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

JUNE 7–8, 2007

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MARC S. PENN, MD, PHD
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Heart-brain medicine: Update 2007

Heart-brain medicine is dedicated to furthering our understanding of the interaction between the body's neurologic and cardiovascular systems. As discussed previously,[1] the advent of subspecialization in health care delivery has led to significant advances in the care of patients with acute disease or acute exacerbations of chronic disease. While these advances have led to improved outcomes, we were reminded several times this past year how difficult it is to further improve outcomes using the "silo"-based, highly subspecialized approach that has yielded results in the past.

The 2007 Bakken Heart-Brain Summit, held last June in Cleveland, further demonstrated real progress in our understanding of the importance of heart-brain interactions in health and disease. A series of presentations—highlighted by the Bakken Lecture given by Peter Shapiro, MD, an investigator with the SADHART trial—reviewed the effect of psychiatric disorders on the incidence of cardiovascular disease and its consequences. These presentations by leaders in the field (many of which are summarized in the pages that follow) offer irrefutable evidence of the following:

- Patients with depression and heart disease have worse outcomes than patients with heart disease without depression[2]
- Patients with depression have decreased vagal tone[3]
- Patients with coronary artery disease (CAD) can be safely treated with and respond to antidepressants.[4]

These data were complemented by a keynote presentation by Kevin Tracey, MD, whose elegant work over the past many years has demonstrated a link between vagal tone and inflammation.[5] His most recent data have shown that the vagus has direct input into the inflammatory state of macrophages in the spleen. The effect is mediated via vagal innervation of the spleen and the α7 subunit of the nicotinic receptor expressed on the cell surface of the resident macrophages.[6,7] The relevance of vagally mediated modulation of systemic inflammation has been shown in sepsis and more recently by our group in left ventricular remodeling following acute myocardial infarction.

'RECONNECTING THE BODY' TO IMPROVE OUTCOMES

The continuing emergence of the link between psychiatric and neurocontrol of systemic inflammation offers an undeveloped strategy for further improving outcomes in patients with cardiovascular disease. One of our interests in pursuing heart-brain medicine is to reconnect the body and exploit the physiologic interplay between the heart and brain to improve patient outcomes.[1] Given the disappointments over the past year for new therapies like cholesteryl ester transfer protein inhibitors[8] and vascular cell adhesion molecule (VCAM) inhibitors, strategies that have a singular organ or cellular target focus, now may be the time for exploiting multisystem approaches for modulating disease states such as CAD, congestive heart failure, and arrhythmia.

Thus, the emerging data linking neuromodulation to systemic inflammation offers mechanistic insights into long-standing expressions such as "scared to death." For example, multiple studies have demonstrated that CAD patients exposed to terrorist events have an increased risk of myocardial infarction and death. Taking this observation one step further in the context of our discussion at this year's summit, patients with post-traumatic stress disorder (PTSD) have been shown to have low vagal tone[9]—and thus presumably to have increased systemic inflammation. Such a state has been shown by many to increase the risk of plaque rupture, acute coronary syndrome, and myocardial infarction. Thus, while the concept of being "scared to death" has been thought to relate more to arrhythmogenic sudden cardiac death, the scope of potential mechanistic mediators should clearly be broadened **(Figure 1)**.

The potential consequences of these pathways are profound and include the following:

- A physiologic mechanism for the increased incidence of myocardial infarction observed with medications that have anticholinergic properties and potentially decrease autonomic tone
- Worse outcomes in patients with CAD and depression
- An increased incidence of CAD in patients with

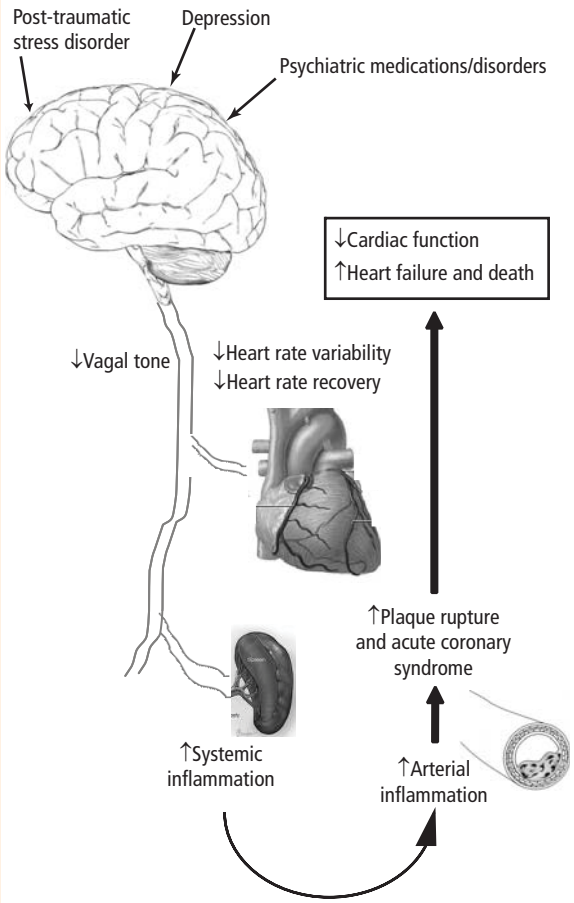

FIGURE 1. Proposed pathways involved in psychiatrically mediated states altering cardiovascular disease and outcomes.

psychiatric disorders that in themselves may be associated with decreased vagal tone, as well as in patients on long-term drug therapies that alter parasympathetic tone

- Increased incidences of CAD, myocardial infarction, and death in patients with PTSD.

AN URGENT NEED FOR CLINICAL TRANSLATION

Clearly the underlying science of heart-brain medicine is fascinating and needs to be pursued vigorously. While the science is ongoing, the need to translate what we know to the bedside has never been greater, given the prevalence of CAD, chronic heart failure, and psychiatric and mood disorders, as well as the likelihood of an increasing incidence of PTSD in light of the Iraq war and terrorist threats.

Multiple studies have been performed to position the field for a trial to test whether treating depression leads to improved outcomes in patients with CAD. We know that patients with depression have decreased vagal tone based on decreased heart rate variability; we know that CAD can be safely treated with selective serotonin reuptake inhibitors; and we know that this patient population is more effectively treated with medications. There was a clear sentiment among faculty and attendees of the 2006 Bakken Heart-Brain Summit that the next step in the clinical science of heart disease and neurologic state is in fact a clinical trial to test the efficacy of this approach. Unfortunately, funding for such a trial from the pharmaceutical industry or government agencies is lacking. The Bakken Heart-Brain Institute is working diligently to secure private financing of such a trial from those with personal interests in moving this field forward. We hope to be able to commence such a trial in the near future. We believe the successful initiation of a multicenter trial not only will demonstrate new avenues for improving outcomes in millions of patients but will validate the concept and usher in a new age of cooperative medicine among multiple disciplines.

As we discussed last year,[1] both the need for and the future of heart-brain medicine are great. The advances seen over the past year and those being pursued in basic and clinical science laboratories throughout the world are very exciting. We thank those colleagues who attended the 2007 Bakken Heart-Brain Summit, and we hope you can join us June 4–5, 2008, in Cleveland to continue this exciting pursuit.

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Depression in coronary artery disease: Does treatment help?

ABSTRACT

Research over the past decade on the link between depression and coronary artery disease (CAD) has moved from establishing the epidemiologic association between depression and CAD to a focus on whether and how treating depression in patients with CAD benefits these patients. Evidence to date indicates that depression therapy does improve depression, albeit somewhat modestly, in CAD patients. The effect of depression therapy on CAD outcomes is less clear, although there is enough positive evidence to encourage further research. The effects of depression treatment on mechanisms mediating increased CAD risk in depressed patients are variable. Future research should perhaps focus on targeting treatment at intermediary mechanisms as well as at depression itself.

Depression's association with incident coronary artery disease (CAD) and recurrent cardiac events became established 10 to 20 years ago. Efforts in the past decade have focused on the specific effects of treating depression in patients with CAD—whether such treatment is beneficial and, if so, exactly how it exerts its benefits. This article briefly surveys the current evidence on these questions after reviewing how we got interested in depression in CAD in the first place.

THE EMERGENCE OF DEPRESSION AS A CARDIAC RISK FACTOR

The shift from a focus on Type A behavior

Not long ago, Type A behavior pattern was the psychosocial variable of greatest research interest as a contributor to CAD. Just 26 years ago, a National Institutes of Health consensus development conference anointed Type A behavior pattern as a CAD risk factor.[1] Five years later, one of the landmark studies in psychosomatic medicine—the Recurrent Coronary Prevention Project—showed that Type A behavior modification, added to usual cardiac care in post–myocardial infarction (MI) patients, not only reduced patients' Type A behavior but also reduced the rate of reinfarction and death.[2]

But that was the high-water mark for Type A behavior in CAD research. The focus soon shifted, especially after the publication of a 1987 review by Booth-Kewley and Friedman showing that larger and later studies found less and less impressive effects of Type A on cardiac outcomes.[3] This same review pointed out the cumulative evidence indicating that depression might be the most important psychological factor associated with coronary disease.[3]

An explosion of research on depression in CAD

In the 10 years following the review by Booth-Kewley and Friedman, there was an explosion of study about depression in CAD.[4] This resulted in what is fair to call a consensus on several key points about this relationship:

- Depression is associated with an approximate 1.5-fold to twofold increase in the risk for incident CAD.[5–8]
- Depression is associated with about a threefold to fourfold increase in the risk of recurrent cardiac events and death in patients with CAD, including patients with a new diagnosis, those with acute coronary events, and those who have undergone revascularization procedures.[9–13]
- Several biobehavioral mechanisms are plausible candidates as mediators of the mind-body relationship linking depression and coronary disease. These include abnormal platelet function, autonomic function, inflammatory processes, and nonadherence to therapy.[4,14]
- Depression is extremely common in CAD, affecting about 15% to 20% of patients, and is a serious illness in its own right, even apart from its effects on cardiac outcomes.[9–11,15–17]

In light of these observations, the obvious research questions are whether treating depression in patients

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

with CAD helps, and if so, what it helps with—the depression itself, the pathophysiology and outcomes of CAD, or both. These questions have been the increasing focus of the past 10 years.

DOES DEPRESSION THERAPY IN CAD PATIENTS IMPROVE DEPRESSION IN THESE PATIENTS?

The short answer to this question is an almost unqualified yes. Even setting aside the literature on tricyclic antidepressants (which is an old literature but impressive in its own right in its systematic working through of issues of efficacy and the delineation and management of adverse effects[18–25]), we have at least half a dozen studies showing that depression treatment helps to relieve depression in patients with CAD with reasonable safety and efficacy. Some are open-label, small-scale studies, while others are more rigorously designed and controlled, but the overall conclusion is unambiguous.[26–34]

Roose, Glassman, and colleagues were among the first to describe the effects of antidepressants other than tricyclics in cardiac patients.[26–29] They demonstrated the safety profile of bupropion, but did not report on its efficacy.[26] They demonstrated safety but found rather low efficacy of fluoxetine in doses up to 60 mg/day in markedly depressed inpatients, many of whom had a "melancholic" profile (early-morning waking, positive diurnal mood variation, guilt, anhedonia, poor appetite).[27,28] In a randomized double-blind trial, these same researchers subsequently demonstrated paroxetine to be at least as effective as the tricyclic agent nortriptyline and to have excellent tolerability at doses up to 40 mg/day.[29]

Strik et al published an early study of the efficacy of depression treatment in 54 patients with major depression after a first MI.[30] Fluoxetine demonstrated superiority over placebo with respect to the percentage of patients achieving a clinical response (48% vs 26%; $P = .05$) (clinical response was defined as a $\geq 50\%$ reduction in the Hamilton Depression Rating Scale [HAM-D] score), but fluoxetine did not have a statistically significant effect on HAM-D symptom ratings except in the subset of patients with mild symptoms to start with. This is somewhat counterintuitive, and to be contrasted with the results of SADHART.

The Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), conducted in depressed patients following MI or unstable angina, is well known.[31,32] Patients with a recent acute coronary syndrome (acute MI in 74%; unstable angina in 26%) were randomized within 30 days of the coronary event to sertraline or placebo (following a 2-week placebo run-in period for all patients). Sertraline was associated with superior scores on the Clinical Global Impression Improvement Scale, particularly among patients with recurrent depression and more severe depression, but its effect on HAM-D scores was not significantly better than that of placebo. As opposed to the finding of Strik et al, the biggest difference in response was among patients with more severe depression symptoms rather than those with mild symptoms to begin with.

The Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) trial tested the hypothesis that psychosocial intervention aimed at depression and low levels of social support would improve cardiac prognosis in post-MI patients.[33] In this large randomized study (N = 2,481), cognitive behavior therapy exerted a modestly significant effect in reducing symptoms of depression as compared with usual medical care. Most patients in the intervention arm underwent 6 to 10 sessions of individual and/or group therapy over 6 months, and their HAM-D scores improved by approximately 10 points from baseline to 6-month follow-up. However, patients in the usual-care arm also had substantial improvements (almost 9 points) in HAM-D scores at 6-month follow-up.

The Canadian Cardiac Randomized Evalution of Antidepressant and Psychotherapy Efficacy (CREATE) used a 2×2 factorial design to assess interpersonal psychotherapy and antidepressant therapy (citalopram) for depression in patients with stable CAD.[34] Citalopram was more effective than placebo in reducing depression symptoms and in achieving response and remission. The mean decline in HAM-D scores was more than 3 points greater in citalopram recipients than in placebo recipients. Interpersonal psychotherapy was no more effective than clinical management.

In none of the studies reviewed above was the benefit of active treatment very powerful—response rates were between 50% and 60%, and remission rates were much lower.

DOES DEPRESSION THERAPY IN CAD PATIENTS IMPROVE CAD OUTCOMES?

In the ENRICHD trial, cognitive behavior therapy–based psychosocial intervention did not result in lower rates of recurrent MI or mortality compared with usual medical care, but the (nonrandomized) use of selective serotonin reuptake inhibitors (SSRIs) by some patients in the study was associated with a 42% reduction in the risk of death.[33,35]

Likewise, depression intervention had no signifi-

cant effect on cardiac outcome in SADHART, although this 369-patient study was not powered to demonstrate such a benefit.[31] Deaths were reduced by more than 50% with sertraline compared with placebo, but there were only 5 and 2 deaths in the placebo and sertraline groups, respectively. The point estimate for sertraline's effect on major adverse cardiac events was a 23% reduction in events (ie, relative risk of 0.77), but the 95% confidence interval corresponding to this relative risk was 0.51 to 1.16, indicating a lack of statistical significance.

Still, this 23% reduction from SADHART was suggestive—certainly enough to interest the cardiologists associated with the study. Together with the ENRICHD trial findings and results from case-control studies indicating that SSRI therapy reduces the risk of incident MI,[36,37] the SADHART findings have encouraged other investigators to suggest additional studies of the effects of antidepressant therapy on CAD outcomes.[38,39]

Notably, in both the ENRICHD trial[40] and SADHART (unpublished data, manuscript in preparation), patients who recovered from depression (regardless of treatment assignment) had better long-term survival, and this was also true in a long-term longitudinal study of patients following coronary artery bypass graft (CABG) surgery.[12] This suggests that interventions to promote recovery from depression should be useful in improving cardiac prognosis, but it does not prove it. It may be that patients whose depression improves are in some way healthier, regardless of their depression intervention.

As noted above, data from observational case-control studies of patients admitted to coronary care units suggest that SSRI therapy reduces incident MI.[36,37] On the other hand, a study of mortality among patients undergoing CABG surgery revealed worse outcomes in those taking SSRIs than in those who were not.[41] Because this study was observational and not randomized, its findings must be interpreted with caution. The effect observed could be due to an adverse effect of SSRI treatment, an adverse effect of depression, or some other mechanism.

DOES DEPRESSION THERAPY HAVE A BENEFICIAL EFFECT ON INTERMEDIARY MECHANISMS LINKING DEPRESSION TO CORONARY EVENTS?

The answer to this question depends on the specific mechanism being considered.

Platelet activation. In the case of platelet activation, the answer may be yes. In a randomized study of depressed patients with ischemic heart disease, paroxetine but not nortriptyline reduced elevated biomarkers of platelet activation.[42] In a substudy of SADHART, blood levels of sertraline and desmethylsertraline were inversely correlated with platelelet activation.[43] Moreover, serotonin reuptake inhibitors appear to reduce platelet activation in proportion to their affinity for the serotonin transporter.[37,44]

Heart rate variability. There is little evidence that depression therapy influences heart rate variability. In SADHART, for instance, sertraline and placebo did not differ in their effects on heart rate variability.[31]

Nonadherence to CAD therapy. It is clear that nonadherence to therapy is more common in depressed patients with cardiac disease than in their nondepressed counterparts[45,46] and that poor adherence is associated with worse cardiac outcomes.[47] But no study in depressed patients has yet demonstrated that depression treatment per se results in improved adherence. One study has demonstrated, however, that adherence tends to "travel with" depression over the course of treatment: as symptoms of depression declined, adherence improved.[48]

FUTURE DIRECTIONS

In the future, a more efficient way to improve cardiac outcomes associated with depression may be to target interventions directly at intermediary mechanisms rather than at depression itself. For example, if depression is robustly associated with a deleterious effect on platelet function that heightens the risk of thrombus formation, it might be helpful to optimize antiplatelet therapy in patients with depression, independent of the depression treatment. Similarly, anti-inflammatory treatments might have added benefit in those cardiac patients who are depressed, because these patients tend to have abnormally elevated inflammatory activity, which is associated with worse outcomes. These hypotheses would need to be specifically tested in randomized controlled trials, of course.

Because depression is associated with smoking, a recent study of a 3-month smoking cessation intervention in patients admitted to a coronary care unit provides an instructive example.[49] At 2-year follow-up, significantly more patients had continuously abstained from smoking in the intervention group than in a usual-care control group (33% vs 9%, respectively), and significantly fewer patients had died in the intervention group compared with the control group (2.8% vs 12%, respectively).

Another desirable objective is the development of treatments that are more robust in their effects on depression for patients with CAD than the interven-

tions tested so far. Higher rates of response and remission of depression would be highly desirable in their own right. Moreover, only with more potent interventions, whose effects separate more robustly from those seen with placebo or usual care, is it likely that depression treatments themselves could affect cardiac outcomes.

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Case study in heart-brain interplay:
A 53-year-old woman recovering from mitral valve repair

ABSTRACT

This article presents the case of a 53-year-old female attorney who underwent successful mitral valve repair for mitral valve prolapse. The patient's postoperative course was marked by refractory pain, fatigue, shortness of breath, refusal to ambulate, frequent episodes of tearfulness, and a postsurgical decline in ejection fraction through postoperative week 4. Her slow recovery prompted a psychiatric consult, during which she reported panic and a fear of "losing it." After respective presentations of the case from the cardiology and psychiatry perspectives, the article concludes with a moderated discussion of the case to explore insights it provides into heart-brain interactions.

CARDIAC CASE PRESENTATION

A 53-year-old woman, a malpractice lawyer, with a history of mitral valve prolapse was diagnosed with severe mitral regurgitation and referred for mitral valve repair.

History and examination

The patient had no other cardiac history. She reported jogging 2 to 3 miles daily and playing tennis regularly, but over the past few months she had become more fatigued during her jogs, to the point that she occasionally had to reduce her pace and even shorten the duration of her runs.

On her initial visit, she expressed surprise regarding the severity of her mitral valve disease, as she had always been healthy. She seemed somewhat nervous but appropriately concerned about the impending surgery, and questioned whether she would be able to return to her previous level of activity. She also mentioned that she hoped the timing of the surgery would permit her to attend her son's college graduation in 9 weeks.

Her medical history was notable for mitral valve prolapse. She had a history of panic attacks, for which she occasionally took alprazolam. There was no family history of cardiac disease. She did not use tobacco and occasionally consumed alcohol. A review of systems was negative.

Her physical examination was unremarkable except for a grade 4/6 holosystolic murmur at the apex that radiated to the axilla, which was consistent with the mitral regurgitation.

A transthoracic echocardiogram demonstrated mitral regurgitation that extended through the left atrium back into the pulmonary veins. The left ventricular ejection fraction was 50%, which is considered low-normal. The degree of mitral regurgitation was 4+. No other significant valvular disease was observed.

An electrocardiogram revealed a normal sinus rhythm. Per our routine, the patient underwent cardiac catheterization, which showed normal coronary arteries.

An uncomplicated repair, but slow recovery

The mitral valve repair was performed without complications. The course in the intensive care unit was uncomplicated, and the patient was quickly extubated and transferred to a regular nursing floor.

On the nursing floor, controlling the patient's pain was difficult. She refused to use her incentive spirometer and initially refused to ambulate or even move from her bed to a chair. She was quite tearful.

A postoperative transthoracic echocardiogram revealed a satisfactorily repaired mitral valve with no mitral regurgitation. Her ejection fraction decreased to 40%, which is not unusual after mitral valve surgery.

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

Her hospital course was notable for an episode of shortness of breath and tachycardia. Sinus tachycardia was evident on review of the telemetry strips. A repeat echocardiogram showed no changes compared with the prior postoperative echocardiogram. Spiral computed tomography was negative for pulmonary embolism.

Pain control remained difficult. The patient expressed concern about the postoperative decrease in her ejection fraction; she was reassured that a decrease in ejection fraction was not unusual, but she remained tearful. The family expressed concern because the patient "wasn't acting like herself," and her ambulation and use of her incentive spirometer continued to be minimal, which had the potential to hamper her recovery and rehabilitation. For these reasons, a psychiatric consult was requested and the patient was seen prior to discharge from the hospital on postoperative day 6.

Wound check at 1 week postdischarge

A routine wound check was performed 1 week after discharge, at which time the patient was still reporting pain that was more severe than would be expected at her postoperative stage. She reported concern about drainage from the incision. She said that she was unable to do much walking or stair climbing, and she reported sleeping in the guest bedroom on the first floor of her house because she was unable to negotiate the stairs to her bedroom.

A check of the wound showed minimal serous drainage at the inferior aspect and was consistent with normal wound healing. The slow progress of her recovery was a concern, as was the possible contribution of her anxiety to this slow progress, so we kept our psychiatric colleagues informed about the patient's recovery.

Follow-up at postoperative week 4

At the follow-up visit at postoperative week 4, the patient reported still being in pain, although the pain had improved, and complained of constant fatigue and shortness of breath that prevented her from returning to work. She had been discharged on lisinopril and admitted to occasional medication noncompliance. She said that if she did not improve dramatically and quickly, she would not be able to attend her son's graduation.

We considered the possibility of new ischemia, a large pleural effusion, postpericardiotomy syndrome, constrictive pericarditis, or a mitral valve leak as potential causes of her symptoms. A chest radiograph was obtained, which demonstrated a small left pleural effusion, and an echocardiogram showed that her ejection fraction remained at 40% and the mitral valve repair remained intact. The patient had a psychiatric visit scheduled later on the day of this follow-up visit and was referred to the cardiac rehabilitation program, to start on week 6 of her postoperative care.

PSYCHIATRIC CASE PRESENTATION

At the time of the first psychiatric consult, postoperative day 6, the patient's chart was reviewed, detailing her presentation and hospital course as described above. The chart confirmed one episode of "panic" following surgery while the patient was on telemetry, showing only sinus tachycardia. This episode was successfully treated with 1 mg of lorazepam. She expressed a fear of "losing it," which is how she characterized her panicky state during the hospital stay, punctuated by the feeling that she was not in control. The nursing staff reported that she was distressed and irritable. Her husband also confirmed that the patient "was not herself."

Her baseline functioning was high; she is a partner in a law firm and is customarily "in control." Before the interview began, the patient had several questions ready, including how quickly she would heal, how soon she could return to work and resume her normal activities, the reason for her low ejection fraction despite having mitral valve surgery, and whether or not she would be able to attend her son's graduation. Even though she knew the psychiatry consult had been ordered, she was not very receptive to it at first and was more focused on her physical symptoms.

Psychiatric history

Her psychiatric history was significant for fear of heights and panic attacks, but she had been able to conquer each. She overcame performance anxiety in high school and was able to be a successful malpractice attorney, deliberating cases in court. She had never seen a psychiatrist or mental health professional, and had never been on psychotropic medications, although for the past couple of years she had been using 0.5 mg of alprazolam to treat flight anxiety. She admitted to postpartum depression that lasted about 2 months; no treatment was sought at the time, and the depression resolved.

Family and personal history

Her mother was a teacher and a "professional worrier," and her father is a retired lawyer. She reported resolving to "suck it up" during times of adversity during childhood, but her childhood was otherwise unremarkable. She is an only child and finished at the top of her class at law school.

Review of symptoms

An assessment of depressive symptoms using the mnemonic SIGECAPS (disturbance of ***s***leep; disturbance of ***i***nterest; presence of ***g***uilt; disturbance of ***e***nergy, ***c***oncentration, or ***a***ppetite; increased or decreased ***p***sychomotor activity; ideas of ***s***uicide) elicited low energy levels, decreased concentration, and a "slowed down" feeling. The WART (withdrawal, anhedonia, rumination, tearfulness) scale, used to assess depressive symptoms in the medically ill, showed the patient to be withdrawn and tearful at times.

Mental status examination

The patient was polite, professionally courteous, and sitting up in bed. Her vital signs were stable (heart rate, 70 beats per minute; blood pressure, 122/72 mm Hg) and her mood was "fine," although she had many concerns about her physical health. Her affect was serious, constricted, and controlling. Her thought process was linear and organized, and her thought content revealed no psychosis, suicidal ideations, or overt hopelessness. She admitted that she was slightly anxious and overwhelmed, and that this anxiety precipitated her "panic" on telemetry and tearfulness, but she believed (and asked for assurance) that this level of anxiety was normal following surgery.

Diagnosis and recommendations

By the end of the consultation, we were able to make a series of recommendations. We arrived at a diagnosis of adjustment disorder with anxious features, and we agreed to treat her with alprazolam at a dose of 0.5 mg twice daily as needed. We provided education about mood and anxiety disorders in cardiac patients. We explained that her postpartum depression was a risk factor for future depression. We discussed coping strategies and relaxation techniques, and scheduled a follow-up appointment with her primary care physician for further monitoring of her mood and anxiety.

One week postdischarge

The cardiology team communicated with us after her wound check at postdischarge week 1. At this time, she was still having pain and was concerned about excessive wound drainage even though it was found to be minimal. The cardiology team was concerned because her progress was slow and she appeared anxious and tense. A follow-up psychiatry consultation was arranged for the patient's next postoperative visit.

Follow-up at postoperative week 4

At her scheduled psychiatric visit at postoperative week 4, the patient was a little surprised to see the fellow, as she expected to see the staff psychiatrist. She appeared tense and frustrated, was fixated on her echocardiogram and her physical symptoms, and reported that she was not yet back to work. She was preoccupied with her son's graduation that was coming up and wondered if she would be able to attend and celebrate it.

We administered the Patient Health Questionnaire depression scale, and the patient's score of 11 indicated moderate depression. Treatment options, including psychotherapy and pharmacotherapy with a selective serotonin reuptake inhibitor (SSRI), were reviewed with the patient. A call to the cardiology team revealed that her ejection fraction was fairly typical for a patient who has had a mitral valve repair but that the continued fatigue was not normal, leading us to suspect that depression may be the actual cause of her fatigue. She remarked, "Let's see how the cardiac rehabilitation program goes and then we'll talk about medications for depression."

Cardiac rehabilitation at postoperative week 6

The patient was entered into the cardiac rehabilitation program, and she was administered a Short Form–36 (SF-36) health survey, which showed a low mental summary score and a low physical component summary score (low scores connote worse health and/or more disability). She was referred to the psychiatrist at the cardiovascular behavioral health clinic for further assessment of her mood as she commenced the cardiac rehabilitation program.

DISCUSSION OF THE CASE

To explore management options in this case and discuss the insights it provides into heart-brain interactions, the case presentation was followed by an interactive discussion (moderated by Dr. James B. Young) between the physicians who presented the case and the Heart-Brain Summit audience.

Dr. James Young: Let's begin by considering whether there were some red flags that may have been apparent up front to predict that this patient might have been challenging in the postoperative period. I think one red flag was the diagnosis of mitral valve prolapse itself, which has been known to occur in type A personalities, who tend to exhibit catecholamine excess and sympathetic nervous system arousal that activates the autonomic nervous system.

Also, I'd be interested to know a few more findings from the patient's physical examination. Was she thin? Did she have a narrow anteroposterior diameter? Did she have pectus excavatum? Did she have

arachnodactyly tendencies? These are important characteristics that might have flagged the anxiety up front, as psychosomatic manifestations of patients with mitral valve prolapse were identified—and hotly debated—20 to 30 years ago. Although the link between mitral valve prolapse and personality type has fallen out of favor in cardiology circles, it clearly seems to describe this patient. The history of anxiety, panic, and possibly agoraphobia has been well described in patients with mitral valve prolapse and excematous degeneration.

I'd like to pose the following questions to the audience. What do you do with this patient now? Do you push medication therapy? Do you push psychotherapy? What is the next step?

Comment from audience: You haven't excluded the post-pump syndrome. This patient is very bright and it wouldn't take much of an insult to impair her sufficiently so that she would interpret the world in a different way. From my point of view, she needs sophisticated neuropsychological testing soon.

Dr. Young: That's a good point. We know that cardiopulmonary bypass is associated with difficulties and problems that have been underreported in the past.

Comment from audience: The last thing that this patient wants to admit or even allude to is a psychological problem. She is the last one who's going to even hint at it, which makes it very easy to miss. Look at how she reacted when she heard that there was a psychiatrist in the room. These patients are not necessarily well disposed to completing screening tests because they recognize that somebody is trying to identify a psychological problem. I don't know that I have the answer, but I think that we should avoid browbeating ourselves for the problem.

Dr. Young: I want to mention the cultural anthropology of physicians and how it affects our approach to treatment. I like being a cardiologist because I write prescriptions for drugs that have proven to be useful, such as beta-blockers and ACE inhibitors, among others. From this experience came my earlier question, "Should we give this patient a drug?" The cardiologist's focus—perhaps excessive focus—on pharmacologic solutions may not be the best way to approach this patient. You allude to some important issues about screening a patient for diseases that can be more easily treated.

Comment from audience: I have seen such situations as a result of drug interactions; many of our patients are on multiple drugs when they leave the hospital. The other issue to consider is sleep deprivation, with or without sleep apnea.

Dr. Young: Many complications, particularly in patients with heart failure, are related to disordered sleep, which certainly causes some heart-brain dysfunction. What about the drugs?

Dr. Thomas Callahan: We considered the effects of her medications, which included an ACE inhibitor and her analgesics. We also considered the lingering effects of anesthesia or other medications that she might have been receiving.

Dr. Young: Remember, she was reporting considerable pain. I suspect that she was on a cocktail of pain medications that might have been contributing to her difficulties.

Comment from audience: Morphine's effects tend to be stronger in women than in men. The other issue is the 10% drop in ejection fraction after the surgery. This patient may be thinking, "Why did I go through all of this if my ejection fraction is going to be worse?"

Dr. Callahan: A drop in the ejection fraction, especially after mitral valve repair, is common. We often address it with patients preoperatively, but perhaps not with everyone, and perhaps not clearly enough.

Dr. Young: Also, this is an example of a patient who had heart failure going into the operation, but "heart failure" would be the worst term to use with this particular patient. An ejection fraction of 50% is not normal for a patient with 4+ mitral regurgitation and, as Dr. Callahan suggested, when you take away the mitral regurgitation, you dump a little more load on the left ventricle, and the ejection fraction will go down. We see this all the time, although I admit that cardiologists or cardiac surgeons don't necessarily do the best job of discussing these subtleties with patients. Something we can take away from this case is a sense of the importance of improving our communications with patients about what they might expect postoperatively, although it still needs to be tailored to the individual patient. If this patient had understood the pathophysiology behind the drop in ejection fraction, it may have helped her. Other patients, on the other hand, may not require detailed conversations about this phenomenon.

Comment from audience: It was mentioned several times that the husband said the patient was not her-

self. Did you interact with the husband and the son to get a sense of the long-term dynamics of this family? It seems that there may have been some issues with the family dynamics.

Dr. Ubaid Khokhar: That's a good question, although no underlying dynamics seemed apparent. The husband and son's primary concern was that the patient's previous characteristics of perfectionism and always being "in control" were so much in contrast with the tearful episodes she was having now. "She is not the same," is how they kept phrasing it. However, there were no other significant changes—no rumination about suicide, no overt unwillingness to go along with treatment, or anything like that.

Comment from audience: I believe strongly that this patient was depressed, although she did not admit it. She had four of the five symptoms. She did not admit to a depressed mood but was tearful, which you reported at every postoperative visit. This is a sign of depression. We know very well that anxiety and depression often are present in tandem, especially in patients with high baseline anxiety. When they have more stress in their lives, they tend to get depressed.

I agree with the preceding comments that drug interactions are a potential worry; however, a few of the SSRIs have favorable drug-drug interaction profiles. I would urge this patient to try SSRI therapy. If she rejected this by responding, "I'm not depressed," you could point out that SSRIs work very well for anxiety. Alprazolam is not a good medication for anxiety because it has a very short half-life, which can leave patients with an increase in anxious feelings after the medication is cleared from their system but before their next dose.

In addition to SSRI therapy as a first-line approach, I would try stress management, biofeedback, or even psychosupportive therapy that relies on patient education to help this patient understand her condition and take back control.

CASE OUTCOME

Our initial approach with this patient was the path of least resistance. Very good points have been made by the discussants and members of the audience. This patient was attached to alprazolam because it was the only psychotropic medication that she had ever taken. For this reason, she was discharged on alprazolam even though it wasn't the ideal medication. As pointed out by the audience, the patient was quite resistant to the concept of having depression superimposed on a history of anxiety. In the cardiac rehabilitation setting she was again reassured by the exercise physiologists that her heart was doing well. A cardiologist personally reviewed the echocardiographic reports and films with the patient, pointed out the absence of unusual abnormalities with her heart, and suggested that something else was causing her symptoms. This direct explanation and reassurance from the cardiologist facilitated the patient's ability to entertain depression as a comorbid condition.

At the visit with the psychiatrist in the cardiac rehabilitation program, the patient finally accepted that her lack of confidence could also be a symptom of depression. We repeated the Patient Health Questionnaire, which still showed moderate depression, and we started her on an SSRI, citalopram. About 3 weeks later, she began to regain her confidence, and she was able to attend and host her son's graduation. By 8 weeks after the start of antidepressant therapy, a repeat Patient Health Questionnaire showed no evidence of depression.

Her progress, both physically and emotionally, was quite pronounced during the 12-week cardiac rehabilitation program. Her physical stamina improved, her fatigue abated, and her sense of confidence was restored. She successfully returned to work and her family concurred that she had returned to her "old self." She benefited from the stress management and lifestyle seminars that were offered in the cardiac rehabilitation program, and her exit SF-36 scores were much improved. The patient pleasantly surprised us all by taking the initiative of forming a monthly women's support group for coping with heart surgery.

She completed a 9-month course of the SSRI, with the depression in full remission, and has continued to follow up with her cardiologist and her exercise regimen.

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Emotional predictors and behavioral triggers of acute coronary syndrome

ABSTRACT

Mounting evidence suggests that depression, anxiety, and hostility/anger may each be an independent risk factor for acute coronary syndrome (ACS) occurrence. Data specific to the role of these negative emotional states in predisposing to imminent ACS risk are limited, however. Additionally, a number of studies have indicated that certain situational triggers (such as intense physical exertion) and behavioral triggers (such as acute anxiety or anger) are predictive of imminent occurrence of an ACS. Despite these findings, the use of emotional or behavioral information to identify persons at high risk for imminent ACS onset is not yet practical. Further research is needed to facilitate such patient identification.

Numerous systematic reviews indicate that psychosocial factors are predictive of an initial acute coronary syndrome (ACS),[1–8] defined as myocardial infarction (MI), unstable angina, or sudden cardiac death. Psychosocial factors under active investigation for their role in ACS onset include chronic negative emotional states (eg, depression, hostility, anxiety) as well as situational and behavioral triggers (eg, acute anger, unusual intense physical activity). This review will present evidence for each grouping of risk markers and then discuss the studies required to better identify and treat patients who have these psychosocial vulnerabilities.

