subjects to an unconditional stimulus in the form of an electric shock. Subjects were also exposed to a visual stimulus (conditional stimulus) in the form of a flashing light. When the functional MRI time series data were analyzed using the visual stimulus as a reference function, the primary activated areas were in the occipital cortex. However, a very different pattern of activation was identified using a reference function that is sensitive to autonomic changes. The reference function from the galvanic skin response during experiments demonstrated the desired activation within the amygdala that was indicative of an autonomic response.

Anterior cingulate. Functional neuroimaging with PET and MRI has also been used to study autonomic activation of the anterior cingulate during a variety of tasks. Critchley and colleagues have used a variety of methods to measure autonomic function, including blood pressure, cardiac sympathetic response, heart rate, and change in pupil diameter.[17] Across the multiple tasks designed to elicit an autonomic response, consistent activation in the anterior cingulate was observed. Further, this relatively consistent response was seen using a variety of methods to determine autonomic response. The findings suggest a central role for the anterior cingulate in autonomic functioning. Critchley also points out that the anterior cingulate is involved in almost all concentration tasks, which may be partially related to autonomic function or to the anterior cingulate being a central processing area for volitional behaviors.[17]

Right insular cortex. Another functional imaging study designed to map autonomic control centers involves correlating changes in galvanic skin response to performance of a gambling task.[17] Skin conductance was measured as subjects attempted to choose a "winning" playing card among two cards presented. Unbeknownst to the subjects, the winning card in this task was chosen randomly, provoking anxiety as subjects attempted without success to develop a decision-making strategy to win. Comparing the functional MRI time series data with the galvanic skin response as a reference function produced a consistent pattern of activation in the right insular cortex. Activation was also observed in medial frontal regions and some parietal regions of the brain as well.

In a study designed to test autonomic interoceptive awareness, Critchley at al tested the ability of subjects to detect their own heart rate **(Figure 2)**.[17,22] In the study, subjects underwent functional MRI scans while they were asked to judge the timing of their own heartbeats to auditory tones that were either synchronized with their heartbeat or delayed by 500 msec. At the

end of 10 heartbeats, the subjects were asked whether the tone matched or did not match their heartbeats. Areas of activation during the task were observed in the right insular cortex, the anterior cingulate, the parietal lobes, and the operculum. However, when activation was compared with subjects' accuracy in detecting their own heart rate, only the right insular cortex showed a significant correlation with conscious perception of heartbeats. Interestingly, the degree of activation in the insular cortex correlated with subjects' perceived anxiety in daily life as assessed by scores on the Hamilton Anxiety Scale. Subjects who reported more anxiety were also more accurate at detecting their own heart rate (interoceptive sensitivity). These findings suggest that interoceptive sensitivity is mediated by the right insular cortex and that sensitivity to autonomic states may play a role in anxiety.

Imaging autonomic brainstem nuclei. Many of the brain regions responsible for autonomic responses lie within the brainstem and are relatively small. Recently, investigators have demonstrated that functional MRI can detect brainstem nuclei as small as 2 mm.[23] Although the studies have been performed largely in normal subjects, they hold the promise that the entire autonomic nervous system can be evaluated, including small brainstem nuclei.[23]

IMAGING IN DISEASE STATES

Few functional brain imaging studies have been performed in patients with disease. In a study comparing activation of brain regions in patients with heart failure and controls upon performance of a cold pressor task, activation in the medulla, the hypothalamus, and portions of the insular cortex was observed in the patients with heart failure but not in the controls.[24]

Functional MRI is an excellent tool for in vivo evaluation of normal subjects. It is also potentially useful for disease states, with several caveats. It is difficult to perform on sick patients because of the unfriendly MRI environment and because extensive physiologic monitoring is required. In addition, the autonomic response may be blunted, making physiologic comparisons and monitoring more difficult. Finally, blood flow and neurovascular coupling may be impaired in disease states.

CONCLUSION

Excellent methods are available for assessing brain injury from cardiac causes. Anatomic imaging can be used to relate neurologic injury to cardiac effects. The potential of functional brain imaging for in vivo testing of autonomic function is strong, and may provide a better understanding of disease states.

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Cortical control of the heart

Neuraxial organization of cardiac control can be considered as a series of hierarchically organized oscillatory networks. Some of the oscillatory activity is determined by intrinsic characteristics of the cells themselves, but it may also be related to neural networks that are either situated inside or distributed between specific brain nuclei. The functional rationale for such hierarchical organization is unclear, but this probably permits integration between cardiac neural regulatory elements and extraceptive and intraceptive perceptions, allowing for contextually appropriate response patterning.

The anatomic locations involved in cardiac regulation extend from the spinal cord to the cortex itself. At the cortical level, the insula has received the most recent attention and this will be the major focus of this article.

INVESTIGATING THE ROLE OF THE INSULAR CORTEX

For many years, the role of the insular cortex was unclear. Recently, viscerotopicity has been demonstrated and chemosensation, taste, and respiratory representation have been shown.[1]

The insular cortex is also of interest because neuroanatomic tracing experiments have shown efferent and afferent connectivity with several diencephalic and brainstem structures known to be involved with cardiovascular representation.[1]

Stimulus choice

One problem with investigating cardiac representation is the difficulty in obtaining specific cardiac effects (ie, changes in heart rate or rhythm) without concomitant changes in blood pressure and respiration. When these occur, uncertainty arises as to whether the resultant cardiac effects are primary or secondary. Overcoming this problem required a different stimulus, which we accomplished by discriminating the R wave of the electrocardiogram (ECG) and using it to trigger a microstimulus delayed by approximately 120 msec (the estimated cortical cardiac time delay from neural transfer between the insular cortex and the sinoatrial node), which reached the heart just prior to the P wave. In this way, cardiac responses could be obtained without changes in the respiratory rate or blood pressure. In chloralose-anesthetized rats, microstimulation of the posterior insular cortex in phase with the ECG R wave produced significant increases in heart rate and bradycardia without concomitant detectable autonomic changes.[2]

Potential arrhythmogenesis

With success in obtaining changes in heart rhythm in these rats, we were next interested in whether or not ventricular arrhythmias could be provoked by phasic microstimulation of the insular cortex. Stimuli were arranged so as not to change heart rate, by generating the neural activity reaching the heart during the early part of the T wave. This was done in hopes of increasing cardiac sympathetic drive at a time when the ventricle might be most vulnerable to destabilizing neural influences.

Results obtained with microstimulation of the left insular cortex were compared with those obtained with peri-insular stimulation in the parietal region, which served as a control.

Prolonged stimulation in parietal locations over approximately 8 hours produced little change in the ECG pattern. In contrast, stimulation within the left insular cortex produced ST-segment depression followed by QT prolongation, broadening of the QRS complex, and increasing degrees of heart block leading to complete heart block and culminating in death in asystole. These changes were associated with myocytolysis, a form of cardiac muscle damage characterized by scattered areas of necrosis with monocytic infiltration and subendocardial hemorrhage adjacent to the left ventricle. This was accompanied by a significant increase in levels of plasma norepinephrine, which, in the rat, is indicative of a neurally mediated mechanism rather than adrenal activation.[3]

These findings suggest that stimulation within the insular cortex mimics the repolarization and structur-

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al changes that occur with catecholamine-induced cardiomyopathy seen under certain clinical circumstances, including death following extreme and prolonged stress, and that these effects are likely associated with neural activation within the ventricular myocardium.

Investigation of patients in the acute phase of insular stroke revealed significant increases in the corrected QT interval and in ventricular arrhythmias, indicating that insular damage may produce effects on cardiac repolarization, extending the experimental observations into a relevant clinical context.[4]

LATERALIZATION OF CARDIOVASCULAR CHANGES

In an attempt to demonstrate lateralization, a series of single localized lesions was placed in either the left or right posterior insula, the left or right anterior insula, and in adjacent peri-insular regions. We found no changes in basal cardiovascular state except with lesions placed in the right posterior insular cortex, which produced elevations in mean arterial pressure and basal heart rate and, interestingly, no change in baroreceptor gain. In contrast, left posterior insular lesions significantly increased baroreceptor gain. These findings suggest a differential effect, with the right posterior insula involved in cardiovascular sympathetic control and the left posterior insula involved in the regulation of cardiac parasympathoregulatory function.[5]

Following these observations, spectral analysis of heart rate variability in the rat was used to explore the effects of microstimulation within the right insular cortex since the previous findings indicate a role specific to sympathoregulatory cardiovascular mechanisms in this location. This appeared to upregulate sympathetic neural activity significantly without changing heart rate or blood pressure, and was associated with a decrease in baroreceptor reflex gain.[6]

Cardiac representation in humans

Whether or not similar lateralizability exists within the human insular cortex was explored in human epileptic patients. In five patients undergoing temporal lobectomy for intractable seizures, exposure of the antero-inferior insular cortex allowed for study of the effects of intraoperative insular stimulation. The caveat here is that prolonged seizures may change synaptic relationships in the brain, and therefore the findings may not necessarily be applicable to normal individuals. Nevertheless, left anterior insular stimulation produced bradycardia in 93% of the stimulations. Stimulation of the right anterior insula produced tachycardia or an increase in diastolic blood pressure. Therefore, we demonstrated that cardiovascular changes could be elicited with human insular cortex stimulation, as well as lateralization of responses for a cortical site. As in the rat, right-sided dominance was demonstrated for sympathetic effects.[7]

Patients with stroke lateralized to the left insular cortex were then compared with age-matched controls. Using spectral analysis, we found a reduction of sympathovagal balance and a decrease in the randomness of heart rate variability. Further, one third of the stroke patients developed sinus tachycardia within 24 hours of admission in the absence of significant coronary artery disease. This implies that ablation of the left insular cortex, where it is believed that parasympathetic regulatory cardiac function is represented, predisposes to the development of adverse cardiac outcomes.[8]

Left insular stroke and adverse cardiac outcomes

To investigate whether or not left insular stroke contributes to adverse cardiac outcomes, we followed patients with left insular stroke and another group with noninsular cortical stroke or transient ischemic attack, and assessed adverse cardiac outcomes over 1 year. Using multiple regression analysis, left insular stroke was found to increase an aggregate measure of adverse cardiac outcomes that included sudden cardiac death, new-onset angina, myocardial infarction, and new-onset left ventricular failure. The association between left insular stroke and adverse cardiac outcomes was extremely significant when the analysis was restricted to patients without symptomatic coronary artery disease.[9] Exclusion of patients with symptomatic coronary disease reduced the likelihood of beta-blocker therapy in the remaining subjects, and we believe that beta-blocker therapy may confound the association between left insular stroke and adverse cardiac outcome by effectively attenuating insula-related cardiac sympathetic upregulation.

CONCLUSION

There is evidence for lateralization and specialization of cardioregulatory function within the insular cortex from both laboratory and clinical observations. The right insular cortex is primarily concerned with sympathoregulatory activity. The left insular cortex is more likely involved with parasympathoregulatory function. State-dependent inhibitory and excitatory pathways descend from these insular regions to other subcortical areas involved in cardiovascular regulation. Lesions that involve primarily the left insular

cortex are associated with destabilization of sympathoregulatory balance, exposing the heart to increased risk of arrhythmia and adverse cardiac outcomes through myocytolysis and other mechanisms.

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Neurological mechanisms of chest pain and cardiac disease

Electrical stimulation of dorsal segments of the spinal cord has been used to treat patients with severe angina pectoris that is refractory to conventional therapies. The concept is based on the "gate control theory" first proposed by Melzack and Wall,[1] in which a neuronal "gate" in the dorsal horn of the spinal cord controls the flow of noxious stimuli to the brain. Thus, spinal cord stimulation (SCS) can be thought of as "closing the gate" on pain. In the most often-used technique, an electrode is inserted over the dorsal columns and placed in the segments where electrical stimulation elicits paresthesias in the painful dermatomes. SCS activates large afferent fibers that have the ability to suppress stimuli from small fibers transmitting nociceptive information, and thereby "closes the pain gate."

This article will briefly review the efficacy of SCS in relieving angina pectoris, provide an overview of the spinal processing of cardiac nociceptive information and the neural mechanisms of referred pain in the thoracic and cervical spinal cord, and examine the effects of SCS on the heart.

SUCCESS RATES WITH SCS

Success rates achieved with SCS for angina pectoris are in excess of 80%.[2–4] In patients with angina undergoing SCS, the severity and frequency of anginal episodes are reduced, and in some cases episodes are eliminated.[5–8] The intake of nitrates to relieve angina pain is also markedly decreased.[9] In addition to pain relief, clinical studies using SCS for the treatment of chronic refractory angina demonstrate increases in exercise tolerance, improvements in ischemia-related electrocardiographic changes (ST segment), and improvements in the quality of life.[3,6,8,10] Animal studies also indicate that SCS reduces the nociceptive signal and improves the function of the heart.[11–16]

* Dr. Foreman reported that he has no financial relationships that pose a potential conflict of interest with this article.

SPINAL PROCESSING OF CARDIAC NOCICEPTIVE INFORMATION

The challenge is to determine the neural mechanisms underlying angina pectoris that contribute to the success of SCS. Fifteen years of research at the University of Oklahoma, focusing on spinal processing of cardiac nociceptive impulses, have identified the C1-C2 and the T2-T4 segments of the spinal cord as critical for processing information in the neural hierarchy regulating cardiac and respiratory control.

Neural mechanisms of referred pain in the thoracic spinal cord

The responses of individual spinothalamic tract (STT) cells, the cells of origin in the gray matter of the thoracic spinal cord, to nociceptive input from the heart have been assessed by transient coronary artery occlusion or injection of algesic chemicals into the heart, followed by examination of somatic fields.[17] A distribution of STT cells with convergence of somatic and cardiac input was found at the T1-T5 segments. Neurons in the C5 and C6, but not the C7 and C8, segments also responded to cardiac or somatic input, primarily in the proximal region. The receptive fields were located primarily in deep muscle rather than cutaneous tissue.

These findings provide insight into the characteristics of referred pain:

- Pain of visceral origin is referred to somatic regions that are innervated from the same spinal segments as the heart.
- The pain is generally referred to proximal, but not distal, somatic structures.
- The referred pain is experienced as deep pain.

Neural mechanisms of referred pain in the cervical spinal cord

Neck and jaw pain in some patients with angina pectoris served as a basis for exploring neural mechanisms of referred pain in the cervical spinal cord. Early clinical observations of neck pain being unmasked after sympathectomy to reduce angina pectoris led to the

hypothesis that STT cells in the C1-C2 region receive cardiac input.[18,19] To address this hypothesis, recordings were made from STT cells located in the C1-C2 spinal segments.[20,21] Coronary occlusion or injection of algesic chemicals into the heart before and after bilateral vagotomy, or electrical stimulation of cardiopulmonary afferent fibers and thoracic vagal afferents, was used to activate the neurons.

Electrical stimulation of vagal and cardiac sympathetic nerves showed that STT cells in C1-C2 were more responsive to stimuli from vagal afferents than from cardiac sympathetic afferents, and that the somatic fields for these cells were located primarily in the jaw and neck regions.[20] In addition, bilateral vagotomy markedly reduced the nociceptive input produced by injecting algesic chemicals in the heart, as evidenced by reduced activity of these STT cells in the cervical region.[21] Since only 6% of the vagal afferents project directly to the C1-C2 spinal neurons, the rest most likely ascend into the nucleus tractus solitarius and then synapse on cells with axons projecting to the C1-C2 segments.[22] This finding suggests that the vagus plays an important role in relaying this information from the heart to the C1-C2 region. These results also support the clinical observations that information transmitted in the vagus contributes to the referral of pain to the neck and jaw.

Effects of SCS on thoracic STT cells receiving cardiac nociceptive information

Spinal cord stimulation of the T1-T2 area in anesthetized primates at an intensity of approximately 90% of motor threshold was performed to record STT cell responses to noxious cardiac input.[14] An increase in cell activity was observed following injection of bradykinin in the heart via the left atrium, which was suppressed with SCS **(Figure 1)**. The limiting factor of this study was using animals with normal hearts; study of hearts with previous infarction or ischemic hearts would be more relevant clinically. Nevertheless, this study shows a significant decrease in the processing of impulses in STT cells when the spinal cord stimulator was turned on. This effect is attributed to inhibitory mechanisms impinging on the STT cells and potentially a reduction in nociceptive input from the heart to the spinal cord.

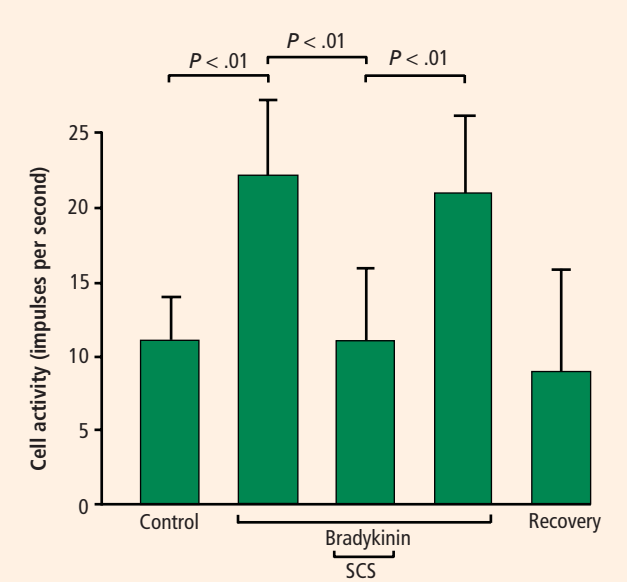

FIGURE 1. Effects of spinal cord stimulation (SCS) on cardiac-evoked activity of thoracic spinothalamic tract (STT) cells. Control: spontaneous activity; bradykinin: intra-atrial injections of bradykinin; SCS: electrical stimulation of the T1-T2 dorsal columns (~80 Hz; 0.25 ms) at an intensity of ~90% motor threshold; recovery: spontaneous activity following the bradykinin response. The line above "bradykinin" indicates that three bars represent responses to bradykinin, and the line above "SCS" represents bradykinin plus SCS (which applies to the second of these three bars). The activity of STT cells in response to bradykinin injection was significantly diminished with SCS to levels observed in controls. Adapted from Chandler et al, Eur Heart J 1993; 14:96–105, by permission of the European Society of Cardiology.

EFFECTS OF SCS ON THE HEART

The intrathoracic intrinsic cardiac nervous system and SCS

Evidence supports the notion that SCS may alter the function of the intrinsic cardiac nervous system to protect the heart. We first looked at the effects of stimulation at the T1-T4 region where processing of several different types of neurons is abundant.[11,15] Recent canine studies have shown that SCS of the T1-T2 dorsal columns using "clinical parameters" (50 Hz, 0.2 ms duration) and an intensity of 90% of motor threshold significantly reduces activity generated by the intrinsic cardiac neurons in their basal conditions and in the presence of regional ventricular ischemia.[15] Another interesting observation is that SCS stabilized these neurons for long periods, even after the stimulus was terminated.[11] Clinical studies support this observation, indicating that a cardioprotective benefit may persist even after discontinuing SCS therapy for long periods.[23]

Infarct size and SCS

The effect of SCS on infarct size was explored in a rabbit model using a transient coronary artery occlusion.[24] The rabbit was chosen as the model because it does not have collateral blood vessels in the heart.[25] It is known that exogenous catecholamines can protect

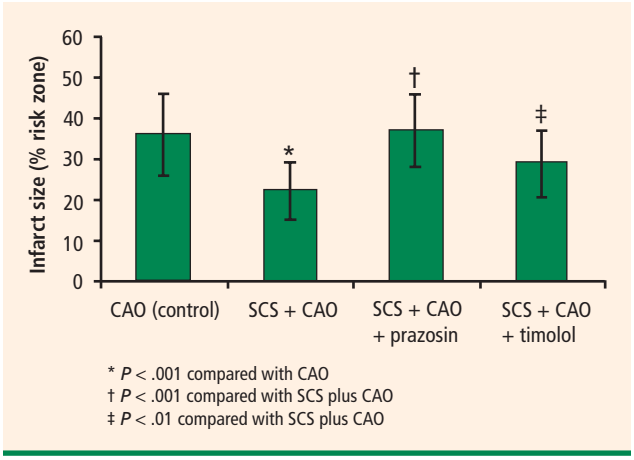

FIGURE 2. Effects of spinal cord stimulation (SCS) on infarct size. The infarct size is plotted as a percentage of risk zone for animals with coronary artery occlusion alone (CAO) compared to animals with preemptive SCS and CAO. Preemptive SCS began 15 minutes before the onset of the CAO, and then both were continued for 30 minutes followed by reperfusion for 3 hours. Vehicle or selective adrenergic blockade (prazosin or timolol) was administered 15 minutes before the onset of SCS. Adapted from reference 24.

the rabbit heart from transient myocardial infarction, an effect that is prevented by alpha-receptor blockade, but endogenous myocardial catecholamines are not essential for protection from ischemic preconditioning in the rabbit.[26–30] It is also known that adrenoceptors are found on subpopulations of neurons within the intrathoracic cardiac neuronal hierarchy.[31,32] Modulation of these receptors can influence the progress of cardiac pathology.[33,34] Our hypothesis, therefore, was that preemptive SCS could reduce myocardial apoptosis, and could reduce infarct size as a result of activation of adrenergic receptors.

Stimulation of the dorsal surface of the T1-T2 segments using "clinical parameters" (50 Hz; 0.2 ms; 90% of motor threshold) was applied approximately 15 minutes before the left coronary artery was occluded and then both the occlusion and SCS continued for 30 minutes **(Figure 2)**. This was followed by a 3-hour reperfusion period. The infarct was measured by using tetrazolium, and the risk zone was determined by using fluorescent microspheres. The infarct size was expressed as a percentage of the risk zone. Infarct size was 36% of the risk zone with only left coronary artery occlusion (control). SCS reduced the infarct size to approximately 22%, which was significantly smaller than the control infarct size. Preconditioning by administering a 5-minute occlusion, waiting 10 minutes, and then occluding the artery for 30 minutes also reduced the infarct size to 22% of the risk zone. Infarct size increased to that observed in the controls following treatment with the alpha-blocker prazosin; beta-blocker treatment with timolol also increased infarct size compared with SCS during coronary artery occlusion without the blockers. From these data, we conclude that SCS has the ability to decrease the infarct size by changing the environment of the heart with respect to the adrenoreceptors.

SUMMARY

SCS is an efficacious, reversible, and safe therapy that improves quality of life, increases exercise tolerance, and relieves angina pectoris, but clinical trials in North America are needed to confirm the data coming from Europe.

Neuronal convergence onto STT cells underlies the referred pain associated with angina pectoris. With pain referred to the chest and upper arm, cardiac nociceptive information is transmitted via sympathetic afferent fibers to thoracic cells. With pain referred to the jaw and neck, cardiac nociceptive information is transmitted via vagal afferent fibers onto cervical cells. SCS can modulate the responses of thoracic STT cells to nociceptive input originating from the heart.

SCS modulates cardiac function. It stabilizes neurons in the intrinsic cardiac nervous system, and can reduce infarct size via adrenoreceptors.

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Hypertension in sleep apnea: The role of the sympathetic pathway

Chronic intermittent hypoxia, a phenomenon that occurs during episodes of sleep apnea, has been shown to produce hypertension independent of obesity, diabetes, and other potentially confounding factors in patients with sleep apnea.

This article discusses the research of our laboratory and collaborating researchers in elucidating the effects of chronic intermittent hypoxia and the mechanisms responsible for the hypertension induced by a reduction in partial pressure of oxygen (P_{O_2}). Using Sprague-Dawley rats as a model, we have focused on the chemoreflex pathway, which arises from the carotid body and is the primary sensor of reduced arterial oxygen levels.

RELATIONSHIP BETWEEN P_{O_2} AND HYPERTENSION

Reduced P_{O_2} could theoretically cause hypertension by a direct effect on smooth muscle, or hypertension could be mediated by endocrine factors or through neural pathways.

Considerable evidence points to the sympathetic neural pathway:

- Some patients with chronic sleep apnea have increased basal sympathetic activity, which can be measured from a nerve containing sympathetic fibers entering a muscle.[1–3]
- Rats exposed to chronic intermittent hypoxia have an exaggerated sympathetic response to acute hypoxia compared with controls, as measured in cervical, renal, and muscle nerves.[4]
- Blocking sympathetic nerve activity in rats using 6-hydroxydopamine prevents chronic intermittent hypoxia-induced hypertension from developing.[5]

THE CHEMOREFLEX PATHWAY: AN IDEAL MODEL

What is the source of increase in sympathetic activity, and why is it not modulated by baroreceptors? To answer these questions, the chemoreflex pathway **(Figure 1)** may be a good model. It consists of:

- Carotid body chemoreceptors that lie in the bifurcation of the common carotid artery. They respond to decreased arterial P_{O_2} by releasing transmitters to activate sensory nerve fibers within the carotid body.
- The carotid sinus nerve, which joins the glossopharyngeal nerve and carries the sensory afferent fibers that are activated by the transmitters. These nerves have their cell bodies within the petrosal ganglia. Their axons project into the brainstem.
- The afferent nerve fibers that enter the nucleus of the solitary tract, where they make synaptic connections with neurons that relay information to the ventral medulla and onward through the intermediolateral columns of the spinal cord and out through the sympathetic ganglia.
- The adrenal glands, blood vessels, and the heart, to which information is ultimately transferred.

The chemoreflex pathway turns out to be an ideal place to look for changes that occur during intermittent hypoxia, for several reasons: the carotid body is a primary sensor for reduced arterial P_{O_2}, electrically stimulating the carotid body pathway increases arterial pressure and heart rate, and severing the nerve in rats has been shown to prevent the hypertension of chronic intermittent hypoxia.[6]

THE HYPOTHESIS: CHEMOREFLEX PATHWAY ACTIVATION LEADS TO SUSTAINED ELEVATION IN ARTERIAL PRESSURE

Our working hypothesis is that increased activation of the carotid body chemoreflex pathway in chronic intermittent hypoxia leads to sustained elevation in arterial pressure. Our research has focused on learning why this occurs.

The protocol

Our protocol, developed by Prabhakar and colleagues,[7] is as follows: Sprague-Dawley rats are exposed to chronic intermittent hypoxia (15 seconds of 5% O_2,

* All authors reported that they have no financial relationships that pose a potential conflict of interest with this article.

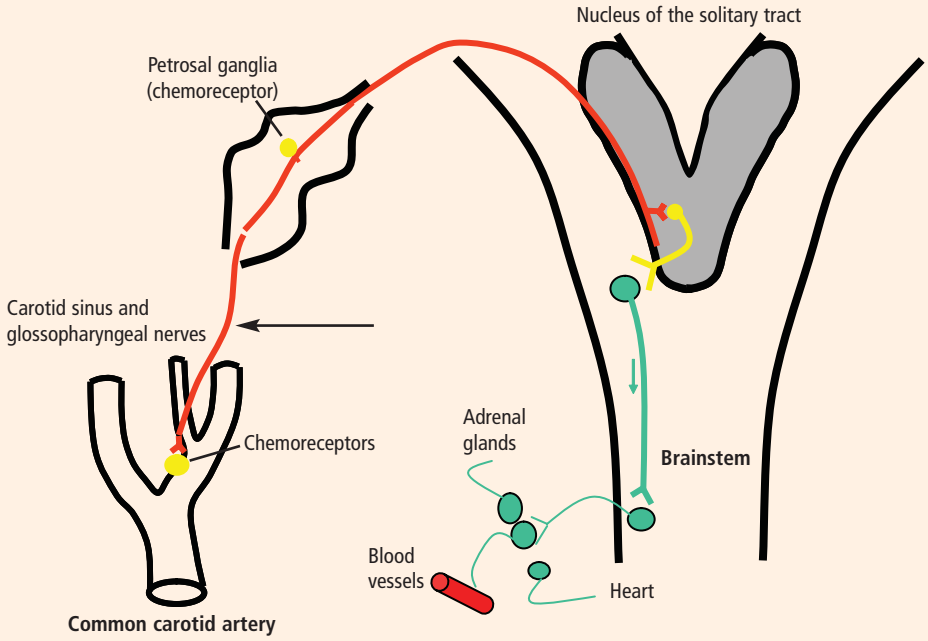

FIGURE 1. The chemoreflex pathway. Carotid body chemoreceptors respond to decreased arterial Po_2 by releasing transmitters to activate sensory nerve fibers within the carotid body. The carotid sinus and glossopharyngeal nerves, whose cell bodies reside in the petrosal ganglia, transfer the sensory afferent fibers to the brainstem via the nucleus of the solitary tract. There the afferent nerve fibers make synaptic connections with neurons, which relay information through the spinal cord and sympathetic ganglia to the adrenal glands, blood vessels, and heart.

followed by 5 minutes of 21% O_2 for 8 hours per day). After 10 days, arterial pressure elevations in the range of 10 to 25 mm Hg are demonstrated[7,8] (other laboratories with different protocols achieve different degrees of blood pressure elevation[6,9]).

Intermittent hypoxia increases carotid body activity

Using this protocol, Prabhakar and colleagues studied carotid body discharge.[7] The carotid body glomus cells respond to Po_2 via nerves that innervate the region. After 10 days of exposure to chronic intermittent hypoxia, the baseline activity in the carotid body was higher than normal and the response to acute hypoxic stimuli was exaggerated.

From this it was concluded that activity from the carotid body was increased from chronic intermittent hypoxia, leading to increased arterial pressure. We would expect baroreceptors to buffer this response, but they do not appear to do so.

Intermittent hypoxia inhibits activity in the nucleus of the solitary tract

To explore whether other sites along the chemoreflex pathway were also susceptible to reduced Po_2, we focused on activity in the afferent fibers at the first synapse in the nucleus of the solitary tract.[10]

Slicing the brain horizontally through the nucleus of the solitary tract in the brainstem leaves the afferent pathway intact, allowing for electrical stimulation of axons on the pathway and measurement of the evoked postsynaptic responses. Placing a small amount of dye on the carotid body allows one to distinguish the cells that receive chemoreceptive input as the dye travels the axons to the presynaptic terminals in the nucleus of the solitary tract.

Using differential interference contrast microscopy, we stimulated the solitary tract under voltage clamp conditions: holding the voltage constant prevents the membrane potential from moving into regions that would activate other ion channels. This enabled us to recognize the responses at specific synapses.[10]

Contrary to our expectations, rats had a dramatically *reduced* evoked synaptic response after 10 days and 30 days of intermittent hypoxia.[10]

As a result of intermittent hypoxia, each action potential arriving from a chemoreceptive afferent fiber releases about half (or even fewer) of the vesicles of neurotransmitter that are normally released. Further experiments verified that the change occurs presynaptically, not in the postsynaptic cell.[10]

Inhibited response following intermittent hypoxia is reversible

The reduced current that occurs from intermittent hypoxia is reversible. Rats that have been through 10 days of intermittent hypoxia followed by 10 days of living in a normal oxygen environment have a near-control postsynaptic current.

Intermittent hypoxia induces increased spontaneous activity presynaptically

To mimic continuous activity arising from carotid chemoreceptors, we delivered a series of 20 stimuli to chemosensory afferent fibers.[10] In normal rats, each stimulus produced a synaptic response. Characteristically, the first one is a large response, and the other responses are diminished.

In rats exposed to intermittent hypoxia, stimulation

produced, in addition to the reduced stimulus-evoked response described above, more spontaneous activity between stimuli, indicating that the synapse has become "hyperactive" and is releasing more transmitter. But the afferent activity arriving from the chemoreceptors is less effective in releasing transmitter.

Intermittent hypoxia alters calcium modulation of transmitter release

Why is the response to stimulation diminished? The spontaneous release of transmitter may deplete the pool available for evoked release. Alternatively, two pools of transmitter may exist that are affected differently by chronic intermittent hypoxia.

Extracellular calcium is directly related to the amount of transmitter released: raising extracellular calcium concentrations increases transmitter release. Presumably, more calcium enters through calcium channels when a fiber is activated, causing more transmitter release. Conversely, reducing calcium concentrations leads to smaller postsynaptic currents.

Chronic intermittent hypoxia appears to affect the handling of calcium presynaptically. In rats exposed to chronic intermittent hypoxia, the entire response is reduced and cannot be enhanced by increasing calcium concentration. However, the response can be further reduced by reducing calcium concentration.

CaM kinase II is involved in calcium changes of chronic intermittent hypoxia

The amplitude of the synaptic evoked potential returns toward normal in the presence of a blocker of calmodulin (CaM) kinase II, implicating this enzyme in the depression of synaptic response in chronic intermittent hypoxia. We recently found that the amount of the phosphorylated form of calmodulin-dependent protein kinase II (pCaM kinase II) increases in rats exposed to chronic intermittent hypoxia as compared with normoxic animals (data submitted for publication).

What information is getting through the chemoreflex pathway?

Despite reduced amplitude of the postsynaptic response, overall transmission through the synapse is increased between the chemosensory afferents and the neurons in the nucleus of the solitary tract. The excess spontaneous activity observed can elicit action potentials, so that more activity continues to the next cell in the synaptic pathway, even though the amplitude of individual impulses is reduced.

FUTURE RESEARCH DIRECTIONS

We believe that the reduced size of the synaptic current may be an adaptive response to tone down the increased activity. Perhaps the calcium defect is more widespread than observed and may also be operating in the carotid chemoreceptors. Whether or not the calcium-induced response can be manipulated to prevent it from occurring is an area of future research.

Other intriguing questions remain:

- How is the increase in chemosensory information conveyed from the nucleus of the solitary tract to the blood vessels? Are there other sites in this pathway where chronic intermittent hypoxia modifies the activity?
- Why is the increase in arterial pressure sustained?
- Why do the baroreceptors not correct for the increase in arterial pressure?
- What causes the hypertension to reverse after normal oxygen conditions are resumed?

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Inflammation: Implications for understanding the heart-brain connection

Autonomic dysfunction is a strong correlate of morbidity and mortality in cardiovascular disease. While increased sympathetic stimulation drives many adverse events in coronary artery disease and heart failure,[1] beta-adrenergic blockade is associated with improved outcomes.[2,3] Similarly, diminished parasympathetic tone is also associated with adverse outcomes in cardiovascular disease, suggesting a key role for this limb of the autonomic system in maintenance of cardiac homeostasis.[4]

The mechanism of parasympathetic protection, however, is not clearly understood. Although an antiarrhythmic mechanism appears intuitive, such a mechanism has not been corroborated by animal studies.[4] Recently, Tracey and colleagues provided new insight by demonstrating that parasympathetic stimulation in mice and in human macrophages results in a decreased release of mediators of systemic inflammation.[5,6] Given the importance of inflammation in atherosclerosis and adverse remodeling in congestive heart failure, it is possible that parasympathetic tone assuages atherogenesis and deleterious cardiac remodeling by directly inhibiting inflammation.[7–9]

PARASYMPATHETIC NERVOUS SYSTEM AND CARDIOVASCULAR MORTALITY

Several studies have shown an inverse relationship between parasympathetic tone and cardiovascular mortality.

In the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study,[10] La Rovere and colleagues studied 1,284 patients with a recent (< 28 days) myocardial infarction by measuring heart rate variability and baroreflex sensitivity, both of which are markers of cardiac vagal tone.[1] Multivariate analysis showed that low heart rate variability and low baroreflex sensitivity (both markers of decreased parasympathetic input) were independently associated with cardiac mortality.[10]

Similarly, Nolan and colleagues measured heart rate variability in 433 patients with congestive heart failure (New York Heart Association classes I to III).[11] Multivariate analysis showed that poor heart rate variability was an independent predictor of all-cause mortality and was the most powerful predictor of death secondary to progressive heart failure.

In exercise testing, correlates of parasympathetic tone, such as heart rate recovery and ventricular ectopy in recovery, are also independent predictors of mortality.[12,13] Moreover, heart rate recovery has been associated with the metabolic syndrome, psychosocial stress, educational level, smoking, and obesity.[14–17] In a recent study by Jouven et al, heart-rate profile during exercise was a strong predictor of sudden death among 5,713 asymptomatic working men.[18]

Taken together, the above studies indicate that the autonomic nervous system, particularly the parasympathetic nervous system, is integral to cardiovascular health, morbidity, and mortality.

PARASYMPATHETIC NERVOUS SYSTEM AND INFLAMMATION

The vagus nerve innervates the cardiovascular system in addition to other visceral organs such as the liver, spleen, and gut. Tracey and colleagues demonstrated that injection of lipopolysaccharides in animals that underwent vagus nerve stimulation resulted in reduced macrophage release of inflammatory cytokines (tumor necrosis factor [TNF]-α, interleukin [IL]-1β, IL-18, and IL-6) and death without affecting release of IL-10, an anti-inflammatory cytokine.[5] However, vagal nerve transection removed this protection. Furthermore, in human macrophage cultures, acetylcholine inhibited TNF-α release when the cultures were exposed to lipopolysaccharide. These results indicated that the vagus nerve plays a role in the anti-inflammatory response.[5]

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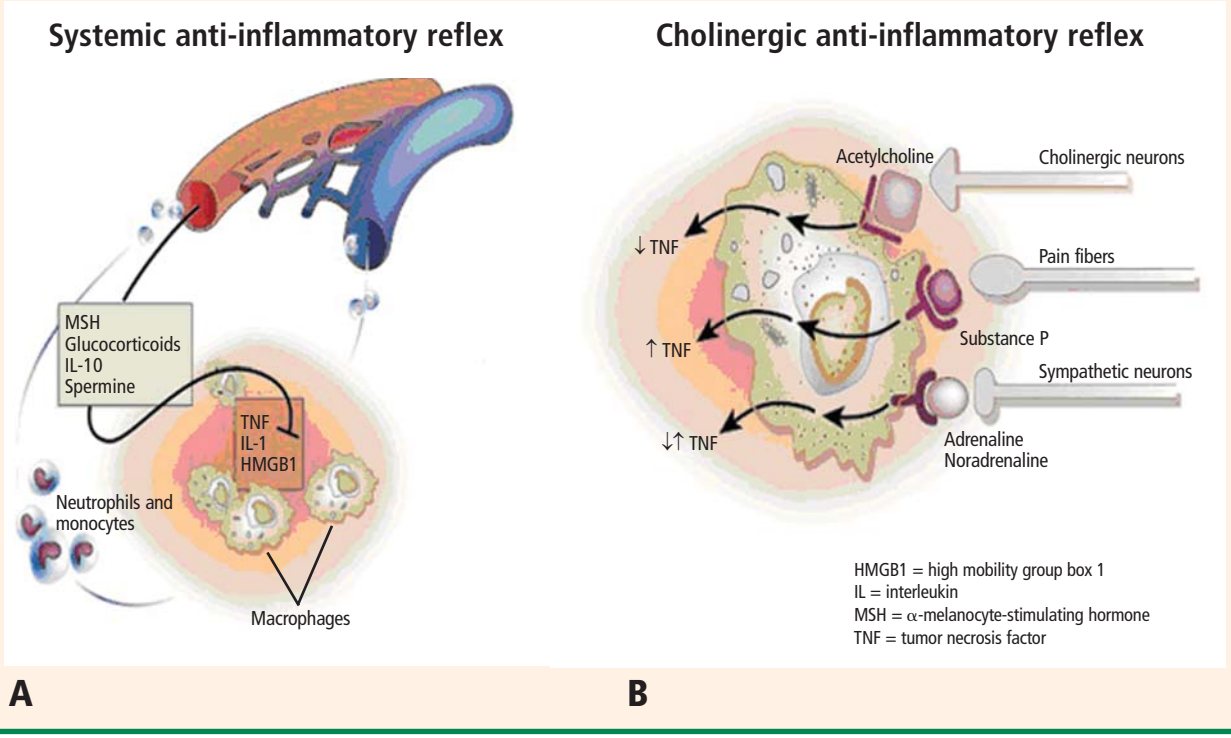

FIGURE 1. (A) The systemic anti-inflammatory reflex, which involves anti-inflammatory cytokines, glucocorticoids, and other humoral mediators, is slow and diffuse. (B) In contrast, the cholinergic anti-inflammatory reflex is quick and integrated. Reprinted by permission from Macmillan Publishers Ltd: Nature 2002; 420:853–859, copyright 2002 (www.nature.com).

In humans, abnormal heart rate variability, a measure of parasympathetic function, is significantly associated with elevated levels of inflammatory cytokines such IL-6 and C-reactive protein (CRP).[19] Lanza et al showed that serum levels of CRP were significantly associated with abnormal heart rate variability in patients with unstable angina.[20] This association has also been observed in healthy subjects, patients with stable coronary artery disease, and patients with heart failure. Overall, in all these studies a significant inverse correlation has been observed between CRP levels and measurements of heart rate variability.

More recently, the mechanisms by which vagus nerve stimulation leads to an anti-inflammatory response have been described by Tracey and colleagues.[6,21,22] Macrophages express nicotinic (cholinergic) receptors, composed of five α7 subunits, which are thought to be involved in the cholinergic anti-inflammatory reflex.[6] In α7 subunit knockout mice, electrical vagal stimulation no longer prevented release of inflammatory cytokines, indicating that this receptor plays an important function in the vagally mediated anti-inflammatory response.[22] In fact, α7 subunit knockout mice demonstrate a greater release of inflammatory cytokines in response to lipopolysaccharides than do wild-type mice.[6] Furthermore, inhibition of this receptor in primary human macrophages stimulated with endotoxin (200 ng/mL) led to a significant reduction in high mobility group box 1 (HMGB1) inflammatory cytokines in a dose-dependent manner.[6] Interestingly, atropine, a muscarinic antagonist, was not able to inhibit this reaction, but α-conotoxin, a nicotinic antagonist, inhibited the action of acetylcholine on this receptor,[6] indicating that acetylcholine inhibits HMGB1 release through the nicotinic cholinergic pathway mediated by the α7 nicotinic acetylcholine receptor. Nicotine also reduces systemic levels of HMGB1 after induction of lethal endotoxemia in animals, and this inhibition led to a significant decrease in mortality in these animals in a dose-dependent fashion.[6]

CHOLINERGIC ANTI-INFLAMMATORY REFLEX

As shown in **Figure 1**, the systemic anti-inflammatory reflex (which involves anti-inflammatory cytokines, glucocorticoids, and other humoral mediators) is slow and diffuse, whereas the cholinergic anti-inflammatory reflex is quick, precise, and integrated, typically releas-

ing inflammatory cytokines at the site of inflammation.[21] As illustrated in **Figure 2**, cytokines activate the afferent vagus fibers that travel to the nucleus tractus solitarius.[21] Subsequently, efferent vagal nerve fibers activate the α7 nicotinic acetylcholine receptor on peripheral macrophages, leading to decreases in systemic inflammatory cytokines such as IL-6, TNF, and HMGB1.[21] In addition, fibers communicating between the brainstem and hypothalamus stimulate release of adrenocorticotropic hormone, leading to increased glucocorticoid secretion, which further suppresses inflammation.

JAK-STAT PATHWAY AND CHOLINERGIC ANTI-INFLAMMATORY RESPONSE

The Janus kinases (JAKs) and STAT (signal transducers and activators of transcription) class of transcription factors are the signaling pathway for a wide variety of extracellular signals, including many cytokines, lymphokines, and growth factors. These signal through a related superfamily of cell surface receptor tyrosine kinases that are associated with and activate the JAKs.[23] The JAK-STAT signaling pathway has been previously described as being involved in the signaling mechanisms of growth hormone, prolactin, epoetin alfa, thrombopoietin, granulocyte macrophage colony-stimulating factor, leptin, and various cytokines.

Mechanistically, once the ligand binds to the associated receptor, it induces the dimerization of the receptor and causes the reciprocal phosphorylation of tyrosine residues on the associated JAKs; this, in turn, phosphorylates tyrosine residues on the cytoplasmic tail of the receptor.[23,24] These phosphorylated tyrosines serve as docking sites for the Src homology 2 (SH-2) domain of the various STAT proteins, and JAK then catalyzes the tyrosine phosphorylation of the receptor-bound STATs. Phosphorylation of the STATs at a conserved tyrosine residue induces SH-2-mediated homodimerization or heterodimerization, followed by translocation of the STAT dimer to the nucleus.[23,24] It is there that the STAT dimers bind to specific DNA response elements in the promoter region of target genes to activate gene expression.

The vagus nerve inhibits peripheral inflammation centrally through muscarinic receptors and, more importantly, peripherally through cholinergic receptors, and acetylcholine released by efferent vagus nerve fibers inhibits peripheral macrophage activation. The molecular mechanism ultimately involves prevention of nuclear factor (NF)-κB p65 nuclear translocation and activation, but the upstream mediators linking the downstream effector vagal stimuli to macrophage deactivation have only recently been uncovered, by Tracey et al. They showed that the anti-inflammatory action of the nicotinic receptor's activation in peritoneal macrophages was dependent on activation of JAK2 by the α7 acetylcholine receptor subunit and on subsequent transactivation of the transcription factor STAT3.[23,24] The anti-inflammatory effect of nicotine required the ability of phosphorylated STAT3 to bind and transactivate its DNA response elements.

Furthermore, an in vivo mouse model showed that stimulation of the vagus nerve ameliorated surgery-induced inflammation and postoperative ileus by activating STAT3 in intestinal macrophages.[6,23] Another study described the effects of inhibiting STAT1 and STAT3 in peritoneal macrophages harvested from rats after being incubated and exposed to lipopolysaccharide.[25] It showed a powerful association between

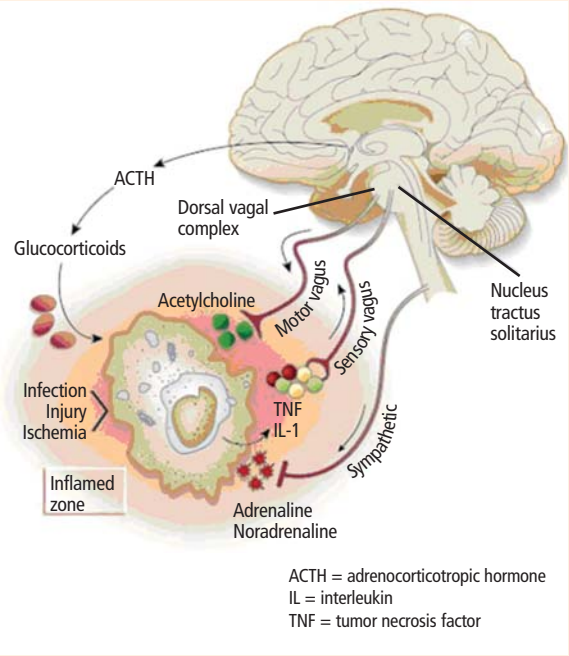

FIGURE 2. The cholinergic anti-inflammatory pathway. Inflammatory cytokines are released at the site of inflammation, activating afferent signals that are relayed to the nucleus tractus solitarius. Subsequently, efferent vagus nerve activates the α7 nicotinic acytelcholine receptor on peripheral macrophages, reducing systemic inflammatory cytokines. Additionally, fibers communicating between the brainstem and hypothalamus stimulate release of adrenocorticotropic hormone, which increases glucocorticoid secretion, further suppressing inflammation. Reprinted by permission from Macmillan Publishers Ltd: Nature 2002; 420:853–859, copyright 2002 (www.nature.com).

lipopolysaccharide stimulation and HMGB1 mRNA synthesis, which decreased significantly ($P < .01$) after specific inhibition of STAT1 and STAT3 with fludarabine and rapamycin, respectively.[25]

Studies have also implicated JAK2, STAT3, and STAT 4 in an experimental model of autoimmune arthritis and multiple sclerosis, in that a powerful inhibitor of IL-12 activation of JAK2, STAT3, STAT4, and tyrosine kinase 2 ameliorates the clinical condition of experimental rats by blocking T-cell proliferation and T helper 1 cell differentiation.[26]

The data suggest that the molecular mechanism of the cholinergic anti-inflammatory pathway seems to involve the concurrent activation of JAK2 and STAT3 within macrophages, in a manner similar to, but independent of, activation of the anti-inflammatory cytokine IL-10, and which ultimately decreases the activation of a central proinflammatory transcription factor NF-κB (p65).

