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INTRODUCTION

LAS October, the 2009 Heart-Brain Summit—the fourth annual summit of this type presented by the Bakken Heart-Brain Institute—was held in Chicago and built on the first three summits’ tradition of open-minded discussion, out-of-the-box thinking, scholarly activity, and engagement of attendees from varied backgrounds.

DEPRESSION AND HEART DISEASE:
A WATERSHED YEAR, OR JUMPING THE GUN?

The year leading up to the 2009 summit may be remembered as a watershed period for the field of heart-brain medicine, in light of the American Heart Association’s (AHA’s) inclusion of the recommendation to screen patients with coronary artery disease (CAD) for depression in its science advisory on depression and CAD.1 As has been discussed at prior Heart-Brain Summits, there is incontrovertible evidence in the literature that CAD patients with depression have a worse prognosis than do their counterparts without depression.2–6 While the link is clear, the etiology or mechanism behind depression’s association with worse CAD outcomes is debated. Possible reasons for the association range from greater nonadherence with medical therapy7 to increased systemic inflammation related to the decreased vagal tone associated with depression.8 Furthermore, there is clear evidence that patients with depression and CAD can be treated for their depression safely with cognitive and pharmacologic therapy.5,9 What is lacking, however, is convincing data that the treatment of depression in patients with CAD leads to improved outcomes.10

The topic for the first half of the opening day of the 2009 summit was whether the AHA has gotten ahead of itself in its science advisory1 and whether we should require demonstrable benefits from the treatment of depression in CAD patients before screening for depression is recommended in all patients with CAD. This is a critically important question for the field as well as for the Bakken Heart-Brain Institute, which under our leadership has been advocating for a clinical trial to address this very issue. Cardiologists addressing this question were well reminded that logical therapeutic targets without proven end points have failed us in the past. For instance, it was a rational concept that the suppression of premature ventricular contractions in patients with a history of acute myocardial infarction would lead to decreased ventricular tachycardia and death. Unfortunately, when this concept was put to the test in a randomized clinical trial, increased death was observed in the treatment group.11 More recent examples—and perhaps more applicable to depression, given its chronic nature—come from recent clinical trials demonstrating that tight blood sugar control is associated with higher mortality than moderate blood sugar control in critically ill patients12 and that intensive blood pressure control does not yield greater reductions in cardiovascular events compared with moderate blood pressure control in patients with type 2 diabetes.13

So we are faced with a chronic disease state—depression—that is clearly linked to adverse outcomes and death in patients with CAD. In the context of this association, we also know the following:

- The AHA science advisory recommends that we screen all CAD patients for depression.
- Treating depression in heart disease patients is safe.
- There is no clear proof that treating depression will reverse the increased risk associated with depression in patients with CAD.
- There is a community of physicians who treat CAD patients who are skeptical about therapies that do not have outcomes data.

The summit’s first morning concluded with a debate on whether now is the time for a large-scale multicenter randomized trial, which raised several important issues:

- The limited effectiveness of treatment for depression (approximately 30% to 40%)
- The ethics of randomizing a patient with depression to placebo
- The required size of the trial, given the efficacy of antidepressant therapy
- Measures to define response to therapy
- The utility of surrogate markers for adverse events in CAD versus a mortality end point.

The discussion and presentations were excellent and animated. In the end, each attendee was left to reach his or her own conclusion. Personally, one of us (M.S.P.) was surprised to be left with the conclusion that we are not ready for a definitive clinical trial.

In the cardiovascular medicine literature we were faced with a similar situation regarding the management...
of patients with atrial fibrillation. In the AFFIRM trial, patients were randomized to conservative treatment (rate control and warfarin) or aggressive treatment (rate control, warfarin, and any and all therapies to convert to and maintain normal sinus rhythm). Ultimately there was no difference between the groups, with a trend toward improved outcomes in the conservatively treated patients. What we really learned was that our therapies to convert to and maintain normal sinus rhythm were inadequate, and that in the case of atrial fibrillation at least we could clearly identify which patients did not respond to therapy. These findings ultimately may have led the field astray, as we still do not know if we have efficacious therapies for the treatment of atrial fibrillation and whether patients would benefit.

### Strategies for Modulating Heart-Brain Interactions

In line with the need for more effective strategies to modulate heart-brain interactions, the summit went on to review and discuss the role of biofeedback. If the effects of depression, post-traumatic stress disorder, and other psychological modulators of vagal tone are the mechanism of action for adverse outcomes in these patient populations, then methods to directly modulate vagal tone may prove efficacious. Within the Bakken Heart-Brain Institute we recently committed half a million dollars to fund a biofeedback program. The program’s goal is to investigate the efficacy of biofeedback in improving outcomes within and across several states of cardiovascular disease and chronic disease. We believe that rigorous and standardized delivery and quantification of the effects of biofeedback are critical in order to robustly determine the role of biofeedback in the treatment of patients with chronic disease.

The group of experts assembled at this year’s summit presented further evidence of the potential importance of biofeedback for the control and treatment of multiple disorders, including heart failure, epilepsy, and chronic headache. As the mechanisms underlying brain interactions with end-organ innervations and systemic inflammation are dissected, it is clear that this field of medicine will have greater impact on the outcomes of many patient populations.

### Cross-Fertilization of Treatment Approaches

The summit abounded with evidence and examples of how neurology, cardiology, and psychiatry continue to cross-fertilize one another and foster interdisciplinary innovation. We were fortunate to have Brian Litt, MD, from the University of Pennsylvania return for the 2009 summit to update us on the progress of detecting, mapping, and extinguishing early seizure activity before there is clinical evidence of a seizure. The lessons learned and clinical advancement of internal cardiac defibrillators offer insights and great hope for this potentially important advancement in the treatment of seizure disorders. Similarly, Irving Zucker, PhD, from the University of Nebraska reviewed how neuromodulation through the baroreceptors can be targeted to modulate arterial blood pressure. Clearly there is great potential for device-based therapies to augment the treatment of chronic hypertension and improve outcomes in clinical populations at risk.

### A Look Ahead

Many of the topics reviewed above are discussed in detail in the proceedings supplement that follows. We continue to be excited and gratified by the progress being made in the field of heart-brain medicine. The continuing commitment to the rigorous multidisciplinary approach that has served this field well to date will continue to advance our understanding of disease and improve outcomes in our patients. We hope you will join us September 23–24, 2010, at the Lou Ruvo Center for Brain Health in Las Vegas, Nevada, for the 2010 Heart-Brain Summit, our fifth annual gathering.

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ABSTRACT

Depression is prevalent in patients with heart failure, and the two conditions share underlying physiologic mechanisms. The prevalence of depression increases sharply with the severity of heart failure symptoms, an important consideration when confronting patients with worsening heart failure. Depression leads to poorer outcomes in patients with heart failure, including increased risk of poor functional status, hospital readmission, and death. Although beta-blockers are often implicated in the development and exacerbation of depression, evidence for this association is lacking, so withholding beta-blocker therapy is not recommended for patients with heart failure and depression. Evidence on whether therapy for depression also improves cardiac outcomes in heart failure patients is inconclusive, and further research on this question is needed. Nevertheless, early identification of depression in heart failure patients is imperative, as it can facilitate intervention attempts.

Depression is common in patients with heart failure

Many studies show that rates of depression among patients with heart failure are higher than expected among other elderly, chronically ill patients. Furthermore, depression has been linked to more severe heart failure symptoms and worse outcomes in some studies. In a 2001 study, Jiang et al screened 374 hospitalized patients with heart failure using the Beck Depression Inventory score and found that 35% had scores of 10 or higher (indicative of at least mild depression).12 Further testing showed that 14% met criteria for major depression.

A 2006 meta-analysis of 27 studies by Rutledge et al found a 21% incidence of clinically significant depression in patients with heart failure.17 Rates of depression depended heavily on the rigor of screening criteria for classifying participants as depressed: rates were as high as 38% with the use of liberal criteria and as low as 14% with strict criteria. New York Heart Association (NYHA) functional status correlated strongly with the prevalence of depression, which increased steadily from 11% in patients with NYHA class I (mild) heart failure to 20% in those with class II, 38% in those with class III, and 42% in those with class IV (severe) heart failure.

In one of the studies included in the meta-analysis, Freedland et al found that the prevalence of major depression was strongly associated with age and functional status in hospitalized patients with heart failure.18 In patients younger than age 60 years, rates of major depression rose particularly sharply as heart failure symptoms worsened.

The Psychosocial Factors Outcome Study found that...
The prevalence of depression in patients with heart failure who participated in the community-based Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) was 36%, based on a score of 13 or greater on the Beck Depression Inventory-II. Similarly, unpublished preliminary data from the Heart Failure Adherence and Retention Trial (HART) show that about one-third of community-based patients with heart failure have depression.

**DEPRESSION AND HEART FAILURE ARE CLOSELY LINKED PHYSIOLOGICALLY**

The underlying relationship between depression and cardiovascular disease is depicted in Figure 1. It shows the commonality of pathophysiologic mechanisms for the two conditions.

The likely psychological and physiologic mechanisms leading to depression in patients with heart failure are almost identical to the list of mechanisms proposed for the development of heart failure itself (Table 1), including autonomic dysregulation, hyperproduction of cortisol, and a prothrombotic and proinflammatory state. One interesting line of study involves a polymorphism in the serotonin transporter gene, which increases the amount of catecholamine secretions secondary to stress in mice. The serotonin transporter gene has also been found to be associated with depression during stress in humans. Likewise, norepinephrine has been found to be a risk factor for adverse outcomes in patients with coronary artery disease and heart failure.

The evidence, therefore, strongly suggests a common pathway between heart failure and depression, and this evidence of a relationship favors a new paradigm that integrates the treatment of the two conditions.

**BETA-BLOCKERS DO NOT RAISE RISK OF DEPRESSION**

Pharmacotherapy is often implicated as a related factor in the development or exacerbation of depression in patients with heart failure, especially in those taking

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**Figure 1.** Numerous alterations in biologic markers observed in depressed subjects may contribute to their increased vulnerability to cardiovascular disease, including sympathoadrenal hyperactivity, diminished heart rate variability, ventricular instability and myocardial ischemia in response to mental stress, and alterations in platelet receptors and platelet reactivity.

Reprinted, with permission, from Archives of General Psychiatry (Musselman DL, et al. Arch Gen Psychiatry 1998; 55:580–592), Copyright © 1998 American Medical Association. All rights reserved.
beta-blockers. Meta-analyses of the incidence of depression associated with various beta-blockers have been conducted in patients with hypertension, heart failure, and recent myocardial infarction. A 2002 meta-analysis of eight trials that randomized patients to treatment with a beta-blocker or placebo found no difference in the incidence of depressive symptoms between the active treatment and placebo groups, or between patients in the two groups who withdrew from the trial, presumably because of depression or other symptoms. An additional study not included in that meta-analysis found no differences in rates of depression among hypertensive patients according to the type of antihypertensive medication they were taking (ie, beta-blockers, diuretics, reserpine, or no drug therapy).

Based on the evidence, I see no reason to avoid a trial of beta-blockers in patients who have depression at baseline or to be overly concerned that patients without depression will develop it as a result of beta-blocker treatment.

**DEPRESSION LEADS TO WORSE OUTCOMES, HIGHER COSTS IN HEART FAILURE**

Not only is depression prevalent in patients with heart failure, but depression adversely affects heart failure outcomes. One study of hospitalized patients older than 70 years found readmission rates to be 67% among heart failure patients with depression versus 44% among heart failure patients without depression. Patients in this study were three times as likely to die if they had heart failure than if they did not have heart failure, and they were twice as likely to die if they had depression than if they did not have depression. The mortality rate was 21% for patients with both heart failure and depression versus 15% for patients with heart failure without depression.

Depressive symptoms also correlate with poorer quality of life in patients with heart failure. Gottlieb et al found that quality-of-life scores were significantly worse in heart failure patients if they had a diagnosis of depression on the basis of the Beck Depression Index.

The 27-study meta-analysis by Rutledge et al discussed earlier found that the presence of depression in a patient with heart failure predicts worse outcomes in terms of hospital readmission rates, functional status, and walk times. This analysis also found twice the rate of death in heart failure patients with depression compared with heart failure patients without depression.

In a large community-based trial involving more than 48,000 patients with heart failure, Macchia et al found that survival was markedly reduced in patients who had a history of depression. This study also showed that depressed patients were less likely to adhere to medication regimens with angiotensin-converting enzyme inhibitors and beta-blockers, which may offer a potential explanation for the reduction in survival among depressed patients.

In a study of patients with coronary artery disease who had no diagnosis of depression or heart failure, May et al demonstrated that those who subsequently developed depression had more than four times the risk of also developing heart failure.

The combination of heart failure and depression also is costly. In a 3-year retrospective study of community-based patients following a first hospitalization for heart failure, Sullivan et al found that annualized adjusted total costs were nearly 30% greater in patients diagnosed with depression and that inpatient and outpatient service utilization was also greater in those with depression.

**DIAGNOSIS AND TREATMENT**

One simple question can effectively screen for depression

Numerous tools are available for the diagnosis of depression, but developing a tool that is readily useful to a busy clinician is challenging. Simply asking the single question, “Are you depressed?” has fairly high sensitivity (55%) and specificity (74%) for diagnosing depression in palliative care patients, a population even more seriously ill than heart failure patients. A variation on the question from British studies—“Do you feel that your life is empty?”—is considered to be a better screening question for elderly patients.

**Effect of depression therapy on heart failure still unclear**

Unfortunately, evidence for the best treatment for depression in patients with heart failure is lacking. Some guidance may be gleaned from studies in patients with coronary artery disease. The Sertraline Antidepressant
Heart Attack Randomized Trial (SADHART) was a multicenter, randomized, placebo-controlled study of the safety and efficacy of treating major depressive disorder with sertraline for 24 weeks in patients hospitalized for acute coronary syndrome.33,34 No significant differences were found between treatment groups in left ventricular ejection fraction, blood pressure, resting electrocardiogram, and cardiac arrhythmias. Although the trial was not powered to detect an effect of treatment on mortality, there were fewer deaths and severe cardiovascular adverse events in the active treatment group. A later study was designed to evaluate 12 weeks of treatment with sertraline in patients with major depression and heart failure.35 Although symptoms of depression improved with treatment, no beneficial effect on heart failure was found. A nursing intervention that was included for both the treatment and placebo groups may have served to limit the impact of sertraline on heart failure surrogate end points.

The abovementioned HART study randomized patients with systolic or diastolic dysfunction and NYHA class II or III functional status to receive either heart failure education (comprising 18 American Heart Association tip sheets and 18 phone calls) or heart failure education plus self-management strategies (comprising the tip sheets, 18 group sessions, and problem-solving and self-management skills) following hospital discharge. Over 3 years, no difference between the two groups was found in the rates and timing of deaths or heart failure hospitalizations.

The best treatment strategies for depression in heart failure are still unclear, and more research is needed. Although guidelines exist for the management of depression in patients with coronary heart disease, no such guidelines have been issued for the management of depression in heart failure.

**CONCLUSIONS**

Although evidence is strong that treatment with medication or cognitive therapies improves symptoms of depression, evidence is lacking for a significant effect of such interventions on cardiac outcomes.39 Because depression and heart failure are so closely linked and appear to share a genetic and pathophysiologic basis, greater understanding of the relationship between these diseases across the stages of heart failure should be pursued.

Any patient with heart failure who is symptomatic has advanced disease, and is therefore closer to death than to health. The same is probably true of depression. Patients with heart failure and depression must be identified early, and interventions must be tried at these early stages of disease. Better screening tools and heightened awareness of the relationship between heart failure and depression are essential.

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The American Heart Association science advisory on depression and coronary heart disease: An exploration of the issues raised

ABSTRACT

The American Heart Association issued a science advisory on depression and coronary heart disease (CHD) in 2008. This paper reviews the purpose and content of the advisory and discusses reactions and new information that have followed the advisory’s release. Both the advisory and subsequent data support routine screening for depression in patients with CHD. Such screening can be done efficiently in primary care and cardiology settings and can effectively identify many depressed patients who would otherwise go undetected. Antidepressant drugs such as selective serotonin reuptake inhibitors are safe for use in patients with CHD, can reduce depression, and can improve adherence with medical therapy. Referral to a practice with the knowledge and resources to manage depression promotes successful management of depressed patients with CHD.

In 2008, the American Heart Association (AHA) published a science advisory on depression and coronary heart disease (CHD).1 Since its publication, the advisory has evoked substantial commentary. The purpose of this article is threefold: (1) to explain the aims of the AHA science advisory, (2) to briefly discuss its content, and (3) to examine some of the comments it has provoked.

WHAT THE ADVISORY SET OUT TO DO

The purpose of an AHA science advisory is to provide rapid, clear, and consistent AHA positioning on a scientific issue. Advisories are statements on an evolving, prominent scientific issue of great interest to the public and health professionals. All AHA science advisories undergo peer review and are also reviewed and approved by the AHA Science Advisory and Coordinating Committee, AHA’s highest science body. Because this particular advisory addressed the interaction of cardiovascular and mental health, the AHA asked the American Psychiatric Association (APA) to review the document; the APA endorsed the AHA advisory.

Two points are worth emphasizing:
• An AHA science advisory is not a treatment guideline.
• Advisories usually are brief and therefore do not exhaustively discuss their topic.

After discussing epidemiologic studies that elucidated the relationships between depression and CHD, the AHA advisory on depression and CHD focuses on screening, referral, and treatment of depression from a cardiology perspective.

The 1-year prevalence of major depressive disorder in the US general population is 7%, and the lifetime prevalence is about 16%.2 Depression in otherwise healthy persons almost doubles the risk of developing CHD.3 About 20% of patients hospitalized for acute coronary syndromes (ACS) have major depressive disorder on admission or within a few weeks thereafter, and these patients have about 2.5 times the mortality rate as patients who are not depressed, after adjusting for infarct severity and cardiovascular risk factors.4-6

ASSESSMENT OF DEPRESSION AND DEPRESSIVE SYMPTOMS

The AHA advisory discusses use of the 2-question Patient Health Questionnaire (PHQ-2) as the first step in screening for depression.7,8 The PHQ-2 inquires about the frequency of depressed mood and anhedonia by asking the following:

Over the past 2 weeks, how often have you been bothered by either of the following problems?
(1) Little interest or pleasure in doing things
(2) Feeling down, depressed, or hopeless.
DEPRESSION TREATMENT

Drug therapy

The safety of fluoxetine, sertraline (SADHART, ENRICHD), citalopram (CREATE), and mirtazapine (MIND-IT) has been evaluated in clinical trials. By far the strongest evidence of safety is for selective serotonin reuptake inhibitors (SSRIs), especially sertraline.

The Sertraline Antidepressant Heart Attack Randomized Trial (SADHART; N = 369), a randomized study of depression after ACS, found no difference in cardiovascular adverse events between the sertraline and placebo groups after 16 weeks of therapy, and there were no significant differences in left ventricular ejection fraction, heart rate, blood pressure, ventricular premature complexes, or electrocardiogram changes. In the group assigned to sertraline, life-threatening cardiovascular events occurred less frequently (15% vs 22%, P = NS).

The Enhancing Recovery in Coronary Heart Disease study (ENRICHD) was a large trial (N = 2,481) to evaluate the effect of cognitive behavioral therapy (CBT) on depression or low perceived social support in patients enrolled within 28 days of myocardial infarction (MI). The ENRICHD protocol required patients randomized to CBT with Hamilton Depression Rating Scale (HAM-D) scores greater than 24, or who showed less than 50% reduction in Beck Depression Inventory (BDI) scores after 5 weeks of CBT, to be referred to a study psychiatrist for consideration of pharmacotherapy, usually sertraline. Of the overall ENRICHD population, 1,834 participants (74%) had a diagnosis of depression, and 446 of these participants (24%) were treated with antidepressant drugs, 301 with an SSRI and 145 with other antidepressants. During mean follow-up of 29 months, the SSRI-treated group had a statistically significant 43% reduction in death or MI.

The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) recruited 284 patients with chronic CHD, major depressive disorder, and a 24-item HAM-D score of 20 or greater and randomly assigned half to citalopram (another SSRI) and half to placebo. Citalopram showed antidepressant efficacy and no evidence of harm.

The Myocardial Infarction and Depression Intervention Trial (MIND-IT) recruited 91 patients within 30 days of hospital admission for MI with depression and randomized them in a 1:1 ratio to mirtazapine or placebo. Mirtazapine showed some evidence of antidepressant efficacy and no evidence of harm.

Strik et al in the Netherlands recruited 54 patients who had major depression after a first MI and randomized them 1:1 to the SSRI fluoxetine or placebo 3 months after the MI. The fluoxetine group showed a trend toward antidepressant efficacy, and no cardiovascular safety problems were detected clinically or by either electrocardiogram or echocardiogram.

Psychotherapy

APA practice guidelines for major depressive disorder indicate that among psychotherapeutic approaches, CBT and interpersonal psychotherapy have the best-documented efficacy for treatment of major depressive disorder. CBT...
Aims to solve problems related to dysfunctional emotions, behaviors, and cognition and is an umbrella term for various techniques that share a theoretical basis in behavioristic learning theory and cognitive psychology. Aaron T. Beck proposed that depressed people are quick to make negative evaluations of themselves and the world, and he designed treatment to reduce these negative cognitions. Interpersonal psychotherapy stems from the work of Harry Stack Sullivan, who believed that emotional reactions were triggered by interpersonal behaviors. Gerald Klerman and Myrna Weissman used this method to treat adults diagnosed with moderate or severe nondelusional clinical depression.

CBT was used in ENRICHD, interpersonal psychotherapy in CREATE, and problem-solving therapy in the Coronary Psychosocial Evaluation Study (COPES). Unintended therapy can also be a confounder in antidepressant drug trials; education and supportive care (e.g., frequent visits or telephone calls with monitoring of depressive symptoms and counseling) are often provided for both the intervention and control (placebo) groups. If a study is blinded, education, supportive care, and attention will be identical for both groups and thus may reduce the likelihood of finding a difference between the drug and placebo, if one exists.

Psychotherapy can be helpful for depression, is preferred over antidepressant drugs by some patients, and can be combined with drugs to increase antidepressant efficacy. We still have much to learn about timing and choice of therapy, as well as about sequencing and combination of antidepressant drugs and psychotherapy.

**Physical activity and exercise**

Aerobic exercise and cardiac rehabilitation can reduce depressive symptoms in addition to improving cardiovascular fitness. Depression can serve as a barrier to participation in cardiac rehabilitation and exercise programs, but cardiologists can help depressed patients overcome this barrier by offering encouragement and follow-up contacts. Cardiologists also should enlist the help of spouses or other family members and friends to promote adherence. The prescription of exercise needs to be based on the cardiac status and exercise capacity of each individual.
SUMMARY OF ADVISORY RECOMMENDATIONS

The AHA advisory1 summarized its recommendations as follows:

1. Routine screening for depression in patients with CHD should be considered in a variety of settings, including the hospital, the physician’s office, clinics, and cardiac rehabilitation centers. The opportunity to screen for and treat depression in cardiac patients should not be missed, as effective depression treatment may improve health outcomes.

2. Patients with positive screening results should be evaluated by a professional qualified in diagnosis and management of depression. Such a clinician can determine whether depression is present and needs treatment, as well as how to connect a patient to an effective care program in the local area.

3. Patients with heart disease who are being treated for depression should undergo careful monitoring for adherence to their medical care and for the efficacy and safety of drug therapy for their medical and mental health conditions.

4. Coordination of care among health care providers is essential for patients with coexisting medical and mental health issues.

COMMENTS ON THE ADVISORY

Since AHA advisories usually address evolving scientific issues, the knowledge base on these issues is constantly growing and a range of opinions and hypotheses are tenable, pending new information. Soon after the AHA science advisory on depression and CHD was issued, a systematic review on depression screening and patient outcomes in cardiac care was published.31 This review posed three key questions that are explored below.

Three key questions

Key question 1: What’s the accuracy of screening instruments for depression in cardiovascular care populations? To answer this question, a case-finding method such as a questionnaire (eg, BD1 or PHQ) must be compared with a structured interview by mental health personnel as the “gold standard” for diagnosis (ie, the truth).

To estimate the accuracy of clinical diagnosis by general practitioners, Mitchell et al pooled data from 50,371 primary care patients across 41 studies in Europe or the United States to evaluate general practitioners’ ability to make an unassisted diagnosis of depression (ie, without specific help from severity scales, diagnostic instruments, education programs, etc).32 They reported a sensitivity of about 50% and a specificity of 81% when the prevalence of depression was about 20%. In other words, general practitioners missed about half the cases of depression when no case-finding tool was used. These researchers pointed out that a low prevalence of depression favors identification of nondepressed cases (false-positive diagnoses), whereas a high prevalence favors diagnosis of depression (true-positive diagnoses).32

Cardiologists focused on treatment of ACS are probably less likely to make a clinical diagnosis of depression and may attribute emotional symptoms to rapidly evolving cardiovascular events. The simple 2-question PHQ-2 case-finding instrument (see page SX) takes only a few minutes to administer and is recommended for use by primary care physicians or cardiologists to evaluate patients at high risk for depression or who manifest symptoms suggestive of depression.7

In the United States, most patients with depression are cared for in primary care venues. The AHA advisory recommends referring ACS patients who screen positive on a PHQ to a professional qualified in the diagnosis and management of depression.1 Enhanced care—using outreach, monitoring, adjustment of therapy, and psychiatric backup—produces significant improvement in depression.33

Key question 2: Is treatment of depression in cardiovascular care patients effective in improving depression? Cardiac outcomes? The evidence for benefit of SSRI therapy for depression detected at the time of ACS is consistent and was discussed above.4,17–21 However, the antidepressant effect of SSRIs is modest in placebo-controlled trials. Most such trials excluded patients who were taking antidepressant drugs when screened, and many patients recruited for antidepressant clinical trials had no previous episodes of depression, had relatively mild symptoms of short duration, and were recruited by screening (ie, they were not seeking treatment for depression).34 Patients with brief and short episodes are likely to remit spontaneously and to respond to psychotherapy or supportive care.34 Moreover, in most antidepressant trials, both the intervention and “control” groups received elements of enhanced depression care, which will reduce the apparent benefit of antidepressant drugs. For instance, because the primary goal of SADHART was to evaluate the safety of sertraline in patients with ACS, monitoring for adverse effects included six or seven visits during 16 weeks of follow-up plus six or seven phone calls, providing several elements of enhanced depression care, including face-to-face education, frequent follow-up, support by a case manager (research coordinator) with a mental health background, and support from a psychiatrist or psychologist.17 Randomization to sertraline or placebo in SADHART was blinded, so the frequent contact and support was the same in both groups.

Whether SSRI treatment for depression will improve survival and cardiovascular outcomes is not established by adequately powered randomized trials. Most randomized (SADHART, CREATE) or nonrandomized (ENRICHED) studies suggest that SSRIs reduce cardiovascular events,
but only ENRICHd produced a statistically significant result. SSRIs—certainly sertraline and citalopram—are not associated with significant cardiovascular adverse effects, even during ACS, when the cardiovascular system is unstable and multiple drugs are being started and titrated. Patients who do not improve significantly during antidepressant drug therapy or psychotherapy have a two- to threefold increase in cardiovascular events compared with patients who do improve substantially.15

Key question 3: Is systematic screening for depression more effective than usual care for identifying patients with depression? Facilitating treatment of depression? Reducing depressive symptoms? Improving cardiac outcomes?

Screening patients with CHD, especially those with ACS, is more effective than usual care (no screening). Indeed, many depressed patients go undetected unless identified by screening. Not surprisingly, those identified by screening tend to have milder depression. For example, half the participants in SADHART had a HAM-D score less than 18 (≥ 25 is considered severe). However, a considerable number identified by screening had above-average HAM-D scores but either viewed their symptoms as appropriate for their medical condition or were simply denying their psychiatric illness. If patients had not been screened, their depression would not have been detected or treated. Even among SADHART participants with baseline HAM-D scores less than 18, those whose depression failed to respond to sertraline/placebo had twice the 7-year mortality rate as did those whose depression remitted.16

The Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT) examined the impact of a care management intervention on suicidal ideation and depression in older primary care patients and reported outcomes over a 2-year follow-up.17 PROSPECT screened 9,072 patients in 20 primary care practices to find 599 study participants aged 60 years or older with major or minor depression (not all had cardiovascular disease). Participants were randomly assigned to either usual care or the PROSPECT intervention, which consisted of services rendered by trained care managers who offered algorithm-based recommendations to physicians and helped patients adhere to treatment during the 24-month trial. Compared with patients receiving usual care, those receiving the intervention had a greater likelihood of receiving antidepressant drugs and/ or psychotherapy (85%–89% vs 49%–62%) and had a 2.2-fold greater decline in suicidal ideation over 24 months. Treatment response started sooner in the intervention group and continued to improve at 18 and 24 months; no appreciable increase in treatment response was observed in the usual-care group during the same period. Among patients with major depression, a significantly greater percentage of the intervention group achieved remission compared with the usual-care group at 4, 8, and 24 months. Patients with minor depression had favorable mental health outcomes regardless of treatment assignment. Sustained collaborative care maintained high utilization of depression treatment, reduced suicidal ideation, and improved the outcomes of major depression during 2 years of follow-up.37

No randomized trial of SSRIs has been designed to show an effect on mortality or cardiovascular events. ENRICHd has produced the strongest evidence that an SSRI can reduce mortality or cardiovascular outcomes. The study was designed with approximately 85% power to detect a 25% to 30% reduction in the primary end point (death or MI) as a result of CBT; as noted above, 2,481 patients (1,834 with depression) were randomized to usual care or CBT within 28 days of MI.4 Depression significantly improved with CBT, but the rate of death or MI did not: during mean follow-up of 29 months, death or MI occurred in 299 patients in the CBT group versus 300 in the usual-care group.4 A post hoc analysis specific to the 1,834 ENRICHd participants who had depression aimed to determine the effects of antidepressant drugs on morbidity and mortality.18 The protocol required patients in the intervention group with scores of 25 or higher on the 17-item HAM-D, or those who had less than a 50% reduction in BDI scores after 5 weeks of treatment, to be referred to study psychiatrists for consideration of pharmacotherapy. Study psychiatrists met with patients who were being treated with antidepressant drugs to monitor medication use. Unless contraindicated or previously ineffective or poorly tolerated, sertraline was the first antidepressant used. Using a time-dependent multivariable Cox proportional hazards regression model to adjust for baseline depression score and cardiac risk factors, the researchers found SSRi use to be associated with a statistically significant 43% lower risk of death or nonfatal MI. Like other SSRI studies, ENRICHd found SSRIs safe for post-MI patients and to possibly, but not certainly, reduce death and MI.18
Medication adherence

One obvious but important way antidepressant drug therapy could prevent death or MI is by improving adherence to post-MI cardiovascular drugs. Four or five classes of cardiac drugs have each been proven to improve survival following ACS (aspirin, beta-blockers, statins, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers), and when all are taken regularly, mortality is reduced by about half.\textsuperscript{38,39} In addition, antihypertensive and antidiabetic drugs are often needed to control blood pressure or blood glucose. However, patients have to actually take these drugs to receive their benefit. Depression in the setting of CHD, especially ACS, is a risk indicator for lack of adherence to medical therapy, mental health therapy, or both.