NEGATIVE EMOTIONAL STATES

Increasing epidemiologic and pathophysiologic evidence suggests that depression, anxiety, and hostility/anger may each be an independent risk factor for initial occurrence of a cardiovascular event.[4,8] The vast majority of evidence has been accumulated for depression, and many meta-analyses and systematic reviews now indicate that depression—as either a clinical diagnosis or an elevation in self-reported symptoms—is a strong, consistent, independent predictor of ACS incidence.[9–11]

For example, in one meta-analysis of studies examining depression and the incidence of coronary heart disease (CHD) events, the presence of depressive symptoms conferred a relative risk of 1.49 for CHD events (95% confidence interval [CI], 1.16 to 1.92), and the presence of clinical depression conferred a relative risk of 2.69 (95% CI, 1.63 to 4.43), which suggests a dose-response–like association between depression and ACS onset.[9] **Figure 1** shows the incident risk of CHD events associated with depression (depressed mood and clinical depression) from this meta-analysis relative to the risk associated with established risk factors for CHD.[4]

Major depression

Major depressive disorder is most appropriately diagnosed through direct patient interview, preferably by trained professionals who look for evidence of severely depressed mood lasting at least 2 consecutive weeks, other concomitant symptoms (such as change in eating or sleeping habits), and evidence of associated functional impairment. Because this interview approach is not convenient for large epidemiologic studies, evaluation of major depression by interview in longitudinal epidemiologic studies has been sparse,[12,13] and only a limited number of other studies have also evaluated the role of a history of depressive disorders[14] or a history of depression treatment.[14–18]

Depressive symptoms

The impact of self-reported depressive symptoms on cardiac outcomes has been studied more widely—in community settings, among the elderly, and in various cardiac settings—using scales such as the Beck Depression Inventory and the Center for Epidemiological Studies Depression Scale. Notably, these scales assess only the presence of recent depressive symptoms. Nevertheless, despite this important limitation, one-

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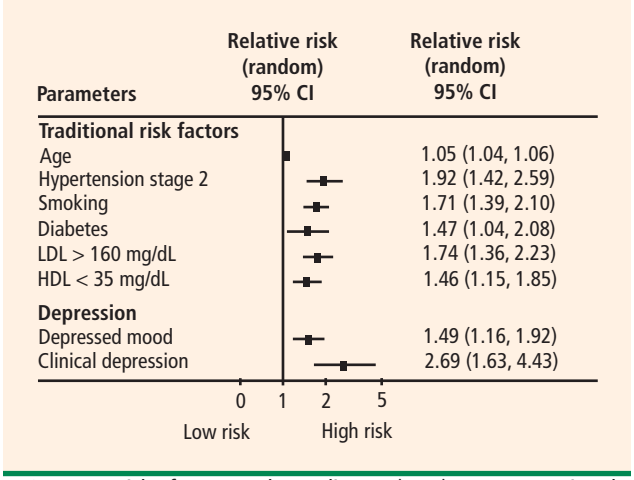

FIGURE 1. Risk of coronary heart disease (CHD) events associated with traditional Framingham risk factors versus the risk associated with depression. Risk ratios for the traditional risk factors are those reported for men followed up in the Framingham study;[45] risk ratios for depressed mood and clinical depression are from a meta-analysis by Rugulies et al.[9]

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time assessment of healthy participants using these scales has generally revealed a significant relationship between depressive symptoms and future adverse cardiac events.[9,18] As further evidence of a gradient relationship, the frequency of cardiac events increases as the level of depressive symptoms increases.[13,19]

Depression is a complex phenotype, and some have argued that subtypes, or intermediary phenotypes, of depression may be particularly predictive of ACS incidence and recurrence.[20] Interestingly, the first article ever published documenting a link between depression and coronary artery disease focused exclusively on melancholic depression, or endogenous depression.[21]

Anxiety

Anxiety is defined as a future-oriented negative emotion resulting from perceived threat and accompanied by perceived lack of control and lack of predictability.[22] Like depression, anxiety occurs along a continuum, but it is characterized as pathological when it becomes chronic, has intensity out of proportion to any real threat, and leaves the affected person with seriously impaired ability to function.

There are many recognized anxiety disorders, including generalized anxiety disorder, panic attacks, obsessive-compulsive disorder, posttraumatic stress syndrome, and various forms of phobia. As a group, these anxiety disorders constitute one of the most common forms of psychiatric illness. Moreover, anxiety disorders and major depression are highly comorbid.[23] Although some interesting epidemiologic studies have indicated that anxiety may predict new ACS events,[24–26] there are a few that have yielded mixed results.[27,28]

Hostility and anger

Angry and hostile feelings are overlapping emotions and, when experienced frequently, indicate broader, more enduring temperaments or personality styles. Hostility is a cynical, suspicious, and resentful attitude toward others; negative social exchanges, such as sarcasm or impatience, typify individuals with hostility. In contrast, individuals with anger difficulties can have warm, appropriate interpersonal skills and may display verbal aggression or other outbursts only when provoked. Unlike depressive and anxiety disorders, professionally diagnosed, syndromal anger and hostility are not yet recognized by psychiatric nosology.

Relatively few longitudinal studies have been conducted using measures of hostility in healthy cohorts. These studies have reported both the presence[29,30] and the absence[31] of positive associations. In a recent systematic review, 7 of 11 studies showed hostility to be a significant risk factor for CHD.[8] A case-control study involving participants in the Multiple Risk Factor Intervention Trial (MRFIT) employed a structured interview (as opposed to a questionnaire) designed to elicit information regarding signs of hostility, including irritation, arrogance, uncooperativeness, and angry feelings.[30] It revealed that men with high hostility levels were more likely to die of cardiovascular disease than men with low hostility levels (adjusted odds ratio = 1.61; 95% CI, 1.09 to 2.39) in this initially healthy but high-risk cohort.[30] The investigators chose the structured interview to overcome participants' potential to underreport or underrecognize hostile tendencies when completing a questionnaire.[30]

Over time, specific measurements of chronic anger,[32–37] including both unhealthy anger expression[34] and suppression,[37] have accumulated, permitting examination of their relationship to adverse cardiac outcomes in longitudinal follow-up of disease-free cohorts. A number of these studies have shown a positive association.[32,33,35–37] Moreover, a recent report from the Framingham study demonstrated an association between anger/hostility and the development of atrial fibrillation and total-cause mortality over a 10-year period,[38] and another study has observed a relationship between anger expression and development of stroke.[39] Combined, these observations suggest that anger is worthy of further study as a factor in the

TABLE 1
Situational and psychosocial triggers of CHD: Profile of studies assessing their association with imminent ACS*

Trigger	No. of studies	Participants	No. of studies showing association with imminent ACS
Earthquakes	7	Vast majority with elevated risk factors for CVD or clinical histories	6
Sporting events	4	Men	3
War	6	Men	2
Emotional distress and anger	5	Men and women	5
Emotional stress	5	Men and women	5

* Studies extracted from Strike and Steptoe.[7]
CHD = coronary heart disease; ACS = acute coronary syndrome; CVD = cardiovascular disease

development of CHD. As with hostility, however, various subscales have been used to study anger, which makes standardization across studies difficult.

Data specific to imminent ACS risk are few

The majority of the negative emotional states have not been tested for their ability to predict an ACS in the near future. Further, negative emotional and cognitive states that may be implicated in the development of CHD or other cardiovascular disease may be quantitatively or even qualitatively different from those psychosocial factors that identify a patient at imminent risk for an ACS.

SITUATIONAL AND BEHAVIORAL TRIGGERS

Evidence for imminent risk or trigger status can be obtained from retrospective reports, from witness accounts (if available), or prospectively from electronic diaries coupled with ambulatory electrocardiogram recordings or an implantable cardioverter-defibrillator (ICD). Triggers of an ACS include external stimuli (eg, cocaine use, air pollution, ambient temperature), patient activities (eg, eating a meal high in saturated fat, unusual physical exertion), and emotional reactions such as extreme anger or anxiety.[1,2,7,40,41] Myocardial stunning has also been reported immediately after acute emotional stress but has generally been reversible in these cases.[42,43] In an observational study, Burg et al found that ICD shocks preceded by an anger episode (as recorded by diary) were more frequent in patients with high trait levels of anger (according to the Speilberger Trait Personality Inventory) and that shocks preceded by an anxiety episode were more frequent in patients with high trait levels of anxiety.[44] A systematic review by Strike and Steptoe showed that physical exertion (particularly in poorly conditioned individuals), emotional stress, anger, and extreme excitement are all probable triggers for an ACS.[7] A recent meta-analysis suggests that emotional stress immediately precedes MI in approximately 7% of MI cases and is a more frequent ACS trigger for women than for men.[1]

Table 1 presents examples of triggers that have been found to predict an imminent ACS. Some of these triggers may represent episodes or situations that can lead to an imminent ACS in any apparently healthy person, whereas some may operate only in apparently healthy persons who have chronic negative emotional states or other psychosocial vulnerabilities.

THE PSYCHOSOCIALLY VULNERABLE PATIENT

This selective overview suggests that patients' emotional states are frequently implicated in the onset of an ACS but that the use of behavioral or emotional information to identify those at high risk for imminent ACS onset is not yet practical. Triggers are, by definition, state-like, but their impact may be amplified by trait-like characteristics, such as high dispositional anger, anxiety, hostility, or chronic environmental stress.

The previously mentioned analysis of the MRFIT study by Matthews et al[30] suggests that patients identified as "high risk" by conventional risk factors, and who additionally possess high trait hostility, should be monitored closely, as they are at risk for cardiovascular death. Additionally, the Burg study of patients with ICDs suggests that arrhythmia may be induced by acute anxiety or anger in those prone to have such emotions chronically.[44]

Such studies have two research implications. First,

controlled laboratory studies that induce acute negative emotion in those with chronic negative emotional states may help reveal the pathophysiologic processes implicated in immediate ACS onset. Interventions for these psychosocially vulnerable patients await such studies. Second, we must begin to consider that in addition to the psychosocially vulnerable patient, we may have psychosocially vulnerable *situations*, about which we know little at this time.

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Impacts of depression and emotional distress on cardiac disease

ABSTRACT

Depression is a primary risk factor for ischemic heart disease (IHD) and a secondary risk factor for worsened prognosis in patients with IHD and heart failure. Mental stress–induced myocardial ischemia appears to be a significant mechanism by which depression increases the risk of death and morbidity in patients with IHD. A number of trials have evaluated the effect of therapy for depression in patients with cardiac disease, and more are ongoing. Selective serotonin reuptake inhibitors (SSRIs) are effective in improving depressive symptoms in cardiac patients and are relatively safe in these patients; tricyclic antidepressants are less safe in these patients. Early evidence suggests that antidepressant therapy with SSRIs may be associated with improved cardiac outcomes in depressed cardiac patients, but further study is needed.

Over the past several decades, a large body of evidence has emerged demonstrating the adverse impact of depressive disorder on heart disease. This evidence confirms the early suspicion of observant clinicians that psychological factors play a significant role in the genesis and course of heart disease, as well as confirming the ancient belief in a mind-body connection in general and a connection between human moods and the heart in particular. Given the high prevalence of these two disorders, we need a better understanding of the impact of depressive disorder on heart disease, the proposed underlying pathophysiologic mechanisms, and the effects of treating depression in relation to risk reduction in patients with heart disease.

In this article, I will focus on (1) reviewing the results of meta-analyses examining the association of depression with cardiac diseases, (2) discussing the relationship between depression and mental stress–induced myocardial ischemia, (3) reviewing the available studies of the treatment of depression in patients with cardiac disease, and (4) discussing future directions for research in this area.

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ASSOCIATION OF DEPRESSION WITH PROGRESSION OF CARDIAC DISEASES

As a disease of the brain, depression is common. The lifetime prevalence of major depressive disorder, a significant form of depression, is 16.2%.[1] The point prevalence of depression in medically ill patients is much higher, ranging from 20% to 50%, and the prevalence of milder depression is even more common. Despite this substantial prevalence, depression (especially in its milder forms) is rarely recognized. It often occurs insidiously, confusing its sufferer into believing that it is part of his or her character rather than an illness.

An invisible killer

The adverse effects of depression manifest in many aspects of life—from relationships to job performance to compliance with medical treatments—and can be so severe as to render the condition an "invisible killer." The first evidence of this emerged in the medical literature in 1937 when Malzberg[2] reported that patients with melancholia had a significantly higher death rate than the general population and that cardiac death occurred in more than 40% of those patients. Although it took another several decades for the field to accelerate, ample data have now been gathered to prove an unshakable association between depression and progression of cardiac diseases. Instead of reviewing results of each study, I will present the results of several meta-analyses.

Prognosis of post–myocardial infarction patients with depression

In a meta-analysis published in 2004, van Melle et al[3] examined data derived from the MEDLINE, EMBASE, and PsycINFO databases between 1975 and 2003 on the prognostic association of post–myocardial infarction (MI) depression with mortality and cardiovascular

events. Twenty-two studies met the selection criteria (post-MI status with measurement of depression and up to 2 years of follow-up); these studies included a total 6,367 post-MI patients and had an average follow-up of 13.7 months. The analysis revealed that post-MI depression was associated with each of the following:

- All-cause mortality (fixed-effects odds ratio [OR] = 2.38; 95% confidence interval [CI], 1.76 to 3.22; $P < .00001$)
- Cardiac mortality (fixed-effects OR = 2.59; 95% CI, 1.77 to 3.77; $P < .00001$)
- Occurrence of cardiovascular events (random-effects OR = 1.95; 95% CI, 1.33 to 2.85; $P = .0006$).

Prognosis of depressed patients with ischemic heart disease

In another 2004 meta-analysis, Barth et al[4] examined the association of depression with mortality among patients with other forms of ischemic heart disease (IHD) (ie, beyond just MI) using data derived from English- and German-language databases (MEDLINE, PsycINFO, and PSYNDEX) from 1980 to 2003. A total of 11,905 patients from 20 cohorts were included. Although depression assessment was heterogeneous among the studies included, the unfavorable impact of depression on mortality among IHD patients was consistently observed regardless of whether the depression was self-reported or detected by psychiatric professionals. The risk of dying in the first 2 years after initial assessment was more than two times higher in patients with high depressive symptoms than in those with low depressive symptoms (OR = 2.24; 95% CI, 1.37 to 3.60). This negative prognostic impact remained over the long term and after adjustment for other risk factors (hazard ratio [HR] = 1.76; 95% CI, 1.27 to 2.43). Although clinical depression had no significant effect on mortality within the first 6 months after initial assessment (OR = 2.07; 95% CI, 0.82 to 5.26), after 2 years it was associated with a greater than twofold higher risk of death (OR = 2.61; 95% CI, 1.53 to 4.47).[4]

Prognosis of depressed patients with heart failure

Several studies over the past decade, including one from my research group,[5] have prospectively examined the impact of depression on outcomes in patients with heart failure (HF). Rutledge et al[6] used meta-analysis to summarize the findings of eight independent cohort studies that tracked the association between depression and mortality or cardiac events in a total of 1,845 patients with HF; follow-up ranged from 6 months to more than 4 years. They found that those patients who were depressed had higher rates of death and secondary events (relative risk [RR] = 2.1; 95% CI, 1.7 to 2.6) compared with their nondepressed counterparts, as well as trends toward increased health care use and higher rates of hospitalization and emergency room visitation.

Development of ischemic heart disease in depressed patients

To assess depression's role as a potential predictor of IHD development, Rugulies[7] reviewed data from MEDLINE (1966 to 2000) and PsycINFO (1887 to 2000), selecting 11 cohort studies based on assessment of patients by standardized psychometric scale (clinical depression or depressed symptoms) and "hard" events (fatal/nonfatal MI, coronary death, or cardiac death). Among the 36,549 individuals in these studies, the overall RR for development of IHD in depressed subjects (as compared with nondepressed subjects) was 1.64 (95% CI, 1.29 to 2.08; $P < .001$). Sensitivity analysis revealed that clinical depression was a stronger predictor of IHD (RR = 2.69; 95% CI, 1.63 to 4.43; $P < .001$) than depressive symptoms were (RR = 1.49; 95% CI = 1.16 to 1.92; $P = .02$).

In summary, individuals with depressive disorder, even mild forms, are more likely to develop IHD than are individuals without depression. The increased likelihood of developing IHD is independent of conventional risk factors. Therefore, depression is a *primary risk factor* for IHD. Depression is also a *secondary risk factor*, independent of conventional risk factors, for significantly worse prognosis in patients with MI, other forms of IHD, and HF. Depression's adverse effect on HF prognosis is independent of the baseline impairment in cardiac function and of the ischemic etiology of HF.

DEPRESSION AND MENTAL STRESS–INDUCED MYOCARDIAL ISCHEMIA

Of the numerous proposed pathophysiologic mechanisms explaining the adverse impact of depression on cardiac diseases, I would like to emphasize the clinical and research significance of mental stress–induced myocardial ischemia (MSIMI).

Myocardial ischemia is an important measure of the clinical manifestation of IHD. Ambulatory electrocardiographic monitoring yielded the insight that myocardial ischemia occurs frequently and transiently during daily living; it usually occurs in the context of a lower heart rate, is asymptomatic or silent, does not necessarily involve high-intensity physical activity, and commonly occurs in conjunction with increased negative emotions.[8,9]

Over the past 2 to 3 decades, several laboratories have consistently demonstrated that mental stress testing elicits myocardial ischemia in patients with

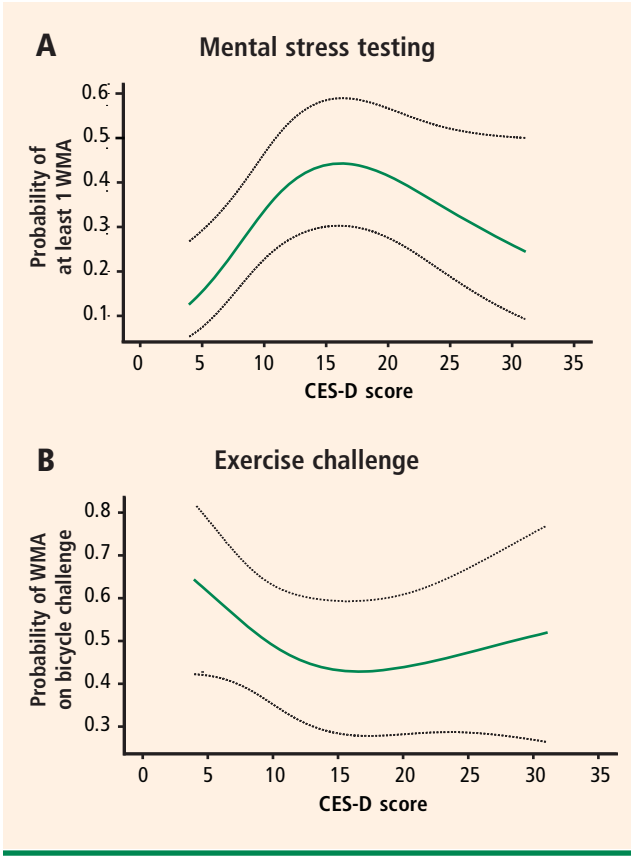

FIGURE 1. Association of myocardial ischemia (as indicated by wall motion abnormality [WMA]) and depressive symptoms (Center for Epidemiological Studies Depression Scale [CES-D] score), according to the source of ischemia, in a study of 135 patients with stable ischemic heart disease.[20] Solid green line represents the fitted probability of WMA; dotted lines are 95% confidence limits.

Adapted from *American Heart Journal* (Jiang W, et al. Depression and increased myocardial ischemic activity in patients with ischemic heart disease. Am Heart J 2003; 146:55–61.), copyright 2003, with permission from Elsevier.

documented IHD.[8,10,11] The prevalence of MSIMI, defined by wall motion abnormality and/or significantly reduced ejection fraction, is comparable to that of exercise-induced myocardial ischemia in the laboratory setting.[12]

Differences from exercise-induced ischemia

MSIMI differs from exercise-induced ischemia in several notable ways. It occurs silently most of the time and rarely results in ischemic electrocardiographic changes. Mental stress induces greater frequency and severity of left ventricular dysfunction. Furthermore, mental stress testing causes a greater diastolic blood pressure response but a modest increase in heart rate, whereas exercise testing elicits a smaller elevation in diastolic blood pressure but a several-fold increase in heart rate.

A key mechanism: Transient coronary vasoconstriction

One of the underlying mechanisms by which mental stress induces myocardial ischemia in susceptible patients is transient coronary vasoconstriction. Yeung et al[13] used an intracoronary Doppler catheter to assess the change in coronary blood flow during mental stress testing and endothelium-dependent vasodilation in a group of patients with IHD. Coronary artery responses varied from 38% constriction to 29% dilation, with changes in coronary blood flow ranging from a decrease of 48% to an increase of 42%. Interestingly, although it has been proposed that mental stress triggers release of catecholamines that induce coronary vasoconstriction, the direction and magnitude of the change were not predicted by changes in heart rate, blood pressure, or plasma norepinephrine level. The change in coronary perfusion was correlated, however, with the response to acetylcholine infusion.[13]

Dakak et al[14] showed that while the coronary microcirculation dilated during mental stress testing in individuals without IHD, it failed to dilate during such testing in IHD patients, a response that is likely mediated by alpha-adrenergic receptor activation. Furthermore, systemic vascular resistance has been found to increase significantly during mental stress and to be positively correlated with increases in plasma epinephrine.[15] In contrast, systemic vascular resistance was reduced significantly during exercise testing, and there was no relationship between the exercise-induced hemodynamic change and the plasma epinephrine level.[15] Compared with exercise-induced ischemia, epinephrine-induced ischemia (which may occur during emotional distress) is marked by smaller increases in heart rate and rate-pressure product and by a marked increase in contractility.[16]

MSIMI predicts cardiac events

From a prognostic standpoint, MSIMI consistently predicts an increase in future adverse cardiac events.[11,17–19] In a sample of 132 IHD patients with a recent positive exercise test,[11] MSIMI was associated with an increase in cardiac events during 5-year follow-up (OR = 2.8; 95% CI, 1.0 to 7.7; $P < .05$) independent of patients' age, history of prior MI, or baseline cardiac function. In contrast, exercise-induced ischemia was not predictive for adverse cardiac events (OR = 1.5; 95% CI, 0.6 to 3.9; $P = .39$) in this same sample.

Depression correlates with MSIMI occurrence

More relevant is the finding that depression is associated with the occurrence of MSIMI **(Figure 1)**. Following withdrawal of antianginal medication for at least 48 hours, we tested 135 patients with stable

IHD using the Center for Epidemiological Studies Depression Scale (CES-D) to evaluate for depressive symptoms and using radionuclide ventriculography to detect the occurrence of wall motion abnormalities during mental stress and exercise testing.[20] The mental stress tasks used in this study included mental arithmetic, public speaking, a mirror trace task, reading, and a type A videotaped structured interview.

The mean CES-D score was 8.2 (SD = 7.4; range, 0 to 47) and the median score was 7. Logistic regression models using restricted cubic splines revealed a curvilinear relation between CES-D scores and the probability of ischemia triggered by mental stress testing and exercise testing. For patients with CES-D scores less than or equal to 19 (81.5% of the study population), a 5-point increment in the CES-D score was associated with a roughly twofold increase in the likelihood of MSIMI **(Figure 1A)**. For patients with CES-D scores greater than 19, the relation between scores and ischemia during mental stress tended to be inverse **(Figure 1A)**, but these patients represented a small portion of the study sample (18.5%). In contrast, depression was not related to the occurrence of exercise-induced ischemia **(Figure 1B)**. This finding strongly indicates that MSIMI may be a significant mechanism by which depression increases the risk of mortality and morbidity in patients with IHD. A few patients in this study had severe depressive symptoms (CES-D scores > 19), which makes interpretation of the result very difficult. Because only 18.5% of the patients had CES-D scores greater than 19, this pattern of results needs to be confirmed in a sample with a greater representation of these more severely depressed patients.[20]

INSIGHTS FROM STUDIES OF DEPRESSION THERAPY IN CARDIAC PATIENTS

To date, six trials evaluating therapies targeting depression or depression-related problems in patients with cardiac diseases have been completed, and an additional trial is ongoing **(Table 1)**.

Among antidepressants, selective serotonin reuptake inhibitors (SSRIs) have been uniformly demonstrated to be effective in improving depressive symptoms and relatively safe for cardiac patients.[21–24] Not surprisingly, tricyclic antidepressants have been found to cause more cardiac problems.[21] Mirtazapine, a central nervous system alpha-2 antagonist, failed to improve depressive symptoms in depressed post-MI patients in the Myocardial Infarction and Depression Intervention Trial (MIND-IT),[25,26] but because the results from this study have been presented only in abstract form, more details will be necessary to gain insight into explanations for this failure.

Although psychotherapy has been found to be quite effective among depressed patients without other medical illnesses, its effectiveness among patients with cardiac disease has not been impressive to date **(Table 1)**.

No evidence of prognostic benefit from psychotherapy

Results from evaluations of psychotherapeutic interventions on cardiac prognosis have been rather disappointing **(Table 1)**. The Enhancing Recovery In Coronary Heart Disease Patients (ENRICHD) study,[27] which involved randomization of 2,481 post-MI patients with depression and/or low perceived social support to usual care or cognitive behavior therapy, failed to show an impact of cognitive behavior therapy on the combined end point of death or nonfatal MI. Similarly, the Montreal Heart Attack Readjustment Trial (M-HART)[28] failed to demonstrate a benefit from home-based psychosocial nursing intervention on cardiac prognosis in IHD patients. These studies suggested that psychotherapeutic intervention might have differing or even opposite effects on the two genders.

Potential prognostic benefit from antidepressant therapy

In theory, adequate treatment of depression could affect dysregulated physiologic factors as well as dysregulated psychosocial factors, thereby leading to improved cardiac outcomes. There is physiologic evidence to support beneficial pleiotropic effects of antidepressant medications in IHD, such as reduced platelet activity[29–31] and improvement in low heart rate variability[32–34] with both sertraline and paroxetine.

The MIND-IT study evaluated mirtazapine for post-MI depression using a randomized placebo-controlled design.[25] However, this trial failed to find a significant treatment effect for either depression or cardiac outcomes.[26] These results may have been related to a lack of statistical power, as only 209 treated patients were compared with 122 patients receiving usual care. This trial also raises the question whether any nontricyclic antidepressant (other than SSRIs) might have beneficial effects on cardiovascular outcomes, or whether such an effect might be limited to SSRIs alone.

Provocative results emerged from the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART),[23] a randomized, double-blind, placebo-controlled investigation of the safety and efficacy of sertraline for major depressive disorder among 369 patients with recent MI or unstable angina. Patients receiving sertraline had fewer cardiac events (death, MI, stroke, worsened angina, or onset of HF) compared with patients taking placebo. The relative risk

TABLE 1
Summary of clinical trials of depression therapy in patients with cardiac disease

Trial (yr)	Therapies	No. pts	Randomized	Treatment period	End points and results
Roose et al[21] and Nelson et al[22] (1998–99)	Nortriptyline vs paroxetine	81	Yes	6 wk	• Depression: both effective • Drug safety: nortriptyline toxic
SADHART (2002)[23]	Sertraline vs placebo	369	Yes	24 wk	• Depression: effective vs placebo • Safety: safe
CREATE (2007)[24]	Citalopram ± IPT	284	Yes	12 wk	• Depression: citalopram effective, IPT not effective
MIND-IT (2006)[25,26]	Mirtazapine vs placebo	331	Yes	24 wk	• Depression: no difference vs placebo • Prognosis: no difference vs placebo
ENRICHD (2001)[27]	CBT vs usual medical care	2,481	Yes	11 sessions over 6 mo	• Depression: CBT modestly effective • Prognosis: no difference vs usual care
M-HART (1997)[28]	Home nursing intervention (vs usual care) for psychological distress	1,376	Yes	1 yr	• Prognosis: no improvement compared with usual care
SADHART-CHF (ongoing)	Sertraline vs placebo	500	Yes	12 wk	• Depression: results pending • Prognosis: results pending

CBT = cognitive behavior therapy; **CREATE** = Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy; **ENRICHD** = Enhancing Recovery in Coronary Heart Disease Patients; **IPT** = interpersonal psychotherapy; **M-HART** = Montreal Heart Attack Readjustment Trial; **MIND-IT** = Myocardial Infarction and Depression Intervention Trial; **SADHART** = Sertraline Antidepressant Heart Attack Randomized Trial

ratio for having at least one cardiac event was 0.77 with sertraline therapy, but this reduction in risk was not statistically significant (95% CI, 0.51 to 1.16). Although these findings suggest that sertraline may improve cardiac outcomes, the study was not adequately powered to detect differences on this measure. Power calculations indicate that in order to confirm a 20% reduction in relative risk in a randomized trial, a sample of at least 4,000 depressed patients with acute coronary syndrome would be required.[23] Based on the cost of SADHART, the estimated expense to complete such a study is approximately $200 million.

The SADHART-CHF trial is a randomized, double-blind, placebo-controlled study examining sertraline's efficacy for major depressive disorder among patients with HF, as well as its effects on mortality and cardiac outcomes. This trial is in its last year of enrollment, and results will be forthcoming in 2008.

FUTURE DIRECTIONS

These recent insights into depression's impact on cardiac disease give rise to several new questions to consider:

- **Expand research to patients with depressive symptoms?** To date, investigations into treatment effects have focused only on patients with cardiac disease who have major depressive disorder. However, depressive symptoms as reported on self-administered questionnaires consistently have been shown to be a risk for poor cardiac outcomes. Should we expand our interventional studies to patients with self-reported depressive symptoms?
- **How thoroughly to test for differences among antidepressants?** Three of the six SSRIs have been studied among depressed cardiac patients. Based on the available findings, can we assume that all SSRIs have the same efficacy and safety profiles and are similarly cardiovascularly protective? Should every antidepressant or SSRI be tested? Should head-to-head comparison studies be conducted? Tricyclic antidepressants are cardiotoxic, and central nervous system alpha-2 antagonists like mirtazapine may not be effective, but what about other types of antidepressants for depressed cardiac patients?
- **Is there a role for studying surrogate end points?** Studies examining the effects of an intervention on mortality and/or morbidity can be very expensive. As research budgets tighten, can we instead test the effects of depression therapy on some surrogate end points?

Our laboratory has been funded by the National Heart, Lung, and Blood Institute to compare the effects

of escitalopram with those of placebo on MSIMI in patients with stable IHD and a score of 5 or greater on the Beck Depression Inventory. This study, the Responses of Myocardial Ischemia to Escitalopram Treatment (REMIT) trial, will provide SSRI therapy to patients with a broad spectrum of depressive symptoms (not just major depressive disorder), assess the ischemic activity induced by mental stress testing as its primary end point, and explore the effects on other hypothesized mechanisms of depression that adversely affect cardiac diseases (platelet aggregation, inflammatory biomarkers, etc). Stay tuned for the results in the near future.

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Inflammation as a link between brain injury and heart damage: The model of subarachnoid hemorrhage*

ABSTRACT

Subarachnoid hemorrhage (SAH) serves as a good model for the study of heart-brain interactions because it is associated with both a high incidence of arrhythmia and a low prevalence of coronary heart disease. The pathophysiology of cardiac abnormalities in SAH is unsettled. Initial theories focused on sustained stimulation of cardiomyocytes at sympathetic nerve endings, but recent data suggest that dysfunction of the parasympathetic nervous system may contribute as well. We believe that the coupling of catecholamine release with parasympathetic dysfunction may allow unchecked inflammation that leads to myocardial dysfunction and cell death. We have developed a novel murine model of SAH to explore these potential inflammatory underpinnings of cardiac damage in SAH.

Subarachnoid hemorrhage (SAH) involves the rupture of an aneurysm in the deep part of the brain, around the circle of Willis, which disperses blood not within the parenchyma but around the brain. Despite this absence of parenchymal interaction, SAH is more potentially damaging than almost any other bleeding syndrome in the brain. Because of its association with heart disease, SAH has been at the nexus of investigation into heart-brain connections for a long time. As early as the 1940s and 1950s, a high incidence of cardiac problems, particularly electrocardiographic (ECG) abnormalities, was described in patients with SAH, especially in those with aneurysmal SAH.

SAH serves as a good model for studying heart-brain interactions because it is associated with both a high incidence of arrhythmia and a low prevalence of coronary heart disease. In a review of five major retrospective studies involving intervention for nontraumatic SAH, Lanzino and colleagues found that 91% of patients had evidence of atrial or ventricular arrhythmias on ECG.[1] In a prospective study of 223 patients with SAH, Tung and colleagues found a low prevalence (5%) of preexisting cardiac disease.[2] This latter finding suggests that the cardiac findings in patients with SAH are a unique phenomenon likely attributable to SAH itself, and this scarcity of confounding cardiac factors makes SAH an ideal model for heart-brain investigations. This review will discuss cardiac responses to cerebral injury in SAH and then look ahead to the use of a novel murine model of SAH to further examine these responses and explore their potential inflammatory underpinnings.

CARDIAC RESPONSES TO CEREBRAL INJURY IN PATIENTS WITH SUBARACHNOID HEMORRHAGE

Cardiac arrhythmias

Cardiac arrhythmias associated with SAH are common and well classified. Sakr and colleagues found rhythm abnormalities in 30.2% of 106 patients with SAH and an abnormal ECG; the most common rhythm abnormality was sinus bradycardia (16%), followed by sinus tachycardia (8.5%) and other arrhythmias (5.7%), which included ventricular premature contraction, ventricular bigeminy, and atrial fibrillation.[3]

Multifocal ventricular tachycardia (torsades de pointes) is associated with a high mortality rate and is a feared complication of SAH, but its importance has been called into question recently. Although Machado and colleagues found in a review of the lit-

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erature that torsades de pointes occurred in 5 of 1,139 patients with SAH (0.4%), they were unable to rule out confounding factors (ie, hypokalemia and hypomagnesemia) as the cause of the arrhythmia.[4] In a supportive finding, van den Bergh et al reported that QT intervals in patients with SAH are actually shorter when serum magnesium levels are lower (prolonged intervals are thought to indicate elevated risk for multifocal ventricular tachycardia).[5] Although it is clear that patients with SAH frequently have a prolonged QT interval (discussed later), which is thought to be a risk factor for torsades de pointes, the electrolyte abnormalities seen in patients with SAH make it hard to definitively attribute the arrhythmia to the direct action of the brain.

Cardiac changes that resemble ischemia

Certain ECG changes seen in patients with SAH are referred to as ischemic changes because of their resemblance to ECG changes seen in acute coronary artery occlusion. In SAH, there is evidence that acute coronary artery occlusion is not present. The myocardial changes are assumed to be due to subendocardial ischemia. ECG abnormalities usually disappear within a few days or without resolution of the neurologic or cardiac condition. They are considered markers of the severity of SAH but not predictors for potentially serious cardiac complications or clinical outcomes.[5]

Repolarization abnormalities, also commonly seen in coronary artery ischemic disease, are common in SAH. Sakr et al found that 83% of patients with SAH developed repolarization abnormalities, with the most common being T-wave changes (39%) and the presence of U waves (26%).[3] Deep, symmetric inverted T waves, usually without much ST-segment elevation or depression, are the typical abnormality. Left bundle branch block, which is sometimes considered a marker of acute, large-vessel ischemia, was present in only 2% of patients.[3]

Prolonged QT intervals were found in 34% of patients in the study by Sakr et al.[3] The presence of this prolonged segment has become the most looked-for clinical tool for determining who might be at risk for cardiomyopathy. Although there is little evidence that the cardiomyopathy seen after SAH is associated closely with prolongation of the QT interval, it is a simple bedside sign that is readily available to all practitioners, given the practice of obtaining an ECG in almost all hospitalized patients at the time of admission.

In older patients with SAH, ECG changes occur with more severe events. In a retrospective study, Zaroff et al identified 439 patients with SAH, 58 of whom had ECG findings indicative of ischemia or myocardial infarction within 3 days of presentation and before surgery to correct an aneurysm.[6] The most common ECG abnormality was T-wave inversions; the next most common abnormalities were ST depression, ST elevation, and Q waves of unknown duration. The most common pattern for ECG abnormalities suggests abnormalities in the anterior descending artery territory or in multiple vascular territories. Follow-up tracings demonstrating reversal of the abnormalities were available for 23 of the 58 patients (40%). There was no significant association between any specific ECG abnormality and mortality. Compared with patients with negative ECG findings, the patients with positive ECG findings were significantly older (mean age, 62 ± 15 years vs 53 ± 14 years), had a higher mean Hunt and Hess grade, and had higher all-cause mortality. Surprisingly, aneurysm location did not differ significantly between the two groups. These data suggest that coronary artery disease (which would be more common in the older population) may be a contributing factor to mortality.

CARDIOMYOPATHY

Regional or focal wall-motion abnormalities on echocardiogram have been observed in some patients with SAH, as have increased levels of creatine kinase, MB fraction (CK-MB). These findings often raise concern about ongoing cardiac ischemia from coronary artery disease and may cause treatment to be delayed. In our experience, patients who have undergone cardiac catheterization for this syndrome have been found not have coronary artery disease as the cause of their cardiac muscle damage.

There is a common misperception among trainees at our institution that patients who have coronary artery disease with neurologic causes do not have elevations in cardiac enzymes. This turns out not to be the case. Cardiac troponin I (cTnI) has been shown to be a more sensitive and specific marker for cardiac dysfunction in patients with SAH than is CK-MB.

In a study of 43 patients with SAH and no known coronary artery disease, Deibert et al found that 12 patients (28%) had elevated cTnI.[7] Abnormal left ventricular function was apparent on echocardiogram in 7 of these 12 patients. cTnI proved to be 100% sensitive and 86% specific for detecting left ventricular dysfunction in patients with SAH in this study, whereas CK-MB was only 29% sensitive and 100% specific. Notably, all patients in whom left ventricular dysfunction developed returned to baseline func-

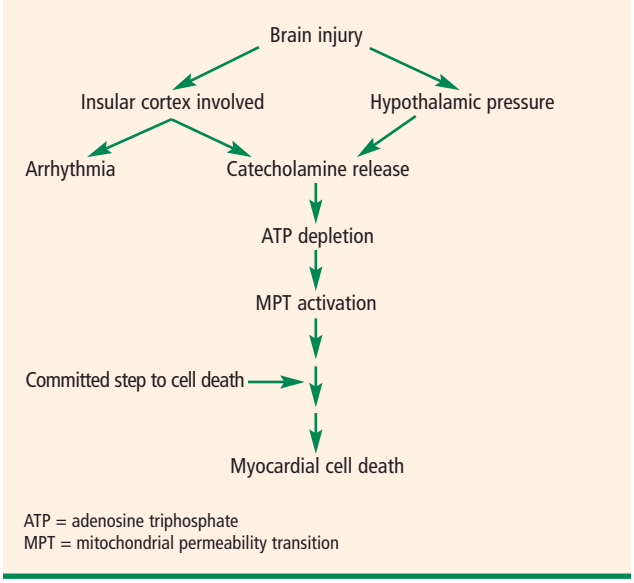

FIGURE 1. Schematic diagram of the possible mechanism of myocardial injury after acute brain injury. The theory suggests that catecholamine excess leads to myocardial death through a cascade of cellular damage. Insular cortical dysfunction likely contributes to arrhythmias. Adapted from reference 15.

tion on follow-up studies.