THERAPEUTIC OPTIONS

The above-mentioned mechanisms bring into focus the importance of the anti-inflammatory properties of these pathways. Although nicotine's therapeutic use is limited by its short half-life in the body and its toxicity at low levels, other compounds are under development that have the same beneficial properties without the associated side effects. One of these, named CAP55, emerged as a leading cholinergic compound and has been shown to significantly inhibit TNF production by lipopolysaccharide-stimulated macrophages. In a recent report, CAP55 was found to inhibit both vascular cell adhesion molecule 1 and E-selectin expression by the endothelium and, hence, endothelial cell activation in vivo by 50%; it also reduced leukocyte activation and migration during acute inflammatory responses.[27] Further experiments delineating how this and other compounds affect clinical outcomes in animals—and eventually humans—are eagerly anticipated.

CONCLUSION

In the past few years, Tracey and colleagues have contributed significantly to our understanding of the cholinergic anti-inflammatory response, bolstering the belief that inflammation has important implications for the heart-brain connection. In vitro and animal studies have revealed a potential mechanistic relationship between the autonomic nervous system (especially the parasympathetic nervous system) and inflammation. The parasympathetic system, through the "cholinergic anti-inflammatory pathway," inactivates macrophages, a critical inflammatory component of atherogenesis, vulnerable plaque, and injured myocardium. This inactivation leads to inhibition of inflammatory cytokines such as nitric oxide, reactive oxygen species, TNF, IL-1, and HMGB1. Many of these cytokines play a significant role in atherosclerosis formation and progression as well as plaque rupture.

Despite the preponderance of evidence linking inflammation to atherosclerosis and cardiovascular morbidity and mortality, few therapeutic options are available for the treatment of low-grade chronic systemic inflammation in coronary artery disease. Recently, novel medications such as CAP55 have shown some promise. As we maximize our therapeutic armamentarium against established risk factors such as hypertension and diabetes, new therapeutic options to treat novel risk factors such as inflammation are on the rise.

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The anti-ischemic effects of electrical neurostimulation in the heart

In 2001, the American College of Cardiology and the American Heart Association introduced electrical neurostimulation (ENS) in their joint guidelines for the treatment of angina pectoris. The introduction of this therapy was supported by many (mainly small) articles examining the beneficial effects of ENS for patients with treatment-refractory angina. Even though ENS is considered to be an antianginal therapy, many physicians question the anti-ischemic benefit that ENS is frequently suggested to confer. This review briefly summarizes the antianginal effects of ENS, with a focus on the therapy's anti-ischemic outcomes.

THE ROLE OF ISCHEMIA IN ANGINA PECTORIS

The complex neurochemical cascades that are responsible for the sensation of angina are initiated by myocardial ischemia. The latter develops when myocardial oxygen demand exceeds oxygen supply, as depicted in **Figure 1**.

Ischemia results in a reduction in the formation of adenosine triphosphate (ATP). As a result, acidosis develops and chemical substances are released, including lactate, serotonin, bradykinin, histamine, reactive oxygen species, and adenosine.[1,2] These substances primarily stimulate chemosensitive receptors of unmyelinated nerve fibers terminating within cardiac muscle fibers and around the coronary vessels.[3] Adenosine can induce angina via stimulation of the A1 adenosine receptor.[4,5] The nerve fibers travel in the sympathetic afferent pathways from the heart and enter the lower cervical and upper thoracic spinal cord (C7 to T4) via the dorsal root ganglia of these segments. Impulses are then transmitted via ascending spinal pathways to the thalamus and ultimately the cerebral cortex, where the angina is "felt" as generally orginating from the chest, the arms, and sometimes the neck and jaw.

* All authors reported that they have no financial relationships that pose a potential conflict of interest with this article.

TWO MAIN TYPES OF ELECTRICAL NEUROSTIMULATION FOR ANGINA

The treatment of chronic stable angina pectoris has involved applying electrical current to various sites of the body (ganglion, nerve, spinal cord, skin, subcutis). To date, ENS is most often applied either to the spinal cord (spinal cord stimulation, or SCS) or to the skin (transcutaneous electrical nerve stimulation, or TENS). For details on the implant procedure involved in SCS, see DeJongste et al.[6]

Patients who are referred to the hospital and fulfill the inclusion criteria for SCS **(Table 1)** may be considered candidates for SCS. A team of clinicians—typically consisting of anesthesiologists, cardiologists, neurosurgeons, nurse practitioners, and psychologists—makes the final decision to implant an SCS device, apply TENS, or consider other alternatives. To achieve a successful outcome, it is essential to first perform cardiac, neurologic, surgical and psychological examinations and provide essential information to the patient up front. In this respect, TENS application may be used before implantation of an SCS device to allow the patient to get acclimated to the paresthesias. Although randomized studies comparing SCS with TENS are lacking, observational studies lead to the conclusion that SCS is more effective than TENS in the treatment of refractory angina.

ANTIANGINAL PROPERTIES OF ELECTRICAL NEUROSTIMULATION

Patients are candidates for ENS if they suffer from chronic stable angina pectoris that is refractory to conventional antiaginal therapies despite maximal tolerable dosing and if coronary revascularization is not an option.[7] ENS has been used for these "no option" patients for years—by means of stellate ganglion stimulation since 1967,[8] by TENS since 1982,[9] and by SCS since 1987.[10]

Both observational and randomized studies of ENS for angina have demonstrated long-term beneficial effects, including a reduction in severity of angina

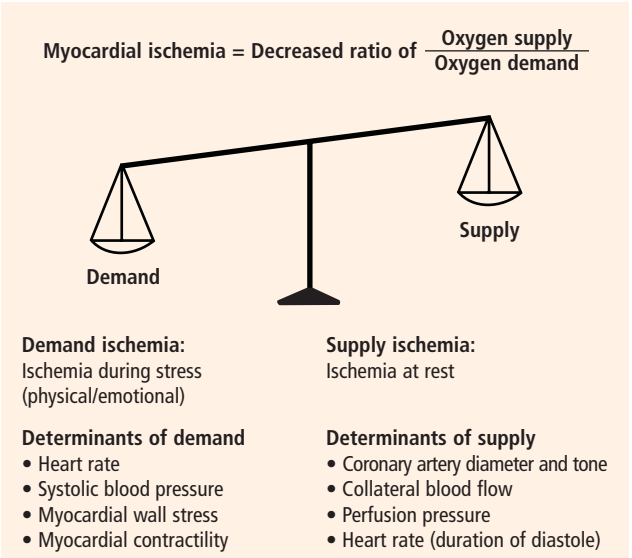

FIGURE 1. Schematic of myocardial ischemia and the determinants of the oxygen ratio. Myocardial ischemia occurs when the ratio of oxygen supply to oxygen demand decreases—as a result of a decreased oxygen supply, an increased oxygen demand, or both.

TABLE 1
Inclusion and exclusion criteria for spinal cord stimulation

Inclusion criteria
Stable angina pectoris (Canadian Cardiovascular Society scale III to IV), despite optimal medical treatment, resulting from documented significant coronary artery disease
Patient is not suitable for revascularization
Patient understands the therapy and is able to use the device
Exclusion criteria
Cardiac pacemaker dependence/implantable cardioverter defibrillator
Likelihood of magnetic resonance imaging in the future
Psychological instability
Insurmountable technical and anatomic problems (specifically in the spine)

complaints, a decreased intake of short-acting nitrate tablets, and an improved quality of life, in conjunction with an improvement in exercise capacity.

There has been concern over the safety of SCS out of fear that it might deprive the patient of an important angina "warning signal." However, fear of an inability to experience angina during ischemic events seems unjustified. Rather than abolishing angina, ENS is thought to enhance the angina threshold. As a result, patients report an increase in exercise capacity and a reduction in angina severity. There is abundant literature dealing with "natural occurrence" of angina, specifically during acute myocardial infarction, in patients treated with ENS. This is congruent with the absence of an adverse effect on mortality as demonstrated in prospective and retrospective studies. Moreover, SCS was not able to suppress the conduction of cardiac nociceptive signals to the cerebrum during cardiac distress.[11]

ANTI-ISCHEMIC PROPERTIES OF ELECTRICAL NEUROSTIMULATION

Many diagnostic tests are available to assess myocardial ischemia, each with its own limitations.[12] Because the different measures of ischemia are found to be independent, it is recommended that efficacy be assessed separately for each clinical end point before appropriate treatment is considered.[13]

One of the major problems with studies of ENS is their design. Patients feel the paresthesias, so they cannot be blinded, and the physician sees the stimulation artefacts on the electrocardiogram (ECG). Nevertheless, randomization and crossover designs are still feasible. In this review we will specifically address the anti-ischemic studies performed with ENS in patients with chronic refractory angina.

Studies of (neuro)chemicals

A very accurate test for ischemia involves measuring lactate metabolism. Mannheimer et al used atrial pacing to show that TENS improved lactate metabolism during atrial pacing, in conjunction with less-pronounced ST-segment depression,[14] and later showed that these effects were seen both in the presence and in the absence of treatment with the endorphin blocker naloxone.[15] The latter study further demonstrates that the heart is capable of producing endorphins following ENS.[15]

Another study found that ENS decreased total body norepinephrine by 18% (P = .02).[16] Moreover, total body norepinephrine levels increased during pacing by 47% (P = .02), whereas total cardiac norepinephrine spillover remained unchanged during pacing and active SCS. These findings suggest that the anti-ischemic effects of ENS are not exerted via cardiac sympathetic activity, even though the overall sympathetic activity is decreased. The authors concluded that the heart may benefit from ENS through a reduction in oxygen demand.[16]

TABLE 2
Improvements in exercise stress test parameters with electrical neurostimulation*

	Improvement in maximum exercise†	Increase in time to angina (sec)	Reduction in ST-segment depression at maximum workload (mm)	Reduction in ST-segment depression at comparable workload (mm)	Improvement in rate-pressure product‡ at maximum workload
Mannheimer et al, 1985[14]	73 W	NA	NA	0.6	3.6
Mannheimer et al, 1988[19]	28 W	216	0.3	0.6	0.57
Sanderson et al, 1992[20]	64 sec	NA	1.5	0.9	0.5
De Jongste et al, 1994[21]	168 sec	171	0.4	NA	0.9
Hautvast et al, 1998[22]	80 sec	69	0.3	0.4	1.5
Mannheimer et al, 1998[23]	1.6 W	NA	0	0	–0.2
Murray et al, 2004[25]	35 sec	30	0.1	0.4	0.4

* Results are the differences between baseline and follow-up after electrical neurostimulation (either transcutaneous or spinal cord stimulation), except for the study by Murray et al, for which results are the differences between the treatment group and the control group.
† Expressed as workload (watts) or as duration (seconds).
‡ Rate-pressure product = systolic blood pressure × heart rate × 10^3.
NA = not available

Cardinal et al concluded that ENS appears to counteract the deleterious effects that stressors—particularly stressors with effects on the intrinsic cardiac nervous system, such as angiotensin II—exert on ischemic myocardium.[17] Further, it has been shown that ENS modulates these intrinsic cardiac neurons, which contain many substances, and thus may prevent deleterious consequences of myocardial ischemia.[18]

Exercise stress testing

The most frequently used method to demonstrate myocardial ischemia is exercise stress testing. Since the magnitude of ST-segment depression on the ECG is considered a quantitative measure of myocardial ischemic burden, exercise stress testing may also be used to quantify the reduction of myocardial ischemia. **Table 2** summarizes the effects of ENS on exercise stress test parameters from seven different studies.

Mannheimer et al found in 1985 that TENS increased work capacity and reduced ST-segment depression,[14] and in 1988 these same researchers found comparable results with SCS.[19] Subsequent studies are in agreement with these early observations **(Table 2)**.[20–22]

One of the larger randomized controlled trials was the ESBY (Electrical Stimulation versus Coronary Artery Bypass Surgery) study, which was designed to compare SCS with coronary artery bypass graft surgery (CABG) in patients with no proven prognostic benefit from CABG and an increased surgical risk.[23] The primary objective was to examine symptoms, survival, and myocardial ischemia after 6 to 60 months of therapy. Anginal symptoms improved significantly in each group, with no significant difference between the groups. Mortality was significantly lower in the SCS group, but exercise stress tests showed significant increases in maximum workload capacity and in rate-pressure product with CABG, as well as significant decreases in ST-segment depression at comparable workload and maximum workload with CABG, although exercise was performed with SCS off. These effects were maintained after 5 years of follow-up.[24]

The carry-over effect of TENS was studied in a randomized, placebo-controlled, crossover trial in which exercise stress testing was performed at baseline and after 2 and 4 weeks.[25] After 2 weeks of inactive TENS, patients were switched to active TENS, and vice versa. TENS increased total exercise time and time to maximum ST-segment depression. There was no significant difference in the maximum degree of ST-segment depression or in the rate-pressure product at maximum exercise.

Ambulatory ECG monitoring

Monitoring the magnitude of ST-segment depression on ECG during daily activities provides quantitive evidence of ischemia during submaximal efforts. The ECG also provides information about the status of the autonomic nervous system by assessing heart rate variability.

Di Pede et al studied myocardial ischemia and heart rate variability using a Holter monitor for 48 hours in 15 patients who were already being treated with SCS for 9 to 92 months.[26] Active SCS showed a 50% reduction in the number and a 45% reduction in the duration of ischemic episodes, decreasing the total ischemic burden. Since the heart rate variability parameters were unchanged,[26] SCS possibly exerted anti-ischemic effects over a long period of time by increasing myocardial blood flow. Similar findings have been reported by others.[6,22,27]

Moore et al assessed the effect of three different output settings of SCS (zero, half-maximum, and maximum) on short-term heart rate variability in 16 patients.[28] They found that heart rate variability parameters changed with maximum SCS and half-maximum SCS compared with zero SCS, which did not change heart rate or arterial blood pressure.

Noninvasive perfusion (imaging)

As early as 1990 it was suggested that the anti-ischemic effects of ENS may be related to changes in regional myocardial blood flow.[29] With positron emission tomography (PET), it is possible to quantify myocardial perfusion noninvasively.

De Landsheere et al used PET to perform quantitative analysis of regional myocardial perfusion at rest and after exercise, before and during SCS, in eight patients who had been undergoing SCS for at least 2 months.[30] SCS increased regional myocardial clearance significantly in nonaffected segments but not in the affected segments. However, ST-segment depression decreased during SCS treatment.

Hautvast et al evaluated myocardial blood flow with PET in nine patients, at baseline and after 6 weeks of SCS.[31] SCS was associated with a reduction in ST-segment depression during stress testing with the adenosine reuptake inhibitor dipyridamole. The distribution of myocardial blood flow was more homogeneous during SCS. However, SCS may also have blunted the effect of dipyridamole.

Mobilia et al studied myocardial blood flow with PET in 11 patients who had undergone SCS treatment for 2 to 48 months.[32] The first PET scan was taken on day 1 with SCS deactivated, and the second scan was taken on day 2 with SCS activated. Regional myocardial perfusion increased in nine patients, but the mean value of myocardial flow did not change.

Diedrichs et al demonstrated an improved quality of life and physical fitness after 3 months of SCS, with maintenance of these results at 1-year follow-up.[33] Physical fitness was measured using a 6-minute walk test and bicycle ergometry; quality of life was measured with the Seattle Angina Questionnaire. Additionally, MIBI-SPECT (single-photon emission computed tomography) imaging showed myocardial perfusion to be unchanged after 3 months, whereas there was a shift toward improved myocardial perfusion after 1 year. The researchers hypothesized that analgesia is the main effect of SCS and that changes in myocardial ischemia are secondary and might be due to increased physical activity.

Invasive coronary blood flow measurements/ atrial pacing

Chauhan et al measured the effect of TENS on coronary blood flow in 34 patients with syndrome X, 15 patients with coronary artery disease (CAD) affecting the right coronary artery, and 16 heart transplant patients.[34] A Doppler flow wire was used to measure coronary blood flow in the left coronary artery at rest and after 5 minutes of TENS. Coronary blood flow increased significantly in patients with syndrome X and in those with CAD, but no change was observed in the heart transplant patients. No significant changes were seen in the diameter of the left coronary artery or in hemodynamics. Additional assessment of catecholamine levels showed a significant reduction of epinephrine levels in patients with syndome X and in those with CAD, whereas levels were unchanged in the heart transplant patients. Norepinephrine levels were unchanged in all patients.

Norrsell et al measured the effect of SCS on coronary blood flow velocity in eight patients with CAD and four patients with syndrome X.[35] All patients underwent pacing that increased in frequency until they experienced moderate angina, at which point pacing continued for 7 minutes and SCS was begun after 2 minutes. During pacing the average peak velocity increased significantly (53%, $P = .02$), without differences in average peak velocity during pacing when SCS was activated.

Jessurun et al studied the effect of TENS on coronary blood flow using two flow wires, with one wire positioned in an affected artery and the other in a patent artery.[36] They found that TENS increased flow in the patent artery, with a decrease of flow in the affected area and a decrease in ST-segment depression of the ischemic area. This result may be attributable to the flow of blood through collateral pathways from the patent artery toward the ischemic region, bypassing the stenosis in the affected area.

Mechanisms of anti-ischemic effects

Coronary blood flow is influenced by coronary artery

diameter and tone (resistance) as well as by collateral blood flow.[37,38] Coronary atherosclerosis reduces coronary blood flow, leading to a reduction of myocardial oxygen supply, which in turn can lead to angina.

Anti-ischemic effects can be established by improving myocardial blood flow or by reducing the oxygen requirements of the heart. The latter can result from reduced sympathetic activity, by afterload reduction following reduced systemic vascular resistance, and by reduction of myocardial contractility, which also reduces the heart's oxygen needs.

Different outcomes have been reported regarding sympathetic activity and ENS, with some groups finding no differences in parameters of heart rate variability[6,22,26,27] while other groups have reported findings that could be due to decreased sympathetic activity.[14,16,28] Changes in myocardial blood flow were assessed with invasive measurements, SPECT, and PET.[30–36]

CONCLUSIONS

In addition to having an antianginal effect, ENS is thought to exert beneficial effects on myocardial ischemia by improving ischemic tolerance. Ischemic tolerance is the result of both preconditioning and collateral recruitment in the heart. Studies have reported the effect of ENS on adenosine and caffeine handling.[18,39] Furthermore, the heart appears to produce endorphins.[15] Additionally, ENS affects the alpha-receptor. All three of these factors are involved in the upregulation of protein kinase C that subsequently opens the ATP-dependent potassium channels and leads to preconditioning. At the same time, a recent pilot study by our group demonstrated a trend in collateral recruitment by ENS.[40] Moreover, another recent study found that preemptive SCS reduces the size of infarcts via cardiac adrenergic neurons.[41] We therefore hypothesize that ENS improves myocardial ischemia by mobilizing the mechanisms that produce preconditioning and by recruiting collaterals.

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The little brain on the heart

The function of the cardiovascular neuronal hierarchy is ultimately to match cardiac output to regional body blood flow demands. To comprehend how the varied elements of this hierarchy interact to accomplish this task, we must determine how its peripheral (intrathoracic and cervical ganglion) and central neurons communicate on an ongoing basis in the coordination of regional cardiac indices.[1]

The cardiac neuronal hierarchy can be represented as a massively parallel and, for the most part, stochastic control system such that stable cardiac control generally occurs in the absence of obvious cause and effect **(see sidebar below)**. Its peripheral neuronal interactions display emergent properties, functioning as they normally do in a highly optimized fashion to tolerate normal cardiac perturbations.

From a clinical perspective, excessive activation of select elements within the cardiac neuronal hierarchy has been thought to result in the genesis of atrial[2] or ventricular[3] arrhythmias. Indeed, the functional interconnectivity of the various neurons in the hierarchy is so organized that the whole can be catastrophically disabled by cascading failures initiated by relatively minor abnormal inputs. Defining the function of each of its populations may be required to understand how, for instance, excessive activation of select elements initiates cardiac arrhythmias. Such an understanding is required if one is to manage this state from a neurocardiological perspective.

This brief review presents the anatomy and function of this hierarchy's afferent and efferent neurons and discusses the putative interactions that occur among its neuronal populations.

The cardiac neuronal hierarchy

The cardiac neuronal hierarchy can be represented as a massively parallel and, for the most part, stochastic control system such that stable cardiac control occurs in the absence of obvious cause and effect (ie, it displays emergent properties).

This hierarchy displays robust external behavior while matching cardiac output to whole-body blood flow demands.

Its target organ component, the "little brain on the heart," transduces centripetal and centrifugal inputs in the coordination of regional cardiac electrical and mechanical indices.

Although optimized to tolerate *normal* perturbations, the system can be catastrophically disabled by cascading failures initiated by relatively minor input changes.

What it cannot tolerate, as these are not design features, are:

- Rearrangement of its interconnecting parts
- Excessive activation of select components that engender cardiac pathology (cf, arrhythmias).

Therapeutic targeting of select components of the hierarchy should take into consideration the emergent properties of the whole.

ANATOMY

Cardiac afferent neurons

Pain associated with myocardial ischemia is frequently referred to a patient's left upper limb and/or anterior thoracic wall.[4] As a result, the somata of cardiac afferent neurons are assumed to be located primarily in left-sided, cranial thoracic dorsal root ganglia. Anatomic evidence indicates that cardiac afferent neurons are distributed relatively evenly throughout the nodose ganglia and the C7 to T4 dorsal root ganglia bilaterally.[5] They are also located in intrathoracic ganglia, including those intrinsic to the heart.[1,6]

Cardiac efferent neurons

Cholinergic neurons. The somata of parasympathetic efferent preganglionic neurons that synapse with cholinergic efferent postganglionic neurons on the heart are located primarily in the ventral lateral region of the nucleus ambiguous of the medulla;[7] fewer are found in its dorsal motor nucleus and the zone intermediate between these two medullary nuclei.[8] Cardiac preganglionic motor neurons in individual medullary loci project axons to parasympathetic efferent postganglionic neurons distributed throughout each major atrial and ventricular ganglionated plexus.[9]

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Adrenergic neurons. Cardiac sympathetic efferent preganglionic neurons in the spinal cord project axons via the T1 to T5 rami[10] to synapse with cardiac sympathetic efferent postganglionic neurons located in the cranial poles of the stellate ganglia, throughout the right and left middle and superior cervical ganglia and mediastinal ganglia adjacent to the heart.[1] They also project to adrenergic neurons in each intrinsic cardiac ganglionated plexus.

Local circuit neurons

Yet another neuronal population within the intrathoracic nervous system lies interposed between cardiac afferent and efferent neurons. These neurons can project axons to neurons not only within their individual ganglia but also to neurons distributed in other intrathoracic ganglia. Thus, they appear to function as local circuit neurons.[1] Some of these relatively large-diameter neurons (ie, up to ~30 µm) form rosettes within intrathoracic ganglia, including those on the heart, frequently arranged in the periphery of intrinsic cardiac ganglia. Their centrally projecting dendrites synapse with one another within that rosette, and thus may represent an anatomical substrate for local information processing within such ganglia. Intrathoracic neurons display immunoreactivity to various peptides and other chemical markers.[11–13] These anatomical findings indicate that intrathoracic neurons may be involved in a multiplicity of interactions in the coordination of regional cardiac motor outputs.

PHYSIOLOGY

Cardiac afferent neurons

The constantly changing cardiac milieu is transduced to neurons distributed throughout the cardiac neuroaxis via a rich variety of cardiac sensory neurons that are located in nodose, dorsal root, and intrathoracic extracardiac and intrinsic cardiac ganglia. The activity generated by the sensory neurites (nerve endings) of some neurons depends on regional cardiac or major vascular wall mechanics; others transduce the cardiac regional chemical milieu. The vast majority of cardiac afferent neurons transduce regional dynamics and/or the local chemical milieu of their neurites.[14,15] For instance, about 75% of nodose ganglion cardiac afferent neurons transduce chemical stimuli; fewer (about 35%) display mechanosensory capabilities.[14,16]

On the other hand, most dorsal root ganglion cardiac afferent neurons display multimodal (mechanical and chemical) transduction. The varied transduction capabilities displayed by these different cardiac afferent neuronal populations results in a regional specific local dynamic and chemical milieu being transduced to second-order neurons throughout the neuroaxis. The majority of cardiac sensory neurites associated with afferent neuronal somata in intrathoracic extracardiac and intrinsic cardiac ganglia express multimodal properties.[14]

Apparently, the multimodal transduction capacity displayed by individual dorsal root ganglion cardiac afferent neurons permits this relatively limited population of sensory neurons to transduce multiple cardiovascular signals simultaneously to second-order neurons in the central nervous system.[14] Adenosine is released in increasing quantities by the ischemic myocardium.[17] Adenosine activates sensory neurites associated with many ischemia-sensitive cardiac afferent neuronal somata.[14] In fact, it has been proposed that purinergic dorsal root ganglion cardiac afferent neurons are involved in the genesis of ischemic ventricle symptoms.[4]

Mechanosensory neurites associated with a significant population of intrathoracic afferent neuronal somata are also present on major intrathoracic vessels, especially along the inner arch of the aorta. The latter transduce constantly changing aortic wall dynamics that occur throughout each cardiac cycle, as do carotid artery baroceptor neurons that project to nucleus solitarius neurons.[18] These data indicate that multiple populations of intrathoracic and cervical afferent neurons transduce regional vascular dynamics to second-order neurons throughout the neuroaxis, along with the different cardiac afferent neuronal populations described above.

Cardiac motor neurons

Parasympathetic efferent neurons. Medullary (parasympathetic) efferent preganglionic neurons project axons to cholinergic postganglionic neurons distributed throughout the various atrial and ventricular ganglionated plexuses. When activated, cholinergic motor neurons suppress not only atrial rate and force, but also atrioventricular nodal conduction and regional ventricular contractile force. As reflex excitation of these motor neurons involves short-latency medullary reflexes, their activity frequently equates to carotid arterial baroreceptor activity reflective of a constantly changing arterial wall dynamic.[1,18] Indeed, their capacity to influence heart rate depends to a considerable extent on when in the cardiac cycle they become excited.[19]

Sympathetic efferent neurons. Sympathetic efferent postganglionic neurons in each intrathoracic gan-

glion receive inputs from sympathetic efferent preganglionic neurons in the caudal cervical and cranial thoracic spinal cord.[10] Cardiac sympathetic efferent postganglionic neurons are also influenced by cardiac and major intrathoracic vascular sensory neurons.[1] These data indicate that adrenergic motor control of cardiac chronotropism, dromotropism, and regional inotropism ultimately depends on the integration of multiple cardiovascular sensory and central neuronal inputs within the intrathoracic neuroaxis. Intrathoracic local circuit neurons play a key role in such integration.

Local circuit neurons

Interposed between cardiac afferent and efferent neurons are local circuit neurons. Their presence permits information exchange among neurons located not only in one intrathoracic ganglion (including those intrinsic to the heart) but also among neurons in different intrathoracic ganglia.[1]

Neurons of the target organ nervous system are constantly interacting with those in intrathoracic extracardiac ganglia, as well as with central neurons, to influence cardiac motor outputs. Some intrinsic cardiac local circuit neurons even receive inputs from sympathetic and parasympathetic efferent preganglionic neurons, indicating that some neurons process inputs from both efferent limbs of the autonomic nervous system, and not necessarily in a reciprocal fashion.[1]

Intrathoracic local circuit neurons also receive indirect inputs via the spinal cord neurons derived from sensory neurites in extrathoracic tissues.[1] Thus, alterations in the extrathoracic milieu can also influence the intrinsic cardiac nervous system, doing so in an indirect manner. As neurons within the intrathoracic neuronal hierarchy interact via a host of chemicals (including acetylcholine, butyrylcholine, alpha- and beta-adrenoceptor agonists, histamine, nitric oxide donors, peptides, purinergic agents [adenosine and adenosine triphosphate], excitatory and inhibitory amino acids, and serotonin),[1] current cardiac pharmacologic therapy may influence cardiomyocyte behavior directly or indirectly via this nervous system.[1]

Recent data indicate that the target organ nervous system processes centrifugal and centrifugal inputs, doing so via many neurochemical signals. It appears that multiple inputs are required in order that the "little brain on the heart" has sufficient information to coordinate regional cardiac indices on a beat-to-beat basis.[1,20,21] The synapses involved in such cardiac motor neuron control may be targeted therapeutically with agents such as beta-adrenoceptor or angiotensin II receptor blockers. The short-latency reflexes (40 to 100 ms) so engendered apparently influence cardiac motor neurons throughout each phase of the cardiac cycle. On the other hand, the longer latency cardiocardiac reflexes (300 ms to 2 sec) involving intrathoracic extracardiac and central neurons apparently coordinate regional cardiac indices over time scales reflective of multiple cardiac cycles.[1]

POTENTIAL CLINICAL RELEVANCE OF THIS HIERARCHICAL ARRANGEMENT

The cardiac neuroaxis relies to a considerable extent on its capacity to transduce the cardiac mechanical and chemical milieu to cardiac motor neurons on a beat-to-beat basis. Centrally derived parasympathetic efferent neuronal outputs to the heart are dependent to a considerable degree on arterial baroreceptor afferent neuronal function.[18]

Cardiac sympathetic efferent neurons, in contrast, depend to a considerable extent on intrathoracic reflex modulation, thereby placing relatively little demand on central neurons in the routine maintenance of adequate cardiac output.[1,20] The multiple intrathoracic and central reflexes so engendered ultimately assure stable cardiac output during daily activity fluctuations. Understanding the integration of central and peripheral reflexes will require further experimentation.

Interactions so engendered within the peripheral nervous system appear to be optimized to tolerate normal cardiac perturbations. Presumably, the stochastic nature of these interactions results in the fact that cardiac efferent neuronal outputs rarely reflect a simplistic reciprocal (positive and negative) reflex control system **(see sidebar)**.

In contrast, the cardiac neuronal hierarchy appears to be organized in such a manner that the whole can be catastrophically disabled by cascading failures initiated by relatively minor abnormal inputs. Myocardial ischemia modifies the function of many neurons within this hierarchy, doing so in either a direct (local ischemic damage) or an indirect (altered sensory inputs) manner. When sufficient populations of cardiac efferent neurons become excessively activated as a result of such an event, cardiac arrhythmias can be initiated. Concomitant and excessive activation of cholinergic and adrenergic efferent neurons may potentially represent a predisposing factor for the genesis of atrial[2] or ventricular[3] arrhythmias.

Neurons within this hierarchy communicate via numerous receptors, including angiotensin II and beta-adrenergic receptors. Such data indicate that

synapses within this nervous system may be a target for pharmacologic therapies currently used to treat heart disease. In fact, therapy targeting such receptors may influence cardiomyocyte function not only directly, but also indirectly by modifying their autonomic efferent neuronal inputs.[1]

A fuller understanding of how the varied components within the cardiac neuroaxis interact to stabilize cardiac output is required before its individual elements can be targeted therapeutically to improve diseased cardiac status.

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Open heart surgery and cognitive decline

Mild cognitive decline occurs normally as people age, and specific at-risk populations, such as those with cerebral vascular disease or coronary disease, decline faster. Patients who undergo coronary artery bypass graft surgery (CABG) are known to have an increased risk of stroke, other serious adverse cerebral events, and cognitive decline.

This paper reviews the incidence and the short-term and long-term sequelae of neurologic injury following cardiac surgery. Possible causes of neurologic injury are discussed, as well as strategies for prevention. The potential contributions of genomics in identifying patients at high risk for neurologic injury from surgery are also discussed.

SHORT-TERM NEUROLOGIC SEQUELAE FROM CARDIAC SURGERY

Researchers from 24 US institutions evaluated 2,108 patients who had cerebral injury following cardiac surgery.[1] Outcomes were categorized into type I (stroke, coma, or death due to cerebral injury) and type II (confusion, agitation, deterioration in intellectual function, memory deficit, or seizures).

In patients who underwent CABG, the incidence of type I and type II injuries was about 3% each. Patient age was one of the strongest predictors of cerebral injury and was more important than surgical technique. The short-term consequences of neurologic injury were severe. Only 32% of patients with type I injury and 60% of patients with type II injury were discharged home vs 90% of those who did not sustain neurologic injury. In addition, 21% of patients with type I injury and 10% of patients with type II injury died during hospitalization vs 2% of those without neurologic injury. Hospital and intensive care department stays were also longer in patients with neurologic injury.

* Dr. Newman reported that he is a consultant for Guilford Pharmaceuticals, Inspire Pharmaceuticals, KAI Pharmaceuticals, Neuren Pharmaceuticals, Prism Pharmaceuticals, Procter & Gamble Pharmaceuticals, and The Medicines Company.

LONG-TERM NEUROLOGIC EFFECTS

The short-term effects of neurologic injury are likely the tip of the iceberg of neurologic sequelae. Our next step was to assess cognitive function and the long-term neurologic effects of cardiac surgery.

We performed neurologic and cognitive testing on 261 patients before they underwent CABG, as well as at discharge and at 6 weeks, 6 months, and 5 years.[2] Patients who had a deficit at baseline were excluded.

Four domains of cognitive function were identified that accounted for almost 80% of the variability found:

- Verbal memory and language comprehension (short-term and delayed)
- Abstraction and visuospatial orientation
- Attention, psychomotor processing speed, and concentration
- Visual memory.

Neurocognitive outcomes were defined in two ways:

- Cognitive deficit—a decline in performance in any one of the domains by 1 standard deviation or more (a reduction of 1 standard deviation represented an approximately 20% decline in function)
- Composite cognitive deficit—the reduction in the sum of scores of the four domains.

Initial deficit predicts long-term outcome

The pattern of cognitive deficits is outlined in **Figures 1 and 2**. At discharge, about half of the patients had declined in one or more domains; at 6 weeks, the percentage dropped to 36%; at 6 months, 24%; but at 5 years, 42% of the patients again had a deficit. Therefore, the pattern is one of early improvement followed by later decline.

A cognitive deficit from baseline that was evident at discharge predicted long-term outcome, even if short-term gains occurred in the meantime. At 6 weeks, patients who initially had a deficit improved to a level similar to those who never deviated from baseline levels. But after 5 years, patients who had deficits at discharge had significantly worse outcomes than those without initial deficits **(Figure 2)**.

In addition to cognitive deficit at discharge, predic-

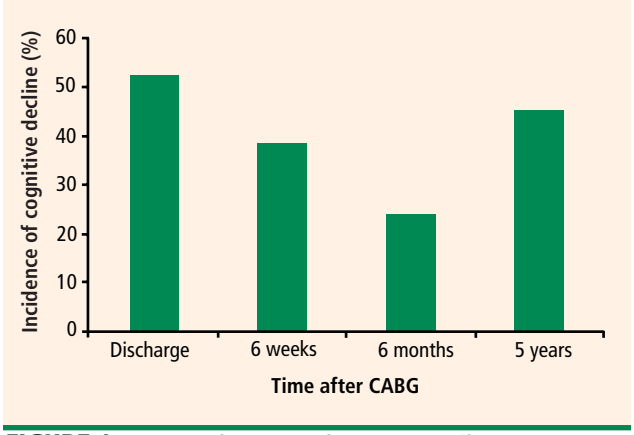

FIGURE 1. Analysis of a subset of 261 patients (from a prospective study of 2,108 patients) who underwent coronary artery bypass graft surgery (CABG) and were followed for 5 years using neurocognitive tests. Results demonstrate cognitive decline following CABG, with short-term improvement followed by a decline in cognitive function.

tors of cognitive dysfunction at 5 years included baseline cognitive level, age, and years of education. Ejection fraction, history of hypertension, diabetes, and surgical variables were found to be insignificant factors.

We also assessed quality-of-life factors 5 years following cardiac surgery.[3] Patients with higher levels of cognitive functioning were more likely to describe their health as excellent or very good rather than as only good, fair, or poor. Patients with higher cognitive function were also likelier to be working, either full-time or part-time, and less likely to be unemployed or disabled.

Lyketsos et al[4] took another approach to measuring neurologic effects of cardiac surgery by comparing patients who underwent CABG to those who did not. Using the Modified Mini Mental State examination, they evaluated 5,092 patients age 65 years or older, and repeated the evaluation after 3 years, then after another 4 years. Those who at baseline reported having undergone CABG or who underwent this surgery between follow-up evaluations had a significantly greater decline from baseline in mental status than those who had never undergone CABG. The decline was not evident immediately following surgery but only 5 years later. The authors noted that the cognitive decline in the CABG recipients was small, and its clinical significance not known.

POSSIBLE CAUSES OF NEUROLOGIC INJURY DURING SURGERY

Understanding the mechanisms that lead to cognitive decline following CABG may yield possible targets for prevention.

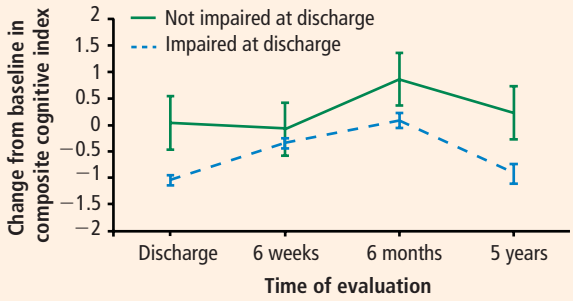

FIGURE 2. Evidence of cognitive decline at discharge, as ascertained by a composite index of four cognitive domains, was a major predictor of cognitive decline over 5 years in a longitudinal study of 261 patients who underwent elective coronary artery bypass graft surgery. Reprinted, with permission, from reference 2, copyright © 2001 Massachusetts Medical Society.

Embolic events

Neurologic sequelae could result from unstable plaques in the aortic or transverse arch breaking off and lodging in the brain during surgery. Transcranial Doppler flow studies indicate that up to several thousand air or particulate emboli commonly occur in patients undergoing bypass procedures. New devices are under investigation that can catch particulate matter or redirect it away from the brain.

More evidence that embolization occurs during cardiac surgery is revealed through alkaline phosphatase staining of the brain at autopsy. Small capillary arterial dilatations, most likely from fat or other lipids, commonly develop immediately after cardiopulmonary bypass or catheterization. These tend to disappear a month or so following the procedure.

Hyperthermia

While hypothermia has been found to be neuroprotective in several animal and human models due to reduction in glutamate release and slowing of the ischemic cascade, hyperthermia is associated with a worsening of neurologic outcomes in those same models.[5] From this work and from our work described below,[6] there has been concern that the rate at which the patients are rewarmed and the peak temperature on rewarming may alter the severity of postoperative cognitive dysfunction. At our institution, Grigore et al[6] compared patients who were rewarmed slowly (maintaining no more than 2°C difference between nasopharyngeal and cardiopulmonary bypass perfusate temperature) with patients warmed in a conventional manner (4°C to 6°C difference) following hypothermic cardiopulmonary bypass. Slower rewarming was associated with better neurocognitive

function 6 weeks following surgery.

It is clear that close monitoring of nasopharyngeal temperature and control of rewarming rate and inflow temperature may have an overall effect on both the incidence and severity of neurologic injury.

STRATEGIES TO REDUCE RISK

To help determine the risk of patients who are about to undergo cardiac surgery at Duke Heart Center, we use transesophageal echocardiography, epiaortic scanning, and a stroke risk index that we developed several years ago. The stroke risk index allows rapid assessment of stroke risk by awarding points for perioperative risk factors (age, unstable angina, diabetes mellitus, neurologic disease, prior CABG, vascular disease, and pulmonary disease). These preoperative measures help us decide how we will manage temperature and mean arterial pressure during surgery.

Unfortunately, many strategies used for reducing risk are not supported by evidence from randomized controlled clinical trials showing efficacy. Once a certain technique or intervention is believed to offer a better outcome, physicians tend to adopt it, and doing otherwise seems unethical.

Hemodynamic management during cardiopulmonary bypass

Through the use of epiaortic scanning, a relationship between atherosclerotic load in the aorta and perioperative stroke risk has been firmly established.[7] Use of epiaortic scanning may represent a simple means to reduce aortic instrumentation during CABG to reduce perioperative stroke risk. In a clinical trial of 15 patients undergoing elective CABG in which intraoperative palpation alone was compared with epiaortic scanning in addition to palpation, epiaortic scanning was more sensitive than palpation alone in identifying cerebral emboli.[8] Eight of the 15 patients had an abnormal epiaortic scan with detection of plaque, whereas 4 of 15 had an abnormal aorta by palpation.

Gold et al[9] randomized 248 patients undergoing primary, nonemergency CABG to either low (50 to 60 mm Hg) or high (80 to 100 mm Hg) mean arterial pressure. The rates of both neurologic and cardiac complications were lower in patients maintained at higher arterial pressures.

Identifying risk by transesophageal echocardiography

Increasing mean arterial pressure is especially important for high-risk patients to increase collateral flow. We use transesophageal echocardiography and/or epiaortic scans to preoperatively assess risk for all CABG patients at Duke Heart Center.

Hartman et al[10] further analyzed the study by Gold et al[9] and found that patients who were at highest risk of stroke or death following CABG were those with advanced atheromatous disease of the thoracic aorta identified by transesophageal echocardiography.

Temperature management

At Duke Heart Center, in accordance with the data described previously,[5,6] we recommend avoiding hyperthermia in all patients: inflow temperature is kept at or below 37°C.

PERIOPERATIVE GENOMICS

We are starting to recognize the importance of genetic variability in the response to surgery (J.P. Mathew, MD, unpublished data, 2006). Patients enter surgery with a unique genome, which in part determines their baseline health status and disease state, as well as their response to surgical injury, cardiopulmonary bypass, anesthesia, and medications. Most patients respond well, but others respond poorly to similar circumstances; the new field of genomics may help better identify patients at high risk.

The Perioperative Genetics and Safety Outcomes Study (PEGASUS) is an ongoing prospective, longitudinal study at Duke University Medical Center involving more than 5,000 patients that is evaluating the association of clinical and genetic factors with perioperative outcomes.

Some of our preliminary findings have been published by Grocott et al.[11] Of 1,635 patients who underwent cardiac surgery, 28 (1.7%) experienced ischemic strokes. Patients having both one of the interleukin-6 minor alleles as well as one of the C-reactive protein (CRP) minor alleles had more than three times the risk of stroke as those who did not.

We also evaluated genetic factors and neurocognitive function and found that two minor alleles—one for CRP and another involved in platelet activation (P1A2)—appeared to be protective: they were associated with less than half the incidence of neurocognitive decline.[5] Genetic differences for platelet activation levels were also found in response to cross-clamp release time.[5]

Future applications

Although the types of intervention that genetic information may lead to are still uncertain, it could provide us with important future targets. We can already deduce by history and clinical factors many patients who are at high risk as well as those at the lowest risk. Patients in a "medium-risk" group, how-

ever, could be further stratified with the use of genetic information, and treated differently if additional risk factors are found.

Many controversies still surround cardiac surgery, including the use of off-pump CABG and the proper use of pharmacologic interventions such as aprotinin. Further defining patient risk could help clarify when the use of these and other interventions is appropriate.

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The heart and the brain within the broader context of wellness

Approximately 40% of all premature deaths (before age 75) can be attributed to unhealthy behaviors, 30% to genetics, 15% to social factors, 10% to poor medical access, and 5% to environment.[1] Unhealthy lifestyles claim about 1 million lives per year in the United States and cause nearly 30 million cases of chronic disease.[1] Tobacco is responsible for approximately 440,000 premature deaths annually.[2] Overweight, a sedentary lifestyle, alcohol abuse, accidents, firearms, and illegal drugs are other lifestyle factors that are associated with premature mortality.

Of the top 10 causes of death in the United States, all of the top six have lifestyle as a primary cause. These six causes account for 1.7 million of the 2.2 million people who died in 2002.[3]

This article will review the impact of lifestyle on heart and brain health, as well as the impact of the heart and the brain in adopting changes in health behavior.

IMPACT OF LIFESTYLE ON HEART-BRAIN HEALTH

A systematic review of prospective cohort studies and randomized controlled studies of patients with coronary artery disease (CAD) revealed that lifestyle changes (ie, combined dietary changes, increased physical activity, quitting smoking) had a larger impact on subsequent mortality than did standard medications for the treatment of CAD (low-dose aspirin, statins, beta-blockers, angiotensin-converting enzyme inhibitors).[4]

The relationship between obesity and the prevalence of medical conditions was assessed by Must and colleagues using data from 16,884 adult participants from the Third National Health and Nutrition Examination Survey (NHANES III).[5] Health conditions examined were type 2 diabetes, gallbladder disease, CAD, hypercholesterolemia, hypertension, and osteoarthritis. The prevalence of any one of these conditions was 9% among men and women with a normal body weight (body mass index [BMI]: 18.5 to 24.9 kg/m^2), and increased steadily with increasing BMI.

Impact of lifestyle on the heart

Evidence indicates that intensive lifestyle changes improve myocardial perfusion abnormalities in patients with CAD. Gould et al randomized 35 patients with documented CAD who were not receiving lipid-modifying therapy to 5 years of usual care directed by their physicians or to risk-factor modification.[6] The risk-factor modification consisted of exercise, stress management, a very low-fat vegetarian diet, smoking cessation, and a weekly support group (the Dean Ornish Heart Disease Reversal Program). Positron emission tomography (PET) and quantitative coronary angiography were performed at baseline and again at 5 years. Myocardial perfusion abnormalities on PET were reduced in size and severity in 99% of patients randomized to intensive risk-factor modification compared with 55% of those randomized to usual care. The extent of coronary artery stenosis improved similarly in the group assigned to the active intervention relative to those assigned to usual care.[6] On June 12, 2006, Medicare announced that it would cover 18 to 54 weeks of the Dean Ornish Heart Disease Reversal Program.