DiMatteo et al conducted a meta-analysis to test the hypothesis that anxiety and depression might explain poor adherence to treatment recommendations and result in poor medical outcomes.\textsuperscript{15} Of the 25 trials that met the inclusion criteria, 13 studied anxiety and 12 studied depression. The associations between anxiety and non-adherence were small and not statistically significant, but depression was strongly associated with nonadherence to medications (odds ratio = 3.03; 95% confidence interval, 1.96–4.89). In other words, depressed patients were three times as likely as nondepressed patients to be nonadherent to treatment recommendations. The authors speculated that depression might increase non-adherence in the following ways: (1) the hopelessness of depression might reduce patients’ hope in the therapy, (2) depression may cause withdrawal from family and social networks that otherwise would provide support and assistance, or (3) the impaired cognitive dysfunction associated with depression may impair memory and follow through on treatment recommendations.\textsuperscript{15}

The findings from this meta-analysis could reflect depression causing medication nonadherence or vice versa. To establish the sequence, Rieckmann et al measured adherence to aspirin therapy during a 3-month period in a consecutive cohort of 172 patients (25 to 85 years old) recruited within 1 week of hospitalization for ACS.\textsuperscript{8} Severity of depressive symptoms was quantified using the BDI during hospitalization and at 1 and 3 months after discharge. Adherence was defined as taking aspirin as prescribed on at least 80% of days. Using an electronic monitoring system that recorded the date and time when the aspirin bottle cap was opened, the study found that more than 30% of patients with post-ACS depression were nonadherent to their aspirin therapy compared with only 15% of nondepressed patients.\textsuperscript{40} The more severe patients’ depressive symptoms were, the greater the nonadherence to aspirin therapy. Moreover, a lagged correlation statistical model determined that improvement in depression preceded improvement in medication adherence.

Adherence to lifestyle recommendations

Ziegelstein et al have shown that depressed patients have poorer adherence to lifestyle recommendations (diet, exercise, smoking cessation).\textsuperscript{41} The Heart and Soul Study, a prospective cohort study of 1,017 outpatients with stable CHD, attempted to determine why depressive symptoms (as determined by PHQ-9 self-report) are associated with an increased risk of cardiovascular events.\textsuperscript{42} Participants were predominantly older men, about half of whom were recruited from Veterans Administration hospitals. A total of 341 cardiovascular events occurred during a mean follow-up of 4.8 years. Participants with baseline depressive symptoms had a 50% greater rate of cardiovascular events during the study period compared with participants without depressive symptoms. However, no significant association between depressive symptoms and cardiovascular events remained after adjustment for health behaviors—most
strikingly, physical activity. This finding was consistent with an earlier study that found that exercise therapy plus antidepressant medication could reduce the risk of cardiovascular events in patients with depression. The ongoing Understanding Prognostic Benefits of Exercise and Antidepressant Therapy (UPBEAT) study is comparing the effects of exercise and antidepressant medication on depression and biomarkers of cardiovascular risk in patients with depressive symptoms and CHD. The study's longer-term goal is to identify an intervention that improves both depression and cardiovascular disease outcomes.

**CONCLUSIONS**

The USPSTF recommends screening for depression in adults. The PHQ-2 is an efficient first-step screening tool that can identify many depressed patients who would otherwise go undetected. It is clear that SSRIs are safe in cardiac patients, can reduce depression, and can improve medication adherence, but it is not enough to screen and report depression. Optimal benefit depends on having (1) a primary care provider who is familiar with managing depression, (2) a case manager with a mental health background to follow and support patients, and (3) regular supervision of the case manager by a psychiatrist or psychologist. Cardiologists see large numbers of patients with chronic CHD, ACS, or recent coronary artery bypass graft surgery who are at high risk for depression. The AHA advisory recommends a care model that is practical for CHD patients with depression. Such a care model must be based on detection of depression and referral to a practice that has resources and knowledge to manage it well.

**REFERENCES**


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ABSTRACT

We systematically searched published empirical research on depression and cardiovascular disease (CVD) and found 494 unique articles published in 2009. Several particularly notable and provocative findings and controversies emerged from this survey of the 2009 literature. First, multiple large observational studies found that antidepressant use was associated with increased risk of incident stroke, CVD, or sudden cardiac death. Second, four randomized controlled trials on depression interventions in CVD patients reported important efficacy results that should guide future trials. Finally, the vigorous debate on whether patients with CVD should be routinely screened (and subsequently treated) for depression continued in 2009 even as some observed that routine screening for CVD in depressed patients is more evidence-based and appropriate. This article reviews these selected provocative findings and controversies from our search and explores their clinical implications.

METHODOLOGY OF OUR SYSTEMATIC SEARCH AND RATIONALE FOR FINDINGS REVIEWED

Previous evidence demonstrated that the presence of depressive symptoms or a diagnosis of a depressive disorder predicts poor prognosis and reduced survival rates after any coronary artery disease diagnosis, including myocardial infarction (MI) and unstable angina, as well as after coronary artery bypass graft surgery (CABG).1

We aimed to see how this evidence base was expanded in 2009 by using a systematic search strategy to retrieve the most relevant articles about depression and coronary heart disease (CHD) from the MEDLINE and PsycINFO (Ovid interface) databases. The most relevant subject headings and free text terms were identified and combined with “or.” The two sets were then combined with “and.” Terms included “depression,” “depressive disorder,” “depress$,” “coronary artery disease” (CAD) “coronary disease,” “acute coronary syndrome” (ACS), “cardiovascular disease” (CVD), “coronary heart disease,” and “heart disease$.” The final set was limited to the English-language literature and identified 494 unique articles published during 2009.

Closer inspection of titles and abstracts revealed well more than 100 articles directly relevant to the science and management of patients with CVD and depression or pronounced depressive symptoms. In light of this quantity, a thorough review of all new findings, editorials, and reviews is not feasible. Thus, we review here a few exciting articles in several distinct topical areas that could influence views of the relationship between depression and CVD as well as how we screen for and treat depression in patients with CVD. As with any review that is not strictly evidence-based, our choice of articles is subjective and incomplete, but we hope it will stimulate discussion and further exploration.

SUMMARY OF KEY FINDINGS AND CONTROVERSIES

The following numbered topics emerged as common themes or controversies from our survey of the 2009 literature. The remainder of this article will review find-
ings in each of these areas in detail and discuss important clinical implications as appropriate.

1. Antidepressant use and adverse cardiac events. In surprising findings, antidepressant use was associated with increased risk of incident stroke, CVD, and sudden cardiac death in multiple large observational cohort studies. It is not known if the association is caused by unmeasured confounders or depressive symptom severity, although controlling for symptom severity did not reduce this elevated risk in some studies. Another interesting possibility is that the treatment-resistant depressed patient is at particularly high risk of CVD and death.

2. Effects of depression intervention in CVD patients. Four exciting randomized controlled trials on depression intervention in patients with CVD reported important efficacy results and suggested future directions for larger, definitive trials of depression treatment for these patients.

3. Depression screening and treatment in CVD patients. In the absence of large randomized controlled trials, the debate continues on whether depression screening or any type of depression treatment is beneficial, harmless, or harmful to patients with CVD. Continuation of this debate does not serve the health and well-being of patients or the public. Less controversial—and thus less discussed—is the important insight that psychiatric patients with depression should be routinely screened for cardiac disease and risk factors, as they are clearly at risk of CVD. We await clinical trials in this area to ensure that screening leads to improved CVD outcomes.

**OBSERVATIONAL EVIDENCE ON ANTIDEPRESSANT USE AND CVD OUTCOMES**

In an analysis of the Nurses' Health Study, Whang et al examined the relationship of depressive symptoms and antidepressant use with sudden cardiac death and adverse cardiac events in 63,469 women without CVD. Depressive symptoms were assessed using the Mental Health Index, a five-item subscale of the Short Form-36 Health Survey. Among women who reported antidepressant use, most (61%) were taking a selective serotonin reuptake inhibitor (SSRI; sertraline, fluoxetine, paroxetine, or citalopram), while 39% reported use of other antidepressants. Women taking antidepressants were more likely to suffer sudden cardiac death, with a fully adjusted hazard ratio (HR) of 3.34 (95% confidence interval [CI], 2.03–5.50).

Krantz et al examined psychotropic medication use and risk of adverse cardiovascular events in 519 women from the Women’s Ischemia Syndrome Evaluation. Enrolled women underwent coronary angiography, were separated into four groups according to their psychotropic medication use (none, anxiolytics only, antidepressants only, or both anxiolytics and antidepressants), and were observed for a median of 5.9 years. Results revealed that women who received both medications had a higher risk for adverse cardiovascular events and higher all-cause mortality compared with those using neither medication, even after controlling for anxious and depressive symptoms. In addition, whereas the use of antidepressant medication was associated with a doubling of risk for subsequent CVD events (HR = 2.16; 95% CI, 1.21–3.93) and all-cause mortality (HR = 2.15; 95% CI, 1.16–3.98), use of anxiolytic medication alone was not. While this study did not examine cause of death, cardiac death is likely to have constituted a large proportion of total mortality in this cohort selected for likelihood of CAD.

Although CVD and death have long been outcomes of interest for those studying the effects of depression, additional end points have recently been investigated as well. In a prospective cohort study of 136,293 community-dwelling postmenopausal women in the Women’s Health Initiative, Smoller et al found that new antidepressant use was significantly associated with increased incidence of stroke and all-cause mortality but not with incidence of CHD. The rate of stroke per 1,000 person-years was 2.99 for subjects with no antidepressant use versus 4.16 for patients with new SSRI use; the rate of all-cause death was 7.79 versus 12.77, respectively. The rate of all-cause death for subjects with new tricyclic antidepressant use was 14.14 per 1,000 person-years. To address potential confounding by indication, the researchers obtained a propensity score from a logistic regression model to predict any new antidepressant use from demographic, lifestyle, risk factor, and comorbidity variables measured at baseline. New SSRI use was associated with a doubling of the risk of incident hemorrhagic stroke as well as fatal stroke. There were no significant interactions between use of SSRIs and use of statins or aspirin in terms of risk of hemorrhagic stroke.

In an interesting observational study of 7,709 patients with confirmed CAD but without a diagnosis of heart failure or depression (and without current antidepressant use), May et al found that a subsequent diagnosis of depression was associated with a significant 50% increase in the risk of heart failure. There was no difference, however, between depressed patients who were using antidepressants and those who were not.

Increased risk of bleeding with SSRI use, particularly in patients with CAD, has also been a concern. Kim et al evaluated 1,380 adults who received any antidepressant before CABG for in-hospital mortality or any bleeding events. After controlling for the percentage of patients taking SSRIs (78%), there were no significant differences between those taking SSRIs and those taking non-SSRIs in the rate of any bleeding events (6.5% vs 7.2%; odds ratio [OR] = 0.93; 95% CI, 0.50–1.76) or in-hospital mortality (3.1% vs 2.3%; OR = 0.88; 95% CI, 0.47–1.65). There was no increased risk of bleeding asso-
associated with SSRI use when the analysis was restricted to patients who received antiplatelet and anticoagulant therapy. Thus, compared with patients who received non-SSRI antidepressants, patients who received SSRIs preoperatively had no increased risk of bleeding or inhospital mortality after CABG; however, this study did not evaluate the effect of no antidepressant use.

Another study hypothesized that the use of any drug with the potential to prolong cardiac repolarization would be associated with an increased risk of sudden death.\(^7\) Use of individual drugs was analyzed among 1,010 cases of sudden unexplained death and 3,030 living primary care controls, all from the community. SSRI use was associated with a doubling of risk of sudden death (OR = 2.21; 95% CI, 1.61–3.05), and tricyclic antidepressant use was associated with a nonsignificant trend toward increased risk (OR = 1.44; 95% CI, 0.96–2.13). Further analysis that stratified patients according to prior CVD showed that most of the association of SSRIs with sudden death was in those with existing CVD and not in those without CVD. Other drugs found to raise sudden death risk included the typical and atypical antipsychotics.

**Summary and clinical implications**

The Nurses’ Health Study analysis by Whang et al suggested that antidepressant use triples the risk of sudden cardiac death in healthy women, and the authors suggested that the association between fatal ventricular arrhythmias and antidepressant use be examined further.\(^2\) The analysis of the Women's Health Initiative by Smoller et al found that use of SSRIs and tricyclic antidepressants doubled the risk of fatal stroke in healthy women.\(^4\) The analysis of the Women's Ischemia Syndrome Evaluation by Krantz et al revealed a doubling of the risk of CVD and death in women taking antidepressants who had been referred for coronary angiography.\(^5\) At the same time, May et al found no increase in the risk of heart failure conversion with antidepressant use in patients with CAD,\(^5\) and Kim et al found no increase in the risk of bleeding with use of SSRIs compared with non-SSRI antidepressants in patients with CAD undergoing CABG.\(^6\) Finally, in a population- and community-based case-control study, SSRI use was associated with an increased risk of sudden death, particularly in patients with CVD.\(^7\) So what are we to make of these findings?\(^8\)

In all observational studies (including those reviewed above), unmeasured confounders pose a threat to the validity of any causal conclusions. A study recently tested some of the proposed confounders that might have existed in the above studies. Waldman et al examined racial differences in depressive symptoms and antidepressant treatment among a cohort of 864 consecutive patients with CHD undergoing diagnostic coronary angiography (727 white and 137 African American).\(^9\)

While levels of depression were similar between the white and African American patients, the African Americans were less likely than their white counterparts to receive antidepressant medications. Patients with only some high school, men, and patients with more severe depressive symptoms were significantly more likely to receive a prescription for antidepressants. Clearly, low education, male sex, and elevated depressive symptoms are related to poor prognosis for CHD, and the simple interpretation that antidepressant use is causing poorer outcomes is problematic.\(^8\)

Two additional interpretations of the observational findings should be considered. First, confounding by indication (depressive symptom severity) might exist in these studies.\(^10\) In other words, patients who are prescribed antidepressant medication may be those with the most severe depressive illness, and it could be this severity, rather than the antidepressant use, that is causally implicated in the CVD incidence.\(^11\) However, all of the studies reviewed above either directly controlled for depressive symptom severity (at least as obtained at baseline) or used propensity scores or stratified subjects based on depression severity. The results showed an increased risk among those who were taking antidepressants. However, none of the studies examined depressive symptom severity during or at the end of the study or depression diagnosis and severity before antidepressant use; these data are needed for a clearer understanding of whether the results were confounded by indication.

Second, these findings are also consistent with a treatment-resistant depression phenotype.\(^12\) Krantz et al caution that it is not clear from their observational study whether medication use itself or depression refractory to treatment is implicated in the increased risk of CVD events and mortality. Depression that is refractory to treatment may be the type of depression that places patients at risk for sudden death, stroke, or CHD recurrence, so it may not be the antidepressant use per se that is associated with this risk. This phenomenon was documented in a secondary analysis\(^13\) of the largest-to-date randomized controlled trial of patients with MI undergoing treatment for depression (ENRICHD).\(^14\) It showed that those whose depressive symptoms did not respond to treatment had a higher risk of late mortality (ie, death ≥ 6 months after acute MI). This finding was replicated in 2009 in an important follow-up\(^15\) of the SADHART trial\(^16\); among patients with MI and major depression, treatment-resistant depression (ie, depression that failed to improve substantially during treatment with either sertraline or placebo) was strongly and independently associated with long-term mortality (HR = 2.39; 95% CI, 1.39–2.44; \(P < .001\)).\(^15\)

What is needed next? Testing the alternative hypothesis—that an unmeasured confounder may exist—is difficult, requiring new observational studies and mea-
measurement of the putative third common causes or previously unmeasured confounder. Other putative confounders would then be hypothesized and would need to be included in additional observational studies. To properly test the putative confounding by depressive symptom severity, future observational studies should examine initial depressive symptom severity prior to antidepressant use and then collect data on depressive symptom severity and antidepressant use as time-varying covariates to CVD outcomes. To test whether treatment-resistant depression is the phenotype driving the spurious observational association between antidepressant use and increased risk of CVD, the phenotype and its underlying causal mechanisms need to be better understood.

Of course, rigorous and adequately powered randomized controlled trials of antidepressant use in patients with CVD would be a more straightforward way to test the observational association between antidepressant use and increased risk of CVD. We turn now to the recently published randomized controlled trials in this field.

**NEW EVIDENCE FROM RANDOMIZED TRIALS IN PATIENTS WITH CVD AND DEPRESSION**

Concerns have been voiced for some time about the ability to effectively treat depression and whether an effective depression treatment will affect the risk of CVD recurrence and mortality.\(^1\) Adding to these concerns is our limited knowledge of the causal pathways and behavioral and biologic mechanisms implicated in this risk association.\(^1\) For these reasons, results from new randomized controlled trials, such as the four summarized below, are important.

Rollman et al compared the effectiveness of telephone-delivered collaborative care (treatment group) and usual physician care (control group) for improving mental health quality of life and reducing depressive symptoms in 302 patients with depression after CABG.\(^17\) Patients were observed for 8 months following randomization. Mental health quality of life and depressive symptoms were both significantly improved in the treatment group relative to the control group. Significantly more patients in the treatment group had a 50% or greater reduction in depressive symptoms (50.0% vs 29.6% in control group, \(P < .001\); number needed to treat = 4.9 [95% CI, 3.2–10.4]). Men particularly benefited from the treatment. This trial suggests that collaborative care can be delivered effectively and potentially cost-efficiently over the phone.

Freedland et al also evaluated depression treatment in 123 patients with major or minor depression who underwent CABG.\(^18\) Their primary objective was to determine the efficacy of two behavioral treatments (cognitive behavioral therapy [CBT] or supportive stress management) compared with usual care. Significantly more patients in both the CBT group (71%) and the stress management group (57%) had a low score (indicating less severe depressive symptoms) on the Clinician-based Hamilton Rating Scale for Depression compared with the usual care group (33%). These results were maintained 6 months after the end of the trial. Secondary measures of depressive symptoms, anxiety, and quality of life were also significantly improved in the depression treatment groups compared with the usual care group. This trial is important for the following reasons:

- The use of a second control group, the stress management group, represents a strict, high-quality design that controls for professional attention, generic or placebo therapy effect, and time or effort on the part of the patient.
- The second control group also provides treatment options for the patient, as both CBT and stress management were beneficial.
- Outcome assessors were blinded to treatment assignment, an important design feature in behavioral trials.

In a rigorously conducted randomized, double-blind, placebo-controlled trial, Carney et al tested whether 2 g/day of omega-3 acid ethyl esters (EPA) and docosahexaenoic acid [DHA]) improved depressive symptoms in 122 patients with major depression and CHD.\(^19\) Patients in both the omega-3 and placebo groups received sertraline (50 mg/day) during the 10-week trial. A deficiency of omega-3 fatty acids has been implicated in both depression and CHD and is a possible causal link between the two diseases. Also, there is some evidence that the efficacy of antidepressants is increased by the addition of omega-3 supplementation. Unfortunately, there were no differences in self-reported or clinician-assessed depressive symptoms or in predefined depression remission at the study’s end. The trial included a 2-week adherence run-in period, ensuring that medication adherence in the trial was excellent (97%), and concluded that omega-3 supplementation, at least at these dosage levels, does not improve depression outcomes.

In the Coronary Psychosocial Evaluation Studies (COPES) randomized controlled trial, Davidson et al compared 6 months of an enhanced care intervention with usual depression care among 157 patients with ACS and persistently elevated depressive symptoms.\(^20\) Under the enhanced care intervention, patients received either problem-solving therapy or antidepressant medication, depending on their preference, and then had the option of later augmentation with the other treatment, intensification of the initial treatment, or switching of treatments, if indicated by depressive symptom severity (stepped care). The purpose of the trial was to determine the acceptability and efficacy of depression treatment among patients with ACS, who often neither agree with the diagnosis of depression nor had been seeking treatment for depression.
more patients were satisfied with their depression care in the intervention arm, and depressive symptoms and major adverse cardiac events (nonfatal MI, hospitalization for unstable angina, or all-cause mortality) were significantly reduced in the intervention arm compared with the usual care arm. The absolute numbers were very small; at the end of the trial, 3 patients in the intervention group and 10 patients in the usual care group had major adverse cardiac events (4% and 13%, respectively; log-rank test, $\chi^2 = 3.93; P = .047$). The results suggested that involving patients in the type of depression care they receive (medication and/or psychotherapy) and stepping treatments aggressively may be methods to improve the treatment of depression in patients with CHD. In addition, persistently depressed patients may be an interesting patient group to select for future trials, as usual care has resulted in large reductions in depressive symptoms in some previous trials but not in this study of patients with persistent depression.

**Summary and clinical implications**

Each of these four efficacy trials adds critical information to the evidence base. Depressed patients who have undergone CABG can be effectively treated in primary care settings with integrative care, and CBT is also extremely effective for these patients. Additional studies of omega-3 supplementation should not be pursued at this time, but using a run-in period to better identify patients who are prepared to engage in treatment is a prudent idea and should be used in future trials in this area. Patients with CHD and persistent depressive symptoms are a promising group to target for depression therapy, and asking patients to choose their type of depression treatment may improve response to therapy for both depression and CHD.

**DEPRESSION SCREENING, REFERRAL, AND TREATMENT IN PATIENTS WITH CVD**

We finish with the least evidence-based and most controversial issue in the area of depression and CVD. This controversy started in 2008 when the American Heart Association recommended in an advisory (endorsed by the American Psychiatric Association) that “screening tests for depressive symptoms should be applied to identify patients who may require further assessment and treatment” if appropriate referral for further depression assessment and treatment is available. Partly in response to this advisory, Thoms et al conducted a systematic review of the evidence on whether screening or treatment improves outcomes of depression or CVD in patients with CVD. They found no trial that tested whether depression screening was beneficial in patients with CVD, and the randomized controlled trials of depression treatment provided evidence of only mild improvement of depressive symptoms and no improvement in CVD outcome. Therefore, they questioned whether routine depression screening was appropriate.

In at least eight editorials, letters, and reviews published on this subject in 2009, investigators continued to debate this issue. Below we provide a simplified list of reasons presented for and against screening and subsequent treatment raised in these articles.

**Arguments for depression screening and treatment**

The proponents of screening contend that depression is highly prevalent in patients with CVD and is clearly a risk marker for increased adverse events, reduced quality of life, and poorer adherence to treatment. They argue that since there are plausible biologic and behavioral mechanisms for this association, and since SSRIs use improves depressive symptoms in other patient populations and is safe in patients with CVD, health care providers should not hesitate to screen and refer patients for appropriate depression treatment. At the same time, they have cautioned that SSRIs interact with anticoagulants and that bleeding should be monitored closely in patients with CVD who are taking SSRIs.

Whooley noted that although there are controversial findings in this area, depression screening provided in conjunction with collaborative care depression management is cost-effective and has a documented positive impact on depression, if not on CVD outcomes. She observed that there are some costs to screening, such as false-positive findings (resulting in stigma for patients incorrectly diagnosed) and diversion of resources from other health care needs. However, Whooley suggested that primary care providers, rather than cardiologists, should conduct depression screening and that patients should undergo screening only when an established collaborative care treatment protocol exists.

Carney et al argued that depression, like age, clearly marks CVD risk, and that health care providers should aggressively treat readily modifiable CVD risk factors. They added that because of the strong association between depression and medication nonadherence, providers should carefully monitor patient adherence to life-saving therapies.

Taking another tack, Shemesh and colleagues advocated the importance of documenting the prevalence of suicidal ideation and intent if recommendations to screen for depression in CVD patient populations were implemented. Using a sample of more than 1,000 patients with CVD, they determined the prevalence of suicidal ideation (12.0%) and the number of patients who required hospitalization for risk of suicide (0.5%) when routine depression screening occurred in a large cardiology clinic. They concluded that identification and stabilization of imminently suicidal patients would be a benefit of universal screening and that there is a
high societal cost to neglecting suicidal ideation, intent, and risk in patients with CVD. However, more patients would need immediate thorough psychiatric evaluations for safety, which would affect resource allocation and cost in cardiology clinics.

Arguments against depression screening and treatment

The main argument against screening for and treating depression in patients with CVD is that there are neither randomized controlled trials nor systematic evidence-based reviews showing that screening for depression and/or referring for additional treatment sufficiently improves outcomes for depression or CVD, and that existing evidence does not support the recommendation to screen all patients with CVD.\footnote{11,12} Furthermore, antidepressant use is associated with only mild improvement in depressive symptoms, even in other patient populations,\footnote{13,14} and publication bias (“the file-drawer problem”) has prevented the publication of antidepressant trials with null results, thereby skewing the evidence base.\footnote{15} In addition, considerable health care resources would be needed to mount such a large screening effort, and these resources would come at the expense of other efforts. Finally, the adverse effects of medications and the inevitability of some false-positive screening results must be weighed against any benefit that might occur with universal screening.\footnote{16,17}

In addition to the arguments above, Ziegelstein et al.\footnote{18} in commenting on the American Heart Association advisory,\footnote{19} wryly observed that there is far greater observational evidence that depressed patients seen in mental health settings are at risk for incident and recurrent CVD and that there should be universal screening and referral for CVD in patients with depression. They contended as well that the evidence is insufficient to recommend that patients with CVD undergo universal depression screening and referral.

Summary and clinical implications

Although we were hesitant to raise this tense and often emotional issue, we are in favor of routine, algorithm-based depression screening by all cardiologists, with the critical proviso that a nationwide and/or Centers for Medicare and Medicaid Services–coordinated randomized controlled trial be conducted to evaluate this practice. All patients with pronounced depressive symptoms should be referred to the trial, and two depression treatments should be evaluated, such as usual referral versus telephone-based collaborative care\footnote{20} or enhanced depression care.\footnote{21} Such a trial would allow us to ensure that data are collected on the cost,\footnote{22} the benefit, and even the possible harms associated with routine depression screening for patients with CVD, and we could ascertain if there is an acceptable, beneficial treatment for depression that can be delivered and definitively tested.

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Recovery of consciousness after severe brain injury: The role of arousal regulation mechanisms and some speculation on the heart-brain interface

**ABSTRACT**

Recovery of consciousness after severe brain injury involves reconstitution of brain arousal mechanisms and cerebral integrative function. This review discusses several aspects of neuroanatomy and neuropathology relevant to the process of recovery. Particular emphasis is placed on the role of the anterior forebrain and circuit mechanisms linking the frontal lobe, striatum, and central thalamus. The article concludes with some observations on the heart-brain interface and future research directions in the context of recovery from severe brain injury.

**WHY WE NEED TO UNDERSTAND MECHANISMS OF RECOVERY AFTER SEVERE BRAIN INJURY**

The problem of recovery of consciousness after severe brain injury is one that easily captures the imagination of both the lay public and the professional. Puzzling reports continue to arise of late recovery of speech, language, memory, and other higher cognitive functions in rare patients, yet a scientific framework for the systematic assessment of these phenomena has been lacking. Some of these cases provide intriguing hints to the possible role of various medications (such as dopaminergic, serotoninergic, and noradrenergic agents) as well as spontaneous changes in brain function arising over time. As discussed below, the varying levels of recovery following coma seen after multifocal traumatic or nontraumatic brain injuries may share some common underlying mechanisms at the “circuit” level. Severe brain injuries producing coma have many causes (see Posner et al for a comprehensive review), but careful review reveals an overlap of structural pathologies and functional disturbances isolated to specific cerebral structures across several clinical syndromes grouped under the framework of “disorders of consciousness,” with an emphasis on the role of particular substructures. Perhaps most important is a consideration of the pathologic, anatomic, and pathophysiologic role of the anterior forebrain, particularly the relationships of the brainstem and basal forebrain arousal systems, the central thalamus, and frontostriatal pathways, as reviewed below.

Figure 1 indexes neurologic disorders of consciousness on a two-dimensional grid that highlights the independence of the degree of impairment of cognitive function and motor function that may be encountered in a patient. In the bottom left corner of the figure, coma and vegetative state are both considered unconscious brain states as judged by the bedside behavioral examination in the context of appropriate neurologic history. In both coma and vegetative state, patients do not demonstrate responses to environmental stimuli or initiate goal-directed behaviors. Comatose patients also show no state variation and usually remain close-eyed. In vegetative state, an observable cycling of irregular periods of eye opening and eye closure is evident, but this cyclical variation in behavioral state does not correlate with identifiable electroencephalographic features of either sleep or normal wakefulness. To the right of vegetative state in the figure is the minimally conscious state. Patients in minimally conscious state show unequivocal but inconsistent evidence of awareness of self or the environment through a wide range of behavioral response patterns that can be elicited by bedside examination. Patients may track objects with their eyes, exhibit stereotyped automatic motor behaviors, follow simple commands with small motor movements, or intermittently communicate through verbal or gestural means. The functional boundary indicating emergence from minimally conscious state is the demonstration of reliable verbal or gestural communication. Operationalizing this level of function is a topic of current research, as even simple “yes” versus “no” communication can be unreliable in brain-injured patients who recover past the level of minimally conscious state.