Similarly, Parekh et al found that cTnI is elevated in 20% of patients with SAH and that these patients are more likely to manifest echocardiographic and clinical evidence of left ventricular dysfunction.[8] Patients with more severe grades of SAH in this study were more likely to develop an elevated level of serum cTnI.

PATHOPHYSIOLOGY OF CARDIAC DYSFUNCTION IN SUBARACHNOID HEMORRHAGE

The pathophysiology of cardiac abnormalities in SAH is unsettled; one hypothesis that has support from human and experimental data proposes that sustained sympathetic stimulation of cardiomyocytes at the sympathetic nerve endings results in prolonged contraction and structural damage to the myocardium.[5] Contraction band necrosis, a pathological pattern indicating that injury to the heart has occurred from muscles that have been energy-deprived from prolonged contraction, is a classic finding in autopsy specimens from patients with SAH. Transient low ejection fraction is the physiologic parameter that correlates with this pathologic finding.

A model has been proposed for how SAH can cause cardiac damage. Brain injury can damage the insular cortex of the cerebral hemisphere or cause hypothalamic pressure, either of which causes catecholamine release at the nerve terminal at the cardiac myocyte. As the heart muscles contract, adenosine triphosphate (ATP) is depleted, mitochondria malfunction, and there is ensuing myocardial cell death **(Figure 1)**. However, some studies have reported no correlation between concentrations of plasma catecholamine and ECG abnormalities, which suggests a more complicated pathophysiology.[9]

We recently presented an interesting finding that may suggest complementary mechanisms of cardiac dysfunction.[10] Twenty-nine consecutive patients with SAH and no record of preexisting coronary artery disease were enrolled in a study of ECG abnormalities in SAH at Alexandria University Hospitals in Egypt. Each patient had ECGs during the preoperative period, during surgery, and during the first 3 days of postoperative treatment. We found that patients who had ECG abnormalities that fluctuated over the course of their early treatment had worse outcomes. This finding suggests that part of the mechanism of cardiac damage may occur later than the initial ictus.

The area that our laboratory has actively pursued is the interaction between the sympathetic nervous system, the parasympathetic nervous system, and inflammation in cardiac damage after SAH. There are reasons to believe that dysfunction of the parasympathetic system may be involved in the pathology of cardiac damage. The next section explains the underpinnings of why we believe this avenue of research needs to be explored.

ROLE OF VAGAL ACTIVITY AND INFLAMMATION

In the body, the sympathetic and parasympathetic systems work as the yin and yang in controlling many bodily functions. Rate and rhythm control of the heart is the prime example. Until relatively recently, the cardiac muscle was thought to be innervated predominantly by the sympathetic system, with the parasympathetic system largely innervating the conduction system. Fibers from the vagus nerve are now known to innervate the myocardium and therefore may play a role in the cardiac damage in SAH.

The role of the vagal system in inflammation is described elsewhere in this proceedings supplement. Briefly, there exists a recent body of research on the role of the vagal system in modulating the inflammatory system through acetylcholine receptors.[11] The "neuorinflammatory reflex" (a term coined by Tracey[11]) is a vagally mediated phenomenon that may relate to parasympathetic nervous system activation (debate continues over whether this is a parasympathetic function or a function of the vagus nerve that is not autonomic) that suppresses inflammation.

Evidence of parasympathetic dysfunction in SAH

is becoming more abundant. Kawahara et al measured heart rate variability in patients with acute SAH and determined that enhanced parasympathetic activity occurs acutely.[9] This acute activation could potentially contribute to ECG abnormalities and cardiac injury. In addition, the parasympathetic response may also affect the inflammatory response. It has long been known that cardiomyopathy in patients with SAH and other brain traumas is accompanied by inflammation. It is unclear whether the neutrophil infiltration seen in this cardiac damage is due to the primary response from the brain (and therefore possibly contributory) or is in reaction to the cardiac damage.

Evidence from the transplant literature

Support for the role of inflammation in cardiac damage following SAH comes from the cardiac transplant literature. Data indicate that the cause of death in an organ donor has an impact on the organ recipient's course of transplantation. Tsai et al compared outcomes among 251 transplant recipients who received hearts from donors who died of atraumatic intracranial bleeding (group 1; n = 80) or from donors who died of other causes (group 2; n = 171).[12] They found that mortality among transplant recipients was higher in group 1 (14%) than in group 2 (5%).

Yamani et al performed cardiac biopsies 1 week after transplantation and then performed serial coronary intravascular ultrasonography over 1 year in 40 patients, half of whom received hearts from donors who died from intracerebral hemorrhage (ICH) and half from donors who died from trauma.[13] At 1 week, heart biopsies from the ICH group showed greater expression of matrix metalloproteinases, enzymes that are responsible for matrix remodeling and associated with proinflammatory states, compared with biopsies from the trauma group. The injury in the ICH group translated to an increase in vasculopathy and myocardial fibrosis. At 1 year, hearts from donors who died of trauma had much less fibrosis and less progression of coronary vasculopathy (as measured by change in maximal intimal thickness on intravascular ultrasonography) than did hearts from donors who died from ICH, even after correction for differences in age.

Yamani et al also found that mRNA expression of angiotensin II type 1 receptor (AT1R), which is upregulated during acute inflammation, was elevated 4.7-fold in biopsies of transplanted hearts from the donors who died of ICH compared with the donors who died of trauma.[14] There was likewise a 2.6-fold increase in AT1R mRNA expression in spleen lymphocytes from donors who died of ICH compared with donors who died from trauma, indicating that systemic activation of inflammation occurred *before* transplantation.[14] AT1R mRNA expression has also been found to be seven times greater in the cerebrospinal fluid of patients with SAH than in a control population (unpublished data). The fact that upregulation of an inflammatory mediator in the heart of transplant recipients is associated with ICH suggests that there is a potential for the cerebral injury–induced inflammation seen in Tracey's sepsis model[11] to affect the heart in a setting other than sepsis.

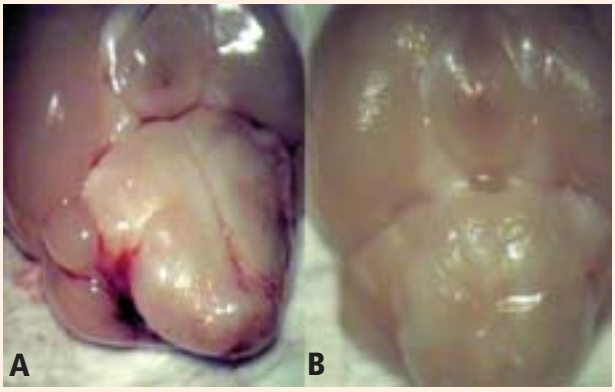

FIGURE 2. Development of subarachnoid hemorrhage in the mouse. **Panel A** shows the ventral view of the brain of an animal with a subarachnoid hemorrhage; note the blood in the pontocerebellar angle. **Panel B** shows an animal given a saline injection to the subarachnoid space.

A MODEL FOR SUBARACHNOID HEMORRHAGE

A murine model of SAH offers a number of advantages for studying the inflammatory underpinnings of cardiomyopathy. First, many of the immunological reagents needed to evaluate this problem are more easily available in mouse than in other species. Second, there are genetic manipulations of the inflammatory system that are more readily possible in mouse than in other species. Finally, at our institution, we have normative echocardiographic data that are better developed in the mouse than in other species.

We are in the process of developing a murine model of SAH and characterizing the cardiac effects. Our hope is that this model will allow us to investigate the mechanism of cardiac damage in SAH. Our preliminary work shows that we can develop consistent SAH in mice with low mortality **(Figure 2)**.

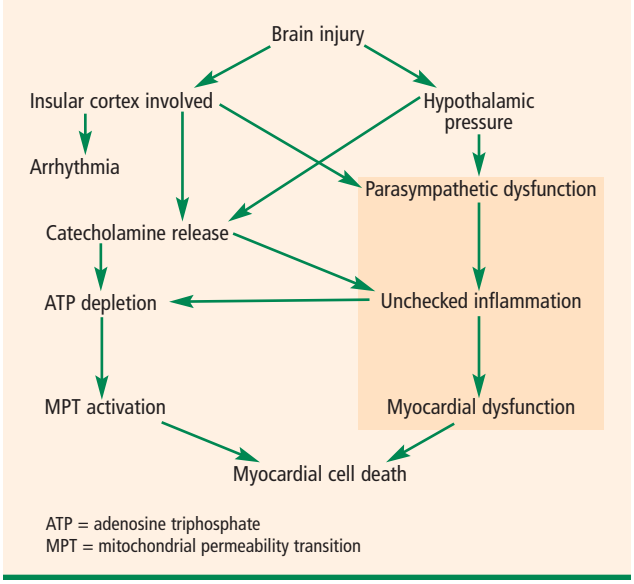

FIGURE 3. A new model of heart-brain interaction based on combined sympathetic hyperactivity and parasympathetic dysfunction (shaded area).

A NEW MODEL FOR BRAIN-HEART INTERACTION

Recent data have prompted us to rethink the previous model of the mechanisms of cardiac injury from SAH. We believe that parasympathetic dysfunction may also play a role and, coupled with catecholamine release, may allow unchecked inflammation, which leads to myocardial dysfunction and cell death **(Figure 3)**.

We hope that with better understanding of these two processes—ie, parasympathetic dysfunction and catecholamine release—we will be able to mitigate harm to the heart. If agents can be found that suppress sympathetic activation or heighten parasympathetic activation, it might be possible to improve outcomes in patients with SAH. This line of research will likely shape future efforts to further understand the pathophysiology of cardiac damage after brain injury and identify targets for clinical intervention.

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Biofeedback: An overview in the context of heart-brain medicine

ABSTRACT

Biofeedback involves the monitoring and use of physiologic information to teach patients to modify specific physiologic functions. Common modalities for biofeedback include surface electromyography, respiration rate and depth, skin surface temperature, cardiovascular reactivity, and electrodermal response. Clinical biofeedback therapy broadly involves either the direct feedback learning model or the therapeutic/stress-management/biofeedback model, which emphasizes the need to understand each patient as an individual. Biofeedback interventions have been deemed efficacious or probably efficacious in treating a number of medical disorders, and are increasingly embraced by the public as well as by health care providers and payors.

Clinical biofeedback therapy is one of the many new approaches in health care aimed at helping individuals take responsibility for their well-being, including responsibility for the cognitive, emotional, and behavioral changes needed to effect healthy physiologic change. This article provides a brief survey of biofeedback therapy by defining what biofeedback involves, reviewing the various modalities that it can serve to monitor, discussing major models of biofeedback therapy, and outlining criteria for evaluating the efficacy of biofeedback interventions.

BIOFEEDBACK: BOTH PROCESS AND INSTRUMENTATION

Biofeedback refers to both a process and the instrumentation used in that process.

The process is one of learning to use physiologic information that is monitored and "fed back" through biofeedback instruments. The term dates from 1969, when it was coined to describe laboratory procedures that had been developed in the 1940s in which research subjects learned to modify heart rate, blood flow, and other physiologic functions that were not normally thought of as being subject to conscious control. Feedback itself has been present through much of human history, particularly through the use of mirrored surfaces to practice the expression of emotion.[1]

Biofeedback instruments monitor one or more physiologic processes, measure what is monitored and transform that measurement into auditory and/or visual signals, and present what is monitored and measured in a simple, direct, and immediate way. Biofeedback equipment typically is noninvasive. The instruments provide continuous monitoring and transformation of physiologic data into understandable feedback for the patient being monitored. Current computerized instruments can provide simultaneous displays and recording of multiple channels of physiologic information. The goal is to enable the individual being monitored to change some physiologic process, guided by the information provided by the biofeedback equipment. How many training sessions are necessary varies with the individual and the disorder, ranging from a few to 50 or more. Our experience is that the great majority of patients obtain benefit in 8 to 12 sessions.

MULTIPLE MODALITIES FOR MONITORING

Multiple modalities can be monitored via biofeedback. Surface electromyography is perhaps the most commonly used instrumentation. Other commonly used measures in a psychophysiologic/biofeedback assessment are respiration rate and depth, skin surface temperature (particularly at the fingertips), cardiovascular reactivity (particularly heart rate and blood pressure), and electrodermal response.[2]

Feedback of real-time physiologic data is limited only by one's creativity and technological capabilities. Most of the early noncomputerized equipment provided feedback through the onset and offset of

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

sounds, the changing of tones and volume, the turning on and off of lights, and digital numeric displays indicating both the direction of change and absolute values (such as digital peripheral temperature). Current computerized equipment uses such feedback features as computer games, which the patient "wins" by reaching a goal (such as a systolic blood pressure level below 130 mm Hg), mandalas that can be filled in with colors of the patient's choosing as he or she progresses in the desired direction, and complex computer-generated figures and graphs.

Electroencephalographic biofeedback (neurofeedback) has become a separate area of study and application, with particular use in the treatment of attention deficit disorder. A baseline electroencephalogram is used in neurofeedback assessment to identify abnormal patterns, and follow-up training is provided to teach the patient to change these patterns in a healthy direction.[3]

More recently, heart rate variability has come into use as a measure of adaptability or autonomic balance. Soviet scientists were the first to study heart rate variability biofeedback, working with cosmonauts in measuring autonomic function. They found that the low-frequency (0.1-Hz) bands produced the highest frequency-specific oscillations in heart rate variability, and training typically proceeds in increasing amplitude of the low-frequency band (also called the baroreceptor band). Because diminished heart rate variability is a predictor of increased risk for cardiac mortality, teaching patients to increase heart rate variability made sense. The training involves instruction in breathing at an identified resonant frequency that is related to optimal low-frequency band power.[4]

LEARNING AND MODELS OF BIOFEEDBACK

Accurate feedback facilitates the learning of any skill, whether it be sinking a golf putt, solving an algebra problem, or controlling physiologic behavior. A man playing darts blindfolded is unlikely to achieve as good a score as he would with the blindfold off, because feedback makes a difference.[5]

Four conditions are important for effective learning;[5] the learner must:

- Have the capacity to respond
- Be motivated to learn
- Be positively reinforced for learning
- Be given accurate information about the results of the learning effort.

Direct feedback learning model

The direct feedback learning model assumes that adding feedback to the other important conditions of learning will result in a patient gaining control of the relevant physiology being targeted. This model has been used in treating many disorders, including Raynaud phenomenon and urinary and fecal incontinence.

Biofeedback training in this model may involve a coach/instructor/therapist only to the extent of explaining the equipment and its use. In other words, the coach "teaches the patient how to use the mirror." More commonly—particularly for training in lowered arousal for patients in whom stress reactivity is a significant factor in the development and maintenance of excessive (sympathetic nervous system) arousal that leads to symptoms—a skilled therapist is present. The therapist not only teaches the patient how to use information from biofeedback instruments but also guides the patient in identifying and changing cognitive, emotional, and behavioral patterns that contribute to excessive reactivity. The relationship of physiologic reactivity to the subject matter under discussion also helps diagnostically in identifying stressful areas of life, particularly in psychophysiologic responders who are repressive and denying and who are not good at identifying the stressors in their lives. The equipment becomes a mirror that lets the patient see a problem that he or she had not identified as such.[5]

Therapeutic/stress-management/biofeedback model

When treating patients with disordered physiology (including autonomic imbalance) in the therapeutic/stress-management/biofeedback model, it is essential to understand each patient as an individual. In this model, stress management and psychotherapeutic interventions address particular vulnerabilities that lead to excessive arousal. This approach starts with a psychophysiologic assessment in which resting levels of relevant physiologic dimensions are measured; this is followed by imposition of stressors to measure reactivity and then by a recovery period in which rate and extent of recovery are measured. An interview and psychological test help determine which cognitive, emotional and behavioral patterns contribute to vulnerability. Patients typically respond well to this approach. It is common for patients to use such descriptions as, "I break out in a cold sweat when I'm stressed," or "I feel heartsick when I'm stressed," which suggests that the notion of mind-body interaction resonates with patients.[6]

The complexity of biofeedback-assisted psychotherapeutic stress-management training is high. Content analyses of patient–therapist interactions suggest at least a dozen possible different processes operating, as detailed in **Table 1**.[6]

CRITERIA FOR EVALUATING EFFICACY OF BIOFEEDBACK INTERVENTIONS

Several years ago a task force of the Association for Applied Psychophysiology and Biofeedback and the Society for Neuronal Regulation published criteria for evaluating the clinical efficacy of biofeedback/psychophysiologic interventions.[7] These criteria are detailed below.[3,7]

Level 1: Not empirically supported

This designation applies to interventions supported only by anecdotal reports and/or case studies in non–peer-reviewed venues (ie, not empirically supported).

Level 2: Possibly efficacious

This applies to interventions supported by at least one study of sufficient statistical power with well-identified outcome measures but which lacked randomized assignment to a control condition internal to the study.

Level 3: Probably efficacious

This applies to interventions supported by multiple observational studies, clinical studies, wait-list–controlled studies, and within-subject and intrasubject replication studies that demonstrate efficacy.

Level 4: Efficacious

a. In a comparison with a no-treatment control group, alternative treatment group, or sham (placebo) control using randomized assignment, the intervention is shown to be statistically significantly superior to the control condition, or the intervention is equivalent to a treatment of established efficacy in a study with sufficient power to detect moderate differences, *and*
b. The studies have been conducted with a population treated for a specific problem, for whom inclusion criteria are delineated in a reliable, operationally defined manner, *and*
c. The study used valid and clearly specified outcome measures related to the problem being treated, *and*
d. The data were subjected to appropriate data analysis, *and*
e. The diagnostic and treatment variables and procedures were clearly defined in a manner that permits replication of the study by independent researchers, *and*
f. The superiority or equivalence of the intervention has been shown in at least two independent research settings.

Level 5: Efficacious and specific

This designation applies when the intervention has been shown to be superior to credible sham therapy, pill therapy, or alternative bona fide treatment in at least two independent research settings.

TABLE 1
Processes potentially at work during biofeedback-assisted psychotherapeutic stress management[6]

1. Operant conditioning, with success in changing physiology representing immediate positive reinforcement.
2. Feedback learning, with the biofeedback equipment representing imposition of an external psychophysiologic feedback loop upon already existing internal feedback loops.
3. Feedback learning, with the biofeedback equipment affecting general arousal through impact on already existing feedback loops of the homeostatic adaptive control systems.
4. Learning the relaxation response via imagery and cognitive exercises.
5. Modifying assumptions, attitudes, and expectations that lead to psychophysiologic stress reactions.
6. Enhancing self-awareness in general, including awareness of bodily functioning, by getting specific information about bodily functioning and experimenting with the relationship of physiologic functioning to thought patterns.
7. Resolving conflicts by discussing them with a therapist, thus reducing self-generated stressors leading to psychophysiologic reactions.
8. Responding to hypnotic suggestion of greater well-being while in an altered state of consciousness induced by narrowing of attention.
9. Faith healing, with belief in the process being a curative agent leading to placebo healing.
10. Changing behavior to reduce stressors, in response to specific counseling of the therapist.
11. Experiencing an increase in self-esteem secondary to warmth, genuineness, and empathy of the therapist, thereby reducing stress.
12. Emulating a relaxed therapist who is not upset thinking about and discussing emotionally laden topics.
13. Articulating values and shifting them to enable attitudinal, behavioral, and emotional change.
14. A cathartic re-experiencing and emotional release that reduces stress.
15. Changing the locus of control so that the patient takes greater responsibility for his or her own well-being.

Adapted, with permission, from SLACK Incorporated: McKee MG (1978). Using biofeedback and self-control techniques to prevent heart attacks. Psychiatric Annals, 8(10), 92–99.

Efficacy ratings for specific disorders

In their recent text on biofeedback and neurofeedback, Yucha and Gilbert[3] rated the available evi-

TABLE 2
Efficacy ratings for biofeedback interventions in various medical conditions*

Level 5: Efficacious and specific
Urinary incontinence in females[8]

Level 4: Efficacious
Anxiety[9]
Attention deficit disorder[10]
Headache (adult)[11]
Hypertension[12]
Temporomandibular disorders[13]
Urinary incontinence in males[14]

Level 3: Probably efficacious
Alcoholism/substance abuse[15]
Arthritis[16]
Chronic pain[17]
Epilepsy[18]
Fecal elimination disorders[19]
Headache (pediatric migraine)[20]
Insomnia[21]
Traumatic brain injury[22]
Vulvar vestibulitis[23]

*Ratings are by Yucha and Gilbert[3] based on data from the cited references.

dence on the efficacy of biofeedback interventions in various diseases and conditions according to the above efficacy criteria. **Table 2** lists the disorders that met the three most stringent levels of evidence.[3]

Despite high standards, biofeedback thrives

The above criteria represent high standards. Since biofeedback training is often more like physical therapy or learning a language, double-blind protocols usually are not feasible, nor is sham training. Moreover, the effectiveness of training is perhaps even more difficult to assess in daily practice, with the inevitable multiplicity of confounding variables. Nevertheless, biofeedback training for many disorders is standing the test of both time and outcomes research, and it is increasingly embraced by the public and recognized by health care insurers and professionals alike.

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Biofeedback therapy in cardiovascular disease: Rationale and research overview

ABSTRACT

Biofeedback has much therapeutic potential in cardiovascular diseases, since many of these diseases involve dysregulation of the autonomic nervous system. Studies have clearly demonstrated that patients can use biofeedback techniques to regulate the input of the autonomic nervous system to the heart, but the clinical utility of these techniques has not been well explored in systematic trials. Much biofeedback research to date has focused on patients with hypertension, but outcomes have been inconclusive. Preliminary studies suggest that heart rate variability biofeedback may be useful in improving symptoms and quality of life in patients with cardiac disease, and early studies suggest a possible effect of biofeedback on remodeling of the failing heart. Both of these areas require further research, however. Biofeedback is increasingly used as an adjunct to stress management in cardiac rehabilitation programs, providing the impetus for a large-scale, systematic study of self-regulation in cardiac disease.

The potential of biofeedback therapies in cardiovascular disease is only recently beginning to be explored in a systematic way. This article reviews the rationale for the use of biofeedback therapy in cardiovascular disease and briefly surveys research on the usefulness of biofeedback for several specific cardiovascular parameters and conditions.

RECOGNIZING THE POTENTIAL OF BIOFEEDBACK IN CARDIOVASCULAR DISEASE

Biofeedback is part of a group of modalities known as "self-regulation therapies," in which a subject is taught to control the activities of his or her autonomic nervous system. The autonomic nervous system has also been called the "visceral," "involuntary," and "automatic" nervous system, which suggests that the physiologic processes governed by this branch of the nervous system are largely beyond conscious control. Until the 1950s, this was largely believed to be true. Physicians and scientists had been convinced that the functions regulated by the sympathetic and parasympathetic branches of the autonomic nervous system, such as digestion, blood pressure, and body temperature, were not amenable to self-regulation.

During the 1950s, however, it became clear that functions of the autonomic nervous system could be controlled by conscious thought and training. Subjects could be taught to correctly perceive and also to control heart rate, blood pressure, skin temperature, and other seemingly involuntary functions. The field of biofeedback and applied psychophysiology became possible with these discoveries and with the advent of technologies capable of measuring physiologic variables with enough sensitivity to detect small changes.

Key role of sympathetic/parasympathetic balance

In cardiovascular medicine, biofeedback has a great deal of therapeutic potential because many diseases of the heart and vasculature involve inappropriate regulation of the autonomic nervous system.

Under normal conditions, the sympathetic branch of the autonomic nervous system serves to augment cardiac function in times of stress, increasing heart rate, contractility, and blood pressure, as well as favoring clotting processes that would be mainly adaptive during the "fight or flight" response. The parasympathetic branch of the autonomic nervous system plays the opposite role during health, exerting a calming influence on cardiovascular function.

Normal cardiovascular function is regulated by a balance between sympathetic and parasympathetic inputs to the heart and blood vessels. Heart rate, for example, is governed by the parasympathetic nervous system under resting conditions, when the intrinsic firing rate of the sinus node is decreased by vagal

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

input. Under stressful conditions, this inhibition is released and sympathetic excitation can increase the heart rate even further. In many pathological cardiac conditions, such as arrhythmias, an imbalance between the two branches of the autonomic nervous system causes at least some of the disease manifestations and often contributes to progression.

Biofeedback as a 'physiologic beta-blocker'

Another good example is heart failure, where overactivation of the sympathetic nervous system results in many of the phenotypic changes in the myocardium and contributes to the downward spiral from compensatory cardiac hypertrophy to end-stage decompensated failure. The role of sympathetic overactivation in heart failure is clearly evident by the success of beta-adrenergic blocking agents in ameliorating symptoms and delaying disease progression. Given the role of autonomic nervous system dysregulation in cardiovascular diseases, biofeedback therapy has the potential to teach patients a skill that may allow them to decrease activation of their autonomic nervous system, theoretically acting as a "physiologic beta-blocker."

An adjunct to stress management

The potential of biofeedback to have an impact in the arena of cardiovascular disease has not been well explored. Clinically, biofeedback is often used in the context of stress management programs, but biofeedback is not synonymous with stress management. Stress management programs most commonly involve some type of relaxation training and perhaps cognitive behavioral therapy. Biofeedback can be used to augment relaxation, helping the subject to be more aware of physiologic responses and thus be better able to elicit the relaxation response. Biofeedback can also be used to train subjects to control particular physiologic responses that contribute to symptoms or to disease progression. In cardiovascular disease, although stress management is frequently a component of cardiac rehabilitation programs, the question of whether stress management is more effective with or without biofeedback has not been systematically investigated.

PIONEERING STUDIES OF BIOFEEDBACK IN CARDIOVASCULAR DISEASE

Some of the earliest studies of physiologic regulation using biofeedback were attempted in patients with cardiovascular abnormalities. In 1971, Weiss and Engel reported success in using operant conditioning of heart rate in eight patients with premature ventricular contractions.[1] All eight patients were able to achieve some degree of control, and five of the patients were able to decrease the frequency of premature beats, demonstrating increased success over a 21-month follow-up period. Interestingly, use of pharmacologic agents to understand the mechanisms of control suggested that one patient was able to decrease sympathetic control of his heart rate while another increased the parasympathetic influence.

Several years later, Pickering and Gorham reported their work with a single subject, a 31-year-old woman who had a ventricular parasystolic rhythm.[2] Using a biofeedback technique, they were able to teach the woman to voluntarily control her heart rate, demonstrating that she could both increase and decrease the rate, avoiding the ranges in which the arrhythmia occurred. In the same year, Benson et al demonstrated that they could teach patients the relaxation response and decrease the incidence of premature ventricular contractions.[3] Using Holter monitors for validation, these investigators showed that 4 weeks of relaxation training resulted in 8 of 11 patients being able to control their heart rates sufficiently to have therapeutic impact.

These pioneering studies were very early in the development of the field of biofeedback, but they showed what has been clearly established since—that the input of the autonomic nervous system to the heart can be regulated by biofeedback techniques.

BIOFEEDBACK STUDIES OF SPECIFIC CARDIOVASCULAR PARAMETERS AND DISEASES

A host of parameters for assessment

Many cardiovascular parameters can be used for biofeedback. Commonly these include heart rate, blood pressure, skin temperature, and, more recently, heart rate variability. In each case, the parameter is measured and displayed for the subject, and the subject is taught to make it change in a positive direction through relaxation, thought patterns, imagery, or some combination of techniques. Many times the display of the physiologic parameter and the demonstration that it can be controlled are quite surprising to the subject and lead to an enhanced desire to participate in the therapy.

Heart rate variability: A focus of recent interest

The newest parameter in use, and one that has gained considerable interest in the field of cardiovascular biofeedback, is heart rate variability.[4] Heart rate variability refers to the variation within the R-R interval of the electrocardiogram during a fixed cycle. It is associated with adaptiveness of the cardiovascular system, and high variability is believed to be a sign of

health. Low variability is associated with a number of disease states. Heart rate variability reflects the balance between sympathetic and parasympathetic input to the heart, and many cardiac disease states have been shown to be associated with low variability. Therapies that increase heart rate variability have been shown to improve prognosis.

On the basis of these observations, heart rate variability biofeedback is used to train patients to increase the variability in their heart rate, using feedback from equipment that records the R-R interval from the electrocardiogram or from blood pulse volume sensors. Patients learn to make the variability greater, primarily by breathing at a resonant frequency, as described by Lehrer et al.[5]

Several preliminary studies have been conducted with heart rate variability in cardiac patients, but much remains to be understood about its use. In 63 patients with established coronary artery disease, Del Pozo et al showed that six biofeedback sessions coupled with daily practice resulted in significantly increased heart rate variability.[6] Similarly, Nolan and colleagues found that five sessions of biofeedback improved symptoms and quality of life in 46 patients with coronary artery disease.[7] In 14 patients with heart failure, Luskin et al demonstrated that eight sessions of heart rate variability biofeedback produced reductions in perceived stress and improved function on the 6-minute walk test.[8]

It remains unclear whether heart rate variability biofeedback has more or less potential than other types of biofeedback in patients with cardiovascular disease, but these preliminary observations suggest that it may be useful in improving symptoms and quality of life.

Biofeedback in hypertension: Despite decades of study, conclusions elusive

Among diseases of the cardiovascular system, biofeedback has been used most frequently in hypertension, where it has been under investigation for more than 30 years, since the early days of biofeedback study.[9] The field of biofeedback in hypertension is fraught with difficulties, rendering conclusions about its efficacy difficult.

Biofeedback has been assessed in many different types of hypertension, often within the same study. Essential hypertension and "white coat" hypertension, now known as excessive cardiovascular reactivity, have been most commonly investigated, but with no apparent consensus. The biofeedback techniques used in these studies have ranged from blood pressure biofeedback to electromyography, finger temperature, and skin conductance. More recently, heart rate variability biofeedback has also been used in this population.

In general, biofeedback has been more successful in the treatment of hypertension when respiratory training has been a component of the biofeedback. McGrady has established that certain types of patients with hypertension fare better with biofeedback than others.[10] These include patients with higher baseline blood pressure, higher heart rate, cool hands, high electromyographic response, and high plasma renin activity—in short, patients who can be seen to have a high degree of sympathetic arousal.

Blood pressure can be lowered by 6 to 10 mm Hg when biofeedback is effective, which is less of an effect than that observed with most drug therapy for hypertension. Biofeedback does have the advantage, however, of improving overall cardiovascular reactivity and giving the patient a greater sense of control over his or her physical well-being, which may prove valuable in the setting of hypertension. Typically, the most effective interventions for hypertension (and perhaps for cardiovascular disease in general) are individualized for the patient and not protocol-driven. Thus, although biofeedback has potential in hypertension, its efficacy is not proven and systematic trials are lacking.

Biofeedback in heart failure: Targeting sympathetic overactivation

In patients with heart failure, the sympathetic nervous system is overactivated, as noted previously. High levels of plasma norepinephrine correlate with worse prognosis. Decreasing activation of the sympathetic nervous system improves both symptoms and prognosis, as demonstrated in patients taking beta-adrenergic blocking agents or those treated with a left ventricular assist device.

Several studies have suggested that biofeedback may be able to provide a similar reduction in sympathetic nervous system activation in patients with heart failure. Moser and colleagues showed that a single session of skin temperature biofeedback plus relaxation training increased cardiac output in patients with heart failure,[11] while studies by Weiner et al,[12] Bernardi et al,[13] and Mangin et al[14] showed that training heart failure patients to breathe more slowly increased their exercise tolerance. Although these studies are preliminary, they support the speculation that if biofeedback can decrease activation of the sympathetic nervous system in patients with heart failure, it may actually cause some degree of remodeling of the failing heart, such as that observed with beta-blockers or left ventricular assist device therapy.

BIOFEEDBACK AND STRESS MANAGEMENT: AN OPPORTUNITY FOR WIDER IMPACT

As mentioned earlier, biofeedback can serve as a component of stress management programs. Biofeedback is often a very effective adjunct to stress management because it teaches the subject to control physiologic reactions that are part of the stress response and gives the subject feedback to suggest that he or she is adequately practicing relaxation. Biofeedback-mediated stress management may actually be the most practical use of biofeedback in the setting of cardiovascular disease because it is easy to practice and can have an effect on large numbers of patients.

Mental stress has been well documented as a significant risk factor for many forms of cardiovascular disease, and stress management programs have been shown to have an impact on disease progression and symptoms. Many studies, including those reported by Sheps et al for the Psychophysiological Investigations of Myocardial Ischemia (PIMI) study,[15] have shown that patients who exhibit ischemia in response to a mental stress test have increased mortality from cardiovascular disease. Jiang and colleagues,[16] among others, have shown that mental stress predicts cardiac events in patients with lower ejection fractions, and Blumenthal et al[17] have repeatedly demonstrated that stress management training reduces the incidence of wall motion abnormalities in patients with cardiovascular disease. Stress management is included in many cardiac rehabilitation programs, and it is likely that routine use of biofeedback as a component of stress management programs would benefit patients with cardiovascular disease, in whom reproducibly decreasing activation of the autonomic nervous system should be helpful.

According to a recent article in the *Heart Advisor*, 84% of physicians believe that stress is a risk for cardiovascular disease but only 35% say they feel knowledgeable about stress and a mere 5% feel that they succeed in helping stressed patients.[18] Anything that could improve these numbers would be beneficial.

CONCLUSIONS

Cardiovascular conditions in which biofeedback has been shown to be helpful include arrhythmias, hypertension, Raynaud phenomenon, ischemia, infarction, and heart failure, but we have barely begun to explore the potential of biofeedback therapy. Given that many cardiovascular diseases involve inappropriate regulation of the autonomic nervous system, instruction in the use of biofeedback to control activation of the sympathetic and parasympathetic nervous systems is likely to be useful in cardiac patients. Systematic trials are needed.

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Helping children and adults with hypnosis and biofeedback

ABSTRACT

Hypnosis and biofeedback are cyberphysiologic strategies that enable subjects to develop voluntary control of certain physiologic processes for the purpose of improving health. Self-hypnosis has been used with and without biofeedback for a wide range of therapeutic applications, and both laboratory studies and clinical trials have shown it to be effective in improving symptoms and outcomes in various disorders. More formal Cochrane reviews of hypnotherapeutic interventions are currently under way.

Thorough patient assessment should precede training in self-hypnosis in order to properly tailor training strategies to patient preferences and characteristics, especially for children. Workshops offered by various clinical societies are available to train health professionals in self-hypnosis.

Training in self-hypnosis, with or without biofeedback, is a valuable adjunct for children and adults with chronic illnesses or behavioral problems. After defining terms and briefly reviewing the evolution of medical hypnosis, this article provides an overview of the clinical utility and applications of self-hypnosis and various issues in its use, including patient assessment, concurrent use with biofeedback, and how health care providers can become trained in self-hypnosis instruction. Because my experience is primarily with medical hypnosis in children and adolescents, portions of this discussion will devote particular attention to the use of hypnosis in children.

DEFINITIONS

Hypnosis is a state of awareness, often but not always associated with relaxation, during which the participant can give him- or herself suggestions for desired changes to which he or she is more likely to respond than when in the usual state of awareness. Spontaneous self-hypnosis may happen while reading, listening to music, watching television, jogging, dancing, playing a musical instrument, doing tai chi, doing yoga, or performing similar activities. Terms often used to describe mind-body training include *relaxation imagery*, *guided imagery*, or *visual imagery*. These include the same training strategies as those used in hypnosis.

Biofeedback is a term coined in 1969 to describe procedures (developed in 1940s) for training subjects to alter physiologic responses such as brain activity, blood pressure, muscle tension, or heart rate. With biofeedback, participants are trained to improve their health and performance by using signals from their own bodies. In so doing, they strengthen awareness of the connections between their mind and body.

Cyberphysiology was defined by Dr. Earl E. Bakken at the first Archaeus Congress, held in Santa Fe, New Mexico, in 1986. "Cyber" derives from the Greek *kybernan*, meaning steersman or helmsman. From *kybernan* came the Latinate term *govern*, meaning "to control." Thus, *cyberphysiology* means to control a physiologic response. In scientific terms, cyberphysiology is the study of how neurally mediated autonomic responses—usually viewed as automatic, reactive reflexes—can be modified by a learning process that appears to be significantly dependent on modification of mental images. Both hypnosis and biofeedback are cyberphysiologic strategies that enable the user to develop voluntary control of certain physiologic processes.

HISTORICAL BEGINNINGS OF HYPNOSIS

Franz Mesmer developed a training system that he called *animal magnetism*. Mesmer believed that normal body processes were disrupted when there was improper distribution of magnetism, a kind of fluid that could penetrate all matter. He described his ability to direct this magnetic fluid through his presence

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

with the waving of a metallic rod and contact with a a large wooden tub called a *baquet*. Mesmer was convinced that the successful therapeutic effects he observed depended on the magnetic rods he used.