Lifestyle changes combined with medical therapy was the best strategy to prevent cardiovascular events in a study by Sdringola and colleagues.[7] They measured the impact of various levels of treatment on the probability of cardiovascular events in 409 patients with CAD. Patients whose treatment was categorized as "poor," defined as neither lifestyle changes nor treatment with lipid-modifying drugs, had the greatest 5-year incidence of coronary events (30.6%). Patients on moderate treatment (American Heart Association diet and lipid-modifying drugs, or a diet from which < 10% of calories were derived from fat with no lipid-modifying drugs) had a 5-year incidence of CAD events of 20.3%, and those on maximal

* Dr. O'Donnell reported that he has no financial relationships that pose a potential conflict of interest with this article.

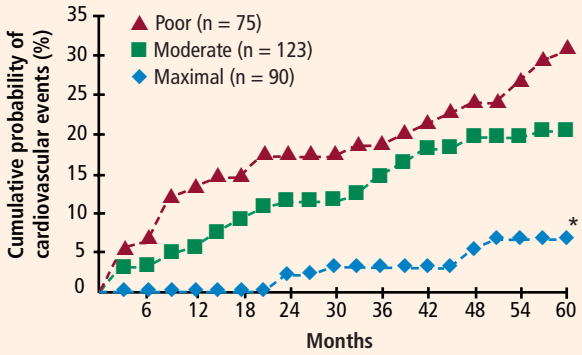

FIGURE 1. Among 409 patients with coronary artery disease (CAD), the incidence of cardiovascular events was lowest among those treated with combined intense lifestyle and lipid-modifying drug therapy (maximally intensive treatment) compared with moderately intense treatment (defined as an American Heart Association diet plus lipid-modifying drugs or a diet with 10% or fewer calories derived from fat without lipid-modifying drugs) or poor treatment (defined as no specific treatment for CAD). Reprinted from reference 7, copyright 2003, with permission from the American College of Cardiology Foundation.

treatment (a diet from which < 10% of calories were derived from fat, regular exercise, and lipid-modifying treatment dosed to meet target goals) had the lowest incidence of CAD events, 6.6% **(Figure 1)**.

Death rates and other health outcomes have been calculated according to the quality of self-reported diets. Among 42,254 women who completed dietary questionnaires in a prospective cohort study, those with a Recommended Food Score in the lowest quartile had rates of death, cancer, heart disease, and stroke that were significantly higher than those for women with a Recommended Food Score in the highest three quartiles **(Table 1)**.[8] The Recommended Food Score was an index developed by the authors that gauged how often a subject ate foods recommended by dietary guidelines (fruits, vegetables, whole grains, low-fat dairy products, and lean meats and poultry).

Current or former smoking is an especially powerful risk factor for stroke and myocardial infarction.[9] In fact, of all the identified risk factors for these two diseases, a substantial number are related to lifestyle.

Impact of lifestyle on the brain

Several lifestyle factors have been found to influence the incidence of dementia and Alzheimer disease as well as the rate of mental decline. These factors include mental stimulation, physical activity, nutrition, tobacco use, alcohol consumption, and social interaction.

TABLE 1
Likelihood of death based on diet*

	Odds ratio			
	Worst diet	Poor diet	Good diet	Best diet
All deaths	1.79	1.41	1.12	1.00
Death from cancer	1.45	1.19	1.03	1.00
Death from heart disease	1.67	1.37	1.25	1.00
Death from stroke	1.49	1.12	1.05	1.00

* Based on a prospective cohort study of 42,254 US women from 1987 to 1989 with median follow-up of 5.6 years. Subjects' diets were classified into four quartiles (worst to best) according to their responses to a 62-item diet questionnaire (see text). Derived from data in reference 8.

Ott and colleagues examined the relationship between smoking habits and dementia in 6,870 men and women.[10] After adjusting for age, sex, alcohol use, and education, former smokers were found to have a 30% to 40% increased risk and current smokers a doubling in the risk of dementia, compared with never smokers.

The association between occupational complexity and the risk of Alzheimer disease was assessed in a study of 10,079 Swedish twins.[11] Participants were categorized by the complexity of their work with data, people, or things. Study subjects who had greater complexity with people or data in their jobs had lower rates of dementia and Alzheimer disease after adjusting for education. Among 55 pairs of twins in whom complexity of occupation differed, the relationship between job complexity with people and a reduced risk of Alzheimer disease and dementia was maintained, as was the relationship between complexity with data and a reduced risk of Alzheimer disease.

Physical activity has also been correlated with cognitive function. In older women, an increase in time spent walking was associated with superior cognitive function on five measures.[12]

IMPACT OF THE HEART AND BRAIN ON LIFESTYLE

The condition of the heart and brain affects a person's lifestyle. Exercise can be dangerous or even impossible with a diseased heart. Brain chemistry and structure influence mood, personality, and health-related behaviors, such as addiction, compulsive behavior, and food cravings. It is also known that cognition can influence behavior through awareness, motivation, and skills.

Four components of behavior change

Cognitive functions of the brain have a direct impact on a person's behavior. However, cognitive functioning is just one component of behavior change. Successful behavior change requires awareness, motivation, skill, and opportunity. A model I developed uses a point system to predict the likelihood of successful health behavior change: awareness contributes 10% to the total score; motivation, 25%; skill, 25%; and opportunity, 40%.[13] Success is considered unlikely with accrual of 40 points or less, possible with 40 to 65 points, and likely with more than 65 points.

Information and education by themselves are not sufficient to effect behavioral change. As an example, despite repeated national educational campaigns about the health benefits of physical activity, the number of Americans who partake in at least 30 minutes of moderately intense physical activity at least 5 days a week remained unchanged from 1986 to 2000.[14] Effecting change will mean moving beyond education to discovering what motivates people to change their behavior, offering training to give people the appropriate skills to engage in healthier behaviors, and providing opportunities to change behavior.

Are there uniquely American factors at work?

A recent study found that self-reported health was superior in English adults aged 55 to 64 years compared with their counterparts in the United States, and the finding was independent of education and income.[15] One explanation that has been offered is that the higher rate of obesity in the United States has more than offset the higher rates of smoking and alcohol consumption in England, but the authors acknowledge that this did not explain all of the differences between the countries. Approximately two thirds of the US population is overweight, with one third being obese. One contributor to the obesity epidemic in the United States is a built environment that has engineered activity out of daily living (ie, streets not friendly to pedestrians), which serves to further hinder the motivation for people to engage in physical activity.

CONCLUSION

Lifestyle influences the health of the heart and the brain, and both organs influence the healthfulness of our behavior and our overall health. The interaction of both within the context of the body and life must be considered.

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The heart-brain interaction during emotionally provoked myocardial ischemia:

Implications of cortical hyperactivation in CAD and gender interactions

Stress has been defined as a state of threatened homeostasis that is reestablished by physiologic adaptive responses. If the adaptive responses are inadequate or excessive and prolonged, homeostasis is not attained and pathology ensues.[1]

Among the pathologies that are related to stress and its associated emotional manifestations is coronary artery disease (CAD). It has been established by multiple laboratories that 30% to 50% of CAD patients exhibit transient, symptomless myocardial ischemia during mental stress performed in a laboratory setting.[2–4] The clinical manifestations of this mental stress-induced ischemia include profound left ventricular dysfunction[5,6] and the triggering of acute coronary syndrome[7] and potentially fatal arrhythmia.[8,9] Furthermore, up to 75% of ischemic episodes seen during ambulatory electrocardiographic monitoring in patients with chronic CAD occur during routine daily activities that carry a considerably lower metabolic demand than is required to provoke ischemia during exercise diagnostic testing.[10] Furthermore, these ischemic episodes occur without symptoms.[10] This ischemia in response to emotional provocation differs from exercise-induced ischemia with regard to several pathophysiologic determinants and clinical presentation.

Among patients with CAD, exercise has been shown to initiate various homeostatic responses and attendant changes in myocardial blood flow and ventricular function that are indices of myocardial ischemia. Emotional provocation with the attendant cognitive demand is associated in the brain with activations in regions involved in processing of cognitive stimuli. Simultaneous with these activations in regions known to be involved with cognitive and emotional function are activations of the effectors responsible for cardiovascular physiologic funtion. Accordingly, studies of the brain during emotional provocation that culminates in myocardial ischemia are cardinal to our understanding of ischemic clinical presentations.

* Both authors reported that they have no financial relationships that pose a potential conflict of interest with this article.

MENTAL STRESS VS EXERCISE STRESS

The physiologic responses to mental stress and exercise stress differ in several important ways. For example, exercise produces a substantially greater increase in heart rate and a somewhat greater increase in systolic blood pressure compared with mental stress, largely as a function of the increased metabolic demands associated with exercise stress.[2] Diastolic blood pressure and systemic vascular resistance, which rise with mental stress, are flat or decrease in response to exercise.[11] In patients with CAD, angina accompanies ischemia provoked by exercise stress, particularly when the level of exercise stress approaches maximal exercise capacity. Angina, however, occurs rarely during ischemia provoked by mental stress.

In 1984, Deanfield et al measured uptake of rubidium-82 with positron emission tomography (PET) after mental arithmetic challenges and again after physical exercise in 16 patients with chronic stable angina.[12] After mental arithmetic, 12 of the 16 patients had regional perfusion abnormalities but only 6 had ST-segment depression and 4 had an anginal episode. Six patients with perfusion abnormalities had neither angina nor ST-segment changes. Subsequent research in a number of laboratories has served to highlight several important pathophysiologic elements that distinguish mental stress-provoked ischemia, most notably an apparently primary role for dysfunction in the epicardial vessels[13] and microvascular bed.[14]

Mental stress-induced ischemia carries poor prognosis

Clinical studies have demonstrated the negative prognostic impact of mental stress-induced myocardial ischemia. Patients with a perfusion deficit on PET, or left ventricular dysfunction on echocardiog-

raphy, when subjected to laboratory mental stress are at increased risk for subsequent myocardial infarction, unstable angina, and revascularization[15–17] and have a greater 5-year mortality than those patients who do not demonstrate this ischemic response.[4] Treatment strategies tailored to patients with stress-induced myocardial ischemia (ie, cognitive behavioral therapy and stress management) decrease the incidence of cardiovascular events compared with usual care.[18,19]

New approaches needed for ischemia from mental stress

Given the apparently different underlying pathophysiology of mental stress-induced ischemia compared with exercise-induced ischemia, it is clear that conceptual constructs that serve as a basis for diagnostic testing and treatment of patients with chronic CAD are not sufficient to address patients with vulnerability to mental stress-induced ischemia and the associated poorer prognosis. Pathophysiologic constructs need to be established, and associated diagnostic and treatment models need to be developed and tested, so that patients who are vulnerable to mental stress can be identified and can receive appropriate treatments. Clearly, new approaches are needed. Their development requires an understanding of the differences between the conditions associated with exercise (demand) and those associated with mental stress-induced ischemia (cognitive).

The stimulus for myocardial ischemia that results from mental stress is cognitive and thereby differs fundamentally from the physical stimuli that provoke demand-related ischemia. Hostility and anger, emotional concomitants of mental stress, are associated with an increase in levels of inflammatory markers,[20] and episodes of anger are associated with an increased risk of myocardial infarction.[7] Although negative reactivity to stress has been shown to increase the risk of a poor outcome, individuals have different thresholds for expressing negative emotions as a result of stress, so that the risk of an event may depend not only on the individual's cardiovascular substrate but on his or her coping mechanism as well. Given the cognitive and emotional constituents of mental stress, an examination of the neurobiology of this phenomenon, with an eye toward "downwind" effects on the cardiovascular system, is in order if we are to proceed to the day when prognostic testing for mental stress-induced ischemia becomes a routine part of clinical practice.

The neurobiology of mental stress

When stress occurs, the stimulus for ischemia is located in the brain.[2,11,21] CAD patients who exhibit myocardial ischemia in response to laboratory mental stress should exhibit activation in subcortical regions associated with visceral effectors, such as the frontolimbic structures, compared with those who do not become ischemic.

The evaluative component of a psychosocial stress or confrontation occurs in the frontal cortex—specifically in the medial prefrontal cortex, where there are functional interconnections between it and the limbic system. The limbic system has visceral effectors and functional interconnections between the hypothalamus and pituitary, initiating the adrenal stimulation of epinephrine, which returns to the locus coeruleus to potentiate norepinephrine production. These interconnections shape the function of the amygdala and the hippocampus, and are important in coping mechanisms.

A prevailing theory is that differentially less activation of the frontal to the limbic reaction results in an unbalanced output of visceral effectors from the limbic system, which augments catecholamine output and various physiologic outcomes such as parasympathetic withdrawal and potentiation of coronary vascular dysfunction that results in myocardial ischemia.

The hippocampus provides the context from which we evaluate situations (eg, distinguishing a bear in the woods from a bear in the zoo). Patients with posttraumatic stress disorder have dendrite atrophy in the hippocampus, impairing their ability to accurately put into context their retrieval of long-term traumatic memories.

The amygdala has visceral effectors that shape the response to fear. The interaction between the amygdala and the limbic system may determine the appropriateness and the output of visceral neurosectors and the subsequent effect upon the heart.

BRAIN ACTIVATION PATTERNS IN MENTAL STRESS

We conducted O_{15} PET studies of the brain to map brain activation in response to laboratory stress (mathematical calculation) in subjects with or without CAD.[11] Echocardiography was also performed during the O_{15} PET imaging, enabling us to map patterns of brain activation in CAD subjects who experienced myocardial ischemia during stress and compare these patterns to those of the CAD subjects who did not exhibit myocardial ischemia during stress.

Different activation patterns in subjects with vs without CAD

Compared with otherwise healthy controls, subjects with CAD exhibited significantly increased blood flow in the left anterior cingulate, the left parietal cortex, and the left parahippocampus, areas that are involved in emotion, memory, and attention. In these CAD subjects there was greater limbic to prefrontal activity. This pattern of activation implies that the

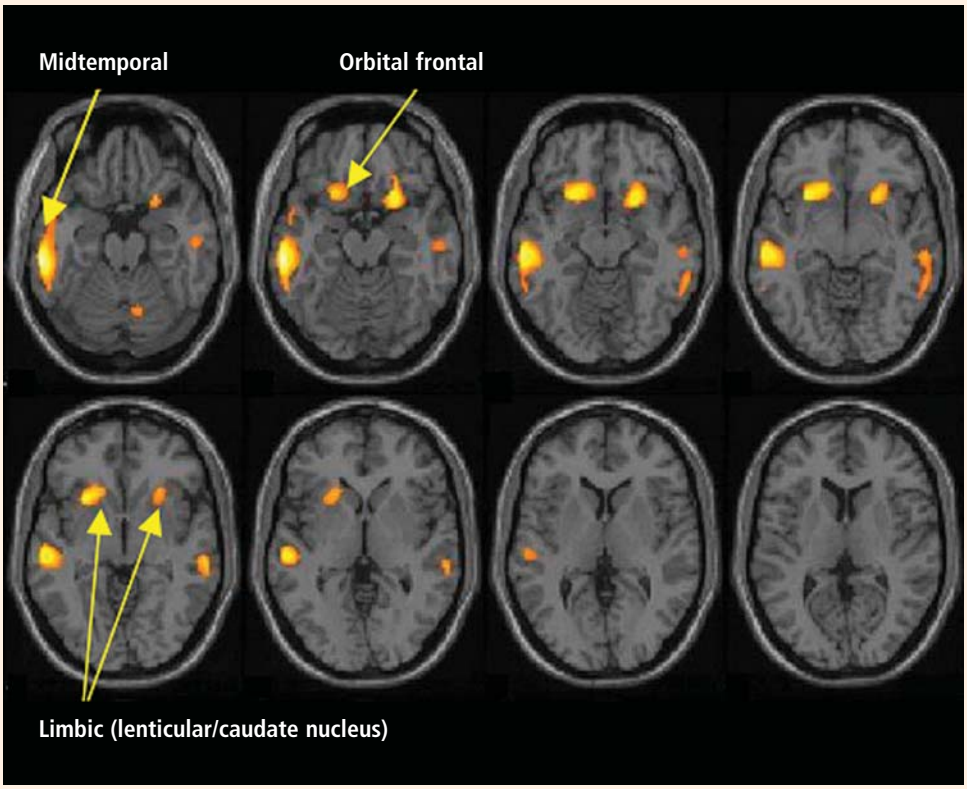

FIGURE 1. Subtraction scans showing areas of cortical activity in association with mental stress ischemia vs ischemia provoked by dobutamine. Activation is observed in the midtemporal, orbital frontal, and limbic lobes, the anterior cingulate gyrus, and the amygdala/hypothalamus (all $P < .01$), confirming that mental stress-induced ischemia is associated with a distinct pattern of central nervous system activation compared with demand-provoked ischemia. These areas are referable to the cognitive nature of mental stress and are associated with memory/emotion and sympathetic activation.

hyperactivation of limbic regions associated with fear and anxiety has a greater effect on cardiovascular function via effectors, which regulate neurohormonal responses and autonomic balance. Healthy subjects did not significantly exhibit these activations but instead exhibited activations that were referable to the cognitive effect of the task.

Thus, CAD subjects with ischemia had marked activation in the hippocampus and the anterior cingulate gyrus, both of which are involved in emotional processing and the processing of neurohormonal effectors. The subjects who developed ischemia had marked deactivation throughout their nondominant hemisphere, which suggests that the coping mechanism in response to stress that exists in the nondominant hemisphere is deactivated in subjects who exhibit ischemia.

Furthermore, during mental stress, CAD subjects also have specific activation patterns distinct from those in subjects without ischemia. These findings suggest pathways that may account for the silent nature of mental stress-induced ischemia, namely deactivation in the cingulate anterior gyrus.[22] The latter has been associated with varying thresholds for pain sensations.

Different activation patterns in men vs women

We next examined patterns of brain activation during mental stress in men and women with CAD and men and women without CAD.[23] We found no difference in patterns of brain activity between men and women without CAD during laboratory stress. Both had activation of the visual association cortex and other areas referable to numerically based tasks. The women with CAD, when compared to their counterparts without CAD, had greater activation in areas associated with neocortical and subcortical limbic structures. Of note, activation occurred in the prefrontal cortex (middle frontal gyrus and inferior frontal gyrus) in the women with CAD, which suggests an evaluative component to their central nervous system response to mental stress.

Women with CAD also had greater bilateral and medial temporal activation during mental stress (amygdala/hippocampus) when compared to men with CAD. Interestingly, men with CAD had deactivation in the same areas that were significantly activated in women with CAD during stress: the anterior cingulate, orbital frontal, and medial temporal anterior regions. Brain activation in women with CAD was also mainly bilateral, whereas it was more medial in men with CAD.

Different activation patterns as a function of ischemia during mental stress

We hypothesized that patients with mental stress-induced ischemia would show increased activation in brain regions that involve memory and emotion relative to subjects without mental stress-induced ischemia. We further hypothesized that this pattern of activation would differ from that seen in demand-related ischemia.

To test these hypotheses, we studied 58 patients

with CAD who underwent simultaneous measurement of brain activation with O_{15} PET and cardiac wall motion analysis (to evaluate myocardial ischemia) with echocardiography during arithmetic mental stress and dobutamine stress conditions.[24] Eight of the 58 subjects had ischemia to both mental stress and dobutamine stress. Thirteen had myocardial ischemia to mental stress but not in response to dobutamine stress.

When brain PET images were analyzed, cerebral hyperactivation was observed in the subcortical limbic and neocortical regions of the brain during mental stress relative to dobutamine stress. Again, activation was observed in frontolimbic circuits associated with emotion, memory, fear, and anxiety, which are areas also involved in neurohormonal and autonomic regulation. These findings suggest that ischemia to mental stress has a distinct cerebral activation pattern compared with ischemia that results from demand stimulus. Activated areas with ischemia that results from mental stress are referable to the cognitive nature of mental stress, and activation occurs in regions associated with memory, emotion, and sympathetic activation **(Figure 1)**.

SUMMARY

Mental and emotional stress can provoke transient ischemia and acute coronary syndrome in vulnerable patients. Furthermore, those patients so provoked are at increased risk for recurrent cardiac events and early death. Viable psychological treatments to improve prognosis exist, and preliminary trials demonstrate their efficacy with regard to short- and long-term outcomes, as well as economic savings.

These findings heighten the need for efforts directed toward the complete identification of the differential pathophysiology of mental stress-induced ischemia, with an eye toward development of diagnostic tests and establishment of risk stratification algorithms that can be applied in the clinical setting. Ongoing research in this vein is identifying unique aspects of the brain-heart relationship during mental stress that underlie the cognitive and emotional aspects of mental stress, and the "downwind" pathways by which distinct patterns of brain activity during mental stress can provoke otherwise silent myocardial ischemia. This research is making important contributions to the larger clinical goals associated with diagnostic testing, risk stratification, and treatment of patients at risk for mental stress-induced ischemia and poorer prognosis.

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Depression and heart disease

Considerable evidence strongly supports an association between depression and cardiac disease: depression (both major depressive disorder and depressive symptoms) is a predictor of short-term and long-term mortality in patients following myocardial infarction (MI) and is also a predictor of having an acute coronary event in the general population.

The nature of the association has been contested. Does depression cause heart disease because of behavioral factors, autonomic dysfunction, or enhanced inflammation? Or does another factor—such as dietary intake of foods rich in omega-3 fatty acids—simultaneously affect both depression and heart disease? Evidence supports each theory.

Despite the well-proven association between heart disease and depression, attempts thus far to target depression to improve heart disease outcomes have been unsuccessful.

This article reviews the strength of the epidemiologic data linking depression and heart disease and discusses possible mechanisms to explain this relationship.

DEPRESSION AS A RISK FACTOR FOLLOWING MI

There is much epidemiologic evidence to support an association between depression and increased mortality following MI.

In 1993, we followed 222 patients for 6 months after an MI and found that major depression was a significant predictor of mortality.[1]

A follow-up study[2] with 896 patients showed that the increased risk was not restricted only to those with major depression. The level of depression symptoms during admission, as assessed by the Beck Depression Inventory (BDI), had a dose-response relationship with cardiac mortality **(Figure 1)**. Even patients with only low levels of depressive symptoms at baseline had an increased risk of cardiac mortality over 5 years of follow-up. The risk associated with depression symptoms was independent and of about the same magnitude as having a previous MI, or having diabetes or ventricular dysfunction.

Welin et al[3] followed 275 patients younger than 65 years old who experienced a first MI and found that the increased risk of mortality associated with baseline depression was still evident for up to 9 years.

DEPRESSION AS A RISK FACTOR FOR A CARDIAC EVENT

Depression is also a risk factor for an incident cardiac event among initially healthy people. Rugulies[4] evaluated 11 cohort studies that assessed depression and coronary heart disease and found that people with clinical depression had more than 2.5 times the risk of an MI or coronary death as the general population. Those with symptoms of depression who did not meet the criteria for a diagnosis of clinical depression had about 1.5 times the chance of a future cardiac event.

HOW MIGHT DEPRESSION AFFECT HEART DISEASE?

Several plausible pathways could link depression with cardiac disease. Whether depression is actually the cause of, a consequence of, or only coincidentally associated with cardiac disease is still uncertain.

Risky behaviors. Depression may adversely influence behavioral factors, such as smoking, diet, exercise, and compliance with medical care, increasing the risk of cardiac mortality.

Autonomic function. Depression may enhance sympathetic nervous system activity, leading to increased cardiac mortality. Carney et al[5] found that patients with depression following an acute MI had greater autonomic dysfunction, as measured by heart rate variability indices, than patients after MI without depression.

Consequence model: Inflammation

Alternatively, atherosclerosis or MI may induce physiologic changes that cause depression. Atherosclerosis is associated with a subchronic elevation of cytokines, whereas acute MI triggers a more intense rise. These peripheral cytokines induce production of cytokines

* Dr. Lespérance reported that he has received honoraria from GlaxoSmithKline, Lundbeck, and Wyeth; has received grant support from IsodisNatura and GlaxoSmithKline; and is a consultant for Servier. Dr. Frasure-Smith reported that she has received honoraria from Solvay and Tromsdorff and grant support from IsodisNatura and GlaxoSmithKline.

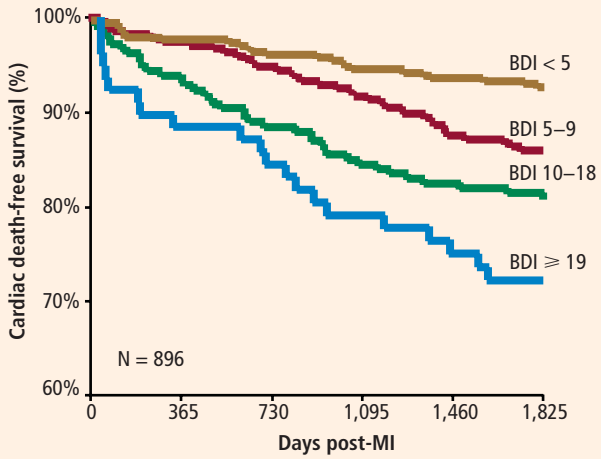

FIGURE 1. A dose-response relationship between depressive symptoms, as measured by scores on the Beck Depression Inventory (BDI), and long-term prognosis following myocardial infarction (MI) was evident in this study of post-MI patients who were followed for at least 5 years. Reprinted, with permission, from Lespérance et al. Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. Circulation 2002 (Mar 5); 105:1049–1053.

TABLE 1
Relationships between depression and markers of inflammation among post-ACS patients

Inflammatory marker	BDI-II < 14 (n = 450)	BDI-II ⩾ 14 (n = 152)	*P*
Soluble intercellular adhesion molecule 1 (ng/mL)	179.1 (156.5–210.2)	192.6 (166.9–233.3)	.001
Interleukin-6 (pg/mL)	2.03 (1.41–3.14)	2.22 (1.41–3.64)	.30
C-reactive protein (mg/L)	1.66 (0.91–3.87)	2.02 (1.02–4.91)	.042

Levels of inflammatory markers expressed as median levels; numbers in parentheses represent the 25th and 75th percentiles.

ACS = acute coronary syndrome; BDI-II = Beck Depression Inventory II

Adapted from Frasure-Smith et al. Depression, C-reactive protein and two-year major adverse cardiac events in men after acute coronary syndromes. Biol Psychiatry 2006; vol. 60. In press. Copyright 2006, with permission from the Society of Biological Psychiatry.

in the brain, which then activates the hypothalamic-pituitary axis and the stress response and inhibits serotonin activity. This activation leads to "sickness behavior," such as is exhibited with the occurrence of an upper respiratory viral infection.[6]

Evidence indicates that MI may cause physical changes in the brain that cause depression, which is mediated by an inflammatory response.

Wann and colleagues[7,8] developed a rat model of post-MI depression. They found that 14 days after having an acute MI, rats showed behavioral changes consistent with depression (ie, reduced sucrose intake [an equivalent to anhedonia] and reduced performance on the forced swim test [an equivalent to behavioral despair]). In addition, these behavioral changes were associated with the presence of apoptosis in the prefrontal cortex, hypothalamus, and amygdala, a phenomenon that was suppressed by treating rats with pentoxifylline, an inhibitor of cytokine synthesis, or antidepressants.

Tyring et al,[9] in a randomized controlled study involving 618 patients with psoriasis, found that those taking etanercept, an inhibitor of the inflammatory marker tumor necrosis factor (TNF)-alpha, had improvements in scores measuring fatigue and depression. Improved scores did not completely correlate with improved joint pain and skin clearance. It is possible that the anti-inflammatory effects of the medication directly improved sickness behaviors.

At the Montreal Heart Institute, we evaluated the association between depression and inflammatory markers (soluble intercellular adhesion molecule 1 [sICAM-1], interleukin-6 [IL-6], and C-reactive protein [CRP]) in 602 men 2 months after hospitalization for an acute coronary syndrome.[10] Levels of sICAM-1 and CRP were significantly higher in men with depression **(Table 1)**. Two-year follow-up showed that the impacts of depression and CRP on major cardiac events were not additive (ie, that depression and CRP appear to be overlapping risk factors).[11]

Depression and inflammatory markers are also associated in people without known cardiac disease. Penninx et al[12] evaluated a community-based sample of well-functioning people aged 70 to 79 years and found that those with depressed mood had higher median plasma levels of IL-6, TNF-alpha, and CRP.

It is impossible to know at this point whether the link between heart disease, inflammation, and depression is unidirectional or bidirectional: each factor may give rise to the other.

Coincidence model: Omega-3 fatty acids

Evidence suggests that depression is linked to a worse prognosis in acute coronary syndromes by several mechanisms:

- Autonomic dysregulation, as shown by decreased heart rate variability and increased risk of ventricular arrhythmias

- Platelet changes
- Inflammation
- Endothelial function.

It is possible that dietary factors affect both depression and heart disease through these mechanisms. One such potential dietary factor is omega-3 fatty acids.

Omega-3 and omega-6 fatty acids are polyunsaturated fatty acids that are so named because of the position of the first double bond on their carbon atom chain. Their molecular structure determines their three-dimensional configuration and biological properties. Arachidonic acid (an omega-6 fatty acid) and eicosapentaenoic acid (an omega-3 fatty acid) are both 20-carbon polyunsaturated fatty acids that are included in multiple biologic molecules such as prostaglandins and leukotrienes and have different physiologic actions.[13]

Omega-3 fatty acids are found in flax seed, canola, nuts, and fish. Eating more fish may improve prognosis in acute coronary syndromes by increasing heart rate variability and by antiarrhythmic, antithrombogenic, and anti-inflammatory actions. Increasing dietary consumption of omega-3 fatty acids also promotes nitric oxide-induced endothelial relaxation.

The GISSI-Prevenzione trial[14] randomized 11,324 post-MI patients to daily supplementation with either omega-3 fatty acids (1 g), vitamin E (300 mg), both, or neither for 3.5 years. Omega-3 fatty acid supplementation significantly reduced the combined incidence of death, nonfatal MI, and stroke compared with controls, whereas vitamin E supplementation had no effect.

Hibbeln[15] found an inverse relationship between average per capita annual fish consumption and the prevalence of major depression in nine countries. Other studies have also found an association between omega-3 fatty acid consumption and postpartum depression[16,17] or bipolar disorders.[18]

In a case-control study of patients recovering from an acute coronary syndrome, we found that depressed patients had significantly lower concentrations of omega-3 fatty acids than their nondepressed counterparts **(Table 2)**.[19]

TABLE 2
Relative levels of fatty acids between depressed cases and controls with recent acute coronary syndrome

	Age- and sex-matched controls (n = 54)	Depressed cases (n = 54)	*P*
Alpha linolenic acid *18:3n-3*	0.25 ± 0.08	0.25 ± 0.09	.71
Eicosapentaenoic acid (EPA) *20:5n-3*	1.20 ± 0.51	1.14 ± 0.58	.38
Docosahexaenoic acid (DHA) *22:6n-3*	3.85 ± 1.13	3.32 ± 1.03	.013
Total EPA and DHA	5.05 ± 1.44	4.46 ± 1.32	.024
Omega-3 total	6.63 ± 1.47	6.09 ± 1.43	.044
Omega-6 total	33.28 ± 1.60	33.50 ± 2.29	.57
Omega-6/omega-3 ratio	5.28 ± 1.27	5.84 ± 1.57	.044
Arachidonic acid (AA)/EPA ratio	10.46 ± 3.64	12.63 ± 6.63	.044
AA/DHA ratio	3.14 ± 1.05	3.88 ± 1.40	.002

Adapted from reference 19.

TREATING DEPRESSION TO REDUCE CARDIOVASCULAR RISK

No secondary prevention trial has successfully reduced cardiovascular risk by targeting depression.

The Enhancing Recovery in Coronary Heart Disease (ENRICHD) study[20] was a multicenter clinical trial involving 2,481 patients following an acute MI who were either depressed or had low social support. Patients were randomized to either 16 weeks of cognitive behavior therapy supplemented by treatment with a selective serotonin reuptake inhibitor (SSRI) or usual care. After 3.5 years, no difference was detected in survival rates between the two groups.[21] However, physicians of usual care patients were informed that their patients were depressed, and by the end of the trial a good proportion of the usual care patients had been treated with SSRI antidepressants. Thus, it is difficult to know if treating depression has no effect on cardiovascular risk or whether the intervention chosen for this trial was inadequate.

The Sertraline Antidepressant Heart Attack Trial (SADHART)[22] was a randomized controlled trial that tested the safety and efficacy of the SSRI antidepressant sertraline in 369 patients with major depression hospitalized for acute MI or unstable angina. Sertraline was found to be safe and mildly to moderately effective for treating depression in this population, but the incidence of serious adverse cardiac events and changes in surrogate cardiac markers were not significantly different between the treated and untreated groups.

The Canadian Cardiac Randomized Evaluation of

Antidepressant and Psychotherapy Efficacy (CREATE),[23] evaluating the SSRI citalopram and interpersonal psychotherapy for treating major depression in patients with coronary artery disease, has just been completed. Results will be forthcoming.

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Sick at heart: The pathophysiology of negative emotions

The notion that emotional states can influence health is an enduring idea. In 1628, William Harvey noted that a mental disturbance can affect the heart and impair its function. However, it is only in the past several decades that rigorous and methodologically sound epidemiologic research has begun to provide compelling evidence of the link between emotions and cardiovascular diseases, with relative risk estimates that are comparable to those for known risk factors such as smoking. As a result, negative psychological states are beginning to be recognized as risk factors for the development of cardiovascular disease, believed to adversely affect cardiovascular health through multiple pathways.

This article reviews the epidemiologic evidence supporting the role of negative emotion in the development of one form of cardiovascular disease—coronary heart disease (CHD)—and briefly discusses the mechanisms that may help us to understand this relationship. It is worth noting, however, that there is evidence of similar relationships between negative emotions and other cardiovascular outcomes (eg, stroke), as well as between the related experience of chronic stress (eg, caregiver burden, work stress, marital stress) and a range of cardiovascular diseases.

EPIDEMIOLOGIC STUDIES

Clinicians have long been familiar with the possibility that acute or extreme emotion can bring on cardiac arrest. As reviewed in other articles in this supplement, there is growing scientific evidence for this phenomenon, which has been variously referred to as acute myocardial stunning, voodoo death, fatal pleasures, and tako-tsubo cardiomyopathy.

However, there is also growing evidence that negative emotions have cumulative pathophysiological effects and can ultimately lead to CHD events, via accumulation of damage through a steady activation of key neurohormonal systems and other mechanisms.[1–3]

For example, in one of the most compelling demonstrations of this association, a recent case-control study of 29,972 patients from 52 countries, known as INTERHEART, assessed the impact of nine conventional risk factors on incident acute myocardial infarction (MI).[4] Psychosocial distress conferred a greater adjusted relative risk of acute MI than did hypertension, abdominal obesity, diabetes, and several other traditional risk factors. A high level of psychosocial distress increased the relative risk of MI more than 2.5-fold compared with a low level of psychosocial distress, and this relationship was maintained after including all the other risk factors in the models simultaneously. The population-attributable risk (ie, the incidence of disease in the population that would be eliminated if the exposure were removed) of psychosocial distress for acute MI was 32.5%.

How might negative emotions play a role in CHD?

Negative emotions may have direct physiologic effects on the development of CHD via repeated sympathetic nervous system and hypothalamic-pituitary-adrenocortical axis activation, immune dysregulation, and inflammation. Negative emotions might indirectly influence CHD via motivation of behaviors detrimental to health. For example, individuals who experience high levels of anxiety are more likely to smoke and less likely to engage in physical activity. As alluded to earlier, negative emotions may be involved in triggering a coronary event. Finally, negative emotions may also exacerbate disease progression or reduce survival either via direct physiological effects or through reduced compliance with recommended medical regimens.

It is generally accepted that emotions may influence health behaviors or compliance with medical regimens. Thus, for the remainder of the article, I will focus on the most controversial of these possible links, the role of negative emotion in the etiology of CHD.

* Dr. Kubzansky reported that she has no financial relationships that pose a potential conflict of interest with this article.

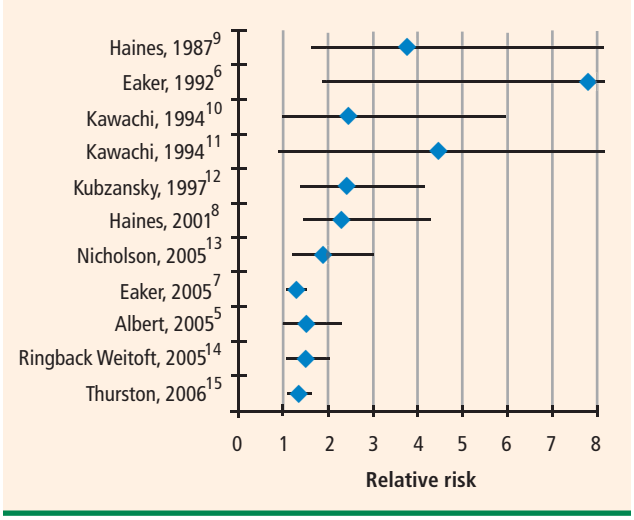

FIGURE 1. In 11 prospective studies in which an association between chronic anxiety and incident coronary heart disease was explored, the risk ranged from 1.5 to nearly 8.0.

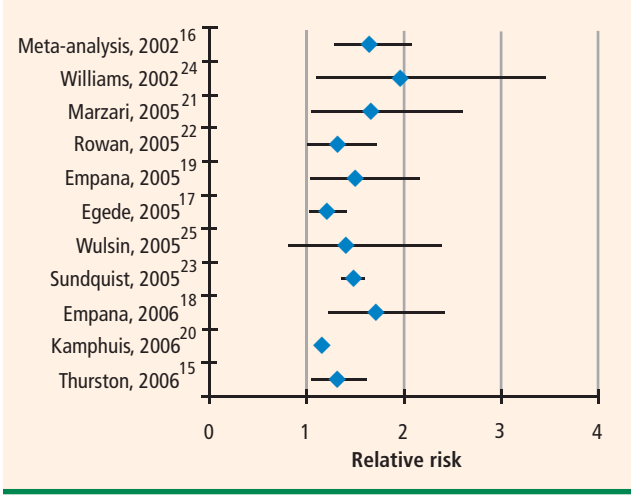

FIGURE 2. A meta-analysis of 11 studies and 10 subsequent prospective studies revealed a strong association between depression/depressed mood and incident coronary heart disease.

Three negative emotions influence CHD

To date, consistent with findings from the INTERHEART study,[4] a body of epidemiologic evidence supports an etiologic link between three negative emotions and development of CHD: anger, anxiety, and depression. Numerous prospective studies that have controlled for a broad range of CHD risk factors have established a positive association between these three emotions and incident CHD events. Most of these studies also controlled for a number of health behaviors, including smoking; if such behaviors are believed to be on the pathway between negative emotions and CHD, then risk estimates derived from these studies are likely to be underestimates.

The evidence presented below is derived solely from prospective studies, designed to look at incidence of CHD, considering only "hard" disease outcomes (eg, nonfatal MI, sudden death) in population-based samples with individuals who are disease-free at the start of the study. Not all studies include men and women, but findings across studies to date suggest that effects are similar.

Anxiety and CHD. Chronic anxiety appears to increase the risk of incident CHD, with risk estimates from 1.5 to 7, depending on the type of anxiety measure used and the form of the analysis **(Figure 1)**.[5–15] The landmark Northwick Park Heart Study followed 1,457 initially healthy men for about 10 years.[9] Those with the highest levels of phobic anxiety had a relative risk (RR) of fatal CHD of 3.77 (95% confidence interval [CI]: 1.64–8.64) compared with men reporting no anxiety, after controlling for a range of known coronary risk factors.

Since then, 10 additional studies have produced largely consistent findings. For example, the most recent study used data from a nationally representative study of the US population and found that anxiety was associated with 60% excess risk of CHD in both men and women, an effect that was independent of smoking and other known risk factors.[15]

Depression and CHD. To date, most of the research on negative emotions and CHD has focused on depression. In 2002, a meta-analysis of 11 published studies demonstrated a strong positive association between depression and incident CHD, with a RR of 2.69 (95% CI: 1.63–4.43) for individuals with clinically relevant levels of depression, and a RR of 1.49 (95% CI: 1.16–1.92) for individuals with depressed mood.[16] Since then, 10 additional prospective studies have confirmed a significant association of similar magnitude between depression and development of CHD **(Figure 2)**.[15,17–25] Risk was increased not only for clinically relevant levels of depression, but also as depressive symptoms increased. This graded effect has also been identified with both anger and anxiety.

Post-traumatic stress disorder (PTSD) is linked closely with both anxiety and depression and has long been hypothesized to be associated with development of CHD. Interestingly, findings in select samples are beginning to emerge that are consistent with studies on anxiety or depression and CHD.[26] However, further work is needed to confirm this association and determine whether it holds in diverse populations.

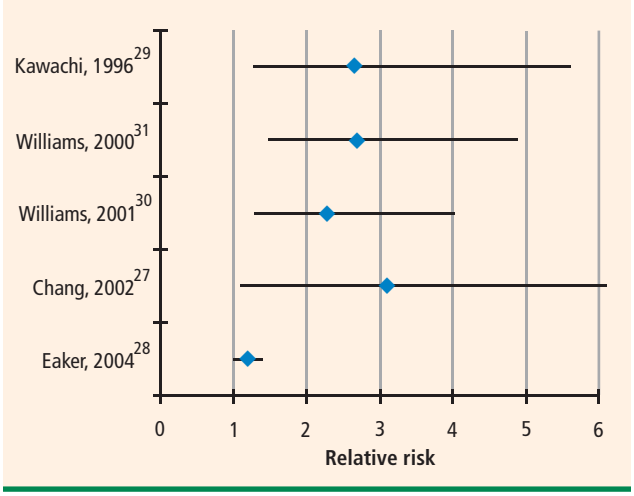

FIGURE 3. Five prospective studies showed significant associations between anger symptoms and incident coronary heart disease with follow-up of 5 to 15 years.

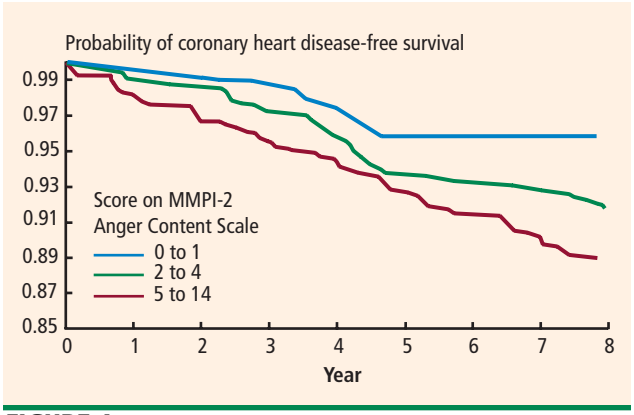

FIGURE 4. Among 1,305 participants in the Normative Aging Study who completed the revised Minnesota Multiphasic Personality Inventory (MMPI-2), men reporting the highest levels of anger (score of 5 to 14) had a relative risk of 2.66 for developing coronary heart disease compared with men reporting the lowest levels of anger (score of 0 or 1). Adapted from data in reference 29.

Anger and CHD. Similar to findings with anxiety and depression, although there are fewer studies, those on anger and CHD suggest increased relative risk associated with higher levels of anger. In five prospective studies that included initially disease-free individuals, higher levels of anger symptoms were significantly associated with a 1.5- to 3-fold excess risk of incident CHD over follow-up periods of 5 to 15 years **(Figure 3)**.[27–31]

Dose response between emotions and CHD risk

While clinicians often think of emotional disturbance as occurring at a certain level of symptomatology or when a specific set of criteria are met, in fact, emotions occur on a continuum that ranges from normal to pathologic, and the components (cognitive, biological, and behavioral) that characterize an emotion are the same regardless of where on the continuum they fall. The pathologic end of the spectrum is defined not by different components, but rather by a high frequency and intensity of emotion, occurring in generally inappropriate situations. As a result, the study of emotion and CHD does not fit neatly into traditional epidemiologic models that compare exposure with nonexposure, because all humans are exposed in some way to emotion, even if at a level defined as normal.

Studies of negative emotions and CHD incidence consistently suggest a dose-response relationship between levels of emotion and risk, rather than a threshold effect. These findings suggest that individuals with subclinical levels of symptoms may still be at increased risk for CHD.

Several studies looking at anxiety or anger provide a clear illustration of this type of dose-response relationship. Using data from the Normative Aging Study, Kawachi et al followed 1,305 initially disease-free community-dwelling men for 7 years.[29] Anger was measured using self-reported symptoms from the revised Minnesota Multiphasic Personality Inventory. Men with the highest levels of anger had more than 2.5 times the risk of incident CHD relative to those with the lowest levels of anger **(Figure 4)**. Those with only slightly elevated levels of anger also had a significantly elevated risk of developing CHD.

Similar findings were obtained in this sample when examining effects of worry, a cognitive component of anxiety, over approximately 20 years of follow-up among initially disease-free men. Men reporting the highest levels of a particular type of worry had an adjusted RR of 2.41 (95% CI: 1.40–4.13) for nonfatal MI compared with men reporting the lowest levels of worry, and those with a moderate level of worry also demonstrated a somewhat elevated risk of developing CHD.[12] In positing possible mechanisms, such studies have considered atherogenic pathways as well as alterations in the electrical stability of the heart.

However, these studies may not rule out the possibility that extreme emotion states may "trigger" CHD. There is some evidence for this type of effect as well, more specifically in relation to "triggering." For example, in a case-crossover study by Mittleman et al designed to look at whether emotions might have strong short-term effects, the risk of MI was found to more than double in the 2 hours after an episode of either anger or anxiety.[32] Interestingly, chronic aspirin use appeared to mitigate this increased risk of MI with episodes of extreme emotion.