The large gray box in Figure 1 indicates the disquietingly high degree of uncertainty in assessing cognitive...
level in some patients who lack controllable motor output channels. The locked-in state (bottom right corner of figure) defines patients who retain total preservation of cognitive function but otherwise appear no different from those in deep coma. Although locked-in state often arises in the context of neurologic injuries that selectively damage motor output pathways distal from their cortical origins or that slowly reduce primary motor neuron function, this syndrome and closely similar conditions arise in patients with complex brain injuries. Such patients likely retain full or nearly normal consciousness but unfortunately are unable to produce consistent goal-directed movements that allow for communication. In principle, such patients could retain significant cognitive capacity near the normal range of cognitive function yet be indistinguishable from patients in minimally conscious state.

**ROLE OF THE CENTRAL THALAMUS IN SEVERE BRAIN INJURIES**

Recent studies have yielded evidence for common anatomic pathologies following severe injuries associated with vegetative state and minimally conscious state as well as pathologies underlying severe to moderate cognitive disability. Autopsy studies of patients remaining in vegetative state at the time of death have identified widespread neuronal death throughout the thalamus as the common finding following either anoxia or diffuse axonal injury that produces widespread disruption of white matter connections. The severe bilateral thalamic damage after either trauma or anoxia seen in permanent vegetative state is not, however, invariably associated with diffuse neocortical neuronal cell death. This is particularly true of traumatic brain injury, in which only approximately 10% of brains at autopsy show widespread neocortical cell death. Specific subnuclei of the thalamus show the greatest neuronal cell loss following global and multifocal cerebral injuries produced by traumatic brain injuries. In particular, the central thalamic nuclei (intralaminar nuclei and related paralaminar nuclei) demonstrate progressive neuronal loss following severe traumatic brain injuries, and there is some evidence that a similar pattern might be identified in hypoxic-ischemic injuries.

Progressively severe disability grades with neuronal loss along a rostrocaudal axis: the anterior intralaminar and surrounding regions initially show volume loss associated with moderate disability, while neuronal loss in the ventral and lateral nuclei of the central thalamus (posterior intralaminar group) appears with worsening disability associated with minimally conscious state and vegetative state. This progressive and relatively specific involvement of the nuclei of the central thalamus likely results from the unique geometry of these neurons, which have wide point-to-point connectivity across the cerebral hemisphere. The marked neuronal volume loss in these cells is likely due to their integration of the effects of neuronal cell death across large cerebral territories after diffuse trauma, hypoxia, and other nonspecific severe brain injuries.

Importantly, however, focal bilateral injuries to these regions of the central thalamus are also associated with global disorders of consciousness (coma, vegetative state, and minimally conscious state). This observation indicates that these neurons also play a causal role in the production of disorders of consciousness. Abrupt injuries of the central thalamus on both sides of the brain are associated with acute coma, reflecting these cells’ key contribution to normal mechanisms of arousal regulation (reviewed by Schiff). The central thalamus receives ascending projections from the brainstem/basal forebrain “arousal systems” that control the activity of many cortical and thalamic neurons during the sleep-wake cycle. Importantly, the central thalamus is strongly innervated by the cholinergic, serotonergic, and noradrenergic afferents of the brainstem arousal systems (see Schiff for review). These same neurons also are innervated by descending projections from frontal cortical regions supporting “executive” functions that underlie goal-directed behaviors. Collectively, these ascending and descending influences on the central thalamus appear to modulate the level of arousal associated with generalized alertness and variations in cognitive effort, stress, sleep deprivation, and other variables affecting the wakeful state.
Neuroimaging and electrophysiologic studies offer further evidence that the anatomic specializations of the central thalamus play an important role in regulating brain activation during attentive wakefulness. The central thalamus shows selective activation in normal subjects performing tasks requiring a short-term shift of attention,19,22 sustained cognitive demands of high vigilance,22 or memory holds over extended time periods.23,24 Central thalamic activation associated with varying levels of vigilance correlates with global cerebral blood flow19 and specifically covaries within the anterior cingulate cortex and pontomesencephalon.22 Brain activity in the anterior cingulate cortex grades with increasing cognitive load and is recruited by a wide range of cognitive tasks, apparently reciprocally increasing activity along with the central thalamus in response to increasing demands of cognitive effort.20,21

CIRCUIT MECHANISMS UNDERLYING RECOVERY AFTER SEVERE BRAIN INJURY

In addition to the studies reviewed above providing evidence for the role of specific disconnecton of neurons within the central thalamus in disorders of consciousness, Figure 2 illustrates a key vulnerability of the anterior forebrain in the setting of widespread deafferentation and neuronal cell loss seen with severe brain injuries. This vulnerability places the role of the central thalamus in a wider context. A “mesocircuit”-level25 model has been proposed that suggests that functional alterations across very large connected neuronal populations of the anterior forebrain may arise primarily as a result of global reductions of excitatory neurotransmission.26,27 The majority of etiologies associated with coma and related disorders of consciousness diagrammed in Figure 1 effectively produce a broad decrease in background synaptic activity and excitatory neurotransmission (eg, diffuse axonal injury, anoxia, hypoxia-ischemia, cerebral vasospasm with strokes; see Posner et al8 for review).

In addition to the wide point-to-point connections of the central thalamus with the cerebral cortex (predominantly connections to frontal and prefrontal cortices; see Van der Werf et al15 Groenewegen and Berendse,28 Morel et al29), these neurons have important projections to the striatum that return via projections from the globus pallidus.30 These projections from the central thalamus (both central lateral nucleus and parafascicularis nucleus) diffusely innervate the striatum and project onto the medium spiny neurons (MSNs), the output neuron of structure.31 Because the specific thalamostriatal projections from these central thalamic neurons use glutamate transmitters with a high probability of synaptic release,32 they likely also have a strong role in modulating background activity in the striatum.

The MSNs represent an important point of vulnerability in this anterior forebrain mesocircuit, as they have a key role in maintaining activity in the anterior forebrain through their inhibitory projections to the globus pallidus interna, which in turn inhibits the central thalamus.33 MSNs have intrinsic cell membrane properties that keep them below their firing threshold unless a high level of spontaneous background synaptic activity arising from excitatory corticostriatal and thalamostriatal inputs is present in concert with sufficient concentrations of the neurotransmitter dopamine.33 In the setting of diffuse deafferentation or neuronal loss following severe brain injury of any type, it is expected that background

![Figure 2. Proposed “mesocircuit” linking behavioral fluctuations following severe brain injuries and improvements in response to interventions. The model focuses on the modulatory role of the anterior forebrain in overall corticothalamic dynamics. The anterior forebrain (frontal/prefrontal cortical-striatopallidal thalamocortical loop system) is particularly vulnerable to large-scale dysfunction following multifocal brain injuries that produce widespread deafferentation or neuronal cell loss. At least two mechanisms related to this mesocircuit appear to play a key role after severe injuries: (1) the high demands of striatum output neurons for background activity and dopaminergic innervations and (2) the anatomic connections and physiologic specializations of the thalamocortical projections from the central thalamus. These central thalamic neurons have a potent activating role strongly driving both cortical and striatal neurons and wide point-to-point connections that make them more sensitive reporters of global neuronal loss than other thalamic nuclei. Withdrawal of thalamocortical transmission from the central thalamus is known to associate with coma and other disorders of consciousness (see Schiff and Plum5). The thalamostriatal projection from the central thalamus contacts the medium spiny neurons (MSNs) of the striatum, forming axodendritic (centromedian32) or axospinous (central lateral, parafascicular31) synapses. The MSNs, in turn, send inhibitory projections to the globus pallidus interna (GPI); without MSN output, the GPI tonically inhibits the central thalamus.33 Thus, a suppression of MSN output resulting from a loss of dopaminergic modulation or marked reduction in background synaptic activity can potentially catalyze a shutdown of the anterior forebrain. The mesocircuit model economically accounts for several clinical observations and aspects of normal physiology (see text for further discussion). (DBS = deep brain stimulation)](image-url)
excitatory synaptic activity is considerably reduced. Under these circumstances, a broad withdrawal of direct excitatory striatal projections from the central thalamus and corticostriatal inputs is likely to cause MSN output to shut down. Observations of regional changes in brain metabolism following severe brain injuries, specific responses to pharmacologic and electrophysiologic interventions in brain-injured subjects, and normal variations in brain state are all consistent with this mesocircuit model (see Schiff26 for comprehensive review). Similarly, a consistent pattern of selective metabolic downregulation within the anterior forebrain has been shown to specifically grade with severity of behavioral impairment following diffuse axonal injury,34 and application of dopaminergic agents in such patients often will produce behavioral facilitation.35,36 These medications may facilitate the output of the MSNs and directly modulate mesial frontal cortical neurons, possibly restoring anterior forebrain activity within the loop connections of the frontal cortex, striatum, pallidum, and central thalamus. This model provides context for understanding another paradoxical observation—ie, the association of the sedative zolpidem (Ambien), a nonbenzodiazepine hypnotic that potentiates GABAA receptors, with behavioral improvement of alertness and interactive behavior in severely brain-injured patients.37–41 Zolpidem’s primary direct action in patient responders, as originally proposed by Schiff and Posner,27 may be upon on the globus pallidus interna, producing a release of tonic inhibition of the central thalamus in the setting of a broad reduction in background excitatory neurotransmission (as seen, for example, following diffuse hypoxic-ischemic injury) and leading to a shutdown of the inhibitory projection of the MSNs. The GABAA, alpha-1 subunit is expressed in large quantity in the globus pallidus interna, and experimental studies support this mechanism of action.42

**SINGLE-SUBJECT STUDY OF CENTRAL THALAMIC STIMULATION IN MINIMALLY CONSCIOUS STATE**

A further implication of the mesocircuit model is that direct activation of the central thalamus is expected to be the causal step in reactivating a downregulated anterior forebrain system, suggesting that direct modulation of the central thalamus might facilitate behavioral responsiveness in some patients with severe brain injuries. A recent study offers evidence that direct electrical stimulation of the central thalamus can produce behavioral facilitation.

In this single-subject study of central thalamic deep brain stimulation (DBS), a 38-year-old man remained in minimally conscious state for 6 years following a severe closed head injury following blunt trauma to the right frontal lobe.43 After 3 months in a vegetative state, the patient exhibited the first evidence of clear behaviors in response to sensory stimulation consistent with minimally conscious state and advanced to eventually demonstrating a best behavioral response of inconsistent command-following and communication using eye movements. This behavioral level remained unchanged at the start of the DBS study 4 years later, as confirmed by evaluation with the Coma Recovery Scale–Revised (CRS-R), a formal behavioral assessment tool.

The patient entered into a study of central thalamic DBS according to the timeline in Figure 3A. An initial 4-month quantitative behavioral assessment was completed prior to placement of the DBS electrodes, which were implanted bilaterally in the anterior intralaminar thalamic nuclei (central lateral nucleus and adjacent paralaminar regions of the thalamus; Figure 3B). Following electrode placement and brief contact-by-contact testing of the electrodes, 2 months of behavioral testing was conducted with the electrodes remaining off to reassess the patient’s postsurgical behavioral baseline, which had not changed as a result of electrode placement. Two subsequent phases of the study focused on evaluation of DBS effects. A 5-month titration phase focused on establishing tolerance of DBS and evaluating several combinations of different electrical stimulation parameters (contact geometry, frequency, intensity) as well as the duration of the stimulation period. Following this titration phase, the patient entered a 6-month double-blind alternating crossover study. Through all phases of the study, the patient received standard rehabilitation efforts amounting to 3 hours a day, 4 days per week.43

Figure 3C summarizes results of the alternating cross-over study and compares the prestimulation baseline assessments of various behaviors with the “on” versus “off” testing of the DBS electrodes during the crossover phase. The results demonstrate the overall impact of DBS compared with approximately 6 months of ongoing rehabilitation efforts in the absence of DBS exposure. Overall the findings show marked improvement in behavioral responsiveness compared with prestimulation frequencies of the highest-level behavioral response across six categories. The primary outcome assessments were prospectively chosen from subscales of the CRS-R, which is a well-validated psychometric tool used in patients with disorders of consciousness. CRS-R subscale items that had shown variation during the presurgical baseline assessment were chosen prospectively as the primary outcome measures. Notably, the CRS-R oral motor subscale was not chosen because no variation in this measure had been identified during the baseline assessment period. In addition, an object-naming scale and two other tailored secondary measures were developed later, during the titration phase, as the patient’s behavior changed, and were calibrated to be tested using these secondary measurement scales. All six measures showed marked change from prestimulation baseline levels, with five of the six measures showing...
higher-level behaviors than those seen prior to stimulation, regardless of whether the electrodes were on or off.43

As shown in Figure 3C, the behaviors captured by secondary measures had never occurred before the titration phase of the study; i.e., the patient initially lacked a capacity for object naming, oral feeding, and the complex controlled goal-directed movements captured in the secondary limb movement measure, thus setting a prestimulation baseline frequency of 0 for these measures (see supplementary material in Schiff et al43). Three outcome measures—one primary (CRS-R arousal subscale) and two secondary (oral feeding and limb control)—showed statistically significant dependence on DBS during the 6-month period, as indicated by a significantly higher frequency of maximal score rating during “on” versus “off” periods (Figure 3C). The continuation of improvements during the “off” periods of the crossover trial (relative to the prestimulation baseline assessments) showed that the DBS effects produced carryover changes that remained after the extensive exposure to DBS during the titration period (for further analysis of the dynamic of these data, see supplementary material in Schiff et al43).

Importantly, these observations are limited to a single human subject and do not provide a guide to their generalizability;44,45 although they are consistent with the proposed mesocircuit model reviewed above. While the precise mechanism underlying this patient’s improved behavioral responsiveness with central thalamic DBS is unknown, it is likely that DBS served to partially reverse the markedly depressed cerebral global metabolism earlier measured in this patient using fluorodeoxyglucose position emission tomography (FDG-PET)46 and also seen in other patients in minimally conscious state.47 The depressed cerebral metabolism seen in minimally conscious state likely reflects volume loss of neurons, deafferentation of remaining neurons, and neuronal functional impairments. All of these mechanisms may result in low firing rates of neurons in the neocortex, thalamus, and striatum. The mesocircuit model in Figure 2 suggests that direct activation of the central thalamus in patients with such chronically downregulated background synaptic activity may produce excitatory output from central

FIGURE 3. Overview of a 6-month alternating crossover study of central thalamic deep brain stimulation (DBS) in a patient in minimally conscious state following severe traumatic brain injury.43 (A) Study timeline. (B) Electrode lead placements within central thalamus of patient’s right (R) and left (L) hemispheres displayed in T1-weighted coronal magnetic resonance image. (C) The patient’s responsiveness on six cognitive and functional measures at prestimulation baseline (“Pre”) and during periods when DBS was on (“On”) and off (“Off”) during the crossover phase. Responsiveness measures are shown with 95% confidence intervals (whiskers). Asterisks denote measures for which there were statistically significant differences between DBS “on” versus “off” periods. Dagger is present after “Oral feeding” to note that oral feeding data were not available before titration (hence no “Pre” value for this measure); also, oral feeding scores 1 and 2 are combined for dichotomy. See text for further explanation (including explanations of outcome measures). Reprinted from Schiff et al.43
thalamic neurons that acts to partially normalize firing rates and possibly firing patterns within the cortico-striatopallidal-thalamocortical system.

**SPECULATIONS ON THE IMPORTANCE OF HEART-BRAIN RESEARCH IN FUTURE STUDIES OF RECOVERY OF CONSCIOUSNESS**

As this conference is focused on the heart-brain interface, it is appropriate to consider the relevance of heart-brain research to the general set of problems reviewed above. In fact, the linkage is quite natural, and classical physiologic psychology research has shown that cerebral arousal regulation is associated with patterned modulation of cardiac rhythm and autonomic function linked to the behavioral state. Among the most relevant observations are demonstrations that sustained focused attention is associated with several stereotyped cardiac and autonomic changes, including anticipatory bradycardia, pupillary dilatation, and others (eg, galvanic skin response). Neurologic cases have shown that such couplings of effort to reflex bradycardia, pupillary dilatation, and other autonomic markers are altered by focal cerebral lesions in the right frontal lobe and left anterior cingulate cortex.

In the single-subject central thalamic DBS study reviewed above, there were several unpublished observations that are potentially relevant to these mechanisms. During initial bedside testing of the individual DBS electrode contacts in first 2 postoperative days, electrical stimulation above threshold voltages associated with visible arousal response (for details, see supplementary material in Schiff et al) consistently produced marked changes in heart rate and audible modulations of heart rhythm during interactions with the patient. Notably, the patient's basal heart rate rose from a stable level of approximately 50 to 55 beats per minute to approximately 70 to 75 beats per minute—a nearly 50% increase. While increases in blood pressure and heart rate typically accompany arousal, the heart rate change observed here may reflect a marked change in cerebral metabolic rates. Earlier quantitative FDG-PET imaging in this patient revealed a global metabolic rate across the brain of approximately half the normal level. Considering that the brain consumes approximately 23% of the cardiac output, the increased heart rate observed in this setting may reflect an increase in demand in cardiac output, possibly as much as 100%. At the same time that these changes occurred, there was an audible cardiac deceleration noted when the patient was attentionally engaged by the examiner (this occurred without scoreable variation in most of the quantitative neurobehavioral metrics; see supplementary material in Schiff et al). Of note, although the patient had suffered a complex severe brain injury, the right ventral frontal lobe showed the largest structural lesion; injuries to the right hemisphere are associated with loss of such anticipatory changes in heart rate during attentional task performance.

These anecdotal observations suggest that future studies that include measures to track patterns of heart rate variation during recovery of consciousness might provide an indirect index of increasing brain demand for allocation of cardiac output or emergent neural control of mechanisms linking cardiovascular response to attentive behavior. Ongoing coupling of electroencephalographic measures to autonomic and basal cardiac rhythms may be particularly interesting to examine during social interactions, as it is likely that behavioral responsiveness is linked to social stimuli. Emotional reactivity has been proposed as an essential component of arousal per se, and although not formally studied in the DBS trial reviewed above, emotional reengagement seems to be a clear concomitant of the collection of gestural and verbal behavioral improvements operationally tracked using quantitative behavioral scales. Beyond tracking heart-brain interactions as an index of brain recovery, it is possible that the integrity of heart-brain interactions may also be a target for optimization in support of recovery of consciousness after nonprogressive brain injury. Moreover, studies of optimization of cardiac function in severely brain-injured patients may provide insight into the recovery process as well.

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ABSTRACT

Important recent publications in the area of neuroscience and heart-brain medicine center largely around three topics: (1) mechanisms of cardiac sympathetic denervation in Parkinson disease, (2) cytoplasmic monoamine metabolites as autotoxins, and (3) the validity of power spectral analysis of heart rate variability to indicate cardiac sympathetic tone. Findings by Orimo et al support a centripetal, retrograde pathogenetic process involving alpha-synuclein deposition and degeneration of cardiac noradrenergic neurons in Parkinson disease. Several studies suggest that processes increasing cytoplasmic monoamines lead to neuronal loss from auto-oxidation or enzymatic oxidation. Lack of correlation between commonly used indices from power spectral analysis of heart rate variability and cardiac norepinephrine spillover casts doubt on the validity of power spectral analysis to indicate cardiac sympathetic tone.

This review highlights important recent publications in the area of neuroscience and heart-brain medicine. Abnormalities of regulation of the circulation by catecholamine systems figure as a general theme of the topics highlighted. These topics, which are reviewed in turn below, are (1) mechanisms of cardiac sympathetic denervation in Parkinson disease (PD), (2) cytoplasmic monoamine metabolites as autotoxins, and (3) the validity of power spectral analysis of heart rate variability to indicate cardiac sympathetic tone.

MECHANISMS OF CARDIAC SYMPATHETIC DENERVATION IN PARKINSON DISEASE

The movement disorder component of PD is well recognized as resulting from loss of dopaminergic neurons in the nigrostriatal system of the brain. The finding of myocardial 6-[18F]fluorodopamine–derived radioactivity by positron emission tomography provided the first neuroimaging evidence for loss of catecholaminergic neurons outside the brain in PD. Many reports using 123I-metaiodobenzylguanidine scanning have concurred with this finding. Beginning in the early 2000s, postmortem neuropathologic studies demonstrated virtually absent immunoreactivity for tyrosine hydroxylase, the rate-limiting enzyme in norepinephrine biosynthesis, in epicardial nerves in PD. These results provided clues to the mechanism of autonomic dysfunction in PD, a prominent nonmotor manifestation of the disease.

Alpha-synuclein is a key protein in the pathogenesis of PD. It is abundant in Lewy bodies and Lewy neurites, and mutations or multiplications of the gene that encodes it cause rare inherited forms of PD. In 2001 we reported evidence for cardiac sympathetic denervation, neurogenic orthostatic hypotension, and baroreflex failure in familial PD from mutation of the gene encoding alpha-synuclein. Subsequently we reported analogous denervation in familial PD from triplication of the normal gene. This past year Orimo’s group in Tokyo provided the first pathological confirmation of cardiac sympathetic denervation in familial PD from inherited alpha-synucleinopathy, based on severely decreased epicardial neuronal tyrosine hydroxylase immunoreactivity (Figure 1). In contrast, patients with familial PD from parkin gene mutation, which is not thought to be a Lewy body disease, have been found to have normal cardiac 123I-metaiodobenzylguanidine–derived radioactivity and normal epicardial neuronal tyrosine hydroxylase immunoreactivity. These findings establish a link between alpha-synucleinopathy and cardiac sympathetic denervation.

Some individuals who die without clinical parkinsonism have Lewy bodies detected pathologically. Growing evidence shows that incidental Lewy body disease represents early, presymptomatic PD. Orimo’s group therefore studied cardiac tissues and paravertebral sympathetic ganglia from patients with incidental Lewy body disease. Postmortem tissues were likewise obtained from comparison subjects with multiple system atrophy and from control subjects. Immunohistochemical analyses were performed using antibodies against alpha-synuclein, tyrosine hydroxylase, and dopamine-

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tyrosine hydroxylase, phosphorylated neurofilament as a marker of axons, and phosphorylated alpha-synuclein as a marker of abnormal alpha-synuclein deposits. Key findings from this study\(^9\) were as follows:

- Alpha-synuclein aggregates in distal epicardial nerve fascicles were more abundant in incidental Lewy body disease with preserved tyrosine hydroxylase–immunoreactive (THir) axons than in incidental Lewy body disease with decreased THir axons (Figure 2).
- Alpha-synuclein aggregates in the epicardial nerve fibers were closely related to the disappearance of THir axons.
- In incidental Lewy body disease with preserved THir axons, alpha-synuclein aggregates were consistently more abundant in the epicardial nerves than in the paravertebral sympathetic ganglia.
- Distally dominant accumulation of alpha-synuclein aggregates was reversed in incidental Lewy body disease with decreased THir axons and in PD, because both conditions involve fewer alpha-synuclein aggregates in axons and more abundant aggregates in the paravertebral sympathetic ganglia (Figure 2).

Thus, accumulation of alpha-synuclein aggregates in distal cardiac sympathetic axons precedes aggregation in neuronal somata or ganglionic neurites, heralding centripetal degeneration of cardiac sympathetic nerves in PD. This chronological and dynamic relationship between alpha-synuclein aggregation and distally dominant degeneration of cardiac noradrenergic nerves may represent the pathological mechanism behind a common degenerative process in PD.

In conclusion, cardiac noradrenergic denervation in Lewy body diseases, even in early stages, accounts for reduced cardiac uptake of \(^{123}\)I-metaiodobenzylguanidine and \(^{6-[^{18}F]}\)fluorodopamine in PD. Alpha-synuclein aggregation appears to be intimately involved in the cardiac noradrenergic denervation that attends Lewy body diseases. The pathogenetic process seems to proceed in a centripetal, retrograde direction.

### CYTOPLASMIC MONOAMINE METABOLITES AS AUTOTOXINS

Current concepts about mechanisms of PD emphasize pathologic alpha-synuclein accumulation, oxidative injury, impaired proteasomal or mitochondrial functions, neuroinflammation, or abnormal kinase signal-
ing. These concepts do not explain relatively selective nigrostriatal dopaminergic and cardiac noradrenergic denervation in PD.

A potential explanation is that cytoplasmic catecholamine metabolites are autotoxins (Figure 3). The mechanisms of autotoxicity include spontaneous auto-oxidation, to form quinones and chromes leading to increased production of reactive oxygen species, and enzymatic oxidation.

Catecholamines in the neuronal cytoplasm undergo enzymatic oxidative deamination to form catechol-aldehydes (dihydroxyphenylacetaldehyde [DOPAL]) from dopamine, which are cytotoxic, as predicted by Blaschko more than a half century ago.10 DOPAL is detoxified mainly by aldehyde dehydrogenase (ALDH). In the substantia nigra, aldehyde dehydrogenase 1A1 (ALDH1A1) is the main isoform of ALDH, and post-mortem studies have noted decreased nigral ALDH1A1 gene expression11,12 and protein content13 in PD patients.

All neurons express alpha-synuclein. Current concepts about mechanisms also do not explain the relatively selective aggregation of alpha-synuclein in catecholaminergic neurons. Alpha-synuclein appears to play a role in the cycling of catecholamines across vesicular and cell membranes.14

In the past year, a few important studies have been published related to autotoxicity of cytoplasmic catecholamine metabolites and to pathogenic interactions with alpha-synuclein. In 2006, Mosharov et al reported that alpha-synuclein overexpression increases cytoplasmic dopamine concentrations in rat pheochromocytoma PC-12 cells.15 Recently, the same group, using intracellular patch electrochemistry, directly measured cytoplasmic dopamine in cultured midbrain neurons and found that increases in dopamine and its metabolites are neurotoxic, whereas manipulations that reduce cytoplasmic dopamine are neuroprotective (Figure 4).16 Levodopa (L-dopa) increased cytoplasmic dopamine more in substantia nigra neurons than in ventral tegmental neurons, suggesting that this difference might help explain the greater susceptibility of nigral neurons to the pathogenic process. The greater buildup of cytoplasmic dopamine seemed to depend on dihydroxyamine-sensitive calcium (Ca²⁺) channels. Finally, dopaminergic neurons lacking alpha-synuclein were resistant to L-dopa–induced cell death. These findings led the authors to propose a “multiple-hit” model (Figure 5) in which interactions between intracellular ionized calcium, cytoplasmic dopamine, and alpha-synuclein underlie susceptibility of nigral neurons in PD.17

Burke et al added a potentially important clue, demonstrating that DOPAL potently oligomerizes and aggregates alpha-synuclein.17 This finding introduces the possibility of multiple pathogenetic positive feedback loops.

Under resting conditions, most catecholamine turnover results from leakage from vesicular stores into the cytoplasm and subsequent oxidative deamination by monoamine oxidase. Ordinarily, however, catecholamines in the cytoplasm are efficiently recycled back into the vesicles via the type 2 vesicular monoamine transporter (VMAT-2). Accordingly, interference with VMAT functions would be expected to tend to build up cytoplasmic catecholamines, with potentially cytotoxic consequences. In 2007, Caudle et al reported that mice with severely decreased VMAT-2 have aging-associated decreases in striatal dopamine that begin in the terminal fields, alpha-synuclein deposition in substantia nigra neurons, and L-dopa–responsive behavioral deficits.18 More recently the same group noted nonmotor signs associated with PD in VMAT-2–deficient mice, such as anosmia, gastrointestinal hypomotility, sleep distur-
VALIDITY OF POWER SPECTRAL ANALYSIS OF HEART RATE VARIABILITY TO INDICATE CARDIAC SYMPATHETIC TONE

Power spectral analysis of heart rate variability is simple, relatively inexpensive, noninvasive, and widely used to indicate cardiac sympathetic “tone” or sympathovagal “balance.” Almost 2,000 studies to date have used this modality. Relatively increased cardiac sympathetic tone, reflected by low-frequency (LF) power or the ratio of LF power to high-frequency (HF) power, is an adverse prognostic sign in a variety of conditions. Nevertheless, the validity of LF power, or the LF:HF ratio, as an index of cardiac sympathetic tone remains unsettled.

In 2007 we assessed the validity of power spectral analysis rather directly, by taking advantage of our ability to delineate cardiac sympathetic innervation. We compared LF power in patients with cardiac sympathetic denervation, indicated by low myocardial levels of 6-[18F]fluorodopamine–derived radioactivity or low rates of norepinephrine entry into coronary sinus plasma (cardiac norepinephrine spillover), with val-

monooamine oxidase inhibition. These findings fit with the concept that the aldehydes produced by the action of monooamine oxidase on cytoplasmic monoamines generate toxic free radicals.

bances, anxiety, and depression. Since VMAT-2 serves to recycle not only dopamine but also norepinephrine and serotonin, this single abnormality could help explain loss of all three types of monoaminergic neurons in PD.

Finally, Pena-Silva et al recently tested whether serotonin induces oxidative stress in human heart valves. They showed that in heart valves from explanted human hearts not used for transplantation, incubation of homogenates of cardiac valves and blood vessels with serotonin increased generation of the superoxide free radical. Inhibitors of monooamine oxidase prevented this effect. Dopamine also increased superoxide levels in heart valves, and this effect was also attenuated by oxidation.

...
ues in patients with intact innervation. LF power was unrelated to myocardial 6-[18F]fluorodopamine–derived radioactivity or cardiac norepinephrine spillover, but it was related to baroreflex-cardiovagal gain. Patients with a low baroreflex-cardiovagal gain had low LF power, regardless of cardiac innervation. From these findings we concluded that LF power reflects baroreflex function, not cardiac sympathetic innervation.

Recently Baumert et al also examined the relationship between indices from power spectral analysis of heart rate variability measures (LF = low frequency; HF = high frequency) versus cardiac norepinephrine in healthy subjects (squares) and patients with major depression (triangles) and panic disorder (circles). They found, as we did, that none of the standard heart rate variability parameters was correlated with cardiac norepinephrine spillover (Figure 6). The same group reported a positive correlation between the heart rate–corrected QT interval and cardiac norepinephrine spillover. Among patients with major depression, the distribution of cardiac norepinephrine spillover seemed bimodal. Overall, cardiac norepinephrine spillover was not increased, although a subgroup had clearly increased spillover.