When jealous and hostile colleagues challenged Mesmer's clinical successes, King Louis XVI of France called for an investigative commission chaired by Benjamin Franklin, who was then the American ambassador to France. Other commission members included Dr. Antoine Lavoisier, the first to isolate the element of oxygen, and Dr. Antoine Guillotine, well known for developing a machine for beheading.[1] After the commission conducted some clever experiments, they concluded that Mesmer's success was related to application of the imagination. In fact, we are not far beyond that concept today, although we now have brain imaging documentation of changes in the brain associated with the practice of hypnosis.[2–5]

CORRECTING MISCONCEPTIONS ABOUT HYPNOSIS

Hypnosis is not sleep

Modern hypnosis is considered to have begun with Mesmer, although the term *hypnosis* was first used by James Braid, a Scottish ophthalmologist, in 1843. His decision to derive the word from *hypnos*, the Greek word for sleep, was unfortunate. Hypnosis is not sleep, but the name confuses people.

All hypnosis is self-hypnosis

Another major misconception about hypnosis is that someone—ie, the hypnotist—is in control of a person. In fact, the hypnotist is a coach or teacher who helps the patient to increase his or her self-regulation abilities.[6] All hypnosis is self-hypnosis; after the initial training, the learner must reinforce the training with daily practice. Adult learners should anticipate practicing approximately 10 minutes twice daily for about 2 months in order to condition the desirable physiologic change or outcome. Children learn more easily and often can achieve desired changes over a period of a few weeks.

IMPORTANCE OF PATIENT ASSESSMENT BEFORE TEACHING SELF-HYPNOSIS

Every candidate for self-hypnosis therapy deserves a thoughtful, careful diagnostic assessment that includes appropriate laboratory procedures, radiologic procedures, or both prior to decisions about treatment. Patients are sometimes referred for specific cyberphysiologic interventions, such as hypnosis, without adequate diagnostic assessments.[7] When a patient is referred for hypnosis training, the health professional who will provide the training should evaluate the extent of the previous diagnostic assessment and do more if indicated. It is also important that the health professional be knowledgeable and competent with respect to the patient's specific problem. For example, a dentist who is board-certified in dental hypnosis should not be teaching hypnosis to children with migraine, just as a pediatrician who is board-certified in medical hypnosis should not be extracting teeth using hypnosis.

Mental imagery varies from individual to individual. Many children have visual, auditory, kinesthetic, and olfactory/taste imagery abilities and can use these easily in the process of self-hypnosis. In contrast, many adults do not generate multiple types of mental imagery, and many lack clear visual imagery. It is important that the therapist identify which types of mental imagery the patient prefers before embarking on a therapeutic approach.

CONCURRENT USE OF BIOFEEDBACK AND HYPNOSIS

Much common ground exists between hypnosis and biofeedback. Both have the potential to provide a powerful validation of mind–body links, contribute to a lowered state of sympathetic arousal, heighten awareness of internal events and sensations, facilitate imagery abilities, narrow the focus of attention, and enhance the internal locus of control.

Adding biofeedback games to self-hypnosis training can make the experience much more interesting for children. Children see evidence on the screen that, by changing their thinking, they have control over a body response such as skin temperature, electrodermal activity, or pulse rate variability. Adults also benefit from the addition of biofeedback to self-hypnosis training. A patient cannot effect a change in a biofeedback response without a change in his or her mental imagery.

A WIDE RANGE OF THERAPEUTIC APPLICATIONS

As outlined in **Table 1**, hypnosis has been used, both with and without biofeedback, for a wide range of therapeutic applications.

Hypnosis training is valuable as a primary intervention for prevention of juvenile migraine[8,9] as well as for many performance problems (eg, fear of public speaking or playing tennis), insomnia, and many habit problems (eg, nail-biting, tics, hair-pulling). For treatment of juvenile warts, hypnosis is at least as effective as topical treatment and associated with fewer relapses.[10]

Hypnosis is valuable as an adjunctive intervention during painful procedures,[11–13] and many adults and children use self-hypnosis to teach themselves to be

comfortable through procedures without any pharmacologic treatment.[14]

Training in self-hypnosis is a valuable adjunct for both children and adults with chronic illnesses such as cancer, cardiac failure, asthma, hemophilia, sickle cell disease, and arthritis. Self-hypnosis helps to reduce anxiety and increase comfort, and it provides a therapeutic tool over which the patient has control. Several recent studies have demonstrated the efficacy of hypnosis in the treatment of irritable bowel syndrome.[15]

Hypnosis and cardiac disease

With respect to cardiac disease, training in hypnosis can help to reduce symptoms both preoperatively and postoperatively, to enhance the success of rehabilitation following myocardial infarction, and to reduce anxiety associated with chronic heart disease.[16]

Hypnosis also is helpful for motivating behaviors associated with prevention of cardiac disease, such as regular exercise, eating a low-fat diet, and smoking cessation. Several studies have found hypnosis to be a helpful adjunct to cognitive behavioral therapy for treatment of obesity.[17] Additionally, a number of studies have demonstrated that hypnosis is useful as an initial intervention for smoking cessation,[18] although only about 45% of persons who stop smoking with hypnosis continue to abstain 6 months later. In the case of both obesity and smoking cessation, hypnosis has modestly better efficacy compared with other treatments for these conditions.

TEACHING SELF-HYPNOSIS: SPECIAL CONSIDERATIONS WITH CHILDREN

Self-hypnosis has great potential in children, as children delight in recognizing their own control over problems such as bed-wetting or wheezing or test anxiety.

As noted above, success with hypnosis requires that the patient practice self-hypnosis daily. In the case of children, it is essential that the coach or teacher emphasize that the child is in control and can decide when and where to use self-hypnosis. The message should be that self-hypnosis belongs to the child and that he or she needs to practice to become more skilled (as with learning soccer or some other sport), but that no one can force him or her to practice.

The choice of strategies for teaching self-hypnosis varies depending on the child's age and developmental stage. As children mature, their cognitive abilities change. Preschool children are concrete in their thinking, so therapists working with children of this age must select words carefully. Children between ages 2 and 5 years spend a great deal of their time in various types of behavior based on imagination and fantasy. They enjoy stories and may enter a hypnotic state as a parent or teacher reads a story to them. Unlike adults, they often prefer to practice their self-hypnosis with their eyes open. Although adolescents may enjoy learning self-hypnosis methods that are similar to those preferred by adults, immature adolescents may prefer methods that also appeal to younger children. A child with cognitive impairment can learn self-hypnosis if the therapist selects a teaching approach appropriate for the child's actual developmental stage. Because of developmental changes, a child of 9 years is unlikely to enjoy a method he or she was taught at age 4. Therapists who work with children should be familiar with a variety of hypnosis induction strategies and be capable of creative modification to accommodate a child's changing developmental circumstances.[19,20]

TABLE 1
Therapeutic applications of hypnosis with or without biofeedback

Anxiety	Migraine
Asthma	Painful procedures
Burns	Performance anxiety
Chronic pain	Pruritus
Conditioned fears	Sleep problems
Enuresis	Sports performance
Habit problems	Warts
Irritable bowel syndrome	

HYPNOSIS RESEARCH WITH CHILDREN

Substantial research in child hypnosis has been done over the past 50 years. Initial research measured child hypnotic susceptibility using scales such as the Stanford Hypnotic Clinical Scale for Children.[21,22] Research laboratory studies have demonstrated children's ability to control voluntarily autonomic responses such as peripheral temperature[23–25] and immunologic responses.[26,27] Several controlled laboratory studies have revealed an association between learning self-hypnosis and changes in humoral and/or cellular immunity in children. This work was the basis for a clinical trial by Hewson-Bower, who demonstrated that training in self-hypnosis for children with frequent upper respiratory tract infections resulted in a reduction of infectious episodes and

Organizations that offer training in hypnosis instruction

Society for Developmental and Behavioral Pediatrics (www.sdbp.org)

Society for Clinical and Experimental Hypnosis (e-mail: dabby@MSPP.edu)

American Society of Clinical Hypnosis—bimonthly training workshops (www.asch.net)

fewer illness days when infections did occur.[28,29]

Most subsequent research has consisted of clinical studies documenting the efficacy of hypnosis with children in areas such as pain management, habit problems, wart reduction, and performance anxiety. A recent study completed in Cleveland, Ohio, taught stress-reduction methods, including self-hypnosis, to 8-year-old schoolchildren.[30] This study concluded that a short daily stress-management intervention delivered in the classroom setting in elementary school can decrease feelings of anxiety and improve a child's ability to relax. Many of the children in the study continued to use self-hypnosis in their daily lives after the study was completed.

A host of variables complicate research design

The variability in preferences, learning styles, and developmental stages among children complicates the design of research protocols for studying hypnosis in children. These protocols are often written to describe identical hypnotic inductions, often tape-recorded, to be used at prescribed times. Measured variables do not include whether or not a child likes the induction, listens to the tape, or focuses on entirely different mental imagery of his or her own choosing. Learning disabilities, such as auditory processing handicaps, may interfere with children's ability to learn and remember self-hypnosis training. Furthermore, learning disabilities are often subtle and may not be recognized without detailed testing.

Each of these variables complicates efforts to perform meta-analyses of hypnosis and related interventions. Analyses of studies on the efficacy of hypnosis in children should include all strategies that induce hypnosis in children—eg, visual imagery, guided imagery, and/or progressive relaxation. Some research studies that are defined as controlled nevertheless mix different therapeutic interventions. An example would be a comparison of hypnosis with guided imagery.

The International Society of Hypnosis is currently sponsoring Cochrane reviews of hypnotherapeutic interventions, including those with children.

TRAINING IN HYPNOSIS INSTRUCTION

Health professionals who wish to teach self-hypnosis should take workshops sponsored by the American Society of Clinical Hypnosis or its component sections, or by the Society for Clinical and Experimental Hypnosis. The Society for Developmental and Behavioral Pediatrics also provides annual workshops to prepare health professionals for teaching self-hypnosis to children. Contact information for these organizations is provided in the sidebar on this page.

The basic workshops should include at least 22 hours of supervised practice of hypnosis techniques and didactic information. After completing such basic training, the professional should seek a mentor who, by phone or e-mail, can provide guidance and support. The professional who is developing skills in self-hypnosis instruction should also attend follow-up workshops, watch videotapes of other teachers, and read basic textbooks and hypnosis journals recommended by professional hypnosis societies.

Hypnosis board examinations are given in four areas: medicine, dentistry, psychology, and social work. The American Society of Clinical Hypnosis has developed a hypnosis certification program for professionals who use hypnosis in their practice and teaching.

Importantly, the professional who is developing skills in self-hypnosis instruction should learn self-hypnosis for him- or herself. Learning self-hypnosis is a valuable lifelong skill that provides many benefits.

THE FUTURE

We anticipate that appropriate and early training in self-hypnosis and biofeedback can enable children to learn to control autonomic responses relating to cardiovascular function. Preventive work by pediatric health professionals may include monitoring of autonomic responses early in life, identification of children most at risk because of autonomic lability, and interventions to reduce that risk via hypnosis and biofeedback training. We anticipate that laboratory and brain imaging studies will provide increasing documentation of the impacts of hypnotic suggestions on neural processing, and that Cochrane reviews will demonstrate increasing evidence for the clinical value of hypnosis.

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Clinical hypnosis for reduction of atrial fibrillation after coronary artery bypass graft surgery

ABSTRACT

The belief that postoperative atrial fibrillation (PAF) results from transient autonomic dysfunction suggests that interventions such as clinical hypnosis may reduce the incidence of PAF. To explore this hypothesis, we retrospectively compared outcomes between two groups of patients undergoing coronary artery bypass graft surgery: 50 consecutive patients who received preoperative hypnoidal explanation of the surgical procedure and 50 case-matched historical controls who received no clinical hypnosis. The patients who received hypnosis were significantly less likely to experience an episode of PAF ($P = .003$) and showed nonsignificant trends toward superior outcomes in terms of length of stay, narcotic use, and total hospital charges. Our findings indicate that prospective randomized trials are warranted to further delineate the potential benefit of clinical hypnosis for prevention of PAF.

Postoperative atrial fibrillation (PAF) is the most common complication of coronary artery bypass graft surgery (CABG), affecting approximately 20% to 40% of patients undergoing this procedure.[1] Occurrence of PAF has been associated with prolonged hospital and intensive care unit (ICU) stays, a decline in neurocognitive ability, an increased risk of stroke and transient ischemic attacks, increased surgical mortality, and increased resource utilization and cost.[2]

The role of the autonomic nervous system in atrial fibrillation (AF) has been studied extensively, but the impact of the autonomic nervous system on PAF has received little attention. Research on the mechanisms of AF has shown imbalance in the autonomic nervous system when measured using heart rate variability. These studies have demonstrated an increase in sympathetic activity approximately 20 minutes prior to the onset of AF, with a shift to parasympathetic activity directly prior to onset. A correlation between mental stress and changes in the autonomic nervous system, as assessed by heart rate variability, has also been shown.[3–7]

Pharmacologic interventions, including beta-blockers and amiodarone, have been proposed as preventive measures for PAF, but the incidence of PAF remains high.[1] Beta-blockade may not be tolerated by patients postoperatively, and there is no consensus on dosing parameters. A meta-analysis on the use of amiodarone in the prevention of PAF was inconclusive,[8] and the optimal dosing regimen and incidence of adverse events with amiodarone have not been determined.

There are a small number of studies linking clinical hypnosis to changes in the autonomic nervous system.[9] Clinical hypnosis also has been associated with reductions in anxiety and depression before and after surgical procedures.[10,11] If PAF is a result of transient autonomic dysfunction, then interventions that alter autonomic tone should influence the incidence and duration of PAF. We report here a retrospective analysis of the impact of clinical hypnosis on the occurrence of PAF in patients undergoing CABG.

METHODOLOGY

Fifty consecutive patients undergoing first-time CABG between October 2004 and May 2005 received preoperative hypnoidal explanation of the surgical procedure as part of their preparation for surgery. A group of 50 case-matched patients who had undergone CABG at the same center between October 2003 and May 2004 were chosen as historical controls.

The treatment group (hypnosis group) and the control group were case-matched for presence of diabetes mellitus, use of beta-adrenergic blocking agents, and use of antiarrhythmic medications. The groups were also matched for various predictors of postoperative PAF, such as age, gender, and coronary artery

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TABLE 1
Clinical characteristics of the study population

Characteristic	Treatment group (n = 50)	Control group (n = 50)	*P* value
Age (mean, in years)	66.8 ± 10.1	66.3 ± 9.6	.79
% Male	72.0	72.0	.59
Body mass index (mean)	29.2 ± 5.6	29.1 ± 4.9	.92
% Smoker	54.0	58.0	.42
% Current smoker	8.0	26.0	.02
% Diabetic	44.0	34.0	.21
% Dyslipidemic	76.0	70.0	.33
% With renal failure	10.0	4.0	.22
Last preoperative creatinine level (mean, in mg/dL)	1.2 ± 0.6	1.1 ± 0.3	.43
% Hypertensive	72.0	76.0	.41
% With MI	44.0	32.0	.15
% With recent MI (≤ 7 days before surgery)	20.0	10.0	.13
% With CHF	10.0	24.0	.41
% With angina	74.0	76.0	.50
% With arrhythmia	8.0	10.0	.50
% Receiving preoperative beta-blocker	70.0	70.0	.59
Predicted risk of mortality (SD)	0.02903 ± 0.03801	0.02092 ± 0.02045	.20

MI = myocardial infarction; CHF = congestive heart failure; SD = standard deviation

TABLE 2
Postoperative outcomes in the study groups

Outcome	Treatment group (n = 50)	Control group (n = 50)	*P* value
No. (%) of patients with PAF	3 (6.0)	12 (24.0)	.003
No. (%) of patients discharged on antiarrhythmics	7 (14.0)	14 (28.0)	.03
Postoperative ICU stay (mean, in hours)	34.5 ± 41.3	36.0 ± 68.2	.08
Postoperative hospital stay (mean, in days)	5.0 ± 2.1	5.4 ± 3.2	.08
Postoperative narcotic use (mean, in mg of morphine)	48.3 ± 39.4	56.3 ± 49.1	.11
No. (%) of patients referred for extended care	8 (16.0)	10 (20.0)	.50
Total hospital charges (mean, in dollars)	9,362 ± 5,582	9,791 ± 7,365	.06

PAF = postoperative atrial fibrillation; ICU = intensive care unit

disease. The patients were all treated by the same surgeon (R.N.), with no significant alterations to surgical or pharmacologic protocols.

The surgeon used indirect Ericksonian techniques during the preoperative explanation of the surgery. Milton Erickson, one of the most prominent hypnotherapists in recent times, used an indirect approach to weave suggestions into the dialogue rather than giving direct commands. This approach encourages active participation and gives the patient a sense of greater control in the hospital environment. The surgeon also instructed patients in self-hypnosis using respiration and imagery.

RESULTS

The clinical characteristics of the study population are outlined in **Table 1**. The groups were considered equivalent on a given characteristic if the *P* value for that characteristic was greater than .10, so the only factor on which the groups differed was the percentage of current smokers, which was higher in the control group **(Table 1)**.

Table 2 presents outcomes in the two study groups. Patients who were treated with clinical hypnosis were less likely to experience PAF: the percentage of patients with one or more episodes of PAF was 6.0% in the treatment group versus 24.0% in the control group ($P = .003$). Likewise, the percentage of patients who were discharged on amiodarone was 14.0% in the treatment group versus 28.0% in the control group ($P = .03$).

Additionally, favorable trends toward superior outcomes in the treatment group were observed for length of stay in the ICU, postoperative length of stay in the hospital, postoperative narcotic use, and total hospital charges, although these trends did not reach statistical significance **(Table 2)**.

Clinical characteristics were tabulated and compared between the subjects who experienced new-onset PAF and those who did not experience PAF to determine whether there was a covariate responsible for the results observed. With the exception of age, the difference in clinical characteristics between these groups of patients was not statistically significant (using $P > .10$ as the threshold for significance) **(Table 3)**.

TABLE 3
Clinical characteristics of the study population based on incidence of PAF

Characteristic	Patients with PAF (n = 14)	Patients without PAF (n = 86)	*P* value
Age (mean, in years)	70.9 ± 7.8	65.8 ± 10.0	.06
% Male	83.6	71.9	.19
Body mass index (mean)	27.7 ± 5.1	29.4 ± 5.5	.28
% Smoker	71.4	52.3	.37
% Diabetic	42.9	38.3	.93
% Dyslipidemic	64.3	76.7	.23
Last preoperative creatinine level (mean, in mg/dL)	1.1 ± 0.3	1.1 ± 0.5	.68
% Hypertensive	85.7	70.9	.57
% With MI	57.1	34.9	.19
% With recent MI (≤ 7 days before surgery)	28.6	12.8	.18
% With angina	71.4	76.7	.87
% Receiving preoperative beta-blocker	85.7	66.3	.76

PAF = postoperative atrial fibrillation; MI = myocardial infarction

Multiple regression analysis revealed that age was not a significant factor in the prediction of postoperative hospital charges (P = .51), length of stay in the ICU (P = .78), or postoperative length of stay in the hospital (P = .85). Patients who experienced PAF had higher mean postoperative hospital charges ($12,627 vs $9,003 for those without PAF; P = .05), a longer mean stay in the ICU (76.0 vs 28.1 hours, respectively; P = .002), and a longer mean postoperative stay in the hospital (6.5 vs 5.0 days, respectively; P = .05).

DISCUSSION

Adverse effects of PAF are well established

The onset of PAF following CABG is a common complication that has been linked to increases in morbidity and mortality, length of stay in the ICU and hospital, and total hospital charges. Villareal et al found that the odds ratio for early mortality (within 30 days) for patients who experienced PAF after CABG was 1.4 (95% confidence interval, 1.12 to 1.68; P = .002).[12] In addition, patients with PAF had significantly higher rates of postoperative infections, renal failure, shock, failure of multiple organ systems, and cardiac arrest compared with those who did not have PAF.[12] A literature analysis by Maisel et al found that PAF increases the likelihood that cardiac surgery patients will need to return to the operating room, be readmitted to the ICU, and require prolonged ventilation or reintubation.[13] Nickerson et al showed that PAF following cardiac surgery corresponded with an increase in length of stay in both the ICU and hospital.[14]

Our study showed statistically significant increases in postoperative hospital charges, postoperative hospital stay, and ICU stay among patients who experienced PAF following CABG. These findings are consistent with the current literature. In a study of 720 subjects undergoing CABG, Hravnak et al reported a 1.4-day increase in length of hospital stay and a 0.3-day increase in length of ICU stay among patients who had PAF compared with those who did not.[15] A significant increase in postoperative hospital charges was also observed.[15] Similarly, in a multicenter study of 2,417 patients undergoing isolated CABG procedures, Mathew et al observed increases in ICU stay and hospital stay among those patients who experienced PAF.[2] These findings indicate that the onset of PAF after CABG is a serious complication and that further study is warranted.

Hypnosis to prevent PAF: Suggestive evidence and mechanisms

Clinical hypnosis has been shown to reduce stress and anxiety in surgical patients and can be highly individualized to address the patient's needs during the stressful preoperative period. Saadat et al found that hypnosis administered directly before ambulatory surgery using Ericksonian techniques reduced patients' levels of anxiety by 56% from baseline.[11] In a South African study specifically in men undergoing CABG, de Klerk et al found that preoperative hypnotherapy led to reductions in both anxiety and depression at discharge that were maintained through 6-week follow-up.[10]

These findings, taken together with research linking clinical hypnosis to changes in the autonomic nervous system[9] and the belief that PAF may result from transient autonomic dysfunction, suggest that hypnosis may reduce the incidence of PAF.

In a study of R-R interval dynamics prior to PAF in patients who had undergone CABG, Hogue et al showed that patients who experienced PAF had higher heart rates directly before PAF onset.[16] Higher heart rates are associated with increased activity of the sympathetic nervous system and/or decreased activity of the parasympathetic nervous system. This finding supports our hypothesis of a relationship between PAF fol-

lowing CABG and excessive adrenergic activation. Chen et al have noted that catecholamine-mediated AF usually occurs in the presence of heart disease and that these types of attacks often happen during the daytime in association with physical or emotional stress.[4]

Bettoni and Zimmermann found that the onset of AF is preceded by a primary increase in adrenergic drive, which changes to increased vagal activity immediately before the occurrence.[3] Tomita et al reported that sympathetic tone increases immediately before an occurrence of daytime AF.[7] These results were supported by Lombardi et al, who detected signs of predominant sympathetic modulation and reduced vagal modulation of sinus node in AF episodes that started during the daytime.[6] These episodes were characterized by atrial ectopic beats prior to onset.[6]

Modulations in baroreceptor reflex activity may provide further evidence of the importance of the sympathetic/parasympathetic balance in the initiation of AF. Suboptimal functioning of the baroreceptor reflex has been associated with arrhythmias and adverse cardiac events in patients and animal models. Loss of the protective effects of vagal activation has been postulated to increase vulnerability to sympathetically driven ischemia and malignant arrhythmias.[17]

Multiple studies have shown that the only conclusive predictor of PAF is age. Notably, heart rate variability is reduced with increased age.[18] By measuring heart rate variability, Taggart et al showed that autonomic balance was improved in patients under induced stress when they were in a hypnotic state.[19] Although no attempts were made to determine heart rate variability in our patient set, other studies have demonstrated an increase in heart rate variability during hypnosis. The results of our study suggest that clinical hypnosis using a personalized Ericksonian approach may have a beneficial effect on the incidence of PAF.

CONCLUSIONS

Clinical hypnosis appears to lower the incidence of PAF in patients undergoing CABG as well as to yield favorable trends toward reduced ICU and postoperative hospital stays, reduced hospital charges, and reduced use of narcotics. Although our study had a small sample size and lacked randomization, its positive results and the absence of side effects suggest that prospective randomized trials should be conducted to further delineate the role of hypnosis in the prevention of PAF. A better understanding of AF, and of the autonomic nervous system's role in triggering and maintaining PAF, will allow more appropriate treatment of this condition.

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Depression and coronary heart disease: Association and implications for treatment

ABSTRACT

Growing evidence indicates that depression is an important primary and secondary risk factor for coronary heart disease (CHD). Depression is quite common among patients with CHD: prevalence estimates are 14% or higher, and an additional 20% of patients have subclinical or minor depression. This review summarizes evidence that depression is a risk factor for cardiac events in patients with established CHD, suggests potential mechanisms underlying the relationship between depression and adverse cardiac outcomes, and provides evidence for the efficacy of exercise in improving both depression and clinical outcomes in depressed patients with CHD.

Depression refers to an emotional condition ranging from a transient negative mood state of sadness or mild dysphoria to a chronic and severe psychiatric illness. The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) identifies two depressive disorders: major depressive disorder (MDD) and dysthymic disorder.[1] The essential feature of MDD is a clinical course characterized by one or more major depressive episode (whose diagnostic criteria are presented in **Table 1**) without a history of manic, mixed, or hypomanic episodes. The diagnosis requires the presence of a total of at least five symptoms over a period of at least 2 weeks, which must include either depressed mood or loss of interest or pleasure. Dysthymic disorder is marked by mild depressive symptoms that are more chronic in nature, lasting at least 2 years.[1]

Minor depressive disorder (mDD) is not an official DSM-IV diagnosis but is used for research purposes; it is similar to MDD in duration but requires that only two to four symptoms be present.

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EPIDEMIOLOGY OF DEPRESSION

Depression is a widespread and often chronic condition. Lifetime prevalence estimates for MDD are approximately 15% to 20%;[2,3] 1-year prevalence estimates are 5% to 10%;[2,4] and point prevalence estimates range from 4% to 7%.[3,5] Moreover, MDD is characterized by high rates of relapse: 22% to 50% of patients suffer recurrent episodes within 6 months after recovery.[6]

Women are twice as likely as men to be diagnosed with MDD, with lifetime prevalence rates of 10% to 25% in women versus 5% to 12% in men.[1]

Although rates of depression do not appear to increase with age, MDD often goes undertreated in older adults[3] and in cardiac patients.[7]

DIAGNOSING AND ASSESSING DEPRESSION

The gold standard for diagnosing MDD is a clinical interview. Commonly used instruments include the Diagnostic Interview Schedule[8] and the Composite International Diagnostic Interview.[9] The Structured Clinical Interview for DSM-IV Axis I Disorders[10] and the Schedule for Affective Disorders and Schizophrenia[11] are frequently used semistructured interviews.

The most common clinical instruments for assessing the severity of depressive symptoms are the Hamilton Rating Scale for Depression (HAM-D),[12] which is a clinician-rated scale, and various psychometric questionnaires, including the Beck Depression Inventory (BDI)[13,14] and the Center for Epidemiological Studies Depression Scale (CES-D).[15]

THE DEPRESSION–HEART DISEASE LINK

Depression as a primary risk factor

Evidence that depression is a primary risk factor for coronary heart disease (CHD) in healthy individuals has been reviewed previously.[16] A recent meta-analysis of 11 prospective cohort studies of initially healthy individuals indicated that depression (either depressive mood or clinical MDD) conferred a relative risk of 1.64 for adverse cardiac events, including myocardial infarction (MI) and cardiac death; the presence

TABLE 1
DSM-IV criteria for major depressive episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
   (1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad or empty) or observation made by others (eg, appears tearful). *Note:* In children and adolescents, can be irritable mood.
   (2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
   (3) Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
   (4) Insomnia or hypersomnia nearly every day.
   (5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
   (6) Fatigue or loss of energy nearly every day.
   (7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
   (8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
   (9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
B. The symptoms do not meet criteria for a mixed episode.
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication) or a general medical condition (eg, hypothyroidism).
E. The symptoms are not better accounted for by bereavement, ie, after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

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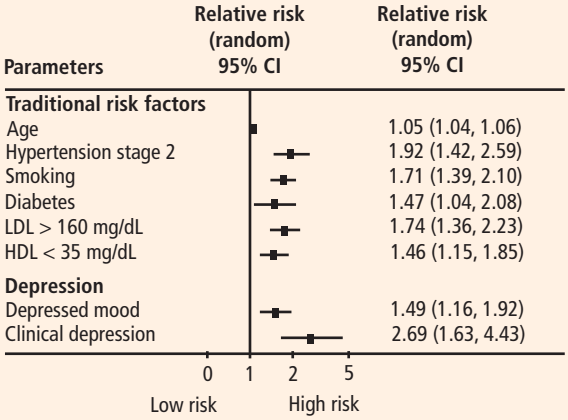

FIGURE 1. Risk ratios of traditional risk factors for coronary heart disease (CHD) observed in the Framingham study as compared with risk ratios of depressive symptoms and depressed mood as derived from the recent meta-analysis by Rugulies.[17] The risk of CHD conferred by depressive symptoms is comparable to that conferred by traditional risk factors, and the presence of clinical depression appears to raise this risk. For traditional risk factors, risk ratios were calculated for cardiac death, myocardial infarction, coronary artery insufficiency, and angina. For depressed mood and clinical depression, risk ratios were calculated for cardiac disease and myocardial infarction.[18]

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of MDD was associated with the greatest risk (relative risk of 2.69).[17] **Figure 1** shows that clinical depression is comparable to traditional risk factors for CHD, such as smoking and elevated blood lipid levels, as observed in the Framingham study.[18]

Depression as a secondary risk factor

Depression is an even stronger risk factor for cardiac events in patients with established CHD. Point estimates range from 14% to as high as 47%, with higher rates in patients with unstable angina and in patients awaiting coronary artery bypass graft (CABG) surgery; an additional 20% of patients exhibit elevated depressive symptoms or minor depression (mDD).[19–25]

Prospective studies have shown that depression increases the risk for death or nonfatal cardiac events approximately 2.5-fold in patients with CHD. For instance, Frasure-Smith et al followed 896 patients with a recent acute MI and found that the presence of depressive symptoms as indicated by an elevated BDI score was a significant predictor of cardiac mortality after controlling for multivariate predictors of mortality (odds ratio [OR] = 3.29 for women and 3.05 for men).[26]

Two recent meta-analyses confirmed the association between depression and adverse clinical outcomes in patients with CHD.[27,28] For example, van Melle et al reported that post-MI depression was associated with a 2- to 2.5-fold increase in the risk of adverse health outcomes.[28] In this analysis, depression's effect on cardiac mortality and all-cause mortality was especially pronounced in older studies (before 1992) (OR = 3.2) compared with more recent studies (after 1992) (OR = 2.01).[28]

Duke University researchers have conducted several

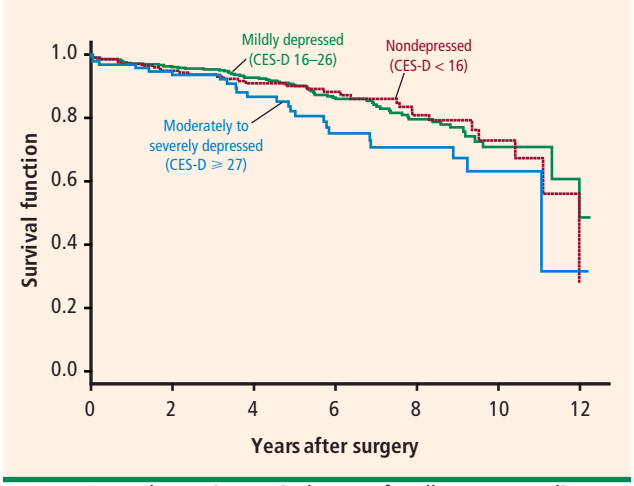

FIGURE 2. Kaplan-Meier survival curves for all-cause mortality among coronary surgery patients according to their presurgery (baseline) depressive symptoms as measured by the Center for Epidemiological Studies Depression Scale (CES-D). Compared with the absence of depressive symptoms, the presence of moderate to severe symptoms was associated with a hazard ratio of 2.4 (95% CI = 1.40 to 4.00; $P = .001$) for all-cause mortality. Mild symptoms were associated with no difference in risk relative to the absence of symptoms (hazard ratio = 1.08, 95% CI = 0.70 to 1.67; $P = .723$).[30]

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prospective studies in various cardiac populations.[29–31] Barefoot et al assessed 1,250 patients with documented CHD using the Zung Self-Rating Depression Scale at the time of diagnostic coronary angiography and followed them for up to 19.4 years.[29] Results showed that patients with moderate to severe depression were at 69% greater risk for cardiac death and 78% greater risk for all-cause death than were their nondepressed counterparts.

In a prospective study of patients undergoing CABG surgery, we assessed the effect of depression on mortality in 817 patients followed for up to 12 years (mean, 5.2 years).[30] Using the CES-D instrument, patients were categorized on the day before surgery as having either no depression (CES-D score < 16), mild depression (score of 16 to 26), or moderate to severe depression (score ⩾ 27). We found that moderate to severe depression was independently associated with a twofold to threefold increase in the risk of death, even after controlling for age, gender, number of grafts, diabetes, smoking, left ventricular ejection fraction, and history of acute MI **(Figure 2)**. Moreover, patients who exhibited persistent depression, with CES-D scores of 16 or greater at baseline and after 6 months, had more than a doubling in risk relative to patients who were never depressed.

We also recently reported results from a prospective study that followed 204 patients with heart failure over a median interval of 3 years.[31] Clinically significant symptoms of depression (BDI score ⩾ 10) were associated with a hazard ratio of 1.56 (95% CI, 1.07 to 2.29) for the combined end point of death or cardiovascular hospitalization. These observations included adjustment for plasma NT-proBNP level, ejection fraction, and other established risk factors, suggesting that heightened risk of adverse clinical outcomes associated with depressive symptoms is not simply a reflection of the severity of heart failure.

In summary, a number of observational studies have demonstrated that depression is associated with increased risk of morbidity and mortality both in healthy populations and in a variety of populations with established cardiac disease.

BIOBEHAVIORAL MECHANISMS LINKING DEPRESSION AND CHD

A number of biobehavioral mechanisms have been hypothesized to underlie the relationship between depression and CHD. Most evidence is derived from cross-sectional studies and suggests that depression is associated with traditional risk factors for CHD, such as hypertension, diabetes, and insulin resistance,[32,33] as well as changes in platelet reactivity,[34] dysregulation of the autonomic nervous system[35] and hypothalamic-pituitary-adrenal axis,[36] and alterations in the immune response/inflammation.[37] Depression is also associated with behavioral factors that are in turn associated with CHD risk, such as reduced treatment adherence,[38] smoking,[39] and physical inactivity.[40]

STUDIES OF DEPRESSION TREATMENT IN CARDIAC PATIENTS

Successful treatments for depression in patients with CHD may have the potential to improve not only quality of life but also cardiovascular and physical health. Several treatments for depression exist for use in the general population, such as antidepressant medication or psychotherapy.[41] However, only three studies have tested the efficacy of these treatments in patients with CHD: SADHART, ENRICHD, and CREATE.[42–44]

SADHART (Sertraline Antidepressant Heart Attack Randomized Trial) was a safety and efficacy evaluation of antidepressant medication in patients with MDD and a recent MI or unstable angina.[42] It showed only modest differences in reductions in depressive symptoms between sertraline recipients and placebo recipients, and it lacked statistical power

to examine the impact of treatment on hard clinical end points.

ENRICHD (Enhancing Recovery in Coronary Heart Disease Patients) assessed the effect of psychosocial treatment on survival among more than than 2,400 post-MI patients.[43] Although this trial found that cognitive behavior therapy resulted in significant, albeit small, improvements in depressive symptoms compared with usual care, it failed to demonstrate that treating depression and low social support was associated with increased survival.

CREATE (Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy), a recent placebo-controlled trial, assessed the value of antidepressant medication and clinical management in patients with CHD.[44] The study's 284 patients, all of whom had CHD as well as MDD and a HAM-D score of 20 or greater, underwent two separate randomizations: (1) to 12 weeks of interpersonal therapy plus clinical management or 12 weeks of clinical management alone, and (2) to 12 weeks of citalopram therapy or matching placebo. There was no difference between interpersonal therapy and clinical management alone; however, citalopram was superior to placebo in reducing HAM-D scores and demonstrated better remission rates (35.9% with citalopram vs 22.5% with placebo). The same therapists who provided interpersonal therapy also performed the clinical management, so it could be argued that this was why additional interpersonal therapist time did not result in greater reductions in depressive symptoms than did clinical management alone. Furthermore, this study did not examine the effects of depression therapy on clinical outcomes.

EXERCISE AS A TREATMENT FOR DEPRESSION

There is growing evidence that exercise may be an effective treatment for depression.[45] Most of the existing studies of exercise for depression have focused on aerobic exercise.

In the relatively large SMILE study (Standard Medical Intervention and Long-term Exercise),[46] conducted at Duke University, 156 adult noncardiac patients with MDD were randomized to 4 months of treatment with supervised aerobic exercise, antidepressant medication (sertraline), or a combination of exercise and medication. Although antidepressant medication was associated with faster reductions in depression in the first 4 weeks of treatment among mildly depressed patients, exercise was as effective as antidepressant medication in treating depression by the end of the 16-week intervention for all participants.

Six-month follow-up among patients from the SMILE study who had achieved remission revealed that those who had been randomized to exercise were less likely to have relapsed than those randomized to the medication or combination-therapy groups **(Figure 3)**.[47] Moreover, across the entire follow-up population, those patients who reportedly engaged in regular aerobic exercise during the 6-month follow-up period were only half as likely to have relapsed compared with those who did not engage in regular exercise.