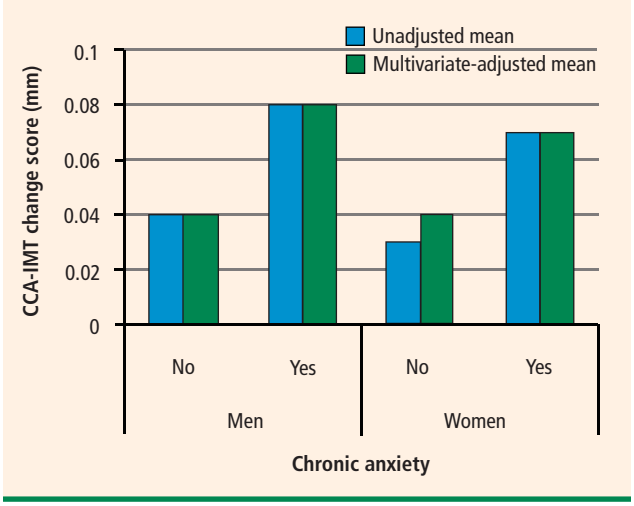

FIGURE 5. Chronic anxiety in both men and women was associated with an increase in common carotid artery intima-media thickness (CCA-IMT), indicating increased atherosclerosis progression, over 4 years of follow-up in a population-based sample of 726 subjects with no history of coronary heart disease at baseline. Adapted from data in reference 34.

PROPOSED MECHANISMS

Mechanisms by which negative emotions may predispose to CHD are beginning to be explored. Both animal and human studies have considered a variety of pathophysiologic effects of distress, including sympathetic nervous system hyperresponsivity and endothelial injury. Research in humans has explored two pathways in some detail. For example, research on anxiety suggests that one key mechanism linking anxiety and CHD may be altered cardiac autonomic control. Data from the Normative Aging Study, which previously identified an excess risk of CHD associated with anxiety, have also shown a link between high levels of anxiety and reduced heart rate variability.[33] With each increase in anxiety symptoms, there was a corresponding decrease in heart rate variability.

An atherogenic pathway, promoted by recurring activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, has also been explored. For example, in a population-based sample of 726 men and women who were healthy at baseline, Paterniti and colleagues showed that high levels of sustained anxiety were associated with increased progression of atherosclerosis over a 4-year period as measured by changes in common carotid artery intima-media thickness **(Figure 5)**.[34] Findings from this study were all the more convincing because the primary effects were maintained after controlling for a wide array of potential confounders.

A general effect of distress?

The consistency of findings across the three negative emotions in relation to CHD risk raises the question of whether effects of anxiety, depression, or anger are unique, or if there is some general effect of distress. Little work to date has been able to clearly tease apart these relationships due to methodological and data limitations. However, limited work in the area hints at several important issues.

It is clear that general distress shared by these negative emotional states is a key factor.[35] However, anxiety has been shown to predict CHD outcomes independently of depression, although depression has received far more attention from investigators.

The uniqueness of these three negative emotions as risks for incident CHD was recently explored in a prospective study of a population that was disease-free at baseline and was followed for 11 years.[36] General stress, anxiety, and depression measured at study entry were each strong predictors of incident CHD over the follow-up period; anxiety and depression (but not anger) remained independent predictors even when entered into the model together and after controlling for known CHD risk factors. Such findings suggest the importance of continuing to consider these specific emotions separately as well as considering general distress, and perhaps focusing more attention on anxiety as an important risk factor.

FUTURE DIRECTIONS

Identification and use of biomarkers

A critical next step to understanding the epidemiologic findings reported above is to examine the biology of the relationship between psychological distress and CHD. To better understand this biology, appropriate biomarkers need to be identified. Numerous studies have linked anger, anxiety, and depression to a range of biomarkers that have also been linked to CHD, including C-reactive protein, fibrinogen, cortisol, and interleukin-6.[3,37] Other work in animals has shown that nuclear factor kappa beta controls various genes that are upregulated in both atherosclerosis and psychosocial stress.[38] To date, however, few studies in humans have yielded sufficient information on psychological factors, biomarkers, and disease outcomes to allow formal testing of these pathways, so new studies are needed.

Gene-environment interactions

Another productive avenue for exploration may be to consider gene-environment interactions. For example, genes may contribute to variation in response to the environment or susceptibility to infection. They

may also alter the effectiveness of interventions or susceptibility to adverse effects from interventions. One recently identified gene, stathmin, may be of particular interest. Stathmin has been linked to fear and anxiety. Recent studies in mice have found that it is enriched in the amygdala, which is the location of the fear circuitry in the brain.[39] Knockout mice lacking stathmin show an absence of fear.

The catechol-*O*-methyltransferase (COMT) gene is also of potential interest. In a recent investigation using data from 1,234 women who participated in the Nurses Health Study (a study of 120,000 nurses), a polymorphism in the COMT gene was linked to phobic anxiety.[40] In a separate study that included these same women in the sample, phobic anxiety was associated with an increased risk of developing CHD (RR = 1.59, 95% CI: 0.97–2.60).[5]

Other work has suggested the importance of a polymorphism of the serotonin transporter gene, 5HTT. In a variety of studies, this polymorphism has been linked to anxiety and depression as well as to longevity, and may therefore be worthy of exploration in relation to CHD.

Work on mechanisms and pathways clearly highlights the importance of bringing together multiple approaches, including research on animals and humans as well as experimental and observational studies.

Psychological resilience?

Another area of interest is whether psychosocial factors may confer resilience. Most research to date has focused on pathologic effects, but other evidence suggests that positive social interactions offer a degree of protection from illness. Studies have just begun to explore whether positive psychological factors and emotional states may also confer resilience in relation to CHD.

One prospective study found that optimism was associated with reduced risk of CHD. Thus, after controlling for known coronary risk factors as well as negative emotions, individuals with the highest levels of optimism had approximately half the risk of developing CHD as did individuals who were more pessimistic.[41] Other work has since replicated these findings in other samples.[42,43] In another study, optimism was associated with a slower rate of atherosclerotic progression over a 3-year period.[44] A greater understanding of how psychological factors may impact CHD risk may be obtained by considering a fuller spectrum of psychological factors in relation to CHD, including both positive and negative states.[3]

Randomized trials needed

Ultimately, randomized clinical trials are needed to fully understand the relationship between emotional states and disease, as well as to determine whether the observed epidemiologic associations are truly causal. Thus far, with the limited evidence available, psychosocial interventions have not been shown to reduce consistently the incidence of cardiac events in randomized controlled trials of post-MI populations.

It is important, however, to distinguish onset from progression when considering work in this area. Effects of emotions on coronary health may not be identical among individuals who are initially healthy and those who are already diseased. Moreover, we still have much to learn about the relationships between negative emotion and CHD. For example, most studies of incident CHD measure chronic negative emotional experiences in middle to later adulthood. As negative emotions are generally fairly stable and recurrent, it is likely that these individuals have long been exposed to such potentially toxic states. To date, however, the duration, intensity, or reversibility of exposure has not been established. Because patients with negative psychological states have likely had lifetime exposure to negative emotions, an intervention at one point in time after disease is already initiated may be insufficient to modify the disease process.

One recent study of depression in post-MI patients found that 53% of subjects had a lifetime history of depression prior to the occurrence of their MI, which suggests long-term exposure and potentially irreversible damage.[45] Thus, interventions may not yet have found the appropriate etiologic window—earlier intervention may be needed. Trials in this area have shown that patients can be successfully recruited and enrolled, and that distress can be reduced, which is a desirable outcome in and of itself. With better information on the nature of the exposure-disease relationship, interventions will likely be better able to target the appropriate etiologic window and thereby reduce the risk of adverse outcomes and cardiotoxic effects of negative emotions.

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Role of the brain in ventricular fibrillation and hypertension: From animal models to early human studies

Sudden cardiac death is caused by ventricular fibrillation (VF), not by myocardial ischemia. Ventricular tachycardia, the precursor to VF, results dynamically from a "rotor"[1,2] that occurs in the excitable medium of the myocardium. The rotor is a self-sustaining vortex with its wave front of depolarization extending outward from a pivot point, with the inner circles moving more slowly than the outer. The rotor is a couple of centimeters in diameter, and the pivot point meanders randomly. When its outer edges strike nonexcitable tissues, such as an artery or an old infarction, the initial rotor breaks up into secondary and tertiary rotors to produce the disorganized excitability of VF.

VENTRICULAR FIBRILLATION IS A BRAIN PROBLEM

Pathology studies have shown that sudden cardiac death is often, but not always, associated with infarction or thrombosis in the heart. One seventh of patients experiencing sudden cardiac death have no detectable cardiovascular pathology, and half have insignificant pathology compared with controls.[3]

In a compelling experiment, Ebert and associates[4] showed that if all the nerves projecting to the heart (including the intrinsic ones) are blocked, then coronary artery occlusion and ischemia do not result in VF—not in a single case among 13 anesthetized dogs. This demonstrated that VF is clearly a brain problem, not a heart problem.

Joaquin Fuster showed in an early report[5] that brief electric pulses delivered through an electrode in the hypothalamus, which activated local neurons and fibers of passage, would elicit ventricular tachycardia. This evocation of arrhythmogenesis in a normal heart was later confirmed by others and shown to result in lethal VF if stimulation continued for longer periods (see review by Skinner[6]). **Figure 1A** presents an example of one such brain stimulation.[6]

A CEREBRAL DEFENSE SYSTEM?

Skinner and Reed[7] backtracked from the cutting of nerves in the periphery to blocking the higher cerebral sources of the nerves. We obtained results similar to those of Ebert et al, but in conscious animals, ie, in a conscious pig model of left anterior descending coronary artery occlusion.[7] This work, however, was guided by previous results that had considered Walter B. Cannon's early theory about brain-heart relationships.[8]

Cannon suggested that the focus of natural selection that led to the hypertrophy of the human brain was a "cerebral defense system" in which novel stimuli evoked cerebral "orchestration" of both the sensory input channels and the autonomic output channels. He believed that this orchestration had important survival value in moments of crisis, as it led to superior escape from predators or superior attack of prey.

Skinner and Lindsley[9] studied this hypothesized orchestrator, which Cannon proposed to lie in the most recently encephalized centers of the brain. We found it to be located in the orbitofrontal cortex and to control sensory input by thalamic inhibition in channels conveying irrelevant information—ie, the regulation of sensory input by the cerebral defense system worked by selective *in*attention.[10] Thus it was knowledge of where the autonomic output arose (the frontal cortex) that guided Skinner and Reed[7] in locating the descending projections to the peripheral nerves that, when blocked, would prevent VF in the conscious pig model of heart attack.

Insights from sleep

Sleep is initiated by the frontal lobes, as blockade in these structures, or blockade of their connections with the nonspecific nuclei of the thalamaus, will pre-

* Dr. Skinner reported that his employer, Vicor Technologies, holds patents for the nonlinear PD2i algorithm discussed in this article.

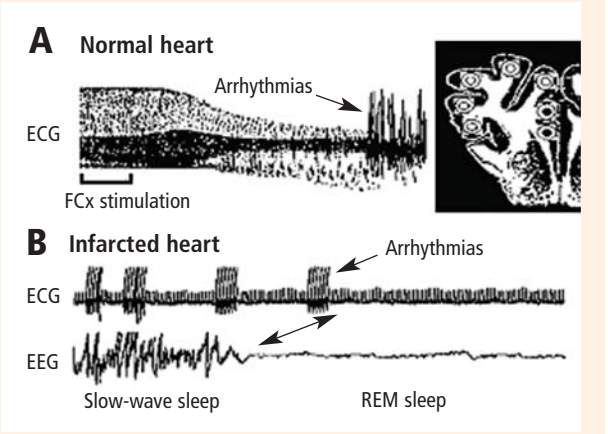

FIGURE 1. (A) Effect of electrical stimulation of the frontal cortex (FCx) on the electrocardiogram (ECG) of the normal heart in an unanesthetized pig.[6] (B) Salutary effect (after a 10-second latency, indicated by double-headed arrow) of rapid eye movement (REM) sleep on arrhythmogenesis in the acutely infarcted pig heart.[12]

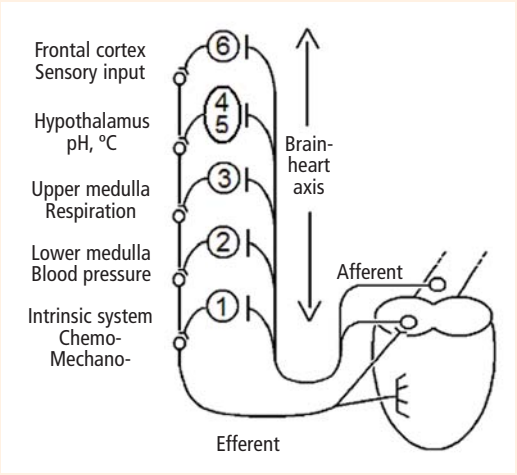

FIGURE 2. The sensory-motor loops of the brain-heart axis that compete with one another to control the heartbeat intervals.

vent occurrence of the sleep spindles that initiate the sleep process.[11] **Figure 1B** depicts the salutary effect of a particular sleep state (rapid eye movement [REM] sleep) on cardiac arrhythmias resulting from an acute myocardial infarction.[12] The 10-second latency between the onset of REM sleep and the salutary effect on arrhythmogenesis (double-headed arrow in figure) suggests that the release of a neuroendocrine molecule may underlie the effect.

Brain-heart axis

A brain-heart axis regulates the vulnerability of the heart, especially the ischemic heart, to lethal arrhythmogenesis. As illustrated in **Figure 2**, blockade at any point in the descending pathway will prevent VF in the conscious pig model of heart attack, and, conversely, electric stimulation will evoke lethal arrhythmias. Thus, by Cartesian logic, the brain–VF relationships are both necessary and sufficient (causal), whereas ischemia–VF relationships are not. So what normally causes the brain-mediated VF that is especially easy to evoke in the ischemic heart?

STRESS AS AN ENABLER OF VENTRICULAR FIBRILLATION: EVIDENCE FROM ANIMAL MODELS

Cannon's subjects would be expected to be "stressed" by the sudden appearance of a novel stimulus in a jungle setting. For example, a monkey sitting quietly in a tree would not know whether to move toward or away from an object producing a novel stimulus, but meanwhile its heart would be racing and it would feel anxious. With the additional evolution of the frontal lobes, as in the human primate, any stimulus event may come to evoke anxiousness.

For example, complex "stressor events" are known to have a relationship to the incidence of sudden cardiac death (VF) in humans. Bereavement, job insecurity, marital strife, and recently having moved are among the defined psychosocial stressors that Rahe et al[13] found were statistically related to the incidence of sudden cardiac death. Although pigs are not capable of being stressed by bereavement, job insecurity, or marital strife, as these events require considerable neocortex for their perception, Skinner and associates[14] considered another psychosocial stressor identified by Rahe et al—"recently having moved"—as a possible way to simulate human psychosocial stress in pigs. In our conscious pig model of heart attack, we found that coronary occlusion always resulted in VF in pigs unadapted to the laboratory, whereas it did not result in VF—not in 1 of 16 animals—among those pigs that had been adapted to the laboratory by having been fed and played with daily for about 1 week.[14] A subsequent study showed that this daily adaptation to the unfamiliar surroundings of the laboratory systemically reduced the sympathetic drive on the myocardium at rest and did this (ie, reduced phosphorylase activation) without changing heart rate or blood pressure.[15]

THE SEARCH FOR A CEREBRAL MEDIATOR OF THE STRESS RESPONSE

Meanwhile, the search was on by Skinner and associates for a cerebral mediator of the stress response.

Both novel stimuli and conditioned stressors were found to evoke a cortical event-related slow potential (of greatest amplitude in the frontal lobes) that was mediated by the following:

- Noradrenergic release[16]
- Slow postsynaptic potentials in the dendrites of pyramidal neurons[17]
- Cyclic AMP as the intracellular messenger[18]
- Activation of a slow outward membrane current (K^+).[19]

Focus on intracerebral beta-receptors

When it was realized that these neurophysiologic and neurochemical results implicated a cerebral beta-receptor as a way to intervene in the stress response, experiments were quickly performed[20,21] to determine where the site of action was, since beta-blockers had already been determined in the Beta-Blocker Heart Attack Trial to prevent VF (ie, reduce mortality by 26% in post-myocardial infarction patients).[22] What was not known was whether the target receptor of the beta-blockers is in the brain or the heart. In the pig model, short-term injections of propranolol into either the interstitial compartment of the brain or the larger compartment of the circulation soon made clear that it is the blockade of the intracerebral beta-receptors, not the cardiac beta-receptors, that results in the antimortality effect.[20,21]

This interpretation is further supported by observing the antimortality efficacy of different beta-blockers with varying lipophilicities. Fat-soluble molecules get into the brain at higher levels. The straight-line negative slope that Hjalmarson[23] found for this comparison indicates that the more lipophilic beta-blockers have a much greater efficacy for preventing VF in post-myocardial infarction patients.

Blood pressure elevations maintained by hypothalamic fibers of passage

Since beta-blockers were first developed using bioassay models of hypertension, there was reason to suspect that this same cerebral defense system, which involves the frontal lobes, might also play a role in the maintenance of hypertension, especially since hypertension is a harbinger for sudden cardiac death. Skinner and associates[24] showed that blood pressure elevations are not maintained by the hypothalamus, as was previously interpreted by others after they placed permanent lesions in this structure, but rather that it is blockade of the fibers of passage through the hypothalamus that produces normalization of blood pressure. These hypothalamic fibers of passage were understood to arise from the frontal cortex because blockade of that structure also normalized blood pressure in the several animal models of hypertension that were studied. Even more convincingly, we found that cryoblockade in the hypothalamus, at temperatures that blocked the local synaptic activity but not the fibers of passage, had no effect on blood pressure elevations, whereas cooling only 5°C more, which also blocked the fibers of passage, quickly normalized blood pressure in the various hypertensive models.[24]

The above result explains why reducing blood pressure elevations with a neuroactive beta-blocker also has an antimortality effect. That is, both hypertension and lethal arrhythmogenesis originate in the same noradrenergic frontocortical tissues. In contrast, reducing blood pressure with a diuretic (which reduces blood volume by expelling water) has no effect on mortality. It was interpreted that hypertension per se does not lead to sudden cardiac death but rather that activation of the frontal cortices produces both, in parallel.

A UNIFYING INSIGHT: BETA-BLOCKERS ARE ANXIOLYTIC

A single piece of scientific evidence ties all of this brain-heart business together and makes it consistent—the unexpected finding that beta-blockers are also anxiolytic (ie, anti-"stress"). Beta-blocker pills have been used by actors for decades to reduce stage fright. This anecdotal efficacy has gained scientific support more recently in studies that have shown beta-blockers to prevent the behavioral (psychiatric) sequelae in posttraumatic stress disorder.[25] Anxiety reduction in humans is perhaps somewhat predicted by the action that beta-blockers have in pigs that are unadapted to the laboratory. That is, with this deleterious brain state of "stress," VF always occurs after coronary artery occlusion, whereas with this deleterious brain state *and* intracerebral beta-blockade, VF does not occur.

But the beta-blocker effect did not have to be mediated through the perception of anxiety—it just turned out that way. The antimortality effect could have worked farther downstream in the brain-heart axis **(Figure 2)** without there being any anxiolytic effect, but it didn't—there is an anxiolytic effect, and this means that the drug is likely working on the higher cerebral centers underlying the perception of anxiety to reduce mortality. The frontal cortex, the highest center in the brain-heart axis, is well recognized as underlying the perception of anxiety, as frontal lobotomies were at one time prescribed to alleviate it.

The role of changes in neocortical gamma activity

The early realization that "intelligence" centers were part of the mechanism underlying sudden cardiac death and VF is what first led Skinner and associates[26] to examine the effects of beta-blockers on the olfactory bulb, a tissue that is often employed as a simple-system model of the more complex neocortex. We found in the conscious rabbit that the beta-blocker propranolol, when administered to the interstitial space of the olfactory bulb, would prevent the rabbit from learning anything new about an odor (eg, that the odor forewarned a noxious stimulus).[26] The important control observation was that blockade of the beta-receptor exerted its effect without reducing the cellular excitability and without preventing the raw perception of the odor and a sniffing response to it (ie, propranolol did not simply anesthetize the tissue). The rabbit could tell that the odor was there, but it could not learn what it signified.

The effect of the beta-blocker was on *learned* changes in the electric "gamma" activity in the bulb—ie, activity that oscillates within the higher frequency ranges (the gamma band). Gamma activity can also be recorded in the neocortex of humans and is recognized to be the low-voltage fast activity that we formerly called "EEG desynchronization," a cerebral reaction that always occurs in conjunction with attentive behavior.

What the learned changes in the gamma activity signify in the neocortex was later revealed by Gray and Singer,[27] who presented compelling evidence that it is the gamma activity that links various "cell assemblies" together in a "global phase synchrony" to form a more complex perception, that is, as more and more learned significance is attached to an initially simple sensory stimulus. This work is still fresh and productive in neuroscience, as evidenced in recent publications.[28,29]

Francis Crick, codiscoverer of the structure of DNA and later a theoretical neuroscientist, has stated that this "global phase synchrony" is a breakthrough discovery about higher cognitive processes of the brain.[30] Through studies of neocortical gamma activity we may someday come to understand what "stress" is and how it comes to organize the autonomic outflow that seems to cause VF in normal hearts and in ischemic hearts with lability of refractoriness.

HOW TO ASSESS THE IMPACT OF HIGHER CEREBRAL ACTIVITY ON THE HEART?

What is needed in medicine now, however, is not this complete understanding of the higher brain functions that lead to VF, but rather a simple way to assess the impact of the higher cerebral activity on the heart, especially the ischemic heart. It is known that there are at least the six sensory-motor loops shown in **Figure 2** that compete with one another to control the heart rate. In a person at rest there is a natural "jitter," or variation in the lengths of the heartbeat intervals, that results from this neural competition.

Skinner and associates[31] initially proposed to measure the neural impact on the heart by assessing the "degrees of freedom" in the heartbeat series, since conventional heart rate variability algorithms did not seem to work very well as a predictor of VF in our pig model. The degrees of freedom calculated from the heartbeat series, if they could be measured, would indicate how many of the different neural generators were contributing to the control of the heartbeats at any one moment.

We encountered several problems, however:

- Heartbeats are not randomly distributed around a mean (as is required for the use of measurement algorithms based on the linear stochastic model, eg, the mean, the standard deviation, the power spectrum, etc)
- The data do not remain stationary for very long, as is also required by linear stochastic algorithms as well as by most nonlinear ones
- Long data segments are required for most algorithms.

Applying nonlinear dynamics to assess heartbeat

A nonlinear algorithm, the point correlation dimension (PD2i), was finally developed[31] that did not require either random variation or stationary data yet did accurately express the degrees of freedom for various short segments of test data that had different known degrees of freedom. Skinner et al then tested this algorithm in our conscious pig model of heart attack.[31] If the left anterior descending coronary artery is closed 90%, then half of the unadapted (stressed) pigs will manifest VF within 24 hours and the other half will not (ie, they can be the controls). High-resolution digitization rates (> 500 Hz) were required to prevent discretization error, as the PD2i is a nonlinear algorithm and thus is sensitive to noise. We observed that the pigs that went into VF after 90% occlusion (pulsed-Doppler flow) had a low time-dependent excursion of the PD2i of the heartbeats that could predict the outcome before it happened. Those pigs that would not manifest VF were also accurately predicted. That is, with two common statistical tests of event predictability we found the PD2i to have a sensitivity of 100% and a specificity of 100%—a black-and-white result.[31]

We then tested the nonlinear PD2i algorithm in a retrospective clinical study of human subjects.[32] We studied 24-hour electrocardiographic recordings (analog Holter tapes, digitized at 500 Hz) in which the patient had manifested VF on the day of the recording. Control tapes were found that were matched to the VF subjects on important clinical variables: number and degree of coronary artery narrowings, degree and type of cardiac arrhythmias (ie, nonsustained ventricular tachycardia), low ejection fraction, etc. The only difference was that the controls did not manifest VF for at least the 3 years of follow-up after their Holter tape recording. The results were the same as for the pig model—the VF and non-VF patients were predicted by the PD2i of the heartbeat intervals with a sensitivity of 100% and a specificity of 100%.[32]

Only a few tapes were rejected from study because of overly high arrhythmia rates. Arrhythmias of the usual types encountered in high-risk subjects were well tolerated,[32] as the PD2i algorithm internally rejects analysis of such aberrant beats. Tolerance of small amounts of continuous noise in the data (± 5 integers) was designed into the algorithm by setting slopes in the correlation integral less than 0.5 to 0.

Figure 3 presents an example of the "jitter" in the heartbeat (R-R) intervals and its corresponding "degrees of freedom" (PD2i) for three randomly selected 15-minute segments (A, B, and C in the figure) taken from a 24-hour Holter tape. This recording is from a patient who had manifested VF just after the C segment. It is clear that there are low excursions of PD2i values in time (asterisks in figure) throughout all of the segments. Excursions of PD2i values to levels this low never occurred in patients who did not manifest VF within the 3 years of follow-up—another black-and-white result.[32]

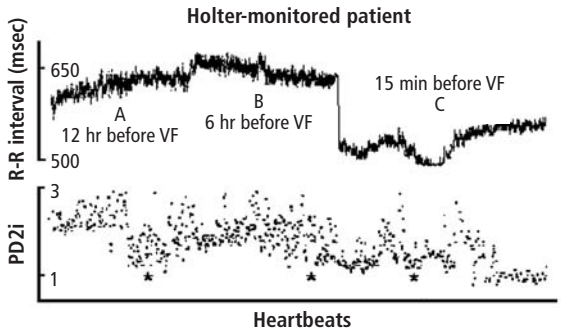

FIGURE 3. The R-R intervals (top panel) and corresponding PD2i series (bottom panel) of heartbeats in a patient with ventricular fibrillation (VF). Reprinted from reference 32, copyright 1993, with permission from Elsevier.

CONCLUSIONS AND FUTURE DIRECTIONS

Future studies of the brain-heart axis involved in VF initiation may lead to important insights into consciousness itself, especially those studies related to the selective attention and complex perception that are involved in anxiety and psychosocial stress. The study of neocortical gamma activity is an important lead in this direction. Until these insights come, however, the application of nonlinear dynamics to assess heartbeats, as with the PD2i algorithm, appears to constitute a new clinical paradigm in which to determine the impact of the brain on the heart, especially the heart at risk of VF. Salutary molecules released during particular brain states, such as REM sleep, may become the basis for important new cardiovascular drugs to treat lethal arrhythmogenesis, the ischemic myocardium, or both. Furthermore, the state-dependent release of natural biomolecules may be a new paradigm for the discovery of important new drugs. See the next article in this supplement for a detailed review of these new paradigms.

After examining all of the neuroanatomic, neurochemical, neurophysiologic, and neurobehavioral correlates of the sensory and autonomic regulation that occurs during defined defensive events, it now seems that Cannon was right: the cerebral defense system was the focus for the natural selection that gave us our big brains (especially the frontal cortex). At the same time, natural selection also gave us psychosocial stress and sudden cardiac death as unfortunate side effects of human intelligence.

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New paradigms in heart-brain medicine: Nonlinear physiology, state-dependent proteomics

Two pivotal studies using a conscious pig model of heart attack suggest new paradigms for the discovery of cardiac devices and drugs. The first study[1] showed that nonlinear analysis of heartbeat intervals, which are controlled by the nervous system, could predict with high sensitivity and specificity whether or not ventricular fibrillation (VF) would later occur following occlusion (90% reduction of blood flow by pulsed-Doppler recording) of the left anterior descending coronary artery. This predictive ability was later confirmed by retrospective data from humans exhibiting coronary artery narrowing and nonsustained ventricular tachycardia.[2] The second pivotal study[3] showed that the state-dependent release of a salutary molecule during rapid eye movement (REM) sleep would suppress arrhythmogenesis in the acutely infarcted heart. It is presumed that neurosecretion explains the salutary effect, as the latency is on the order of seconds.

This article reports previously patented data from additional investigations by me and my colleagues to further explore these two new paradigms in heart-brain medicine. First I review results from a prospective multicenter study of heartbeat analysis using a nonlinear algorithm to predict future arrhythmic death in emergency room patients. Then I discuss insights from state-dependent proteomics in the hibernating woodchuck and resulting efforts to isolate, identify, and synthesize an anti-infarction molecule from the woodchuck and test its efficacy using bioassay models.

NONLINEAR ANALYSIS OF HEARTBEAT INTERVALS

Background and methods

Heartbeat intervals were assessed using the PD2i nonlinear algorithm, details of which are provided in three published patents.[4–6] In brief, the algorithm produces a descriptor of deterministic chaos in the heartbeat, the "point correlation dimension" (PD2i) of interbeat intervals.[1,2] This nonlinear algorithm, unlike others in the field, does not require random data variation or stationary data.

Using a prospective, multicenter design, we tested the nonlinear PD2i algorithm in 400 patients presenting in the emergency room with chest pain. All patients were determined to be at high cardiac risk (> 7% probability of acute myocardial infarction [MI]) by the protocol developed by Lee et al[7] to rule out low-risk patients. All patients had 15-minute electrocardiograms (ECGs) recorded, each of which was digitized at 1,000 Hz. Hinkle-Thaler criteria[8] for suddenness and unexpectedness of out-of-hospital death were used to adjudicate arrhythmic death (AD) during 1-year follow-up. This is the first preliminary report of our study results, which have been submitted for archival publication.[9]

Results

All-cause mortality at 1-year follow-up was 10.2%, with 7.6% of cases judged to be AD. Many of the cases of AD occurred in subjects without a history of MI or a hospital diagnosis of acute MI.

Nonlinear PD2i analysis of the heartbeat intervals recorded in the emergency room accurately predicted patients who later died of arrhythmic death (AD, documented VF, or fulfillment of the Hinkle-Thaler criteria):

- For predicting AD at 30 days, the algorithm had a sensitivity of 100%, a specificity of 56%, and a relative-risk statistic >13.5 ($P \leq .001$)
- For predicting AD at 360 days, the algorithm had a sensitivity of 95%, a specificity of 57%, and a relative-risk statistic >22.8 ($P \leq .001$).

Figure 1 shows the R-R intervals and corresponding PD2i values for 18 AD patients who died suddenly and 18 matched controls who had an acute MI but who survived through at least the 1-year follow-up period. It is readily apparent that all of the AD subjects had time-dependent PD2i excursions and that

* Dr. Skinner reported that his employer, Vicor Technologies, holds patents for the nonlinear PD2i algorithm discussed in this article and has applied for patents on molecules discovered with the state-dependent proteomics method.

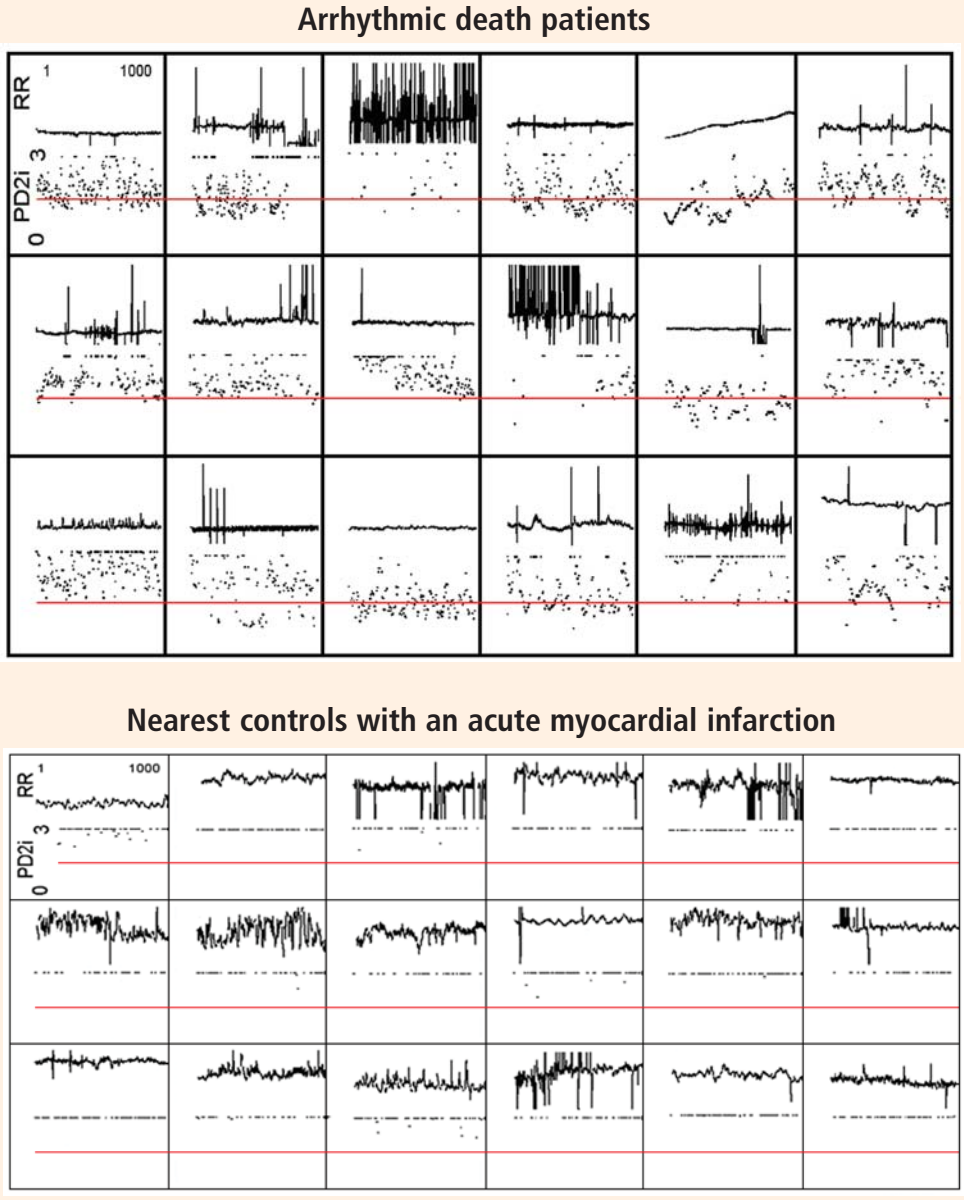

FIGURE 1. R-R intervals and corresponding PD2i values for 18 arrhythmic death (AD) patients and 18 control patients with acute myocardial infarction (MI) in a prospective emergency room study of patients with chest pain.[9] The AD patients all exhibited low-dimensional excursions of PD2i values, with most values less than 3.0. The acute MI controls did not manifest AD over 1 year of follow-up and did not exhibit low PD2i excursions. Red lines indicate a PD2i of 1.4, which served as the best separator between AD patients and controls.

the controls did not. Most of the PD2i values in the AD patients were less than 3.0, whereas most of these values in the controls with acute MI were greater than this level (shown on the line at 3 in **Figure 1**). The best separator between the two groups, as in our previous retrospective study,[2] turned out to be a PD2i value less than or equal to 1.4 (red lines in **Figure 1**).

The relative-risk statistic is thought to be the best measure for prospective clinical studies, as it emphasizes the ratio of true-positive predictions (which physicians want to make) to false-negative predictions (which physicians never want to make). **Table 1** presents the relative-risk statistics for the PD2i measure of heartbeat intervals compared with those of other algorithms previously proposed as predictors of AD. As shown in the table, the PD2i has a highly statistically significant superiority in predictive ability relative to the other algorithms across all patient subgroups. The comparative measures include other nonlinear algorithms (DFA, ApEn, 1/f Slope), all of which require stationary data, and the more common linear ones based on the stochastic model (LF/HF power, LF(ln)

power, MNN, and SDNN), all of which require stationary data *and* random variation (see **Table 1** for expansions of algorithm abbreviations).

Figure 2 depicts the PD2i values of heartbeat intervals in relation to refractoriness, as expressed by T waves, in three patients who manifested AD at various times following ECG recordings. In **Figure 2A**, the patient went into documented VF within minutes after the ECG. At the right are shown three samples of five successive heartbeats in which the large R waves and their preceding PQ intervals are aligned. There is an apparent lability (L) in the T waves throughout the period of recording. In **Figure 2B**, the patient did not manifest AD until 2 days after the ECG. Lability of the T waves did not begin until the PD2i transiently descended to the vicinity of 1.4 (horizontal line). In **Figure 2C**, the patient did not manifest AD until 2 weeks after the ECG. Note that there is no T-wave lability in this patient yet there are still PD2i excursions below 1.4 that predict the subsequent AD. These results show that the PD2i values are not related to T-wave lability per se, but it can appear this way in some patients (eg, **Figure 2B**).

TABLE 1
Relative-risk statistics for arrhythmic death at 1 year for various linear and nonlinear algorithms applied to the same prospective data set

	Patient subgroups			
Algorithm	**AMI**	**Non-AMI**	**Post-MI**	**Non-post-MI**
PD2i	> 7.39*	> 12.17*	> 4.51*	> 16.85*
DFA	0.70	0.44	0.63	0.48
1/f Slope	1.67	0.56	0.87	0.90
ApEn	0.50	1.44	0.00	0.72
SDNN	0.68	1.75	0.83	1.34
MNN	1.94	> 20.82*	3.00	> 3.61†
LF/HF	1.08	0.66	2.52	0.61
LF(ln)	1.08	> 5.13†	0.73	2.09

* $P < .01$, Fisher's exact test

† $P < .05$, Fisher's exact test

AMI = acute myocardial infarction; MI = myocardial infarction; PD2i = point correlation dimension; DFA = detrended fluctuation analysis; 1/f Slope = 1/f slope of power spectrum; ApEn = approximate entropy; SDNN = standard deviation of normal to normal beat intervals; MNN = mean of normal to normal beat intervals; LF/HF = low-frequency/high-frequency power spectrum; LF(ln) = normalized (natural logarithm) low-frequency power spectrum

Discussion

The PD2i of the heartbeats is believed to predict AD better than the other algorithms for two reasons:

- The data requirements of its underlying mathematical model are met by the physiologic data; ie, the PD2i does not require random data variation or data stationariness, as do the linear and nonlinear mathematical models of the comparator algorithms in **Table 1**
- The heartbeat PD2i measures something relevant to the underlying neurophysiology of heartbeat generation—namely, the degrees of freedom of neural controllers at work at any one moment in time.

The significance of the reduced number of degrees of freedom in the ischemic heart that predicts AD (VF) is not yet fully understood. That the maximum PD2i value in the heart at rest is 6.0 suggests a relationship to the six well-known afferent-efferent loops that compete with one another to control the heartbeats:

- Intrinsic cardiac neurons
- Baroreflex
- Respiratory sinus arrhythmia
- pH modulator
- Temperature controller
- The cerebral defense system (the only loop that receives primary sensory inputs as well as visceral afferents).

These same loops all contribute efferent fibers to the same descending cerebral pathway that has been identified in the pig model of heart attack to regulate the vulnerability of the ischemic heart to VF. That is, the heartbeat is regulated by the same integrated neural system that controls cardiac vulnerability to VF. Thus the heartbeat PD2i is a continuous physiologic measure of the cerebral impact on the heart that controls vulnerability to lethal arrhythmogenesis.

Of special interest is the finding that the PD2i of the R-R intervals in heart transplant recipients is exactly 1.0.[10] This observation is perhaps expected, as only the intrinsic cardiac nervous system remains intact. The mechano- and chemoreceptors located in this most peripheral neural loop enable the heartbeats to increase and decrease in rate (ie, have 1 degree of freedom), but the beat series lacks the more complex jitter caused by the competitive contributions of the other five afferent-efferent loops. Interestingly, at the time the cardiac nerves begin to regenerate back into the transplanted heart, the heartbeat PD2i begins to increase systematically.

The significance of the low-dimensional PD2i excursions (to ≤ 1.4, the separator that best divides the high-risk emergency room patients into those who are and are not at risk of AD) would seem at first

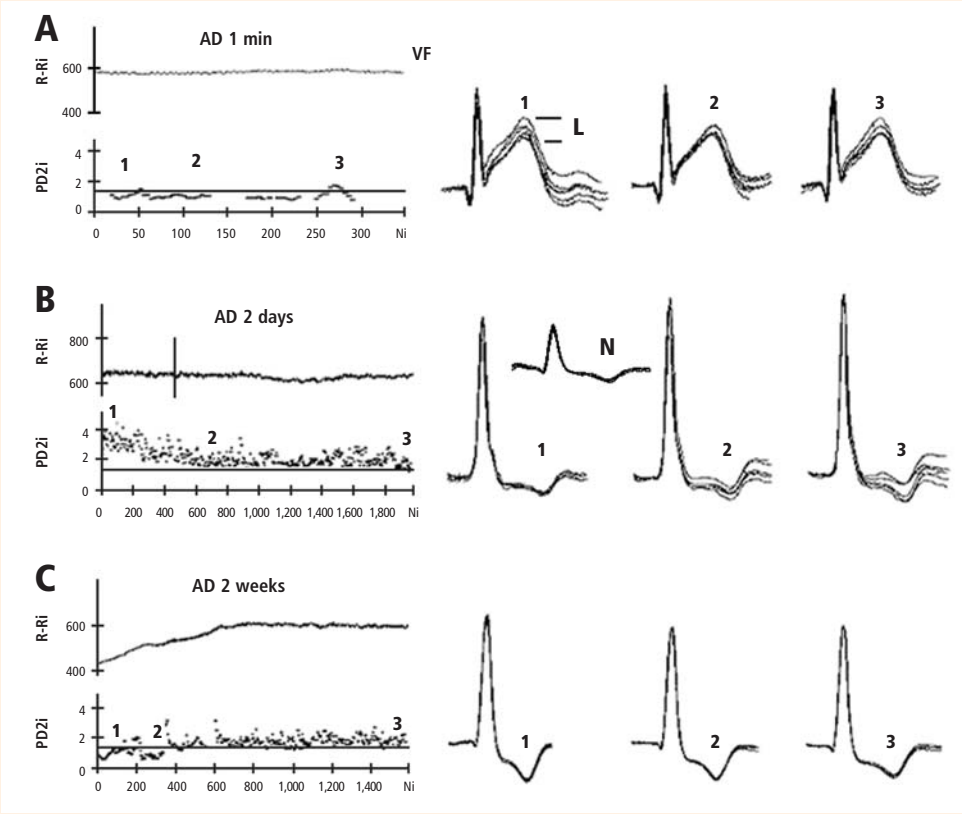

FIGURE 2. Heartbeat intervals (R-Ri), degrees of freedom (PD2i), and T-wave lability (L) in three patients who manifested arrhythmic death (AD) at different times after undergoing electrocardiographic recordings. T-wave lability (L) is indicated by the range of variation of the T waves when five successive heartbeats are superimposed; the superimposed traces were aligned by the PQ intervals preceding each R wave and were sampled at three different locations, indicated by the numbers (1, 2, 3) above the PD2i plots. "N" indicates the trace of a normal patient.

thought to be related to a turning off (inhibition) of many of the afferent-efferent loops. But the low value ($\leq$ 1.4) suggests that there would not be sufficient numbers of vital controllers that remain functional. Furthermore, it does not make sense that 1.4 is a fractional value.

Therefore, a collapse of the orthogonal dimensions of the variations would seem to be a better explanation, as all systems could still participate in heartbeat regulation and actually have a coordinated overall fractional-dimensional effect. So the best interpretation is that cooperation among the previously independent afferent-efferent loops along the brain-heart axis is what best explains the reduced dimensionality. This cooperation is like that of six ensemble musicians who start playing together in harmony instead of in disharmony (resonant cooperativity) or, alternately, like six musicians in an orchestra who follow the conductor (driven cooperativity).

Figure 2 demonstrates what this orchestrated neural harmony descending from the brain does to the heart at risk of VF. As noted above, this figure, which presents findings in three patients who suffered AD at various intervals after their ECG recordings, shows apparent lability in the T waves in two patients who manifested AD either immediately or within a few days. For the patient represented in **Figure 2B**, lability of the T waves did not begin until the PD2i temporally descended to the vicinity of 1.4 (horizontal line), a finding that indicates some relationship between PD2i and the lability of refractoriness. The patient represented in **Figure 2C**, however, did not manifest VF until 2 weeks after the ECG, and in this case there was no T-wave lability, yet there still were PD2i excursions below 1.4 that predicted the later AD. Perhaps the T-wave lability needed more time to develop in this patient's heart and that is why he did not manifest AD more imminently.

Verrier and associates have studied T-wave lability in patients by observing the T-wave difference in alternate beats (T-wave alternans, or TWA). They found that TWA also is a predictor of AD.[11] It would seem, however, that PD2i predicts AD at a time when TWA does not **(Figure 2C)**. This might be because TWA is a measure of a "bad heart" (lability of refractoriness) while PD2i is a measure of a "bad brain" (autonomic cooperativity) and it takes both a bad heart *and* a bad brain to generate the physiologic

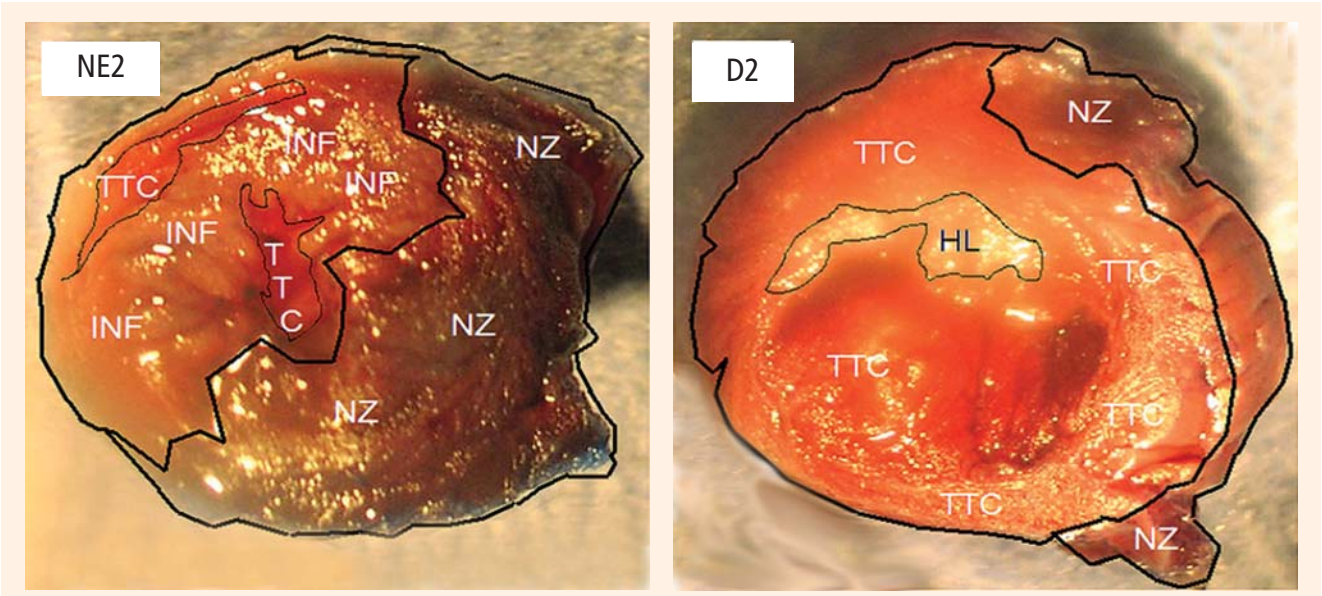

FIGURE 3. Effects of state-dependent molecular fraction with the anti-infarction molecule (D2) on the prevention of myocardial infarction in the rat. The anesthetized and respirated animal underwent 45-minute occlusion of its left anterior descending coronary artery (LAD), after which either the D2 molecule or its control was injected. After 24 hours the heart was sectioned and incubated in triphenyltetrazolium chloride (TTC). **Right panel:** The bright TTC stain indicates normal functioning of heart muscle; highlights are indicated by "HL"; "NZ" indicates nonischemic zones that were perfused during the LAD occlusion and injected later with a blue dye (after retying the LAD). **Left panel:** The control injection (NE2) resulted in unstained infarcted tissue (INF) with islands of TTC staining only at the epicardial and endocardial surfaces.

dynamics underlying initiation of the rotor that Winfree has modeled mathematically[12] and suggested to be the root cause of VF.