In congestive heart failure, baroreflex-cardiovagal gain tends to be low and cardiac sympathetic outflow markedly increased, yet the LF:HF ratio is not increased during supine rest. It therefore appears that power spectral analysis of heart rate variability may provide a measure of baroreflexive modulation of autonomic outflows to the heart but not a measure of those outflows themselves. The search continues for a valid, noninvasive means to assess cardiac sympathetic function.

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**FIGURE 6.** Relationships of heart rate variability indices with cardiac norepinephrine spillover. Graphs show time and frequency domain heart rate variability measures (LF = low frequency; HF = high frequency) versus cardiac norepinephrine in healthy subjects (squares) and patients with major depression (triangles) and panic disorder (circles). 22

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Pathophysiologic mechanisms linking impaired cardiovascular health and neurologic dysfunction: The year in review

ABSTRACT

The nervous system and cardiovascular system have long been known to interact. Only more recently, however, have the mechanisms driving this interaction become more clearly understood. Although many psychological disturbances, including depression and anxiety, are known to predict poor outcomes in patients with cardiovascular disease, other neurologic disturbances, such as migraine and stroke, have been connected to poor cardiovascular outcomes as well. Although these connections were traditionally thought to be due to shared risk factors, recent research has focused on pathophysiologic mechanisms underlying these interactions, including neuroendocrine dysregulation, genetic predisposition, and vascular dysfunction.

The complex interaction between the nervous system and cardiovascular (CV) health is well recognized. In addition to stroke, migraine, and other disorders, the focus has shifted to depression and related negative-affect states including anxiety, chronic stress, posttraumatic stress disorder, and social isolation. Although all of these conditions have been linked to poor CV health, the mechanisms responsible for this brain-cardiovascular interaction have been poorly understood until recently.

At first, it appeared that the link between CV disease and such states as depression and anxiety was mediated by a clustering of shared risk conditions such as smoking, high low-density lipoprotein cholesterol, and obesity. As more research uncovered the pathophysiologic mechanisms underlying these negative-affect states, however, it became apparent that some of these mechanisms overlapped with those leading to vascular dysfunction (Figure 1). For instance, regulation of neurotransmitters such as serotonin is known to play a key role in mood dysfunction as well as in sleep and appetite, but only recently has this regulation been identified as an important component in moderating platelet function as well. Several other common pathways have been identified, including the hypothalamic-pituitary-adrenal (HPA) axis, endothelial progenitor cell (EPC) regulation, and inflammatory cell dysfunction. The role of genetic predisposition as a common factor leading to psychological and vascular dysfunction has been studied as well. In addition, research has recently expanded to examine other forms of central neurologic dysfunction besides mood, including stroke and migraine, and their connection with CV health.

This paper reviews a sample of the more recent advances in our understanding the pathophysiologic mechanisms underlying this complex brain-vascular interaction—including the roles of genetic predisposition, endothelial cell dysfunction, and endocrine dysregulation—and discusses future directions for research in this area.

GENETIC PREDISPOSITION

Increasing evidence highlights the importance of genetic predisposition in both psychological dysfunction and CV disease. The importance of common genetic variability in these two conditions originated from studies of twins that established that both depression and coronary artery disease (CAD) tended to run in families. However, recent studies focused on identifying specific genes that may link depression/negative affect and CAD through various pathways related to platelet reactivity, inflammation, and autonomic nervous system regulation, among many others. A candidate gene study by McCaffery et al1 sought to identify specific genes influencing depressive symptoms in CAD patients. Genes were selected based on their role in biologic pathways involved in inflammation, platelet activation, and the HPA axis and sympathetic nervous system. Among the 59 genes analyzed, the strongest associations were between markers involved in endothelial dysfunction and platelet aggregation—specifically, the involvement of von Willebrand factor in platelet recruitment and of

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vascular cell adhesion molecule–1 in recruitment and adhesion of inflammatory cells to injured endothelium. Other recent studies have analyzed the role of various genes in mediating neurologic and CV dysfunction.

**Serotonin: A multitude of cardiovascular effects**
Serotonin (5-HT) is best known as a neurotransmitter involved in mood regulation, but it also directly affects endothelial cells and vascular smooth muscle. Human brain microvascular endothelial cells have 5-HT2A receptors, which are thought to be involved in blood-brain trafficking.2 Polymorphisms in this receptor have been associated with impaired glucose tolerance and type 2 diabetes.

However, the role of serotonin within the CV system has only recently been realized. Along with its associated serotonin transporter (SERT), serotonin has been best studied within the CV system for its role in the development of pulmonary hypertension via vasoconstrictor. However, serotonin and SERT exhibit other effects on the CV system, including regulation of factors involved in vascular integrity, such as platelet activity, endothelial dysfunction, and smooth muscle cell and endothelial cell mitogenesis. Serotonin is stored peripherally in platelets and, when released at sites of endothelial damage, promotes platelet aggregation. Cardiomyocytes also are a source of serotonin within the heart, resulting in positive chronotropy, positive inotropy, and activation of mitogen activity.4

Serotonin also affects endothelium through effects on bone marrow production of EPCs. It has been shown in mice to increase the proliferative activity of hematopoietic stem cells in the bone marrow via 5-HT2 receptors.5 It also seems to have an effect on regulation of inflammatory cells6 and has also been shown to enhance ex vivo production of CD34+ hematopoietic stem cells in mice.7 It also seems to have an effect on regulation of inflammatory cytokines by regulating different secretory pathways. Activity of several different serotonin receptors, including 5-HT2A, 5-HT4, and 5-HT7, inhibits tumor necrosis factor production in peripheral cells.8

**Insights from genetic analysis of SERT**
These areas of recent research continue to highlight the importance of serotonin within the CV system, and its overlapping role in depression and other forms of psychological dysfunction underscores the importance of understanding its regulation.

The best-studied component of serotonin regulation is SERT, a sodium-dependent transporter that removes serotonin from outside the cell, bringing it back into the cell for repackaging. It is recognized as the site of action of the selective serotonin reuptake inhibitors (SSRIs).

Analysis of the serotonin transporter gene has traditionally focused on polymorphisms within the promoter region (5-HTTLPR). Two common alleles, the long (L) and short (S) variants, are the best characterized. The S variant is associated with a lower expression of SERT, leading to reduced uptake and release of serotonin. The SS genotype of SERT has been linked to major depressive disorder and to increased risk of subsequent cardiac events after myocardial infarction (MI).10

A study of the effects of environmental stress and gender on associations between depression and 5-HTTLPR found that this link varied according to gender and stressful life events.11 Specifically, women with the SS genotype of SERT, which leads to less transcriptional activity of 5-HTTLPR, tended to be more susceptible to depression under stressful life conditions. However, in men the LL genotype was associated with increased transcriptional activity and the same increased susceptibility to depression.11 Expression of the LL genotype also resulted in upregulation of SERT, leading to higher MI risk.12

Another study investigated the relationship between genetic variability in two serotonin-related gene polymorphisms and found that the 5-HTTLPR gene polymorphism was associated with adverse cardiac events after coronary artery bypass graft surgery in combination with depression, specifically in patients with the L allele compared with SS.13

Humans who possess the L variant of the SERT protein have more rapid platelet serotonin uptake.14 Inhibitors of SERT have been shown to reduce platelet serotonin content, leading to disruption of thrombosis.
and increased bleeding due to inhibition of serotonin reuptake. A study in middle-aged men also found that genetic variability within SERT was associated with increased depressive symptoms and elevated levels of interleukin-6, a marker of inflammation. This indicates a common source of genetic vulnerability accounting for both depression and inflammation, and could help to explain the increased risk of CV disease in patients with depression.

**Mental stress–induced myocardial ischemia**
The association between mental stress and activation of the sympathetic nervous system is well established. Stress leads to increases in blood pressure and heart rate. In patients with CAD, mental stress–induced myocardial ischemia (MSIMI) is a well-characterized phenomenon whereby ischemia is provoked by psychological stress. Sympathetic nervous system activation from stressful life events can increase vulnerability to CV outcomes such as MI, arrhythmias, and sudden cardiac death. MSIMI has been identified as a risk factor for poor outcomes in patients with known CAD. Proposed mechanisms include mismatch of myocardial blood supply and demand, as well as coronary spasm.

A recent study by Hassan et al evaluated associations of beta-1-adrenergic receptor gene (ADRB1) polymorphisms with MSIMI in CAD patients. The researchers found a threefold increase in MSIMI in patients with a particular allele of the ADBR1 gene. This is the first report to highlight a specific genetic predisposition to susceptibility to MSIMI; it could help explain why some patients are at increased risk and also suggest targeting specific behavioral or pharmacologic therapies to reduce MSIMI.

**ENDOTHELIAL DYSFUNCTION**
Dysfunctional endothelium is important in the link between neurologic dysfunction and CV disease. Circulating EPCs have been recognized as playing an important role in maintaining vascular health. These cells originate in the bone marrow and may be identified by their surface markers and various functional characteristics. They have been shown to be a key part of the process involved in repair of biologic risk factor–mediated damage to endothelium and are reduced and/or dysfunctional in patients with CV risk factors such as tobacco use, diabetes, and hypertension. Low EPC levels have also been found in patients with cerebrovascular disease and are key in vascular neogenesis after ischemic insult.

**Genetic effects on endothelium in migraine and stroke**
A more recent area of interest in brain and cardiovascular health has been the role of EPCs in migraine, which is often debilitating. The association between migraine and increased risk of depression, as well as stroke and MI, has been well recognized. A recent study by MacClellan et al evaluated whether polymorphisms in genes regulating endothelial function and vascular tone influenced susceptibility to migraine and stroke in a large subset of young women. Analyzed genes included endothelin-1 (EDN), endothelin receptor type B (EDNRB), and nitric oxide synthase-3 (NOS3). Several polymorphisms within these genes were associated with stroke in white women but not in black women. However, the study did not show whether the association between migraine and stroke was mediated by the polymorphisms studied from the candidate genes. Others have found no association with EDNRB but found that the homozygous minor genotype (present in 5% of cases) of the EDNRA SNP rs2048894 showed association with migraine with aura (odds ratio [OR] = 1.61, 95% confidence interval [CI], 1.12–2.32; P = .010) when adjusted for gender and sample origin. Early age at onset (< 20 years) also was associated with rs2048894 (OR = 1.69, 95% CI, 1.13–2.54; P = .011) in the pooled sample. Studies on larger samples will be needed to confirm these findings.

**Depression may alter endothelial homeostasis**
One mechanism by which depression may lead to increased CV disease risk is through effects on endothelial homeostasis. Several studies have found an association between depression and attenuated flow-mediated vasodilation. However, it has been postulated that this effect was mediated by atherosclerosis, as these studies were performed in older cohorts. To evaluate this association without the possibility of confounding severe atherosclerosis, a recent study evaluated this association in adolescent women with no known health problems. Regression analysis demonstrated a significant inverse relationship between depression and endothelial function as measured by pulse-wave amplitude. Most patients in this study had evidence of subclinical depression, suggesting that even those with mild symptoms can have endothelial dysfunction. These findings provide evidence to suggest that there may be some factors that underlie the vascular dysfunction associated with both depression and early subclinical atherosclerosis.

**Focus on endothelial progenitor cells**
EPCs from bone marrow and likely other sites (eg, spleen, perivascular omentum, liver, mesentery) play an important role in maintaining vascular integrity. The interaction between the bone marrow, nervous system, HPA axis, and progenitor cells, together with the effect of this interaction on vascular integrity, has become an area of increasing research. Specifically, the sympathetic nervous system has been identified as playing an important role in progenitor cell egress from the bone marrow. Mice with abnormal nerve conduction produce virtu-
Endothelial progenitor cell counts in headache patients. The counts were lowest in patients with migraine with aura, followed by migraine without aura, followed by tension headaches. Box plots show the median count (white lines), interquartile ranges (green boxes), 5% to 95% percentiles (whiskers), and outliers (dots). P values were calculated using a two-tailed Student t test.

Decreased number and function of endothelial progenitor cells in patients with migraine. Neurology 2008;70:1510–1517.

Psychosocial factors influence activation of the sympathetic nervous system. An innovative recent study examined the effect of psychosocial determinants on bone marrow–derived progenitor cells; the psychosocial variables and progenitor cell counts were associated independently from traditional biological and behavioral risk factors. This is one of the first studies to examine the effect of psychosocial stressors on progenitor cells and should open the way for further research exploring this association and its effects on CV health.

Another area of interest has been the ability of progenitor cells to aid in repair after neurologic damage following vascular insult. Two areas related to progenitor cells have been stroke and migraine, which is a risk factor for stroke as well as depression. Compared with patients with tension headaches, patients with migraines (with and without aura) had lower levels of EPCs, with the lowest levels observed in migraine patients with aura (Figure 2). The EPCs in patients with migraine with and without aura also showed reduced migratory capacity and increased senescence.

Another study examined the relationship between EPCs and ischemic stroke, finding that an increase in circulating EPCs after acute ischemic stroke was associated with better outcomes and reduced infarct growth (Figure 3). This suggests that EPCs may play an important role in neurovascular repair after ischemic insult.

Platelet activity
Platelets play a critical role in endothelial hemostasis. Alterations in platelet function have been hypothesized as a mechanism by which depression may lead to CV disease. A recent study analyzed the effects of persistent depressive symptoms on platelet activation in a cohort of spousal dementia caregivers. P-selectin, measured as an index of platelet activation, and depression, mainly in the subclinical range, were associated with elevated platelet reactivity and recovery. This may be one mechanism by which elderly caregivers are at risk of CV disease even without evidence of clinical depression.

Serotonin is also known for its effect on platelet function and vascular tone and is one of the main targets of antidepressant therapy. Several studies have analyzed the effect of depression treatment with SSRIs on platelet function. An initial analysis from the SADHART trial in 2003 found that in depressed patients treated with sertraline after acute coronary syndrome, reductions in platelet/endothelial activation occurred despite concurrent treatment with antiplatelet drugs, including aspirin and clopidogrel. This suggests that the antiplatelet
properties of sertraline differ from those of aspirin and other antiplatelet therapies. A study by van Zyl et al.10 yielded similar results with a different SSRI, citalopram, along with enhanced production of nitric oxide.

**HORMONES, NEGATIVE AFFECT, AND CV DISEASE**

Patients with CAD have different patterns of cortisol excretion compared with controls. A dysfunctional HPA axis has been implicated, leading to a failure in containing inflammatory activity.3,4 In healthy older patients without known CAD, heightened cortisol reactivity is associated with a greater extent of coronary artery calcification.32 Cynical hostility is also associated with CAD, but the mechanism is unclear. Higher levels of cynical hostility were associated with attenuation of the decreasing phase of the cortisol awakening response.33 Another recent study also found a higher cortisol awakening response and a larger ratio of total cholesterol to high-density lipoprotein cholesterol in response to stress in socially isolated men.34

Although cortisol is the most studied end product of the HPA axis, aldosterone is also released. Recent research has focused on the role of aldosterone in CV injury through its increase in superoxide generation and its upregulation of genes involved in inflammation, fibrosis, and atherosclerosis.35,36 Several studies have demonstrated the increased incidence of CV disease, including atrial fibrillation, stroke, and MI, among patients with primary hyperaldosteronism compared with patients with similar blood pressure elevations.37,38 Continued evidence supports the importance of the endocrine pathways in modulation of CV disease, and future research should continue to explore the role of various hormones in this interaction.

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ABSTRACT

New reports have emerged exploring the use of electrical stimulation of peripheral nerves in patients for the treatment of depression, heart failure, and hypertension. Abolishing renal sympathetic nerve activity in resistant hypertension has also been described. Since nerve bundles carry a variety of signals to multiple organs, it is necessary to develop technologies to stimulate or block targeted nerve fibers selectively. Mathematical modeling is a major tool for such development. Purposeful modeling is also needed to quantitatively characterize complex heart-brain interactions, allowing an improved understanding of physiological and clinical measurements. Automated control of therapeutic devices is a possible eventual outcome.

Biomedical engineering is a rapidly growing field, as indicated by a recent threefold increase in the number of students enrolled in the more than 80 programs granting biomedical engineering degrees. The field is known primarily for contributing to the development of devices that aid diagnosis (such as chemical sensors and medical imagers) or help to restore lost function (such as pacemakers, cochlear implants, and artificial limbs). At the same time, biomedical engineering has also contributed to the understanding of physiology and is now a participant in the more recent molecular- and cellular-based discoveries and their potential clinical applications.

This article reviews the contributions of biomedical engineering to heart-brain medicine and looks ahead to where its future contributions may be expected. The focus is on the autonomic control of the heart, with special emphasis on stimulating or blocking the activity of peripheral nerves for therapeutic purposes.

AUTONOMIC MECHANISMS

One way biomedical engineering has contributed to heart-brain medicine is through systems physiology, attempting to characterize complex cardiac control mechanisms by mathematical models ranging from the relatively simple to the very complex. In particular, investigation of the effect of the baroreceptor reflex (baroreflex) on heart rate led to recording of efferent vagal activity, demonstrating that the respiratory variations in heart rate are attributable to complete stoppage of vagal efferent activity, at least in anesthetized dogs. The results suggested that respiratory sinus arrhythmia was a measure of parasympathetic cardiac control. Extensive further work investigated heart rate variability in humans, resulting in the generally accepted concept that rapid variations in heart rate are primarily due to the parasympathetic nervous system, while slower variations are primarily due to sympathetic contributions. It has been amply demonstrated that in a variety of disease states, a high degree of parasympathetic control is correlated with improved outcome.

Heart rate variability: Much is still unknown
Because heart rate variability is derived through analysis of easily recorded single-lead electrocardiograms (ECGs), techniques are still being described for determining the degree of variability. Measurements may be based on heart rate or heart period (interbeat interval); they may be made during spontaneous, deep, or timed periodic breathing; and the recordings may last for a few minutes or for 24 hours. The results are rarely reported for different states, yet variability depends on whether the subjects are awake, in quiet sleep, or in REM sleep.

The present incomplete understanding of the physiological basis and clinical significance of heart rate variations makes it difficult to judge what the optimum measurement is. For example, recent publications have still debated whether the respiratory variations are primarily of central origin or a result of the baroreflex. The reviewed evidence leaves little doubt that most respiratory variations are caused by vagal modulation induced by breathing, independently of the baroreflex. On the other hand, breathing affects blood pressure and thus must have some influence on heart rate through the baroreflex as well. These effects are likely to be important when considering low-frequency variations. It also has been suggested that the branch of the vagus...
that contributes to the slow variations may be different from the one responsible for the rapid changes.15

A role for mathematical modeling

Untangling the above relationships requires at least an approximate physiologically based quantitative model of the entire system. What is the “entire system”? It includes all components that significantly affect the clinical condition or physiological/biological phenomenon studied. Developing such models is challenging since they can be misleading if they are too simple. However, if they are too complex, they may obscure rather than illuminate. Even though mathematical modeling has been a major component of biomedical engineering for decades, there is still great need for physiological and clinical studies that are aided by biomedical engineers with mathematical skills and a discerning eye toward the life sciences.

For example, following numerous previous efforts to develop models of cardiorespiratory control systems, a model has been developed to describe changes in heart rate, stroke volume, and blood pressure caused by disordered breathing during sleep.16 The model was initially tested in animals but recently has been evaluated in children with obstructive sleep apnea.17 It was found to be more effective in identifying and characterizing cardiac control abnormalities than was spectrum-derived variability of heart rate or blood pressure alone.

To enhance the usefulness of heart rate variability as a clinical tool, it is necessary to go beyond observing that decreased high-frequency heart rate variations are ominous in a particular disease state because there is an “imbalance” of autonomic control. This gives the physician little guidance as to what to do. Should he or she treat the brain to get more parasympathetic outflow? Should attention be concentrated on making the heart more tolerant to the imbalance? Or should both approaches be tried?

In addition to the building of models, biomedical engineers can also contribute to heart-brain medicine by developing sensors that can measure appropriate physiological variables in animal experiments—and eventually in humans. Such variables include neural activity and chemical signals controlling the heart, as well as neural and chemical signals that arise from the heart and are sensed by the brain. These variables must be included in any model for a comprehensive characterization of heart-brain interactions.

NEURAL INTERVENTIONS

A second and complementary way in which bioengineering can contribute to heart-brain medicine is through the development and evaluation of technology that applies selective electrical, chemical, or mechanical stimulation to the physiological system. External interventions may have therapeutic effects even though the underlying physiological mechanisms are not fully understood. For example, deep brain electrical stimulation is increasingly used or explored to treat epilepsy, Parkinson disease, and depression.18,19 The development of technology to deliver drugs locally is advancing rapidly and is almost certain to play a major role in exploring heart-brain interactions. The remainder of this paper concentrates on interventions applied through peripheral nerves.

Vagal stimulation

A major recent development is the demonstration that vagus nerve stimulation may have beneficial effects. The vagus nerve is large, easily accessible, and well studied. Its afferents carry sensory information from the periphery to the brain, while its efferents provide central control of numerous organs, including the heart (Figure 1).
Because of its accessibility, it can be easily stimulated. Vagal stimulation is being used to treat epilepsy, but now it is also being explored for the treatment of drug-resistant depression and chronic migraine. The intensity, frequency, pulse width, and train duration of the apparently single-channel stimulation are set telemetrically. Preliminary data indicate a long-term success rate of about 20% for depression and improvement in 2 of 4 patients with chronic migraine. Side effects include discomfort caused by the electrical stimulation and vocalization impairments.

The modesty of the success in these trials was likely due in large part to the method of stimulation. Current preferentially stimulates large nerve fibers as well as those closest to the electrode. Yet the vagus contains a variety of afferent and efferent nerves that have varying fiber sizes at different distances from the stimulating electrode. The complex structure of peripheral nerves such as the vagus is schematically illustrated in Figure 2. Simple electrodes cannot control the location and function of the nerves that are actually stimulated.

The selective stimulation of nerves has received much attention in rehabilitation engineering since electrical activation of peripheral motor fibers can restore at least some function in patients with spinal cord injury. The stimulation must be selective: different muscles to restore movement need to contract in the appropriate sequence and with appropriate intensity. Thus, fascicles of motor nerves innervating these muscles must be stimulated accordingly.

Electrodes have been developed in a variety of configurations for selectively activating the desired fibers in a nerve bundle. Multiple electrodes around the nerve allow targeting of the desired fascicles and preferential stimulation of small nerve fibers. Gentle compressing the nerve using a flat electrode sleeve enhances selectivity by increasing the surface area of the stimulated nerve. A tripolar sleeve electrode along the nerve (one cathode at the middle and an anode on each side) may be used to preferentially stimulate small fibers by “anodal blockade” of the propagation of activity in large fibers. Mathematical models of nerve excitation, combined with models of the tissue surrounding the nerve fibers, show that positioning the anodes at different distances from the cathode can generate unidirectional propagation. Mathematical analysis also shows that the stimulating pulse should have a slowly decaying trailing edge to assure effectiveness of the blockade.

Similar technologies are likely necessary for stimulating the vagus for specific purposes. If the goal is to induce central effects, appropriate afferents should be stimulated. If the goal is to influence the heart directly, cardiac vagal efferents need to be stimulated without confounding the effect by also stimulating afferents. Since cardiac efferent fibers are small and constitute only a small portion of vagal trunk, their stimulation requires special care to reverse the normal “largest first” recruitment of stimulated fibers.

The recently reported first pilot study of vagal stimulation in heart failure patients used an electrode that seems to partially satisfy such requirements. Although the details appear to be proprietary, the implantable electrical stimulator has multiple electrodes and induces anodal blockade to preferentially stimulate efferent rather than afferent nerve fibers. In the pilot study, 8 patients received intermittent vagal stimulation (2 to 10 sec “on” and 6 to 30 sec “off”) of the right cervical vagus using a pulse delivered 70 msec after each R wave of the ECG. The stimulating current, limited by a threshold or the onset of side effects, was adjusted to achieve a heart rate reduction of 5 to 10 beats/min. Patients were evaluated up to 6 months; no permanent side effects were reported. There was a modest improvement of cardiac function as judged by a reduction in left ventricular volumes, as well as a clear improvement in a measure of quality of life. The study shows feasibility and suggests further investigations.

The primary task seems to be optimization of stimulation parameters. Since natural vagal impulses are distributed through the cardiac cycle, artificial
stimulation might be more effective if it emulated the natural firing pattern. Since long-term heart rate reduction was minimal, parameters might be tuned further to stimulate small cardiac efferent fibers that may be far from the electrodes. Measurements of heart rate variability during controlled conditions may reveal the pacemaker’s responsiveness to vagal stimulation. Comparison of duty cycles (duration of “on” and “off”) may show whether the study’s choice, to some extent already mimicking the breathing-induced modulation of natural vagal activity, is most effective. Such studies to optimize effectiveness may be best performed in chronically instrumented animals.

**Baroreceptor stimulation**

An extensively studied mechanism that modulates the autonomic nervous system is the baroreceptor reflex that is known to be depressed in heart failure. Former efforts to use this reflex therapeutically were recently revived in both animal experiments and human studies. For example, bilateral carotid sinus stimulation nearly doubled the survival time of dogs with pacing-induced heart failure. Although measures of left ventricular function, obtained while the stimulator was turned off, were similar in dogs with stimulated and unstimulated carotid sinuses, plasma norepinephrine was lower in the animals receiving stimulation. This suggests that carotid sinus stimulation led to a general decrease in sympathetic activation. It is noteworthy that the stimulation was applied intermittently (9 min “on”, 1 min “off”) to avoid the resetting (or adaptation) of baroreceptors, a phenomenon that had led to the now-doubted traditional belief that the baroreflex regulates only acute rather than long-term changes of blood pressure.

Chronic bilateral baroreceptor stimulation was also applied in 21 patients with essential hypertension that could not be controlled by medication. Measurements were taken 1 month after implantation with the stimulator turned off and 3 months after chronic stimulation with the stimulator on. Stimulation moderately reduced both blood pressure and heart rate; heart rate variability suggested an increase in parasympathetic activity and a decrease in sympathetic activity.

**Renal sympathetic ablation**

Technology-based approaches encompass not only the stimulation of nerves but also the abolition of nerve activity. In an exploratory study, bilateral sympathetic denervation was performed in 45 patients with drug-resistant hypertension. A catheter, introduced through the femoral artery, was positioned at the entrance of each renal artery. Sympathetic denervation was produced by radiofrequency energy applied for a maximum of 2 minutes. The details of the technology appear proprietary, complete ablation could not be ascertained, and both efferents and afferents are likely to have been stimulated. Nevertheless, the procedure appeared safe and resulted in a significant reduction in both diastolic and systolic pressures over 12 months. In addition to lowering blood pressure, catheter-based sympathetic denervation might also prove therapeutic in heart failure and chronic kidney disease.

**Automated control of physiologic variables**

These initial experiences with baroreceptor stimulation, together with the results obtained by stimulating the vagus and ablating renal sympathetic nerves, indicate that device-based approaches may be useful additions to the treatment of drug-resistant hypertension and heart failure. The incorporation of control features that automatically respond to the changes in physiological states is natural extensions. As a recent example, in anesthetized dogs with heart failure and paced heart, systemic arterial pressure, cardiac output, and left atrial pressure were automatically regulated at set levels by a model-based infusion of nitroprusside, dobutamine, and volume expanders. When the heart rate was reduced, cardiac energetics (based on a reduction in left ventricular oxygen consumption) improved while the hemodynamic variables remained constant.

**Conclusions**

Biomedical engineering played a major role in linking measures of heart rate variation to sympathetic and parasympathetic contributions to cardiac control, as well as in demonstrating that the balance of control was correlated with a variety of disease states of heart and brain. However, much work remains to be done to fully realize the field’s potential for aiding clinicians in preventing or treating diseases. Further studies, some to be performed in chronically prepared animals, are needed to quantitatively characterize the many interacting mechanisms that determine cardiac function. Such studies would benefit from recording naturally occurring neural activity to and from the brain, and are already starting to benefit from the artificial electrical stimulation of nerves in both experimental animals and preliminary trials in patients.

The appropriate use of mathematical modeling is an essential tool for gaining in-depth understanding of physiological function. Mathematical modeling is also essential for developing stimulators that selectively stimulate those nerves that control the function to be influenced. The determination of stimulation parameters, based on understanding rather than on trial and error, is highly desirable. The use of “intelligent” stimulators, automatically controlled by appropriate physiological measurements, is an ambitious but achievable goal for improving human health.
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Sudden death in epilepsy, surgery, and seizure outcomes: The interface between heart and brain

ABSTRACT
A significant body of literature suggests that sudden unexpected death in epilepsy (SUDEP) has a cardiac mechanism. Although a correlation has been established between freedom from seizures and reduced SUDEP risk, the exact relationship between seizure outcomes following epilepsy surgery and SUDEP is still being studied. Emerging evidence suggests that seizure outcomes following epilepsy surgery and risk for SUDEP may both be governed by a common underlying biologic process linked to cardiac changes and autonomic dysregulation.

Sudden unexpected death in epilepsy (SUDEP) is most often defined as the sudden, unexpected, nontraumatic, and nondrowning death of patients with epilepsy. The death may be either witnessed or unwitnessed, and may occur with or without evidence of a seizure, excluding documented status epilepticus. In cases of definite SUDEP, postmortem examination does not reveal a structural or toxicologic cause of death.1

The reported incidence of SUDEP ranges from 0.7 to 1.3 cases per 1,000 patient-years in large cohorts of epilepsy patients2,3 and from 3.5 to 9.3 cases per 1,000 patient-years in antiepileptic drug registries, medical device registries, and epilepsy surgery programs.4–6 SUDEP is currently accepted as the most important epilepsy-related mode of death5,7 and is associated with standardized mortality ratios in patients with ongoing seizures as high as 24 to 40 times those of the general population.8 The exact mechanism or mechanisms leading to SUDEP remain unknown,1,5,9,10 and despite the identification of several potential risk factors, elimination of seizures still represents the main intervention correlating with risk reduction.5,11

This review will first discuss evidence for a cardiac mechanism of SUDEP, then review data traditionally used to support freedom from seizures following epilepsy surgery as a method for reducing SUDEP risk, and finally examine recent evidence suggesting that both SUDEP and seizure outcomes following epilepsy surgery are governed by a common pathway with certain cardiac manifestations.