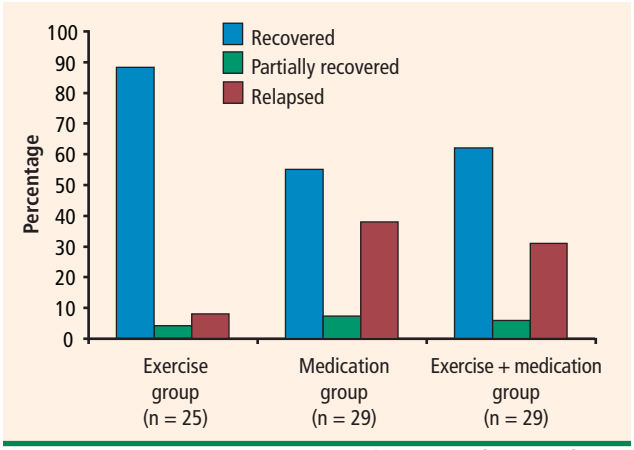

FIGURE 3. Clinical status at 10 months (6 months after end of treatment) among 83 patients who achieved remission from major depressive disorder following 4 months of treatment in the SMILE study,[46] according to the three treatment groups. Compared with participants in the other treatment groups, those in the exercise group were more likely to remain fully or partially recovered and less likely to have relapsed.[47]

Reprinted, with permission, from Babyak MA, et al. Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. Psychosom Med 2000; 62:633–638.

Exercise generally is considered safe for most patients with stable CHD.[48] Some studies of exercise treatments for patients with CHD have tracked depressive symptoms and thus have provided insight into the potential efficacy of exercise as a treatment for depression in this population. Although most of these studies have reported significant improvements in depression after completion of an exercise program, many have had important methodologic limitations, including absence of a control group. In one of the few controlled studies in this area, Stern et al[49] randomized 106 men who had a recent acute MI and elevated depression, anxiety, or low fitness to 12 weeks of exercise training, group therapy, or usual care (control). At 1-year follow-up, subjects in both the exercise and counseling groups showed improvements in depression relative to controls.

EFFECT OF EXERCISE ON CARDIOVASCULAR RISK FACTORS AND OUTCOMES

Exercise is a particularly promising intervention for depression in patients with CHD because it has well-

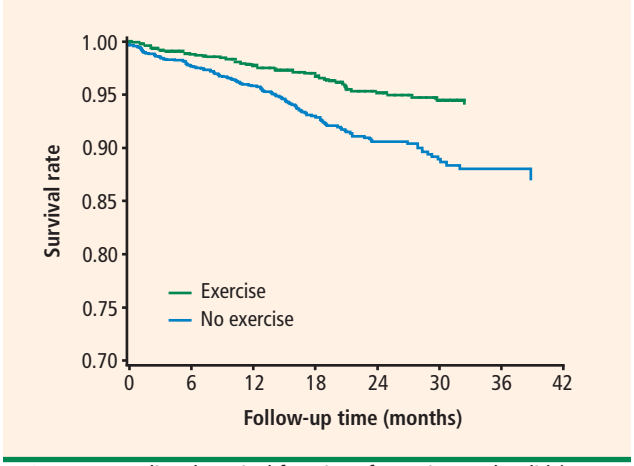

FIGURE 4. Predicted survival functions for patients who did (n = 952) and did not (n = 1,096) exercise regularly during the 6 months following an index myocardial infarction in the ENRICHD trial. There were a total of 187 fatal events; the mortality rate was 5.7% among the exercisers compared with 12.0% among the nonexercisers.[52]

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documented cardiovascular benefits. In addition to the well-established role of exercise interventions in primary prevention, such interventions have been shown to improve outcomes for patients with CHD.[50]

Jolliffe et al conducted a meta-analysis comparing exercise-only interventions, comprehensive rehabilitation (including educational and behavioral components such as dietary changes and stress reduction in addition to exercise), and usual care.[51] Exercise-only interventions were associated with reductions in both all-cause and cardiac mortality relative to usual care. Comprehensive rehabilitation, on the other hand, was not associated with statistically significant reductions in all-cause mortality relative to usual care, but it was associated with a decreased risk for cardiac mortality, to a slightly lesser extent than exercise-only interventions.

Recent data from the ENRICHD trial suggest that exercise may reduce rates of death and recurrent nonfatal infarction in post-MI patients with depression or low levels of social support.[52] Self-reported data were used to categorize participants as exercising regularly or not exercising regularly. After adjustment for medical and demographic variables, regular excercise was found to be associated with a nearly 40% reduction in the risk of death and a nearly 30% reduction in the risk of recurrent nonfatal infarction. **Figure 4** depicts the Kaplan-Meier survival curves for patients who did and did not exercise regularly.

The evidence that exercise affects depression, CHD risk factors, and CHD outcomes suggests that exercise is a particularly promising intervention for depression in this population.

UPBEAT trial promises further insight

A new Duke University study known as UPBEAT (Understanding Prognostic Benefits of Exercise and Antidepressant Treatment) is randomizing 200 patients with elevated depressive symptoms to exercise, antidepressant therapy (sertraline), or placebo for 4 months.[53] A variety of "biomarkers" of risk are being assessed, including measures of heart rate variability, vascular function, inflammation, and platelet aggregation. Results of this 5-year trial should be available by 2011.

CONCLUSIONS

Although depression has emerged as an important risk factor for CHD, there is no consensus on the optimal way to treat depression in patients with CHD. Interventions that are guided by an understanding of the mechanisms linking depression to CHD may prove to be most effective in improving both depression and physical health outcomes.

Exercise targets many of the mechanisms by which depression may be associated with increased risk, including autonomic nervous system activity, hypothalamic-pituitary-adrenal axis function, platelet activation, vascular function, and inflammation. Moreover, a growing body of evidence suggests that exercise is an effective treatment for depression that may be comparable in effect to antidepressant medication, at least in select subgroups (eg, patients who are receptive to exercise as a treatment for depression). The value of exercise training—not only for improving quality of life, but also for improving "biomarkers" of risk and other relevant health outcomes—is the focus of our current research efforts.

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Cardiovascular autonomic dysfunction in patients with movement disorders

ABSTRACT

Autonomic dysfunction is common in parkinsonian syndromes, particularly those involving dysregulation of alpha-synuclein, and may result from neurodegeneration in autonomic regulatory regions of the brain or peripherial autonomic ganglia. The most limiting cardiovascular autonomic dysfunction in these diseases is orthostatic hypotension, which is particularly prominent in multiple system atrophy. Postprandial hypotension and supine hypertension, as well as dopaminergic therapy, often complicate the management of orthostatic hypotension in patients with parkinsonian syndromes.

The Lewy body is the pathologic hallmark of both Parkinson disease and dementia with Lewy bodies. Lewy bodies are seen microscopically as neuronal inclusions containing alpha-synuclein and associated proteins. In contrast, glial inclusions involving alpha-synuclein are seen in multiple system atrophy. Because Lewy bodies are observed in autonomic regulatory regions of the brain, they are of interest in the study of the autonomic dysfunction that figures prominently in several parkinsonian syndromes. Cardiovascular autonomic dysfunction in parkinsonian syndromes includes orthostatic hypotension, postprandial hypotension, and supine hypertension.

This article will describe the major clinical and pathologic features of movement disorders with Lewy body pathology, the likelihood of autonomic dysregulation in these disorders, and issues involved in the treatment of autonomic dysfunction in patients with these movement disorders.

OVERVIEW OF PARKINSONIAN SYNDROMES

Parkinsonian syndromes can be divided grossly into idiopathic Parkinson disease, secondary parkinsonism, and Parkinson-plus syndromes. Secondary parkinsonism is defined as parkinsonian symptoms resulting from damage to motor circuits in the brain attributable to known insults to the brain from infectious, metabolic, toxic, ischemic, neoplastic, or other causes. Parkinson-plus syndromes include multiple system atrophy, dementia with Lewy bodies, corticobasal ganglionic degeneration, and progressive supranuclear palsy; each syndrome is a separately identifiable neurodegenerative disease with distinct pathology, and each presents with parkinsonian features as well as its own characteristic clinical features. **Table 1** presents the incidence and prevalence of idiopathic Parkinson disease and the Parkinson-plus syndromes.

Tauopathies versus synucleinopathies

Pathologically, parkinsonian syndromes can be divided into two groups: the tauopathies and the synucleinopathies.

The tauopathies, so named because of the presence of hyperphosphylated tau protein, include progressive supranuclear palsy and corticobasal ganglionic degeneration as well as a number of other neurodegenerative conditions (ie, Pick disease, FTDP-17, primary progressive aphasia, argyrophilic grain disease) that do not cause parkinsonian features.

Synucleinopathies, the focus of this article, are disorders in which the protein alpha-synuclein accumulates in the cytoplasm. They include idiopathic Parkinson disease, multiple system atrophy, dementia with Lewy bodies, and pure autonomic failure. In multiple system atrophy, deposits of alpha-synuclein are prominent in glial cytoplasmic inclusions. In both Parkinson disease and dementia with Lewy bodies, alpha-synuclein is present in Lewy bodies. Although primary autonomic failure is not a movement disorder, its pathology is similar to that of the other synucleinopathies, with alpha-synuclein accumulation in both the central and peripheral nervous systems, as well as the presence of Lewy bodies.

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IDIOPATHIC PARKINSON DISEASE

Autonomic dysfunction usually occurs late in idiopathic Parkinson disease, and its severity is less than that observed with other parkinsonian syndromes. However, the lifetime risk of significant autonomic dysfunction in patients with Parkinson disease is approximately 1 in 3.[1] Almost 60% of patients with idiopathic Parkinson disease meet the criterion for a diagnosis of orthostatic hypotension—ie, a fall in systolic blood pressure of at least 20 mm Hg—and orthostatic hypotension is symptomatic in about 20% of patients.[1]

MULTIPLE SYSTEM ATROPHY

The nomenclature of multiple system atrophy has been evolving slowly. In 1900, Dejerine and Thomas described olivopontocerebellar atrophy, a progressive cerebellar degeneration with parkinsonism. In 1960, Shy and Drager described the Shy Drager syndrome, which has prominent autonomic features common to Parkinson disease, such as orthostatic hypotension, urinary and fecal incontinence, loss of sweating, iris atrophy, external ocular palsies, rigidity, tremor, loss of associated movement, and impotence.[2]

Also in 1960, Van der Eecken described striatonigral degeneration, an akinetic, rigid, parkinsonian syndrome that did not respond well to medications and was associated with autonomic dysfunction.[3]

In 1969, Graham and Oppenheimer realized an overlap to these syndromes and coined the term *multiple system atrophy*. They used it to refer to a gradually progressive idiopathic neurodegenerative process of adult onset characterized by varying proportions of cerebellar dysfunction, autonomic failure, and parkinsonism, and which is poorly responsive to levodopa therapy.[4]

Newer terminology is more specific for the predominant symptoms in the syndrome. A predominance of parkinsonism with this syndrome is referred to as "parkinsonian type of multiple system atrophy" (MSA-P), whereas a predominance of cerebellar signs is termed "multiple system atrophy with cerebellar-predominant symptoms" (MSA-C). The parkinsonian type is about four times as common as the cerebellar type.[5] Autonomic dysfunction is common to both types, and its severity varies.

Parkinsonism is the most common symptom in multiple system atrophy, followed by autonomic failure and cerebellar signs. Approximately one fourth of patients with multiple system atrophy have all three categories of symptoms. Pyramidal signs are present in approximately 60% of patients, and help distinguish this syndrome primarily from idiopathic Parkinson disease.[6]

TABLE 1
Epidemiology of parkinsonian disorders*

	Incidence†	Prevalence‡
Idiopathic Parkinson disease	4.5–19	100–200
Corticobasal ganglionic degeneration	? (rare)	? (rare)
Dementia with Lewy bodies	100	~ 750
Multiple system atrophy	0.6	4.4
Progressive supranuclear palsy	1.1	1.4

* Data compiled by the author from multiple published sources.
† Number of new cases per 100,000 population per year.
‡ Number of patients per 100,000 population.

Diagnostic criteria

Autonomic dysfunction in the form of orthostatic hypotension and/or urinary incontinence is a key diagnostic criterion for multiple system atrophy.

Parkinsonism. Parkinsonian features of the syndrome are bradykinesia, rigidity, postural instability, and tremor.

Cerebellar dysfunction. Features of cerebellar dysfunction include gait ataxia, ataxic dysarthria, limb ataxia, and sustained gaze-evoked nystagmus.

Corticospinal tract dysfunction (extensor plantar response with hyperreflexia) also helps establish the diagnosis because this feature separates multiple system atrophy from idiopathic Parkinson disease as well as some of the other parkinsonian syndromes.

Diagnostic categories

The above diagnostic criteria can be combined to make a diagnosis of possible, probable, or definite multiple system atrophy.

Possible. For a diagnosis of possible multiple system atrophy, one of the above diagnostic criteria must be present along with two features from separate domains. If the case meets the criteria for parkinsonism (bradykinesia plus at least one of the other aforementioned features of parkinsonism), a poor levodopa response qualifies as a feature.

Probable. A diagnosis of probable multiple system atrophy must meet the criterion for autonomic dysfunction plus either the criterion for parkinsonism (with poor levodopa response) or the criterion for cerebellar dysfunction.

TABLE 2
Criteria for clinical diagnosis of dementia with Lewy bodies*

Central feature
Progressive cognitive decline
Core features
Fluctuating cognition with pronounced variations in attention
Recurrent visual hallucinations
Parkinsonism
Suggestive features
REM sleep behavior disorder
Severe neuroleptic sensitivity
Low dopamine transporter activity in the basal ganglia by SPECT or PET
Possible dementia with Lewy bodies
Central feature + 1 core feature *or*
Central feature + 1 or more suggestive features
Probable dementia with Lewy bodies
Central feature + 2 core features *or*
Central feature + 2 core feature + ⩾ 1 suggestive feature

* Revised criteria from the third report of the Dementia with Lewy Bodies Consortium, 2005.[7]

REM = rapid eye movement; SPECT = single-photon emission computed tomography; PET = positron emission tomography

Definite. Definite multiple system atrophy requires pathological confirmation.

Extrapyramidal features in multiple system atrophy

In addition to prominent autonomic and/or cerebellar dysfunction, differences in extrapyramidal features help distinguish multiple system atrophy from idiopathic Parkinson disease. Tremor is less common in multiple system atrophy than in idiopathic Parkinson disease, and the akinetic/rigid symptoms tend to be symmetric in multiple system atrophy, rather than asymmetric as in Parkinson disease. Postural instability occurs early in multiple system atrophy but does not occur until late in idiopathic Parkinson disease. Moreover, multiple system atrophy responds poorly to levodopa and is characterized by more rapid disease progression. The presence of early autonomic and cerebellar symptoms is diagnostic for multiple system atrophy.

Pathology

The pathologic hallmark of multiple system atrophy is alpha-synuclein deposits in the glial or glial cytoplasmic inclusions (Papp-Lantos inclusions), which are diffuse through the central nervous system but are present particularly in the brainstem and spinal cord.

DEMENTIA WITH LEWY BODIES

Dementia with Lewy bodies is also known as diffuse Lewy body disease, senile dementia of the Lewy body type, Lewy body variant of Alzheimer disease, and Parkinson disease with dementia.

Dementia with Lewy bodies is descriptive for the entire series of these diseases. Pathologically, it is identical to Parkinson disease with dementia, with the only difference being an objective criterion based on the duration of dementia. Dementia less than 1 year after onset of parkinsonism is considered dementia with Lewy bodies, whereas dementia more than 1 year after the onset of parkinsonism is considered Parkinson disease with dementia. Whether these are separate disorders or two ends of a spectrum of disease is unclear.

Clinical criteria

The clinical diagnosis of dementia with Lewy bodies is based on revised criteria from the third report of the Dementia with Lewy Bodies Consortium, issued in 2005 **(Table 2)**.[7]

Central feature: progressive cognitive decline. Dementia with Lewy bodies is characterized by prominent progressive cognitive decline that is uncharacteristic of Parkinson disease. In particular, patients with dementia with Lewy bodies have fluctuating cognition, pronounced variations in attention, and early hallucinations when either off medications or on low doses of dopamimetic medications.

Supportive features that are not diagnostic. Rapid eye movement (REM) sleep behavior disorder suggests a diagnosis of dementia with Lewy bodies; however, this feature is common to all synucleinopathies, so it is not diagnostic. Other supportive features (ie, depression, severe autonomic dysfunction) increase the likelihood of a diagnosis of dementia with Lewy bodies but are not alone diagnostic **(Table 3)**.

Pattern of dementia is more subcortical than cortical. The cognitive changes are different from those present in Alzheimer disease. In contrast to patients with Alzheimer disease, those with dementia with Lewy bodies have more subcortical than cortical dementia, resulting in executive dysfunction and inattention, whereas patients with Alzheimer disease have dysfunction of naming and memory.[8]

Pathology: diffuse distribution of Lewy bodies. As in Parkinson disease, the pathology is characterized by the appearance of Lewy bodies (positive stain for alpha-synuclein), but their distribution is more diffuse than in Parkinson disease and includes the brainstem, subcortical nuclei, limbic cortex, and neocortex,

which may lead to hallucinations in affected patients.

Autonomic features are also diffuse. Autonomic features are also more common in dementia with Lewy bodies than in idiopathic Parkinson disease, which may relate to the different distribution of pathology in these diseases. Significant autonomic failure is present in 62% of patients with dementia with Lewy bodies,[9] and the autonomic failure is believed to result from dysfunction of peripheral postganglionic neurons in addition to numerous cortical and brainstem Lewy bodies. Patients with dementia with Lewy bodies also have significant deposits in intermediolateral columns of the spinal cord and autonomic ganglia and sympathetic neurons.

PURE AUTONOMIC FAILURE

The pathology of pure autonomic failure is similar to that of dementia with Lewy bodies and idiopathic Parkinson disease. In contrast to these disorders, however, pure autonomic failure is characterized by a less significant presence of Lewy bodies in the cortex and brainstem, although the pathology in the spinal cord and peripheral nervous system is quite prominent.

Pure autonomic failure is a sporadic disease with onset after age 60 years. It is characterized by slowly progressive isolated impairment of the autonomic nervous system, which manifests particularly as orthostatic hypotension and also as significant bladder and sexual dysfunction. The condition is ultimately disabling as a result of the orthostatic hypotension.

CARDIOVASCULAR AUTONOMIC DYSFUNCTION

Orthostatic hypotension is the most limiting of the cardiovascular autonomic dysfunctions in the neurodegenerative disorders discussed here. Postprandial hypotension is also prevalent in these disorders, as is supine hyp*er*tension, which makes successful treatment of cardiovascular autonomic dysfunction difficult.

Orthostatic hypotension is defined as a decrease in systolic blood pressure of at least 20 mm Hg, or a decrease in diastolic blood pressure of at least 10 mm Hg, upon tilting or standing.

In contrast, in normal subjects the initial response upon standing is a pooling of 500 to 1,000 mL of blood and a reduction in venous return and cardiac output. A resultant decrease in blood pressure would occur if not for the baroreceptor reflex, which increases sympathetic tone and decreases vagal parasympathetic tone. Vasopressin is then released from the posterior pituitary, which increases peripheral vascular resistance, venous return, and cardiac output. As a result, the normal response to standing is a modest decrease in systolic blood pressure—ie, by 5 to 10 mm Hg—and an increase in diastolic blood pressure by a similar amount, as well as a compensatory increase in pulse rate of 10 to 25 beats per minute.

TABLE 3
Supportive but nondiagnostic features for dementia with Lewy bodies

Repeated falls
Syncope
Transient loss of consciousness
Neuroleptic sensitivity
Systemized delusions
Hallucinations in other modalities
REM sleep behavior disorder
Depression
Severe autonomic dysfunction
Relative preservation of medial temporal lobes on imaging
Generalized low uptake on SPECT/PET perfusion with reduced occipital activity
Abnormal (low-uptake) MIBG myocardial scintigraphy
Prominent slow-wave activity on electroencephalogram with temporal transient sharp waves

REM = rapid eye movement; SPECT = single-photon emission computed tomography; PET = positron emission tomography; MIBG = [^{123}I]meta-iodobenzylguanidine

Approaches to therapy for orthostatic hypotension

Nonpharmacologic approaches to orthostatic hypotension include raising the head of the patient's bed by 30 degrees, use of compression stockings, and liberalizing the use of fluids and salt.

Often, however, patients require pharmacologic therapy. Fluorohydrocortisone and midodrine are the primary drugs used for this purpose, but pyrodostigmine also has shown some efficacy in doses of 60 mg or greater in small clinical trials. Less-effective options include nonsteroidal anti-inflammatory drugs, vasopressin analogs, erythropoietin, and caffeine.

Management of postprandial hypotension

Reducing meal size while increasing the frequency of meals and adding caffeine are dietary approaches to treat postprandial hypotension. Somatostatin analogs may be helpful, although data to support their use for this indication are limited.

Treatment of supine hypertension is more difficult

The management of supine hypertension is difficult in patients with neurodegenerative disorders. Supine hypertension is defined as a blood pressure greater than 140/90 mm Hg, but the threshold for concern is uncertain. Most patients with neurodegenerative disorders are plagued more by hypotension than by hypertension, but the hypertension can be deleterious to their health, particularly when they are being treated for their hypotension during the day. Some clinicians choose to treat the hypertension if it is significant in the evening. Most important is to remove the midodrine at night and minimize the use of fluorohydrocortisone. Other options are nitrate derivatives, hydralazine, and calcium channel blockers. The proposed benefits of minoxidil and clonidine are controversial.

Autonomic complications of dopaminergic therapy

Complicating the management of autonomic dysfunction in patients with parkinsonian features is that drug therapies for Parkinson disease exacerbate orthostatic hypotension to varying degrees. Selegiline, amantadine, and dopamine agonists exacerbate orthostasis to a greater degree than levodopa does. Therefore, we are apt to start treatment with levodopa as patients develop more features of autonomic dysfunction, as well as in patients with advanced Parkinson disease or in patients who are older than 70 years of age.

Multiple system atrophy may respond only to high doses of levodopa (> 1 g), and when autonomic symptoms are prominent, patients with multiple system atrophy may not tolerate dopaminergic therapy at all. In patients with dementia with Lewy bodies, the use of dopaminergic therapies is limited not so much by autonomic dysfunction but because of hallucinations and cognitive decline.

SUMMARY

Central autonomic dysfunction predominates in patients with multiple system atrophy. Peripheral autonomic dysfunction predominates in the other parkinsonian disorders with Lewy body pathology, and this includes idiopathic Parkinson disease, dementia with Lewy bodies, and the related disorder, pure autonomic failure, in which there are no parkinsonian features.

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Deep brain stimulation: How does it work?

ABSTRACT

Deep brain stimulation has significantly improved the motor symptoms in patients with Parkinson's disease (PD) and other movement disorders. The mechanisms responsible for these improvements continue to be explored. Inhibition at the site of stimulation has been the prevailing explanation for the symptom improvement observed with deep brain stimulation. Research using microelectrode recording during deep brain stimulation in the MPTP monkey model of PD has helped clarify how electrical stimulation of structures within the basal ganglia–thalamocortical circuit improves motor symptoms, and suggests that activation of output and the resultant change in pattern of neuronal activity that permeates throughout the basal ganglia motor circuit is the mechanism responsible for symptom improvement.

Whether deep brain stimulation can dramatically help patients with Parkinson's disease (PD) and other movement disorders is no longer questioned. Rather, *how* it works is not well understood: how do patients with seemingly diverse conditions show improvement with the same intervention?

Patients with advanced PD often freeze when trying to walk and have tremor, rigidity, bradykinesia, and gait and balance problems. With deep brain stimulation, a patient typically experiences a marked improvement in these motor symptoms.

Similarly, patients with hypokinetic disorders such as generalized dystonia who have extensive involuntary movements involving multiple body parts may experience a significant reduction in these movements and regain function during deep brain stimulation. In my experience, it is not unusual for patients who were not ambulatory as a result of their dystonic movements to regain function to the point where they can walk unassisted and, in some cases, participate in physical activities such as racquetball or jogging on a treadmill. One of my patients with generalized dystonia could walk no farther than several meters before deep brain stimulation but afterward was able to run on a treadmill. This patient did not gain this type of function immediately after stimulation, but after sustained efforts at programming his stimulation device over the course of 1 year he was able to travel to Europe, hike in the mountains, and jog on a treadmill.

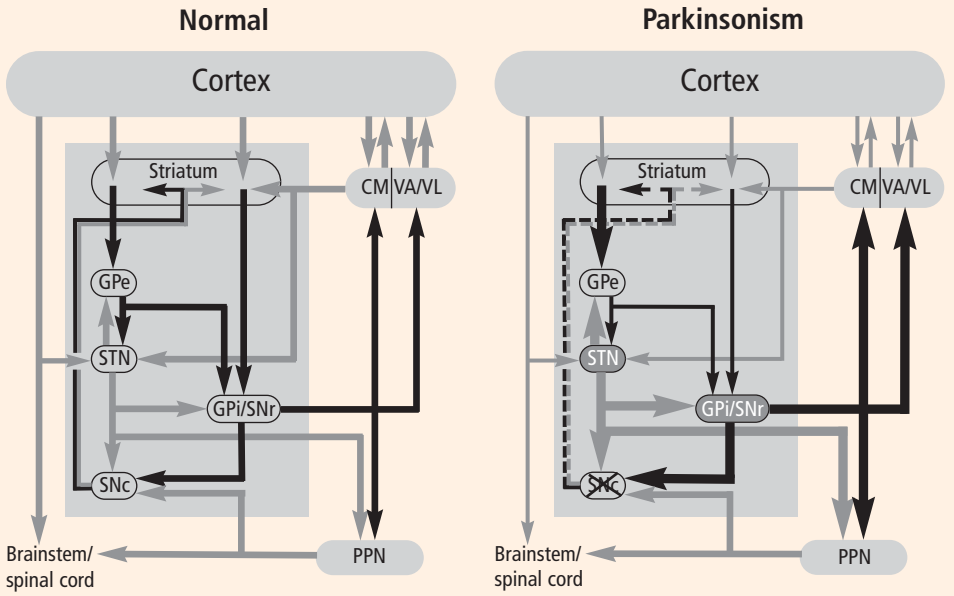
In addition to treating movement disorders, deep brain stimulation is being used experimentally to treat patients with behavioral disorders such as depression and obsessive-compulsive disorder that are refractive to standard therapy. Broadening our understanding of the mechanisms responsible for success with deep brain stimulation is important since it may help to improve current applications and develop new ones. This article discusses our research in deep brain stimulation using microelectrode recording of structures within the basal ganglia–thalamocortical circuit in the MPTP monkey model of PD.

INSIGHTS INTO MECHANISMS OF STIMULATION PROMISE TECHNOLOGICAL REFINEMENTS

One rationale for attempting to better understand how deep brain stimulation works is that such knowledge may enable us to improve the technology to better apply the technique.

Electrode design is one important area of potential improvement. Diseases that may one day be treated with deep brain stimulation will likely require electrodes of different shapes than those used currently, to accommodate other targets in the brain. At present, a single lead shape is used to stimulate the subthalamic nucleus (STN) and the globus pallidus internus (GPi) for treating PD. Possible future targets include the globus pallidus externus (GPe), various subnuclei of the thalamus, portions of the striatum, and other subcortical and cortical structures that have different geometric configurations and physiologic characteristics. Since these structures and regions of the brain differ from one another in size and shape, it is highly likely that new electrode designs will be needed to take advantage of

Dr. Vitek reported that he serves as a consultant and board member for Advanced Neuromodulation Systems, Inc., and serves as a consultant for Medtronic, Inc., from which he has also received fees for teaching/speaking.



GPe = external segment of the globus pallidus
GPi = internal segment of the globus pallidus
STN = subthalamic nucleus
SNr = substantia nigra pars reticulata
SNc = substantia nigra pars compacta
CM = centromedian nucleus of thalamus
VA/VL = ventroanterior and ventrolateral nuclei of thalamus
PPN = pedunculopontine nucleus

FIGURE 1. Schematic diagram of the basal ganglia–thalamocortical circuitry under normal and parkinsonian conditions. Inhibitory connections are shown as black arrows, excitatory connections as gray arrows. Parkinsonism leads to differential changes in the two striatopallidal projections, which are indicated by the thickness of the connecting arrows. Basal ganglia output to the thalamus is increased.

Reprinted, with permission, from Wichmann T, et al. Basal ganglia: anatomy and physiology. In: Factor SA, Weiner WJ, eds. Parkinson's Disease: Diagnosis and Clinical Management, 2nd ed. New York, NY: Demos; 2008:255.

this geometric and physiologic variability. Future electrodes may vary in size and shape from those used currently, incorporate three-dimensional designs, and require a current source that allows the pattern of stimulation to be varied based on the physiologic changes that characterize each neurologic disorder.

Directionality may be another important feature of electrode design. With presently used electrodes, electric current spreads in all directions. To spread the current or increase the volume of tissue affected by stimulation, one must increase the voltage being passed through the lead. This results in a larger region of tissue being affected by stimulation, but the current density varies based on distance from the stimulation site, with neural tissue close to the site being affected differently from tissue that is farther away. Moreover, the current cannot be directed or aimed in one direction or the other. A split-band design could spread current in opposing directions, and a three-dimensional directional design involving several contacts could affect a volume of tissue more homogeneously.

PROGRESS IN DEFINING PD PATHOPHYSIOLOGY

As with any disease, defining the problem and understanding the underlying pathophysiology are essential first steps to finding an effective treatment for PD. In the 1930s and 1940s, numerous attempts were made to treat PD with surgical therapies. Surgical targets were chosen throughout the length of the neuraxis, including the cortex, the internal capsule, the basal ganglia, the thalamus, the cerebral peduncle, and the spinal cord itself. The underlying pathophysiology was not well understood, however, so the rationale for surgery was weak at best. For example, lesioning the cortex improved parkinsonian tremor, but it also caused paralysis and was associated with considerable morbidity.

Evidence of a common circuit

Over time, a number of anatomic and physiologic studies provided evidence that there may be a common anatomy or circuit that malfunctions between the diverse disorders that are now improved with deep brain stimulation. It is now recognized that PD and dystonia—disorders that involve a paucity of movement and excessive movement, respectively—both result from disorders of the basal ganglia. Similarly, the basal ganglia–thalamocortical circuit appears to play an integral role in behavioral disorders such as depression, schizophrenia, autism, and obsessive-compulsive disorder. This basal ganglia–thalamocortical circuit includes connections from the cortex, through the basal ganglia, and back to the cortex through the thalamus **(Figure 1)**. Different regions within nodal points (striatum, GPe, GPi, STN, thalamus) of the circuit affect movement, cognition, and behavior, so that malfunction in different regions of each nodal point in the circuit may result in different neurologic disorders.

In PD, degeneration of dopamine-producing neurons

in the substantia nigra pars compacta reduces dopamine levels in the striatum. In MPTP monkey models of PD there is also a loss of dopamine-producing cells in the substantia nigra pars compacta. These animals develop the cardinal motor symptoms of PD and are considered a good model of the human disorder. By recording from the basal ganglia–thalamocortical circuit in this model, we and others have observed excessive activity in the STN and GPi.[1–4] In addition, cells in these regions in the monkey model were more likely to discharge in bursts compared with cells from healthy monkeys, and they showed a higher degree of synchronized oscillatory activity among neighboring neurons.[5,6]

Ultimate goal: The ability to individualize therapy

Understanding how such changes relate to parkinsonian symptoms will enable us to develop stimulation strategies that are focused on ameliorating the particular physiologic changes in PD. Since PD can lead to distinctly different clinical pictures, it would be ideal to be able to individualize therapy based on the particular motor symptoms each patient experiences. This may require stimulation strategies that affect either a particular region of the targeted structure or a particular physiologic change that occurs in the disease state.

THE 'RATE HYPOTHESIS': ALTERED CELLULAR DISCHARGE RATES CAUSE PARKINSONIAN MOTOR SYMPTOMS

A good model for PD was lacking prior to the 1980s. As a result, there was little understanding of the pathophysiologic basis for this disorder. A breakthrough in the mid-1980s revolutionized research in this field. A group of young people developed parkinsonian symptoms, and it was discovered that they had all used recreational "designer drugs" containing an impurity: the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Now given to primates to simulate PD, MPTP causes all of the classic symptoms of PD except tremor (this may vary from species to species), including freezing, slowness, stiffness, and gait and balance problems. Like humans with PD, primates with MPTP-induced PD even develop dyskinesia after prolonged treatment with levodopa.

Experimentation with MPTP monkeys in the late 1980s led to the "rate hypothesis," which basically states that when dopamine production is reduced from the substantia nigra compacta (as in PD), changes in striatal activity lead to suppression of GPe activity and a reduction in inhibitory output from the GPe to the STN. This decrease in inhibitory output allows the STN to be overactive, which, in conjunction with a reduction of direct striatal inhibition of the GPi, causes excessive GPi activity and a suppression of thalamic activity to the cortex **(Figure 1)**.

When recording electrodes were placed in these structures in the monkey brain, rate changes were reported to occur in each of these structures in the parkinsonian state.[1–4,7] Action potentials recorded from the GPi in MPTP-treated monkeys occurred at a much faster rate than those in healthy monkeys.

Pallidotomy revisited: Dramatic symptom improvement is possible

On the basis of the above and other studies in the MPTP monkey model of PD, investigators in the 1990s reasoned that reduced dopamine in PD led to excessive activity in portions of this circuit. While I would like to say that this led to the rationale for lesioning the STN and GPi for the treatment of PD, this approach had already been taken in the early 1930s and 1940s and continued into the 1960s; it was largely stopped with the introduction of levodopa and was restarted again after the realization that chronic levodopa therapy was associated with a variety of side effects, including the development of excessive involuntary movement and motor fluctuations.

Pallidotomy (lesioning of the pallidum), although tried as a treatment for PD in the 1930s and 1940s, had been abandoned as a result of its inconsistent benefit and lack of effect on parkinsonian tremor. It underwent a resurgence in the 1990s through the work of a group in New York[8] that revived Lars Leksell's pallidotomy approach of the 1960s[9] at a time when basic science studies provided the rationale for surgical therapy to create lesions in the GPi. These basic science studies also provided critical new information about the optimal site for lesioning, which led to improved and more consistent outcomes.[10–13] In the early years, lesions were created in the anterior (nonmotor) portion of the pallidum but led to inconsistent results. In the 1990s, with a better understanding of the portion of the pallidum involved in motor control, destroying brain tissue by creating a lesion in the posterolateral "motor" region of the pallidum resulted in such dramatic improvement in motor signs that waiting lists of up to 4 years were common for patients who wanted the procedure.

Although unilateral pallidotomy led to marked improvement in motor symptoms on the contralateral side, attempts at bilateral lesions to improve both sides of the body, as well as axial symptoms, were associated with marked hypophonia and, in some reports, cognitive decline. This led physicians and scientists to search for a procedure that could be performed

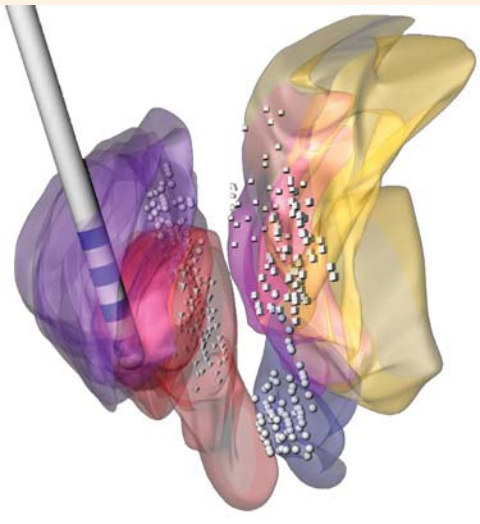


FIGURE 2. Image generated by software designed to assist in lead placement in a monkey model of Parkinson's disease.[16] The various subcortical structures are represented in different colors. In this example, the thalamus is yellow, the subthalamic nucleus is gray, the globus pallidus externus (GPe) is purple, and the globus pallidus internus (GPi) is red/pink. The lead is passing through the GPe and GPi with the contacts denoted by the purple bands. Each cell from which recordings are made is denoted by a white symbol.

bilaterally without the high incidence of side effects associated with lesioning procedures—and thus to the birth of deep brain stimulation.

Deep brain stimulation as lesion simulation

During the early experience with pallidotomy, the area to be lesioned would first be stimulated with the lesioning probe to observe its effects and thereby determine the precise area in which to create a lesion. At the time, no mechanism existed to leave the stimulator in place rather than create a lesion. But after the development of implantable stimulation devices, chronic stimulation could be delivered bilaterally to the pallidum and STN, resulting in a markedly improved treatment. Since side effects associated with stimulation are reversible, the ability to perform such procedures on both sides of the brain and to adjust stimulation parameters in order to optimize benefits while minimizing side effects made deep brain stimulation the procedure of choice for patients with advanced PD and led to its exploration for treatment of other neurologic disorders.