Future studies and clinical applications

New clinical studies will first look at the ability of heartbeat PD2i to predict the risk of sudden death in certain high-risk populations. Since only 19% to 21.4% of patients implanted with an automatic defibrillator ever have the device "fire" and shock their hearts out of VF,[13] it would seem that PD2i analysis of individuals referred for such surgery may, as a group, benefit from risk stratification to reduce the number of unnecessary implant surgeries. A large multicenter trial (VITAL) is under way to examine this possibility. Manufacturers of implantable cardioverter defibrillators should appreciate that large-scale and cost-effective screening with the PD2i technology may identify yet more candidates for implantation, as sudden cardiac death remains a major medical problem.

Early application of PD2i analysis is likely to target other high-risk populations. First among these are likely to be patients with ischemic and nonischemic cardiomyopathy, followed by patients with hypertrophic obstructrive cardiomyopathy and hypertensive cardiomyopathy, for which risk stratification is completely lacking. The possibility that such individuals could be successfully identified and directed toward life-saving treatment is exciting. Similarly, patients with the "channel-opathies"—long QT syndrome, Brugada syndrome, etc—would also seem to be good candidates for PD2i analysis.

Eventually, studies will be planned for evaluation of PD2i analysis in large populations at low risk, such as competitive school-aged or professional athletes. Such studies would require an enormous number of (typically young) subjects, but these are the populations in which a rare case of sudden death creates considerable parental concern and media interest. Lastly, studies may be done in individuals who are at moderate risk but may in the future, if the test becomes widely available, simply wish to be screened. Examples would include asymptomatic adults with hypertension or hyperlipidemia.

STATE-DEPENDENT PROTEOMICS

Background and rationale

For our second paradigmatic approach—use of state-dependent proteomics to identify an anti-infarction molecule—a research problem arose because REM sleep is so brief that one cannot expect to sample very many molecules during this period. A better model of REM sleep was sought. Consideration of hibernation

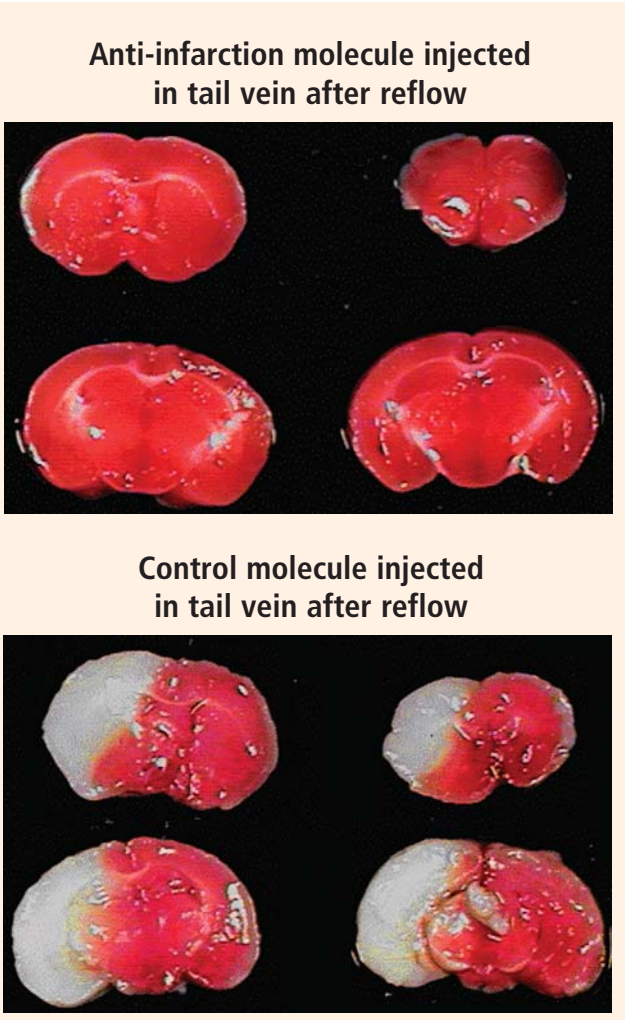

FIGURE 4. Effects on the mouse brain of injection of the isolated anti-infarction molecule (top panel) or its control (bottom panel) following 1-hour occlusion of the middle cerebral artery. Red triphenyltetrazolium chloride (TTC) staining indicates brain tissue that was viable 24 hours after injection. The large white zones in the control mouse indicate a typical cerebral infarction.

was a natural, as it has several of the physiologic features of REM sleep: muscle atonia, autonomic shutdown, and neurosecretion of regulatory proteins and peptides. For these reasons, we chose as our model the hibernating woodchuck; details of the patented state-dependent proteomic methods used to isolate and identify the endogenous molecules in the plasma of hibernating woodchucks are described in another patent (pending).[14]

The early substate of hibernation in the woodchuck was found to have the salutary effect on arrhythmogenesis. To find the proteins and peptides that are expressed in abundance during this substate, high-resolution two-dimensional gels (sodium dodecyl sulfate) and high-performance liquid chromatography were applied to plasma withdrawn during that state and its nearest control state (ie, midhibernation). Differential substate comparisons were used to isolate the salutary molecules. Tandem mass spectrometry fingerprinted the differential upregulated molecules, leading to their identification in worldwide databases. The peptide molecules and their pharmacophores were then synthesized and tested for efficacy in bioassay models.

Methods and results of bioassay models

Coronary artery occlusion in the rat was the first bioassay model. The hibernation-related molecules were indeed found to have a salutary effect on the ischemic heart—they prevented infarctions. An example of this is shown in **Figure 3** for control and experimental molecule subfractions.

The protocol was to occlude the left anterior descending coronary artery for 45 minutes, release the ligature (and electroconvert reperfusion VF, if it occurred), intravenously inject the experimental or control subfraction, and then 24 hours later examine staining of viable tissue in the distal myocardium (the stain triphenyltetrazolium chloride [TTC] is taken up only by functioning mitochondria in viable tissue).

Figure 3 provides a comparison of the widespread bright-red TTC staining in the section of the heart from the rat injected with the salutary molecule (right panel) with the very few such spots in the specimen from the rat injected with the control molecule (left panel).

In the wake of this evidence that the salutary molecule worked in the heart, as expected, it was then quickly tested in another model of ischemia—stroke in the mouse.

The mouse stroke model involved occlusion of the middle cerebral artery for 1 hour. After 1 hour of no blood flow (documented by 0 flow in the parietal cortex by laser Doppler recording), reflow was established (ie, to model the effect of clot-breaking drugs as used in a modern hospital). Immediately after reflow was established, the experimental or control molecule was injected into a tail vein of each of the mice. After recovery, 24 hours later, each animal's behavior was observed for limb paralysis and its brain was extracted and examined for TTC staining. More than 25% of the experimental animals had no histologic or behavioral signs of stroke, whereas severe paralysis and lack of TTC staining occurred in all of the controls.

With the mouse stroke bioassay, we easily isolated

the best peptide molecule, identified it, and then synthesized it. The synthesized molecule and many of its amino acid substrings all worked very well as anti-infarction compounds. With the best pharmacophore, the mean percentage of tissue saved was 77%. An example of a 100% result with that candidate drug is shown in **Figure 4**.

Additional compounds and future studies

Other hibernation-related drugs are still being discovered. For example, pregnant polar bears make proteins for their fetuses during hibernation, but they do not urinate. So what do they do with their blood urea? It was found that they recycle the blood urea back into amino acids.[14] A nonhibernating mammal (the rat) seems to have a small basal level of urea recycling. A hibernation-related molecule was isolated that can stimulate the recycling rate in this nonhibernating animal to a level that approaches the load-handling capability of normal kidney function.[14]

Additional hibernation-related molecules regulate the ongoing physiologies, and these, like the anti-infarction and urea-recycling molecules, may be the basis for discovery of important new drugs. So far, all of the molecules of interest found in hibernating species are also found in nonhibernating species. Regulatory molecules that readily come to mind include anticoagulants, soporifics, antihypertensives, and appetite suppressants, each of which would seem to regulate one or another of the physiologies of hibernation. This plethora of hibernation-related molecules appears to be a gold mine that has been stumbled upon in the quest to unravel the role of the brain in cardiovascular disorders.

CONCLUSION

Successful application of these two new paradigms suggests that heart-brain medicine holds a wealth of possibilities for discovery. The early theories of the pioneer in heart-brain relationships, Walter B. Cannon, have now been supported by neurophysiologic, neurochemical, and neurobehavioral studies, as presented in the preceding article in this supplement. The integration of these results within the framework of Cannon's early ideas about the evolution of the brain, using the new paradigmatic methods of state-dependent proteomics and nonlinear dynamics, presents meaningful new ways of developing devices and drugs in a new era.

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Subarachnoid hemorrhage: A model for heart-brain interactions

Research on the brain-heart connection has traditionally focused on intentionally altering the brain and observing the effect on the heart, but natural brain injury also confers a specific signal to the heart and causes observable effects. Subarachnoid hemorrhage serves as a good model for how brain injury affects the heart because it causes characteristic cardiac responses, including arrhythmias, contraction band necrosis, and ischemia-like changes.

This article summarizes research relating to the cardiac effects of subarachnoid hemorrhage, proposes a physiologic model of how brain injury leads to cardiac damage, and suggests future directions for research.

POSSIBLE BRAIN-HEART MODELS

Epilepsy. The seminal study of brain-heart interaction was done by Oppenheimer et al,[1] who found that stimulating the insula in patients with epilepsy produced cardiovascular changes. Other authors have investigated the phenomenon of sudden unexpected death in epilepsy for possible cardiac involvement, but evidence is lacking. In the absence of death, cardiac arrhythmias during epilepsy are uncommon, making this a poor model of heart-brain interaction.

Stroke. Patients with strokes, especially strokes involving the insula, tend to have cardiac conduction abnormalities. Eckardt et al[2] found that QT dispersion was present in 82.6% of patients who had a stroke involving the insula vs 40.7% of those without insular involvement. Because the origin of stroke is diverse (ie, lesions can exist in many areas of the brain), requiring evaluation of many patients to find an adequate study sample, stroke does not serve as a good human model for heart-brain interactions.

Traumatic brain injury is associated with cardiac injury, but because trauma usually involves systemic injury, a resultant cardiac abnormality rarely can be attributed directly to the brain. Traumatic brain injury serves as a good model, therefore, only when a specific injury can be induced in an animal model.

Neurodegenerative disease frequently involves autonomic dysfunction but causes a low incidence of cardiac problems. Typical autonomic sequelae of neurodegenerative diseases are hypotension and gastric abnormalites. Direct conduction or myocardial involvement is far less likely.

SUBARACHNOID HEMORRHAGE: A GOOD MODEL

Subarachnoid hemorrhage serves as a good model to study heart-brain interactions for two major reasons—its association with a high incidence of arrhythmias and a low prevalence of coronary artery disease. The occurrence of heart abnormalities in patients with subarachnoid hemorrhage has been recognized since the 1950s: much of the initial work centered on classifying the associated arrhythmias. More recently, Lanzino et al[3] reviewed five major retrospective studies involving interventions for nontraumatic subarachnoid hemorrhage and found that 91% of patients had evidence of cardiac abnormalities (atrial and ventricular arrhythmias) observed on electrocardiography (ECG). At the same time, in a prospective study involving 223 patients with subarachnoid hemorrhage, Tung et al[4] found a low prevalence of cardiac disease (5%), an ideal situation that limits confounding of the data.

CARDIAC ARRHYTHMIAS

Cardiac arrhythmias associated with subarachnoid hemorrhage are common and have been well classified by Sakr et al.[5] Sinus bradycardia occurs most frequently, at nearly twice the rate of sinus tachycardia. Multifocal ventricular tachycardia (torsades de pointes) is associated with a high mortality rate and is a feared complication of subarachnoid hemorrhage. The importance of torsades de pointes has been called into question recently. Although Machado et al,[6] in a retrospective review of the literature, found that tor-

* Dr. Provencio reported that he has no financial relationships that pose a potential conflict of interest with this article.

sades de pointes occurred in 5 of 1,139 patients (0.4%) with subarachnoid hemorrhage, they were unable to rule out confounding factors (ie, hypokalemia and hypomagnesemia) as the cause of the arrhythmia. In support of this, van den Bergh et al[7] found that QT intervals are actually shorter with lower serum magnesium levels (prolonged intervals are thought to be indicative of patients at risk for multifocal ventricular tachycardia).

Current research: Long-term cardiac outcome after subarachnoid hemorrhage

Current clinical research at the Cleveland Clinic involves assessing patients at the time of hospitalization for subarachnoid hemorrhage with a battery of tests, including computed tomography, angiography, prolonged inpatient Holter monitoring, and biochemical tests. Further comprehensive testing is also performed at 3 months and 6 months following discharge to discover whether cardiac changes persist past the acute stage, when most studies that evaluate patients with subarachnoid hemorrhage end. It is too early in the study to report results.

CARDIAC CHANGES THAT RESEMBLE ISCHEMIA

Certain ECG changes are referred to as ischemic changes, although no evidence exists that ischemia is actually present. The myocardial changes associated with subarachnoid hemorrhage do not appear to be due to coronary artery disease. Repolarization abnormalities are common in subarachnoid hemorrhage. Sakr et al[5] found that 83% of patients with subarachnoid hemorrhage developed repolarization abnormalities, with most being T-wave changes (39%) or the presence of U waves (26%). Deep, symmetric inverted T waves, usually without much ST-segment elevation or depression, are the typical abnormality. Prolonged QT intervals were found in 34% of patients. Left bundle branch block, which is sometimes considered a marker of acute, large-vessel ischemia, was present in only 2%.

Contraction band necrosis, a pathological pattern indicating that injury to the heart has occurred from muscles that have been energy-deprived from prolonged contraction, is a classic finding in subarachnoid hemorrhage. Transient low ejection fraction is the physiologic parameter that correlates with the pathologic finding. Despite the pattern of ECG changes commonly seen in patients with subarachnoid hemorrhage, until recently there was little evidence that they are independently associated with poor neurologic outcomes. Naidech and colleagues found in a retrospective analysis that cardiac abnormalities were associated with worsened outcome in subarachnoid hemorrhage patients.[8] Owing to the retrospective nature of the study, causal relationships could not be established.

At the Cleveland Clinic, we typically see approximately five patients each month with subarachnoid hemorrhage. We evaluate almost all of them with echocardiography, and typically find one patient each month with an ejection fraction in the range of 20% to 25%, which is much lower than we would expect in a relatively young, healthy population. On cardiac catheterization, which is performed infrequently in this population, the typical finding is normal coronary arteries. In almost all cases, the ejection fraction returns to almost normal in 1 week to 3 months.

In older patients, ECG changes occur with more severe events. In a retrospective study, Zaroff et al[9] identified 439 patients with subarachnoid hemorrhage, 58 of whom had ECG findings indicative of ischemia or myocardial infarction within 3 days of presentation and before surgery to correct an aneurysm. The mean age of patients with ECG findings was higher than that of patients without ECG abnormalities (62 vs 53 years, respectively), indicating that heart disease was more likely to be present and could contribute to a confounding effect. The Hunt and Hess grade—a clinical scale for evaluating subarachnoid hemorrhage, which ranges from 1 (mild headache, alert, and oriented) to 5 (comatose, signs of severe neurologic damage)—was also higher in patients with ECG abnormalities than in those without (3.1 vs 2.5, respectively). Surprisingly, the location of the aneurysm did not differ significantly between the two groups.

Based on the findings of Oppenheimer, we would expect that posterior communicating artery aneurysms, which originate between the middle cerebral artery and the posterior communicating artery which is in close proximity to the insular cortex and hypothalamus, would be more likely to be associated with ECG abnormalities.

The importance of cardiac troponin levels in subarachnoid hemorrhage is controversial. Some argue that high levels are proof that cardiac damage originates in the heart and not from the brain. Deibert et al[10] found that the troponin level is routinely elevated in patients with subarachnoid hemorrhage. Troponin levels do not correlate well with the amount of cardiac damage as measured by ejection fraction or contractility.[11] Among 39 patients with aneurysmal subarachnoid hemorrhage, the mean

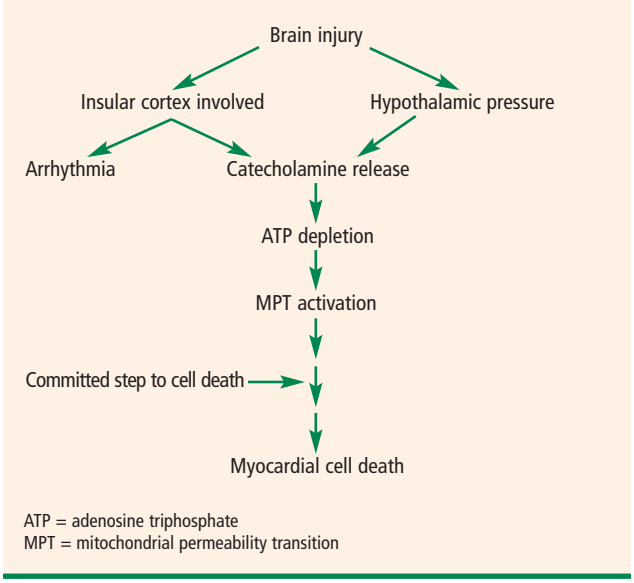

FIGURE 1. Schematic diagram of the possible mechanism of myocardial injury after acute brain injury. The theory suggests that catecholamine excess leads to myocardial death through a cascade of cellular damage. Insular cortical dysfunction likely contributes to arrhythmias. Adapted from reference 12.

ejection fraction was lower among patients who had elevated troponin I levels relative to normal troponin I levels (53% vs 72%), but the range of ejection fractions was wide (< 30% to > 80%) in patients with raised levels of troponin.[11]

HOW MIGHT SUBARACHNOID HEMORRHAGE LEAD TO CARDIAC DAMAGE?

A model of how subarachnoid hemorrhage can cause cardiac damage has been proposed.[12] Brain injury can damage the insula or cause hypothalamic pressure, either of which causes catecholamine release, either systemically or at the nerve terminal at the heart. The heart contracts, leading to adenosine triphosphate depletion, mitochondrial dysfunction, and myocardial cell death **(Figure 1)**.

Arrhythmias appear to be more likely to occur from insular involvement rather than generalized damage caused by hypothalamic pressure, although differentiating between effects caused by specific areas of aneurysm involvement requires further study.

PARASYMPATHETIC ACTIVITY AND INFLAMMATION ALSO INCREASE

The above model, however, is likely too simplistic. In the body, the sympathetic system and the parasympathetic system work as the yin and yang in controlling many bodily functions. Inflammation and cardiac control are importantly modulated by both the sympathetic and parasympathetic systems. I believe that the parasympathetic system may play an important role in cardiac injury from acute subarachnoid hemorrhage.

Evidence of parasympathetic dysfunction in subarachnoid hemorrhage is now becoming more abundant. Kawahara et al[13] measured heart rate variability in patients with an acute subarachnoid hemorrhage and determined that enhanced parasympathetic activity occurs acutely. This acute activation could potentially contribute to ECG abnormalities and cardiac injury.

The parasympathetic response may also affect the inflammatory response. The "neuroinflammatory reflex" (a term coined by Tracey[14]) is a vagally mediated phenomenon that relates to parasympathetic nervous system activation that suppresses inflammation. Thus, parasympathetic dysfunction resulting from subarachnoid hemorrhage could result in enhanced inflammation.

Previous theories (as depicted in **Figure 1**) speculate that norepinephrine is the sole cause of heart injury in acute brain injury, but this notion is doubtful. In fact, patients given large doses of intravenous norepinephrine for the treatment of sepsis or hypovolemic shock typically do not develop cardiomyopathy. Cardiomyopathies of the type seen in patients with subarachnoid hemorrhage only develop from an excess of catecholamines when exposure occurs over weeks or months, such as in patients with pheochromocytoma. The cardiac abnormalities seen in subarachnoid hemorrhage develop in a matter of hours, which is unheard of in other disease processes involving only sympathetic activation.

Evidence of inflammation at transplant

Data indicate that the cause of death in an organ donor has an impact on the organ recipient's course of transplantation. Tsai et al[15] compared outcomes among 251 transplant recipients who received hearts either from donors who died of atraumatic intracranial bleeding (group 1; n = 80) or from donors who died from other causes (group 2; n = 171). Mortality among transplant recipients was higher in group 1 (14%) than in group 2 (5%).

Yamani et al[16] performed cardiac biopsies 1 week after transplantation and then performed serial coronary intravascular ultrasonography over 1 year in 40 patients, half of whom received hearts from donors who died from intracerebral hemorrhage (ICH) and half from donors who died of trauma. At 1 week, heart biopsies from the ICH group had greater expression of

matrix metalloproteinases, enzymes that are responsible for matrix remodeling and associated with proinflammatory states, compared with biopsies from the trauma group. The injury in the ICH group translated into an increase in vasculopathy and myocardial fibrosis. At 1 year, hearts from donors who died of trauma had much less fibrosis and less progression of coronary vasculopathy (as measured by the change in maximal intimal thickness on intravascular ultrasonography) compared with hearts from donors who died from ICH, even after correcting for differences in age.

Yamani et al[17] also found that mRNA expression of angiotensin II type 1 receptor (AT1R), a receptor that becomes upregulated during acute inflammation, was elevated 4.7-fold in biopsies of transplanted hearts from donors who had ICH compared with those from donors who died of trauma. A 2.6-fold increase was also found in AT1R mRNA expression in spleen lymphocytes from donors who died of ICH compared with donors who died from trauma, indicating that systemic activation of inflammation occurred before transplantation. AT1R mRNA expression has also been found to be seven times greater in the cerebrospinal fluid of patients with subarachnoid hemorrhage than in a control population (unpublished data).

INSIGHTS FROM ANIMAL RESEARCH

Animal research of subarachnoid hemorrhage has traditionally been difficult because of a lack of suitable models. Recently, a successful mouse model was developed at the University of Virginia using injected blood from a genetically identical sibling into the cisterna magna following microsurgery to mimic a subarachnoid hemorrhage.[18] A study done by the same group found that suppressing brain inflammation by injecting an antibody to E-selectin (a necessary protein for inflammatory cell traffic into the brain) into the blood of mice diminished the inflammatory side effects of subarachnoid hemorrhage, especially a condition of delayed stroke after subarachnoid hemorrhage called vasospasm.[19] In preliminary data from our laboratory, we have found that another anti-inflammatory antibody can also diminish the cardiac pathology seen after subarachnoid hemorrhage (unpublished work).

These recent data have caused us to rethink the previous model of the mechanisms of cardiac injury from subarachnoid hemorrhage. We believe that parasympathetic dysfunction also plays an important role and, coupled with catecholamine release, allows unchecked inflammation, which leads to myocardial dysfunction and cell death **(Figure 2)**.

We hope that with better understanding of these two processes—parasympathetic dysfunction and catecholamine release—we will be able to mitigate harm to the heart. If agents can be found that can suppress sympathetic activation or heighten parasympathetic activation, it might be possible to improve outcomes in this patient population. This line of research will likely shape our future efforts to understand the system further and look for targets for clinical intervention.

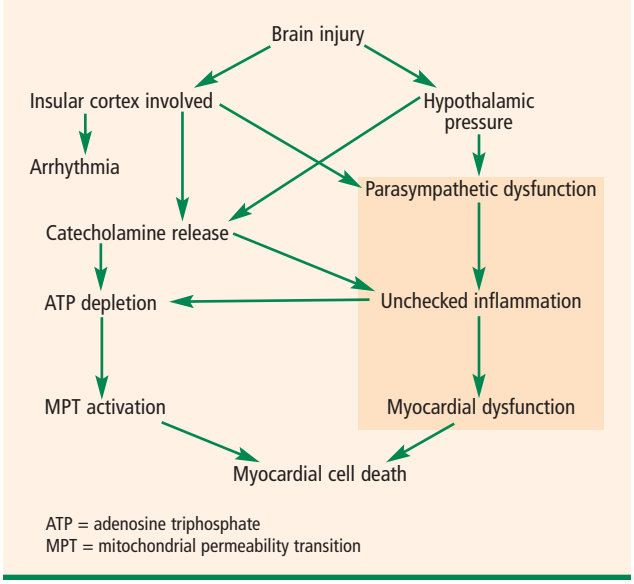

FIGURE 2. A new model of heart-brain interaction based on combined sympathetic hyperactivity and parasympathetic dysfunction (shaded area).

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Cardiac denervation in patients with Parkinson disease

Until relatively recently, Parkinson disease (PD) was viewed as mainly a movement disorder, resulting from loss of nigrostriatal dopamine terminals in the brain. Almost all patients with PD, however, have symptoms or signs of dysfunction of the autonomic nervous system,[1] such as constipation, urinary incontinence, orthostatic or postprandial light-headedness, heat or cold intolerance, and orthostatic hypotension. Recent studies focusing on the sympathetic noradrenergic component of the autonomic nervous system have supported the concept that PD is not only a movement disorder but also a form of dysautonomia. This review provides an update on the status of the innervation of the heart in PD.

SYMPATHETIC INNERVATION OF THE HEART

The autonomic nervous system has multiple components—enteric, parasympathetic cholinergic, sympathetic cholinergic, sympathetic noradrenergic, and adrenomedullary hormonal—and failure of a particular component produces characteristic clinical manifestations. In particular, sympathetic noradrenergic failure presents as orthostatic hypotension, which can cause or contribute to susceptibility to falls and other accidental trauma. Moreover, orthostatic hypotension is amenable to treatment, and administration of drugs for the movement disorder can worsen orthostatic tolerance and decrease blood pressure when the patient stands. Orthostatic hypotension occurs in about 40% of patients with PD and can be an early finding.[2]

Sympathetic nerves in the heart emanate from thoracic ganglia and course with the epicardial coronary arteries before diving into the myocardium. The fibers seem to develop along the coronary vascular trunk, since after cardiac transplantation, reinnervation begins in and often is confined to the anteroseptal base of the heart.

EVIDENCE FOR CARDIAC AND EXTRACARDIAC NORADRENERGIC DENERVATION IN PD

Since 1997, more than 40 neuroimaging studies have assessed the sympathetic innervation of the heart in PD. There has been universally consistent evidence for loss of sympathetic noradrenergic nerves. Several postmortem pathology studies demonstrating profoundly decreased tyrosine hydroxylase immunoreactivity in epicardial nerves or myocardial tissue have confirmed cardiac sympathetic denervation in PD.[3] In remarkable contrast, more than 15 neuroimaging studies have reported intact cardiac noradrenergic innervation in multiple system atrophy, a finding confirmed also by postmortem immunohistochemistry.

Cardiac denervation and orthostatic hypotension: Association but no causation

Although orthostatic hypotension in patients with parkinsonism has been thought to be a side effect of treatment with levodopa, the neurocirculatory abnormalities attending PD with orthostatic hypotension occur independently of levodopa treatment.[4]

Whereas cardiac sympathetic denervation, as indicated by 6-[^{18}F]fluorodopamine-derived radioactivity, seems to be virtually universal in PD patients who have neurogenic orthostatic hypotension, about one half of patients with PD who do not have orthostatic hypotension also have neuroimaging evidence for loss of cardiac noradrenergic innervation **(Figure 1)**. Therefore, cardiac noradrenergic denervation does not cause the orthostatic hypotension in PD.

Etiologic link with alpha-synucleinopathy

Patients with familial PD from mutation of the gene encoding alpha-synuclein or from triplication of the normal gene have low myocardial concentrations of 6-[^{18}F]fluorodopamine-derived radioactivity,[5,6] whereas

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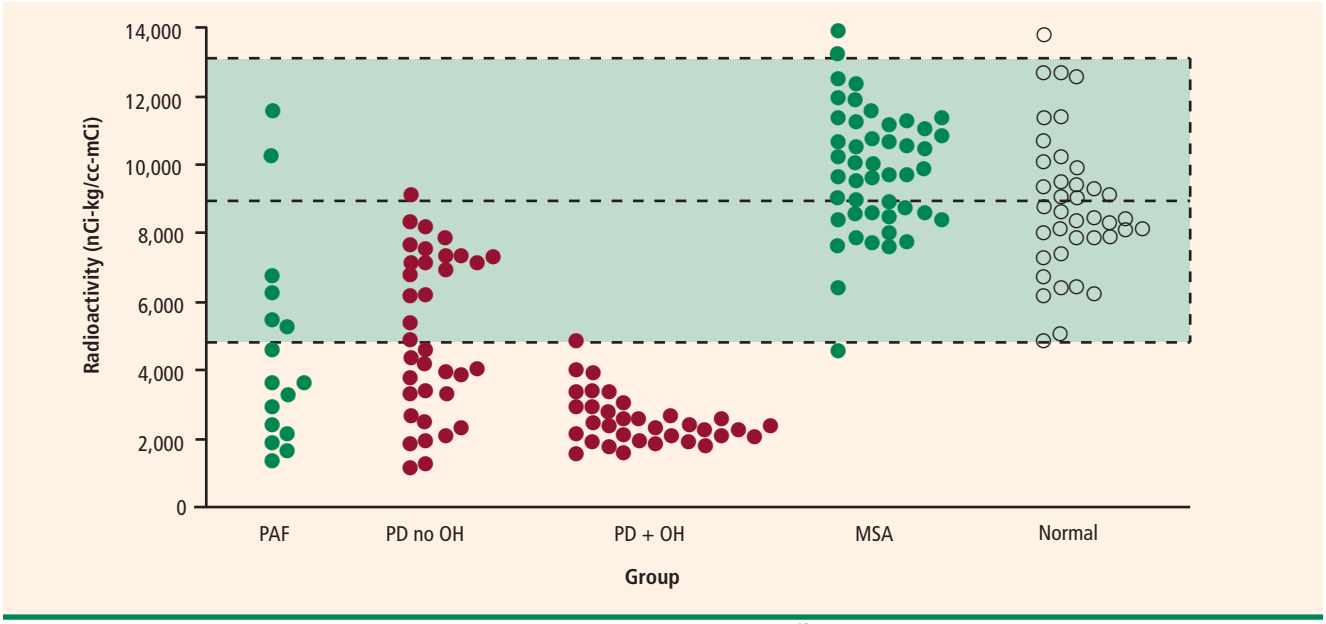

FIGURE 1. Individual values for interventricular septal myocardial concentrations of 6-[^{18}F]fluorodopamine-derived radioactivity in patients with pure autonomic failure (PAF) or multiple system atrophy (MSA) (green circles), patients with Parkinson disease (PD) with or without orthostatic hypotension (OH) (red circles), and normal volunteers (empty circles). Rectangles with dashed lines indicate normal mean value ± 2 standard deviations. Note that virtually all "PD + OH" patients have low radioactivity and that virtually all MSA patients have normal radioactivity.

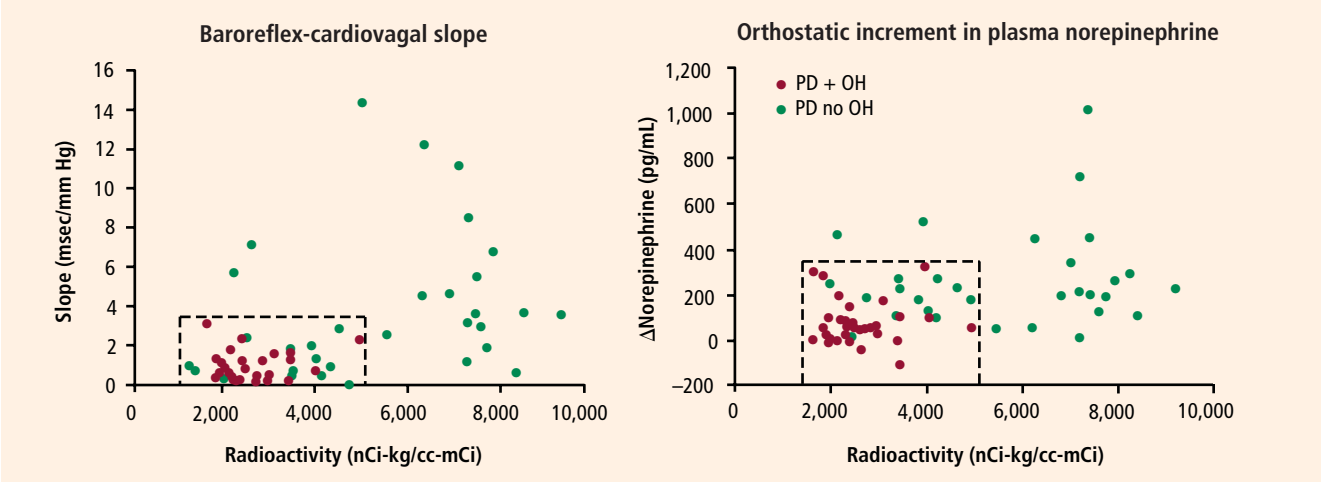

FIGURE 2. Individual values for baroreflex-cardiovagal slope and the orthostatic increment in plasma norepinephrine, expressed as functions of interventricular septal myocardial concentrations of 6-[^{18}F]fluorodopamine-derived radioactivity, in patients with Parkinson disease (PD) with (red circles) or without (green circles) orthostatic hypotension (OH). Note the low values for both baroreflex-cardiovagal slope and the orthostatic increment in plasma norepinephrine in patients with OH.

patients with familial PD from mutation of the gene encoding parkin have normal cardiac innervation,[7] indicating an etiologic link between cardiac sympathetic denervation and alpha-synucleinopathy.

Progression over years

The loss of cardiac innervation in PD progresses over years, in a pattern suggesting a "dying-back" pathogenetic sequence[8] that seems to be the mirror image of the sequence of partial reinnervation after cardiac transplantation.[9] Compared with patients who do not have orthostatic hypotension, PD patients with orthostatic hypotension have lower plasma levels of norepinephrine and of its main neuronal metabolite, dihydroxyphenylglycol, consistent with extracardiac noradrenergic denervation.

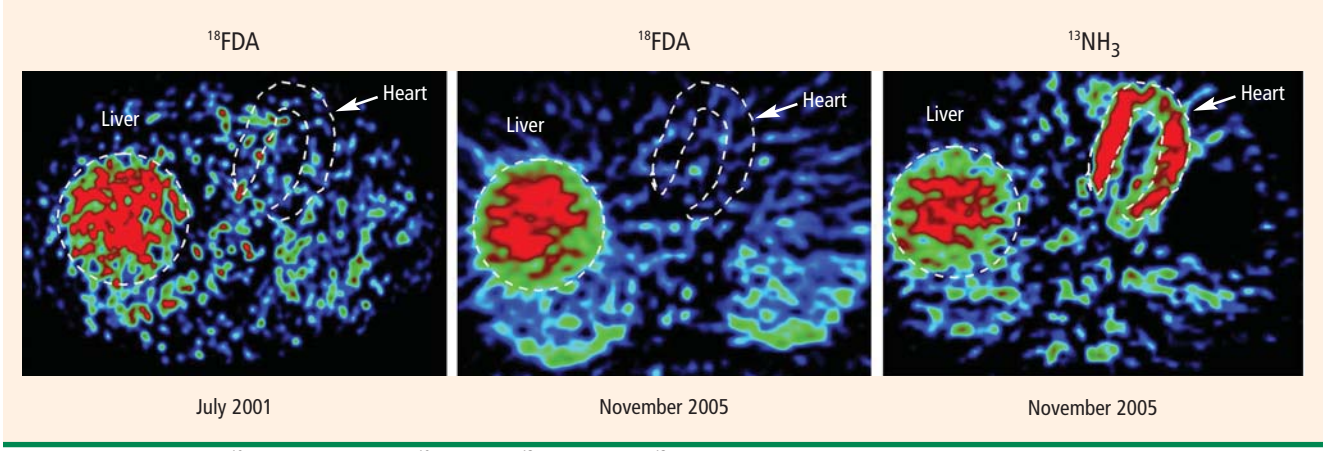

FIGURE 3. Thoracic 6-[^{18}F]fluorodopamine (^{18}FDA) and ^{13}N-ammonia ($^{13}NH_3$) images from July 2001 and November 2005 in a patient who first developed symptoms of Parkinson disease in about May 2005. Note the absence of left ventricular myocardial ^{18}FDA-derived radioactivity in both 2001 and 2005, indicating cardiac sympathetic denervation. Myocardial perfusion, as indicated by $^{13}NH_3$-derived radioactivity, was normal.

Extracardiac denervation

Patients with PD and orthostatic hypotension also have relatively low concentrations of 6-[^{18}F]fluorodopamine-derived radioactivity in the renal cortex, indicating noradrenergic denervation not only of the heart but also of the kidneys.[10]

Associations with baroreflex-cardiovagal and baroreflex-sympathoneural failure

The arterial baroreflex constitutes a classic, frequently studied neurocirculatory reflex. Distortion of stretch-sensitive cells in the walls of large arteries and the heart evokes reflexive increases in vagal outflow to the heart, resulting in bradycardia, and also decreased sympathetic outflows to the cardiovascular system, resulting in vasodilation and decreased force of contraction of the heart. One can estimate baroreflex-cardiovagal gain from the slope of the relationship between interbeat interval and systolic blood pressure during phase II of the Valsalva maneuver.[11] Baroreflex-sympathoneural gain can be assessed by the increment in plasma norepinephrine during orthostasis. In PD patients with orthostatic hypotension, both baroreflex-cardiovagal and baroreflex-sympathoneural gain are virtually universally very low and correlated with the myocardial concentration of 6-[^{18}F]fluorodopamine-derived radioactivity **(Figure 2)**. Thus, PD with orthostatic hypotension features not only cardiac noradrenergic denervation but also baroreflex-cardiovagal and baroreflex-sympathoneural failure.

The site or sites of central neural lesions producing baroreflex failure in PD remain largely unknown. Cells of the rostral ventrolateral medulla that contain phenylethanolamine-*N*-methyltransferase, the enzyme catalyzing conversion of norepinephrine to epinephrine (C1 cells), project to sympathetic preganglionic neurons, and PD patients have been reported to have a loss of C1 cells.[12] The dorsal motor nucleus of the vagus nerve can have cell loss or Lewy bodies in PD,[13,14] but the main source of vagal effer-

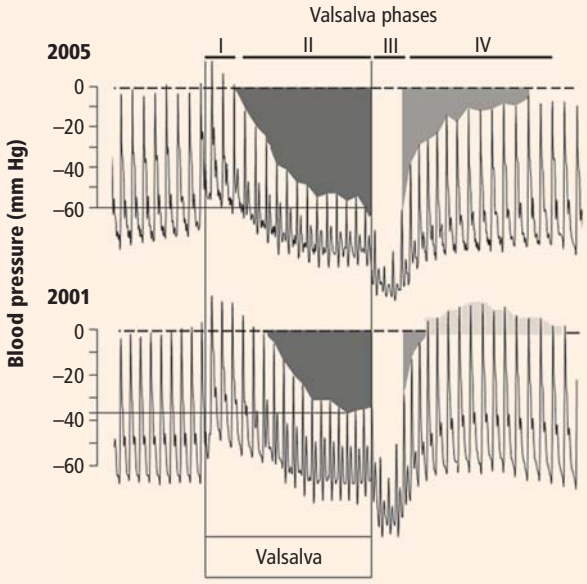

FIGURE 4. Beat-to-beat blood pressure responses to the Valsalva maneuver in November 2005 and July 2001 in the same patient as in Figure 3. In 2001, 4 years before the onset of PD, the patient had relatively little increase in heart rate for a given decrease in blood pressure during phase II of the Valsalva maneuver. In the 2005 recording, note the progressive decline in blood pressure during phase II and the absence of pressure overshoot and delayed return of pressure toward baseline in phase IV, consistent with declining baroreflex-sympathoneural function.

ents mediating reflexive bradycardia is the nucleus ambiguus, and the nucleus ambiguus does not appear to be involved.[15]

NEUROCARDIOLOGIC TESTING FOR DETECTING EARLY PD?

As indicated by the data in **Figure 2**, combined cardiac denervation and baroreflex hypofunction characterizes virtually all patients with PD and orthostatic hypotension. Others have reported this combination in de novo PD,[16,17] consistent with early involvement of peripheral autonomic or lower brainstem centers. Whether these abnormalities can actually *precede* symptomatic PD has been unknown. We recently evaluated a patient who had both cardiac noradrenergic denervation, detected by 6-[^{18}F]fluorodopamine positron emission tomography, and baroreflex-cardiovagal failure, detected by abnormal beat-to-beat blood pressure and heart rate responses to the Valsalva maneuver, 4 years before the onset of PD **(Figures 3 and 4)**. The findings in this potentially important case suggest that neurocardiologic testing may provide a biomarker for detecting presymptomatic or early PD.

SUMMARY

More than 40 neuroimaging studies have reported evidence for loss of sympathetic noradrenergic nerves in PD. Cardiac sympathetic denervation is virtually universal in patients with PD and neurogenic orthostatic hypotension. About one half of patients with PD who do not have orthostatic hypotension also have evidence for loss of noradrenergic innervation. The loss progresses over years, in a pattern suggesting "dying-back." Because patients with familial PD from mutation of the gene encoding alpha-synuclein or from triplication of the normal gene have low myocardial concentrations of 6-[^{18}F]fluorodopamine-derived radioactivity, cardiac sympathetic denervation seems linked etiologically with alpha-synucleinopathy. Baroreflex-cardiovagal failure and cardiac sympathetic denervation can occur before onset of the movement disorder, suggesting that neurocardiologic testing might provide a biomarker for detecting presymptomatic or early PD and for following responses to putative neuroprotective treatments.

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Aging and the brain renin-angiotensin system: Insights from studies in transgenic rats

Aging is characterized by increased systolic blood pressure resulting from activation of the sympathetic nervous system, reduced vagal activity, and reduced vascular distensibility. Imbalances in sympathetic and parasympathetic outflow to vessels, heart, kidney, and other organs contribute to the increase in systolic blood pressure as well as the associated impairment in the gain of the baroreceptor reflex. The reduced heart rate variability linked to increased mortality in patients with cardiovascular disorders could be attributed in part to impaired reflex function. Alterations in reflex control of autonomic outflow may also contribute to the constellation of cardiovascular and metabolic changes known to accompany hypertension, especially during aging. Understanding the factors that regulate the function of the brainstem areas controlling autonomic outflow during aging is critical as the elderly proportion of the population continues to increase.

PROTECTIVE EFFECTS OF RENIN-ANGIOTENSIN SYSTEM BLOCKADE DURING AGING

One factor with a close anatomic association with both the sympathetic and parasympathetic limbs of the autonomic nervous system is the renin-angiotensin system (RAS).[1] Abundant evidence of functional interactions between the RAS and the autonomic nervous system at sites in the brain and periphery provides a strong rationale for therapeutic interventions involving RAS blockade during aging. Indeed, RAS blockade extends lifespan and improves or prevents age-related deficits in cardiovascular and metabolic function in rats.[2,3] Multiple benefits are derived from long-term inhibition of angiotensin-converting enzyme (ACE) or angiotensin II type 1 (AT_1) receptor blockade in normotensive rats at doses that do not lower blood pressure at the outset of treatment in early adulthood: attenuation of the age-related decline in cognitive function, the increase in body weight gain, and the decline in mitochondrial function, as well as preservation of renal function.[2–8]

However, during aging there is a decrease in plasma renin activity and circulating angiotensin (Ang) peptide levels,[9–11] which raises questions about whether the beneficial actions of RAS blockade may signal a role of excess Ang II in tissue rather than plasma Ang II. It is well known that local tissue renin-angiotensin systems exist in a variety of tissues and organs, including the brain, kidney, heart, pancreas, and adrenal gland.[12,13] The brain cardiovascular nuclei influencing many of the age-related changes in the autonomic system exhibit high levels of AT_1 receptors and other RAS components.[14–17]

THE BRAIN RENIN-ANGIOTENSIN SYSTEM AND AGING IN THE RAT

To understand whether the brain RAS plays a role in the aging process with respect to metabolic and cardiovascular function, our recent studies compared Sprague-Dawley (SD) rats with transgenic rats that have a deficiency in brain angiotensinogen (ASrAogen rats). The ASrAogen transgenic rats have a glial fibrillary acidic protein (GFAP) promoter-linked angiotensinogen antisense sequence overexpressed in brain glia.[18] Since glia are the major source of angiotensinogen in the brain, this "knockdown" reduces cerebral levels of angiotensinogen to less than 10% of normal.[18,19] ASrAogen rats have slightly lower values of resting arterial pressure but otherwise exhibit similar circulating levels of leptin, insulin, and glucose in early adulthood.[20] SD rats demonstrate an increase in systolic blood pressure during aging that is associated with increased circulating insulin and leptin levels.[20] There is also activation of the intrarenal RAS in SD rats during aging, as demonstrated by increases in excretion of urinary Ang peptides, preceding the increase in systolic pressure in these animals.[10]

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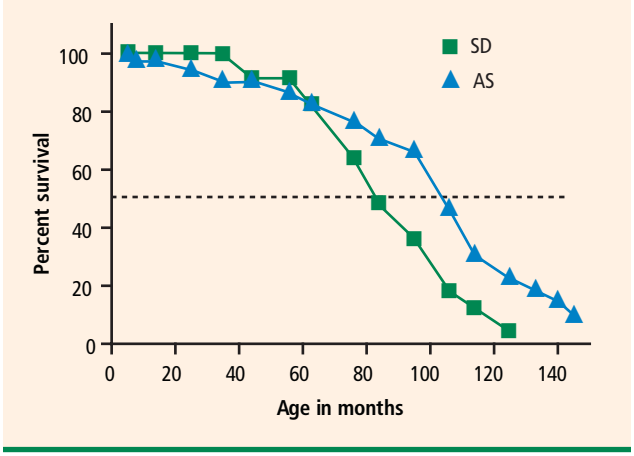


FIGURE 1. Comparative lifespans of Hannover Sprague-Dawley (SD) and ASrAogen transgenic (AS) rats.