CENTRAL AUTONOMIC NETWORK
A tightly interconnected neuronal network controls various elements of the cardiovascular autonomic system. Consideration of a cardiac pathophysiology of SUDEP requires a fundamental understanding of this network (Figure 1).7,12,13 The insula, the anterior cingulate gyrus, and the ventromedial prefrontal cortex are key to central cortical control of autonomic function. The insula represents the primary viscerosensory cortex, whereas the cingulate gyrus and prefrontal cortices constitute the premotor autonomic region. At the subcortical level, the hypothalamus provides an interface with endocrine stimuli and triggers autonomic responses to maintain homeostasis. The amygdala, which is an integral component of the limbic system that links the previously mentioned cortical and subcortical centers, mediates the autonomic response to emotions. Beyond their centrality to autonomic control, the insula, amygdala, cingulate gyrus, and prefrontal cortex also represent the most common foci of partial epilepsy, a finding that might explain the frequent observation of autonomic changes in relation to epileptic seizures.14

EVIDENCE FOR A CARDIAC MECHANISM OF SUDEP
The most significant and broadly discussed cardiac mechanism of SUDEP is cardiac arrhythmia brought about by seizure discharges acting through the autonomic nervous system.5,2,15,16

Clinical evidence
A wide spectrum of cardiac arrhythmias—from ictal asystole to atrial fibrillation to repolarization abnormalities to bundle branch blocks—has been reported during seizures.14–19 In one study, ictal cardiac arrhythmias occurred in 42% of hospitalized epilepsy patients, the most common being an irregular series of abrupt rate changes near the end of the electroencephalographic (EEG) seizure discharge.17 In another study, R-R interval analysis dur-
ing the first 10-second period of EEG discharge showed a significant early heart rate increase in 49% of seizures and an early heart rate reduction in 25.5%.18

Certain clinical seizure characteristics have been correlated with the occurrence of ictal electrocardiographic (ECG) abnormalities. One study found that mean seizure duration was longer in patients with ECG abnormalities than in those without such changes.16 Others observed that ictal ECG abnormalities occurred more often and were more severe in generalized tonic-clonic seizures than in complex partial seizures.15,16,19 These same clinical seizure characteristics were correlated with a higher risk of SUDEP,20 which suggests an interrelation among seizure semiology, ECG abnormalities, and SUDEP.

FIGURE 1. The cardiovascular autonomic system. **Afferent pathways (violet tracings):** The afferent loop of the cardiac autonomic system receives input from chemo- and baroreceptors in the carotid sinus (cranial nerve [CN] IX) and the aortic arch (CN X). 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 tracings):** 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. Parasympathetic influence on the heart arises primarily from the nucleus ambiguous. 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 arrows):** 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. Reprinted from Schuele et al,12 which was modified from Britton and Benarroch.13
Additionally, direct evidence of seizure-related cardiac changes occurring specifically in SUDEP victims has come from a study that compared EEG and ECG data between 21 SUDEP patients and 43 clinically similar historical controls with refractory partial epilepsy. The patients who eventually succumbed to SUDEP had a higher ictal maximal heart rate, a greater increase in heart rate with seizures arising from sleep, and a higher incidence of ictal cardiac repolarization and rhythm abnormalities.

**Experimental evidence**

Electrical brain stimulation of the limbic system and insular cortex has repeatedly been shown to provoke heart rate changes, including bradycardia, tachycardia, and asystole. Some studies have even suggested a lateralized influence of the insulae on cardiovascular autonomic control, with intraoperative stimulation of the left posterior insula eliciting a cardioinhibitory response and hypotension, and with stimulation of the right anterior insula eliciting tachycardia and hypertension. Other studies have suggested that the limbic system has a localization-related influence on cardiovascular responses, with stimulation of the amygdala alone being insufficient to produce the ictal tachycardia so commonly seen in epileptic seizures, which suggests that cortical involvement is essential for the increase in heart rate. Such cortical stimulation–induced heart rate changes may explain how massive seizure-related discharges can affect cardiac rhythm during the seizure itself.

There is also, however, evidence of a baseline epilepsy-related autonomic dysfunction. Abnormalities in cardiac uptake of meta-iodobenzylguanidine (MIBG) have been demonstrated interictally in patients with chronic temporal lobe epilepsy relative to controls. A recent study specifically showed a pronounced reduction in cardiac MIBG uptake in patients who had ictal asystole compared with other epileptic patients and nonepileptic controls, a finding that suggests a postganglionic cardiac catecholamine disturbance in patients with epilepsy. The authors proposed that epilepsy-related impairment of sympathetic cardiac innervation limits adjustment and heart rate modulation, and may thus increase the risk of asystole and, ultimately, SUDEP.

### EPILEPSY SURGERY AND SUDEP RISK

The above findings make it reasonable to postulate that recurrent uncontrolled seizures may lead to significant cardiac changes—namely, arrhythmias—which may then lead to a higher risk of SUDEP. Successful epilepsy surgery, the treatment of choice for uncontrolled partial epilepsy, would eliminate seizures and would thus be expected to reduce SUDEP risk.

Several studies support this hypothesis. Reductions in all-cause mortality and in SUDEP following successful epilepsy surgery have been observed when patients who became seizure-free after surgery were compared either with patients who had ongoing postoperative seizures or with patients with intractable epilepsy who did not undergo epilepsy surgery. In one study with a mean follow-up of 3.82 years, no deaths occurred among 199 patients who were seizure-free following epilepsy surgery, whereas there were 11 deaths—including 6 cases of SUDEP—among 194 patients who had persistent seizures following epilepsy surgery. A separate study compared 202 patients who underwent epilepsy surgery with 46 patients with medically treated intractable epilepsy over a mean follow-up period of greater than 5.7 years. In this study, death occurred in only 7% of the surgical patients compared with 20% of the medically treated patients, which suggests that epilepsy surgery (or lack thereof) may be an independent predictor of mortality. Favorable outcome was linked closely to seizure control, as 81% of the patients who died had 2 or more seizures per year at last follow-up, compared with only 47% of survivors in the overall cohort.

**Complete seizure resolution—not just reduction—seems necessary for SUDEP risk reduction**

In our experience at the Cleveland Clinic Epilepsy Center, we have found that a reduction in seizure frequency following epilepsy surgery is not enough to eliminate SUDEP risk—complete freedom from seizures is required. Of 37 SUDEP cases identified so far in a cohort of 3,481 patients evaluated in our epilepsy monitoring unit between 1990 and 2005 (Jehi et al, in preparation), 7 patients had undergone epilepsy surgery. None of these 7 patients was seizure-free at the time of death; four had a greater than 50% reduction in seizure frequency. No cases of SUDEP occurred in patients who were seizure-free after surgery.

Our findings mirror earlier results reported by Sperling et al, who also found that epilepsy surgery improves mortality only when seizures resolve completely, not when they merely “improve.” It seems plausible, therefore, that elimination of seizures postoperatively eliminates the risk for the several seizure-related cardiac arrhythmogenic changes discussed above, thereby eliminating the risk for the series of events that eventually leads to SUDEP.

**A role for stabilized baseline autonomic control?**

Alternatively, some data suggest that the “autonomic” impacts of epilepsy surgery may extend beyond the immediate seizure-related manifestations to the baseline interictal period in epilepsy patients. One study found that surgery for temporal lobe epilepsy is followed by a reduction of sympathetic cardiovascular modulation and baroreflex sensitivity. The authors proposed that this finding may be attributable to decreased influences of interictal epileptogenic discharges on brain areas.
involved in cardiovascular autonomic control. These researchers continue to postulate that surgery for temporal lobe epilepsy seems to stabilize cardiovascular control in epilepsy patients by reducing the risk of sympathetically mediated tachyarrhythmias and excessive bradycardiac counterregulation, potentially lowering SUDEP risk.25

**CARDIAC FINDINGS, SUDEP, AND SEIZURE OUTCOMES**

Whether it is the elimination of seizure-related cardiac arrhythmias achieved by rendering patients seizure-free after surgery, or whether it is the stabilization of baseline autonomic cardiac control by reducing interictal epileptiform discharges, this line of thought assumes that the autonomic dysfunction contributing to SUDEP is caused by epilepsy and that freedom from seizures following epilepsy surgery should therefore be responsible for reducing the risk of death. An alternative hypothesis for the infrequent occurrence of SUDEP in seizure-free patients may be that seizure outcomes following epilepsy surgery and SUDEP risk are actually both governed by the same underlying biologic process. This would suggest that the same patient cohort is at a higher baseline mortality risk and in a prognostically poorer seizure outcome group following epilepsy surgery.

This idea is supported by a recent prospective study among 21 consecutive candidates for temporal lobe epilepsy surgery in which spectral analysis of heart rate variability performed preoperatively was correlated with seizure control 1 year after surgery.26 The study found that patients with poor seizure outcomes (Engel class II to IV, signifying ongoing postoperative seizures) had significantly lower power in all domains of heart rate variability than did patients with favorable seizure outcomes.26

In another study, heart rate was recorded in 16 patients before and after temporal lobe epilepsy surgery, and sympathetic and parasympathetic cardiac modulation was determined as powers of low-frequency (LF, 0.04–0.15 Hz) and high-frequency (HF, 0.15–0.5 Hz) heart rate oscillations.27 The LF/HF ratio was calculated as an index of sympathovagal balance. Cardiac MIBG uptake was measured with MIBG single-photon emission computed tomography and compared with control data. Baseline sympathetic LF power and LF/HF ratio were higher in patients who eventually had persistent seizures than in those who became seizure-free. Following surgery, both measures decreased in seizure-free patients but increased in patients with persistent seizures. MIBG uptake was lower in patients than in controls and even lower yet in patients who had persistent seizures. In this subgroup, MIBG uptake declined further after surgery.

Essentially, both of the above studies demon-## REFERENCES


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Biofeedback in the treatment of heart failure

**ABSTRACT**

Biofeedback training can be used to reduce activation of the sympathetic nervous system (SNS) and increase activation of the parasympathetic nervous system (PNS). It is well established that hyperactivation of the SNS contributes to disease progression in chronic heart failure. It has been postulated that underactivation of the PNS may also play a role in heart failure pathophysiology. In addition to autonomic imbalance, a chronic inflammatory process is now recognized as being involved in heart failure progression, and recent work has established that activation of the inflammatory process may be attenuated by vagal nerve stimulation. By interfering with both autonomic imbalance and the inflammatory process, biofeedback-assisted stress management may be an effective treatment for patients with heart failure by improving clinical status and quality of life. Recent studies have suggested that biofeedback and stress management have a positive impact in patients with chronic heart failure, and patients with higher perceived control over their disease have been shown to have better quality of life. Our ongoing study of biofeedback-assisted stress management in the treatment of end-stage heart failure will also examine biologic end points in treated patients at the time of heart transplant, in order to assess the effects of biofeedback training on the cellular and molecular components of the failing heart. We hypothesize that the effects of biofeedback training will extend to remodeling the failing human heart, in addition to improving quality of life.

**BIOFEEDBACK: AN OVERVIEW**

Biofeedback is a self-regulation therapy that aims to teach individuals the skills that will allow them to change their physiology in healthy directions. Biofeedback involves a client, a trained biofeedback coach, and appropriate instrumentation. Sensors are connected to the client, and various physiologic parameters (such as heart rate, blood pressure, and digital peripheral temperature) are displayed on a computer screen. The client is guided through a brief mental stress test and a relaxation exercise to learn to recognize differences between hyperarousal and a more relaxed physiology. Biofeedback training involves a series of sessions in which the goal is to help the client gain control of his or her own physiology by learning relaxation techniques such as deep breathing, progressive muscle relaxation, and guided imagery. Although biofeedback can be used solely as operant conditioning, it is more commonly and more effectively combined with techniques of stress management. Biofeedback training is commonly (although not exclusively) used to decrease activation of the sympathetic branch of the autonomic nervous system (the “fight or flight” response). The reduction in sympathetic nervous system (SNS) activity is manifest as an increase in digital peripheral temperature and decreases in skin conductance, heart rate, and blood pressure, as well as changes in the frequency distribution of heart rate variability. While the SNS is becoming less activated, the parasympathetic portion of the autonomic nervous system (“rest and digest”) is becoming more involved in regulating body functions. More parasympathetic nervous system (PNS) activation and less SNS activation produces a healthier physiologic state, and thus biofeedback can be used to move the body in the direction of health and wellness.

**HEART FAILURE: BIOLOGIC MECHANISMS OF INJURY**

Heart failure is the end result of most untreated cardiovascular diseases. Heart failure involves inadequate cardiac pump function, such that appropriate perfusion of end organs does not occur. The process of developing heart failure is a gradual one that begins with compensatory processes. In response to an injury or insult, such as chronic high blood pressure or long-standing coronary artery blockage, the heart compensates by activating various neurohormonal pathways in an attempt to preserve cardiac function and end-organ perfusion. When these pathways are activated, they initially help the heart to compensate for the ongoing challenge of increased pressure or decreased tissue oxygenation and allow the cardiovascular system to pump sufficient blood. Over time, however, these compensatory processes become maladaptive. Cellular signaling pathways, which were activated in order to help the heart compensate, actually become as much of a problem as the decreased cardiac function.
Hyperactivation of the SNS
Chief among these pathways is the SNS, which is the most powerful means by which cardiac function can be augmented. In response to decreased cardiac function, cardiac sympathetic nerves are activated, releasing norepinephrine locally, and both norepinephrine and epinephrine increase in the circulating blood. Beta-adrenergic receptors on cardiac myocytes and on vascular smooth muscle cells are stimulated, and the resulting augmentation of cardiac contraction helps the heart to overcome an immediate challenge. If the insult or injury to the heart is acute and time-limited, this system compensates and the situation is resolved. However, chronic activation of the SNS creates more problems than it solves for the failing heart, including:

- Myocardial cells are challenged by the need for increased energy production to support the chronic stimulation
- Oxidative stress ensues
- Receptors are downregulated
- Pathways that result in necrosis and apoptosis are activated
- Myofilament proteins respond to chronically elevated intracellular calcium.

As a result, the heart begins to spiral more quickly into a decompensated state. The toxicity of SNS overactivation is the reason for the success of beta-adrenergic blocking drugs in treating heart failure, but this situation is complicated further by adrenergic receptor polymorphisms and nonhomogeneous responses to beta-blocking agents. It is safe to say that the goal of much heart failure therapy is inactivation of the once-compensatory SNS and its resulting biologic effects.

Hypoactivation of the PNS
In addition to hyperactivation of the SNS, heart failure is also accompanied by a decrease in the role of the PNS. Under normal resting conditions, the human heart is governed more by the PNS than the SNS, with the SNS becoming a major source of cardiac control only during periods of decreased cardiac function. In heart failure, however, this relationship is reversed, with the SNS taking over the governing role and PNS input becoming less significant. Studies have suggested that the lack of contribution of the PNS to cardiac regulation in heart failure may be as deleterious as overactivation of the SNS. Most recently, stimulation of the vagal nerve has been shown to be beneficial in both animal models and humans with heart failure, confirming that augmenting PNS activity may be as important as inhibiting SNS activity. Although vagal nerve stimulation may be the first heart failure therapy aimed specifically at the PNS, it is likely that the future will hold more therapies with this goal.

PNS as regulator of inflammation of the failing heart?
It has recently been suggested that beyond its role in regulating cardiac function under baseline conditions, the PNS may participate in regulating the inflammatory state of the failing heart. It has been established since the observations of Packer and colleagues in the early 1990s that proinflammatory cytokines such as tumor necrosis factor–alpha, interleukin-6, and interleukin-1 are elevated in the circulation of heart failure patients, that these cytokines are correlated with clinical prognosis, and that they play a role in the activation of deleterious cardiac signaling pathways. Trials of anti-inflammatory therapies in heart failure have been less than successful, but this may be because the complexity of the activation has been underestimated. In elegant work reported several years ago, Kevin Tracey’s group showed that stimulation of the vagus nerve could inhibit inflammatory processes associated with sepsis. Since that time, the reflex activation and inactivation of inflammatory processes by the PNS have become more widely accepted. Although it has not yet been directly demonstrated, it is possible that part of the benefit of vagal nerve stimulation in heart failure will prove to be due to its ability to reduce the chronic inflammatory state of the failing heart.

BIOFEEDBACK IN HEART FAILURE: RATIONALE
The failing heart is characterized by autonomic imbalance (hyperactivation of the SNS and hypoactivation of the PNS) and by a chronic inflammatory state. It has been hypothesized both directly and indirectly that these two major pathophysiologic processes may be intertwined. Biofeedback-assisted stress management is a therapy that has the potential to interfere with both processes. If the patient with heart failure can be trained to reduce activation of the SNS and to increase control by the PNS, it is likely that the negative consequences of autonomic imbalance will be decreased or possibly even reversed. Whether these effects are limited to quality of life and clinical status, or whether they extend to an effect on myocardial remodeling processes, remains to be established. Since the chronic inflammatory state can also be affected by increasing PNS control of the cardiovascular system, we further hypothesize that biofeedback training may have a direct effect on the inflammatory processes involved in the downward spiral of heart failure.

BIOFEEDBACK IN HEART FAILURE: STUDIES
We are certainly not the first group to hypothesize that self-regulation may have a role in the treatment of cardiovascular diseases in general or heart failure in particular. It has been shown that patients with heart failure manage their disease better and experience less emo-
tional distress when they have a greater sense of control over their condition. In addition to giving patients a greater sense of control, some mind-body therapies have been shown to be beneficial in those with heart failure. Pischke et al showed as part of the Multicenter Lifestyle Demonstration Project that patients with left ventricular ejection fractions in the range associated with heart failure (≤ 40%) were able to learn and benefit from stress management techniques equally as well as those with more normal cardiac function. Both relaxation training and meditation have been shown to improve quality of life in heart failure patients, but meditation also reduced circulating norepinephrine, a marker of SNS activation. Mindfulness training improved clinical symptoms of heart failure and also reduced both anxiety and depression in patients with heart failure. Training heart failure patients to breathe more slowly is an intervention that is normally part of biofeedback training, but even when used alone it has resulted in decreased dyspnea, increased oxygen saturation, and improved exercise tolerance.

To our knowledge, three studies to date have specifically used biofeedback training in patients with documented heart failure. As early as 1997, Moser and colleagues showed that heart failure patients were able to raise their finger temperature in spite of disease-related vascular changes, and that a single session of finger temperature biofeedback resulted in meaningful clinical improvement. Luskin et al randomized 33 heart failure patients to either biofeedback-assisted stress management or a control group, and showed improvement with the intervention in perceived stress, emotional distress, exercise tolerance, and depression. Most recently, Swanson and colleagues demonstrated improved exercise tolerance after cardiorespiratory biofeedback in patients with higher left ventricular ejection fractions (≥ 31%), although improvement could not be accomplished in those with ejection fractions below 30%.

**ONGOING STUDY IN END-STAGE HEART FAILURE AND FUTURE DIRECTIONS**

We are currently involved at Cleveland Clinic in a study of end-stage heart failure patients who are awaiting cardiac transplantation. Each patient is provided with eight sessions of biofeedback training, including respiratory rate, digital peripheral temperature, muscle tension, and heart rate variability. Clinical status, quality of life, and heart failure-specific symptoms are being monitored throughout the training period. Success with biofeedback training is being analyzed, and we are testing the hypothesis that the degree of success in learning self-regulation will predict change in clinical status, quality of life, and the biology of the heart. What is unique to our study is that we will obtain the heart tissue at explant, when the patient receives a cardiac transplant, and we will conduct experiments to determine whether the cellular and molecular phenotype of the heart have been changed by the intervention, particularly components of the SNS, PNS, and inflammatory pathways.

We have been studying human heart failure for many years, and we have previously shown the changes in receptors and signaling pathways that occur in the failing human heart. We were also among the first to demonstrate that the cellular and molecular changes that occur in the failing human heart are not actually irreversible but can be changed by interventions such as a left ventricular assist device. Thus we hypothesize that biofeedback training, by interfering with overactivation of the SNS and by allowing the PNS to more adequately contribute to cardiac regulation, will have a meaningful effect on the biology of the failing human heart in addition to improving clinical status and quality of life. We hope to be among the first to demonstrate that effect.

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Biofeedback in the treatment of epilepsy

ABSTRACT
This review traces the application of electroencephalographic (EEG) operant conditioning, or biofeedback, from animal research to its emergence as an alternative treatment for the major types of seizure disorder. Initial animal studies focusing on brain mechanisms that mediate learned behavioral inhibition revealed a uniquely correlated 12- to 15-Hz EEG rhythm localized to sensorimotor cortex. We labeled this the sensorimotor rhythm, or SMR. The similarity of the SMR to the known EEG spindle pattern during quiet sleep led to the novel idea of attempting to increase the SMR using EEG operant conditioning. The hypothesis was that this might produce a corresponding increase in sleep spindle activity, thus establishing a common EEG marker for the state of motor inhibition. Results supported this hypothesis but led also to the accidental discovery of an anticonvulsant effect on drug-induced seizures in cats and monkeys. Continuing animal studies identified a pattern of neurophysiologic responses correlated with the SMR in primary motor pathways. These and other findings were indicative of reduced motor excitability. Simultaneously, we undertook studies in human epileptic subjects that documented a significant reduction in seizure incidence and severity, together with EEG pattern normalization. This work expanded internationally, resulting in numerous well-controlled group and single-case studies summarized in recent meta-analyses. Exciting new findings in functional neuroimaging/EEG correlation studies provide a rational model for the basis of these clinical effects. In recognition of the diversity of clinical applications of EEG biofeedback and the complexity of seizure disorders, this review also details specific methods used in our EEG biofeedback program.

INITIAL APPLICATION IN HUMANS
This application was officially added to the broader field of biofeedback with the publication of a 1972 paper by Sterman and Friar titled, “Suppression of seizures in an epileptic following sensorimotor EEG feedback training.” In this paper we documented a sustained and progressive reduction of generalized nocturnal tonic-clonic seizures in a 23-year-old female epileptic with a 7-year history of frequent and medically refractory seizures of unknown origin. The patient’s clinical EEG showed left sensorimotor cortex spikes and slow 5- to 7-Hz activity. Seizure reduction occurred in response to an experimental course of EEG operant conditioning aimed at increasing 12- to 15-Hz EEG activity in the left sensorimotor cortex while suppressing slower activity at this same site. The 12- to 15-Hz EEG rhythm was discovered in animal research and labeled as the sensorimotor rhythm (SMR). Although the patient had previously been worked up and treated unsuccessfully with anticonvulsant medications at several prestigious medical institutions, over the course of 2.5 years of twice-weekly EEG feedback training sessions she became essentially seizure free (Figure 1) and was ultimately issued a California driver’s license.

BACKDROP TO THE CLINICAL APPLICATION: KEY ANIMAL STUDIES
The above landmark study was predicated on the observation of a discrete 11- to 19-Hz EEG rhythmic pattern in cats, which occurred intermittently over the sensorimotor cortex during behavioral quiescence. When animals were trained to suppress a learned bar-press response for food if a tone was sounded in the chamber, a 12- to 15-Hz version of this EEG pattern always accompanied inhibition of the bar-press response. If animals later fell asleep, a similar rhythmic EEG pattern, known as the...
sleep spindle, was localized to the same cortical area at the same frequency (Figure 2). Our interest at the time was in the neurophysiological control of sleep. Because both of these patterns occurred uniquely in the absence of movement, we sought to determine if the underlying neural mechanisms were related.

To accomplish this, we attempted to facilitate the SMR during wakefulness using an operant conditioning paradigm with a liquid food reward, and then study any resulting changes in sleep spindle activity and sleep structure. Necessary quality controls included alternate training to suppress this rhythm and a counterbalanced design employing two separate groups of cats. Six weeks of three training sessions per week to satiation led to profound and differential changes in sleep EEG and sleep architecture. SMR training, whether it preceded or followed suppression training, led to a significant increase in EEG sleep spindle density, as well as a significant reduction in sleep period fragmentation due to arousals. No changes occurred in the control condition.

FIGURE 1. A carefully documented 6-year seizure data log from an adult female subject (aged 23 years at the start of the log) with nocturnal tonic-clonic seizures, often with incontinence. The log starts 1 year before initiation of electroencephalographic (EEG) feedback training ("Pre-SMR"), continues through 2.5 years of twice-weekly EEG training sessions ("Post-SMR"), and continues through 2.5 years after withdrawal from this training ("Withdrawal"). Training consisted of auditory and visual reward for increased 12- to 15-Hz EEG activity over the left sensorimotor cortex, which has been labeled the sensorimotor rhythm (SMR). Medications were held constant during training and adjusted downward after withdrawal from training. In 1977 this patient was issued a California driver’s license.


As interesting as this finding was, the most profound outcome of the study emerged later. A different cat study under way in our laboratory, funded by the US Air Force, was seeking to determine the effects on behavior of low-dose exposure to monomethyl hydrazine (MMH). This compound is a highly toxic component of the liquid rocket fuel used for launching virtually all space vehicles. Significant MMH exposure via any route causes profound nausea and gradual onset of convulsions, which are lethal at adequate doses. The mechanism for this effect was ultimately determined to be a disruption of the synthesis of gamma-aminobutyric acid, the primary inhibitory neurotransmitter in the central nervous system. We were investigating the effects of low-dose exposure to determine the possible disruption of cognitive functions such exposure might cause in flight crews. Our first objective for studies in cats was to establish the dose-response curve for convulsive effects in that species. We had succeeded in determining a curve showing that 9 mg/kg of MMH was the threshold dose for reliably producing
nonlethal convulsions after a prodrome of approximately 40 to 67 minutes. This prodrome consisted of a sequence of reliable autonomic and behavioral events. When data from animals provided with SMR operant conditioning as the final training procedure were added to this curve, the same prodrome was observed but there were no seizures at 60 minutes. Instead, the latency to seizures was delayed to a range of 80 to 220 minutes, and several animals failed to seize at all. This finding then led to the test in the human epileptic subject described above.1

Platform for a dual research approach
These two studies provided several interesting conclusions that directed our subsequent scientific efforts. First, in the cat study we observed a common prodrome in both SMR-trained and control animals even though the SMR-trained animals had acquired protection against seizures. This suggested a direct effect on the seizure process and not on MMH toxicity in general. Second, in our human epileptic patient, the seizures that were suppressed arose out of the unconscious state of sleep, a fact that eliminated the possibility of any voluntary countermeasure and again indicated a direct effect on the seizure mechanism. Accordingly, we undertook a dual approach to understanding the basis of this effect, involving both additional animal electrophysiologic and human clinical studies.

Animal studies evaluated motor behavior, motor reflexes, motor and thalamic unit firing, and somatosensory pathway correlates of the SMR response. Clinical studies, as reviewed in the following section, sought to further document the anticonvulsant effects of SMR operant conditioning and examine this effect on various seizure types. Possible alternative explanations, such as altered medication compliance and placebo effects, were also addressed in several comprehensive studies. Additionally, by this time other laboratories were beginning to add to the research literature in this new field.

Neurophysiologic studies in cats revealed a convergent pattern of changes that were directly correlated with the SMR pattern in the EEG and clearly indicated reduced motor excitability. These included a specific attenuation of cellular activity and reflex excitability in the motor pathway, a reduction in muscle tone and associated motor unit firing, and cessation of behavioral movements. Further, unit studies in afferent nuclei of the somatosensory pathway revealed evidence of reduced somatic afferent firing and the onset of reciprocal burst oscillation between the thalamic reticular nucleus and the adjacent ventrobasal relay nucleus. This oscillation provides the thalamic source of the cortical SMR pattern. These findings are summarized in Figure 4. Details of the studies and resulting publications are provided in recent review articles. They represent empirical evidence for significant reorganization of neuronal function when SMR activity appears in the sensorimotor EEG.

**CLINICAL STUDIES**
A series of human studies followed our initial clinical report, including group studies involving crossover and placebo-controlled designs. These studies consistently reported significant seizure reductions in epileptic
patients in response to reward for increasing sensorimotor EEG rhythmic activity.

Two independent meta-analyses of the peer-reviewed papers in this literature have appeared in the last decade.8,10 In a review of 24 studies involving 243 patients with predominantly partial complex seizures provided with central cortical SMR feedback training, Sterman determined that 82% of these subjects registered seizure reductions greater than 50%.8 More recently, Tan and colleagues evaluated data from 63 studies and selected for comprehensive analysis 10 studies that met stringent criteria for controls and population and seizure details.10 They reported that 79% of the patients treated with SMR feedback training experienced a statistically significant reduction in seizure frequency despite a collective history of failed medication therapy.

Data from one of the studies11 evaluated in both of these systematic reviews are summarized in Figure 5. In this study, 24 subjects with complex partial seizures, many with seizure foci confirmed through depth recordings, were randomly assigned to three experimental treatment groups:

- One group simply tabulated their seizure experiences for 6 weeks using a comprehensive logging method.
- The second group received EEG feedback training for 1 hour three times a week for 6 weeks; however, the EEG signal responsible for reward was previously recorded from a different individual. This noncontingent feedback constituted a “yoked control” group.
- The third group received 6 weeks of contingent training for increasing SMR activity in somatosensory cortex while simultaneously suppressing slower 4- to 8-Hz activity.

After the initial 6 weeks, all 24 subjects were combined into one contingent SMR training group for 6 additional weeks and then gradually withdrawn from training. A final 6-week follow-up seizure tabulation period completed the analysis. Data are plotted against group baselines. A significant reduction in seizures was registered after contingent training only, and this effect increased progressively across subsequent conditions. Data are from Lantz and Sterman.11
logical testing showed that responding SMR-trained subjects also improved significantly in performance of tasks specific to the hemisphere contralateral to their frontotemporal lesion, indicating a reduced corrosive disturbance from the seizure focus.11

EEG BIOFEEDBACK IN PRACTICE:
PROFILE OF THE AUTHOR’S PROGRAM

EEG operant conditioning methods for biofeedback training have diversified as various hardware and software products have emerged and as individuals with differing backgrounds and credentials have entered the field. A lack of methodologic standards and professional regulations has contributed to an undesirable inconsistency in the competence and effectiveness of therapeutic applications. Nevertheless, abundant peer-reviewed research by qualified investigators has proven the worth of this method as a viable alternative treatment for seizure disorders, so I will attempt to provide some idea of a systematic and evidence-guided approach to treatment as used in our program.