Because stimulation produced the same or similar benefit as a lesion, most physicians thought that stimulation must work in a similar manner, ie, by decreasing output from the stimulated structure. The rationale for this hypothesis received support from the "rate" model of PD, which postulated that PD motor symptoms occur as a result of overactivity in the STN and GPi. It was postulated that deep brain stimulation improved clinical symptoms by suppressing output from the stimulated structure—in other words, deep brain stimulation effectively caused a physiologic ablation.[14,15]

FURTHER RESEARCH GIVES RISE TO THE 'PATTERN HYPOTHESIS'

Deep brain stimulation in the monkey model

To test the effects of deep brain stimulation, we have performed it in primates with MPTP-induced parkinsonism. Custom-made leads sized to fit a monkey brain are implanted in the same deep brain structures that are targeted when treating PD in humans. Each animal lead has four contacts 0.5 mm in size. We implant a pulse generator, connect the pulse generator to the lead, and set stimulation parameters to improve motor symptoms to mimic a human therapeutic setting as closely as possible. We then record from the basal ganglia structures before, during, and after stimulation that improves the monkey's motor symptoms. This allows us to determine which changes in neuronal activity in the basal ganglia circuit during stimulation are associated with an improvement in motor symptoms.

Chamber placement and orientation as well as lead placement are determined with the help of a software program and information from magnetic resonance imaging and computed tomography, similar to the process for neurosurgery in humans.[16] The software also allows for mapping the location of every cell from which recordings are taken **(Figure 2)**.

In earlier studies examining the mechanism underlying deep brain stimulation, neural activity was recorded only after stimulation, so that activity that occurred during stimulation had to be inferred from that which occurred immediately after stimulation was stopped. We developed a method to subtract artifact produced from stimulation without losing data. This method has been validated, is now used in a number of laboratories, and has revolutionized our ability to study the effect of stimulation on neuronal activity.[17]

A paradoxical finding

Based on the rate hypothesis, we expected that increased output from the GPi would cause parkinsonian symptoms and predicted that stimulation of the STN should suppress its output, which would suppress excitatory activity to the GPi from the STN and thereby reduce its output. Reduction of the inhibitory output from the GPi to the thalamus would, in turn, lead to a restoration of thalamocortical function and a reduction in the motor signs associated with PD. However, stimulating the STN was found to *increase* GPi activity.[18]

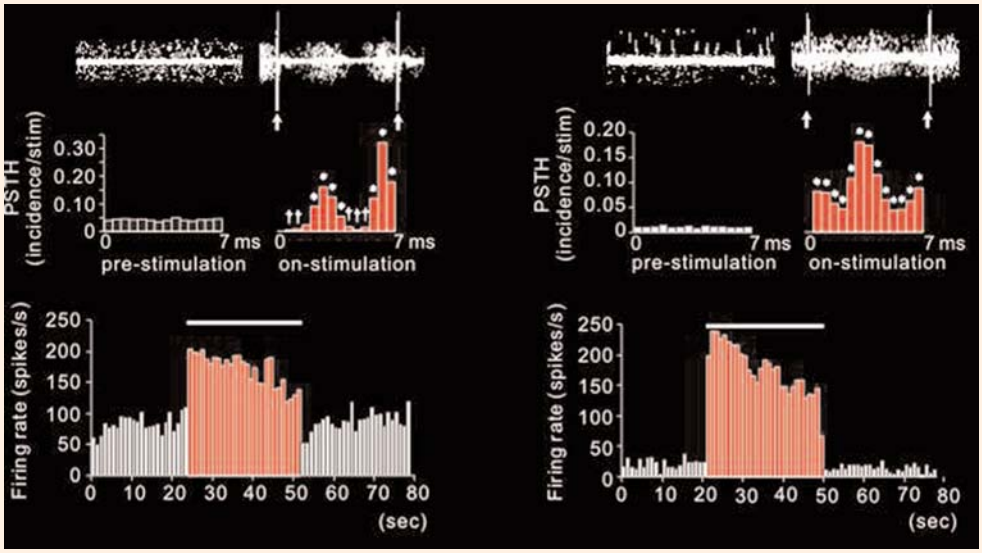


FIGURE 3. Examples of neuronal responses occurring during subthalamic nucleus stimulation in (A) a GPi cell and (B) a GPe cell. **Top:** Analog signal overlays of 100 sweeps made by triggering at 10-ms intervals in the prestimulation period (before start of stimulation) and by triggering on the stimulation pulse in the on-stimulation period. Arrows indicate residual stimulation artifacts after artifact template subtraction. **Middle:** Peristimulus time histograms (PSTHs) reconstructed from successive 7.0-ms time periods in the prestimulation period and from the interstimulus periods (7.3 ms) in the on-stimulation period. The first PSTH bin is omitted in the on-stimulation period because of signal saturation and residual stimulation artifacts. Asterisks denote a significant increase at $P < .01$, and daggers denote a significant decrease at $P < .01$ (Wilcoxon signed rank test). **Bottom:** Mean firing rate calculated every 1 sec on the basis of the PSTH, illustrating the time course of the firing rate.

Despite increased rates, the incidence and intensity of symptoms were reduced. Further complicating the picture, we were contemporaneously exploring the effect of creating lesions in other parts of the basal ganglia that also led to increased rates of GPi activity, but in this case we observed that the increased rates were associated with a worsening of motor symptoms. In short, we had two laboratories working in parallel that had apparently obtained opposite results: increased GPi activity was associated with improved symptoms in one laboratory and with worse symptoms in the other.[18,19]

Patterns of activity are more important than rate

This seeming paradox may be explained by evaluating the data with a post-stimulus time histogram **(Figure 3)**. Simple recordings of activity show seemingly random action potentials over time; however, if activity is recorded repeatedly during stimulation and the overall data are averaged, action potentials are observed to occur in a definite pattern, with action potentials in GPi neurons occurring mainly at 3 ms and 6 ms after a stimulation pulse in the STN. The number of cells showing a particular pattern of response could be changed by varying the stimulation parameters. This shift in the population of neurons that showed such a stereotyped pattern of response under stimulation parameters that improved motor symptoms may offer part of the explanation for our apparent paradox: stimulation that improved motor symptoms regularized that spike train, while the lesions we produced in the GPe that increased the rate did not change the irregularity in the spike train. These observations provided compelling data to support the hypothesis that motor symptoms associated with PD, and possibly other movement and nonmovement disorders, may occur as a result of changes in the pattern of neuronal activity rather than changes in rate.

Knowledge that stimulation activated output from the stimulated region and changed the pattern of neuronal activity led us to ponder whether other targets, or even other ways to deliver stimulation, might work better to improve parkinsonian symptoms.

A focus on GPe stimulation

As a result of these observations, we reasoned that since GPe activity is also altered in PD and its rates are reduced, driving the output from this region that is inhibitory to the STN and GPi may help to reduce and regularize that activity at a point in the circuit that could provide even greater improvement in the motor symptoms associated with PD. Based on this hypothe-

sis, we performed direct stimulation of the GPe in the MPTP monkey model of PD and evaluated its effect on motor behavior and neuronal activity in the circuit.

As an interesting sidelight, it should be noted that long before we developed this hypothesis, we had observations from a 1994 experiment (only recently published[20]) in which bradykinesia was improved upon acute stimulation in the GPe prior to making a lesion in the GPi. With sustained stimulation in this patient, we observed development of dyskinetic movements. Since we reasoned that lesions in this region would worsen parkinsonian symptoms—a rationale recently supported by a publication from our laboratory in 2006[19]—and since we had no means by which to stimulate this region chronically at the time, this observation was filed away and we continued with lesioning the GPi for the treatment of these patients.

However, with the advent of chronic deep brain stimulation, we opted to reexplore this series of experiments in MPTP-treated monkeys. A lead was placed such that three of its contacts were in the GPe and one was in the GPi. Bradykinesia was assessed by determining the time it took for the monkey to retrieve raisins from a Klüver board. By inducing symptoms on one side only, we were able to use the healthy side as a control. We observed that before stimulation, retrieval took more than twice as long on the affected side. Stimulation of only 2 V had no effect, but increasing the voltage to 5.5 V significantly improved retrieval time.[21]

Plotting the data using post-stimulus time histograms showed that stimulation of the GPe inhibited the STN, confirming our hypothesis that stimulation activated the output from the stimulated structure (the GPe sends inhibitory projections to the STN). The responses observed were dramatic, with the majority of cells in the STN showing almost complete suppression of activity (Vitek et al, unpublished data).

In light of this observation, we expected that the rate of activity in the GPi would be reduced. Interestingly, although the rate was changed in most cells compared with control, what was most striking was the relatively stereotyped pattern of inhibition and excitation that occurred following each pulse of GPe stimulation. Although shifted in absolute frequency, the pattern that occurred was similar to that observed during STN stimulation, with alternating periods of excitation and inhibition evident in the post-stimulus time histogram.

Further evaluation of the data revealed a change in burst and oscillatory activity in the STN. Analysis of the data showed a shift in the distribution of power from low to high frequencies. Stimulation reduced activity in the low-frequency range and increased power in higher frequencies, similar to that in normal movement.

Further analysis of the spike trains revealed that entropy (a reflection of noise in the spike signal) was reduced under stimulation parameters that resulted in a reduction in symptoms. In contrast, stimulation parameters that resulted in worsening symptoms increased measures of entropy (Dorval, data submitted for publication).

PATTERN CHANGES AFFECT INFORMATION PROCESSING ACROSS THE BASAL GANGLIA–THALAMOCORTICAL NETWORK

There is a lack of consensus about the precise physiologic effect of deep brain stimulation for improving symptoms in movement disorders. Many researchers continue to believe that deep brain stimulation works through inhibition. An alternate explanation is that at effective stimulation parameters, the net effect is activation of output from the stimulated structure. Various modalities, including modeling,[22,23] microdialysis,[24] functional magnetic resonance imaging,[25] and positron emission tomography,[26,27] provide additional evidence that activation occurs during stimulation.

While one cannot discount a role for rate changes in mediating the effects of deep brain stimulation, there is now increasing evidence suggesting that pattern changes induced in the network as a result of stimulation-induced activation of output from the stimulated structure play an integral role in this process.

Research often leads to unpredictable outcomes. The prevailing hypothesis a decade ago concerning the pathophysiologic basis of PD (and still believed in many centers) was that rate is the controlling factor. But we have seen in our animal models that symptoms improve with increased rate in the GPi during stimulation in the STN. Similarly, GPi rates are abnormally low in patients with dystonia and in PD patients during dyskinesia, yet lesioning in the GPi that further reduces its output leads to improvement in these conditions. Based on these observations, it would appear that rate is unlikely to be the critical factor; we now must take into account other factors, such as pattern, oscillation, and synchronization, as well as changes in the network dynamics. Deep brain stimulation is changing the informational content of the neural network, and these changes are occurring across populations of neurons through the whole basal ganglia circuit. Knowing how these changes result in improvement in the neurologic disorder being treated will be critical to our understanding of not only how deep brain stimulation works, but how to make it work better and how to apply it effectively to other neurologic disorders.

FUTURE DIRECTIONS

Future research should focus on multiunit recording simultaneously across nodal points in the basal ganglia–thalamocortical circuit to assess population and network dynamics. This approach would provide information on the real-time effects of stimulation in the network. Until now, most studies have collected recordings from one cell at a time. This is a very labor-intensive process and limits our ability to relate what happens at one point in the circuit to what happens at another point. Multiunit recording across multiple nodes within the basal ganglia–thalamocortical circuit will help us address this question and tell us what happens across populations of neurons at multiple sites in the motor circuit and how this is changed during stimulation. Such an approach will help us to better understand the pathophysiologic basis for the development of neurologic disorders and how stimulation works to improve these disorders. This information is a critical step toward the ability to knowingly change network activity in a way that is predictable and more compatible with the normal state, as well as toward the application of this technology to other disorders.

The potential for clinical applications of deep brain stimulation is dramatic, but we must proceed with caution. Indications should be based on sound scientific rationale, and outcomes must be accurately and systematically documented. Move forward we must, but with caution—most certainly.

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Sudden unexpected death in epilepsy: Impact, mechanisms, and prevention

ABSTRACT

Patients with refractory epilepsy face an elevated risk of sudden death, with rates as high as 1% per year. This phenomenon, known as sudden unexpected death in epilepsy (SUDEP), is believed to be a seizure-related occurrence, but the exact underlying mechanisms are uncertain. Both pulmonary and cardiac pathophysiologies have been proposed. The cardiac mechanism of greatest interest is the precipitation of arrhythmias by seizure discharges via the autonomic nervous system. SUDEP prevention has centered on effective seizure control, and epilepsy surgery has reduced SUDEP incidence in a number of studies. Additional prophylaxis methods are needed, however, for the large number of patients with treatment-refractory epilepsy. Future research should aim to clarify whether the association between seizures and autonomic dysfunction and cardiac arrhythmias extends to a demonstrable cardiac mechanism for SUDEP.

The intimate interplay between heart and brain is well illustrated in epilepsy and may underlie the mechanism of one of its most devastating consequences: sudden unexpected death in epilepsy (SUDEP). This article will briefly describe the potential mechanisms of SUDEP, elaborate on the evidence for a likely cardiac pathophysiology, and review considerations in SUDEP prevention. We begin with a couple of brief case presentations and an epidemiologic overview to illustrate the concept and significance of SUDEP.

CASE PRESENTATIONS

A patient with near-SUDEP

The following is an actual message received by one of the authors:

Dr. Najm: A quick note regarding a 27-year-old male patient of yours with cerebral palsy and seizure disorder. Yesterday, while being transported from floor to floor, he had a cardiac arrest and was successfully resuscitated. Immediately after the code he developed seizures, which were treated with phenytoin and lorazepam. He is now in the neurointensive care unit. Thank you.

This case represents a scenario of near-SUDEP in which death was prevented by the fortuitous presence of immediate medical assistance at the time of cardiac arrest. Had this patient been home at the time of this incident, he almost certainly would have simply been found dead in his bed, like many SUDEP victims.

A typical case with multiple risk factors

A 32-year-old man underwent left temporal lobectomy at the Cleveland Clinic for treatment of medically refractory focal epilepsy. His seizure frequency improved after surgery, but he continued to have rare convulsions. Nevertheless, he discontinued all his anticonvulsant medications on his own. One year later, he was found dead on his bathroom floor. No obvious cause of death was identified.

This case illustrates several characteristics of the patient typically at risk for SUDEP: young, male, with intractable poorly controlled epilepsy, and not taking antiepileptic medications.

EPIDEMIOLOGY AND RISK FACTORS

Epilepsy affects 1% of the US population. Among those affected by epilepsy, SUDEP is a common cause of mortality. Estimates of SUDEP incidence range from 0.7 to 1.3 cases per 1,000 patient-years in large cohorts of patients with epilepsy[1,2] and from 3.5 to 9.3 cases per 1,000 patient-years in anticonvulsant drug registries, medical device registries, and epilepsy surgery programs.[3–5] SUDEP accounts for up to 17% of all deaths in patients with epilepsy[6,7] and exceeds the expected rate of sudden death in the general population by nearly 24 times.[6,8]

Several potential risk factors for SUDEP have been investigated, but results from different studies are

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

conflicting. Consistently identified risk factors include young age, early onset of seizures, refractoriness of epilepsy, the presence of generalized tonic-clonic seizures, male sex, and being in bed at the time of death. Weaker risk factors include being in the prone position at the time of death, having one or more subtherapeutic blood levels of anticonvulsant medication, having a structural brain lesion, and being asleep.[9] The current consensus is that SUDEP is primarily a "seizure-related" occurrence, but the exact mechanisms underlying SUDEP are unknown.

PROPOSED MECHANISMS

Pulmonary pathophysiology

Central apnea and acute neurogenic pulmonary edema are the two major proposed pathways linking seizures to SUDEP. Evidence exists for each pathway.

Central apnea. In a prospective study of patients in an epilepsy monitoring unit, central apnea lasting at least 10 seconds was observed postictally in 40% of the recorded seizures.[10] Otherwise healthy young epilepsy patients have been reported to develop central apnea immediately following complex partial seizures.[11] Neurotransmitters mediating the brain's own seizure-terminating mechanism could also be inhibiting the brainstem and causing postictal apnea.

Acute neurogenic pulmonary edema has been well described in relation to severe head injury and subarachnoid hemorrhage. Pulmonary edema is frequently found in SUDEP patients at autopsy.[12] Intense generalized vasoconstriction induced by massive seizure-related sympathetic outburst can lead to increased pulmonary vascular resistance, and thereby may mediate acute pulmonary edema.

These two mechanisms—central apnea and acute neurogenic pulmonary edema—are not mutually exclusive. In the only animal model of SUDEP, one third of animals died from hypoventilation and had associated pulmonary edema at autopsy.[13] Limited opportunities for realistic and practical interventions to reverse SUDEP risks related to pulmonary causes have hindered further development of these concepts.

Cardiac pathophysiology

The most significant and widely discussed cardiac mechanism of SUDEP is cardiac arrhythmia precipitated by seizure discharges acting via the autonomic nervous system.[14–19]

Centers of autonomic control are also key epileptic foci. A tight interconnected network exists throughout the neuraxis to control various elements of the cardiovascular autonomic system. A solid understanding of this network provides useful insights for consideration of a cardiac pathophysiology of SUDEP. Key components of the central cortical control of autonomic functions include the insula, the anterior cingulate gyrus, and the ventromedial prefrontal cortex. The insula represents the primary viscerosensory cortex, while the cingulate gyrus and prefrontal cortices form the premotor autonomic region. At the subcortical level, the hypothalamus provides the interface with the endocrine stimuli and triggers corresponding autonomic responses to maintain homeostasis. The amygdala, an integral component of the limbic system linking the cortical and subcortical centers already mentioned, mediates the autonomic response to emotions. In addition to playing a key role in autonomic control, the insula, amygdala, cingulate gyrus, and prefrontal cortex also represent the most common foci of partial epilepsy, which leaves no mystery behind the frequent observation of autonomic changes in relation to epileptic seizures.[19] **Figure 1** provides an overall illustration of those changes.

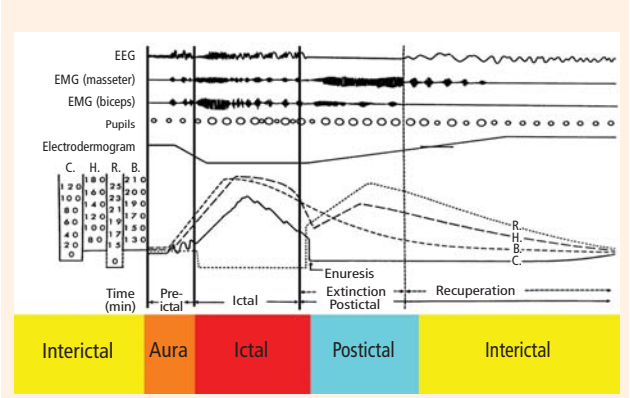

FIGURE 1. Autonomic changes during a motor seizure. Clear increases in the heart rate (H) and blood pressure (B) correspond to a suppression in the respiratory rate (R) during the ictal phase. Autonomic changes continue well after the ictal event is finished. C = cystogram.

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Experimental evidence. Heart rate changes, including bradycardia, tachycardia, and even asystole, have been repeatedly provoked by electrical brain stimulation of the limbic system and insular cortex.[19] Some studies have suggested a lateralized influence of the insulae on cardiovascular autonomic control. In one study, intraoperative stimulation of the left posterior insula elicited a cardioinhibitory response and hypotension, whereas stimulation of the right anterior

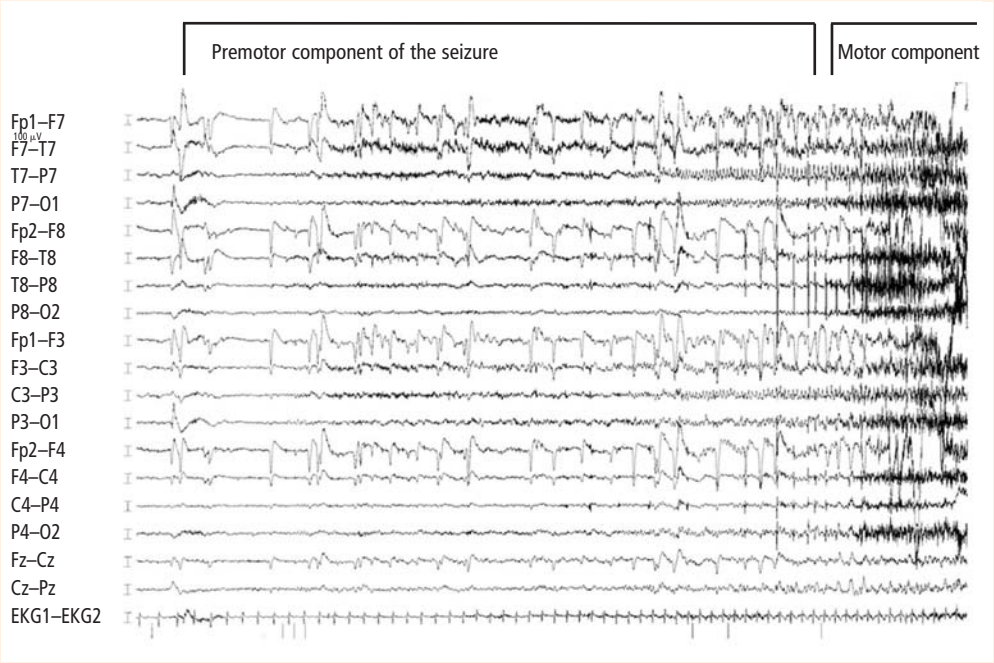

FIGURE 2.
Electroencephalographic and electrocardiographic tracings from a patient with ictal tachycardia during a left temporal lobe seizure.

insula elicited tachycardia and hypertension.[20] Such results have not always been reproducible.[21–23] Other studies have suggested a localization-related influence of the limbic system on cardiovascular responses. Stimulation of the amygdala has not led to the ictal tachycardia that is commonly seen in epileptic seizures, suggesting that cortical involvement is needed for the development of tachycardia.[24]

Clinical evidence. Clinically, a similarly wide spectrum of cardiac arrhythmias has been reported during seizures.[10,14,25–28] Illustrative examples are shown in **Figures 2 and 3**. Ictal cardiac arrhythmias occurred in 42% of hospitalized epilepsy patients in one study, with the most common being an irregular series of abrupt rate changes toward the end of the electroencephalographic (EEG) seizure discharge.[14] In another study, analysis of R-R intervals during the first 10-second period of EEG discharge showed a significant early heart rate increase in 49% of seizures; the corresponding figure for an early heart rate reduction was 25.5%.[26] Ictal asystole, atrial fibrillation, repolarization abnormalities, and bundle branch blocks have also been reported.[10,16,17,27,29] The hypothesis that such arrhythmias are more prominent in SUDEP patients than in the general epileptic population could provide a direct extension of these observations to a specific subgroup of epilepsy patients. Evaluation of clinical and EEG characteristics of SUDEP patients would then represent an indirect investigation of the experimentally observed heart rate changes with various cortical stimulation experiments.

ECG abnormalities and seizure characteristics. The occurrence of ictal electrocardiographic (ECG) abnormalities has been correlated to certain clinical seizure characteristics. In one study, mean seizure duration was longer in patients with ECG abnormalities than in those without such changes.[16] In other studies, generalized tonic-clonic seizures have been associated with increased occurrence and severity of ictal ECG abnormalities relative to complex partial seizures.[16,17] Those same clinical seizure characteristics were correlated with a higher risk of SUDEP.[30] This suggests an interrelation between seizure semiology, ECG abnormalities, and SUDEP.

SUDEP PREVENTION

Epilepsy control is first line of defense

A careful consideration of the incidence of SUDEP in various patient populations suggests that controlling patients' epilepsy might just be the best method of preventing SUDEP. While estimated SUDEP incidence ranges from 0.7 to 1.3 cases per 1,000 patient-years in population-based studies of patients with epilepsy,[1,2] this rate escalates by nearly tenfold (3.5 to 9.3 cases per 1,000 patient-years) in cohorts with severe epilepsy, such as those derived from anticonvulsant drug registries, medical device registries, and

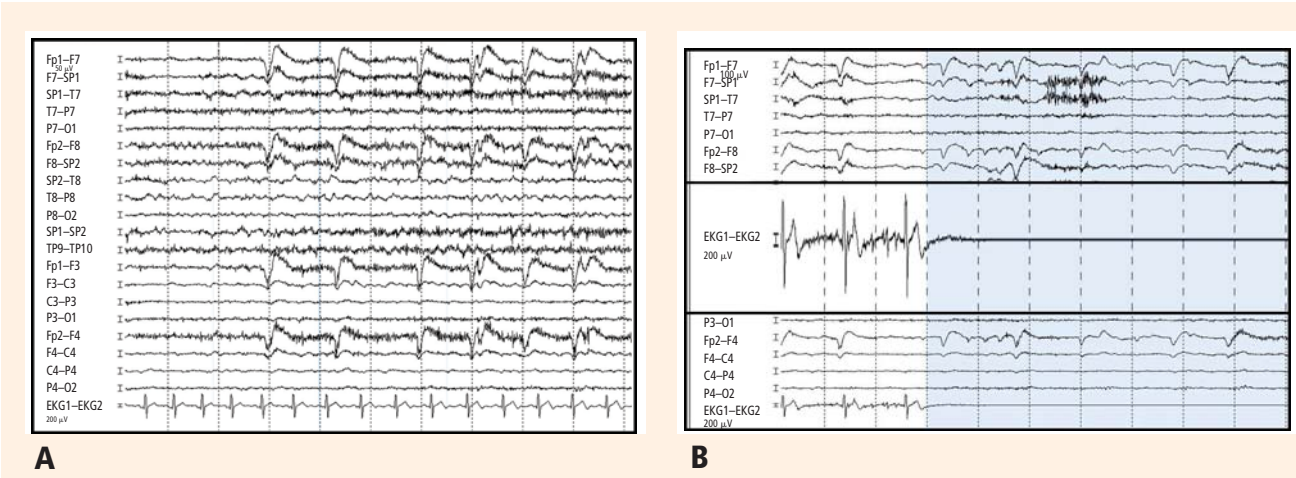

FIGURE 3. Electroencephalographic and electrocardiographic tracings from a patient with ictal bradycardia (A) and then asystole (B) during a right temporal lobe seizure.

referral centers.[3–5] Therefore, medical control of seizures might reduce the incidence of SUDEP.

Epilepsy surgery cuts SUDEP risk for many patients

Studies involving epilepsy surgery programs also suggest that successful epilepsy surgery reduces the impending risks of SUDEP. In cohorts in which the estimated risk of SUDEP is almost 1% per year without surgery, SUDEP incidence was significantly lower following epilepsy surgery. In a study of 305 patients who underwent temporal lobe epilepsy surgery in the United Kingdom, the incidence of SUDEP following surgery was 2.2 cases per 1,000 person-years, and only one-third of SUDEP cases were among seizure-free patients.[31] A similar incidence of 2.4 cases per 1,000 person-years was seen following epilepsy surgery in 596 Swedish patients; none of the 6 SUDEP patients in that study was seizure free.[32] In a US study, no SUDEP cases occurred among 256 seizure-free patients with a follow-up of about 5 years after epilepsy surgery.[33]

In our own experience at the Cleveland Clinic, we have reported on outcomes among 70 patients who underwent frontal lobectomy[34] and among 371 patients who underwent temporal lobectomy.[35] In the frontal lobectomy study,[34] 2 of the 39 patients who had persistent seizures following surgery died of SUDEP during follow-up, whereas none of the 31 patients who remained seizure free were dead up to 10 years after surgery. In the temporal lobectomy report,[35] 2 of the 141 patients with ongoing postoperative seizures died of SUDEP, as compared with none of the 230 patients who were seizure free after a mean follow-up of 5.5 years.

Additional means of prophylaxis needed

Unfortunately, as many as 30% to 40% of patients with epilepsy continue to suffer intractable epilepsy despite all the available treatment modalities, including epilepsy surgery. For these patients, controlling seizures to reduce the risk of SUDEP is neither a possible nor a realistic means of avoiding this devastating condition, and alternative methods of prophylaxis must be sought.

CONCLUSIONS AND FUTURE RESEARCH

Patients with refractory epilepsy currently face a lifelong risk of sudden death as high as 1% per year.[3] Elucidating the mechanisms of SUDEP might lead to preventive measures, which could have significant implications in reducing mortality in this patient population. Abundant evidence exists that autonomic dysfunction and cardiac arrhythmias are associated with seizures. The missing links in establishing a cardiac mechanism for SUDEP now include the following: (1) evidence of cardiac arrhythmias generally observed in seizures as a risk factor for SUDEP, (2) determination of clear electrophysiologic characteristics—from EEG and ECG standpoints—of patients at risk for SUDEP, and (3) clarification of the role of cardiac mechanisms in SUDEP and the role that cerebral influences on autonomic function might play. Early identification of patients at risk of SUDEP would offer a unique opportunity for early intervention to prevent this devastating condition.

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Evaluating brain function in patients with disorders of consciousness

ABSTRACT

Evaluating brain function in patients with disorders of consciousness may offer important clues to their state of awareness and help to predict prognosis. Disorders of consciousness mainly comprise the comatose state, the vegetative state, and the minimally conscious state. These disorders typically stem from acute brain insults caused by hypoxic-ischemic neural injury or traumatic brain injury, and the type of brain injury frequently determines the neuropathology. Current knowledge, including results from our laboratory, supports a model of extended brain tissue damage from the midbrain to the cortex in anoxia patients and a model of focal or multifocal cortical lesions in trauma patients. These differing models may help to explain differences in prognosis and outcomes in these excruciating life situations. Although the neural basis of consciousness remains puzzling, findings from normal volunteers and pathologies of consciousness show that widely distributed networks such as thalamofrontal and parietofrontal systems may be critical.

Consciousness has long been a fascinating subject to both philosophers and scientists, yet consciousness has only recently been taken into account by neuroscientists as a topic for research. This article discusses research done over the past 10 years evaluating brain function in patients with disorders of consciousness—specifically those in a vegetative or minimally conscious state. We highlight physiologic, sensory, perceptual, cognitive, and behavioral commonalities and disparities between patients with anoxic and traumatic brain injuries, with the aim of characterizing the neurophysiologic and neuroanatomic differences between these two main causes of disorders of consciousness.

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WHAT IS CONSCIOUSNESS?

Although consciousness is difficult to describe, it can be defined as a combination of wakefulness and awareness.[1] As for the brain systems supporting these two aspects of consciousness, it has been suggested that the brainstem ascending reticular formation system and its thalamic projections support alertness and the sleep-wake cycle, and that conscious awareness relies on a functional thalamocortical and corticocortical system.

DISORDERS OF CONSCIOUSNESS: A VARIETY OF STATES

Disorders of consciousness **(Figure 1)** mainly comprise three states: the comatose state, the vegetative state,[2] and the minimally conscious state.[3]

Coma: Near-complete unresponsiveness

Coma is a condition of almost complete unresponsiveness in which the patient lies with eyes closed, very limited reflexes, no cyclical wakefulness, and, above all, no signs of awareness. Coma is normally attained after an acute brain insult and may last about 2 weeks, although chronic coma cases have been described, and is usually caused by either temporary or permanent damage to the reticular system.

Vegetative state: Wakefulness without awareness

Following a coma, some patients may enter a vegetative state, which involves a complete absence of consciousness of one's environment but with preserved sleep-wake cycles and autonomic functions. The vegetative state is easily differentiated from brain death, in which the electroencephalogram shows no brain wave or activity.[4] Brain death is the irreversible end of all brain activity and should not be confused with a persistent vegetative state.

The vegetative state is a condition of wakefulness without awareness in which the patient exhibits a partially preserved sleep-wake cycle and a variable portfolio of reflexes and spontaneous nonvolitional behav-

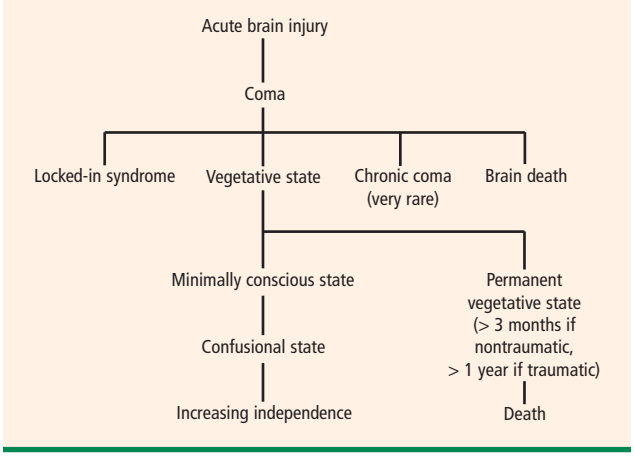

FIGURE 1. Flow chart outlining various disorders of consciousness and related disorders that may follow acute brain injury (traumatic or nontraumatic) and coma.

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iors. A patient who has been in a vegetative state for more than 1 month with no improvement is often said to be in a *persistent vegetative state*. The term *permanent vegetative state*, implying no chance of recovery, is sometimes used when the vegetative state persists for 3 months after a nontraumatic insult, such as cardiac arrest, or for 1 year after a traumatic brain injury.

Minimally conscious state: Conscious awareness is evident despite impairment

Some patients in a vegetative state may start to recover by entering a minimally conscious state, in which conscious awareness is evident despite profound physical and cognitive impairment. Although communication capabilities are absent, cognitively mediated (or voluntary) behavior occurs in the minimally conscious state, which may be inconsistent but is reproducible enough to be differentiated from reflexive behavior. For example, patients may occasionally be able to smile when asked to do so or follow an object with their eyes. In the minimally conscious state, patients show those basic behaviors seen in the vegetative state along with islands of presumably conscious processing such as inconsistent responses to simple commands and sustained visual pursuit.[5] Patients in a minimally conscious state have a better prognosis than those in a persistent or permanent vegetative state.[3]

Locked-in syndrome: Not a true disorder of consciousness

Another pathology that is often confounded with vegetative or minimally conscious states is the locked-in syndrome, which is characterized by complete paralysis of voluntary muscles in all parts of the body except those controlling eye movements. Individuals with locked-in syndrome are conscious and can think and reason, but they are unable to speak or move. The disorder confines the patient to paralysis and a mute state. Communication may be possible with blinking eye movements.

WHAT CAUSES DISORDERS OF CONSCIOUSNESS?

Disorders of consciousness mostly stem from acute brain insults, which may be caused by hypoxic-ischemic neural injury or traumatic brain injury. Although traumatic brain injury is currently the most common cause of vegetative and minimally conscious states, nontraumatic causes are becoming more frequent as a result of scientific and technological developments in resuscitation. Nontraumatic causes of disorders of consciousness include stroke, cardiopulmonary arrest, and meningoencephalitis; additionally, patients in the final stage of certain neurodegenerative diseases, including Parkinson, Alzheimer, and Huntington diseases, may lapse into a minimally conscious or vegetative state.[6]

NEUROLOGIC FINDINGS IN COMATOSE SURVIVORS OF CARDIAC ARREST

Structural magnetic resonance imaging (MRI) of patients in a vegetative state following cardiac arrest often reveals abnormalities. Most frequently there is a white matter signal in the cerebellum, the thalamus, the frontal and parietal cortices, and the hippocampus. Widespread abnormalities may indicate little to no prospect for recovery. Pupillary light response, corneal reflexes, motor responses to pain, myoclonus status epilepticus, serum neuron-specific enolase, and somatosensory evoked potential studies can assist in predicting efficiently and accurately a poor outcome in comatose patients after cardiopulmonary resuscitation for cardiac arrest.[7]

DEFINITION PROBLEMS AND MISDIAGNOSIS

The diagnosis of vegetative state emerges from a negative finding—namely, the lack of behaviors that would signal conscious capabilities. Using the nonoccurrence of events as a criterion to establish a fact is inherently problematic, since the causes of a nonoccurrence are theoretically infinite. More specifically, the reasons behind the lack of evidence of voluntary movement in presumably unconscious patients can be classified in terms of malfunctioning of either sensoriperceptual, output/motor, or central processing.

Deficits in sensoriperceptual processing

A patient might have deafness that may lead to a deficit in speech comprehension, or perhaps the auditory pathway and first cortical pathways are spared but the patient is aphasic and cannot process additive events such as speech. In a cohort of 42 patients, we found 17 who lacked the fourth or fifth components of the brain auditory evoked potentials to clicks presented binaurally, signaling severe damage to the auditory pathway.[8] It is useless to ask such patients to follow commands, since the sensory input is damaged and the movement (or lack of movement) has no validity for the diagnosis. A similar argument can apply for patients who may show some fixation but exhibit delayed or absent visual evoked potentials when presented with written commands.

Deficits in motor processing

The second type of lesions that may contribute to misdiagnosis in these patients are those found in the effector systems. If the motor voluntary pathways are damaged—either in the motor cortex or in the corticospinal or corticobulbar pathways—then movement might be impaired enough to prevent responses by the patient. Patients of this type are sometimes diagnosed as being in a vegetative state although they might actually have locked-in syndrome,[9] with preserved cognition but an inability to initiate voluntary responses as a result of a lesion in the pontine peduncle.