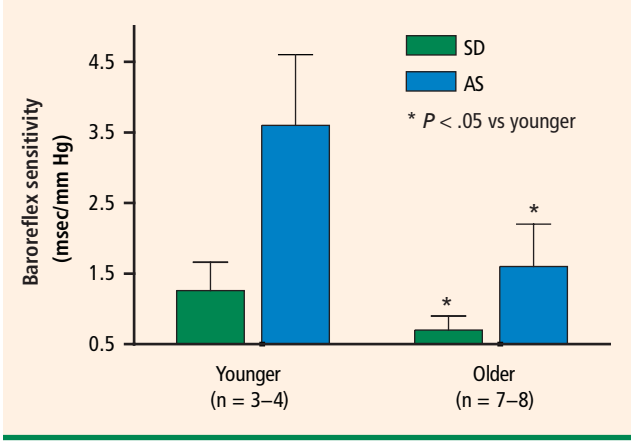


FIGURE 2. Baroreflex sensitivity in conscious Hannover Sprague-Dawley (SD) and ASrAogen (AS) transgenic rats at younger (~15 weeks) and older (~65 weeks) ages.

Renin-angiotensin system blockade prolongs survival

That the brain RAS plays a key role in these age-related changes is supported by the remarkable finding that ASrAogen rats do not exhibit increases in systolic pressure and maintain a lower body weight relative to SD rats over the same time span of aging.[20] Moreover, ASrAogen rats experience no increase in insulin or leptin during the aging process[20] and no activation of the intrarenal RAS, as evidenced by maintenance of a low level of excretion of Ang peptides.[10] Lifespan is also increased by approximately 30% in ASrAogen rats relative to the SD control strain **(Figure 1)**, to a length comparable to that seen in rats receiving lifetime treatment with an ACE inhibitor or an AT_1 receptor blocker begun in early adulthood.[2,3] These findings—that selective knockout of the glial angiotensinogen source has minimal effects at an early age but mitigates many age-related pathologies and mimics almost completely the effects of long-term RAS blockade in humans and rats—strongly argue that it is blockade of the brain RAS that makes a major contribution to the beneficial effects.

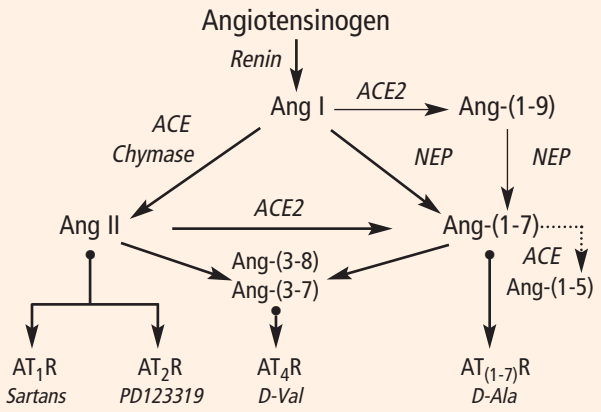
Ang II and Ang-(1-7) in baroreflex regulation

Impairment in the gain of the baroreflex to levels comparable to those seen in overt hypertension accompanies the increase in systolic pressure in older humans, which is similar to observations in the older SD rats in our studies **(Figure 2)**. At the level of the nucleus tractus solitarius (nTS) in the dorsal medulla oblongata, Ang II is known to provide tonic inhibition of the sensitivity of the baroreceptor reflex control of heart rate, a vagally mediated component of the reflex control of arterial pressure.[15,16] This effect of Ang II is counteracted within the nTS, in part, by Ang-(1-7) **(Figure 3)**. Ang-(1-7) is another active component of the RAS that opposes many of the actions of Ang II in the brain and systemic circulation, and increases in Ang-(1-7) contribute to the beneficial actions of ACE inhibition and AT_1 receptor blockade.[16,21–23] A deficit in endogenous Ang-(1-7) at the level of the nTS may be one mechanism for the impairment in the reflex in the SD rats during aging.[24]

Figure 4, adapted from data reported by Sakima et al,[24] demonstrates that in older SD rats, blockade of endogenous Ang-(1-7) by the receptor antagonist D-Ala^7-Ang-(1-7) does not inhibit the sensitivity of the baroreflex, in contrast to what is seen in younger SD rats. These data reveal that facilitation of the reflex by endogenous Ang-(1-7) is reduced or absent in older animals. On the other hand, there is no difference between older and younger rats in the response to blockade of endogenous Ang II by an AT_1 receptor antagonist **(Figure 4)**.

Whether these observations on blockade of Ang II and Ang-(1-7) hold true for older ASrAogen rats is not known, but there is a decline in reflex function in the transgenic animals at the older age **(Figure 2)**. However, note in **Figure 2** that the reflex sensitivity in the older ASrAogen rats, while lower than that in their younger counterparts, is comparable to that seen in the younger normotensive SD rats. Therefore, the functional impact of the decline in reflex sensitivity in the ASrAogen rats is hard to assess at this stage of our investigations.

As shown above, Ang-(1-7) and Ang II initiate opposing actions in baroreceptor reflex regulation of heart rate at the level of the nTS. If an imbalance in



Ang = angiotensin; ACE = angiotensin-converting enzyme; NEP = neprilysin
Sartans = drugs of the AT_1 receptor antagonist class (candesartan, irbesartan, losartan, olmesartan, valsartan)
D-Val = Ang IV receptor antagonist D-valinal-Ang IV
D-Ala = Ang-(1-7) receptor antagonist (D-Ala^7)-Ang-(1-7)

FIGURE 3. Diagram of renin-angiotensin system processing pathways and receptors for active peptides.

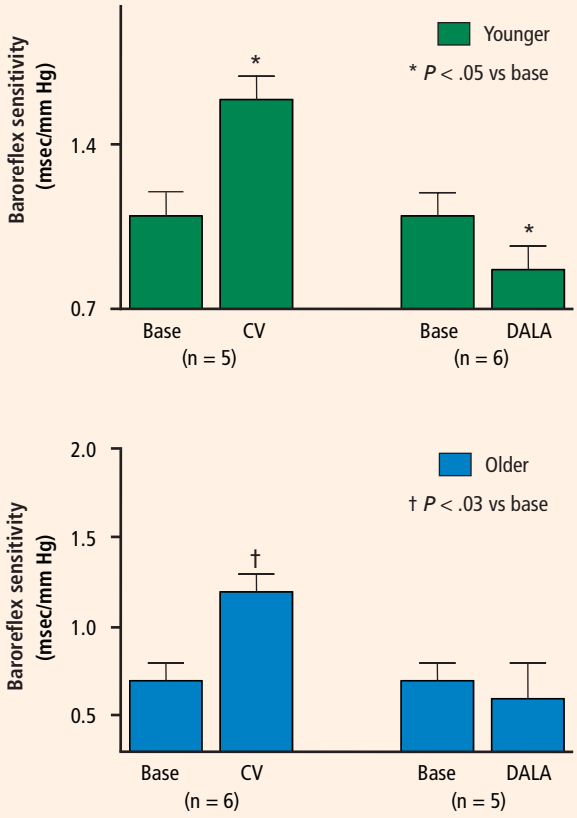


FIGURE 4. Baroreflex sensitivity in anesthetized Hannover Sprague-Dawley rats at younger (~15 weeks) and older (~70 weeks) ages before (Base) and after microinjection of either the AT_1 receptor antagonist candesartan (CV) or the Ang-(1-7) receptor antagonist (D-Ala^7)-Ang-(1-7) (DALA) into the nucleus tractus solitarius. Adapted from data published by Sakima et al.[24]

these two peptides contributes to the changes in reflex function seen during aging, then an understanding of the factors that regulate the levels of these peptides and their receptors during aging in brainstem areas controlling sympathetic outflow is of considerable importance. Little is known about the regulation of the local RAS within each tissue during aging. There may be overt elevation of components of the system, as reported for Ang II in the heart during aging,[11] consistent with observations on the intrarenal RAS.[10] Preliminary studies from our laboratory reveal that reductions in enzymes in the dorsal medulla oblongata, such as neprilysin and ACE2, may be responsible for reduced formation of Ang-(1-7) in older animals. The mRNA for neprilysin and ACE2 is lower in older SD and ASrAogen rats, respectively, than in younger animals of the same strains.[25] This may indicate that rather than frank elevation of the early precursor substrate or initial enzymes of the system, a shift in the processing favoring Ang II at the expense of Ang-(1-7) could underlie the development of age-related pathologies. This hypothesis is currently under investigation.

A LINK WITH AGING-RELATED METABOLIC CHANGES

The above studies focused on the age-related changes that occur in nTS pathways involved in autonomic function directed toward baroreflex function. It must be emphasized that these same brain areas are involved in control of appetite and body energy metabolism. A variety of peptide transmitters, including those identified as part of the gut-brain connection, as well as insulin and leptin, act at receptors on vagal sensory and motor fibers in the periphery as well as within the nTS and other dorsal medullary sites to influence food intake and satiety and contribute to regulation of autonomic outflow.[26–30] Of particular significance is the report that the forms of the leptin receptor and melanocortin receptor present in the dorsal medulla are similar to those in the hypothalamic centers known for regulation of temperature, ingestive behaviors, and energy metabolism.[30,31] Our early studies showed that the distribution of Ang II receptors in brainstem nuclei clearly overlapped the distribution of the entire vagal sensory and motor pathways, and was not confined to vagal fibers associated solely with the cardiopulmonary system.[16,32,33] As reviewed previously, the anatomic distribution pat-

tern suggested a widespread influence of the RAS on autonomic function.[1,34] Thus, we propose that the alterations in the brain RAS during the aging process, including changes in the balance of actions between Ang II and Ang-(1-7) in brain nuclei of the dorsal medulla, may provide a link between impairments in autonomic reflex function and the metabolic changes of aging.

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Contextual cardiology: What modern medicine can learn from ancient Hawaiian wisdom

I ka `olelo no ke ola (our words bring life)
I ka `olelo no ka make (our words cause death)
—2,000-year-old Hawaiian proverb

A Hawaiian *mo`olelo* (legend) speaks of the importance of loving connection, a concept that 2,000-year-old Hawaiian medicine considers to be the essence of health. To Hawaiian *kahuna* (healers), all illness takes place in the context of some form of disconnection, and all healing requires reconnection by "restorative justice" through which responsibility for the disconnection is taken and amends are made. To Hawaiians, health is an interpersonal matter, and the *pu`uwai* (heart) develops and functions in interaction with other hearts.[1] This power of heart-to-heart connection is illustrated in the Hawaiian legend of Naupaka.

THE LEGEND OF NAUPAKA

The Hawaiian princess Naupaka fell in love with Kaui, who was not of royal birth. Because marriage between a commoner and royalty was strictly *kapu* (forbidden), Naupaka and Kaui traveled together to a *heiau* (sacred temple) to see the *kahuna* (healer priest) to ask for special dispensation, but he feared breaking the *kapu*. "Your *aloha* (love) is stronger than any *kapu* and your *pu`uwai* (hearts) are joined forever, but I must banish you, Naupaka, to the sea and you, Kaui, to the mountains. Pray that your hearts will always beat as one."

As the couple knelt together to pray, rain began to fall and mixed with tears on their cheeks. As the lovers embraced for one final time, Naupaka took a plain white flower from behind her ear, tore it in half, and gave one half to Kaui. "We will always be of one heart, as two halves of the same whole," sobbed the princess.

The lovers separated, but to this day the tear-stained half blossom of the naupaka plant blooms at the same time on the same day—one half at the mountain and the other at the sea—and Hawaiians seeing these half flowers feel the sacred power of *aloha* (loving heart-to-heart connection) to transcend time and space.

ANCIENT *PU`UWAI*-OLOGISTS (CARDIOLOGISTS)

Far beyond metaphor, Hawaiians use the legend of Naupaka to teach about what they believe to be the literal connection that exists between loving *pu`uwai* (hearts). *Pu`uwai* translates as "lump" (*pu`u*) of water (*wai*), and ancient *kahuna* could be seen as some of the first cardiologists—"*pu`uwai*-ologists."

Hawaiian *kahuna* thought that the heart, like water, could be fouled and hardened by behaviors that interfered with the natural rhythm of the energy (*mana*) resonating from the lump of water in the center of our being (the *na`au*) that flows between all beings. Unlike Western medicine's "rock" logic that tends to focus on individual patients and the currently popular "statins and stents" approach to the heart as an isolated organ pumping inside an individual body, Polynesian oceanic "water" logic does not value concepts like separateness, boundaries, independence, and personal health. It sees well-being as existing between people, not within a person. As one *kahuna* put it, "One rock plus one rock is still two rocks, but water plus water is just more water."

THE INTERPERSONAL CARDIOVASCULAR SYSTEM

To Hawaiians, the cardiovascular "system" was just that, an interactive union of hearts and minds existing in *lokahi*, or infinite, loving, mutually dependent connection. They felt that healing was impossible without first finding the context not only of the illness but also of the strengths that could lead to a return to health. Treatment was a process of looking for the place where a disconnection between hearts had occurred or where hearts had begun to beat with-

* Dr. Pearsall reported that he has no financial relationships that pose a potential conflict of interest with this article.

out synchronization with other hearts, diagnosing how and why the disconnection had occurred, and then working to reestablish loving connections. Any use of plants or procedures took place only in the context of a system, and treatments were never prescribed after assessing only the individual.

Western medicine neglects interdependence

While acknowledging that social support systems are important to health, modern medicine has continued Western society's emphasis on independence, self-esteem, personal power, and assertive self-representation. Even when modern medicine does acknowledge the importance of social connection, it is often from the individual point of view that it is "good for the individual's heart" to have a "social support system." The idea of a vibrant interdependent context of interactive hearts and how that system might impact the cardiovascular system either receives little attention, is seen as "touchy-feely" pseudoscience, or, at best, is viewed as secondary to the individual heart in an individual's body.*

With some notable exceptions, most of our approaches to the diagnosis and treatment of heart disease and other conditions still focus on "what's within the person" more than "what's within the relationship." Every cardiologist knows the research showing that if you want to predict how long a patient will live and you don't know anything about her genes, family history, diet, or exercise, you should at least find out about the nature of her social relationships.

A contextual cardiology

Data from psychoneuroimmunology, cardiac psychology, and other fields have demonstrated that strong social relationships strengthen our immune system, extend our life more than smoking cessation does, speed recovery from surgery, and reduce the risks of the anxiety and depression that make us more vulnerable to disease.[2] *Contextual* cardiology asks if our daily practice of cardiology reflects the relevance of these data to the interactive system in which two or more hearts exist.† It asks whether our evaluation of cardiovascular systems looks at the interpersonal system in which hearts live and whether the energy emanating from the hearts of cardiologists and other health care professionals has an influence on the hearts of those who bring their hearts to us for healing.

INTERPERSONAL NEUROBIOLOGY

Recent findings in human development, neurobiology, and affective neuroscience have led to the formation of a new discipline, called *interpersonal neurobiology* (IN), that establishes a precedent for a field of contextual cardiology. Publications such as the *Journal of Integrative Neuroscience* regularly publish articles in this fascinating new field. For example, data from a Russian study recently published in this journal suggest that cardiac rhythmogenesis relates to changes in the efferent structure of the medulla oblongata and its interactions with hierarchical brain structures, and that rhythmogenesis is not limited to intercardiac rhythm generation and sympathetic and parasympathetic neural mediation.[3] The authors suggest that the intrinsic cardiac rhythm generator is life-sustaining during stages of deep inhibition (under anesthesia or during unconsciousness) and that the brain generator provides interactive behavioral and psychological heart adaptive reactions.

Is medicine losing its mind—or finding it?

In the United States, the impetus for IN came in the early 1990s from the research of psychiatrist Daniel J. Siegel. His work showed that what we refer to as "mind" emerges at the interface of interpersonal experience and the structure and function of the brain.[4] While the rapid expansion of research in the neurosciences upon which IN is based has led some critics to argue that medicine is "losing its mind" in favor of the brain and that medicine is returning to reductionism and "biologic determinism," the data from IN lead to the possibility that we are finally *finding* the mind. Research in IN suggests that our interactions with the environment, especially with other people, have profound influences on the structure and function of our brains. In other words, what we call "mind" is a much broader concept than we ever imagined, and it emerges from an interactive system of brains not only prenatally but throughout the entire life cycle.

Three fundamental hypotheses of IN

IN is organized around three fundamental hypotheses that continue to receive strong research support:

* For a discussion of the fields of neurocardiology, cardioendocrinology, and energy cardiology, see Pearsall P. The Heart's Code: Tapping the Wisdom and Power of Our Heart's Energy. New York, NY: Broadway Books; 1998.

† For reviews of data directly related to the concepts presented in this paper regarding "loving intimate connections," see Cohen S, Herbert TB. Health psychology: psychological factors and physical disease from the perspective of human psychoneuroimmunology. Annu Rev Psychol 1996; 47:113–142; and Waise LJ, Gallagher M. The Case for Marriage: Why Married People are Happier, Healthier, and Better Off Financially. New York, NY: Doubleday; 2000.

1) What we call "mind" is a manifestation of the flow of energy and information within the brain and between brains.
2) Development of the "mind" is continuous and determined by the interaction between internal neurophysiologic processes and our interactions with others in our environment.
3) The structure and function of the brain are determined by our experiences, especially the nature and quality of our interactions with others, that help shape our nervous system's genetically programmed predispositions.

Findings from IN have important implications for understanding human behavior, health, healing, and particularly cardiology. They offer evidence that how we interact with others directly influences a neurobiologic system that influences how we think and feel, which in turn impacts our overall physiologic well-being.

This "contextual" approach is not new. Studies in animals have long indicated that a major interactive factor, such as short episodes of maternal deprivation, can have pronounced negative neuroendocrinolgic effects on an animal's ability to cope with future stressful events.[5] Studies of human development have long documented that different patterns of child-parent interaction are associated with how children come to see and interpret their world and the kinds of physiologic responses that are associated with their "cognitive style."[6] The condition of "failure to thrive" has an established research history documenting important interpersonal dimensions of health.

IN prompts key questions about contextual cardiology

Using IN as a point of departure, a number of questions related to contextual cardiology emerge:

1) If the brain's structure and function are influenced by our interactions with our environment and the persons with whom we lead our lives (as supported by recent work in IN and affective neuroscience), is the heart similarly influenced?
2) To supplement the focus on what is going on within our patients, is it productive to look at what is also going on between our patients and the persons with whom they interact?
3) Should our understanding, diagnosis, and treatment of the cardiovascular system be done in the context of our patients' interpersonal interactions?
4) Are our patients' hearts literally affected by the hearts of those closest to them (including their physicians and other health care workers), and vice versa?
5) Should cardiologists and other cardiology-related health care professionals look beyond a patient's genetic, dietary, exercise, temperament/emotional profile, and personal health profile to the system in which the patient lives, loves, and works?
6) Can and should a thorough cardiology evaluation include analysis of the context of the patient's interpersonal system, and is it realistic to do so?
7) Is there research available that documents a significant impact of the quality of our relationships on our cardiovascular system?
8) Would the development of a field of contextual cardiology that studies the nature and quality of our relationships yield helpful new approaches to the research, prevention, and treatment of heart disease?

At a time when dealing with the various diseases of the heart requires as much valid, research-based information as possible and when IN and related approaches are yielding such important information about illness and health existing *between* rather than just *within*, it would seem that the answer to all of these questions is "yes."

HARD MARRIAGE, HARD HEART

One recent example of research done from a contextual cardiology perspective is a study conducted by University of Utah researchers from 2002 to 2005 involving 150 married couples aged 60 to 70 years with no history of heart disease.[7] The researchers analyzed 6-minute verbal interactions between the married couples about a topic on which the spouses disagreed, evaluating patterns of speech. Two days later, both spouses underwent computed tomography of the chest, and the findings illustrate what can be learned about hearts in the context of the interpersonal relationships in which they exist (ie, the "naupaka effect").

The results revealed different impacts on the cardiovascular system for men and women in response to their spouses' words:[7]

- The more hostile the wives' comments (eg, "You can be so stupid sometimes"), the greater the extent of calcification or hardening of their cardiovascular arteries. Particularly high levels of calcification were found in the wives who spoke in a hostile manner and who were interacting with husbands who responded with hostility.
- The more controlling the husbands' or wives' words (eg, "I'll do what you want to get you off

my back"), the greater the calcification observed in the husbands' hearts.

The researchers concluded that hostile words during marital disputes resulted in more calcification in women's hearts but not men's. Controlling words during disagreements led to calcification in men's hearts but not women's.

These findings come in the context of prior research showing that women tend to place greater value on interdependence and to be uncomfortable with factors that seem to threaten it, such as hostile behaviors, and that men place more value on independence and become stressed by behaviors that seem to challenge that orientation, such as controlling statements. In that context, is not surprising that "hard" marriages—characterized by verbal expressions that cut at the core of each gender's general cognitive and emotional style—could result in "hardened" hearts.[8] Whether these findings merit a new kind of "interpersonal verbal stress test" or perhaps a different kind of electrocardiography—"expression cardiography," in the form of a 6-minute verbal content analysis of a couple's discussion of a stressful topic to supplement the electrocardiogram—is a question asked by the proposed field of contextual cardiology.*

'HOT' AND 'COOL' INTERACTIVE STYLES

A truly contextual cardiology would have to take into account factors beyond gender-based predisposition to interactive styles. Many other factors potentially influence such styles, not the least of which is cultural. For example, in Hawaiian culture, the female orientation toward interdependence and the male orientation toward independence are not dominant patterns, and significant variations exist between the genders on these axes and within *`ohana* (families).

Placing heart health and disease in the context of "affective style" may be helpful. Affective style is the balance between our "approach" and "withdrawal" systems as they manifest within interpersonal systems. New research from affective neuroscience indicates that this balance exists at birth and can be read by electroencephalographic measures from the forehead region.[9]

Persons with certain brain-wave patterns measured as coming from the left forehead region consistently report more feelings and behaviors characteristic of the "approach" orientation—more happiness, less anxiety and shame, more ease with establishing and maintaining interpersonal relationships—than persons with these same waves coming from the right forehead area. "Cortical lefties" also tend to be significantly less intense ("cooler") in their reactions to stress than "cortical righties," who tend to be intense ("hot") in their reactions to stress. What happens when these patterns intersect in our most intimate relationships may have bearing on the cardiovascular system.

Research has consistently shown that a good marriage is one of the life factors that is strongly and consistently associated with happiness.[10]† Part of the "marital benefit effect" on health and happiness may derive from the possibility that happy people (cortical lefties)—who are more prone to cooler (less reactive) "approach"-style behaviors—are more appealing as dating partners and easier to live with as marital partners.[11] However, just being in a marriage—and thus benefiting from the "naupaka effect"—seems to offer a statistically significant buffer against illness and to elevate the happiness associated with good health.[12]‡

In keeping with this proposal of a contextual cardiology, it may be helpful to learn more about the impact of inherited "approach" vs "withdrawal" orientations and their associated cool/underreactive and hot/overreactive styles. It seems possible that these styles, particularly in the context of interpersonal relationships, could have a significant impact on the cardiovascular system. Whether busy physicians, whose hands are already full doing heart "pump maintenance," have the interest, time, or heart for considering such factors is another matter. It may be that we need a true systems orientation to cardiovascular health consisting of a team of several health care professionals from different disciplines working together to analyze the context in which our patients' hearts live.

* For a description of the process and findings related to content analysis of verbal expression (CAVE), see Gottshalk LA. Content Analysis of Verbal Behavior: New Findings and Clinical Applications. New York, NY: Lawrence Erlbaum Associates; 1995.

† However, whether married people are happier than people who never marry is not clear because unhappily married people are the unhappiest group of all and "bring down the marital average" of happiness. For a thorough analysis of the issue of marriage, health, and happiness, see DePaulo BM, Morris WL. Singles in society and science. Psychol Inq 2005; 16:57–83.

‡ While most of the research to date shows clear benefits of marriage for health and longevity, a recent longitudinal study failed to find any long-lasting benefits of marriage on self-reported well-being. This may be due to the "happiness set point" differences between left and right cortical orientations. See Lucas RE, Dyrenforth PS. Does the existence of social relationships matter for subjective well-being? In: Vohs KD, Finkel EJ, eds. Interpersonal Processes and Interpersonal Relationships: Two Halves, One Self. New York, NY: Guilford. In press.

SENTIMENT STYLES AND THE HEART

The research of psychologist John Gottman serves as another potential basis for a field of contextual cardiology.[13] Using extensive analysis of videotapes of marital couples' communication patterns (reviewed by Gladwell[14]), Gottman argues that most marital partners exist in one of two states within their relationship, with each state having different impacts on the spouses' cardiovascular systems.

The state that Gottman calls "positive sentiment override" (PSO) has salutary impact on the heart. The positive emotions felt by the spouse in this state seem to act as a buffer against the marriage-induced stressors that lead to the "flooding response" of accelerated heart rhythm and severe spikes in blood pressure. When his or her spouse does something bad, the partner in PSO says something like, "Oh, he/she is just in a crummy mood." In the "negative sentiment override" (NSO) state, a spouse draws and persists in lasting conclusions about his or her partner. Even if the spouse does something positive, it is seen as an action by a selfish person doing a rare nice thing, probably for an ulterior selfish motive. It may be that PSO relates to the cool cortical-leftie style and NSO to the hot cortical-rightie style, but when Gottman graphed and statistically analyzed sentiment override states, he found that they had significant impact on the marriage and the spouses' cardiovascular systems.

The sentiment styles identified by Gottman also result in differing marital patterns. "Validation marriages" involve partners who share a PSO orientation. In these marriages, spouses work calmly and cooperatively to solve their problems to mutual satisfaction. In "conflict-avoiding marriages," the partners seem well aware of "hot spots" in their interactions and their respective sentiment styles. They agree to disagree and rarely delve into the problem areas that they sense could cause their hearts to race and their blood pressures to rise. In "volatile marriages," the pattern with the most damaging consequences for the participants' cardiovascular and immune systems, conflicts constantly arise that erupt into passionate disputes reflected in severe and lasting heart rhythm changes, blood pressure elevations, and negative impacts on immunoefficiency.*

CONTEMPT AND DISGUST AS RISK FACTORS

Gottman also observed that contempt is one of the most dangerous emotional states in marriage and one that signals severe danger for marital viability and the spouses' cardiovascular health. In contrast to criticism, which is characterized by more specific and behavior-based nonpersonal complaints about a correctable behavior, contempt is a generalized state of discontentment accompanied by emotional disgust. Once contempt and disgust find their way into a marriage, the marriage and the hearts of those in it are in serious trouble. To ignore this "cardio-context" is as neglectful as not asking about a patient's diet or genetic background.

One of the healthiest responses spouses can learn for saving their marriage—and, to some extent, their hearts—is for both partners to avoid the devastating effects of disgust and contempt by being willing to blind themselves to the annoying flaws and failings we all bring to relationships. For example, research shows that the bigger the discrepancy between the more objective view that close friends may have of our partner and our own more favorable illusions about our partner's foibles, the greater the chance of a healthy relationship that protects and enhances our health and our partner's health in this reality-denying but forgiving union. Thus, when it comes to a healthy marriage, delusion and denial seem essential.[15]†

HEALTH IN CONTEXT: RESEARCH QUESTIONS FOR A CONTEXTUAL CARDIOLOGY

If we consider the above hypotheses and research in contextual cardiology, together with the basic assumptions of IN, several questions emerge that seem worthy of further investigation:

- Is what we call "heart" a manifestation of the flow of energy and information between the brain and the heart, as well as between multiple brains and hearts?
- Is the heart's development continuous and determined by the interaction between internal neurophysiologic processes and our interactions with others in our environment, particularly those with whom we interact most intimately and regularly?
- Is the structure and function of the heart determined in part by our experiences, especially the nature and quality of our interactions with others that help shape our cardiovascular system's genetically programmed predispositions?

* For a review of some of the research related to lasting, loving relationships, see Pearsall P. The Last Self-Help Book You'll Ever Need. Repress Your Anger, Think Negatively, Be a Good Blamer, and Throttle Your Inner Child. New York, NY: Basic Books; 2005.

† For the Hawaiian view of loving relationships, see reference 1.

For more than 2,000 years, Hawaiian medicine has answered "yes" to these questions. Continuing progress in cardiology may be promoted by considering this ancient wisdom and applying modern science to trying to answer these questions.

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Cardiocerebral resuscitation: The optimal approach to cardiac arrest

Cardiac arrest highlights one of the critical interactions between the heart and the brain, and it remains a leading cause of death in the United States, Canada, and Europe. This summit provides an opportunity to advocate cardiocerebral resuscitation as an alternative to traditional cardiopulmonary respiration (CPR) for out-of-hospital cardiac arrest. Because cardiocerebral resuscitation results in improved survival and cerebral function in patients with witnessed cardiac arrest with a shockable rhythm (the subgroup with the greatest chance of survival), it should replace CPR for out-of-hospital cardiac arrest.[1–4] CPR should be reserved for respiratory arrest.

This discussion will explore the rationale for abandoning traditional CPR for out-of-hospital cardiac arrest and explain what cardiocerebral resuscitation is and why it should replace CPR in this setting.

WHY DOES CPR FOR CARDIAC ARREST NEED TO BE REPLACED?

Past, present CPR guidelines flawed

Despite the development and periodic updating of guidelines for CPR and emergency cardiovascular care from the American Heart Association (AHA)[5] and the International Liaison Committee on Resuscitation (ILCOR),[6] survival rates for victims of out-of-hospital cardiac arrest are dismal and have remained essentially unchanged for decades.[7,8] An important reason for these continued poor outcomes is that both sets of guidelines, despite being updated in 2005, recommend an approach to out-of-hospital cardiac arrest that is far from optimal.

Different approaches required for cardiac and respiratory arrest

Specifically, both the AHA and ILCOR guidelines continue to advocate CPR for two different pathophysiologic conditions: primary cardiac arrest and cardiac arrest secondary to respiratory failure.[5,6] Thus, both sets of guidelines recommend mouth-to-mouth ventilations for all cardiac arrests. This approach has three major drawbacks:

- Most bystanders to a person who unexpectedly collapses are willing to activate emergency medical services (EMS) but are not willing to initiate rescue efforts because they do not want to perform mouth-to-mouth assisted ventilation.[9] Bystanders are more willing to perform chest-compression-only resuscitation for a person who unexpectedly collapses, an approach that all agree is dramatically better than doing nothing. (As it turns out, chest compression alone for cardiac arrest is as good as or better than the guideline-recommended approach of interrupting chest compressions for mouth-to-mouth ventilations; see below.)
- Interrupting chest compressions for ventilation during cardiac arrest decreases survival.[10,11]
- Positive pressure ventilation during CPR for cardiac arrest increases intrathoracic pressures, which decreases venous return to the thorax and subsequent perfusion of the heart and the brain.[12,13]

Any delay in chest compressions can be deleterious

The importance of uninterrupted chest compressions to cerebral function was forcefully brought home to me and my colleagues as we listened to a recording of a woman trying to resuscitate her husband. She asked, "Why is it that every time I press on his chest he opens his eyes, and every time I stop to breathe for him he goes back to sleep?"[3] Brain perfusion during resuscitation efforts for cardiac arrest is so marginal that any interruption in chest compressions, even for ventilations, has the potential of being deleterious.

CARDIOCEREBRAL RESUSCITATION ELIMINATES VENTILATION

In contrast to CPR, cardiocerebral resuscitation eliminates mouth-to-mouth ventilation for bystander-initiated resuscitation efforts, dramatically decreases the

* Dr. Ewy reported that he has no financial relationships that pose a potential conflict of interest with this article.

role of positive pressure ventilation by EMS responders, and emphasizes chest compressions prior to and immediately after a single shock for cardiac arrests not witnessed by EMS personnel.[2,3,14–18]

The evidence base

Bystander-initiated chest-compression-only resuscitation for witnessed unexpected collapse in adults (cardiac arrest) is based on extensive CPR research in swine. The University of Arizona Sarver Heart Center CPR Research Group found that chest-compression-only resuscitation for cardiac arrest in swine not only was dramatically better than no CPR but also was associated with dramatically better survival than CPR consisting of two ventilations before each 15 chest compressions,[19] the practice recommended in 2000 consensus guidelines from the AHA and ILCOR.[20]

In a human study, investigators from Japan found that among witnessed victims of out-of-hospital cardiac arrest who had a shockable rhythm upon the arrival of EMS personnel, chest-compression-only resuscitation resulted in better survival than did chest compressions plus mouth-to-mouth ventilation.[21]

Why guidelines slight chest compression alone

Unfortunately, the findings of these Japanese investigators were published only in abstract form at the time the 2005 AHA guidelines were considered. Therefore, chest-compression-only resuscitation by bystanders is recommended in these guidelines only "if the individual is unwilling or unable" to perform chest compression and mouth-to-mouth ventilation.[5,20]

Another putative reason the guidelines continue to recommend both ventilation and chest compression is that patients with respiratory arrest do need ventilation and might not receive ventilation if chest-compression-only resuscitation were advocated. However, in Tucson, Arizona, where I practice, there is approximately one death from drowning for every 100 cardiac arrests. This shows that any desire to avoid "complicating the message" about resuscitation for the sake of respiratory arrest victims is actually jeopardizing a vastly larger group of cardiac arrest victims.

What the public should be taught about resuscitation

The message that needs to be promulgated is twofold but nevertheless simple: cardiocerebral resuscitation is for cardiac arrest, while CPR with ventilation is recommended for respiratory arrest. The lay public should be taught that an unexpected collapse in an adult is, in all likelihood, a cardiac arrest, to be differentiated from obvious respiratory arrest, such as choking or drowning, where assisted ventilations may be appropriate.

CORONARY PERFUSION PRESSURE IS ESSENTIAL DURING PROLONGED CARDIAC ARREST

In the absence of early defibrillation, survival beyond the first 5 minutes of ventricular fibrillation (VF) arrest is predominantly dependent on adequate coronary and cerebral perfusion pressures, both of which are generated by chest compressions. It is well established that in the absence of early defibrillation or bystander-initiated resuscitation efforts, survival is rare.

The Sarver Heart Center CPR Research Group has now published six experimental studies that included a total of 169 swine, all of which showed that with prolonged cardiac arrest due to VF, survival is the same with chest-compression-only resuscitation as with ideal CPR—ie, CPR in which chest compressions were interrupted for only 4 seconds for respiration.[3] After the 2000 AHA/ILCOR guidelines were published, Assar et al[22] found that when single lay rescuers perform CPR, they interrupt chest compressions for an average of 16 seconds to deliver the two recommended mouth-to-mouth ventilations. Subsequently, our CPR Research Group compared survival in a realistic porcine model of out-of-hospital cardiac arrest using 16-second interruptions for the two recommended ventilations between each 15 chest compressions, and we found that 24-hour survival was only 13% in this group, compared with greater than 70% survival in all of our studies of chest-compression-only resuscitation prior to the simulated arrival of EMS personnel.[19]

The decades-old recommendation of two ventilations before each 15 chest compressions has recently been acknowledged not to be optimal, as this ratio was changed from 2:15 to 2:30 in the 2005 AHA guidelines[5] to increase the recommended number of chest compressions. However, this change did not address the major problem, which is bystanders' reluctance to initiate resuscitation if ventilation is involved, regardless of the ventilations-to-compressions ratio. The greatest impediment to the initiation of bystander resuscitation is the public's aversion to and/or the complicated nature of performing mouth-to-mouth resuscitation.

WHAT IS THE ROLE OF GASPING OR AGONAL RESPIRATIONS?

When a person collapses with VF, or if VF is induced in an animal model, gasping is present in a significant number of individuals and animals. This abnormal breathing, which varies in duration, can be either for-

tunate or unfortunate. When chest compressions are promptly initiated, gasping is fortunate in that the subject is likely to continue to gasp and provide self-ventilation (negative intrathoracic pressure). However, gasping also may be unfortunate in that most laypersons interpret it as an indication that the subject is still breathing, causing them not to initiate bystander resuscitation or call for EMS personnel as soon as they should. Education will be essential to ensure prompt initiation of bystander chest compressions in patients who gasp with cardiac arrest, as well as to ensure that chest compressions are not stopped because of continued gasping.

IMPLEMENTING CARDIOCEREBRAL RESUSCITATION INTO EMS PROTOCOLS

The Sarver Heart Center CPR Research Group has been advocating chest-compression-only resuscitation by bystanders since the early 1990s. In our programs, laypersons are taught to "be a lifesaver." They are instructed to call 911 as soon as possible and then to begin chest compressions alone. If an automated external defibrillator (AED) is available, they should obtain it and follow its directions. Rescue breathing is not recommended. The technique for chest compressions is ideally taught with emphasis on a metronome-guided rate of 100 per minute. Additionally, full chest recoil after each compression is specifically emphasized.

Guidance from the three phases of cardiac arrest

Adoption of the cardiocerebral resuscitation technique will prompt some changes in EMS protocols; these are best understood in the context of the three phases of cardiac arrest due to VF. The three-phase time-dependent conception of cardiac arrest due to VF was articulated by Weisfeldt and Becker.[23]

The electrical phase is the first phase, lasting about 5 minutes. The most important intervention during this phase is defibrillation. This is why the availability of AEDs and programs to encourage their use have saved lives in a wide variety of settings, including airplanes, airports, casinos, and the community.

The circulatory phase is next. It varies in duration but runs approximately from minute 5 to minute 15 of VF arrest. During this time, generation of adequate cerebral and coronary perfusion pressure before and after defibrillation is critical to neurologically normal survival. Ironically, if an AED is the first intervention applied during this phase, the subject is much less likely to survive.[24,25] If preshock chest compressions are not provided, defibrillation during the circulatory phase almost always results in a pulseless rhythm, asystole, or pulseless electrical activity. The previous stacked-shock protocol for the use of AEDs resulted in prolonged interruption of essential chest compressions, not only for rhythm analysis before shocks but also for rhythm analysis after shocks during this circulatory phase of cardiac arrest.[24,26] Successful resuscitation from these pulseless rhythms requires not only preshock chest compressions but also prompt, effective postshock resumption of chest compressions.[3,4]

The metabolic phase occurs late (sometime after 15 minutes) in cardiac arrest due to VF. This is when resuscitative efforts are least successful and is the phase for which new innovative concepts are needed.

Changes in cardiac life-support protocols

One reason why survival of out-of-hospital cardiac arrest has been so poor is that paramedics, who almost always arrive after the electrical phase of cardiac arrest due to VF, spend only half their time doing chest compressions.[27,28] Interruptions are frequent because EMS personnel have been following existing guidelines. One of the more unfortunate recommendations of the old guidelines is the emphasis on stacked defibrillation,[20] which results in a lack of chest compressions during prolonged and repeated analysis by AEDs during the circulatory phase of cardiac arrest due to VF—delays that have proved to be lethal.[25]

Similarly problematic has been the use of endotracheal intubation by EMS rescuers. Not only does the placement of endotracheal tubes interrupt chest compressions, but intubation also causes adverse effects related to positive pressure ventilation and frequent hyperventilation.[3]

In contrast, cardiocerebral resuscitation discourages endotracheal intubation during the electrical and circulatory phases of cardiac arrest due to VF.[2–4] Defibrillator pad electrodes are applied and the patient is given 200 chest compressions and then a single defibrillation shock that is immediately followed by 200 more chest compressions before the rhythm and pulse are analyzed.[4]

These additional 200 chest compressions applied after the shock but before rhythm and pulse analysis represent another important aspect of cardiocerebral resuscitation.[3,4] This practice is based on our swine model of out-of-hospital cardiac arrest, in which we observed that after prolonged VF an effective shock rarely (almost never) produced a perfusion rhythm.[2] Therefore, chest compressions were immediately initiated until an arterial pressure was established.

A new approach to oxygenation

In our later versions of cardiocerebral resuscitation, a new approach to oxygenation is recommended.[4] Aufderheide has documented that positive pressure ventilation during VF arrest is detrimental, concluding that "there is an inversely proportional relationship between mean intrathoracic pressure, coronary perfusion pressure, and survival from cardiac arrest."[12] Adverse effects of positive pressure ventilation include an increase in intrathoracic pressure as well as the inability to develop a negative intrathoracic pressure during the release phase of chest compression.[12] Positive pressure ventilation inhibits venous return to the thorax and right heart, resulting in decreased coronary and cerebral pressures. Additionally, hyperventilation and increased intrathoracic pressure have adverse effects on intracranial pressure and cerebral perfusion pressure. These effects are compounded by the fact that ventilation rates by physicians and paramedic rescuers are often much faster than the rate recommended by the guidelines,[20] even after extensive retraining.[3,13] During cardiac arrest, faster ventilation rates increase the mean intrathoracic pressure and further impede forward blood flow.

Accordingly, cardiocerebral resuscitation recommends opening the airway with an oropharyngeal device, placement of a nonrebreather mask, and administration of high-flow (about 10 L/min) oxygen.[4]

INITIAL DATA ON CARDIOCEREBRAL RESUSCITATION IN HUMANS

Data comparing cardiocerebral resuscitation with standard CPR in humans are beginning to emerge. Kellum and colleagues reported their initial experience after instituting the current version of cardiocerebral resuscitation by EMS personnel in two rural Wisconsin counties in 2004.[4] Among the first 33 patients with witnessed out-of-hospital cardiac arrest and a shockable rhythm treated after institution of cardiocerebral resuscitation, neurologically normal survival was achieved in 48% of patients. This represents a significant improvement from the 15% rate achieved during the previous 3 years when standard CPR (according to AHA guidelines) was followed.

CONCLUSIONS

Uninterrupted perfusion of the heart and brain prior to defibrillation during prolonged cardiac arrest is essential to neurologically normal survival. It is our conviction that the widespread implementation of cardiocerebral resuscitation for cardiac arrest will dramatically improve survival.

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Heart transplantation: A magnified model of heart-brain interactions

The heart-brain interaction is a burgeoning area of science that has been gaining visibility among researchers interested in the relationship between the central nervous system and cardiovascular system. This review explores heart transplantation as a model for providing insight into the heart-brain link, with an emphasis on findings from recent human investigations.

PROGRESS IN TRANSPLANT OUTCOMES

Cardiac transplantation has become a widely accepted therapy for patients with end-stage heart failure. Approximately 2,000 heart transplants are performed annually in the United States. Long-term outcomes after transplantation have improved with advances in transplant candidate selection, surgical techniques, immunosuppressive medications, and postoperative care.

The current survival rate after heart transplantation has been reported as approximately 50% at 10 years by the International Society for Heart and Lung Transplantation registry.[1] Primary graft failure is the most common cause of early death (within 30 days after transplantation), and transplant coronary artery vasculopathy is the most common cause of late death (> 1 year after transplantation).[1]

TRANSPLANT RECIPIENT SURVIVAL AND MODE OF DONOR BRAIN DEATH

The mode of donor brain death has recently been found to contribute to the pathophysiology of coronary allograft vasculopathy and graft ventricular dysfunction.[2–5] Spontaneous intracranial bleeding in the donor culminated in progression of vasculopathy in the heart recipient, as confirmed by intravascular ultrasonography,[5] a highly sensitive technique for measuring the thickness of the inner lining (intima and media) of the coronary arteries in humans. Several animal models have demonstrated impairment of myocardial function and hemodynamic performance after brain death.[6–8] Atraumatic intracranial bleeding, which occurs in approximately 39% of donors suffering brain death, is a potential independent risk factor for death after cardiac transplantation.[2,3]

Proposed mechanisms

Although the exact causes of cardiac dysfunction after brain death remain unknown, one proposed mechanism is the excessive catecholamine surge that accompanies the endocrine perturbations associated with intracranial bleeding.[9–11] Further, spontaneous intracranial bleeding has been associated with an increased incidence of post-transplant ischemic injury complicated by myocardial fibrosis.[2] The myocardial dysfunction accompanying brain injury is associated with marked alterations in beta-adrenergic signal transduction as well as changes in the contractile apparatus.[10]

The type and extent of myocardial injuries are related to the type of brain injury. In a study of 27 patients whose hearts were systematically examined after an acute fatal episode of intracranial brain hemorrhage, Baroldi et al found evidence of myocardial necrosis in up to 89% of these patients, as compared with only 4% of 45 control cases of fatal head trauma.[8] Increased donor age is another confounding factor among heart donors who die from brain injury caused by intracranial bleeding.[3] This may potentially contribute to the higher incidence of post-transplant ischemic injury complicated by fibrosis.

The increased risk of coronary allograft vasculopathy, myocardial fibrosis, and worse survival has prompted us to further evaluate the link between the brain and the heart at the tissue level.

INTEGRIN αVβ3 AND THE HEART-BRAIN LINK

We have recently shown that the vitronectin receptor (αvβ3), a member of the integrin family,[12] is upregulated in coronary allograft vasculopathy.[13] Integrin αvβ3 is expressed by many cells, including platelets,

* Both authors reported that they have no financial relationships that pose a potential conflict of interest with this article.

lymphocytes, monocytes, macrophages, smooth muscle cells, and vascular endothelial cells,[14] and it interacts with several ligands, including metalloproteinase, fibronectin, osteopontin, thrombospondin, vitronectin, von Willebrand factor, prothrombin, and fibrinogen,[15] thus playing a significant role in bone resorption, angiogenesis, endothelial cell migration, tumor invasion, atherosclerosis, apoptosis, and the cellular immune response.[16,17] Integrin αvβ3 also mediates transmembrane signaling,[18] regulating gene expression and contributing to vascular cell survival.[19]

Systemic activation in donors with intracranial bleeding

We recently demonstrated the presence of systemic activation of αvβ3 in hearts from donors with spontaneous intracranial hemorrhage (ICH).[20] We evaluated mRNA expression of αvβ3 (using TaqMan polymerase chain reaction) in endomyocardial biopsies at 1 week following transplant in 20 recipients of hearts from ICH donors and 20 recipients from trauma donors. To investigate whether systemic activation of αvβ3 was present in the donor before transplantation, αvβ3 expression was also evaluated in the corresponding donor spleen lymphocytes. All patients underwent serial coronary intravascular ultrasonography to evaluate for coronary vasculopathy. Compared with the trauma group, the ICH group showed a significant increase in mRNA expression of αvβ3 in the heart biopsies (3.8-fold, $P = .012$) and in the corresponding donor spleen lymphocytes (3.5-fold, $P = .014$). At 1 year, the ICH group also showed increased progression of coronary vasculopathy.