Patients are subjected to a quantitative multichannel EEG evaluation (QEEG) using hardware and software complying with both technical and learning-theory principles critical to valid data collection and operant conditioning applications. Data obtained from this study are combined with medical reports from other studies and information gained in a comprehensive intake interview. QEEG and background information guide the design of an empirical protocol, often with several training components, that is used consistently throughout the treatment period, which consists of one or two 60- to 90-minute treatment sessions per week for at least 20 weeks. Subjects are seated in front of a large-monitor screen and instructed on the requirements for reward. Reinforcement consists of visual images and tones, as well as a numeric display of scores achieved and the time remaining in a trial. On rare occasion a committed parent may be seated next to a more challenged patient and provide additional reinforcement in the form of earned treats, such as raisins and pieces of candy (Figure 6).

The display that subjects see can vary within limits but must always be as simple as possible and must provide information exclusively relevant to achieving the desired EEG changes. One such display is shown in Figure 7. It consists of a series of four rectangular boxes, each with a segment of band-passed EEG data for selected frequency bands and enclosed by reward threshold guidelines. If the objective is to increase the amplitude and/or incidence of a particular frequency band, the band-pass display must exceed the upper threshold guideline. If the objective is to suppress that frequency band, the display must drop below the threshold line. The duration of the required response can be adjusted and is typically 0.25 to 0.5 seconds. When the desired response is achieved a small horizontal bar at the upper right of each band-pass display turns from red to green, and a large blue ball appears above, together with a chime or other tone. The display is frozen for 2 seconds and then becomes active again, thus providing for discrete trials. A yellow score bar at the bottom of the screen advances by one unit. The timing of each performance set (typically 3 minutes) is indicated by a moving blue bar at the bottom of the screen.

With each box monitoring the same electrode site and each frequency tuned to the same band, thresholds can be set to promote facilitation or suppression through “successive approximation,” or sequencing from left to right with sequentially more difficult thresholds. Numerous other configurations are possible. In the case shown in Figure 7, the band-pass at the far left is set at 12 to 15 Hz (SMR) for the C3 electrode site, and the remaining three bands to the right are set to 3 to 5 Hz at the left medial frontal location Fz, with successively lower thresholds to promote suppression of this band at this site.

Performance outcome is measured systematically by tracking the scoring rate per trial, together with associated EEG patterns. Data from the 12-year-old female subject described above provide an example. The top of Figure 8 shows a plot of reward rate across four successive 3-minute EEG feedback trials. The patient was rewarded for simultaneously increasing 12- to 15-Hz

FIGURE 6. This 12-year-old girl has suffered since early childhood from frequent multiple seizure types and myoclonic jerks that are unresponsive to pharmacologic treatments. She currently functions at about third-grade level but is aware and behaviorally compliant. Here she is responding to visual feedback in the context of sensorimotor rhythm training. Her mother assists by providing raisin and candy rewards when certain response criteria are achieved. Her seizures have declined in frequency and severity.
SMR activity at C3 and reducing 3- to 5-Hz activity at Fz, as described above. Smoothed EEG plots for the targeted frequency bands are shown below these reward curves, starting with the C3 12- to 15-Hz channel. Activity in this band became increasingly stable across trials. Data from three frontal recording sites are also shown, with the targeted Fz 3- to 5-Hz band output at the bottom. Amplitudes decreased progressively at all frontal sites but most markedly at the bottom Fz location. Thus, SMR stabilization and simultaneously suppressed frontal slow activity resulted in a progressive pattern of incremental reward both within trials and across the session. The resulting profiles are indicative of learning.

**A RATIONAL MODEL FROM RECENT NEUROIMAGING STUDIES**

While it is difficult to evaluate neurophysiologic changes in human subjects to a degree similar to that in animals, certain parallels can be drawn. Further, new imaging...
methods allow for assessment of localized metabolic changes in the human brain during and after EEG feedback training. Behaviorally, during successful SMR training, human subjects become behaviorally quiet and direct their attention to the task. It is safe to presume that the SMR response develops as a result of reduced motor excitation and resulting intrathalamic ventrobasal oscillations, since this mechanism is well established as a basis for mammalian sensorimotor EEG rhythm generation. These changes, as well as others documented in our animal studies, set the stage for the development of SMR training on the neural substrates of selective attention in children with attention-deficit/hyperactivity disorder.12

Several recent studies have suggested a specific pattern of motor inhibition output from the striatum of the basal ganglia as the source of these changes. Birbaumer observed increased striatal metabolic activity with functional magnetic resonance imaging (fMRI) analysis in subjects producing SMR activity (personal communication, 2005). Further, Lévesque and colleagues studied pre-/post-fMRI blood oxygenation level–dependent response patterns in learning-disabled children trained to increase SMR activity and found a specific increase in the metabolic activity of the striatum and substantia nigra (Figure 9).11 The SMR-trained subjects showed significant academic improvement as well.13

These facts provide a rational model for a threshold-altering process that could affect seizure discharge propagation to motor networks. Although there are many different neurotransmitters used within the basal ganglia (principally acetylcholine, gamma-aminobutyric acid, and dopamine), the overall effect on thalamus and premotor networks in the mesencephalic tegmentum and superior colliculus is inhibitory.14-15 If activation of these inhibitory basal ganglia networks can become labeled by the SMR through contingent feedback training, and if responsible circuits can be potentiated by this association, motor inhibitory regulation would be generally facilitated.

CONCLUSIONS

Despite the encouraging findings and concepts reviewed here, there are significant issues at virtually every step of the thinking and practice behind this new therapy. This method depends on a comprehensive understanding of the EEG signal and the technical requirements of valid quantitative analysis and feedback applications. This includes a basic knowledge of the principles essential for effective operant conditioning. Further, in light of the complexity of seizure disorders, accurate history and seizure classification must be evaluated and understood. Alternative explanations for therapeutic results include such considerations as short-lasting expectation effects and changes in patient behavior. However, it must again be noted that the prolonged anticonvulsant effect documented in our animal studies, as well as in relation to nocturnal seizures arising out of sleep in a human subject, would seem to rule out placebo or nonspecific effects. This conclusion is supported further by the finding of improved neuropsychological performance after SMR training in tasks mediated by the hemisphere contralateral to disrupting localized epileptogenic lesions. Additionally, an alternative explanation for improved seizure control based on increased medication compliance has been rejected through studies that carefully monitored blood levels of prescribed anticonvulsant drugs before, during, and after training.

Finally, the epileptic patients who have demonstrated clinical improvement in EEG biofeedback research studies, along with many who seek this treatment today, represent unquestionable failures of anticonvulsant drug therapy. Notably, positive outcomes have frequently been achieved in patients with complex-partial seizures, an extremely difficult-to-treat seizure type. It is therefore unfortunate that some professionals still criticize neurofeedback therapy for a lack of more consistent or successful outcomes. On the contrary, as noted here, evidence has shown that most of these difficult-to-treat patients benefit beyond any chance or placebo outcome, in some cases dramatically so. In light of the frequent adverse effects and costs associated with lifelong pharmacotherapy, we view EEG biofeedback therapy not as a “last resort” option to be restricted solely to pharmacotherapy-resistant cases but rather as a...
generally viable consideration for any patient suffering from seizures. Moreover, in contrast to drug-dependent management approaches, the altered modulation of striatal and thalamocortical inhibition that is possible through neurofeedback training may sufficiently raise seizure thresholds to greatly increase the prospects for the long-term nondependent management of epilepsy.

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The effects of biofeedback in diabetes and essential hypertension

ABSTRACT

The metabolic syndrome is likely to develop in patients in whom genetic predisposition, chronic stress, negative emotion, and unhealthy lifestyle habits converge. In light of the psychophysiologic aspect of most of these factors, biofeedback, relaxation, and other psychophysiologic interventions have been studied and used in patients with elements of the metabolic syndrome, particularly diabetes and hypertension. This article reviews the rationale and evidence for biofeedback for the treatment of diabetes and hypertension, which has been shown to effectively lower blood glucose and blood pressure in numerous studies. Patients with prehypertension may be a particularly appropriate target population for biofeedback for blood pressure reduction. Further research is needed to guide identification of the best candidates for psychophysiologic intervention for these conditions, although patient readiness for change is a clear prerequisite.

ETIOLOGY OF METABOLIC SYNDROME: THE INTERSECTION OF BIOLOGY, LIFESTYLE, STRESS

Type 2 diabetes, essential hypertension, obesity, and hyperlipidemia are the major components of the metabolic syndrome. Understanding the psychophysiologic basis of the metabolic syndrome is important since its prevalence has been increasing dramatically over the last decade. In the past, type 2 diabetes was diagnosed almost exclusively in persons in their 40s or older. Health care providers are now reporting emergence of type 2 diabetes and the metabolic syndrome in individuals in their 30s and even their late 20s.1,2

This article outlines the psychophysiologic bases for components of the metabolic syndrome and reviews the application of biofeedback and other psychophysiologic interventions on the two components for which such interventions have been most studied—diabetes and essential hypertension.

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

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Importance of sleep
Sleep disruption is often ignored in discussions of the mind-body interface in hypertension and diabetes. However, Knutson and Van Cauter\(^1\) suggested that sleep quality and sleep length have important effects on leptin levels and risk for diabetes. Very short sleepers have stronger appetites, as a result of lower leptin concentrations, and are much more likely to be obese compared with long sleepers (≥ 10 hours). This indicates that sleep length and quality affect metabolism. With regard to hypertension, a very important reduction of blood pressure occurs during the night, and a lack of nighttime blood pressure “dipping” is one of the markers for sustained blood pressure elevation.\(^2\)

Factors overlap and begin to affect self-care
In addition to the effects of stress on mood and anxiety, repeated necessary demands for adaptation have marked effects on self-care behavior. Patients who suffer from anxiety are less efficient in managing their time and may be distracted from monitoring blood glucose and blood pressure. Anxious people often turn to the use of high-calorie comfort foods to soothe themselves during stressful times. Alcohol may be chosen as a means of reducing worry and tension. Depressed people lack the energy needed to maintain medical regimens and tend to be poor adherents to treatment recommendations. They also may choose comfort foods and addictive substances instead of nutritious, high-quality food and drink.\(^3\)

Both anxiety and depression affect sleep routines and efficiency. Anxious people have trouble getting to sleep and may wake up often during the night, while depressed individuals frequently wake up early and cannot get back to sleep. Additionally, psychological distress influences social behaviors. Overt depressive and anxious symptoms tend not to foster social interactions with family and friends. Lack of social support and a scarcity of personal resources eventually contribute to the risk for diabetes and hypertension.\(^4,5\)

In short, the metabolic syndrome is most likely to emerge when there is a combination of genetic factors, chronic stress, negative emotion, and unhealthy habits. The application of psychophysiologic interventions to diabetes and hypertension is based on our understanding of the etiology of these disorders, particularly the roles of psychological distress and behavior on blood glucose and blood pressure.

### BIOFEEDBACK IN TYPE 2 DIABETES

Diabetes is characterized by elevated blood glucose and resistance of cell membranes to insulin, such that glucose is impeded from crossing from the blood into the cells. Standard treatment consists of oral antihyperglycemic agents, exogenous insulin, diet, and exercise.\(^6\) Type 2 diabetes may be the most behaviorally demanding of all chronic illnesses because patients must take an active role in daily management. Typical requirements are to measure blood glucose and take oral medicine, perhaps along with insulin, as well as to exercise, monitor diet, and adjust calories depending on activity level.

**Therapy goals and a sampling of evidence**

The goal of psychophysiological therapy is not to replace standard treatment with relaxation training or biofeedback but rather to use biofeedback-assisted relaxation therapy to improve control of blood glucose. For example, McGinnis and colleagues compared the effects of 10 sessions of biofeedback (both surface electromyography and thermal feedback) and relaxation therapy versus three sessions of education in a sample of 30 patients with type 2 diabetes.\(^7\) No medicines were changed unless medically necessary. Patients kept daily logs of blood glucose, and had their hemoglobin A\(_1c\) measured before and after treatment. Significant between-group differences in hemoglobin A\(_1c\) and average glucose emerged in favor of the biofeedback group.\(^7\) However, patients with high scores on the Beck Depression Inventory\(^7\) (indicating more severe depressive symptoms) tended to drop out of the study or did not do as well as patients who were not symptomatic.

Another application of biofeedback in type 2 diabetes has been demonstrated by Rice and Schindler\(^8\) and Fiero et al.\(^9\) These investigators showed that patients with peripheral neuropathy, a common long-term complication of diabetes, were able to warm their hands and feet with the use of thermal biofeedback. Increased peripheral blood flow mediated the decrease in neuropathic pain.

### Possible mechanisms of biofeedback in diabetes

Several explanations can be suggested to account for the results of biofeedback on blood glucose levels. Forehead muscle tension feedback (surface electromyography) helps patients to reduce facial tension and relax skeletal muscles, while increased finger temperature is an indicator of general relaxation. In the patients who completed the above study by McGinnis et al.,\(^7\) both depression and anxiety scores decreased, which suggests a psychological mechanism for blood glucose reduction. Patients also reported improved sleep duration and quality with the use of relaxation therapy at bedtime.

#### BIOFEEDBACK IN ESSENTIAL HYPERTENSION

Biofeedback-assisted relaxation therapy has also been applied to control essential hypertension. The definition of hypertension, according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNCT7),\(^10\) is systolic blood pressure greater than 139 mm Hg and diastolic blood pressure greater than 90 mm Hg. Prehypertension refers to systolic blood pressures between 130 and 139 mm Hg and diastolic pressures between 80 and 89 mm Hg. Standard treatment for established...
hypertension is antihypertensive medications, diet, and exercise. For patients in the prehypertensive blood pressure range, lifestyle changes are the primary intervention, unless the patient has multiple risk factors.

Representative clinical evidence
Linden et al. reported on the effects of 10 weeks of individualized psychophysiological treatment on ambulatory blood pressure in patients with essential hypertension. Patients were initially screened for anxiety, depression, and anger, after which a program was designed for each patient based on his or her psychological risk factors. All patients received some form of relaxation therapy, and some received biofeedback. Over time significant reductions in ambulatory systolic and diastolic blood pressure were observed. In a separate study, Yucha et al. provided a multimodal training program to hypertensive individuals and also reported significant decreases in blood pressure.

Elliott et al. trained hypertensive patients to use the RESPReRATE™ device to achieve the slow, deep breathing associated with the “relaxation response” sought in relaxation training. After initial training, patients were instructed to practice this device-guided breathing technique at home. Significant reductions in systolic blood pressure were observed over 8 weeks in the patients who used the device compared with controls who simply monitored their blood pressure at home. A maximum mean systolic blood pressure reduction of 15 mm Hg was achieved in the group of patients who practiced device-guided breathing for the greatest number of minutes during the 8-week study. Similar results with device-guided breathing using this device have been reported in two separate studies.

More general stress reduction programs have also achieved success when offered to patients with essential hypertension in the clinic or the workplace. Studies of programs focusing on meditation and repeated practicing of centered breathing and relaxation responses, without use of biofeedback, have reported reductions of approximately 10.7 mm Hg in systolic pressure and 6.4 mm Hg in diastolic pressure. McCraty and colleagues provided a stress management program to hypertensive individuals at their place of work, based on the premise that individuals’ work demands are a source of chronic stress and thus create an ideal setting for the application of new coping skills. In this study, stress reduction training was associated with significant reductions both in blood pressure and in global measures of distress.

Prehypertensive patients: An ideal target population
Although meta-analyses demonstrate that there is support for the efficacy of biofeedback in patients with essential hypertension, the field has been handicapped by the reality that most patients with hypertension are already being treated pharmacologically, which means that their blood pressure levels when starting biofeedback treatment are often low, limiting the potential effects of the intervention. The new category of patients with prehypertension may thus be the ideal population for stress management therapies, since their blood pressure is elevated, but not elevated enough to have prompted medication prescriptions in most cases. Lifestyle modifications, which could certainly include stress management, are the recommended first-line therapies for these prehypertensive patients.

Possible mechanisms of biofeedback in hypertension
One can hypothesize on the mechanisms of action of relaxation-based therapies in hypertension. Relaxing the muscles of the face via electromyography biofeedback and increasing finger temperature facilitates whole-body relaxation and decreased sympathetic adrenergic activity. Parasympathetic dominance is facilitated by the use of breathing techniques to increase heart rate variability. The improved deep sleep that results from relaxation may also reduce blood pressure by restoration of nighttime blood pressure dipping.

IDENTIFYING THE BEST CANDIDATES IS NOT EASY
Some individuals are excellent candidates for biofeedback, while others do not benefit despite their best efforts. The likelihood of response is generally associated with adherence to medical recommendations and willingness and ability to follow instructions for home practice of relaxation. Nevertheless, some patients who attend sessions and practice still do not succeed, perhaps because they have few signs of overarousal in the system, such as a high degree of sympathetic activation, muscle tension, or low heart rate variability. Further, patients must be able to demonstrate that they learned the skill that was trained, such as consistent warming of the hands. If the training was for heart rate variability, the patient should be in the optimal range of heart rate variability and be able to demonstrate high-frequency waves. Patients with specific characteristics, such as stress sensitivity, may benefit more than those whose blood pressure and blood glucose are chronically elevated with few fluctuations.

CONCLUSIONS
The etiology of the metabolic syndrome is complex and multifactorial. Psychophysiological interventions such as biofeedback and relaxation training are sometimes warranted for multiple aspects of metabolic syndrome, and they target several specific associated disruptions, particularly chronic stress, negative mood, and behavior. Initial patient evaluation should aim to assess the patient’s readiness for change, which must be present to a sufficient degree before continuing with biofeedback or relaxation techniques. Use of motivational interviewing techniques is recommended to increase patients’
preparedness for change. Understanding patients’ characteristic responses to stress will guide decisions on the type of biofeedback and relaxation therapies to use and whether or not psychotherapy will be necessary. Specific modalities of biofeedback or particular types of relaxation do not appear to be as critical as the total package of individualized psychophysiological therapy.

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ABSTRACT

Biofeedback-related approaches to headache therapy fall into two broad categories: general biofeedback techniques (often augmented by relaxation-based strategies) and methods linked more directly to the pathophysiology underlying headache. The use of general biofeedback-assisted relaxation techniques for headache has been evaluated extensively by expert panels and meta-analyses. Taken together, these reviews indicate that (1) various forms of biofeedback are effective for migraine and tension-type headache; (2) outcomes with biofeedback rival outcomes with medication therapy; (3) combining biofeedback with medication can enhance outcomes; and (4) despite efficacy in many patients, biofeedback fails to bring significant relief to a sizeable number of headache patients. Biofeedback methods that more directly target headache pathophysiology have focused chiefly on migraine. These headache-specific approaches include blood volume pulse biofeedback, which has considerable supportive evidence, and electroencephalographic feedback.

Biofeedback has long been employed for helping ameliorate symptoms of recurrent headache; seminal work was performed in the late 1960s and first reported in the early 1970s. This early work focused mainly on electromyography (EMG) or muscle tension and hand temperature. Today a greater array of approaches are available, and they fall within two broad categories: (1) biofeedback-assisted relaxation and (2) specific or more specialized approaches.

The first category employs the two types of biofeedback mentioned earlier (EMG and thermal feedback), as well as feedback on sweat gland activity, to counteract the sympathetic nervous arousal that occurs in response to stress for a host of disorders, not just headache. These types of biofeedback are commonly augmented with a variety of allied relaxation-based strategies (guided imagery, diaphragmatic or paced breathing, autogenic training, meditation, etc) as well as training in cognitive and behavioral stress coping. The second category takes a different approach, applying techniques that seek more directly to target the aberrant physiology underlying specific headache types. This latter category has focused chiefly on migraine headache and its variants.

This article reviews the supportive evidence for each category of biofeedback approaches to headache therapy and identifies select areas for future research attention.

EVIDENCE BASE FOR GENERAL BIOFEEDBACK TECHNIQUES IN HEADACHE

Biofeedback-assisted relaxation approaches for headache have been evaluated extensively over the past several decades. These evaluations have consisted of two basic types—comprehensive reviews by expert panels, and meta-analytic statistical analyses—as detailed below.

Expert panel reviews

A wide variety of groups have assessed biofeedback and related relaxation-based procedures by reviewing all relevant published studies according to rigorous predetermined criteria. These groups include the National Institutes of Health, the Canadian Headache Society, the American Psychological Association, the Society of Pediatric Psychology, the Association for Applied Psychophysiology and Biofeedback, and the US Headache Consortium.

The 2000 evidence review by the latter group, the US Headache Consortium, merits particular mention, for several reasons. First, their review was sponsored by diverse medical societies—namely, the American Academy of Family Physicians, American Academy of Neurology, American Headache Society, American College of Emergency Physicians, American College of Physicians–American Society of Internal Medicine, American Osteopathic Association, and National Headache Foundation. Second, this review panel applied objective criteria, grading the evidence quality as A, B, or C (see Table 1 for details). Third, the panelists examined a diverse array of behavioral and physical treatments (acupuncture, transcutaneous electrical nerve stimulation, occlusal adjustment, cervical manipulation, and...
TABLE 1
Treatment recommendations on behavioral and physical treatments for migraine from US Headache Consortium evidence-based guidelines

- Relaxation training, thermal biofeedback combined with relaxation training, electromyographic biofeedback, and cognitive-behavioral therapy may be considered as treatment options for prevention of migraine (Grade A evidence*)

- Behavioral therapy (ie, biofeedback, relaxation) may be combined with preventive drug therapy to achieve additional clinical improvement for migraine relief (Grade B evidence*)

- Evidence-based recommendations are not yet possible on the use of hypnosis, acupuncture, transcutaneous electrical nerve stimulation, cervical manipulation, occlusal adjustments, or hyperbaric oxygen as preventive or acute therapy for migraine (Grade C evidence*)

*Grade A: Multiple well-designed randomized controlled trials (RCTs) revealing a consistent pattern of positive findings. Grade B: Some supportive evidence from RCTs, but not optimal support (often because RCTs were few or findings were judged to be inconsistent). Grade C: Consensus on the recommendation achieved among consortium members in the absence of acceptable RCTs.

TABLE 2
Patient characteristics for which behavioral treatments for migraine may be particularly well suited*

- Preference for a nondrug approach
- Intolerance of, or medical contraindication to, drug treatment
- Absent or minimal response to drug treatment
- Pregnancy, plans to become pregnant, or current nursing status
- History of long-term, frequent, or excessive use of analgesics or other acute medications that aggravate headache symptoms or are reducing medication effectiveness
- Presence of significant life stress or lack of adequate stress-coping skills

*From US Headache Consortium evidence-based guidelines.

Meta-analytic reviews
The other major type of evaluation applied to biofeedback for headache is more quantitative in nature, applying meta-analytical statistical analyses to available studies to determine the range and mean level of clinical effects across pooled studies. Biofeedback and related approaches to headache have been subject to an extensive number of quantitative reviews, the first being published in 1980. Since then, approximately 15 other quantitative reviews have compared behavioral treatments with one another, with various placebo conditions, or with various prophylactic medications for migraine and tension-type headaches in adults and in children and adolescents. The most recent meta-analysis, by Nestoriuc et al, focused extensively on biofeedback and will be discussed in detail here.

Nestoriuc et al identified and screened 150 clinical trials, including randomized controlled trials and quasi-experimental designs. Ninety-four of these trials met predefined inclusion criteria (headache diagnostic criteria specified, biofeedback evaluated as treatment alone or in combination with behavior therapy, outcome assessed using a structured headache diary, 5 or more patients per condition, and sufficient data to permit calculation of effect sizes). It was possible to include a sufficient number of studies to permit comparisons with two types of control groups: waiting list and placebo.

For migraine, biofeedback treatment yielded small to medium effects overall compared with waiting-list control and placebo, although these effects failed to reach statistical significance. For tension-type headache, biofeedback treatment yielded a medium to large effect compared with waiting-list control and a medium effect compared with placebo, both of which were statistically significant.

The accompanying figures provide a more detailed snapshot of results from the meta-analysis by Nestoriuc et al. Figure 1 shows effect sizes in terms of headache pain for various biofeedback treatments for migraine. Figure 2A shows effect sizes for all biofeedback treatments combined for migraine, while Figure 2B shows effect sizes for EMG biofeedback alone for tension-type headache (this was the only type of biofeedback with a sufficient number of studies in tension-type headache to permit analysis). Both panels of Figure 2 show effect sizes on the four main pain outcome measures used in...
headache research, along with reductions in medication (considered a behavior motivated by pain). Figure 3 shows effect sizes from biofeedback on the secondary outcome measures of anxiety, depression, and self-efficacy, again for all biofeedback procedures for migraine and for EMG biofeedback alone for tension-type headache. These latter results show that biofeedback has the added advantage of favorably affecting cognitive and emotional functioning.8

Additionally, Holroyd and colleagues have conducted a number of meta-analyses and randomized controlled trials that compare behavioral and prophylactic pharmacologic treatments, as well as their combination.9-13 These reviews and studies have consistently shown that outcomes for the individual treatments are similar in magnitude and that the combination of both behavioral and pharmacologic treatment leads to even greater effects—a conclusion tentatively offered by the US Headache Consortium back in 2000.4

**Interim conclusions**

Consideration of the findings from individual studies and reviews discussed, plus those not singled out here, leads to the following conclusions:

1) Various forms of biofeedback are effective for migraine and tension-type headache.

2) Outcomes with these forms of biofeedback rival outcomes with medication alone.

3) Combining biofeedback with medication can enhance outcomes.

4) Outcomes from biofeedback are similar to those obtained with other behavioral approaches. Whether biofeedback has a unique advantage over other similar approaches is not known, but at least one investigation suggests that biofeedback may be of particular value to a subset of patients.14

5) Although not reviewed here, the outcome effects from biofeedback seem to endure for extended periods,15 whether booster treatments are provided or not.16

6) Although biofeedback has been shown to be effective for a number of patients, a sizeable number of patients do not achieve significant relief.

**Remaining questions and challenges**

Unfortunately, little attention has been devoted to identifying variables predictive of outcome. Certain headache types—chronic forms of headache (presence of pain ≥ 15 days per month), headaches associated with the menstrual cycle, headaches accompanied by medication overuse (of ergotamine, triptans, analgesics, or opioids), posttraumatic headaches, and cluster headaches—have shown minimal response to biofeedback alone.

Headaches complicated by medication overuse are particularly difficult to treat. The first order in treatment is to have the patient withdrawn from the offending agents, which often requires a brief hospitalization, after which a more appropriate course of treatment is begun. Unfortunately, relapse is high. Mindful of this, we conducted an investigation that assigned 61 consecutive patients who had undergone a course of inpatient withdrawal to either medication alone or medication plus biofeedback-assisted relaxation training to determine if...
EVIDENCE BASE FOR HEADACHE-SPECIFIC BIOFEEDBACK APPROACHES

As noted above, a number of biofeedback approaches have been suggested that are tied more directly to the underlying physiology of headache.

Blood volume pulse biofeedback

One of these approaches, blood volume pulse (BVP) biofeedback, has undergone a sufficient number of trials to be included in the recent meta-analysis by Nestoriuc et al.8 mentioned earlier. This approach involves monitoring blood flow in the temporal artery and providing feedback to patients to enable them to decrease or constrict blood flow. This approach, when first envisioned,18 was viewed as the nondrug counterpart to the abortive agent ergotamine. Although BVP biofeedback is not very common in clinical practice, the meta-analysis by Nestoriuc et al.8 found it to produce the greatest effect size of the biofeedback methods assessed for migraine relief (Figure 1).

such training could enhance outcome.17 At 1-year follow-up evaluation, the two patient groups showed similar levels of improvement. However, at 3-year follow-up, patients receiving biofeedback showed more sustained improvements and, most importantly, had lower rates of relapse back to analgesic overuse (Figure 4). Thus, biofeedback seemed to help these patients cope more effectively over the long term. Unfortunately, we did not collect sufficient data over the intervening 2 years, so we could not determine with precision what mediated this differential outcome.

EEG-based methods

The next most investigated approach involves electroencephalographic (EEG) biofeedback, of which there are two types. The first derives from research investigating links between certain EEG frequency bands and the experience of pain.19 This research suggests that the experience of pain is associated with lower amplitudes of slow brain wave activity (delta, theta, and alpha) and higher amplitudes of faster brain wave activity (beta). Several uncontrolled series suggest that EEG biofeedback may be of value, but more well-controlled investigations are needed before further statements can be made.

The second line of EEG research takes a different approach, focusing on the contingent negative variation response (CNV). The CNV is a slow cortical event-related potential that examines EEG activity occurring between presentation of a warning stimulus and an imperative stimulus (in this case 3 seconds later), a stimulus requiring a response by the individual. This potential is related to the level of excitability upon activation in the striothalamocortical loop, reflecting different stages of information processing.20 Studies in child and adult migraineurs reveal that these patients have a heightened response to novel stimuli and do not habituate as readily over repeated trials as do non-migraine controls.21 The CNV is believed to reflect anticipation of a migraine attack because its amplitude and habituation patterns change during the headache-free interval. Abnormalities gradually increase in the days before a migraine attack, with the most pronounced changes occurring just prior to the attack.22

On the basis of these etiopathologic findings, Sina-atchkin et al conducted an initial test to determine whether child migraineurs could learn, via biofeedback, to change their CNV activity and whether such learning...
would alter the subsequent course of migraine attacks. Ten child migraineurs without aura each received 10 sessions of CNV biofeedback. They were taught how to increase and decrease EEG negativity (as bidirectional control of a physiologic response is assumed to reflect a greater level of self-regulation). By the end of training, the children could indeed regulate their CNV activity when feedback was provided, but they were unable to do so when the feedback was removed.

The number of training sessions administered was low, as most treatment investigations using EEG biofeedback typically use 20 to 40 sessions. A greater number of sessions may have led to greater response generalization. Interestingly, baseline or tonic levels of EEG negativity changed over the course of treatment, so much so that the child migraineurs were no longer distinguishable from a matched sample of healthy controls, which suggests that the migraineurs’ level of cortical excitability may have diminished. CNV biofeedback led to improvements on most measures of headache activity relative to a second group of child migraineurs who comprised a waiting-list control group. These preliminary findings add to those briefly mentioned for other EEG biofeedback approaches, suggesting that further investigations are warranted.