Although the effector systems are difficult to test in unresponsive subjects, some strategies may be tried. Before testing for volition, it is necessary to assess all possible hand, leg, and face reflexes in order to map reflexive behavior. Commands should then specifically target those muscles that showed total or partial preservation of reflexes. To test the output pathways from the cortex to the medulla, a more specialized assessment is needed; the Impaired Consciousness Research Group at the University of Cambridge has developed a simple protocol to assess the ability of the motor cortex to elicit muscle twitches by measuring the motor evoked potentials to simple pulses of transcranial magnetic stimulation. The minimal pulse intensity is determined by electromyographic recordings when transcranial magnetic stimulation pulses are applied to the left or right motor cortices for the hands and feet. The results have shown 2 out of 34 patients to have no detectable motor evoked potentials and 5 patients to have severe delay at maximum pulse intensity [unpublished data]. These results confirm the need for a full neurologic and neurophysiologic assessment in subjects who are unresponsive or show low levels of response, both acutely and more chronically, to minimize the risk of misdiagnosis.

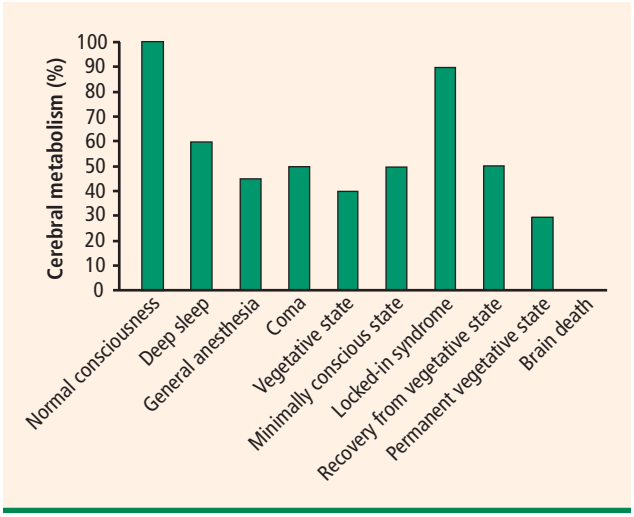

FIGURE 2. Relative levels of cerebral metabolism across various states of consciousness.

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Deficits in central processing

The key element in the assessment of cognitive processing in patients in a vegetative or minimally conscious state is determining deficits in their capacity to process external stimuli in a conscious manner (central processing). This is by far the most difficult characteristic to be determined since the only accepted criteria for awareness are verbal report or voluntary movement, both of which are absent in the vegetative state and are inconsistent and difficult to determine behaviorally in the minimally conscious state.

CLUES TO BRAIN FUNCTION IN DISORDERS OF CONSCIOUSNESS

It is important to differentiate a patient in a persistent vegetative state from a patient in a minimally conscious state, as the latter patient has a much higher chance of a favorable outcome. Evaluation of cerebral metabolism and imaging studies can both provide clues to brain function.

Cerebral metabolism

Cerebral metabolism in the vegetative state is similar to that in a patient under general anesthesia, which is about 40% of the cerebral metabolism in a healthy person in a resting state **(Figure 2)**. In contrast, a person with brain death has no detectable cerebral metabolism.

Neuroimaging studies

In the past few years, studies have found that some patients in a vegetative or minimally conscious state can activate cortical networks in response to auditory, visual, and tactile stimuli.[10] A challenge in neuroscience is to devise a reliable, objective test to assess awareness without relying on explicit voluntary movements or verbal responses. Such a test would have important theoretical and practical implications. Recent evidence from functional neuroimaging and neurophysiology suggests that some patients with disorders of consciousness exhibit partially preserved conscious processing despite having no clinical or verbal output.[11]

During a positron emission tomography study, Menon et al showed photographs to a 26-year-old woman who was in a vegetative state 4 months after becoming comatose from an acute febrile illness.[12] They found significant activation in the right fusiform gyrus and extrastriate visual association areas when the woman was shown photos of people familiar to her as compared with repixellated versions of the same photos with the faces made unrecognizable. The activation pattern she exhibited was similar to that of healthy volunteers. Interestingly, a few months after this study, the patient became increasingly responsive.

Our group conducted the first evaluation of emotion in the minimally conscious state using functional MRI (fMRI) in a 17-year-old male following a traumatic brain injury.[13] The patient was able to localize noxious stimuli, exhibited spontaneous eye opening, and occasionally smiled appropriately and followed people with his eyes. Imaging was performed while he listened to two recordings—one of his mother reading a story about his life, and one of a matched control voice reading the same story. Digital subtraction imaging disclosed strong activation of two areas related to emotion, the amygdala and the bilateral insula, while the recording of the patient's mother was played. Activation was also evident in the auditory cortex in the superior temporal lobe. The patient recovered 6 months following this study.

Classical conditioning

Classical conditioning represents an alternate approach to MRI for assessing brain function in patients with disordered consciousness.[8] Trace conditioning of the eyeblink response is considered to be an objective test of awareness.[14] This test involves highly specific learning, requiring an anticipatory electromyographic response to a paired stimulus (eg, a tone followed by an aversive stimulus such as an air puff to the eyes) but not to an unpaired stimulus (eg, a white noise that is not followed by an aversive stimulus). This effect increases in amplitude as the aversive stimulus approaches. Our laboratory is applying this method to study learning and memory in patients with disordered consciousness.

DETERMINING AWARENESS WITHOUT REPORT

The proposed neural correlates of consciousness do not usually take into account the levels of consciousness.[15,16] In order to build the framework for a cognitive neuroscience of consciousness, we must consider the content of the consciousness experience in fully awake subjects and patients as well as the cognitive processes occurring in unconscious and conscious subjects.

Two main approaches can be used to assess conscious processing in unresponsive patients. The first is to look for neural correlates in direct intentional actions or imagined actions,[11] and the second is to look for physiologic correlates of the cognitive processes required during the conscious processing of stimuli.[17]

Searching for neural correlates of intended actions

The first approach can have enormous impact in the diagnostic arena (as well as in the legal and ethical arenas), such as in the case reported by Owen et al in which a patient showed brain activity related to imagining actions as prompted by spoken instructions during fMRI evaluation.[11] Unfortunately, cases such as these are scarce. Moreover, imagining of actions relies not only on a spared comprehension capacity and preserved memory but also on the subject's willingness to perform the task. It would seem that only a minority of patients in a vegetative state seem to have the cognitive abilities preserved to accomplish these types of tasks.

Searching for physiologic correlates of cognitive processes

The second approach would tend to work with memory and switching attention capabilities in unresponsive patients, assuming that conscious processing does not exist without these cognitive processes. The evidence for this approach comes from electrophysiology. Cognitive evoked potentials are commonly applied to assess basic auditory or visual cortical processing, automatic attention, and focus attention.[18] Both the mismatch negativity wave (a correlate of automatic attention) and the p300 (a correlate of focus attention) are sometimes present,[19] specifically in patients in vegetative or minimally conscious states, and they are a good predictor of awakening in stroke, hemorrhage, and traumatic brain injury.[20]

In day-to-day practice in a neurology clinic or

emergency room, it is more feasible to assess cognitive capabilities using event-related potentials than fMRI since they are more widely distributed, more easily validated, shorter, and statistically more powerful in single-subject analysis,[21] and because they do not frequently rely on speech comprehension.

NEUROPATHOLOGY AND fMRI

The cause of the brain injury leading to a vegetative or minimally conscious state frequently determines the neuropathology.[22] It has also been demonstrated that severely disabled patients (such as those emerging from a minimally conscious state) differ from vegetative state patients in terms of lesions and severity.[23]

The most frequent nontraumatic causes of vegetative and minimally conscious states are cardiorespiratory arrest as a consequence of disease or medical accidents (often under anesthesia), but other causes can be found, such as intracranial hemorrhage, infection, and hypoglycemia. Interestingly, a subgroup of these patients with vegetative state from a nontraumatic cause exhibit lesions not in the cerebral cortex but in the thalamus and subcortical white matter, as illustrated in **Figure 3**, which shows anatomic differences between the vegetative state in patients with and without traumatic brain injury. The figure's left panel shows severe subcortical lesions as a consequence of an anoxic event; in contrast, the right panel, from a patient who suffered traumatic brain injury, shows only some cortical lesions and much less atrophy. Moreover, the activation during a simple auditory fMRI task was much more widespread in the temporal lobe in the patient with traumatic brain injury (right panel) compared with the patient with the anoxic event (left panel). These results illustrate and support, in a neurophysiologic manner, a common finding in severely disabled and vegetative state patients—ie, that stroke is often more disruptive (physiologically and cognitively) than traumatic brain injury.

Although residual activity as seen on functional neuroimaging may be unequivocal in some cases, it may represent only fragmentary cognitive processing; it is important not to assume that normal awareness is present. Much still needs to be learned, but results from neuroimaging studies demonstrate that a small proportion of patients in a vegetative or minimally conscious state have some preserved cognitive processes. These findings have ethical and legal implications. For instance, careless bedside chatter among family members or medical personnel is inappropriate and should be avoided. Whether functional neuroimaging can effectively evaluate neuroprocessing in patients in whom cognitive output is difficult to assess remains to be determined. Such evaluation may one day help to predict prognosis. It may also someday help to facilitate communication with patients with locked-in syndrome, who are cognitively intact but are without verbal or motor output.

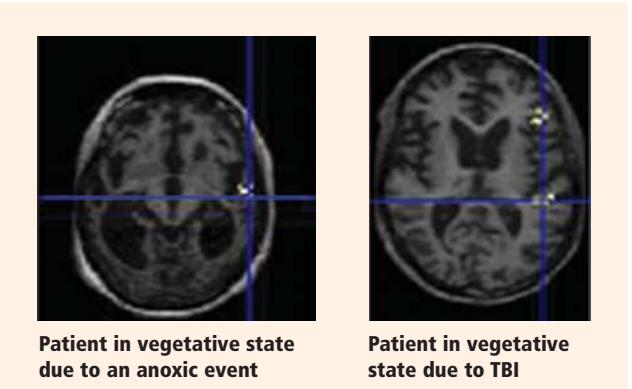

FIGURE 3. Comparative axial brain MRIs taken during speech processing in two patients in a vegetative state: one following an anoxic event (left) and one following a traumatic brain injury (TBI; right). The image from the patient with the anoxic injury shows subcortical hyperintensities and severe atrophy and ventriculomegaly, although there still is left focal brain activity to presented words. The image from the TBI patient depicts moderate cortical atrophy, left parietotemporal focal lesions, and activity in the temporal (auditory) cortex and inferior frontal gyrus to speech presentation. Images are reprinted from Bekinschtein.[8]

CONCLUSIONS

It is highly improbable to find patients with preserved cortical connectivity, since structural[22] and functional[19] studies have demonstrated only a small proportion of patients in a vegetative or minimally conscious state who have relatively preserved brains and cognitive processing. The more we study patients who are unresponsive or show low levels of response, the more complex cognitive processes we find in subpopulations of these patients. Language-related cortical activation is now the most common finding.[13,19,24] More recently, a few researchers working with severely damaged patients have started to test paradigms with the aim of uncovering conscious processes that have no need of verbal or movement responses.

The time has come for clinicians in acute care centers to immediately follow their administration of coma scales in unresponsive patients with the use of more sophisticated methodology to assess not only reflexive and intentional behaviors but also these patients' physiologic and cognitive characteristics. In the field of neurodegenerative disease, it took several

years for clinicians to start using more sensitive cognitive tools than just the mini-mental state examination and computed tomography or three-dimensional T1-weighted structural MRI, but nowadays volumetric MRI and detailed cognitive assessments are widely used to diagnose and characterize patients with neurodegenerative disorders. The same path should be taken for patients with severe brain damage. The information yielded by such an approach may one day help to determine a diagnosis or prognosis, guide treatment, or facilitate communication in patients with pathologies of consciousness.

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Preconditioning paradigms and pathways in the brain

ABSTRACT

Preconditioning is a phenomenon in which the brain protects itself against future injury by adapting to low doses of noxious insults. Preconditioning stimuli include ischemia, low doses of endotoxin, hypoxia, hypothermia and hyperthermia, cortical spreading depression, anesthetics, and 3-nitropropionic acid, among others. Understanding of the mechanisms underlying preconditioning has been elusive, but NMDA receptor activation, nitric oxide, inflammatory cytokines, and suppression of the innate immune system appear to have a role. Elucidation of the endogenous cell survival pathways involved in preconditioning has significant clinical implications for preventing neuronal damage in susceptible patients.

The brain relies upon internal defense mechanisms for protection from injurious stimuli. Preconditioning is a phenomenon whereby low doses of these noxious insults shield the brain from future insults rather than inflicting damage. Preconditioning stimuli include but are not limited to transient global and focal ischemia,[1–4] cortical spreading depression,[5–7] brief episodes of seizure, exposure to anesthetic inhalants,[8–10] low doses of endotoxin (lipopolysaccharide [LPS]),[11,12] hypothermia and hyperthermia,[13,14] and 3-nitropropionic acid treatment.[15,16]

Depending on the specific preconditioning stimulus, a state of neuronal tolerance can be established in at least two temporal profiles: one in which the trigger induces protection within minutes (rapid or acute tolerance),[17] and one in which the protected state develops after a delay of several hours to days (delayed tolerance).[4] Some preconditioning paradigms induce both phases of ischemic tolerance, while others can induce only the acute phase or only the delayed phase.[18–21] The acute phase is most likely due to rapid posttranslational modifications of proteins.[22,23] In contrast, the delayed phase is dependent on de novo protein synthesis.[24,25]

Preconditioning by ischemic tolerance was first identified in the heart by Murry et al,[26] and was subsequently found to occur in the brain[4,27] and a variety of organs including the liver, intestine, kidney, and lung. Preconditioning stimuli can be cross-tolerant, safeguarding against other types of injury. For example, endotoxin preconditioning can protect against subsequent ischemia and vice versa. Thus, there may be some overlapping mechanisms in preconditioning, and unraveling these pathways may uncover an arsenal of neuroprotective therapeutic targets. In this review, we will compare different preconditioning paradigms and discuss potential mechanisms in initiating brain ischemic tolerance.

PARADIGMS TO ESTABLISH PRECONDITIONING

Refinement of various preconditioning models is of great clinical significance. Cardiovascular or cerebrovascular surgery has a negative impact on brain function due to stoppage of blood flow during surgery. In fact, more than 25% of patients who receive coronary artery bypass surgery suffer from temporary or permanent memory loss.[28,29] As a result, it is of premier importance to develop strategies to protect the brain either prior to vascular surgeries or in patients at high risk of stroke. While it would be dangerous and impractical to precondition at-risk patients with ischemia, the identification of underlying preconditioning mechanisms may lead to safer therapeutic factors that can be administered before surgery.

Ischemia

Global ischemic preconditioning in the brain is accomplished by occlusion of the bilateral common carotid

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arteries. In contrast, in focal ischemic preconditioning, occlusion of one side of the middle cerebral artery is induced for about 1 to 20 minutes, depending on methods and animal species.[4,30–32] Twenty-four hours after ischemic preconditioning, stroke is induced in these animals. Preconditioning-induced neuroprotection is observed not only in terms of infarct volume but also in terms of neurological scores and behavior studies.

Lipopolysaccharide

Tolerance to ischemic injury can also be induced by a small dose of LPS injected into the peritoneal cavity. Dosages vary from 0.05 to 1 mg/kg body weight in small rodents such as mice and rats.[11,33–36] This dose of LPS usually does not bring abnormal signs and symptoms to the animals. The ischemic protection yields a reduction of infarct volume of approximately 30%. This tolerant state can be sustained for about 1 week, with maximum protection occurring around 2 to 3 days after injection of LPS.

Hypoxia

A relatively convenient method for preconditioning animals is hypoxic exposure. Animals are put in a chamber in which oxygen and nitrogen proportions can be controlled. Oxygen concentration usually ranges from 8% to 13% with normobaric pressure. Exposure time ranges from 1 to 6 hours. Twenty-four to 72 hours later, transient or permanent focal stroke is induced in the animals.[37–40] Hypoxia-preconditioned neuroprotection usually starts at 1 to 3 days with a significant reduction of infarct size. Hypoxic preconditioning has also been demonstrated for in vitro neuron culture models using oxygen-glucose deprivation injury.[41]

3-Nitropropionic acid

3-Nitropropionic acid (3-NP) is an irreversible inhibitor of succinate dehydrogenase, an enzyme required for oxidative phosphorylation and adenosine triphosphate production. When applied at low doses 1 to 4 days before ischemia, 3-NP can lead to ischemic tolerance in the forebrain of gerbils and rats.[16,42,43] The dose ranges from 1 to 20 mg/kg body weight.[16] Such treatment significantly improves neurological behavior and increases neuronal survival in the CA1 region of hippocampus. In addition, 3-NP preconditioning induces tolerance to hypoxia in hippocampal slice preparations.[15,44]

Hypothermia and hyperthermia

Hypothermia is a well-characterized protective procedure used during and after cerebral surgery. It is also reported that brief hypothermic or hyperthermic exposure can also lead to ischemic tolerance. The temperatures adopted range from 25°C to 32°C[13,45,46] in hypothermia and from 42°C to 43°C in hyperthermia.[14]

Cortical spreading depression

Cortical spreading depression is defined as the electrophysiologic phenomenon of slowly propagating transient depolarization waves across the cortex. Usually 5 M of potassium chloride is infused into the cortex, or a cotton pad soaked with the solution is put on the surface of dura mater, which results in depolarization, firing of neurons, and cortical spreading depression. Cortical spreading depression induces a prolonged phase of ischemic tolerance that lasts 1 to 7 days.[5,6,47,48]

Anesthetics

Exposure to volatile anesthetics such as isoflurane and halothane within pharmacologic concentration ranges also confers delayed-phase ischemic tolerance of the brain.[8–10,49]

MOLECULAR PRECONDITIONING PATHWAYS

Mechanistically, cellular preconditioning can be subdivided into intrinsic neuronal pathways (preventing excitotoxic damage, signaling through anti-apoptotic molecules, and treatment by neurotrophic factors) or extrinsic nonneuronal pathways (peripheral cytokine production, microglial activation, and regulation of the cerebrovascular system). Several neuroprotective molecules are expressed and signal through multiple cell types both within and peripheral to the brain, so that assigning an exact source and paradigm for preconditioning pathways has proven difficult.

NMDA receptor activation and excitotoxicity protection

In neurons, ischemic tolerance is mediated largely by the activation of the *N*-methyl-D-aspartate (NMDA) glutamate receptors through increases in intracellular calcium.[50–52] Although glutamate receptor activation is generally believed to be responsible for much of the neuronal damage caused by excitotoxicity, it appears to also be implicated in the establishment of preconditioning. One study demonstrated that exposure of cortical cell cultures to low levels of glutamate activated NMDA receptors in preconditioning.[50] In addition, preconditioning by oxygen-glucose deprivation was blocked when an NMDA antagonist was applied. NMDA receptor activation can induce a tolerant state through rapid adaptation of the voltage-dependent calcium flux. In addition, activation of NMDA receptors leads to rapid release of brain-derived neurotrophic factor, which then binds to and activates its cognate receptor, receptor tyrosine kinase B. Both NMDA and tyrosine kinase B receptors activate nuclear factor–kappa B (NFκB), a transcription factor involved

in protecting neurons against insults. In sublethal ischemic preconditioning, activation of NFκB and its translocation from the cytosol to the nucleus was required for the development of late cerebral protection against severe ischemia or epilepsy.[53] Other key mediators involved in synaptic NMDA receptor–dependent neuroprotection are phosphatidylinositol 3-kinase (PI3K), Akt, and glycogen synthase kinase 3-beta.[54]

Preconditioning with cortical spreading depression results in the downregulation of the excitatory amino acid transporters EAAT1 and EAAT2 from cerebral cortex plasma membranes.[55] Although these transporters are normally involved in glutamate uptake, it has been suggested that the influx of sodium that occurs during excitotoxicity may cause their reversal and result in additional glutamate release. Downregulating these transporters may thus contribute to ischemic tolerance.

Nitric oxide

Nitric oxide (NO) may play a key role as a mediator of the neuronal ischemic preconditioning response, either in conjunction with or independent of NMDA receptor activation. Both the inhibition of nitric oxide synthase (NOS) and the scavenging of NO during preconditioning significantly attenuated the induced neuronal tolerance, and neither endothelial NOS nor neuronal NOS knockout mice showed protection from rapid ischemic preconditioning.[56,57] Treatment with the inducible NOS (iNOS) inhibitor aminoguanidine abolished the induced protection. The mechanisms responsible for NO-induced tolerance are not clear. Downregulation of the glutamate transporter GLT-1 might play a role.[58] A common link to NMDA receptor activation and NO is $p21^{ras}$ (Ras). Preconditioning induces $p21^{ras}$ activation in an NMDA- and NO-dependent manner and leads to the downstream activation of Raf kinase, mitogen-activated protein kinases, and extracellular regulated kinase.[59] Inhibition of these kinases attenuates subsequent protection from ischemia.[60,61] Pharmacologic inhibition of Ras, as well as a dominant negative Ras mutant, blocked preconditioning, whereas a constitutively active form of Ras promoted neuroprotection against lethal insults. An important consideration regarding NO is also that preconditioning by volatile anesthetics appears to involve NO pathways.[9]

NO and reactive oxygen species (ROS) are also implicated in regulating the peripheral cerebrovascular system. Ischemia generated by occlusion of the middle cerebral artery causes defects in cerebrovascular function for not only the infarcted area but also the surrounding ischemic region. LPS preconditioning has been reported in some cases to increase this regional cerebral blood flow both before and after ischemia.[1,21,36,62–64] LPS also improves microvascular perfusion.[33,64] It was recently reported that LPS-stimulated cerebral blood flow is induced through reactive oxygen and nitrogen species (ROS or NO).[1] Mouse knockouts of iNOS (NO production) or of the nox2 subunit of NADPH oxidase (ROS production) eliminated the LPS-upregulated cerebrovascular activity. Furthermore, blockage of these ROS and NO pathways reduced the preconditioning effect of LPS. Therefore, LPS may play a more direct role in preventing ischemic damage by increasing blood availability to the affected brain region.

Inflammatory cytokines and the innate immune system

LPS, a component of the gram-negative bacterial cell wall, can illicit a potent innate immune response. While this systemic inflammatory response can be destructive (at doses of 5 mg/kg),[65] tolerable LPS doses of 0.05 to 1 mg/kg injected intraperitoneally render the brain,[11] heart,[66,67] liver,[68,69] kidneys,[70] and pancreas[71] transiently resistant to subsequent ischemic injury. This preconditioning paradigm relies on the ability of a peripheral signal to cross into multiple organ systems. LPS injected into the gut can signal through peritoneal macrophages and circulating monocytes. Toll-like receptor 4 is a pattern-recognition receptor that binds to pathogen-associated molecular patterns in LPS and initiates a signaling cascade through the NFκB pathway. This pathway culminates in the expression and secretion of several proinflammatory cytokines to fight off the infection and anti-inflammatory cytokines to control the immune response.

The major output of LPS signaling is innate production of proinflammatory cytokines to fight infection and clear cellular debris. Central cytokines, including tumor necrosis factor–alpha (TNFα), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β), can be neurodestructive if administered after ischemia. TNFα administration by cerebroventricular injection after ischemia augmented the extent of injury, and blockage of TNFα signaling proved neuroprotective.[11,72,73] However, in LPS preconditioning, cytokine production precedes ischemia. Intracisternal injections of TNFα before middle cerebral artery occlusion (MCAO) were protective in reducing the infarct size of pretreated mice.[74] Furthermore, intracisternal injection of ceramide analog, a downstream component of the TNFα signaling pathway, was also capable of reducing the MCAO infarct area.[75] Preischemic treatment with IL-6 and IL-1 also reduced neuronal damage.[76,77] TNFα knockout mice eliminated the LPS

protective phenotype,[72] demonstrating that cytokine production is a critical feature of LPS preconditioning in ischemia. Additionally, ischemic damage in the absence of LPS preconditioning was exacerbated in TNFα receptor 1 knockout mice.[78,79] Consistently, TNFα protein levels are upregulated after LPS treatment but are downregulated following LPS-preconditioned MCAO.[72] A unifying theme in LPS preconditioning comprises early activation of the innate immune system with ensuing suppression in ischemia.

As a potential mechanism, the initial inflammatory response induced by LPS appears to render the innate immune system hyporesponsive to subsequent insults such as ischemia. This may occur by persistence of anti-inflammatory cytokines produced by the primary insult. These molecules are expressed in tandem with proinflammatory cytokines to control the innate immune response, but may also play a role in delayed preconditioning. For instance, intravenous or intracerebroventricular IL-10 injection can reduce the infarct size with MCAO.[80] Alternatively, several proinflammatory cytokine signaling pathways may be downregulated by negative feedback inhibition.[20,81] This inhibition may occur extracellularly, using soluble cytokine receptors, decoy receptors, or receptor antagonists. For example, intravenous injection of IL-1 receptor antagonist can provide neuroprotection against ischemic injury from MCAO.[82,83] Cytokine feedback inhibitors that act intracellularly are also induced with the innate immune response. Intracellular inhibition may involve direct downregulation of cytokine transcription (peroxisome proliferator-activated receptor gamma [PPAR-γ]) or inhibition of intracellular signaling pathways that promote cytokine production (suppressor of cytokine signaling [SOCS] and PI3K). Antisense mRNA knockdown of SOCS-3 exacerbates ischemic injury from MCAO.[84] The MCAO infarction area is increased after treatment with PPAR-γ antagonists and decreased by PPAR-γ agonists.[85,86] Administration of compounds that increase PI3K signaling is also capable of reducing ischemic damage.[87] Thus, several defense mechanisms designed to suppress the innate immune response may play an active role in LPS ischemic preconditioning.

Role of microglia in ischemic preconditioning

Microglia represent the resident central nervous system (CNS) component of the innate immune system. Microglia and macrophages become activated with ischemia in the infarcted and surrounded area.[88] Upon activation in ischemia, microglia will become phagocytic and secrete a multitude of noxious chemokines and cytokines.[89] Accordingly, anti-inflammatory antibiotics such as doxycycline and minocycline reduce microglial activation and diminish the ischemic infarction area.[90] Preconditioning the brain with LPS ameliorates microglial activation, neutrophil infiltration, and circulating monocyte activation following MCAO.[35] However, primary ischemic damage is not correlated with CNS infiltration of peripheral leukocytes but rather with an increase in proliferating resident microglial cells.[91] Alternatively, microglia can exhibit neuroprotective properties within the brain.[92] In fact, greater ischemic damage from longer periods of MCAO is correlated with fewer proliferating microglia, suggesting a protective microglial role.[91] Consistently, ablation of proliferating microglia increases the infarction area following MCAO.[93] Therefore, microglia can be protective in ischemia, and preconditioning with LPS may render microglia more capable of reacting to ischemic conditions.

CONCLUSIONS

Preconditioning represents an adaptive response to prime the brain for protection against future injury. Elucidation of these endogenous cell survival pathways has significant clinical implications for preventing neuronal damage in susceptible patients. For this reason, understanding the underlying mechanisms in establishing a tolerant state will be a critical step in adapting preconditioning for safe patient applications. The field of ischemic research has made great strides in deciphering causative preconditioning factors but has been hampered by the complex, multifactorial nature of preconditioning paradigms. The study of tolerance is further complicated by the fact that signaling takes place both peripheral to and within the brain in multiple cell types. Future research will require the exploration of interactions between multiple pathways and roles of individual cell types in establishing ischemic tolerance. Only with a more thorough understanding of preconditioning mechanisms can we adapt these pathways for the most efficient and protective treatments.

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Post-stroke exercise rehabilitation: What we know about retraining the motor system and how it may apply to retraining the heart

ABSTRACT

A plateau in recovery within the first few months of rehabilitative therapy was assumed to be the norm in stroke survivors. Recent studies in our laboratory examined the effect of 6 months of treadmill exercise training in chronically disabled stroke survivors. Treadmill exercise improves fitness and walking ability in patients when initiated 6 months or more following their index stroke. Functional imaging studies show that such exercise also induces subcortical reorganization in these patients. Future investigations will explore the relationship between these functional and structural effects and characterize the therapeutic mechanisms of post-stroke rehabilitation. Nonetheless, treadmill exercise appears to have motor, cardiac, and daily functional benefits in stroke survivors.

Ideally, rehabilitation following a stroke that leads to functional deficit will result in a rapid return to normal function. In the real world, however, a rapid improvement in function is rarely achieved. Between 80% and 90% of stroke survivors have a motor deficit, with impairments in walking being the most common motor deficits.[1] Most stroke survivors have a diminished fitness reserve that is stable and resistant to routine rehabilitative interventions. Recent research has begun to assess the value of exercise and other modalities of training during this period of stability to improve function long after cessation of other therapeutic interventions. This article will review this research and provide insight into those issues in post-stroke rehabilitation that remain to be addressed and may affect heart and brain physiology.

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STROKE REDUCES AEROBIC CAPACITY

At all ages, the fitness level of stroke survivors, as measured by maximum oxygen consumption, is reduced by approximately 50% below that of an age-matched normal population. In a study comparing peak oxygen consumption during treadmill walking between stroke survivors and age-matched sedentary controls, we found that the stroke participants had an approximately 50% lower level of peak fitness relative to the control subjects.[2] During treadmill walking at self-selected speeds, the stroke volunteers used 75% of their functional capacity, compared with 27% for the age-matched healthy controls. Furthermore, compared with the controls, the stroke subjects demonstrated a poorer economy of gait that required greater oxygen consumption to sustain their self-selected walking speeds.

CLINICAL TRIALS OF POST-STROKE EXERCISE REHABILITATION

In light of the efficacy of treadmill exercise in cardiac rehabilitation, we are evaluating whether treadmill exercise can similarly improve fitness, endurance, and walking velocity in stroke survivors. We have completed 6 months of treadmill training in two separate cohorts that show highly consistent results in terms of improved walking abilities in hemiparetic stroke subjects.[3,4] A third cohort is in progress to confirm these findings and examine the effects of intensity on the functional benefits[5] and mechanisms[6] underlying the effects of treadmill training.

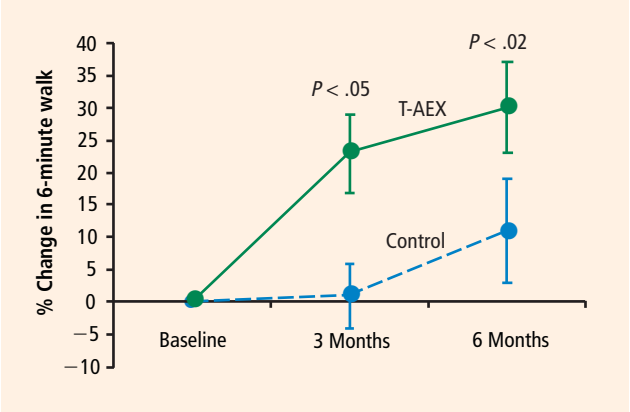

FIGURE 1. Mean change in distance during a 6-minute walk test after treadmill aerobic exercise training (T-AEX) and control therapy among ischemic stroke survivors with hemiparetic gait (25 T-AEX subjects, 20 controls). The between-group difference demonstrates the functional benefits provided by treadmill exercise therapy.[4]

Reprinted, with permission, from Macko RF, et al. Treadmill exercise rehabilitation improves ambulatory function and cardiovascular fitness in patients with chronic stroke. A randomized, controlled trial. Stroke 2005; 36:2206–2211.

Treadmill exercise results in functional benefits and improved glucose metabolism

The first cohort was a before-and-after comparison of stable stroke survivors who underwent a three-times-weekly treadmill exercise program for 6 months.[3] Peak exercise capacity testing (VO_2peak) revealed functional benefits with minimal cardiac and injury risk compared with baseline, demonstrating the feasibility and safety of treadmill exercise therapy in stroke-impaired adults.

The second cohort involved patients with chronic hemiparetic gait following ischemic stroke who were randomized to either treadmill aerobic training (three times weekly for 6 months) (n = 25) or a control rehabilitation program of stretching (n = 20).[4] The aerobic training group selected its own walking speed and increased its speed as tolerated; some participants in this group started with as little as 2 minutes on the treadmill. As shown in **Figure 1**, performance on the 6-minute walk test improved significantly in the aerobic training group, relative to the control group, over the 6-month study. Six-minute walk results paralleled the improved functional performance.

Potential mechanisms for the benefits

These findings raise the question of whether these beneficial effects of treadmill exercise are attributable to muscle training effects, cardiopulmonary circulatory training effects, or perhaps neural mechanisms involving economy of gait movements and neuroplasticity of the motor system.

This question is being examined in our third cohort, now under investigation. This cohort will evaluate the effects of treadmill exercise on 32 chronically disabled stroke survivors in a single-center study design that is randomizing 64 subjects to 6 months of three-times-weekly treadmill training or conventional physiotherapy.[6] Similar to our prior studies, subjects are randomized at least 6 months after their index stroke; this lengthy interval is deliberate because subjects are considered to be in a "plateau" phase of recovery, as they have previously completed rehabilitative therapy.

This group of 32 subjects will undergo both treadmill training and functional magnetic resonance imaging (fMRI) during unilateral knee movements to assess alterations in brain function during such movements over the 6-month study **(Figure 2)**. Previous fMRI studies of healthy controls and stroke patients identified activation of regions in the right side of the cerebral hemisphere with left knee movement.[7,8] In the new fMRI study, functional activation patterns of paretic and nonparetic knee movement will be compared between the exercise group and the control group, and the relationship between the activation pattern and the location of the brain-activation region will be characterized for the paretic and nonparetic knee movements.

Activation will be measured in five prespecified "regions of interest": the precentral gyrus, the postcentral gyrus, the supplementary motor area, the midbrain, and the cerebellum (anterior/posterior lobes). Difference activation maps of post-training minus pretraining fMRIs of paretic knee movement across all patients undergoing treadmill therapy will then be analyzed. The control group, which will receive dose-matched stretching activity from physical therapy, can be contrasted by comparing the patterns of pre/post differences in each region. This will allow for assessment of increased regional activation in the brain that should be specific to the treadmill training intervention. Furthermore, if a specifically localized regional activation difference is found, then individual fMRI and VO_2 training responses (VO_2peak, increase in walking speeds) can be correlated to further assess the relationship between regional activation and magnitude of functional response to the treadmill intervention.

DISCUSSION AND CONCLUSIONS

Central control of walking

Control of gait in animals is mediated by the cortex, brainstem/cerebellum,[9,10] and spinal cord—the so-called cervical gait and lumbar gait pattern-generating areas of the spinal cord. In humans, cortical and spinal gait pattern areas are thought to be major regulatory cen-

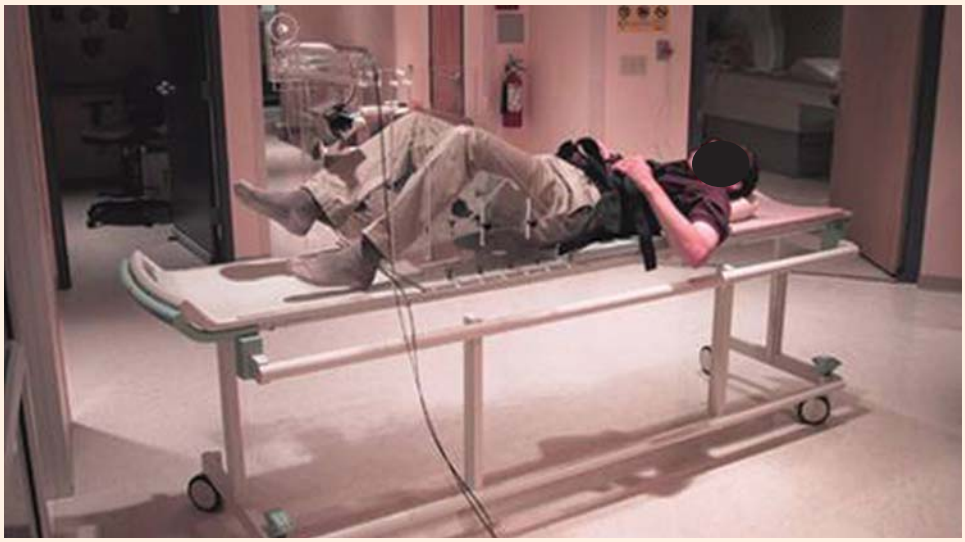

FIGURE 2. Brain activation before and after treadmill training is sampled in a stroke survivor using functional magnetic resonance imaging during unilateral knee movements. A plexiglass scaffold has been custom-designed to define range of motion and minimize concomitant head motion.

ters of ambulation. Whether the cortical areas influence ambulatory recovery mediated by exercise training or whether the recruitment of spinal gait areas is needed to improve motor control after stroke is not known in humans. We will test the hypothesis that the recruitment of cortical and/or subcortical areas is relevant to some or all of the exercise-induced neuroplasticity response to treadmill rehabilitation. If a consistent pattern of brain regional activation is associated with an improvement in walking ability, this finding will suggest potential brain targets for neurally directed rehabilitation interventions. If brain targets for rehabilitation produce viable therapeutic improvement in walking and cardiocirculatory performance (such as V_{O_2}), this will be further evidence of heart-brain interactions.

Future research directions

Studies to date demonstrate that long-term treadmill exercise affects both the brain and cardiac physiology. This has holistic implications for the function of the whole person as well. Yet several pressing issues continue to confront researchers in post-stroke rehabilitation. One is the optimal therapeutic target and the intensity of the rehabilitative effort. Is this improvement solely a response of muscle and cardiac tissue to exercise, or is it possible that improved neuromotor control is a critical component to a major recovery of walking function? Furthermore, the most efficacious elements of rehabilitative therapy are not known. Should treadmill training be high- or low-intensity, and should it be accompanied by strength training, agility and flexibility activities, or other elements directed at reacquisition of finer degrees of gait-related motor training and neuropsychological input, as achieved by tai-chi or yoga? Another issue is the proper dose of rehabilitative therapy, which has barely been explored, although recent preliminary work suggests that the response is dose-dependent. Finally, predictors of response have not been established because the mechanisms of therapy and surrogate markers for early response are not well understood.