Resulting hypotheses

Our findings of significantly increased mRNA expression of αvβ3 in heart biopsies 1 week after transplantation in recipients of hearts from donors with ICH highlights the potential impact of donor cause of death on postcardiac transplant outcomes. Further, our findings of increased mRNA expression of αvβ3 in the corresponding donor lymphocytes in the presence of ICH suggests systemic activation of αvβ3 and therefore indicates that the index insult occurred prior to transplantation.

We hypothesized that disruption of the blood-brain barrier as a result of ICH is associated with systemic activation of αvβ3. It is unknown whether this activation serves as a protective counterregulatory effect in the donor. Recently, the importance of alpha v integrins in vascular function has been demonstrated in knockout mouse models in which alpha v null mice have been noted to exhibit intracerebral hemorrhage.[21] Since we have shown that this effect is systemic, we also hypothesized that the donor heart is affected prior to transplantation and in response to vascular injury; thus, smooth muscle cells migrate from the media into the intima, where myointimal proliferation leads to the development of vasculopathy, as confirmed by intravascular findings we have reported.[20]

Our clinical observation shed light on the relationship between αvβ3 and allograft vasculopathy in relation to donor cause of death. Animal transplant models are needed to further explore mechanistic cause-and-effect relationships. Such models may be difficult to design, however, since alpha v knockout mouse models may result in lethal complications, with the mice not surviving transplantation, which would preclude evaluation of the relationship to vasculopathy.

THE METALLOPROTEINASE SYSTEM AND THE HEART-BRAIN LINK

We have observed that heart transplant recipients who develop myocardial ischemic injury or interstitial fibrosis following transplantation are more likely to have received their transplants from a donor whose death was related to brain injury.[22] We have also shown that myocardial ischemic injury following cardiac transplantation is associated with activation of the matrix metalloproteinase (MMP) induction system.[23] Heart biopsies from ICH donors show a significant increase in mRNA expression of MMP-2 (17-fold, $P < .0001$) and MMP-9 (20-fold, $P < .0001$) compared with biopsies from trauma donors.[24] This upregulation is associated with increased myocardial fibrosis (29% ± 10% vs 19% ± 6%, $P = .003$), as shown by picrosirius staining, and subsequent development of coronary vasculopathy, as evidenced by intravascular ultrasonography.[24]

Evidence supporting systemic activation

The extracellular matrix molecules, such as type IV collagen, laminin, and fibronectin, constitute the basement membrane underlying the vasculature and play a critical role in maintaining integrity of the blood-brain barrier.[25] MMP-2 and MMP-9 have been shown to degrade the extracellular matrix components of the basement membrane and to be involved in the progression of hemorrhagic strokes.[26] We have also shown that there is increased mRNA expression of MMP-2 and MMP-9 in the corresponding donor spleen lymphocytes in the presence of intracranial bleeding, which suggests systemic activation of the metalloproteinase system and that the precipitating insult occurs prior to transplantation.[24]

We have thus postulated that intracranial bleeding is associated with MMP release and subsequent disruption of the blood-brain barrier, resulting in a systemic activation process as evidenced by the splenic upregulation of MMP expression. Subsequently the donor heart coronary vasculature is subject to the effects of systemic activation of MMP, resulting in vascular injury prior to transplantation. After transplantation, smooth muscle cells migrate from the media into the intima, where they contribute to the development of neointimal lesions. Increased MMP expression contributes to the migratory response of smooth muscle cells by releasing them from their surrounding extracellular matrix.[27] In the presence of intracranial bleeding, this injury is translated into increased vasculopathy and myocardial fibrosis. In fact, using multivariate regression analysis, MMP-9 in donor spleen lymphocytes was found to be an independent risk factor for vasculopathy (odds ratio = 2.41, $P = .01$).[24]

Of course, cardiac allograft vasculopathy is a multifactorial process mediated by immune and nonimmune factors, so we acknowledge that these isolated findings are merely part of a more complex process.

THE RENIN-ANGIOTENSIN SYSTEM AND THE HEART-BRAIN LINK

The renin-angiotensin system is activated during transplantation of the heart and other organs and promotes ischemia-reperfusion injury and fibrosis. Inflammatory effects of the renin-angiotensin system may be caused by the production of tumor necrosis factor–alpha, transforming growth factor–beta, and monocyte chemoattractant protein–1.[28–30] Angiotensin II may mediate T-cell proliferation and thus may contribute to alloimmune responses.[31] The interplay between angiotensin II receptor subtype 1 (AT1R) and metalloproteinases has been illustrated by the modulatory impact of AT1R blockade on the extracellular matrix regulatory system in animal experiments.[32,33]

Both clinical and experimental investigations suggest that activation of the renin-angiotensin system occurs along with increased sympathetic drive in patients with spontaneous intracranial bleeding.[34] Angiotensin II interacts with the sympathetic nervous system to maintain adequate cerebral perfusion.[35] It seems plausible that activation of the renin-angiotensin system, which exerts a protective effect by counteracting the elevation in intracranial pressure that occurs following intracranial bleeding (such as subarachnoid hemorrhage),[36] may have a detrimental effect on the donor heart.

We have recently shown that AT1R is upregulated in heart biopsies from recipients of cardiac transplants from donors with spontaneous intracranial bleeding compared with those from trauma donors (4.7-fold increase in mRNA expression of AT1R, $P < .0001$).[37] We have also shown that increased expression of AT1R was present in the corresponding donor spleen lymphocytes, suggesting a generalized activation of the renin-angiotensin system and suggesting that the index insult of angiotensin activation occurred in the donor prior to transplantation.[37] Further, we have shown mRNA expression of AT1R in the donor spleen lymphocytes to be a strong independent predictor of transplant vasculopathy (odds ratio = 4.39, $P = .02$).[37]

SUMMARY

The human heart transplant model unmasks the heart-brain link as an active process that is clinically demonstrated and confirmed at the tissue level. Further studies are needed to elucidate the relative contribution of each of these isolated observations to the pathogenesis of coronary allograft vasculopathy, which remains enigmatic. Recent studies have suggested that mTOR inhibitors may have the ability to attenuate this lethal process that limits the long-term survival of cardiac transplant recipients.[38]

The observations we have discussed here suggest that other targeted therapies, including glycoprotein IIb/IIIa inhibitors, tissue metalloproteinase inhibitors, and angiotensin receptor blockers, may facilitate the attenuation of cardiac transplant vasculopathy, but clinical trials are difficult to conduct in this relatively small population of patients. These observations may shed insight, however, into the pathophysiology of hypertension and its impact on the vascular system, as cardiac transplantation provides a setting in which heart-brain interactions are magnified and the pathophysiology occurs over years rather than decades.

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Patent foramen ovale and migraine

Migraine is a complex disorder in which many psychological, environmental, biochemical, neurophysiologic, and genetic factors may play a role to trigger attacks.[1,2] Although its course is usually benign and it tends to abate with age, migraine has long been suspected as a risk factor for stroke. A number of case-control studies and a recent meta-analysis have demonstrated that the relative risk of stroke is as follows in the following groups of migraineurs compared with nonmigraineurs:[3–6]

- 1.83 in people with migraine without aura
- 2.27 in people with migraine with aura
- 8.27 in female migraineurs who smoke and take oral contraceptives.

Furthermore, migraineurs are more likely to exhibit silent ischemic lesions on magnetic resonance imaging.[7]

STROKE RISK AND THE PFO-MIGRAINE ASSOCIATION

The mechanisms by which migraine conveys an increased risk of stroke had been an object of speculation[6] until the discoveries that the prevalence of patent foramen ovale (PFO) is the same in patients with migraine with aura as in patients with cryptogenic stroke[8–10] and that the frequency of migraine in PFO-associated cryptogenic stroke is twice what would otherwise be expected.[11,12] These findings have prompted a twofold hypothesis:[13,14]

(1) That the association with PFO accounts for the increased stroke risk in patients with migraine through the mechanism of paradoxical brain embolism

(2) That the presence of a right-to-left shunt could serve as a conduit for chemicals that would be normally inactivated by the pulmonary filter to reach the systemic circulation and exert a trigger effect on hyperexcitable neurons.

The latter point would imply that, to a certain extent, PFO may cause migraine attacks. However, PFO and migraine are common conditions and their co-occurrence in a single patient might be coincidental; alternately, PFO and migraine both could derive from a common underlying disorder (eg, a dysfunction in the endothelium) without necessarily being linked in a causal relationship.[14]

Nevertheless, a number of recent findings tend to support an etiologic link.

We recently assessed the extent of right-to-left shunt with contrast-enhanced transcranial Doppler imaging in 420 consecutive patients.[15] Patients with prior stroke had larger shunts than patients without prior stroke (mean bubble count of 91 vs 58, respectively, on transcranial Doppler). Migraineurs with and without aura both had significantly larger shunts than nonmigraineurs (bubble counts of 104, 74, and 46, respectively). As detailed in **Table 1**, patients with both migraine and prior stroke had larger shunts than migraineurs without prior stroke, than nonmigraineurs with prior stroke, and than patients without migraine or prior stroke.

Possible effect of shunt size

These findings suggest that shunt size may have a dose effect in terms of the risk of having migraine and stroke. The plausible hypothesis is that, via the atrial septal defect, a venous-to-arterial passage of activated platelets or chemical substances may trigger headache by overwhelming the filtering capacity of the lung.[16]

Larger shunt might also increase the likelihood of paradoxical embolization to the brain and hence explain the statistically significant increase in stroke risk that is associated with migraine. The presence of a right-to-left shunt may be the most potent trigger of attacks in migraine with aura as well as migraine without aura and may be the main determinant of aura.

Specificity to migraine with aura

However, any interpretation of a causal link between PFO and migraine needs to take into account the fact that although PFO is found in nearly half of patients who have migraine with aura, its frequency in migraine without aura is the same as in nonmigraineurs.[9,10]

For migraine with aura, a common inheritable trait linking migraine with atrial septal abnormalities has

* Dr. Anzola reported that he has no financial relationships that pose a potential conflict of interest with this article.

been suggested by Wilmshurst et al, who studied 71 relatives of 20 probands with a significantly sized atrial shunt.[17] When the proband had migraine with aura and an atrial shunt, 15 of 21 (71.4%) first-degree relatives with a significant right-to-left shunt also had migraine with aura compared with 3 of 14 (21.4%) first-degree relatives without a significant shunt ($P < .02$), which suggests that migraine trait may be inherited in association with atrial shunts, at least in some kinships, and that the occurrence of atrial shunts is consistent with autosomal dominant inheritance.

CAN PFO CLOSURE IMPROVE MIGRAINE?

Further along the migraine-PFO connection are the effects of PFO closure on migraine severity. When Wilmshurst et al observed serendipitously that PFO closure to prevent decompression sickness in a cohort of scuba divers resulted in a dramatic decrease of migraine severity,[18] this finding raised considerable interest on the possible curative effect of atrial septal repair on migraine. A number of subsequent publications reported a consistent benefit on migraine following PFO closure in patients who had suffered a stroke.[19–24] The cumulative results of such studies are presented in **Table 2**. Although the validity of these results is limited by major methodologic flaws (retrospective design, lack of a control group, subjective rating of migraine severity, short follow-up, presence of previous stroke in all patients), recent findings from a prospective case-control study[25] have substantially confirmed the favorable effect of PFO closure on migraine, although to a somewhat less dramatic extent (see **Table 2**).

MIST trial raises questions

However, in partial contrast with these results are the recently reported findings of the Migraine Intervention with STARFlex Technology (MIST) trial,[26] the first prospective, multicenter, randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy of PFO closure with the STARFlex® septal repair implant (NMT Medical, Inc., Boston, MA) to prevent refractory migraine headaches. The MIST trial enrolled patients with migraine with aura and moderate to large PFO as assessed by contrast-enhanced transthoracic echocardiography (TTE); patients had to have at least 5 days of migraine in the month preceding enrollment and their migraines had to be refractory to at least two different prophylactic medications. The primary outcome measure was the proportion of patients without headache at 6 months. Of 432 screened patients, 163 were found suitable for randomization and 147 were actually randomized to the interventional (n = 74) or sham (n = 73) arms. At 6-month follow-up, three patients in each arm were migraine-free, which corresponds to a 4% response rate in each arm and a clearly nonsignificant difference between the groups. A secondary post hoc outcome measure, the proportion of patients with a 50% reduction in the number of headache days, showed a statistically significant difference favoring the interventional arm (42% vs 23%, $P = .038$).

The results of the MIST trial generate more questions than answers in that they are presently published solely on the Web and in slide format, and a substantial amount of information is lacking; for instance, the proportion of residual shunts is unknown, as is the proportion of patients who experienced a worsening of their migraines, which has been reported to occur in the initial postoperative period.[16,27] Furthermore, the use of transthoracic echocardiography as the only tool to quantify the amount of shunt and to discriminate between true PFO and atrial septal defect is questionable. Finally, the inclusion criterion of high frequency of migraine attacks, far exceeding the expected frequency of pure migraine with aura, may have allowed the enrollment of patients with mixed forms of headache, including episodic tension-type headache, which has proved unresponsive to PFO closure.[20]

TABLE 1
Age and shunt according to cerebrovascular history and migraine status*

	No migraine		Migraine	
	No prior stroke	Prior stroke	No prior stroke	Prior stroke
No. patients	100	85	139	96
Sex (M/F)	40/60	38/47	21/118	18/78
Age, yr (mean ± SD)†	48 ± 17	55 ± 14	36 ± 14	42 ± 11
Mean bubble count (SE)‡	38 (5)	55 (8)	72 (8)	123 (24)

* In a series of 420 consecutive patients undergoing transcranial Doppler imaging.[15] See text for details.

† Age significantly different in all comparisons (P between < .0001 and .023).

‡ Mean bubble count in migraine patients with prior stroke was significantly higher than in any other group (P between < .0001 and .038).

Reprinted, with permission, from Anzola GP, et al. Different degrees of right-to-left shunting predict migraine and stroke. Data from 420 patients. Neurology 2006; 66:765–767.

TABLE 2
Summary of results of nonrandomized trials on the effects of patent foramen ovale closure on migraine*

Author	Year	Type of study	No. of pts	Mean follow-up (months)	Patients with resolution (%)	Patients with improvement (%)
Wilmshurst et al[18]	2000	Retrospective	21	17	48	38
Morandi et al[19]	2003	Prospective	17	12	29	59
Schwerzmann et al[20]	2004	Retrospective	47	24	Not reported	83
Post et al[21]	2004	Retrospective	26	6	84	Not reported
Azarbal et al[22]	2005	Retrospective	37	3	60	40
Reisman et al[23]	2005	Retrospective	50	12	56	14
Giardini et al[24]	2006	Retrospective	35	20	83	8
Overall results of retrospective trials			**233**	**13**	**60**	**40**
Anzola et al[25]	2006	Prospective case-control	50	12	38	48

* The only case-control study (reference 25) is contrasted with earlier reports.

PINPOINTING WHO MIGHT BENEFIT FROM PFO CLOSURE

Taken at face value, however, the MIST trial results put the therapeutic efficacy of atrial septal repair in a more realistic perspective. The hypothesis that PFO closure improves migraine needs further refinement and has to be stated in different terms, such as with the qualification that a proportion of patients with PFO-associated migraine might, in principle, benefit from PFO closure. Preliminarily, we need to identify which clinical features are most likely to be related to the presence of a right-to-left shunt. In other words, we need to identify the shunt-associated migraine syndrome.

From preliminary results of an ongoing Italian study,[28] it seems that some features help to differentiate patients in whom the right-to-left shunt may exert a pathophysiologic effect: being a female with a positive family history of migraine with aura and a higher frequency of migraine attacks with aura vs without aura appears to represent the core specificity of shunt-associated migraine (Anzola et al, unpublished data).

Future randomized controlled trials comparing PFO closure with medical treatments will have to incorporate the knowledge of which features are pathophysiologically related to PFO in migraine sufferers in order to enroll only those patients in whom investigating PFO closure in a randomized trial is worthwhile.

Finally, it is worth recalling that, even if transcatheter closure of PFO is a safe, effective, and minimally invasive procedure, a number of complications have been reported. Among these, special emphasis should be placed on major arrhythmias, including supraventricular paroxysmal tachycardia and atrial fibrillation, which have been documented in up to 8% of patients within 1 month of the procedure.[29,30]

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Patent foramen ovale and stroke: To close or not to close?

Patent foramen ovale (PFO) is common, with the prevalence being approximately 20% in individuals younger than 50 years. This congenital cardiac anomaly has been found in many referral-based studies to be more common in young patients with cryptogenic stroke than in stroke of known cause. Parodoxical embolism via right-to-left shunt is the presumed mechanism of cryptogenic stroke in patients with PFO.[1]

The diagnosis of PFO is made by either contrast transthoracic or transesophogeal echocardiography during Valsalva maneuver. Transcranial Doppler can also be used to identify paradoxical emboli in the middle cerebral artery.

PFO is considered the most common identified cause of stroke in patients younger than 50 years. However, recent data have called into question the relationship between PFO and cryptogenic ischemic stroke in the population at large, as well as the notion that paradoxical embolism through PFO is a common cause of cryptogenic ischemic stroke.[2]

EPIDEMIOLOGY: REFERRAL-BASED VS POPULATION-BASED STUDIES

In the PFO in Cryptogenic Stroke Study (PICSS),[1] which included 630 patients with stroke, PFO was present in 39.2% of patients with cryptogenic stroke and 29.9% of those with noncryptogenic stroke. The 2-year cumulative risk of recurrent stroke and death was not significantly different between patients with and patients without PFO in the overall study population or in the subset with cryptogenic stroke.

Large PFOs with rapid right-to-left shunting are thought to pose a greater stroke risk than small PFOs. However, in PICSS, the lowest rate of recurrent stroke or death at 2 years was observed in patients with large PFOs (9.5%) compared with patients with small PFOs (18.5%) or no PFO (15.4%).

PFO with atrial septal aneurysm may confer an especially high risk of recurrent stroke. In a study of 581 patients with an ischemic stroke, Mas et al found that PFO alone was associated with a risk of recurrent stroke of 2.3% at 4 years, whereas patients with both PFO and an atrial septal aneurysm had a rate of recurrent stroke of 15.2% and patients with neither had a rate of 4.2%.[3]

Whereas the previously mentioned data that identified PFO as a risk factor for cryptogenic stroke were obtained in referral-based populations, the most recent data, from a population-based study, found no such link between PFO and the risk of cryptogenic stroke or transient ischemic attack (TIA).[2] In this case-control study, Petty et al found no association between PFO or large PFOs and cryptogenic or noncryptogenic stroke, and they suggest that such associations found previously were the result of referral bias.[2]

TREATMENT: MEDICAL THERAPY OR CLOSURE?

The best option for treating patients with PFO and previous stroke or TIA is controversial.

Medical therapy: Evidence is weak

Traditionally, warfarin has been the medical therapy of choice, although evidence to support its routine use is weak and the risk of bleeding with warfarin in this patient population has not been established. In the subgroup of patients in PICSS with PFO and cryptogenic stroke, those treated with warfarin had better outcomes (fewer deaths or recurrent strokes) at 2 years than those treated with aspirin (9.5% vs 17.9%), but because of the small sample size (n = 98), the difference failed to achieve statistical significance (P = .28).[1] Although these data suggest that the risk of death and recurrent stroke in patients with cryptogenic stroke and PFO is low even with aspirin treatment, except possibly in patients with atrial septal aneurysm, drawing a definitive conclusion is not possible because of the small number of patients.

Closure: Evidence plagued by small numbers

The alternative to medical therapy is PFO closure.

* Dr. Furlan reported that he is a consultant for NMT Medical, Inc.

Before the advent of percutaneous closure devices, this decision meant open heart surgery, with its inherent risks. Endovascular devices obviate the need for open heart surgery, which is now performed infrequently for PFO closure. The evidence for efficacy of endovascular closure of PFO comes mostly from case series, and the numbers of patients included in such series are even smaller than those in PICSS **(Table 1)**.[4]

A variety of PFO occluder devices has been used **(Table 1)**, all with reasonable safety. These devices appear to reduce the long-term risk of stroke and TIA, although prospective clinical studies are lacking.

The complication rates and the rates of recurrent events associated with medical therapy and endovascular therapy were compared in a systematic review by Khairy et al.[5] Ten studies of transcatheter closure and six studies of medical therapy were included in the review, with a total of 2,250 patients. A tremendous amount of variability was observed in the rates of recurrent events and complications in these studies. The 1-year rate of recurrent events ranged from 3.8% to 12.0% with medical therapy, and from 0% to 4.9% with transcatheter closure. Major complications occurred at a rate of about 1% per year with warfarin therapy. In the studies of percutaneous closure, the rate of major complications was 1.5% and the rate of minor complications was 7.9%.

Several limitations to the review by Khairy et al are evident.[5] In the studies of medical therapy, treatment was not uniform, as some patients received antiplatelet therapy and others were treated with warfarin. In addition, in those treated with warfarin, there was significant variation in the targets for the International Normalized Ratio (INR). Further, the patients included in these studies were dissimilar to a typical PFO population; they were older, were more likely to be men, and had a higher prevalence of diabetes and smoking. There was also significant selection bias in the studies of catheter closure, and significant variation in the postimplant pharmacologic therapy.

Thus, the available nonrandomized studies suggest a low stroke recurrence rate with either warfarin (and in selected patients with aspirin) or endovascular closure, but the numbers are small. Randomized clinical trials are needed to firmly establish the best stroke prevention therapy for PFO.

FDA INDICATION FOR PERCUTANEOUS CLOSURE

For the past 6 years the US Food and Drug Administration (FDA) has permitted percutaneous closure of PFOs under a Humanitarian Device Exemption (HDE). Two PFO closure devices—the Amplatzer PFO Occluder and the CardioSEAL Septal Occlusion System—have been approved via the HDE process, based on observational data from fewer than 100 patients with each device. The indication specific to the CardioSEAL Septal Occlusion System is worded as follows:

> The CardioSEAL Septal Occlusion System is indicated for closure of a PFO in patients with recurrent cryptogenic stroke due to presumed paradoxical embolus through the PFO who have failed medical therapy. Cryptogenic stroke is defined as a stroke occurring in the absence of potential phanerogenic cardiac, pulmonary, vascular or neurological sources. Conventional drug therapy is defined as a therapeutic INR on oral anticoagulants. The effectiveness of this device in this indication has not been demonstrated.[6]

The HDE for PFO closure does not include TIA, a first stroke, migraine, or failed antiplatelet therapy.

Because the subset of patients who qualified for PFO closure under the HDE has increased beyond 4,000 per year (the HDE limit), the FDA recently asked US PFO device manufacturers to review their existing HDE. Effective October 2006, both NMT Medical, Inc., and AGA Medical Corporation have voluntarily withdrawn their PFO HDE. As a result, there is no longer any FDA-approved indication for

TABLE 1
Comparison of short-term and periprocedural complications between PFO occluder devices

Device	Total (n = 80)	Procedural complications (n = 8)	Residual shunt (n = 21)	Recurrence of paradoxic embolism* (n = 8)
Buttoned device	28	3	11	2
PFO-STAR	19	3	5	1
Amplatzer occluder	14	1	3	2
Angel-wings occluder	10	0	1	2
CardioSEAL	9	1	1	1
Septal occluder	9	1	1	1
P value		0.74	0.26	0.71

* Comprised six transient ischemic attacks and two peripheral emboli.
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PFO closure in patients with stroke or TIA. This means that PFO closure must now be done under an Investigational Device Exemption within a clinical trial. Alternatively, some interventionalists may elect to insert devices not specifically approved for PFO ("off-label" use).

Ongoing clinical trials

Three studies of PFO closure to prevent recurrent stroke are ongoing.

In CLOSURE I (Trial to Evaluate the Safety and Efficacy of the STARFlex® Septal Closure System Versus Best Medical Therapy in Patients With a Stroke and/or Transient Ischemic Attack Due to Presumed Paradoxical Embolism Through a Patent Foramen Ovale), patients with a recent (≤ 6 months) diagnosis of stroke and/or TIA due to a presumed paradoxical embolism through a PFO are being randomized to PFO closure using the STARFlex septal occlusion system or best medical therapy. The goal is to enroll 1,600 patients and follow them for 2 years. The primary end point is the incidence of recurrent stroke/TIA.

The Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT PFO) is randomizing patients with cryptogenic stroke, defined as an acute focal neurological deficit presumed due to focal ischemia, to PFO closure with the Amplatzer PFO Occluder or medical management (antiplatelet or anticoagulant therapy). The primary end points are recurrent nonfatal stroke, periprocedural death, or fatal stroke.

The PC-Trial is a randomized trial comparing PFO closure using the Amplatzer PFO Occluder with best medical management in patients with cryptogenic embolism (mostly cryptogenic stroke). The recommended medical management is warfarin for 6 months followed by antiplatelet therapy. The goal is to enroll 410 patients and follow them for 5 years with primary end points of death, nonfatal stroke, and peripheral embolism.

Enrollment in these studies has been slow for various reasons. Physician and patient bias toward a particular treatment has deterred physicians from entering patients into the trials. Many interventionalists have already accepted that PFO closure is a superior strategy despite an absence of randomized data, whereas neurologists appear to favor medical therapy. Local referral patterns in which patients with PFO are referred directly to the catheterization laboratory, because the procedure is reimbursed, may bypass knowledgeable neurologists and represent another roadblock to enrolling patients.

The FDA has publicly recognized the problem of off-label use of devices in a large number of patients who do not meet HDE criteria, and has admitted that this practice has interfered with completion of important clinical trials.[7] Because of these difficulties, a variety of alternatives to the traditional randomized clinical trial is under discussion with the FDA.

CONCLUSION

Stroke can occur due to paradoxical embolism through a PFO, but the absolute risk is low. Nonrandomized case series suggest a low stroke recurrence rate in patients with PFO who are treated with either warfarin, aspirin, or endovascular device closure. Whether any of these treatments is superior for preventing recurrent stroke is unknown since there has never been a randomized trial comparing any therapy in patients with PFO and stroke. Currently, there is no FDA-approved indication for PFO device closure although many PFOs are closed "off-label" using devices approved for other heart conditions. The only way out of this PFO treatment dilemma is to enroll patients into one of the several ongoing randomized clinical trials.

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Sudden unexplained death in epilepsy: The role of the heart

Sudden unexplained death in epilepsy (SUDEP) is defined as the sudden, unexpected death of an otherwise healthy person with epilepsy without apparent cause. Death occurs during normal activities and under benign circumstances; it does not arise from trauma, aspiration, or intractable status epilepticus.[1]

SUDEP is most commonly attributed to one of three mechanisms: seizure-induced central apnea, cardiac arrhythmia, and neurogenic pulmonary edema. This review will focus on the potential cardiac causes of SUDEP after providing a brief overview of SUDEP and its other proposed mechanisms.

RISK FACTORS AND MECHANISMS OF SUDEP

Sudden unexplained death is 24 times more common in patients with epilepsy than in the general population. SUDEP is responsible for 7.5% to 17% of all deaths in epilepsy and has an incidence among adults between 1:500 and 1:1,000.[2,3]

Factors associated with SUDEP

Because SUDEP is relatively infrequent, research to identify risk factors has focused on cohort and case-control studies. A number of clear associations exist that provide insight into the potential mechanism of SUDEP.

Almost all witnessed cases of SUDEP have occurred in the context of a generalized convulsive seizure.[4] The relative risk of SUDEP is increased in patients with a history of recent generalized tonic-clonic seizures.[5–7] Evidence of uncontrolled epilepsy, demonstrated by continuing convulsive seizures and polytherapy with antiepileptic drugs, is a consistent risk factor for SUDEP in most studies.[7–9] Patients with epilepsy who are not receiving antiepileptic drugs are at an increased risk of SUDEP.[7] Cessation of seizures after successful epilepsy surgery for drug-resistant epilepsy can normalize or at least significantly reduce the risk of SUDEP.[10–12] Associations have been identified between SUDEP and sleeping or living alone[4,13,14] and having seizures that arise from sleep.[6]

Pulmonary causes of SUDEP

The majority of seizures, of course, do not result in death. Other cardiorespiratory factors associated with epilepsy or induced by a convulsive seizure must exist to explain the phenomenon of SUDEP. As noted above, pulmonary conditions—central apnea and neurogenic pulmonary edema—are among the mechanisms most frequently implicated in SUDEP cases.

Central apnea induced by epileptic activity or occurring in the postictal phase is thought to be the most common cause of SUDEP. In the only animal model of SUDEP, one third of cases died from hypoventilation and had associated pulmonary edema on autopsy.[15,16] In a prospective study of patients in an epilepsy monitoring unit, central apnea lasting at least 10 seconds occurred postictally in 40% of the recorded seizures.[17] Respiratory arrest has been reported in the immediate postictal phase of a complex partial seizure in a healthy 20-year-old woman.[18] The mechanism of seizure-induced apnea may be the inhibition of the brainstem by the brain's own endogenous GABA-ergic seizure-terminating mechanism.[13]

Acute neurogenic pulmonary edema can follow severe head injury, subarachnoid hemorrhage, or epileptic seizures. Pulmonary edema is found in many cases of SUDEP at autopsy.[19] A proposed mechanism for seizure-induced neurogenic pulmonary edema is the intense generalized vasoconstriction from the massive seizure-related outpouring of central sympathetic activity, which leads to an increase in pulmonary vascular resistance.[20,21]

* Dr. Schuele reported that he serves on the speakers' bureaus of GlaxoSmithKline and UCB Pharma. All other authors reported that they have no financial relationships that pose a potential conflict of interest with this article.

CARDIAC SUDEP

Fatal arrhythmias are thought to be the mechanism underlying cardiac causes of SUDEP. A prevailing hypothesis is that a lethal cardiac arrhythmia is caused by epilepsy-induced autonomic discharges to the heart.[22] These might occur in a normal heart with no evidence of structural or conduction abnormalities or in a heart with existing myocyte injury secondary to catecholamine excess from prior seizures. The two main potentially lethal arrhythmias implicated in SUDEP are ictal ventricular tachyarrhythmias and ictal bradycardia/asystole.

Mechanisms of fatal cardiac arrhythmias

Ventricular arrhythmias can be provoked by reentry, abnormal automaticity, and triggered activity due to changes in after-depolarization.[23] These can be seen in patients with left ventricular dysfunction and occur at the border of normal and scarred myocardium.[24,25] Increased sympathetic tone and wall stress, combined with electrolyte disturbances, enhance cardiac arrhythmogenicity.[26]

Ventricular tachyarrhythmias are the cause of sudden cardiac death, and primary prevention of sudden cardiac death has been advocated for patients with ischemic left ventricular dysfunction.[23] Only 5% to 10% of cases of sudden cardiac death occur in patients with no definable structural heart disease.[27] These deaths often can be attributed to primary electrophysiologic abnormalities (eg, Brugada syndrome, long QT syndrome, congenital short QT syndrome, preexcitation syndrome).[28] In children, a familial form of catecholamine-induced ventricular arrhythmia has been described that is caused by a mutation in the cardiac ryanodine receptor gene.[29,30]

Syncopal events may be benign or may be the only warning before an episode causing sudden (cardiac) death.[31] Potentially fatal bradycardic and tachycardic arrhythmias may lead to transient cerebral hypoperfusion and present clinically as syncopal events. Patients with underlying heart disease or an electrophysiologic abnormality associated with ventricular arrhythmias may receive potentially life-saving therapy with an implantable cardioverter defibrillator.[32] Patients with bradycardic syncopal events secondary to sick sinus syndrome or intermittent atrioventricular block may profit from implantation of a pacemaker. However, the most common cause of bradycardia associated with symptomatic cerebral hypoperfusion, vasovagal syncope, has a benign prognosis, and recent studies showed no benefit of pacemaker therapy in patients with vasovagal syncope in terms of event frequency or time to first recurrence.[33–35]

Anatomy of the cardiovascular autonomic system

The cardiovascular autonomic system consists of an interconnected network throughout the neuraxis **(Figure 1)**. At the cortical level, the insula represents the primary viscerosensory cortex, whereas the anterior cingulate gyrus and ventromedial prefrontal cortex constitute the premotor autonomic regions.[36] The central nucleus of the amygdala is involved in mediating the autonomic response to emotions, and the hypothalamus triggers the autonomic response to endocrine stimuli to maintain homeostasis.

Figure 1 depicts the efferent pathways in detail.[37] The parasympathetic influence on the heart arises primarily from the nucleus ambiguus, decreasing the heart rate predominantly via the right vagus nerve and decreasing atrioventricular conduction and ventricular excitability via the left vagus nerve.[38] As shown in the figure, the sympathetic output receives tonic excitation from the ventrolateral medulla and projects from the intermediolateral cell columns to the cardiac conduction system and ventricle, leading to increased automatism of the sinus node, atrioventricular conduction, and ventricular excitability and contractility.[39]

The figure also depicts the afferent loop of the cardiac autonomic system.[40,41] Visceral sensations are projected to the nucleus tractus solitarius, mediating a variety of medullary reflexes, including the baroreflex. From the nucleus tractus solitarius, the viscerosensory information is relayed via the parabrachial region, either directly or indirectly through the ventrobasal thalamus, to the primary viscerosensitive cortex in the insula.

The balance between cardiac vagal and sympathetic modulation is regulated by two main influences:[42]

- Medullary reflexes triggered by activation of baroreceptors, cardiac receptors, and chemoreceptors
- Descending influences from the cerebral cortex, amygdala, hypothalamus, and periaqueductal gray matter mediating integrated responses to internal and external stressors, in part by affecting the gain of medullary reflexes.

Hughlings Jackson first recognized the unique value of epileptic seizures in localizing brain function and discussed the visceral manifestations of epilepsy.[43] Visceral phenomena are present in most epileptic attacks but are often overshadowed by motor phenomena and loss of awareness.[44] Penfield was able to confirm that such symptoms may result from localized irritation of the cortex and may be precipitated by electrical stimulation of specific regions of the cortex.[45] Seizures that arise from

or spread to areas in the central autonomic network (mainly the insula, cingulate gyrus, amygdala, hypothalamus, and brainstem autonomic centers) can mimic stimulation of autonomic afferents or modify autonomic expression. Central cardiovascular responses related to motivated behavior and emotion may be inappropriately activated during a seizure.[37] Sympathetic responses predominate during most seizures, but any combinations of sympathetic and parasympathetic activation and inhibition may occur simultaneously or sequentially during individual seizures.[46]

Cardiovascular effects of electrical stimulation

Insight into central localization of autonomic brain function comes largely from lesional and electrical stimulation studies.[47,48] More recently, noninvasive techniques (eg, functional magnetic resonance imaging and positron-emission tomography) have been introduced in the mapping of central autonomic control.[49–52]

In many species the insular cortex seems to play a pivotal role in the integration of interoceptive information and may exert a lateralized influence on cardiovascular autonomic control. Intraoperative stimulation of the left posterior insula elicits a cardioinhibitory response and hypotension, whereas stimulation of the right anterior insula elicits tachycardia and hypertension. Lateralization of parasympathetic activity to the left insula and sympathetic activity to the right insula is supported by some studies of cerebral inactivation during intracarotid amobarbital injection, but results have been controversial.[53–55] Using phasic electrical microstimulation synchronized to the R wave of the electrocardiogram (ECG), a cardiac chronotropic organization was identified in the rat posterior insular cortex.[56] ECG-triggered phasic microstimulation of the rat left posterior insular cortex results in bradyarrhythmia, complete heart block, and asystolic death.[57]

Evidence exists from animal experiments for a synchronization of the cardiac autonomic (sympathetic and vagal) neural discharges with epileptogenic activity. This "lock-step" phenomenon may contribute to the development of cardiac arrhythmias during seizures in epilepsy patients.[58] This is consistent with a study in patients with focal epilepsy that showed that left-sided interictal epileptiform discharges seem to shorten the R-R interval, whereas right-sided discharges seem to prolong the R-R interval, suggesting that interictal epileptiform discharges may influence autonomic control over the cardiac cycle.[59]

Potential mechanisms of cardiac SUDEP

SUDEP may be related to mechanisms similar to those of sudden cardiac death. During sleep, the heart is more susceptibe to catecholamines. SUDEP and sudden cardiac death are both associated with a peak incidence in the morning. Vagal tone is increased in sleep; the addition of a massive sympathetic outpouring related to a seizure from sleep in a patient with epilepsy or awakening in a patient with heart disease may precipitate a lethal cardiac arrhythmia.

This view is congruent with a number of studies suggesting that sympathetic-parasympathetic nervous system imbalance may play a role in the generation of ventricular arrhythmias and sudden cardiac death.[26,60,61] Removal of the epileptic focus through epilepsy surgery can reduce the excess sympathetic response[22] and may reduce mortality.[12] However, most of the evidence linking SUDEP with cardiac etiology is indirect, and the one monitored patient who died in intractable ventricular fibrillation during a seizure possibly suffered a coincident myocardial infarction.[62]

Autonomic modulation is altered in patients with epilepsy, with parasympathetic and sympathetic cardiovascular responses being diminished and more variable.[63–65] Abnormal heart rate variability is more pronounced during sleep and during interictal discharges.[59,66] Patients with refractory temporal lobe epilepsy show greater cardiovascular dysfunction than do those with well-controlled temporal lobe epilepsy,[67,68] which parallels the relative risk for SUDEP (ie, greater cardiovascular dysfunction in refractory epilepsy). A short-term (< 2 years) cohort study of the incidence of SUDEP in patients treated with vagal nerve stimulation found no evidence for a significant effect of vagal nerve stimulation on SUDEP.[69,70]

Increased QT intervals have been reported during epileptic discharges on electroencephalography (EEG) in animal models and in recordings of epilepsy patients with SUDEP compared with those without SUDEP.[71,72] Anecdotal evidence suggests that electrophysiologic abnormalities such as Brugada syndrome may play a role in patients with SUDEP.[73] ST-segment depression during or just after a seizure was described in 40% of patients in one series.[74] However, the incidence of ST changes was not increased in patients who later died of SUDEP compared with control patients who had similar seizures,[75] and cardiac troponin levels were not elevated after monitored epileptic seizures.[76]

Evidence for autonomic dysfunction in patients with SUDEP was provided by a study of ECG and EEG data from monitoring unit evaluations of SUDEP patients compared with non-SUDEP epilepsy controls.[75] Patients who had died of SUDEP displayed a significantly higher maximal ictal heart rate change.

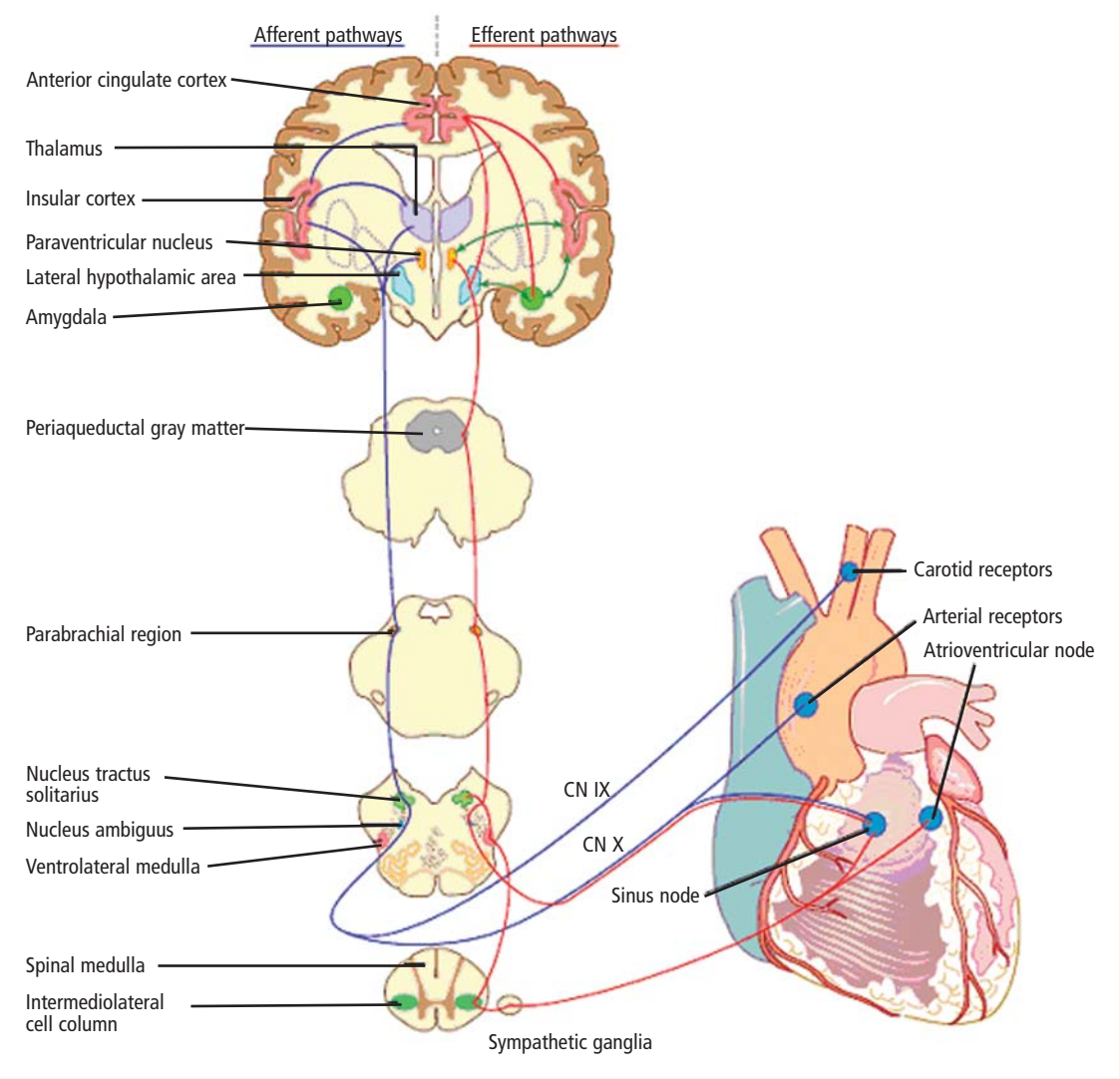

FIGURE 1. The cardiovascular autonomic system. **Afferent pathways (violet):** The afferent loop of the cardiac autonomic system receives input from chemoreceptors and baroreceptors in the carotid sinus (cranial nerve [CN] IX) and the aortic arch (CN X). The incoming visceral sensations are projected via lamina I of the spinal cord to the nucleus tractus solitarius and from there via the parabrachial region to the primary viscerosensitive cortex located in the insula. **Efferent pathways (red):** The anterior cingulate and orbitofrontal cortex send projections to the hypothalamus and amygdala, but also to the autonomic centers within the brainstem: the periaqueductal gray matter, parabrachial nucleus, nucleus tractus solitarius, nucleus ambiguus, and rostral ventrolateral medulla. The parasympathetic influence on the heart arises primarily from the nucleus ambiguus. The sympathetic output receives tonic excitation from the ventrolateral medulla and projects from the intermediolateral cell columns to the cardiac conduction system and ventricle. **Integrated response to emotion and stress (green):** The amygdala has reciprocal connections with the cerebral cortex and mediates autonomic response to emotions via projections to the hypothalamus and brainstem. The paraventricular nucleus of the hypothalamus controls internal homeostasis and innervates the autonomic relay centers in the rostral ventrolateral medulla, nucleus tractus solitarius, parabrachial nucleus, and preganglionic vagal and sympathetic neurons. Modified from reference 37.

The heart rate increase was most pronounced in seizures that arose from sleep. However, ictal cardiac repolarization and rhythm abnormalities occurred at a similar frequency in the two groups (56% vs 39%, P = .39).

Ictal cardiac bradycardia and ictal asystole occur infrequently with seizures, and the possibility that they may be related to SUDEP has been proposed.[77] Ictal bradycardia occurs in fewer than 2% of seizures, mostly those of temporal and occasional frontal lobe origin.[78–83] Rocamora et al reported ictal cardiac asystole, lasting as long as 60 seconds, in 5 of 1,244 monitored patients.[84] Ictal bradycardia and asystole can occur as a primary ictal event or secondary to apnea.[17,18,84] Ictal bradycardia seems to be of localizing rather than lateralizing value, suggesting temporal lobe onset in patients with partial epilepsy.[83] Ictal bradycardia is probably underdiagnosed, as diagnosis

requires the fortuitous occurrence of a clinical event during a combined EEG/ECG recording. In a recent study in which patients were monitored with long-loop ECG over several months, significant bradycardia/asystole (prompting cardiac pacemaker insertion) was noted in 4 (21%) of 19 epilepsy patients.[85]

Various electrophysiologic mechanisms seem to be related to bradycardic arrhythmias during epileptic seizures: the majority of case reports describe a progressive deceleration of heart rate leading into asystole. A few cases of high-grade atrioventricular block have been described, and in one case the atrioventricular block was triggered by epileptic seizure activity limited to the left temporal lobe.[80,86] However, direct evidence linking bradycardic arrhythmias to SUDEP is still lacking.[87]

In an autopsy study, increased levels of deep and subendocardial fibrosis were observed in SUDEP patients compared with controls, which may reflect the result of repetitive sympathetic activation or recurrent hypoxemia from seizures.[88] Subsequent scarring and interstitial fibrosis may lead to discontinuous propagation and dispersion of cardiac conduction, and may predispose to malignant tachyarrhythmias.[88] Other studies have demonstrated microscopic evidence of cardiac disease in SUDEP patients.[89,90] However, cardiac troponin levels are not elevated after seizures, and it has not been proven directly that myocardial damage occurs during seizures.[91]

PREVENTION OF SUDEP

Optimal control of seizures through compliance with antiepileptic drug therapy or epilepsy surgery is of paramount importance in preventing SUDEP. Early and successful epilepsy surgery for drug-resistant epilepsy may significantly reduce the risk of SUDEP.[10–12] In patients with refractory epilepsy, noncardiac causes for SUDEP remain difficult to prevent, and measures are currently limited to optimizing positioning and supervision during the ictal event to ensure adequate respiration. For patients at risk, observation or sound monitoring during the night might detect nocturnal seizures and reduce the risk of SUDEP.

There is increasing hope that cardiac cases of SUDEP may be preventable, at least in part, through the use of medical therapy to block the massive central sympathetic surge during ictal events. Alternatively, implantable loop recorders offer the possibility of detecting patients with ictal bradycardia/asystole, who might then benefit from insertion of a permanent pacemaker. However, so far there is only circumstantial evidence linking ictal bradycardia and asystole to SUDEP, and there is also no proof that the implantation of pacemakers will prevent SUDEP.