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ABSTRACT

Deep brain stimulation has emerged as an experimental treatment option for the sizeable proportion of patients with major depression that is refractory to multiple medications and psychotherapy. Chronic stimulation of the ventral internal capsule/ventral striatum has been shown to improve function and mood in patients with severe obsessive-compulsive disorder, and has likewise been applied to patients with treatment-resistant depression. Multicenter experience with chronic deep brain stimulation of the ventral capsule/ventral striatum in 17 patients with severe treatment-resistant depression has demonstrated sustained improvements across multiple scales of depression, anxiety, and global function. Further research on deep brain stimulation in larger populations of patients with treatment-refractory depression is underway. While such research should benefit from the recent US Food and Drug Administration approval of deep brain stimulation for severe obsessive-compulsive disorder, it must adhere to strict principles for appropriate patient selection.

PSYCHOSURGERY: A CLOUDED HISTORICAL BACKDROP

The use of DBS for depression is best understood within the context of the problematic history of neurosurgery for psychiatric conditions (psychosurgery), which dates back to the development of frontal leucotomy (ie, frontal lobotomy) by Egas Moniz and Pedro Lima in 1935. Walter Freeman, an American neurologist and psychiatrist without surgical training, performed the first prefrontal lobotomy in the United States in 1936. In 1945 Freeman pioneered the transorbital (“ice pick”) lobotomy, which accessed the frontal lobes through the eye sockets rather than by holes drilled in the skull. Freeman’s advocacy of lobotomy as an expedient therapy for psychiatric conditions helped fuel the procedure’s midcentury popularity, as more than 20,000 psychosurgery procedures were performed in the United States for various indications between 1936 and 1955.

Although some symptomatic improvement was seen with these psychosurgery procedures, they quickly became controversial because of their adverse effects, which included personality changes, as well as their perceived barbaric nature and their indiscriminate use by some practitioners. Moreover, little systematic research of these procedures was done, with most studies being poorly designed with little attention to long-term outcomes.

By the 1960s psychosurgery was in decline, largely because of the advent of effective psychopharmacology.

FROM BRAIN LESIONING TO BRAIN STIMULATION

Despite this decline, research on neurosurgery for the treatment of psychiatric conditions continued with small-scale studies of procedures involving smaller brain lesions, such as anterior capsulotomy and anterior cingulotomy using radiofrequency lesioning or gamma knife irradiation. Some of these studies demonstrated significant improvements, particularly in patients with severe obsessive-compulsive disorder (OCD).

These results prompted consideration of DBS for treatment of patients with severe psychiatric illness, especially since DBS offered several potential advantages relative to lesioning.
DEEP BRAIN STIMULATION IN TREATMENT-RESISTANT DEPRESSION

- Reversibility
- The ability to perform double-blind crossover studies
- The ability to vary stimulation sites and parameters.

Briefly, DBS for psychiatric applications involves bilateral implantation of electrodes in the anterior limb of the ventral internal capsule extending into the ventral striatum. Each electrode has four individually programmable contacts. The neurostimulator is placed in a pocket created in the subclavicular area. The leads are connected to each neurostimulator by tunneling under the scalp and the skin of the neck to the pocket, permitting noninvasive adjustment of the electrical stimulation.

■ EXPERIENCE WITH STIMULATION IN OBSESSIVE-COMPULSIVE DISORDER

Greenberg et al reported outcomes of the use of DBS in 26 patients with severe and highly treatment-resistant OCD treated at four collaborating centers from 2000 to 2005. The target for stimulation was the ventral internal capsule/ventral striatum (VC/VS); this target evolved slightly over the course of the study as it became evident that outcomes were superior with targets that were more posterior. Concomitant pharmacotherapy was permitted throughout the study.

At 3 to 6 months after initiation of chronic DBS, scores on the Yale-Brown Obsessive Compulsive Scale, a measure of OCD severity, improved by an average of nearly 50% in these patients with severe refractory disease, which is notably better than the 35% improvement often used as the threshold for response in OCD trials. Improvement in mood was a beneficial side effect of DBS in the study, and in patients with comorbid depression, mood improved to a greater degree than did symptoms of anxiety and OCD.

In the wake of the initial release of this study by Greenberg et al (published online in May 2008) and similar findings, the US Food and Drug Administration (FDA) in February 2009 approved DBS for use in refractory OCD under a humanitarian device exemption. Such exemptions are granted to facilitate the development of devices for rare conditions, and the exemption was applicable in light of the rarity of severe, treatment-resistant, disabling OCD.

■ RATIONALE FOR BRAIN STIMULATION IN DEPRESSION

A large refractory and disabled population

In contrast to OCD, treatment-refractory depression is rather common, as approximately 20% of patients with depression—roughly 4.4 million US patients—have disease that is resistant to the mainstay treatment options of antidepressant medications and psychotherapy. The fact that electroconvulsive therapy is performed more than 100,000 times annually in the United States is another testament to how widespread treatment-resistant depression remains. Even if only some of these patients with severely disabling and refractory depression may be candidates for DBS, they represent a considerable potential patient population.

A pathophysiologic role for the VC/VS

The target for stimulation in OCD—the VC/VS—also has a known anatomic and physiologic role in depression, which makes it an appropriate surgical target for treatment of depression as well. Significantly less VS response to positive stimuli has been observed in depressed patients compared with controls. Moreover, the subgenual cingulate region is known to be metabolically hyperactive in patients with major depressive disorder, and positron emission tomography studies of OCD patients who underwent DBS of the VC/VS showed a reduction in subgenual cingulate activity over time.

White matter tracts in the area 25 region adjacent to the subgenual cingulate cortex represent another target for stimulation. In a pilot study by Mayberg et al, DBS electrodes implanted bilaterally in the subgenual cingulate cortices of 6 patients with treatment-resistant depression resulted in sustained remission of depression in 4 patients at 6 months. The benefit of stimulation continued for up to 4 weeks after stimulation ended.

■ MULTICENTER STUDY OF STIMULATION FOR HIGHLY REFRACTORY DEPRESSION

Our team at Cleveland Clinic partnered with colleagues from Brown Medical School and Massachusetts General Hospital to build on these pilot study findings and evaluate DBS of the VC/VS in patients with chronic, severe refractory depression in a multicenter investigation. The results from the first 15 patients in this series were published in early 2009; results from an additional 2 patients, for a total sample of 17, are now available and summarized below.

Patients and study design

Patients had at least a 5-year history of chronic or recurrent depression that was refractory to at least five courses of medication, an adequate trial of psychotherapy, and at least one trial of bilateral electroconvulsive therapy. Exclusion criteria included significant substance abuse, severe personality disorder that could potentially affect safety or compliance, and psychotic depression.

Outcome measures included the Hamilton Depression Rating Scale (HDRS), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Global Assessment of Function Scale (GAF). Assessments were performed at baseline, postoperatively, and monthly thereafter. A detailed neuropsychological battery was
performed at baseline and again at 6 months.

At the time of electrode implantation, mean patient age was 46.3 years and mean duration of illness was 21.0 years. In their current depressive episode, patients had an average of 6.1 antidepressant trials and 6.1 trials of augmentation or combination of antidepressant medications. The average number of lifetime electroconvulsive therapy treatments was 30.5; of the 17 patients, 15 had an adequate trial of electroconvulsive therapy in their current depressive episode.

Electrodes were implanted bilaterally in the VC/VS. Following a postoperative recovery phase of 2 to 4 weeks, stimulation parameters were titrated over several days on an outpatient basis. The stimulation parameters were selected on the basis of positive mood benefit and absence of adverse effects. Stimulation was at a frequency of 100 to 130 Hz and an amplitude of 2.5 to 8 V. These stimulation amplitudes are higher than those used for treatment of movement disorders, reflecting the different targets (white matter vs gray matter) for the different conditions.

The two ventral contacts (referred to as contact 0 and contact 1) tend to be the most active, providing the best response. Contact 0 is the most distal contact, at the VS below the level of the anterior commissure. Contact 1 is near the junction of the VS and VC.

The time to battery replacement (due to depletion) ranged from 10 to 18 months.

Outcomes
Patients’ mean baseline MADRS score was 34.7, indicating very severe depression. The mean MADRS score improved to 20.6 by 1 month, and declined further to 16.0 at 3 months. This benefit has been maintained to the most recent follow-up (average, 37.4 months; range, 14–67 months). Similar improvements from baseline to most recent follow-up were observed in the HDRS and GAF scores. Additionally, a substantial reduction in suicidality (as measured by mean MADRS suicide sub-scale score) was observed by 1 month (P = .01) and was maintained through 12 months of follow-up (P < .001).7

A clinical response—defined as a 50% or greater decrease in MADRS score—was achieved by 53% of the patients at 3 months, which increased to 71% by the most recent follow-up (Table 1).8 Perhaps the most impressive finding is that 35% of these highly treatment-refractory patients remained in remission (MADRS score ≤ 10) at the most recent follow-up.

Adverse effects
Adverse effects of DBS were observed on occasion and can generally be divided into those related to surgical implantation and those related to stimulation itself.

Effects related to surgical implantation have included infection from lead or battery implantation, adverse cosmetic effects (from placement of the battery-operated neurostimulators into the chest), and repeat surgeries for neurostimulator replacements. A rechargeable battery has recently become available and should enhance tolerability and acceptability by reducing the frequency of replacement surgeries.

Stimulation-induced acute adverse events have included paresthesias, anxiety, mood changes, and autonomic effects. All were reversible with adjustment of stimulation parameters.

## DIRECTION AND GUIDANCE FOR FUTURE RESEARCH

A number of recent developments have enhanced the prospects for better understanding of the use of DBS in treatment-refractory depression:

- The recent FDA approval of DBS for severe, refractory OCD should broaden the base of experience with DBS for psychiatric disorders.
- Two large studies of DBS of the VC/VS and the area 25/subgenual cingulate region in depressed patients are currently under way.
- The aforementioned recent development of a rechargeable stimulator battery should improve patient acceptance of DBS therapy.
- Neuroimaging studies using functional magnetic resonance imaging and positron emission tomography may help to elucidate neuroanatomic pathways in depression and other psychiatric disorders.
- Ongoing studies of DBS for Tourette syndrome will broaden the experience base with DBS and perhaps yield insights for depression.

As investigation of DBS for depression moves forward, it must be conducted in keeping with some basic principles for patient selection and fundamental ethical guidelines, especially in light of the troubled early history of psychosurgery. From the individual patient perspective, patients should be selected only if they meet the following criteria:

### TABLE 1

<table>
<thead>
<tr>
<th>Time point</th>
<th>Response rate*</th>
<th>Remission rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>53%</td>
<td>35%</td>
</tr>
<tr>
<td>6 months</td>
<td>47%</td>
<td>29%</td>
</tr>
<tr>
<td>12 months</td>
<td>53%</td>
<td>41%</td>
</tr>
<tr>
<td>Last follow-up†</td>
<td>71%</td>
<td>35%</td>
</tr>
</tbody>
</table>

* Response defined as ≥ 50% decrease from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) score.
† Last follow-up ranged from 14 to 67 months (average, 37.4 months).
DEEP BRAIN STIMULATION IN TREATMENT-RESISTANT DEPRESSION

- Accurate diagnosis. This may seem obvious, yet inaccurate diagnoses in the psychiatric realm are far more widespread than is appreciated but clearly must be avoided when embarking on an intervention as significant as DBS.
- Ability to provide informed consent
- Sufficient severity of illness
- Nonresponse to less-invasive options (ie, reasonable trials of both pharmacotherapy and psychotherapy).

From the ethical and procedural perspective, research of DBS for psychiatric disease must ensure the involvement of expert and dedicated psychiatric neurosurgery teams, led by psychiatrists, as well as full ethical review (by institutional review boards) and method-safety review (in keeping with FDA policy). Additionally, expert centers must be prepared to make the long-term commitment necessary to follow these difficult-to-treat patients. Centers and investigators must also ensure that DBS be used only to alleviate suffering and improve patients’ lives, and never to “augment” normal function or for social or political reasons.9

REFERENCES


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Abstract 1

Potential Role of the Cardiac Protease Corin in Energy Metabolism

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The melanocortin-mediated pathway plays an important role in energy homeostasis. In the brain, the binding of α-melanocyte stimulating hormone (α-MSH) to melanocortin 4 receptor (MC4r) inhibits appetite, thereby reducing food intake and body weight. Agouti and agouti-related protein block α-MSH binding to MC4r and increase appetite and food intake. In mouse skin, agouti also blocks α-MSH binding to melanocortin 1 receptor, promoting yellow pigment formation. Naturally occurring mutations in lethal yellow (A<sup>y</sup>) mice increase agouti protein expression, causing obesity, hypertension, and diabetes.

Corin is a heart enzyme that converts inactive pro-atrial natriuretic peptide (pro-ANP) to active ANP, a cardiac hormone that regulates blood pressure and cardiac function. In mice, lack of corin blocks ANP production and causes hypertension. In humans, corin gene variants are linked to hypertension and cardiac hypertrophy in African Americans. In functional studies, we found that the corin variants impaired biological activities in vitro and in vivo, suggesting that corin defects may contribute to hypertension and heart disease in patients.

Corin is made primarily in the heart. Unexpectedly, corin expression also was detected in the brain and hair follicle. Corin null mice had a more yellowish coat color than that of controls. This effect was agouti gene-dependent. It appears that lack of corin enhances the agouti pathway in mice. We performed cell-based experiments to examine the effect of corin on the expression of a selected set of peptide hormones that are involved in energy metabolism. In HEK 293 cells, co-transfection of a corin plasmid reduced the expression of recombinant agouti and agouti-related protein. In similar experiments, co-transfection of the corin plasmid also reduced the expression of urocortin III but not urocortin I and II. The observed effect of corin on these peptides depended on its catalytic activity, as corin active site mutant had no such an effect in these experiments.

Our results suggest that corin may participate in energy metabolism by down-regulating peptide hormones that control appetite. Currently, we are testing this hypothesis in additional biochemical studies. We also have made corin transgenic mice to examine the effect of corin expression levels on body weight and food intake. These studies should help to identify a potential role of corin in regulating energy metabolism.

* BHBI = Bakken Heart-Brain Institute
Abstract 2

Anxiety and Type D Personality in ICD Patients: Impact of Shocks

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Quality of life in patients with implantable cardioverter-defibrillators (ICDs) may be impacted by the occurrence of ICD shocks. Although shocks may be life-saving, approximately one-third of patients with ICDs may experience inappropriate shocks. In an observational study of ICD patients, we are testing levels of anxiety and performing a randomized trial of cognitive behavior therapy in patients with moderate-high anxiety. We report here results of an interim analysis of anxiety levels in the first subjects enrolled in this study, testing the hypothesis that anxiety is higher in subjects with non-life-saving ICD shocks.

Methods: Consenting patients presenting to an outpatient ICD clinic completed Beck Anxiety Inventory (BAI) and Type D personality scale (DS14) questionnaires. Type D personality was defined as scoring ≥10 on both negative affectivity (NA) and social inhibition (SI) components of the DS14 scale. Clinical data were collected, including arrhythmia, ICD, and shock data. Data were analyzed using standard parametric and non-parametric statistics.

Results: Among 263 subjects (mean age 62.0 ± 15.1 yrs, 73% male; LVEF 31.9 ± 14.0%), 10% had ICDs implanted for secondary and 89% for primary prevention indications, and 52.7% had CAD. With average time since first ICD implant averaging 4.4 ± 7.6 years, 24.5% perceived having experienced ICD therapies that were life-saving and 16.7% ICD shocks that were non-life-saving (4.5% had shocks for sinus tachycardia and 9.4% for atrial fibrillation). The average total number of shocks experienced was 2.6 ± 7.6 (range 0–71); appropriate shocks averaged 1.4 ± 6.0 (range 0–70), and inappropriate shocks 0.97 ± 4.2 (range 0–50). Recent shocks (within the 4 weeks prior to enrollment) had been experienced in 3.7%. Malfunctioning of the ICD system had been experienced by 3.3%. History of anxiety was reported in 18.8% (10.6% reported current anxiety), and 19.6% had a family history of anxiety. ICD indication was not associated with significant differences in BAI or DS14 scores. Patients who had experienced life-saving ICD shocks were less socially inhibited (SI scores 5.40 ± 5.62 vs 7.80 ± 6.10, P = 0.015) but showed no significant difference in NA or BAI scores. Non-life-saving shocks were associated with a trend toward higher BAI scores (8.94 ± 8.48 vs 6.51 ± 7.05, P = 0.082). The number of inappropriate shocks correlated with BAI, NA, and SI scores (Pearson correlation coefficients 0.148, 0.179, and 0.214, and P values 0.022, 0.006, and 0.001, respectively). History of ICD malfunction was associated with a trend toward higher BAI scores (14.00 ± 7.26 vs 6.96 ± 7.32, P = 0.086). A shock within the past 4 weeks was associated with significantly higher SI (14.00 ± 6.54 vs 6.93 ± 5.96, P = 0.005) and BAI (13.17 ± 9.02 vs 6.66 ± 7.12, P = 0.03) scores.

Conclusions: ICD function significantly impacts anxiety and Type D personality (negative affectivity and social inhibition) scores. Recent or inappropriate shocks, as well as ICD malfunction, may affect quality of life in ICD patients due to anxiety. In contrast, life-saving shocks are associated with less social inhibition. These observations may guide clinicians in better screening for and treatment of comorbid anxiety in ICD patients.

* BHBI = Bakken Heart-Brain Institute
Preconditioning is a phenomenon in which low doses of noxious stimuli shield the brain from future insults. Preconditioning can be induced by a number of stimuli, including hypoxia, ischemia, heat shock, and IP injections of lipopolysaccharide (LPS). While global preconditioning with LPS provides protection against injurious focal ischemia in the brain, the cellular mechanisms involved in LPS neuroprotection are incompletely understood.

In this study, C57BL/6 mice were preconditioned by four daily LPS injections. One day post-LPS treatment, cortical microglia expressed activation markers and directly apposed neuronal cell bodies and proximal dendrites. A 27% reduction in the neuronal circumference occupied by inhibitory GABAergic synapses was observed in preconditioned cortex, and major GABA receptor subunit mRNA and proteins were significantly reduced. In addition, animals preconditioned with LPS showed a significant reduction in the size of cortical induced cryoinjury and the number of apoptotic cells. Cortical mRNA and protein levels of several anti-apoptotic members of the Bcl-2 and the inhibitor of apoptosis (IAPs) families were upregulated and the pro-apoptotic protein BAD was inhibited. Furthermore, the transcription factor cAMP-response-element-binding-protein (CREB) and its regulated neurotrophin brain derived neurotrophic factor (BDNF) were significantly upregulated by LPS preconditioning.

These data support microglia activation as part of a CNS neuroprotective response that involves preferential reductions in GABAergic axosomatic synapses and the activation of anti-apoptotic pathways in cortical neurons through CREB. Reductions in inhibitory innervation may transiently favor neurotrophic activity through synaptic NMDA receptor activation and the subsequent induction of anti-apoptotic pathways in neurons.

This investigation was supported by a grant from the Bakken Heart-Brain Institute and a postdoctoral fellowship (to W.J.) from the National Multiple Sclerosis Society.
Abstract 4

Brain MRI Correlates of Atrial Fibrillation

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While the influence of the central nervous system on cardiac rhythm and function is well accepted, the mechanisms of this control are poorly understood. A preponderance of data implicates the autonomic nervous system in the development of many cases of atrial fibrillation (AF), for which new therapies are needed since both surgical and minimally invasive ablative techniques have substantial failure rates and complications. Efforts to better understand the role of the central nervous system in AF may lead to new treatment strategies that improve outcomes and reduce complications associated with available therapies.

Recently developed functional magnetic resonance imaging (fMRI) techniques make it possible to simultaneously image brain anatomy and assess patterns of regional activation and function. By using specific tasks to cause autonomic activation in subjects and recording heart rate variation, blood pressure variation, and galvanic skin response as independent measures of autonomic arousal, studies have compared these measures to fMRI to determine regions of the brain that are active during sympathetic or parasympathetic arousal (Figure 1, previous page). These studies have identified activation within the anterior cingulate region and insular cortex during sympathetic activation, and in the insular cortex during parasympathetic activation.

Our long-range goal is to determine the relationship between levels of autonomic activation and the development of AF. The central hypothesis of this study is that patients with AF will have diminished central autonomic activation as assessed by fMRI and pupillometry that will persist despite cardioversion to sinus rhythm.

The techniques to measure autonomic tone on subjects while acquiring fMRI data are difficult and subject to patient movements, paradigm selection, and noise pickups. We will present initial results from these techniques on healthy subjects, prior to initiating imaging on AF patients both before and after ablation.

FIGURE 1. (A) Examples of functional magnetic resonance imaging (fMRI) activation obtained in a healthy subject performing five task paradigms designed to alter autonomic tone. (B) Example of noninvasive autonomic recordings obtained from a healthy subject while performing a handgrip task during MRI. Measures are heart rate, systolic blood pressure surrogate, and galvanic skin response.

* BHBI = Bakken Heart-Brain Institute
Abstract 5

Identification and Characterization of Autonomic Dysfunction in Migraineurs With and Without Auras: Phase I

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Objectives: To identify and characterize the presence, if any, of autonomic dysfunction among migraineurs suffering from orthostatic intolerance (postural dizziness, presyncope, and syncope) and to simultaneously compare neurocardiac physiological parameters with morphometrics of sudomotor innervation on skin biopsy.

Methods: In this phase of the study, 30 male and female adults (ages 18–75) who suffered from migraines without and with auras, as defined by the International Headache Society, and who complained of orthostatic intolerance, underwent the following studies: passive upright tilt table testing, clinical autonomic reflex testing, quantitative sudomotor axon reflex testing (QSART), and punch biopsy for evaluation of sudomotor nerve fiber density. The results of clinical autonomic testing were then compared with the morphometric findings supporting small fiber neuropathy involving sweat gland innervation on skin biopsy.

In phase II, the same studies will be performed on age-matched patients suffering from migraines without and with auras but who do not complain of postural instability or intolerance, including presyncope and syncope. The two populations will then be compared.

Results: Among 30 consecutive migraine patients seen in an active neurology practice between January 2008 and June 2009, there were 27 females and 3 males with a median age of 33 (range 18–71). Fifty-seven percent (17 patients) had migraines with and without auras, 33% (10 patients) had basilar-type migraines, 7% (2 patients) had migraines with auras only, and 3% (1 patient) had migraine without aura.

Seventeen of 30 skin biopsies (57%) exhibited small fiber sensory neuropathies (SFSN) by accepted morphometric standards, and 8 of these (47%) demonstrated reduced sweat gland (sudomotor) innervation in addition to reduced innervation to somatic structures. Eleven of 17 biopsies (65%) qualifying as SFSN were classed as length dependent and 6 (35%) as non-length dependent. Among the SFSN group, 5 (29%) exhibited normal QSART results and 12 (71%) had abnormal QSART results. Of the remaining 13 normal skin biopsies, which demonstrated normal nerve fiber densities to both somatic or sudomotor dermal structures, 10 were from patients who had accompanying QSART studies available for comparison; 3 of these (30%) were abnormal while 7 (70%) were normal.

Of 26 available QSART studies, twelve (46%) were normal and 14 (54%) were abnormal (reduced). Three of 12 normal QSARTs (25%) showed sudomotor involvement on skin biopsy while 9 (75%) had no such morphometric abnormality. Among the 14 patients with abnormal QSARTs, only 5 (36%) had biopsy evidence of sudomotor nerve involvement while the remaining 9 (64%) had normal biopsies.

There was a strong association between an abnormal tilt table response in patients with biopsy-proven SFSN; 17/17 (100%) had either orthostatic hypotension with or without a vasovagal syncopal response, postural tachycardia with or without a vasovagal syncopal response, or both. Among the 13 SFSN-negative patients with migraines and orthostatic intolerance, 12 (92%) had abnormal passive head upright tilt table responses.

Conclusions: In this, the first phase of our study of autonomic dysfunction in migraine sufferers complaining of orthostatic intolerance, we measured clinical neurocardiac parameters of autonomic function—the response to passive head upright tilt table testing, standard autonomic reflex testing, and QSART—and compared the results with morphometric analysis of small fibers, including sudomotor fibers, on skin biopsy. Skin biopsy nerve fiber analysis is presently considered to be the gold standard for diagnosis of SFSN.

In this predominantly female population, all but one patient had migraines with auras and one-third met criteria for basilar-type migraines. While a normal QSART result was able to predict normal sudomotor innervation on biopsy, an abnormal QSART result failed to predict a deficiency of sudomotor fiber innervation of sweat glands. In this symptomatic population, tilt table testing was abnormal and revealed either postural tachycardia or orthostatic hypotension in 29 of 30 patients regardless of biopsy results, suggesting that neurocardiac abnormalities may result not only from peripheral neuropathic autonomic defects but also from central autonomic mechanisms. This may be related to either the migrainous diathesis or another unexplained condition, such as head trauma or surgery.

* BHBI = Bakken Heart-Brain Institute
Sudden unexpected death in epilepsy (SUDEP) is a significant cause of mortality in patients with refractory epilepsy, accounting for up to 17% of all deaths in epilepsy and exceeding the expected rate of sudden death in the general population by nearly 24 times. Most of the identified SUDEP risk factors are unavoidable, and patients with refractory epilepsy currently face a lifelong SUDEP risk as high as 1% per year. Elucidating the mechanisms of this devastating condition might offer an opportunity for preventative measures, and therefore could have significant implications for reducing mortality in this patient population. One commonly postulated mechanism is cardiac arrhythmia precipitated by seizure discharges acting via the autonomic nervous system.

The specific aims of our pilot study are as follows:
1. To evaluate the interictal (between seizures) and ictal (during seizures) cardiac rhythm characteristics of patients with SUDEP, as compared to the general population and to other patients with epilepsy
2. To study the cardiac and neurological clinical characteristics of patients with SUDEP, as compared to the general population and to other patients with epilepsy
3. To evaluate the interictal and ictal EEG characteristics of patients with SUDEP in relation to any identified interictal and ictal cardiac rate/rhythm changes.

The long-range goal is to define better the electrophysiological characteristics of patients at risk for SUDEP. The study is a case-control comparison of SUDEP cases identified through death certificate review of mortalities queried from the Social Security Death Index registry with alive matched controls (who have nonepileptic seizures or medically controlled epilepsy).

307 mortalities were identified out of 3,842 patients monitored in our Epilepsy Monitoring Unit during the years 1990–2005. Of those, 237 (77%) had epilepsy (86 had temporal lobe epilepsy, 27 had frontal lobe epilepsy, 14 had parieto-occipital lobe epilepsy, 7 had multifocal epilepsy, 20 had hemispheric epilepsy, 17 had nonlocalizable focal epilepsy, and 36 had generalized epilepsy), 41 (13%) had nonepileptic seizures, and 29 (9%) had both recorded. Mean age at death was 49.9 years (range 18.6–99.6), with a standard deviation (SD) of 17.9 years. Mean epilepsy duration was 16.1 years (range 2 weeks–66 years) (SD = 15.3). Mean overall seizure frequency was 70 seizures per month (median 14 per month), with a mean monthly generalized tonic-clonic seizure frequency of 5.3 (median 1). The cause of death was identified in 211 of the total (including 158 of the 237 patients with epilepsy, 28 of the 41 patients with nonepileptic seizures, and 22 of the 29 patients with both); death certificates need to be obtained for the remainder.

SUDEP accounted for 21% of the deaths in our cohort with epilepsy. Significant differences between SUDEP cases and controls were observed in mean epilepsy duration (22.9 years ± 2.3) in SUDEP cases vs 13.7 years ± 1.5 in controls; P = 0.005) and in mean monthly seizure frequency (31.3 seizures per month ± 16.9) in SUDEP cases vs 1.4 ± 0.7 in controls; P = 0.005). Patients with SUDEP were more likely to have been discharged on valproic acid (VPA) from the Epilepsy Monitoring Unit. (VPA was only used in controls on admission. In SUDEP cases, it was used 50% of the time on admission only, 33% of the time on admission and discharge, and 17% of the time on discharge only [P = 0.01].) The risk for SUDEP was independent of epilepsy type or localization.

Our current data-collection efforts are focused on obtaining the cardiac data elements and obtaining the remaining death certificates to identify the rest of the SUDEP cases.
Abstract 7

Cardiomyopathy After Subarachnoid Hemorrhage Is Mediated by Neutrophils

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Background: Patients with subarachnoid hemorrhage (SAH) from the rupture of a cerebral aneurysm often experience severe acute cardiomyopathy. The prevailing theory is that this cardiomyopathy is caused by catecholamine release during the stress of the SAH. Although stress catecholamine release is clearly associated with cardiomyopathy, the rapidity and severity of the onset make it unlikely that this is the only mechanism of injury. There is a great deal of research on the "neuroinflammatory reflex" that suggests that there is direct cerebral control of some aspects of inflammation.

Hypothesis: We hypothesize that inflammation due to catecholamine surges and an unchecked vagal response leads to inflammation of the myocardium after SAH.

Methods: C57B/6 mice were separated into three groups: sham surgery, SAH, and SAH with prior neutrophil depletion. Sham surgery was accomplished by visualization of the dura mater over the occiput of the mouse and injection of 50 µL of saline. SAH was done similarly except that a subarachnoid vein was sectioned instead of saline injection. Neutrophil depletion was accomplished by IP injection of the neutrophil-depleting Ly6G/C antibody RB6-8C5 24 hours prior to SAH. Animals then underwent echocardiography 24 and 48 hours after SAH. Ejection fraction (EF), heart rate, and fractional shortening (FS) were recorded. After the final echocardiogram, the mice were sacrificed and the heart was sectioned and stained with antibodies for neutrophils (7/4) and the myocardial cell death marker (annexin V).

Results: SAH animals had decreased echocardiographic EF and FS compared to controls. Neutrophil depletion ameliorated the cardiomyopathy. Histology showed less myocardial cell death after neutrophil depletion and fewer neutrophils in the myocardium.

Conclusions: Neutrophils appear to play a role in the cardiomyopathy of SAH.

* BHBI = Bakken Heart-Brain Institute
Abstract 8

Mindfulness, Yoga, and Cardiovascular Disease

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Introduction: There is increasing evidence that reactions to the stressors of daily life are major contributors to the development and progression of coronary artery disease (CAD). Practices such as yoga and meditation are becoming increasingly popular as means to reduce stress and improve the sense of well-being. There is some evidence that they can beneficially modulate some of the potential pathways linking psychological stress and CAD, such as autonomic nervous system (ANS) activity and stress hormones. However, studies providing insights into whether such changes are associated with decreases in downstream cardiovascular risk factors, including inflammatory markers, are lacking.

Primary objectives: To evaluate the effectiveness of a regular practice of yoga or mindfulness, a meditative practice originating in Buddhism, in (1) improving mood and (2) modulating ANS activity, cardiovascular reactivity to a lab stressor, and inflammatory molecules, compared with conventional relaxation.

Secondary objectives: To determine whether there is an association between any of the physiological outcomes measured and (1) any indicators of stress or well-being and (2) reactivity to a lab stressor.

Design and Method: This study was designed as a three-arm randomized controlled trial among individuals with moderate cardiovascular risk including stress and anxiety. The intervention included 1.5-hour weekly sessions and daily home practice for 12 weeks followed by another 12 weeks of home practice, allowing a follow-up assessment at 24 weeks. Of the 62 participants who enrolled, 16 in the mindfulness group, 17 in the yoga group, and 15 in the conventional relaxation group completed the 12-week intervention and 13, 14, and 11, respectively, completed the 24-week intervention. Self-reported mood, psychological stress, and spiritual and emotional well-being were assessed using psychometric instruments. ANS activity was assessed by blood pressure, heart rate, heart rate variability measurements, and plasma catecholamine level. All of these outcomes were measured at baseline and at 6, 12, and 24 weeks. Blood was collected at baseline and 12 weeks to measure the inflammatory markers IL-1β, IL-6, and IL-10.

Preliminary Results: We have completed the study and a preliminary analysis of the inventories and of the inflammatory marker IL-6 has been performed. Results are summarized in Table 1.

Conclusions: The results of this study indicate that the practice of mindfulness, yoga, or health education, relaxation, and light exercise may lead not only to an overall decrease in negative emotions but also to an increase in well-being in individuals with risk factors for CAD. Moreover, these changes were associated with a 25% increase in IL-6. Upon completion of our analysis, we will be able to see whether these psychological changes translate into similar changes for the other physiological outcomes measured.

| TABLE 1 | P VALUES FOR 12 WEEKS VS BASELINE WITHIN-GROUP AND BETWEEN-GROUP COMPARISONS |
|----------------|------------------|------------------|------------------|------------------|
|               | Control (C) (N = 15) | Yoga (Y) (N = 17) | Mindfulness (M) (N = 15) | Y vs C | M vs C |
| Decrease in negative measures                  |                   |                   |                   |       |
| DASS-21–Depression                              | NS                | NS                | 0.03              | NS    | NS    |
| DASS-21–Anxiety                                 | NS                | NS                | 0.02              | NS    | 0.05  |
| DASS-21–Stress                                  | 0.01              | 0.001             | 0.02              | NS    | (0.08) |
| PSS                                               | (0.11)            | 0.001             | 0.003             | (0.08) | 0.05  |
| POMS–Fatigue                                    | (0.13)            | (0.06)            | 0.001             | NS    | 0.05  |
| Increase in well-being                          |                   |                   |                   |       |
| SWB–Existential                                  | (0.08)            | 0.004             | 0.02              | NS    | NS    |
| MASS                                              | (0.06)            | 0.001             | 0.03              | (0.10) | NS    |
| Decrease in inflammatory marker                  |                   |                   |                   |       |
| Interleukin-6                                    | NS                | NS                | 0.05              | NS    | (0.20) |

Results computed using paired t-test with significance level set at P = 0.05.

DASS-21 = Depression, Anxiety, and Stress Scale; PSS = Perceived Stress Scale; POMS = Profile of Mood State; SWB = Spiritual Well-Being; MASS = Mindful Attention Awareness Scale; NS = nonsignificant

* BHBI = Bakken Heart-Brain Institute
Biofeedback is gaining acceptance as a therapeutic modality that provides added value for patients with many medical conditions and has been shown to aid in recovery from some of those conditions. The Association for Applied Psychophysiology and Biofeedback (AAPB) has recently completed an analysis of research in biofeedback, and the resulting report concludes that there is sufficient data to label biofeedback as efficacious and specific in certain medical conditions, such as female urinary incontinence, while it is rated efficacious in diseases such as anxiety, headache, chronic pain, and epilepsy, only possibly efficacious in depression, coronary artery disease, and asthma, and not well justified in eating disorders or spinal cord injury. There are many prevalent disease states in which biofeedback has not been tested or has been studied only in very small and specific patient cohorts where no far-reaching conclusions can be drawn.

Biofeedback training can be used to regulate activity of the sympathetic and parasympathetic nervous systems, both of which are increasingly recognized to be involved in many diseases. Down-regulation of the sympathetic nervous system has been shown to be advantageous in many conditions and is the reason for the success of beta-blocking drugs. Up-regulation of the parasympathetic nervous system has only recently been shown to be anti-inflammatory, and is the rationale for trials of vagal nerve stimulation in several disease states.

We hypothesize that biofeedback should be an efficacious adjunct to conventional therapy in conditions such as coronary artery disease, diabetes, and multiple sclerosis, where the autonomic nervous system is involved in disease progression or symptom generation. For this reason, we are undertaking a study of patients at the Cleveland Clinic with documented coronary artery disease, diabetes, or multiple sclerosis. Within each disease population, patients will be randomized into two groups. One group will receive eight sessions of biofeedback training while the other group receives a valid sham treatment. Measures of autonomic nervous system activation, inflammation, and quality of life will be obtained in all patients in each group. Disease-specific indicators of symptoms, disease progression, and quality of life will also be monitored. Our hypothesis is that the biofeedback-treated subjects will demonstrate progress in symptom control and quality of life, and that progress in this direction will be positively correlated with the ability to self-regulate.

This study is currently ongoing at the Cleveland Clinic and is supported by the Bakken Heart-Brain Institute.

* BHBI = Bakken Heart-Brain Institute
Complex Regional Pain Syndrome (CRPS I): A Systemic Disease of the Autonomic Nervous System

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Our study aims to assess the extent of systemic autonomic dysfunction in the autonomic pain syndrome known as complex regional pain syndrome type I (CRPS I). This condition, formerly known as reflex sympathetic dystrophy (RSD), is notorious for its pathophysiological complexity. On one hand, it occurs in only certain people after a minor trauma or insignificant trigger and behaves like a focalized pain syndrome to one limb with prominent local autonomic manifestations, such as edema, vasomotor changes, trophic changes, pain, and allodynia. A more recent theory speaks about somatic-autonomic coupling as an explanation for the above, and the most recent consensus seems to be that CRPS I is a disease of the central nervous system that manifests peripherally. Through this study we would like to investigate further the possibility that the autonomic nervous system involvement in this disorder is generalized rather than localized to the painful limb and, in a more general way, to try to open new windows on the role of the autonomic nervous system in generating and maintaining pain.

The study is a bicenter research project at Cleveland Clinic and University Hospitals of Cleveland that will include 20 patients with CRPS I. The control group will consist of 10 patients with small fiber neuropathy (a neuropathic pain condition similar in certain aspects to CRPS I), 10 patients with limb pain due to osteoarthritis of the knee (a nonneuropathic pain), and 10 healthy volunteers. All subject will undergo comprehensive autonomic testing, skin biopsies, pupillometry, and Doppler flowmetry to assess the autonomic nervous system at various levels of the body. Results will be compared between the patients with CRPS I and the control group and subgroups.

To date, one patient has been enrolled, a 27-year-old female with CRPS I of the left foot following a traumatic injury. After consenting to the research protocol, the patient underwent a washout from all medications known to affect the autonomic nervous system for 5 half-lives prior to testing. She then underwent a series of tests of the autonomic nervous system and a skin biopsy. Preliminary data revealed the following:

1. Decreased cardiac response to deep breathing, suggesting a cardiovagal abnormality
2. Abnormal vasomotor sympathetic response characterized by postural tachycardia, consistent with the diagnosis of postural orthostatic tachycardia syndrome (POTS)
3. Abnormal quantitative sudomotor axon reflex test (QSART) results consistent with an underlying small fiber neuropathy
4. A 35% reduction of small fiber at the left distal leg (symptomatic) compared to the contralateral asymptomatic leg
5. Abnormal pupillary response to light in constriction parameters in the right eye, consistent with a parasympathetic pupillary abnormality.

These data, from a single patient, are consistent with our hypothesis that CRPS I is a generalized (systemic) disorder of the autonomic nervous system.

* BHBI = Bakken Heart-Brain Institute
Biofeedback training can be used to regulate the autonomic nervous system. Specifically, patients can be trained to up-regulate the contribution of their parasympathetic nervous system while decreasing the sometimes deleterious overactivation of the sympathetic nervous system. In patients with advanced heart failure, the sympathetic nervous system is up-regulated, in an attempt to compensate for decreased pumping ability of the heart. Numerous studies have shown that increased sympathetic nervous system activity is a predictor of worse prognosis in heart failure patients. The most successful treatments for heart failure include drugs, such as beta-blockers, that interfere with this hyperactivation.

We hypothesized that biofeedback training could be used to train patients with advanced heart failure to augment the activity of their parasympathetic nervous system while decreasing the activity of their sympathetic nervous system. Our study was designed to test this hypothesis, and to further investigate the potential role of this training in altering the cellular and molecular changes in the heart that result in decreased cardiac output.

After obtaining informed consent, we have enrolled patients with end-stage heart failure who are awaiting heart transplantation at the Cleveland Clinic, one of the busiest centers for heart transplantation in the country. While awaiting heart transplant, patients participate in 11 one-hour individual sessions with a certified biofeedback therapist. During these sessions, psychophysiological reactivity is assessed and patients receive training in biofeedback-mediated stress management techniques. Patients are asked to practice the techniques at home between sessions, for 20 minutes per day, using a handheld biofeedback device that is provided. Initial assessment includes functional capacity (measured by 6-minute walk), degree of sympathetic nervous system activation (measured by plasma catecholamines), and overall as well as heart-failure–specific quality of life (measured by standardized and validated questionnaires). Progress in psychophysiological control is monitored and analyzed over the 11 sessions, along with clinical status and quality of life.

At the time of heart transplantation, heart tissue from each patient is studied. Measurements of muscle function, inotropic responsiveness, calcium cycling proteins, beta-adrenergic receptor density, and atrial natriuretic factor are compared between patients who have had biofeedback training and those who have not. Our hypothesis is that changes in relative activation of the autonomic nervous system in patients who are able to regulate their own physiological state using biofeedback will produce meaningful changes in the biology of the heart, in the direction of recovery. Since we have previously shown such changes in heart failure patients with other types of interventions (left ventricular assist device), comparison can be made to a positive control group.
Abstract 12

Change in Depressive Symptom Status Predicts Health-Related Quality of Life in Patients with Heart Failure

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Background: Depressive symptoms independently predict poor health outcomes in patients with heart failure (HF). It has been hypothesized that interventions that target depressive symptoms in patients with HF will improve health-related quality of life (HRQOL). Research is needed to determine whether a change in depressive symptom status over time translates into a subsequent improvement in HRQOL.

Purpose: To determine whether a change in depressive symptom status from baseline to 3 or 6 months predicts HRQOL at 1 year among patients with HF.

Methods: The sample consisted of 318 inpatients and outpatients with HF (36% female, 62 ± 12 years, 58% NYHA class III/IV) enrolled in a multicenter quality-of-life registry for patients with HF. HRQOL was measured at 1 year using the Minnesota Living with Heart Failure Questionnaire. Depressive symptom status was assessed at baseline and 3 or 6 months later using the Patient Health Questionnaire (PHQ-9); scores 10 and higher indicate depression. Based on baseline and 3- or 6-month PHQ-9 scores, patients were categorized as “remained nondepressed” (n = 201), “remitted from baseline depression” (n = 45), “became depressed” (n = 21), or “stayed depressed” (n = 51). One-way analysis of variance and the Bonferroni post-hoc test were used to compare differences among the four groups on HRQOL scores at 1 year. Multiple regression was used to determine whether change in depressive symptom status independently predicted subsequent HRQOL.

Results: Patients who were nondepressed or remitted from depression had better HRQOL scores compared with patients who became depressed or stayed depressed (F = 34, P < .001; Figure 1). A worsening in depressive symptom status from baseline to 3 to 6 months independently predicted poorer HRQOL at 1 year (β = 10.7, P < .001) after controlling for age, gender, ejection fraction, NYHA class, inpatient or outpatient status, and antidepressant use. Overall, the regression model explained 32% of the variance in HRQOL.

Conclusion: Our findings suggest that interventions that successfully reduce depressive symptoms may have a powerful impact on HRQOL in patients with HF.
Abstract 13

Entropy of EKG Time Series Distinguishes Epileptic from Nonepileptic Patients

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Introduction: Autonomic cardiac dysfunction has been reported in small studies of patients with temporal lobe epilepsy (TLE), with a wide range of irregularities being described, varying from arrhythmias to decreased heart rate (HR) variability. We hypothesize that patients with TLE display cardiac dysautonomia in either a subclinical or a clinical manner. There are conflicting reports with regard to the degree of dysautonomia and the outcome of epilepsy surgery, which eliminates the epileptogenic focus. It has been suggested that patients with greater cardiac dysautonomia have a poorer postoperative outcome, although others report the opposite. Many independent studies show that biologic systems are controlled by nonlinear mechanisms that can be quantified by entropies calculated from physiologic time series. We measure the entropy of HR providing an objective, mathematically defined measurement of a system’s “complexity,” which in turn represents the “healthiness” of the system. We hypothesize that by measuring and comparing the entropy of HR, we will be able to distinguish TLE patients from patients with nonepileptic pseudoseizures. In further studies, we extend the application of this method in a prognostic manner.

Methods: On receiving IRB approval, we retrospectively identified (2003–2008) two groups of patients from our epilepsy monitoring unit (EMU). All patients with diagnosed cardiovascular morbidities were excluded. Our control group consists of patients with confirmed pseudoseizures and our experimental group of age- and gender-matched patients who had confirmed right TLE through a seizure-free outcome after temporal lobectomy. All patients were coded, allowing analyses to be done blindly. For each patient we extract three 120-second periods (awake, sleep state, and preceding seizure onset) from EMU files that recorded EEG and EKG simultaneously.

Results: Five patients were included in the control pseudoseizure group (4 women; mean age 31 ± 12 years) and 4 patients in the right TLE group (3 women; mean age 32 ± 15 years). We calculated the configurational entropy from the time-delayed phase portrait of the HR, and found TLE patients to have higher entropies (S = 4.5) than the pseudoseizure group (S = 2.5) in all three states. The value S = 4.5 is close to the value for “white noise,” so this result is consistent with the finding that a normal heart is associated with “fractional noise,” ie, correlations in the HR. We quantified the HR variability using the approximate entropy (ApEn) and found it to be similar for each state of consciousness (Figure 1, A–C). In the TLE group, there is some evidence for greater variability in the awake state than in either the sleep state or the state preceding seizure onset. There also appears to be a distinction between the two groups prior to seizure onset, although more patients in each group are needed to confirm this trend. A similar effect was not observed in the pseudoseizure group. Furthermore, we calculated the Shannon entropy for the HR; preliminary data support the view that TLE patients have greater HR variability than do patients having pseudoseizures.

Conclusions: A combination of entropies calculated from HR

![Figure 1](image-url)
time series is a noninvasive method of distinguishing epileptic from nonepileptic patients. The higher configurational entropy values seen in TLE signify higher rates of HR fluctuations in comparison to autonomic “healthy” nonepileptic patients. This is also supported by preliminary Shannon entropy data. Approximate entropy values also reflect ordinary Brownian statistics of HR in TLE with pseudoseizure patients displaying more fractional Brownian statistics. Further studies are ongoing to confirm these trends in HR dynamics by increasing the patient number and by sampling over a greater number of time periods. The increased complexity, as measured by entropy, seen in TLE relative to the control group reflects a system in greater flux, suggestive of a pathological state, offering a promising new noninvasive prognostic tool.
Abstract 14

Evaluation of Cardiac Autonomic Balance in Major Depression Treated with Different Antidepressant Therapies: A Study with Heart Rate Variability Measures

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Background: Depression, one of the most common psychiatric disorders, is known to increase concomitant cardiac mortality. Cardiac autonomic involvement in depression has been suggested as an explanation for the increased cardiac morbidity in depression. Clinical improvement produced by antidepressant therapy could alter the autonomic balance too.

Objective: To investigate the effect of three modes of antidepressant management—ie, repetitive transcranial magnetic stimulation (rTMS), selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants (TCAs)—on autonomic function measured by heart rate variability (HRV) in drug-naïve patients with major depression.

Methods: 94 drug-naïve patients suffering from major depression (based on DSM IV-TR) were recruited. Their HRV and Hamilton Depression Rating Scale (HDRS) scores were measured before and 1 month after two modes of antidepressant therapy. Group A (n = 30; age = 32.27 ± 10.81 years; 21 males) received rTMS, which consisted of magnetic stimulation of the left dorsolateral prefrontal cortex with 15-Hz frequency, 10-sec trains, and 10 such trains for 12 days. Group B (n = 32; age = 31.44 ± 8.36 years; 18 males) received 10 to 20 mg of the SSRI escitalopram at bedtime daily for 1 month. Group C (n = 32; age = 36.72 ± 7.97 years; 11 males) received 75 to 150 mg of imipramine/amitriptyline (TCA therapy) at bedtime daily for 1 month.

Results: The patients showed a significant and comparable clinical improvement as assessed by HDRS after all three modes of antidepressant therapy. However, there was a significant intergroup variation in terms of HRV measures. The LF/HF ratio (indicator of sympathovagal balance) significantly decreased in the rTMS group (from 1.66 ± 0.81 to 1.19 ± 0.69), whereas it significantly increased in the TCA group (from 1.68 ± 0.93 to 2.09 ± 1.55). There was no significant change in the LF/HF ratio with SSRI therapy (from 1.68 ± 1.03 to 1.46 ± 1.21).

Conclusion: Although there were comparable effects in terms of clinical measures between these three therapy groups, cardiac autonomic function measures showed differential involvement. The rTMS group showed an improvement in sympathovagal balance, whereas the TCA group showed worsening of the balance. Since depression is one of the risk factors for development of heart disease, this alteration of sympathovagal balance has to be kept in mind when designing antidepressant therapies for patients.
Proinflammatory Status in Major Depression: Effects of Escitalopram

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Stress-related psychiatric disorders (eg, major depression, bipolar disorder, anxiety disorders, and posttraumatic stress disorder) have been variably associated with pervasive loss of homeostasis in the autonomic nervous system. This loss, often referred to as allostatic load, leads to dysregulation of the autonomic nervous system with sympathetic overdrive and vagal tone diminution. An efferent vagal pathway has been identified, the cholinergic anti-inflammatory pathway, which is believed to exert an anti-inflammatory action. When vagal tone is diminished, inflammation becomes disinhibited and one would expect specific inflammation biomarkers to become elevated in the brain and the periphery. This provides a plausible mechanism for the elevated blood levels of proinflammatory cytokines and chemokines previously reported in depressed patients compared with healthy controls by other groups and ours (Piletz et al, 2009). When proinflammatory cytokines become chronically elevated, endothelial dysfunction eventually ensues, ultimately leading to atherosclerosis and atherothrombosis. Of interest is whether this proinflammatory status of depression can be reversed by antidepressant treatment and/or whether the proinflammatory changes normalize when the depressed mood is alleviated.

Our previous study using venlafaxine-XR (a serotonin-norepinephrine reuptake inhibitor) to treat depression suggested that the elevated plasma proinflammatory cytokines in depression were not normalized after 8 weeks despite mood normalization (Piletz et al, 2009). Other studies have suggested that selective serotonin reuptake inhibitors (SSRIs) might be unique in exerting down-immunoregulatory effects over 6 to 8 weeks of treatment (Lanquillon et al, 2000; Tuglu et al, 2003; Basterzi et al, 2005). We report here preliminary findings of a follow-up study of six proinflammatory biomarkers (TNFα, MCP1, IL1β, IL6, CRP, and MPO) in the plasma of 14 patients with major depression (MDD) and 8 healthy controls. Seven of the patients were restudied after 12 weeks of treatment with escitalopram (ESC). Prior to treatment, MDD patients had higher concentrations (pg/mL) than controls of TNFα (7.4 ± 0.5 vs 4.0 ± 0.7, P = 0.001) and MCP1 (122.3 ± 17 vs 69.6 ± 9, P = 0.01) but lower concentrations of IL1β (1.8 ± 0.2 vs 4.3 ± 0.5, P = 0.001). Covariate and correlation analyses revealed no biomarker relationships with severity of depression (HAM-D scores). However, the low IL1β finding in depressed patients may have been affected by higher BMIs in our depressed patients relative to controls: BMI was higher in MDD patients (P = 0.003), and BMI was negatively correlated with IL1β among the patients (r = −0.5, P = 0.02). Following 12 weeks of ESC (n = 7), none of the biomarkers normalized even though the severity of depression (HAM-D) and anxiety (HAM-A) significantly normalized in 6 patients. This finding is in line with our prior study of venlafaxine treatment for depression (Piletz et al, 2009).

Thus, our findings confirm previous findings that some proinflammatory biomarkers are high in untreated depressed patients and that successful treatment—in this case with the most selective SSRI—fails to normalize the abnormality. We cannot rule out the possibility that extended treatment beyond 12 weeks may ultimately normalize the proinflammatory status of depression.

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Abstract 16
Heart Rate Variability in Depression: Effect of Escitalopram

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There is high bidirectional comorbidity between depression and cardiovascular morbidity and mortality. Depression has been associated with a higher risk for myocardial infarction even after controlling for hypertension, dyslipidemia, obesity, smoking, and physical inactivity. Altered autonomic tone in depression with sustained sympathetic overdrive and diminished vagal tone leads to pervasive loss of homeostasis, referred to as allostatic load. Such an allostatic load is a likely contributor to the increased risk of mortality in patients with depression. Measuring heart rate variability (HRV) is an accepted method for assessing cardiac autonomic tone and a measure of allostatic load. Depression has been associated with decreased HRV in otherwise physically healthy patients, although not all studies agree. HRV can be determined on the basis of frequency and time domains. High-frequency (HF) measures reflect parasympathetic activity, while low-frequency (LF) measures reflect mainly, but not exclusively, sympathetic activity. A ratio of LF/HF is calculated to determine the degree of homeostatic imbalance.

Of interest is whether the allostatic load of depression is reversible with antidepressant interventions and whether cardiac health is restored when the depressed mood is successfully treated. Previous studies using pharmacological treatments of depression have suggested that the allostatic load defined by diminished HRV in depression is not reversed after 4 to 16 weeks on various antidepressants. Some studies suggest that antidepressants, probably due to anticholinergic- and/or noradrenergic-enhancing properties, aggravate the already reduced HRV (Licht et al, 2008; Van Zyl et al, 2008). We undertook this study to (a) reassess the effect of depression on HRV, and (b) assess the ability of escitalopram (ESC), the most selective of the selective serotonin reuptake inhibitors available on the market, to restore HRV.

We report initial findings of HRV at rest in 17 patients with major depression (MDD) and 6 healthy controls. Eleven of the patients were evaluated again after 12 weeks of ESC treatment.

Supine HRV recordings (10 min) were analyzed to distinguish LF and HF domains. Prior to treatment, most of the MDD patients (12/17) had > 50% LF variability, indicative of sympathetic overdrive, but there was overall no statistical difference from controls in any HRV parameter. Following 12 weeks of ESC treatment (n = 11), there was overall a highly significant (P = 0.006) normalization toward a 50%:50% LF/HF ratio, which is considered to be normal for a short rest. This move toward 50:50 was observed whether the patients started in sympathetic excess (> 50% LF) or parasympathetic excess (> 50% HF).

A logistic regression analysis was conducted using age, sex, ethnicity, HAM-D (severity of depression), HAM-A (severity of anxiety), and an insomnia scale to identify those patients whose HRV ratio increased (N = 4) or decreased (N = 7) after treatment. No predictors were significant, but the pretreatment HAM-A score was marginally significant (P = 0.065). This finding suggests that the extent of anxiety symptoms in depressed patients sometimes results in sympathetic overdrive but that, regardless of pretreatment anxiety, all patients tended to achieve a 50:50 balance in the HRV frequency domains after 12 weeks of treatment with ESC. ESC may be advantageous for restoring cardiac health since other pharmacological agents have not been found to affect HRV favorably in depression.

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Abstract 17
Effects of Omega-3/6 Dietary Ratio Variation After a Myocardial Infarction in a Rat Model
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Background: Following a myocardial infarction, apoptosis occurs in the limbic system via a mechanism involving inflammation. Consumption of high concentrations of omega-3 fatty acid is well known to be beneficial for cardiac health, to reduce inflammatory reaction, and to produce neutral metabolites, whereas omega-6 fatty acid produces proinflammatory metabolites. Since these two essentials fatty acids are metabolized by the same group of enzymes, the resulting competition would affect the level of the different metabolites and thus the balance between proinflammatory and neutral metabolites. The aim of this study is to determine the effect of different omega-3/6 dietary ratios on infarct size and on apoptosis in the limbic system in our rat model of myocardial infarction.

Methods: Male Sprague-Dawley rats were divided randomly into three dietary groups containing 5:1, 1:1, and 1:5 ratios of omega-3 to omega-6. They were fed the special diet for 2 weeks prior to left anterior descending coronary artery occlusion for 40 minutes followed by 24 hours of reperfusion. Myocardial infarct size was determined and apoptosis was evaluated in the hippocampus and amygdala.

Results: A significant 32% infarct size reduction was observed in the group 5:1 and 1:1 against the 1:5 group. Caspase-3 enzymatic activity was doubled in the CA1 and dentate gyrus in the 1:5 group compared with the 1:1 and 5:1 groups. Also, caspase-8 enzymatic activity was increased in the dentate gyrus at 24 hours and caspase-9 was enhanced in the CA1 at 24 hours in the 1:5 group relative to the 1:1 and 5:1 groups.

Conclusions: These results indicate that a high ratio of omega-3 to omega-6 reduced infarct size and helps to reduce apoptosis in the limbic system after a myocardial infarction.
Abstract 18

The Effects of Tai Chi on the Heart and the Brain

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Tai chi, a martial art that originated hundreds of years ago in China, is becoming a popular mind-body practice throughout the world. The effect of tai chi practice is holistic. It has proven benefits for mental and heart health and also enhances overall well-being. The authors, as practitioners of tai chi for 10 to 40 years (one being a grand master), discuss the effects of tai chi on brain and heart health based on previous reports and the authors’ own tai chi experience.

Tai chi practice has been proven to enhance heart functions. While practicing tai chi, one lowers the thoracic diaphragm and breathes deeply and slowly. This allows more air intake and greatly increases the capacity of the lungs. It is shown that tai chi practice leads to an improvement in oxygen use/aerobic capacity without getting “out of breath.” The benefits of tai chi on heart function have been reported in patients with chronic heart failure1 and those who have undergone coronary artery bypass surgery.2 Tai chi practice also has consistently been shown to reduce blood pressure.3

Tai chi practice also enhances mental health and cognitive functions. Tai chi offers a unique way to combat stress. Tai chi is practiced slowly and with a relaxed focus, and one feels calm in mind during and after practice. For the clinical population, tai chi has been shown to improve mental and emotional function in patients with depression4 and brain injury.5,6 Apart from stress relief, tai chi also greatly enhances sensory perception, which is not well known to the public as it is only seen in advanced practitioners and masters. Advanced practitioners show higher sensitivity to sensory stimulation both in perception acuity and in reaction speed.7 In real combat, such superb ability allows a tai chi master to detect the intention of the opponent and react fast. Such fast reaction often happens even before the master himself/herself realizes it. This high sensitivity and perception suggest a different neural mechanism from ordinary people in response to these stimulations.

Apart from the effects on the heart and the brain, tai chi also has been shown to improve coordination, balance, and sleep, and it has an effect on multiple diseases such as pain, osteoarthritis, diabetes, and asthma. Taken together, tai chi improves one’s general well-being. However, so far the underlying mechanisms for these effects remain unexplored. The authors call for attention and support for the investigation of this issue.

**Abstract 19**

**A Randomized Controlled Trial of the Effect of Hostility Reduction on Cardiac Autonomic Regulation**

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**Objective:** To test whether reduction in hostility increases autonomic regulation of the heart.

**Methods:** In this randomized controlled trial, participants were 158 healthy adults, 20 to 45 years of age, who were one standard deviation (SD) above national norms on the Cook-Medley Hostility Scale and the Spielberger Trait Anger Index. Participants also were interviewed using the Interpersonal Hostility Assessment Technique (IHAT). They were randomly assigned to a 12-week cognitive behavior therapy (CBT) program for hostility reduction or a wait-list control condition. The main outcome measure was cardiac autonomic modulation, measured as RR interval variability (RRV) derived from 24-ECG recordings.

**Results:** In a MANOVA assessing psychological outcomes of hostility, anger, and IHAT scores, there was a significant treatment effect with an average reduction across the three outcomes that was approximately 0.7 SD (ES = 0.685, se = 0.184, \( P < 0.001 \)) greater for the intervention group than for the control group.

In contrast, the change in HR was −0.14 bpm (95% CI, −2.43 to 2.14) in treatment participants and −1.36 bpm (95% CI, −3.28 to 0.61) in wait-list participants. HF RRV, an index of cardiac parasympathetic modulation, increased by 0.07 ln msec\(^2\) (95% CI, −0.10 to 0.24) for participants in the treatment condition and decreased by 0.04 ln msec\(^2\) (95% CI, −0.18 to 0.10) for participants in the wait-list condition. These differences were not significant. The findings for other indices of RRV were similar.

**Conclusions:** Reduction of hostility and anger was not accompanied by increases in cardiac autonomic modulation. These findings raise questions about the status of disordered ANS regulation of the heart as a pathophysiological mechanism underlying the hostility–heart disease relationship and about whether hostility itself is a mechanism or merely a marker of elevated risk of heart disease.