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Hydrocephalus and the heart: Interactions of the first and third circulations

Chronic hydrocephalus and cardiovascular disease are related, which may result in a dangerous cycle of pathophysiology in elderly patients. Evidence suggests that patients with chronic adult hydrocephalus, also referred to as normal-pressure hydrocephalus, have vascular disease. Studies have shown an increased incidence of arterial hypertension, cardiac disease (including ischemic heart disease, valvular disease, and congestive heart failure), and cerebrovascular atherosclerotic disease in patients with chronic adult hydrocephalus compared with age-matched controls.[1–6]

A major coordinating factor in the regulation of interactions between the cerebrospinal fluid (CSF) and the cardiovascular system appears to be cardiac impulse control. The CSF spaces of the cranium play a critical role in cardiac impulse absorption by surrounding the cerebral vasculature and controlling blood flow, allowing CSF circulation, when diseased, to reduce blood flow, and CSF manipulation to enhance blood flow. This article briefly reviews proposed mechanisms for interactions between the CSF circulatory system and the cardiovascular system.

CSF AND THE CARDIOVASCULAR CIRCULATION

CSF is produced mainly in the choroid plexus at a rate of about 400 mL/day. It flows through the ventricles of the brain, exits the brain, flows around the hemispheres, and eventually is absorbed through the venous system back into the circulation. This cycle can be obstructed within the ventricular system or outside the brain before absorption, which is termed "obstructive" or "communicating" forms of hydrocephalus, leading to dilation of the ventricles and compression of the brain.

Recent imaging technologies have revealed that CSF moves within the subarachnoid space in harmony with the cardiac cycle. The energy of this movement is several times the energy of its movement through the circulation.

As formally described by Cushing in 1925, the first area of contact between the CSF and the cardiovascular circulation is at CSF secretion and absorption sites. A second contact zone is at the CSF space and cerebral vessels. A third site of interaction is at the brain regulatory nuclei, with expansion of the ventricular system.

CSF VENTRICULAR ENLARGEMENT

Pressure forces within the ventricles, the brain, and the subarachnoid spaces must be balanced for ventricles to retain their size. If these forces become imbalanced, either by an increase in ventricular pressure or a change in the resistance or compliance of the brain, the ventricles may enlarge. A canine model of obstructive hydrocephalus confirmed increased pressures with occlusion of the ventricle, resulting in ventricular enlargement. As chronic hydrocephalus developed, the brain became less compliant.[7] With acute decompression (CSF drainage), the hydrocephalic brain became more compliant.

Hydrocephalic brain: A worn-out spring

To understand this phenomenon, we can apply mathematical spring constants in which compliance is dependent on intracerebral pressure and CSF volume. The hydrocephalic brain can be thought of as a worn-out spring in which the ventricles compress the brain against the skull, decreasing the brain's compliance. With acute CSF drainage, the spring is released and the brain becomes softer (more compliant).

Changing the spring's constant

Chronic hydrocephalus changes the spring's constant; under conditions of large ventricles, the compliance is lower than normal, but under conditions of smaller ventricles, the compliance is higher.

The brain as a sponge

The blood vessels within the brain, and not the brain itself, appear to be the compressible components that

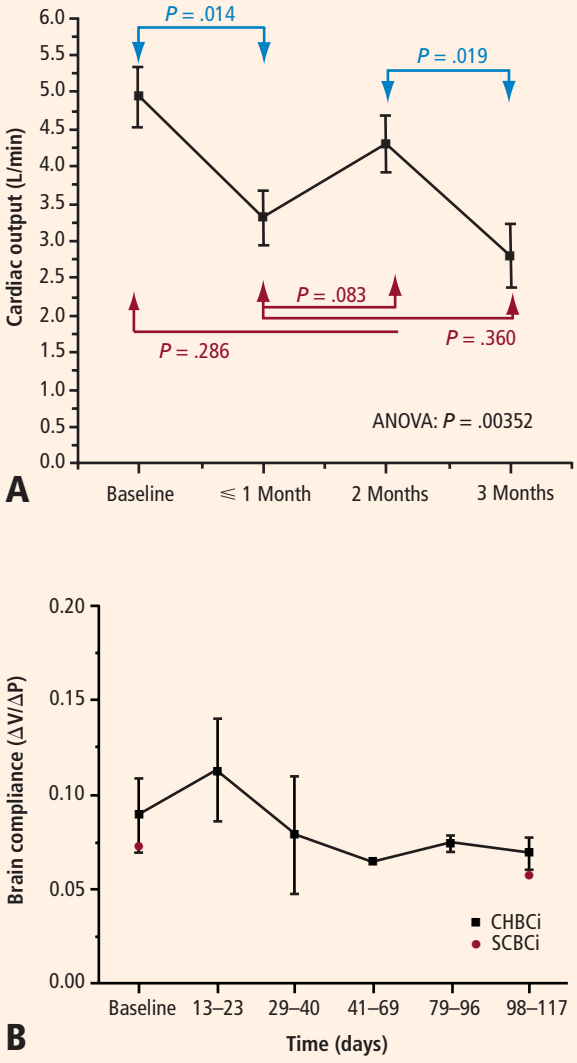
* Both authors reported that they have no financial relationships that pose a potential conflict of interest with this article.

allow for acute changes in volume and re-expansion. If this is so, then changes in blood flow should cause changes in brain compliance. When hydrocephalus is induced in animal models, a reduction in cerebral blood flow occurs, as measured using a microsphere technique, which permits observation of blood flow in any tissue.[8] With obstructive hydrocephalus, we found the same reduction of blood flow in cardiac tissue,[8] which suggests that hydrocephalus is not simply a local brain phenomenon but that blood flow in the brain is part of a response to the general cardiovascular blood supply. In this sense, cerebral blood flow is under the control of the heart. This phenomenon is confirmed by measuring cardiac output, which changes in a pattern similar to changes in blood flow.[8] This pattern of change indicates that cardiac output, and not simply expansion of the ventricles, is responsible for changes in cerebral blood flow.

Brain compliance in these animals was found to be inversely correlated with cardiac output and vascular flow **(Figure 1)**. The inverse correlation suggests that brain stiffness is governed by cerebral blood flow. Also, if the presence of cardiovascular disease decreases blood volume, then the brain may have a smaller vector to oppose the expanding ventricular system.

The amplitude of intracranial pulses serves as an indication of compliance. We found that in animal models of chronic obstructive hydrocephalus, the pulse amplitude is significantly reduced compared with normals, a finding that suggests a softer, more compliant brain (unpublished results). With CSF infusion, pulse amplitude increases to a greater degree in the hydrocephalic animal, indicating less tolerance to the infusion.

Research in the 1970s demonstrated that enlargement of CSF ventricles occurs because of an imbalance of pulsations between the CSF space and brain.[9] Di Rocco et al were able to cause ventriculomegaly by increasing pulsations within the ventricular system without changes in CSF absorption or secretion.[9,10]



CHBCi = chronic hydrocephalus, brain compliance as measured during the cerebrospinal fluid infusion method
SCBCi = surgical control, brain compliance as measured during the cerebrospinal fluid infusion method

FIGURE 1. (A) A significant decrease in cardiac output is observed after surgical induction of chronic hydrocephalus in dogs. (B) In the same animals, brain compliance increased over the same period that cardiac output decreased, indicating that brain compliance is inversely correlated with cardiac output and vascular flow.

HYDROCEPHALUS AND CARDIAC DISEASE: A FEEDBACK LOOP?

Chronic adult hydrocephalus may increase the risk of cardiovascular disease via compression of cardioregulatory nuclei near the hypothalamus, as already described. Early cerebral blood flow is no different in animal models with hydrocephalus compared with controls, but a divergence in cerebral blood flow between hydrocephalic animals and controls is observed with time **(Figure 2)**.[8] Examination of cardiac output and central venous pressure shows similarly late development of congestive heart failure in hydrocephalus.[8] Electrocardiographic data confirm signs of congestive heart failure in chronic hydrocephalus (unpublished results).

A strong relationship between ventriculomegaly and cardiac output was also observed, as was a relationship between cardiac output and cerebral blood flow.[8] Therefore, unlike the intuitive concept that the

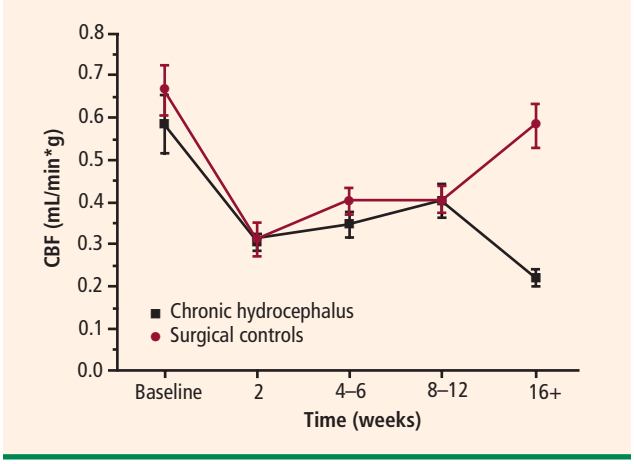


FIGURE 2. Cerebral blood flow (CBF) is not different between control dogs and those with early hydrocephalus, but decreases significantly ($P < .01$) over time in the dogs with chronic hydrocephalus (CH) compared with the surgical controls.

enlarged ventricles have a direct effect on cerebral blood flow, the link between ventriculomegaly and cerebral blood flow may instead be mediated to a great extent by general systemic blood flow and changes in cardiac output.

If changes in cardiac function can increase brain compliance and exacerbate hydrocephalus, and chronic hydrocephalus can result in congestive heart failure, then chronic hydrocephalus and chronic cardiac failure may represent a vicious pathophysiologic cycle in the elderly.

CSF AND CARDIAC IMPULSE ABSORPTION

The CSF spaces play a critical role in cardiac impulse absorption.[11] The direct contact between the CSF space and the cerebral vasculature, which exists in the subarachnoid space, is a dynamic place of CSF movement and pulse changes, and is also believed to be the place where the brain controls its impulses. Like every organ in the body, the brain receives cardiac impulses, and through the elasticity of the blood vessels, arterial pulsations are dampened to a more steady (ie, continuous) stream of blood. This vessel compliance, which makes blood flow more even, is called the Windkessel mechanism.

When an artery expands in the cavity of the rigid skull, some fluid needs to be displaced as a result. CSF fluid movement occurs at the cervical medullary junction into the spinal canal, compressing veins epidurally and within the CSF spaces. If movement of CSF decreases as a result of disease of the dura or the brain, an increase in CSF pressure, or occlusion, then these arteries are less able to enlarge, blood inflow is compromised, and compliance of the vascular system decreases. In this way, cerebral vascular compliance is dependent, to some extent, on CSF space compliance.

CSF: The brain's shock absorber

Patients with chronic hydrocephalus have abnormal compliance waves and abnormal intracranial pulsations, indicating that intracranial pressure is increasing because arteries are unable to expand. The CSF serves as the brain's shock absorber in that the impact of the blood is absorbed by CSF spaces, allowing intracranial pulsations to be absorbed by CSF spaces before they are able to reach the brain and capillary system. However, the spring constant of the hydrocephalus brain is changed, perhaps because the brain is stiffer in certain circumstances and softer in others, allowing dyssynchrony between expansion and contraction of these springs.

The constant of synchrony is important because arriving impulses must be met by an oscillating CSF space system, and this system has its own constant and its own preferred frequency. In control dogs without hydrocephalus, we found that the energy of the cardiac impulse is best absorbed at the normal cardiac frequency, which suggests that the brain and the heart are in tune at this frequency.[12] In dogs in which hydrocephalus is induced, the energy absorption trough at the cardiac frequency is much wider and shallower, which indicates that the hydrocephalic brain does not absorb the cardiac impulse as well as in normal situations.

Effective absorption of cardiac impulses and production of smooth blood flow through the capillary system via the Windkessel effect reduces vessel wall oscillation, capillary trauma, and blood inertial impedance, resulting in more efficient blood flow. Consequently, compromised absorption of cardiac impulses allows more of these impulses into the capillary system and brain, decreasing the efficiency of blood flow. In the future, alterations of the brain's ability to absorb cardiac pulsation may allow improvement in cerebral blood flow.

SUMMARY

Hydrocephalus is not always caused by blockage in absorption; it can result from an imbalance in cardiac impulse distribution that can cause a ventriculomegaly in chronic communicating hydrocephalus. Chronic ventriculomegaly may result in cardiac dysfunction, which may beget a pathophysiologic cycle in the elderly.

The CSF spaces play a critical role in cardiac impulse absorption: cerebral blood flow may be diminished in CSF disease and enhanced by its manipulation.

The interface between the CSF circulatory system and cardiovascular system is based on certain organizing principles, at least one of which appears to be the control and regulation of cardiac impulses that are reaching the brain tissue.

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Cognitive impairment in chronic heart failure

Advances in the treatment of ischemic heart disease have resulted in the survival of an increasingly elderly population with chronic heart failure (CHF). Approximately 5 million Americans suffer from CHF, and an additional 20 million are presymptomatic with a reduced ejection fraction.[1] As the heart fails, so do other organs; renal failure and the profound weight loss of cardiac cachexia are significant determinants of mortality. However, it is the decline in cognitive functioning that can significantly reduce patients' quality of life at a time when physical abilities are limited. This article reviews patient characteristics associated with cognitive impairment in CHF as well as conditions that may contribute to it.

THE SCOPE OF THE PROBLEM: IMPACT ON OUTCOMES AND PATIENT CARE

Within the past several decades, awareness of the presence and impact of cognitive impairment in patients with CHF has grown. Most of our understanding is derived from the detailed study of small numbers of patients or limited testing in larger groups participating in epidemiologic studies or clinical trials. A literature review of heart failure studies from 1966 to 2000 revealed only 13 that reported on the cognitive status of 907 patients.[2] From these data, the message is that some degree of cognitive impairment is common, affecting about half of all patients with CHF.

The presence of cognitive impairment in patients with CHF is significantly associated with increasing age, impaired activities of daily living, reduced independence in daily living, and worsening heart failure.[3,4]

The risk of CHF also increases with age, affecting 10% of those older than 70 years, and is a major cause of hospitalization among the elderly. Cognitive impairment in this group is particularly common. In a study of 92 consecutive patients with CHF admitted to a geriatric unit over a 6-month period, cognitive screening with the Mini Mental State Examination (MMSE) was performed prior to discharge.[5] Confounding causes of dementia, such as Alzheimer disease, vascular dementia, psychiatric disorders, or substance abuse, were excluded, leaving 57 patients (mean age: 77) available for the final analysis. MMSE scores less than 24, consistent with dementia, were present in 53% of patients, with the worst performance observed on tests of complex reasoning. In addition to advanced age, an association between MMSE and left ventricular ejection fraction (LVEF) was evident: subjects with LVEF of 30% or less had worse cognitive scores than those with higher LVEF.[5]

Although age is an important risk factor, cognitive impairment in CHF patients is not exclusive to the elderly. In small studies employing detailed neuropsychological testing in a pretransplant assessment, approximately 50% of patients fulfilled criteria for cognitive impairment.[6–8] In one study, the 62 patients were an average age of 44.7 years.[6] Overall cognitive impairment was documented in 58%, and 13% to 66% of individual test items were abnormal. Most difficulties were observed in reasoning and concept formation, attention, and psychomotor skills.[6] Within this young age group, the older patients (> 50 years) fared worse, as did those with worse CHF as indicated by greater right atrial pressures and lower stroke volume, cardiac output, and cardiac index.[6–8]

In a large pharmacoepidemiologic study, cognitive screening was performed at the time of discharge in 13,635 patients, including 1,583 with CHF.[4] Cognitive dysfunction in patients with CHF was independently associated with disability, as it was present in 57% of those who were disabled vs 13% of those who were independent.[4] Disability in CHF patients is predictive of poorer quality of life, higher medical resource consumption, increased mortality, and more frequent hospitalizations.

Approximately 50% of hospital admissions for heart failure are associated with poor compliance with a prescribed treatment plan. Among patients hospitalized for decompensated CHF, 42% to 80% were noncompliant with medications and 49% to 78% were noncompliant with diet.[9] Addressing these

* Dr. Sila reported that she has no financial relationships that pose a potential conflict of interest with this article.

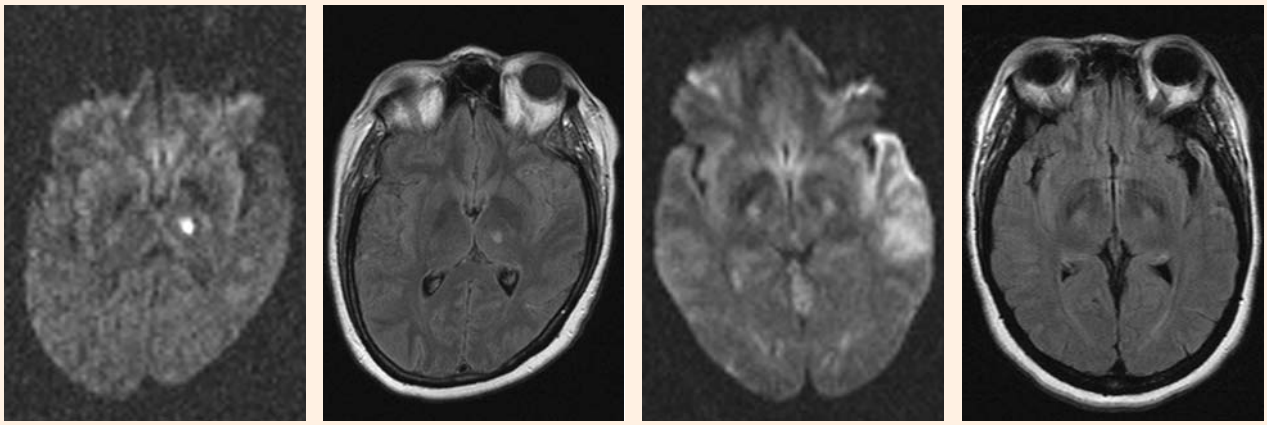

FIGURE 1. (A) A 53-year-old woman with a left ventricular ejection fraction (LVEF) of 20% presented with a sudden onset of hypersomnolence, abulia, and short-term memory loss. She repeated questions and confabulated answers. These effects were persistent and disabling. An acute left mesial thalamic lacunar infarct was identified on diffusion-weighted magnetic resonance imaging (MRI) (left) and T_2-weighted fluid-attenuated inversion recovery (FLAIR) MRI (right). (B) A 43-year-old woman with LVEF of 10% presented with a sudden onset of agitated delirium with memory loss, dysnomia, and poor comprehension. Diffusion-weighted MRI (left) demonstrated an acute left temporal lobe infarct. On follow-up, she had persistent cognitive residual. Follow-up T_2-weighted FLAIR MRI (right) depicts the evolution to temporal atrophy.

issues through intensive postdischarge disease management programs can reduce rehospitalization rates, although the cost to implement these programs exceeds hospitalization cost savings.[10] As cognitive impairment has a significant impact on patients' ability to understand and comply with treatment plans that may be complicated, an improved understanding of this issue could lead to more targeted, and perhaps more cost-effective, treatment of these patients.

FACTORS CONTRIBUTING TO COGNITIVE IMPAIRMENT IN CHF

A number of potential mechanisms have been identified by which CHF can lead to cognitive impairment. These include vascular injury from ischemic or hemorrhagic stroke, injury after cardiac arrest or cardiac surgery, and chronic cerebral hypoperfusion. Brain atrophy, disordered cerebral metabolism, and neurotransmitter dysfunction have also been described as pseudodementia related to depression and sleep deprivation from sleep-related breathing disorders. In addition, it is likely that multiple mechanisms can interact in individual patients.

Stroke

CHF has emerged as the second most common cardiac condition leading to stroke.[11] More than 90% of heart failure is caused by dilated cardiomyopathy, in which the risk of stroke is increased two- to threefold.[11] The development of cognitive impairment after stroke (ie, vascular dementia) is related to the size and location of cerebral injury. Strategic damage to the dominant medial thalamus or temporal lobe will manifest primarily as cognitive impairments, whereas dominant frontal or posterior temporal lesions result in the language impairments so critical to cognitive testing **(Figures 1A and 1B)**.

Most have a cardioembolic mechanism. A multiplicity of infarcts can also produce a subcortical pattern of cognitive inflexibility and prolonged cognitive processing. This pattern may also be a result of a series of inapparent infarcts. Silent cerebral infarcts are common and have been identified in 34% of patients undergoing neuroimaging prior to transplantation.[12] Most of the strokes are ischemic and consistent with a cardioembolic mechanism, which is supported by the relationship between stroke risk and severity of CHF. The overall annual risk of stroke is relatively low, at 1.3% to 3.5%, but certain subsets of patients, such as the elderly, women, those with prior stroke or diabetes, and especially those with worse LVEF, are at increased risk.[13] Stroke risk increases by 18% for every 5% decline in LVEF, from an incidence of 1.5% to 2% with LVEF of 30% to 35%, to an incidence of 2% to 4% with LVEF less than 10%.[14] Worsening left ventricular function leads to increased end-diastolic volume, which, in turn, results in intracardiac stasis and thrombus formation.[1,15]

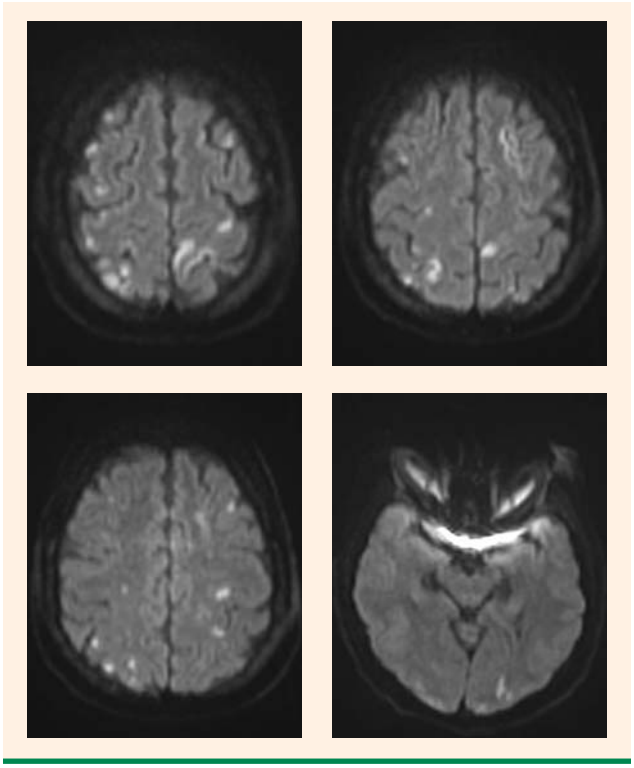

FIGURE 2. A 37-year-old man with a left ventricular ejection fraction of 20% and a 7-year history of ischemic heart disease sustained an acute myocardial infarction with cardiogenic shock requiring intra-aortic balloon support and urgent coronary revascularization. He was slow to awaken after minor sedation, abulic, and disoriented, and had impaired memory but no other focal sensorimotor or visual abnormalities. Note the multifocal infarcts on diffusion-weighted magnetic resonance imaging throughout the cortex.

In elderly patients with CHF, atrial fibrillation is independently associated with cognitive decline, increasing the risk 3.4-fold. This relationship is lost, however, if patients with a history of cerebrovascular events are excluded, implying that the contribution to cognitive impairment is largely exerted through damage from cardioembolic stroke.[3,4]

Other stroke subtypes. Although most strokes are cardioembolic, this population is also at risk for other stroke subtypes. Atherosclerotic risk factors for coronary heart disease, such as hypertension, hyperlipidemia, diabetes, and cigarette smoking, are also risk factors for cerebrovascular disease, resulting in artery-to-artery embolism or stenosis, or occlusion of large cervicocephalic arteries, intracranial arteries, or small perforating arterioles. Intracranial hemorrhage is an established complication of antithrombotic therapies used to prevent ischemic stroke, particularly with anticoagulant use in the elderly.

The risk of stroke after acute myocardial infarction (MI) is 2% to 4%, and is particularly high in the elderly with CHF. Transcranial Doppler (TCD) monitoring of patients within 72 hours of an acute MI detected cerebral microembolism in 17% of patients, with the greatest risk in patients with LVEF less than 65%, akinetic left ventricular segments, and left ventricular thrombus.[16] Of these 17%, 3% had a symptomatic cerebral embolism **(Figure 2)**.

Patients with CHF are likely to undergo various cardiac interventional procedures that can be complicated by cerebral embolism.[17] Stroke complicates less than 0.1% of diagnostic cardiac catheterizations and 0.3% of coronary endovascular interventions. Cardiac surgery risks include a 2% to 5% risk of stroke with coronary bypass alone and a 5% to 10% risk when coronary bypass is combined with valvular surgery **(Figure 3)**.[17]

Optimal prevention therapy unknown. In the absence of atrial fibrillation, the optimum antithrombotic therapy to prevent stroke in patients with reduced LVEF is unknown. When the Warfarin and Antiplatelet Therapy in Heart Failure (WATCH) trial was terminated for poor recruitment, the available data did not demonstrate a significant difference in the primary end point of stroke, MI, or death among those randomized to treatment with warfarin (target International Normalized Ratio [INR]: 2.5 to 3.0), aspirin (160 mg/day), or clopidogrel (75 mg/day). Patients randomized to warfarin, however, experienced fewer strokes but more bleeding complications compared with the antiplatelet regimens, and patients randomized to aspirin had more hospitalizations for heart failure.[18] The ongoing Warfarin Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial continues to compare warfarin (target INR: 2.5 to 3.0) to aspirin (325 mg/day).[19] WARCEF was prospectively designed, and its end points are the same as those in WATCH. These data will hopefully clarify the best therapy for a large range of patients with CHF, and result in guidelines similar in scope to those that emerged from trials of patients with atrial fibrillation.[20]

Cerebral hypoperfusion

In the normal state, resting cerebral blood flow (CBF) is optimized within rather narrow parameters throughout a wide range of systemic blood pressures, a process known as cerebral autoregulation. In CHF, declines in cardiac output result in a redistribution of blood flow to favor the heart and brain at the expense of the skeletal muscle and the cutaneous, splanchnic, and renal vascular beds.[21] As cardiac output continues to decline, however, the capacity of cerebral autoregulation to maintain CBF is exhausted. CBF will begin

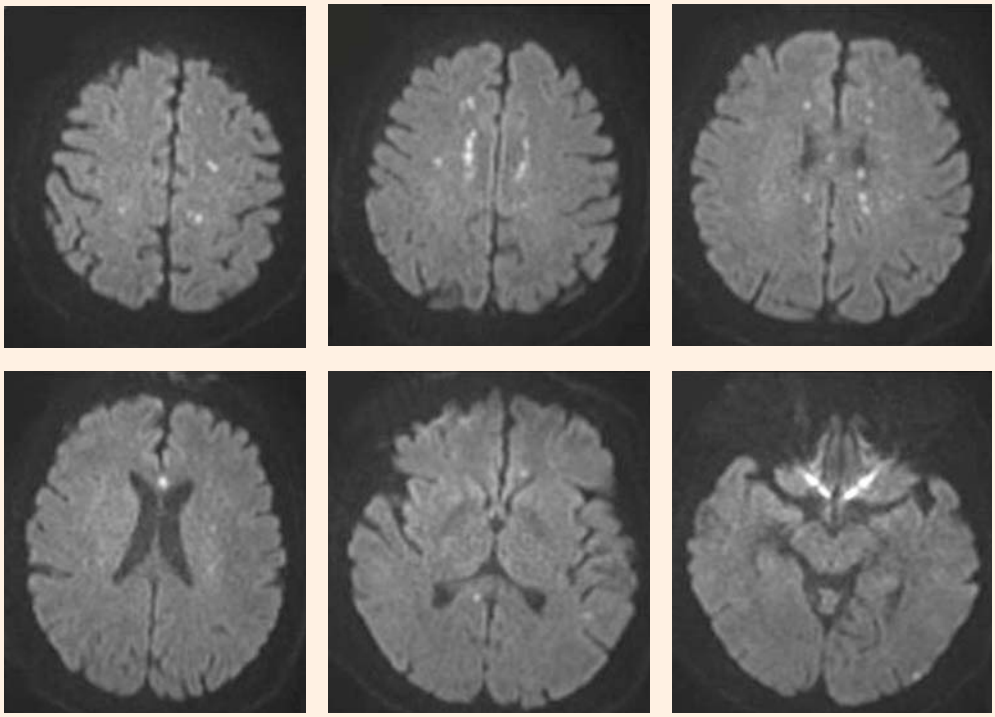

FIGURE 3. After an urgent, but otherwise uncomplicated, coronary artery bypass operation, this patient was abulic with poor attention, concentration, and memory. Encephalopathy following open-heart surgery was diagnosed. The patient had poor memory and exhibited poor attention and concentration. Diffusion-weighted magnetic resonance imaging depicted acute, multifocal ischemic injuries, which have been related to multifocal embolism or reduced clearance of emboli.

to decline when mean arterial pressures decrease to 80% of baseline, or approximately 60 mm Hg. In normal subjects, a 30% decline of CBF results in mild symptoms of cerebral hypoperfusion, and a 50% to 60% decline produces mental confusion.

As part of a pretransplant evaluation, CBF was assessed by ^{133}Xe single photon emission computed tomography (SPECT) and TCD in 12 CHF patients and matched controls.[21] In the CHF patients, resting CBF was 36 mL/min/100 g, which represented a significant 31% reduction compared with 52 mL/min/100 g in the control patients. Resting mean arterial pressures were also significantly lower in the CHF group (76 mm Hg vs 95 mm Hg). CBF and mean arterial pressure values normalized within 1 month of transplantation in the five patients who underwent follow-up testing. In this study, TCD values were somewhat more variable (lower) than SPECT values, but not significantly so, at 36 cm/sec vs 49 cm/sec. However, in another study of 22 patients who underwent heart transplant, TCD velocities increased 53% postoperatively, including 117% in one patient whose increase in CBF was associated with symptoms of hyperperfusion related to impaired cerebrovascular reactivity (an inability to rapidly vasoconstrict when impaired CBF has been rapidly corrected).[22]

The association of cognitive impairment with reduced LVEF is not linear but rather declines sharply with LVEF less than 30%.[5] In young patients with end-stage CHF, cognitive impairment is associated with elevated right atrial pressure, low stroke volume, and low cardiac index.[6] These data support the theory that cognitive impairment in CHF results from cerebral hypoperfusion. The cerebral autoregulatory mechanisms that maintain CBF will begin to fail in the setting of severe hypoperfusion.

It is not clear how the autoregulatory curve shifts in the setting of CHF and chronic hypotension.[23] It is likely to be affected by diseases that alter the function of arteriolar resistance vessels, such as hypertension and diabetes (the classic risk factors for "small vessel disease"), as well as advanced age. The capacity for cerebral vasodilation is an important compensatory mechanism to maintain CBF in the setting of reduced cardiac output. The point at which this capacity becomes exhausted would likely lead to ischemic injury. This capacity, or cerebrovascular reactivity, can be assessed by administering inhaled CO_2. As a potent cerebral vasodilator, CO_2 normally induces immediate increases in CBF that can be measured with TCD monitoring. Cerebrovascular reactivity was demonstrated to be impaired in a group of 50 patients with CHF compared with age-matched and normal controls, an impairment that was also signifi-

cantly related to LVEF and New York Heart Association (NYHA) class.[24]

Cerebral abnormalities

Brain atrophy on magnetic resonance imaging (MRI) studies is more common in CHF patients and correlates with disease duration and cognitive performance. In several small neuroimaging studies of patients with CHF, brain atrophy was present in 77%. In a comparison of 20 CHF patients and 20 age-matched controls, brain atrophy affected cortical structures in 50% of CHF patients vs 5% of controls, ventricular enlargement occurred in 55% of the cases and 15% of the controls, and cerebral infarcts were evident in 20% of the cases and 0% of the controls.[25] Wasting of other tissues—fat, muscle, and bone—occurs in cardiac cachexia, but whether brain atrophy is part of this wasting syndrome is unknown.[26] However, brain atrophy has been demonstrated in other similar chronic illnesses as well as in starvation and eating disorders.

Hydrocephalus can result from the global loss of tissue or specific loss of periventricular white matter tissue in patients with CHF. This hydrocephalus has also occasionally been associated with a fluctuating abulic syndrome similar to normal-pressure hydrocephalus syndrome. It is related to increased central venous hydrostatic pressure and delayed resorption of cerebrospinal fluid within the intracranial cavity during or after treatment of an episode of cardiac decompensation.[27] The importance of recognizing this behavioral and motor syndrome is that therapeutic lumbar punctures can result in rather rapid improvement with more gradual improvement in the neuroimaging abnormalities.

The volume loss exhibited in CHF patients does not appear to occur in a random fashion. Volumetric analyses have demonstrated significant, largely lateralized loss of gray matter in areas related to the control of autonomic and respiratory functions.[28] In a follow-up study, functional MRI was used to image the sympathetic outflow response to a cold pressor test.[29] Aberrant responses in deep and cortical structures were documented, many overlying or neighboring the previously demonstrated regions of gray matter damage. The authors postulated that the aberrant functional neural responses identified in CHF patients could contribute to the progression of the pathology of CHF.[29]

Cerebral metabolic abnormalities have also been demonstrated on magnetic resonance spectroscopy imaging, affecting the gray matter earlier and progressing more rapidly than similar changes in periventricular white matter. Loss of a specific neuronal marker, N-acetylaspartate, in the occipital lobe was associated with duration of CHF symptoms and CHF mortality.[30]

Sleep-disordered breathing

Half of CHF patients have sleep-disordered breathing, 40% due to Cheyne-Stokes respiration and central apneas and 10% to obstructive apneas.[31] The disruption of sleep cycles leads to a reduction of restorative sleep with daytime somnolence and cognitive impairment. This pattern is important to recognize because effective treatment for 1 to 3 months has been demonstrated to improve quality of life and reduce symptoms of daytime fatigue, inattention, and memory complaints, as well as improving LVEF by 5% to 10%.[32]

The presence of central breathing abnormalities may also be an indicator of impending exhaustion of CBF autoregulatory mechanisms. Cerebrovascular reactivity was assessed by TCD monitoring during hypocapnia (voluntary hyperventilation) and hypercapnia (20-second breath-holding) in CHF patients with and without central sleep apnea.[33] Apnea patients had poorer cerebrovascular reactivity, primarily due to poor vasoconstrictor response during hypocapnia, and smaller CBF surges after breath-holding. This impairment was proposed to be the cause of the breathing instability by causing ventilatory overshooting with high P_{CO_2} and undershooting during low P_{CO_2}.

Depression and pseudodementia

Depression is reported by about half of CHF patients and correlates with NYHA class and perceived control of their illness.[34] Depression is significantly associated with abnormalities on neuropsychological testing, and may contribute to cognitive impairment through poor attention and effort. Among young patients with end-stage CHF, 37% reported depressive symptoms in a pretransplant evaluation.[6] Those who went on to transplantation experienced some reduction in anxiety, but both transplanted and non-transplanted patients exhibited increased depression over a mean follow-up of 3 years.[6]

Concomitant dementias

Cognitive impairment has been described in patients after heart surgery, particularly those procedures that require cardiopulmonary bypass or opening the cardiac chambers. A clinically apparent confusional state or encephalopathy identified by simple cognitive screening persists to the fourth postoperative day in 5% to 12% of patients, but 80% of cases resolve by discharge.[17] However, detailed neuropsychological testing reveals cognitive deficits in 35% to 75% of

patients, strongly linked to age.[17] Persistent coma or "failure to awaken" after heart surgery is fortunately rare, at 0.2%.[17] Patients with advanced CHF are also at increased risk for malignant arrhythmias and cardiac arrest. Overall, about 20% of CHF patients have another cause for dementia, such as Alzheimer disease, with or without an element of vascular dementia.[5]

CONCLUSION

Cognitive impairment in CHF is common, affecting half of all patients, and increases with the severity of heart disease and advanced age. It is an important predictor of disability, poorer quality of life, increased frequency of hospital admissions, and mortality. Cognitive screening should be routinely incorporated into patient evaluations, particularly when poor compliance is identified. The mechanism of cognitive impairment is multifactorial, and multiple causes may be present in any individual patient, which increases the complexity of the evaluation but also offers the possibility of multiple avenues for improvement.

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Cardiac events and brain injury: Ethical implications

The collection of work on the interfaces of the heart and brain contains an incredibly rich set of implications and perspectives. Likewise, the set of ethics issues raised by, and as a result of, these research projects encompasses a wide array of topics. This article will explore some of these ethical questions, recognizing that the overarching themes involve bringing the heart and brain back together so that we talk about the *whole person* in health and function, a concept emphasized by Dr. Earl Bakken in his remarks at the opening of this Heart-Brain Summit. Notably, the whole person exists in a network of hearts and brains that compose social networks—a point we must not forget in our exuberance to gain new knowledge and help those who suffer.

BASIC UNDERLYING CONSIDERATIONS

Before approaching a selection of specific ethics questions, the following formulations of ethical points and questions should be kept in mind.

'Because we can' does not mean we should

This first consideration is a cautionary statement about the importance of understanding that some apparently heroic activities may, in fact, entail more harm and suffering than nonaction would. We are obligated to carefully reflect on our goals and practices at each step of innovation, research, and treatment.

How do we act in the face of great uncertainty?

Given the significant uncertainties regarding the complexities of human life—particularly regarding the heart, the brain, and the interaction between the two—we need to be clear about how we wish to act when there is great uncertainty.[1] This requires careful reflection on what valuable things are lost and gained by taking a more cautious or aggressive posture toward research and innovation.

At what cost, and to whom?

When thinking about the posture we take, we need to understand the cost of our endeavors in terms of suffering and harm as well as in terms of resources. This evaluation must take into account *to whom* the cost accrues. It is a matter of justice to assure that no population bears an undue burden in the development of therapies and the advancement of scientific understanding.

RECOGNIZING ASSUMPTIONS AND VALUES IS CENTRAL

The topic suggested for the current discussion was "cardiac events and brain injury: ethical issues." It was not "cardiac events *leading* to brain injury," although that topic will dominate these reflections. There are cases in which brain injuries also lead to cardiac events. The bidirectional importance of each organ creates the foundation for heart-brain research. In fact, these heart-brain research projects call into question many traditional assumptions about the (un)connectedness of the two systems. Since good ethics requires clear understanding of basic assumptions, these new ways of thinking rightfully should cause us to reflect carefully on our ethical balancing.

Two categories of dilemmas in heart-brain medicine

Numerous scenarios allow us to reflect on interesting ethical dilemmas; these fall into two general categories:

- Brain injury after a cardiac event
- Allowing cardiac events that lead to brain injury.

The first category typically involves neurological criteria for death, patients with chronic disorders of consciousness,[2] or patients with diminished motor function. The second category typically involves withdrawal of therapy and cardiac criteria for death.

A balancing of values

Ethical dilemmas exist when there are disagreements over whether one valuable thing must be sacrificed—and to what degree—to preserve another valuable thing. **Table 1** presents several valued things that everyone would likely agree are desirable

* Dr. Ford reported that he has no financial relationships that pose a potential conflict of interest with this article.

in as great a proportion as possible.

Each of these values plays an important role in enabling us to live our lives well. The goal of much heart-brain research should focus on helping people live their lives well by treating them as integrated systems and selves. That means treating the whole person, a concept that echoes a classic ethics issue dating back to Aristotle and well before.

RECENT CASES HIGHLIGHT KEY ISSUES

Several recent high-profile cases of brain-injured patients illustrate how a number of traditional medical ethics questions can be particularly relevant to heart-brain medicine and research.

The case of Terri Schiavo: Medical uncertainty cannot be eliminated entirely

Terri Schiavo and her family recently became central to a heated debate about life-preserving treatments for persons with severe brain damage. At age 25, Ms. Schiavo had a cardiac arrest that resulted in severe brain injury; she was eventually diagnosed as being in a permanent vegetative state. In this case there was a cardiac event leading to a brain injury and then possibly a subsequent cardiac event after the withdrawal of artificial nutrition and hydration many years after the initial events.

A brief look at a 2002 computed tomograph of Ms. Schiavo's brain (released by Ronald Cranford, MD,* with permission from Michael Schiavo and available at http://www.msnbc.msn.com/id/7328639/) is powerful in that it shows severe atrophy of the brain. In spite of the massive brain damage apparent on that scan, some kind of organic life had continued for many years even though there were no indications of a cognitive life. In spite of very aggressive and experimental therapy, including placement of a deep brain stimulator in 1990, Ms. Schiavo's condition did not improve.[3] In March 2005, artificial hydration and nutrition were removed and her heart eventually stopped.

This case involved a number of interesting ethically charged decisions. There is no clear explanation as to when the aim of care shifted from aggressively attempting treatment, such as placement of the deep brain stimulator, to focusing on a respect of Ms. Schiavo's past wishes of not living in a vegetative state. The case also underscores the need to think carefully about the implications of developing better predictors of neurologic outcomes after cardiac events. With better predictors, we might make different decisions at the time of a cardiac event. The case also raises questions of what the cost in human suffering was to those who surrounded Ms. Schiavo and had interacted with her.

To a great degree the troubling choices in this case, as in many cases, hinge on a degree of uncertainty that can never be removed completely. Questions about the cost of being wrong always persist. At the same time, physicians must act in the face of uncertainty.

Much of the discussion about this case contained very deep value suppositions. Likewise, value suppositions were central to the family members' opposing positions up to the end, as revealed by the statement Ms. Schiavo's husband had inscribed on her grave marker:

SCHIAVO
THERESA MARIE

BELOVED WIFE

BORN DECEMBER 3, 1963
DEPARTED THIS EARTH
FEBRUARY 25, 1990
AT PEACE MARCH 31, 2005

I KEPT MY PROMISE

When discussing issues of brain injury we cannot avoid confronting these underlying value assumptions. We should take the wide variety of views about the world into account when we undertake the practice of heart-brain medicine. Reflectively understanding our assumptions will better allow us to understand the true costs of decisions in brain injury cases, particularly as perceived by patients and their families.

The case of Ariel Sharon: When to use innovative therapies, and in whom?

Different issues are raised by the case of former Israeli prime minister Ariel Sharon, who had a stroke related to a cardiac condition—patent foramen ovale (PFO).

TABLE 1
Ethical values at stake

Length of life
Quality of life: maximizing function
Quality of life: minimizing suffering
Fiduciary responsibility/respect for patients
Justice
Improvement of treatments and increase in knowledge (research)

* I am indebted to Dr. Cranford, who recently passed away, for his influence on a number of these points.

This was another well-publicized case, and there was much discussion about the role that Mr. Sharon's PFO played in his neurologic insult.[4] This debate highlights questions about the use of innovative medical therapies and interventions. Although the stroke occurred prior to Mr. Sharon's scheduled PFO closure, it is important to ask about the strength of the evidence concerning the causal connection between PFO and stroke. How strong of a connection must be proved before an innovative treatment is adopted as a standard?

This question is particularly important in light of the difficulties of performing randomized trials after patients begin to demand an innovation despite a lack of the degree of evidence that supports most other established medical therapies. We need to avoid the problems experienced in the 1990s when autologous bone marrow transplants were performed to treat breast cancer even though no proof of benefit existed.

In addition to ensuring that innovative therapies are sufficiently studied before being widely used, great care needs to be taken in considering to whom innovative therapies are applied and in whom they are studied. We need to be careful to balance justice issues for both the powerful and the powerless. The powerful should not be overtreated, and the powerless should not be experimented upon for convenience.

The case of Jean-Dominique Bauby: What makes a life worth living?

A final example involves the case of Jean-Dominique Bauby, the editor of a French fashion magazine who suffered a cerebral vascular event (pontine stroke) that left him with "locked-in" syndrome. This condition did not prevent Mr. Bauby from writing his autobiography, which he composed one letter at a time by blinking his left eye as an assistant pointed to a letterboard. In the resulting book, entitled *Le Scaphandre et le Papillon* (translated in English as *The Diving Bell and Butterfly*), Mr. Bauby describes his mind as being like a butterfly while his body is like a diving suit. After his stroke, he redefines himself in many ways that challenge our conception of which lives are worth living.[5]

Indeed, the diversities of lives that can become worth living must be kept in the forefront of our minds as we explore and develop heart-brain medicine. We must be sure to explore carefully the elements of life most valued by individual patients and research subjects.

DUELING DEFINITIONS OF DEATH

Death forms an implicit thread throughout this discussion, with questions raised about both physical and social death. It is important to point out that the indicators for death are again under debate, with the roles played by the heart and the brain in the declaration of death continuing to be controversial.

Neurological criteria for death appear to make the brain most central in the survival of the self and mind. This definition of death seems to hinge on understanding a person as primarily a thinking being. When properly applied, however, the neurological criteria are extremely reliable in predicting the cessation and permanent absence of a return to life. The increasing belief that death is defined as the failure of the brain has called into question the traditional cardiac criteria for death—ie, cessation of heart and lungs. We can see an interesting lack of consensus even among neurointensivists about cardiopulmonary death when discussing solid organ transplantation after cardiac death.[6] There is considerable discussion about when—ie, how long after the heart stops beating—a patient who has had life support withdrawn is "dead" in the way that allows organs to be harvested for donation. Perhaps current or future heart-brain research projects will result in a set of neuro-cardiac criteria for death that will be more integrative and thus more acceptable to all.

RESEARCH VALUES MAY DIFFER FROM CLINICAL VALUES

In undertaking the fascinating and complicated research of heart-brain interactions, we should make explicit the values underlying innovation and research. These values include good data, benefit to others who are similar to the subject (but not the subject himself or herself), and enhancement of the researcher's career (potential dual-role conflict of interest). These values are not necessarily the same as those espoused strictly for clinical care, and attempts to preserve some of these values of innovation and research can complicate patient treatment. Again, at each step we must consciously balance the risks and benefits for specific patients and subjects.

CONCLUSION

Good ethics starts with a clear understanding of assumptions and good knowledge. In many ways we have a moral obligation to strive for greater scientific understanding. However, this pursuit of knowledge always must be constrained by a careful evaluation of the costs to those around us, those we treat, and those who are willing to participate in research. We need to carefully assess issues as fundamental as even what counts as a harm or a benefit to particular individuals

and communities. Is it always a good thing to restart a heart, reduce intracranial pressure, or generally preserve function?

In our efforts to do work that is performed well and does good, we need to respect the diversity of value choices we find among our fellow persons. This includes carefully providing strong and clear justification for deviating from standard practice both in innovation and in research on those who are sick.

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