Our future research plans are to assess whether a better understanding of neural targets for rehabilitative treatment will be a fruitful avenue to improve recovery. Additionally, this plan will assess whether fMRI can serve as a surrogate marker of recovery by offering a noninvasive means to measure response to rehabilitation.

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Hippocampal volume change in the Alzheimer Disease Cholesterol-Lowering Treatment trial

ABSTRACT

Numerous clinical studies suggest a link between elevated cholesterol and increased risk of Alzheimer disease (AD), and the preponderance of data suggests that statin therapy may reduce the risk of AD later in life. The first clinical investigation of statin therapy in patients with AD, the AD Cholesterol-Lowering Treatment (ADCLT) trial, found that atorvastatin 80 mg/day was associated with improvements relative to placebo on some, but not all, cognitive measures after 6 months and 1 year of therapy. We report here findings from a pilot ADCLT substudy showing a nonsignificant reduction in total hippocampal volume with 1 year of atorvastatin therapy compared with placebo, driven by a highly significant reduction in right hippocampal volume with atorvastatin therapy.

Alzheimer disease (AD) is a degenerative disorder characterized by a gradual deterioration in memory. In its clinically overt stages, obvious signs of neural degeneration on magnetic resonance imaging (MRI) appear as global cerebral atrophy. Even in the earliest stages of the disease, regional cell loss can be observed, particularly in the mesial temporal lobe regions, specifically the hippocampus and entorhinal cortex.[1–3]

MRI is used primarily as a diagnostic tool to rule out conditions other than AD. However, MRI may be useful in understanding whether the underlying processes that are associated with these cognitive changes can be attributed to general or specific effects of the disease process. Volumetric changes observed with MRI in the hippocampal region have been correlated with disease progression[4,5] and predict development of AD in individuals with isolated memory impairment,[6] suggesting that neuroimaging quantification may serve as a useful measure of brain integrity in patients with AD.

New treatments for AD are emerging, and assessing their efficacy is of critical importance. The rationale for testing statin drugs as a therapy for AD was bolstered by ever-mounting preclinical animal and human data suggesting that elevated circulating cholesterol exacerbates AD-like pathology and that statin treatment, in part, reverses the effect of cholesterol. This article surveys current evidence on the association between cholesterol and AD as well as between statin use and AD risk. We conclude by focusing on results from the first clinical investigation of statin therapy in patients with AD and present new results of a substudy of this trial examining the morphologic effects of statin therapy in AD patients.

LINK BETWEEN CHOLESTEROL AND AD

Early epidemiologic surveys suggested an association between a high-fat/high-cholesterol diet and increased risk of AD,[7–10] and this suggestion has been supported by more recent investigations.[11,12] Cholesterol levels are increased in the blood of AD patients,[7,13–16] and increased cholesterol has been observed in the AD brain as a function of the apolipoprotein E allotype.[8,17]

Numerous clinical studies suggest a link between elevated cholesterol and increased risk of AD,[17–23] with one study reporting a threefold increase in the risk of AD with elevated serum cholesterol, even after adjusting for age and presence of the apolipoprotein E4 allele.[19] Another study indicates that persistently elevated cholesterol levels in midlife increase the risk of AD.[23] A retrospective analysis of the Framingham Study suggested, however, that there is no relationship between total cholesterol levels and risk of incident

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AD.[24] A more recent report indicated that language performance in elderly subjects without dementia declined faster among those individuals with higher cholesterol levels, but this effect did not remain significant after accounting for multiple comparisons.[25] In contrast, the Three-City Study, a population-based cohort investigation of 9,294 subjects in France, demonstrated a significant increase in the risk of dementia among subjects who had hyperlipidemia (odds ratio [OR] = 1.43; 95% confidence interval [CI], 1.03 to 1.99).[12]

STATIN USE AND RISK OF AD

The preponderance of clinical data suggests that statin therapy may reduce the risk of AD later in life. Since the initial epidemiologic investigation assessing the effect of statin use on later risk of AD in the elderly, there have been 13 additional studies; all but two of these studies have reported benefit with cholesterol-lowering therapy.

In the two earliest epidemiologic studies, Wolozin et al demonstrated benefit with the use of lovastatin and pravastatin, but not with simvastatin or nonstatin therapy,[26] and Jick et al showed benefit associated with cholesterol-lowering therapy, but not specifically with statin use.[27] Five epidemiologic studies published in 2002 suggested that prior statin use reduced the risk of dementia or AD.[28–32] Meta-analysis of these first seven retrospective studies suggested a significant reduction in the risk of later cognitive impairment with statin use (relative risk = 0.43; 95% CI, 0.31 to 0.62), but the risk reduction with lipid-lowering agents collectively (not just statins) was not statistically significant.[33]

In 2004, Zamrini et al reported a 39% reduction in the risk of AD in statin users compared with nonusers (OR = 0.61; 95% CI, 0.42 to 0.87).[34] That same year, Li et al suggested that there was no association between statin use and a reduced incidence of probable AD using a time-dependent proportional hazards model, but if the data were analyzed (inappropriately) as a case-control study, a significant protective effect was identified.[35]

Data from the Cache County Study cohort demonstrated no significant reduction in the risk of AD with statin use but allowed for the possibility that some benefit could be provided with longer-term statin therapy.[36] In constrast, the Three-City Study of 9,294 individuals in France identified a significant reduction in the risk of AD with statin use (OR = 0.61; 95% CI, 0.41 to 0.91).[12] Rea et al reported that prior statin use did not decrease the risk of dementia or AD, but when they included in their analysis individuals currently using a statin, there was a significant reduction in the hazard ratios for AD and for all-cause dementia.[37] The two most recent epidemiologic studies both suggest that statin therapy slows cognitive decline in AD.[38,39]

COGNITIVE PERFORMANCE AND STATIN USE

A retrospective cohort study that assessed intelligence and cognition at a young age and again when subjects were in their 80s indicated that statin use had a significant beneficial effect on cognitive ability.[40]

In contrast, two very large prospective studies published in 2002 suggested that statins produce no positive effect on cognition in younger individuals at risk for heart disease.[41,42] The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) found that the mean Mini-Mental State Examination (MMSE) score, which was assessed only at subjects' last on-treatment clinical visit, was comparable between the study's pravastatin and placebo groups.[41] Likewise, the Medical Research Council/British Heart Foundation (MRC/BHF) Heart Protection Study, which used the Telephone Interview for Cognitive Status questionnaire at the end of the investigation, reported that simvastatin had no positive effect on cognitive performance compared with placebo, but this finding was obtained in the absence of baseline data.[42] Given the limited cognitive assessments performed in these two studies, no firm conclusions should be drawn.

A more recent prospective comparison of atorvastatin and placebo in younger subjects did include baseline and follow-up assessment of cognitive function, and it identified significantly superior performance in the statin-treated population on the MMSE and on tests of attention, psychomotor speed, mental flexibility, working memory, and memory retrieval.[43]

STATIN TREATMENT OF AD: THE AD CHOLESTEROL-LOWERING TREATMENT TRIAL

The initial clinical investigation of statin therapy in patients with AD—the Alzheimer's Disease Cholesterol-Lowering Treatment (ADCLT) trial—involved atorvastatin.[44] Patients with mild to moderate AD were randomized to either placebo or 80 mg/day of atorvastatin for a 1-year period. Evaluable data were available for 63 patients (32 in the atorvastatin group, 31 in the placebo group). End points included the change in performance on the following measures:

- MMSE
- Alzheimer's Disease Assessment Scale–cogni-

tive subscale (ADAS-cog)
- Neuropsychiatric Inventory Caregiver Distress Scale (NPI)
- Clinical Global Impression of Change scale (CGIC)
- Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (ADCS-ADL)
- Geriatric Depression Scale (GDS).

Cognitive results

In the setting of continued cholinesterase inhibitor use, atorvastatin provided significant benefit on the ADAS-cog at 26 weeks compared with placebo (P = .003) and marginally significant benefit at 1 year (P = .055) while producing a trend for benefit on the CGIC and NPI and a statistically significant improvement on the GDS after 1 year of active treatment.[44] The observed benefit on the MMSE with atorvastatin versus placebo did not reach statistical significance, and no discernible difference was observed on the ADCS-ADL.[44] In contrast, a significant difference in the slope of deterioration on the MMSE and the GDS in the atorvastatin group versus the placebo group suggested disease modification.[45]

Blood test results

Levels of total cholesterol, low-density lipoprotein cholesterol, and very-low-density lipoprotein cholesterol were significantly reduced between 3 and 12 months in the atorvastatin group compared with the placebo group;[44] levels of high-density lipoprotein cholesterol were decreased by 12 months of atorvastatin therapy,[45] but the circulating free radical load was unchanged,[45] as were levels of C-reactive protein.[46] Notably, after assuring fasting compliance, we found that triglyceride levels were significantly increased by atorvastatin treatment in AD patients **(Figure 1)**.

Secondary analysis and initial morphometric substudy

Secondary assessment indicated that the subjects who garnered the greatest benefit from atorvastatin therapy in terms of their 6-month ADAS-cog score were those who had higher cholesterol levels at trial entry, those who harbored the apolipoprotein E4 allele, and those who were less affected by AD at trial entry (ie, with higher entry MMSE scores).[47]

In an ADCLT substudy using new voxel-based morphometry techniques, we quantitatively assessed gray matter density in 15 ADCLT trial participants and compared it with density findings in 15 normal elderly controls.[48] Regional reductions in gray matter density were observed in the AD patients compared with the controls. Large differences in gray matter concentration were observed bilaterally in the temporal lobe. The anterior cingulate, right superior temporal, left superior frontal, and posterior cingulate regions also showed significantly decreased gray matter density in the AD patients compared with the controls. A significant relationship was observed between gray matter density and ADAS-cog error scores—ie, more severe levels of cognitive impairment correlated with reduced gray matter density.[48]

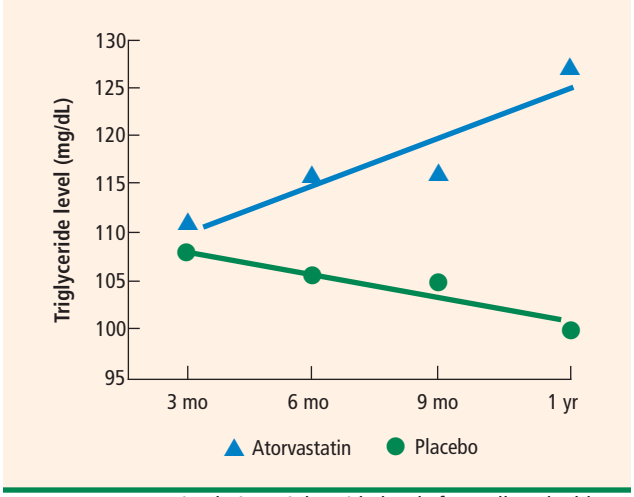

FIGURE 1. Mean circulating triglyceride levels from all evaluable subjects (N = 63) in the Alzheimer's Disease Cholesterol-Lowering Treatment (ADCLT) trial. After insuring compliance for fasting blood draws, triglyceride levels were determined every quarter during the study. Atorvastatin recipients had a significant 30% increase in triglyceride levels compared with placebo controls ($P < .05$).

PILOT SUBSTUDY OF ADCLT: ASSESSING MORPHOLOGIC CHANGES WITH STATIN THERAPY

Eleven of the 15 ADCLT trial participants from the above morphometric substudy returned for MRI assessment after 1 year of treatment with either atorvastatin or placebo. We report here the comparative effects of atorvastatin and placebo on hippocampal volume and the relationship with cognitive performance.

Participants

Subjects were participating in the ADCLT trial, an investigator-initiated, double-blind, placebo-controlled study. Neuroimaging was performed at the Barrow Neurological Institute, Phoenix, AZ, for a subset of the participants in the trial (n = 11) as a pilot study to examine neural changes associated with atorvastatin therapy.

Each patient underwent screening, assignment to either atorvastatin 80 mg/day or placebo, and medical and cognitive assessment at Sun Health Research Institute, Sun City, AZ, prior to imaging at Barrow. All

TABLE 1
Patient demographics and results from pilot morphometric substudy of ADCLT

Placebo group	Age (yr)	Years of education	MMSE change score	ADAS-cog change score	Change in hippocampal volume (mm^3) Left	Right	Combined
Patient 1	65	20	–2	0.5	–497	–109	–605
Patient 2	85	16	–2	1.8	–193	–307	–500
Patient 3	78	12	3	3.5	62	43	105
Patient 4	91	18	–6	7.2	–346	421	75
Patient 5	84	12	–1	–4.0	–208	457	248
Placebo group mean	80.6 ± 4.4	15.7 ± 1.6	–1.6 ± 1.4	1.9 ± 1.8	–236 ± 93	101 ± 149	–134 ± 174
Atorvastatin group							
Patient 1	83	20	1	0.0	1,650	–728	922
Patient 2	81	16	3	0.0	–250	–390	–640
Patient 3	67	16	–3	1.1	–435	–189	–624
Patient 4	79	12	1	–2.4	–407	–292	–693
Patient 5	65	18	–4	8.0	–1,289	–504	–1,793
Patient 6	72	12	–4	2.5	1	–670	–669
Atorvastatin group mean	74.5 ± 3.1	15.7 ± 1.3	–0.9 ± 1.3	1.5 ± 1.5	–121 ± 396	–462 ± 86*	–583 ± 354

* $P = .008$ vs placebo group

ADCLT = Alzheimer's Disease Cholesterol-Lowering Treatment trial; MMSE = Mini-Mental State Examination; ADAS-cog = Alzheimer's Disease Assessment Scale–cognitive subscale

patients met *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, criteria for dementia as well as NINCDS-ADRDA criteria for probable AD. Each patient was free of significant psychiatric and neurological history and had a score of 4 or less on the Hachinski Modified Ischemia Scale. All MRIs were reviewed by a neuroradiologist to ensure that there was no evidence of stroke or cortical or lacunar infarcts.

Both sites' institutional review boards approved this project, and all subjects gave written informed consent.

Cognitive assessment

A primary efficacy measure used in the parent study was the ADAS-cog,[49] and the MMSE[50] was a secondary measure. Change scores were determined by comparing values obtained at baseline, prior to randomization to treatment with either atorvastatin or placebo, and after 1 year of treatment. MMSE scores were obtained at the same session as the ADAS-cog scores. Cognitive assessments were obtained within 2 weeks prior to MRI.

Image acquisition

All participants underwent imaging on a single 1.5-tesla GE scanner at Barrow Neurological Institute. Imaging was conducted both prior to treatment randomization and again after 1 year of treatment. Images of the whole brain were collected using a coronal SPGR (spoiled gradient) T_1-weighted, three-dimensional acquisition with the following parameters:

- Number of acquisitions = 1
- Repetition time = 23 msec
- Echo time = 8 msec
- Flip angle = 35 degrees
- Bandwidth = 12.5 kHz
- Slice thickness = 1.5 mm or 1.9 mm
- 0 skip between slices
- In-plane resolution = 0.9375 × 0.9375.

Hippocampal volumetrics

All imaging analysis was performed within the Analysis of Functional Neuroimages (AFNI) package.[51] We traced the outline of the hippocampus using the three-dimensional SPGR images. The hippocampi were visualized in all three planes, landmarked in the coronal and sagittal planes, and drawn in the coronal plane. We employed the guidelines of Insausti et al[52] and Machulda et al[53] to define the hippocampal boundaries. First we defined the anterior boundary by observing the white matter band and/or the cerebrospinal fluid space between the amygdala and hip-

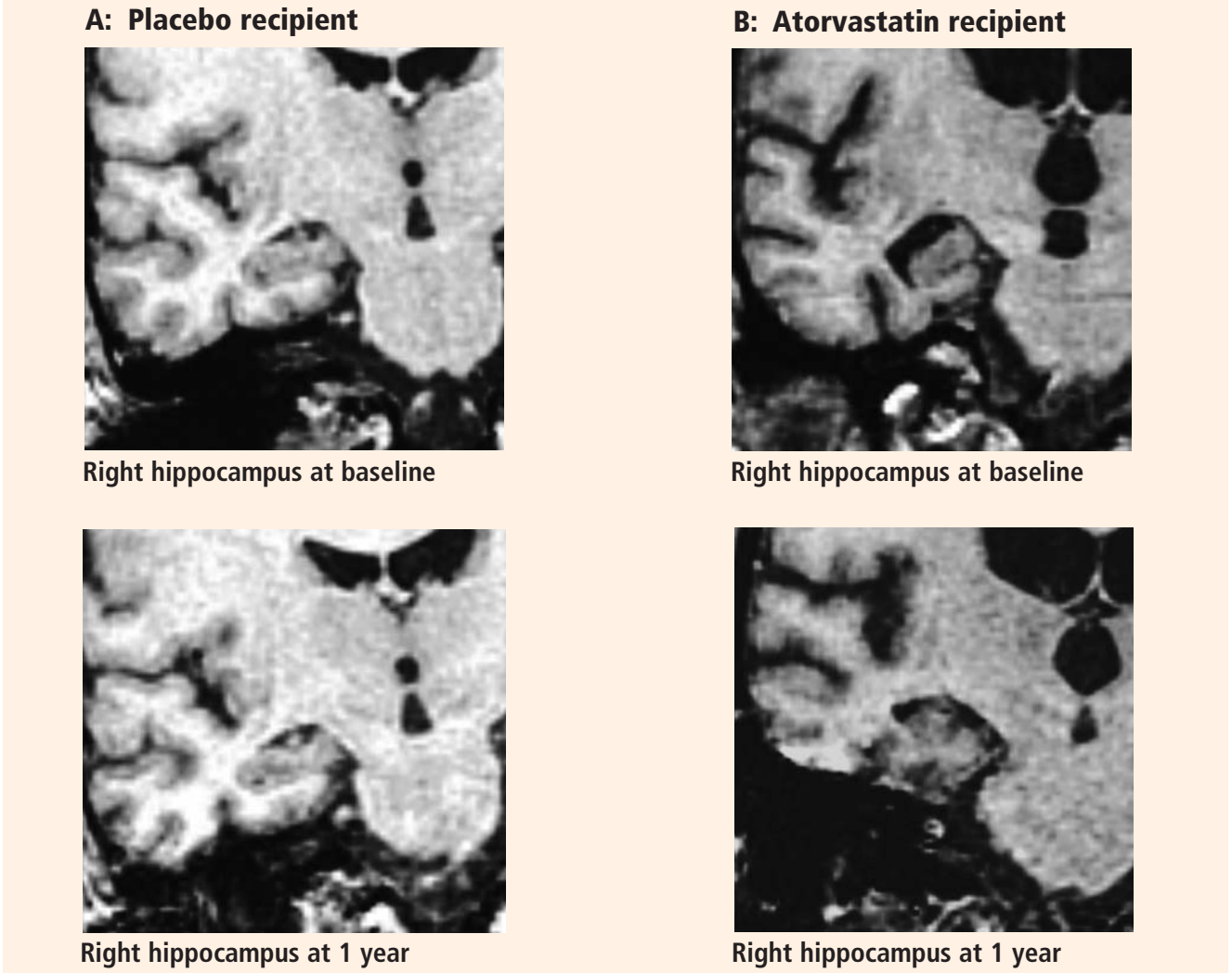

FIGURE 2. Differential effects of placebo and atorvastatin therapy on size of the right hippocampus in a pilot substudy of the Alzheimer's Disease Cholesterol-Lowering Treatment trial of patients with mild to moderate Alzheimer disease. In placebo patient 3 from Table 1 (panel A), the right hippocampus is slightly larger after 1 year of treatment with placebo relative to baseline. In contrast, in atorvastatin patient 2 from Table 1 (panel B), the right hippocampus is much smaller after 1 year of treatment with atorvastatin.

pocampus in the sagittal plane. The posterior aspect of the posterior region was initially landmarked in the sagittal plane by locating the posterior edge of the hippocampus and then checking in the coronal plane to ensure that the fornices were completely visualized. Volumes were calculated by importing the extracted hippocampi into MATLAB to measure the volumes.

Statistical analyses

Mean differences between the atorvastatin and placebo groups were evaluated using two-tailed Student *t* tests. Correlation between changes in cognitive measures and changes in the hippocampal volume for the total population and for the treatment groups was determined using Pearson's *r* coefficient. Significance was defined as a *P* value less than .05; a *P* value between .05 and .10 was deemed a trend.

Results

There was no difference in age or in years of education between the atorvastatin and the placebo groups **(Table 1)**.

In contrast to other studies,[54–58] we found in this pilot study that right hippocampal volume was slightly less than left hippocampal volume (2,015 ± 141 mm^3 vs 2,135 ± 183 mm^3).

Mean changes in performance on the ADAS-cog and MMSE were less pronounced in the atorvastatin group than in the placebo group, but not significantly so **(Table 1)**. However, there was a trend toward superiority in the atorvastatin group on performance on the free word-recall subscale of the ADAS-cog.

The reduction in total hippocampal volume was greater in the atorvastatin group than in the placebo group **(Table 1)**, but the difference was not statistically significant. This effect seems to have been driven by the highly significant reduction in right hippocampal volume in the atorvastatin group relative to the placebo group (P =.008), as illustrated in **Figure 2**.

No significant correlations were found between change in cognitive performance and change in hippocampal volume.

DISCUSSION

The preponderance of evidence clearly indicates that hippocampal volume is reduced in patients with AD compared with individuals with normal cognitive ability for their age. There is also evidence indicating that as cognitive performance deteriorates in AD patients, there are concurrent further reductions in hippocampal volume.[54] Many studies reported that there was no significant volume difference between the right and left hippocampi, but most suggested that the left hippocampus was slightly smaller than the right.[54–58] We identified no significant difference in volume between the sides, but we did find that the right hippocampus was smaller than the left in a very limited population of subjects with mild to moderate AD.

The major finding of this pilot study flies in the face of conventional wisdom in that there seems to be significant shrinkage of the right hippocampus with atorvastatin therapy compared with placebo in a randomized AD treatment trial that demonstrated clinical benefit with atorvastatin therapy.[44] A similar finding was reported from the beta-amyloid immunization (AN1792) treatment trial in AD.[59] In that study the active immunization was associated with significant clinical benefit, reduced beta-amyloid load, and reduced hippocampal volume.[59] The authors suggested that removal of beta-amyloid and/or other protein constituents from the tissue might have caused a "fluid shift" out of the tissue, resulting in shrinkage.

Based on our previous finding of reduced brain tissue density in AD patients compared with age-matched normal controls,[48] an alternative explanation can be proposed. Neuronal loss in the hippocampus may be accompanied by increased fluid balance (reduced density) in an attempt to retain the previous volume at the expense of function. Accordingly, as the hippocampus shrinks, it approaches a more normal density for the remaining neuronal complement, and cognitive function improves.

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Heart-brain interactions in cardiac arrhythmias: Role of the autonomic nervous system

ABSTRACT

The autonomic nervous system plays an important role in the genesis of ventricular arrhythmias and sudden cardiac death. Evidence is substantial for a neural component in sudden cardiac death. Sympathetic nerve sprouting and regional myocardial hyperinnervation following myocardial injury promote cardiac arrhythmia and sudden cardiac death through several potential mechanisms. Modulating autonomic tone is a potential method to reduce the risk of ventricular arrhythmias. Thoracic spinal cord stimulation is showing promise as a treatment for refractory angina. In addition, spinal cord stimulation has protected against ventricular tachycardia/ventricular fibrillation in animal models of postinfarction heart failure.

The autonomic nervous system has an important role in the genesis, maintenance, and interruption of ventricular arrhythmias.[1] In most instances, sympathetic activation precipitates or enhances ventricular arrhythmias, whereas vagal tone suppresses their occurrence.[2,3] Therefore, modulating autonomic tone has been proposed as a method to potentially suppress ventricular arrhythmias.[4]

An important mechanism underlying the development of ventricular arrhythmias is electrophysiologic heterogeneity. Electrical heterogeneity predisposes to the development of reentrant arrhythmias and other types of arrhythmias.[5]

SYMPATHETIC AND PARASYMPATHETIC INNERVATION OF THE HEART

Sympathetic nerve fibers are located subepicardially and travel along the routes of the major coronary arteries. In contrast, the vagus nerve is subendocardial in its location after it crosses the atrioventricular groove. A lesion of the heart produced by infarct or fibrosis can result in denervation of otherwise normal myocardium by interruption of neural axons traveling through the lesion. A defect in sympathetic function following myocardial infarction (MI) has been demonstrated in both animals and humans as measured by iodine-123-metaiodobenzylguanidine (MIBG) and C-11 hydroxyephedrine.[6]

Reduced uptake of MIBG in the inferior wall has recently been observed in patients with idiopathic ventricular fibrillation as compared with controls. Although no difference in survival could be detected between the two groups, patients with reduced uptake of MIBG had an increased incidence of ventricular tachyarrhythmias compared with those who did not have such a defect.[7]

Similar observations of sympathetic dysfunction have been made in a variety of animal models and humans with heart failure, coronary disease, and ventricular tachycardia in the absence of structural heart disease. In such instances, the speculation is that sympathetic heterogeneity may produce electrical heterogeneity and spur the development of ventricular arrhythmias. The arrhythmic mechanism is probably more complex than this description, however, because the response to sympathetic inhibition using beta-blockers is not uniform.

Evidence of nerve sprouting

Using a growth-associated protein antibody that marks axonal growth, nerve sprouting has been demonstrated in mice in areas of denervation following MI.[8] Similarly, using growth-associated protein 43 staining, researchers have demonstrated nerve sprouting in the right atrial free wall, right atrial isthmus, and right ventricle in dogs after radiofrequency catheter ablation.[9]

Neural component in ventricular arrhythmias

Sympathetic hypersensitivity has been shown in areas of denervation, which may be related in part to nerve sprouting. Other sympathetic and electrical phenomena following myocardial injury include an upregula-

Dr. Zipes reported that he serves as a consultant to and has received grant support from Medtronic, Inc., and serves as a consultant to and holds equity interest in Physical Logic.

tion of nerve growth factor, a heterogeneous distribution of sympathetic innervation, and electrical heterogeneity with areas of denervation, hyperinnervation, and normal nerve density.

Two discoveries by Chen and colleagues are perhaps most noteworthy. One is that nerve growth factor infusion and stellate ganglion stimulation following MI increase nerve density and ventricular arrhythmias, with increased burst frequency discharge of the stellate ganglion prior to the onset of ventricular tachycardia/ventricular fibrillation (VT/VF) in dogs.[8] More recently, they have shown that infusion of nerve growth factor into the stellate ganglion prolongs the QT interval and prolongs ventricular arrhythmias.[10]

A relationship has been established between the hyperinnervation that occurs following myocardial injury and ventricular arrhythmias. Using immunocytochemical staining in explanted native hearts of transplant recipients, Chen and colleagues demonstrated colocalization of Schwann cells, sympathetic nerves, and nerve axons, as well as regional cardiac hyperinnervation, with the most abundant nerve sprouting in the areas bordering myocardial injury and normal myocardium.[8] In addition, they demonstrated positive tyrosine hydroxylase staining of cardiac nerves in areas around coronary arteries in patients with coronary disease and idiopathic dilated nonischemic cardiomyopathy. At the origin of ventricular tachycardia (prior to transplant), nerve sprouting was shown by staining for S100 protein and tyrosine hydroxylase. The authors hypothesized that nerve sprouting may give rise to ventricular arrhythmia and sudden cardiac death, in which MI results in nerve injury, followed by sympathetic nerve sprouting and regional myocardial hyperinnervation.[10]

A link with circadian variations in QT interval length?

The observation that nerve growth factor infused into the left stellate ganglion prolongs the QT interval and prolongs ventricular arrhythmias, resulting in an inordinate risk of sudden death, is fascinating in the context of recent findings of a circadian variation in duration of the QT interval. In measuring QT intervals in 3,700 men without ventricular arrhythmias, we found that the QT interval peaked in winter (between October and January), with a 6-msec difference between the longest and shortest QT intervals.[11] This increase in the QT interval in winter coincides with an increase in the incidence of sudden death, which occurs in many regions of the world regardless of climate. Whether or not this increase in sudden death in winter is related to a longer QT interval is supposition, but the potential interaction deserves further exploration. A similar surge in sudden death in winter was observed in patients who were eligible for an implantable cardioverter-defibrillator (ICD) but did not receive one, as opposed to those who did receive an ICD, which suggests that the mechanism responsible for the increase in sudden death in winter is a ventricular tachyarrhythmia that can be prevented by an ICD.[12]

How sympathetic hyperinnervation promotes cardiac arrhythmias is speculative, but increased density of sympathetic nerve endings could promote the release of sympathetic neurotransmitters during sympathetic excitation. The autonomic remodeling is associated with heterogeneous electrical remodeling of cardiomyocytes, resulting in prolongation of action potentials in hyperinnervated regions. Further, acute release of sympathetic neurotransmitters probably accentuates the heterogeneity of excitability and refractoriness, likely contributing to arrhythmia susceptibility.[5]

PHARMACOLOGIC SYMPATHETIC BLOCKADE

Inhibiting sympathetic activity pharmacologically reduces the incidence of sudden cardiac death in patients with heart failure. In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), the aldosterone inhibitor eplerenone was associated with a clear reduction in sudden cardiac arrest in patients with acute MI complicated by left ventricular dysfunction.[13] Beta-blockers and angiotensin-converting enzyme inhibitors have had the same effect. These findings indicate that adverse electrophysiologic consequences from sympathetic stimulation may contribute to the development of a proarrhythmic substrate, and that antagonizing sympathetic activation can reduce the extent of adverse electrical remodeling to reduce the risk of sudden cardiac death.

SPINAL CORD STIMULATION

Acute spinal cord stimulation

The possibility of using spinal cord stimulation to modulate cardiac arrhythmias is intriguing, as electrodes introduced paraspinally may activate nerves that could affect sympathetic function. In Europe, spinal cord stimulation is already approved for treatment of patients with intractable angina and end-stage coronary disease.

The mechanism responsible for elimination of angina pectoris via carotid sinus massage is presumably an increase in vagal activity to the heart. In a study of whether thoracic spinal cord stimulation eliminates angina pectoris via a vagal mechanism, Olgin et al confirmed that spinal cord stimulation at the T1-T2 segments enhanced parasympathetic

activity and that this action is mediated via the vagus.[14] These findings suggest that thoracic spinal cord stimulation may protect against ventricular arrhythmias through its effect on autonomic tone.

This suggestion led to the development of a canine model of spontaneous ventricular arrhythmias to investigate the mechanisms responsible for ventricular arrhythmias related to acute myocardial ischemia in the setting of healed MI.[15] An infarct was produced via occlusion of the left anterior descending coronary artery and a permanent ventricular pacemaker was placed. After a 2-week recovery period, heart failure was induced by continuous rapid ventricular pacing for 2 to 3 weeks. Transient myocardial ischemia was induced by transient occlusion of the proximal left circumflex coronary artery. Seventy-two percent of dogs surviving the rapid pacing period developed VT/VF during acute left circumflex artery occlusion or within 1 to 2 minutes thereafter.

The effect of thoracic spinal cord stimulation applied at the dorsal T1-T2 segments was studied on the surviving dogs.[16] Spinal cord stimulation reduced the occurrence of VT/VF from 59% to 23%.

Another study examined the effect of intrathecal clonidine, an alpha-2 antagonist that reduces concentrations of catecholamines, on ventricular arrhythmias in the canine model.[17] Ischemia-induced VT/VF occurred in 9 of 12 dogs before administration of intrathecal clonidine in contrast to only 3 of 12 dogs after clonidine administration, a degree of efficacy similar to that with spinal cord stimulation.

Chronic spinal cord stimulation

Studies of the effects of chronic thoracic spinal cord stimulation on ventricular function and ventricular arrhythmias in a canine postinfarction heart failure model have recently been completed, and the results will be published in the near future.[18]

CONCLUSIONS

Sudden cardiac death continues to be a major health problem in Western countries. Many approaches have been explored in attempting to reduce this modern-day plague.[19] A better understanding of the risks, mechanisms, and treatments is required.[20] An animal model has demonstrated that acute modulation of autonomic tone with thoracic spinal cord stimulation or intrathecal clonidine reduces susceptibility to ischemic ventricular arrhythmias, presumably via a sympatholytic mechanism. Modulation of autonomic tone—sympatholytic, vagomimetic, or both—may play a significant role in protecting against spontaneous and ischemic ventricular tachyarrhythmias.

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Insular Alzheimer disease pathology and the psychometric correlates of mortality

ABSTRACT

Right hemisphere dysfunction is associated with mortality in Alzheimer's disease (AD) and other neurologic conditions. These associations may be mediated by insular pathology, as insular lesions result in demonstrable changes in cardiovascular and autonomic control. AD affects the insulae at a preclinical stage, and insular AD pathology may be present in up to 40% of nondemented septuagenarians and octogenarians. This pathology can affect in vivo cardiac conduction and thereby dispose to cardiac arrhythmias and sudden death. Thus, AD pathology should be considered as a possible explanation for autonomic morbidity and mortality in nondemented elderly persons.

Only a few brain structures have been implicated in the autonomic control of blood pressure and heart rate. Among them are heteromodal association areas in the cortex, especially the insular cortex. Insular infarction has been associated with both cardiac arrhythmias and mortality. However, stroke may not be the only insular pathology with the potential to disrupt autonomic function. Alzheimer disease (AD) is associated with both insular pathology and autonomic dysfunction.

This article presents the hypothesis that autonomic dysfunction reflects subclinical stages of AD pathology affecting the insular cortex and discusses the resulting clinical implications.

AUTONOMIC DYSFUNCTION AS A PRODUCT OF SUBCLINICAL ALZHEIMER DISEASE

Braak and Braak have demonstrated a hierarchical progression of AD pathology that includes the insular cortex.[1] This may explain why AD has effects on blood pressure and central autonomic cardioregulatory functions. However, AD reaches the insular cortex at a "preclinical" stage in the Braak and Braak sequence (before "dementia" can be diagnosed). Thus, AD pathology should also be considered as a possible explanation for autonomic morbidity and mortality in *nondemented* elderly persons.[2]

Suggestive evidence

The following observations support this possibility:

- Clinical AD is associated with a wide range of dysautonomic phenomena. These can already be demonstrated at the initial diagnosis, which suggests a preclinical onset.
- Only a limited set of brain regions are capable of affecting autonomic control. The insulae are affected at a preclinical stage in the sequence of Braak and Braak (ie, stage III of VI).
- Neurofibrillary tangle (NFT) counts inside the insulae moderate the association between the heart rate–corrected QT interval (QTc) and survival. This has been demonstrated by my colleagues and I in collaboration with the Honolulu-Asia Aging Study, which is examining the association between insular pathology at autopsy and the slope of premorbid change in the QTc.

Implications of AD-mediated autonomic dysfunction

AD-mediated autonomic dysfunction could have important clinical implications:

- The prevalence of preclinical AD is likely to be higher than the number of demented cases. Many apparently well elderly persons may be affected solely on the basis of subclinical AD pathology.
- Autonomic functions have widespread effects; many cardiac and noncardiac "age-related" changes may actually be related to AD.
- Pharmacologic therapies for AD are known to delay the progression of symptoms and to reduce mortality; these medications may also impact AD-related autonomic problems.
- Conversely, the association between other medications and cardiac arrhythmias/sudden death may be mediated via effects on insular function.

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

ALZHEIMER DISEASE DISRUPTS AUTONOMIC CONTROL

AD has been associated with a wide variety of dysautonomic phenomena, including increased pupillary dilation, altered skin conductivity, blunted autonomic response to noxious stimuli, diminished heart rate variability, depressed baroreflex sensitivity, and orthostasis. Autonomic instability has yet to be sought in mild cognitive impairment or even earlier preclinical stages of AD. However, nondemented subjects with mild cognitive impairment and early AD do experience more frequent falls and more gait and balance problems than do age-matched controls.

INSULAR CORTEX: A LIKELY TARGET

The insulae have been specifically implicated in the cortical control of autonomic function.[3] The vulnerability of the insular cortex to AD is easy to understand. NFTs appear to spread retrogradely along cortico-cortical and cortico-subcortical connections.[4] The insulae are mesiotemporal structures with direct connections to the hippocampus and entorhinal cortex.

Insular lesions result in changes in cardiovascular and autonomic control that are readily detectable by a variety of measures and procedures, including blood pressure, tilt table, balance platform, and electrocardiogram. The electrocardiographic effects of insular pathology include diminished heart rate variability, determined in either the time domain or the frequency domain. Diminished heart rate variability has been associated with increased mortality in cardiovascular disease and type 2 diabetes. It is important to note, however, that the effects of diminished heart rate variability are statistically *independent* of disease severity in these disorders, and that they can be demonstrated in the absence of clinically significant cardiovascular disease.[5]

HOLTER MONITOR EVIDENCE

Autopsy studies suggest that as many as 40% of nondemented septuagenarians and octogenarians may have AD pathology that is sufficiently advanced to affect the insular cortex.[1] This might explain the high prevalence of supraventricular arrhythmias and longitudinal decreases in heart rate variability among well elderly persons who are free of cardiovascular disease. In fact, unexplained supraventricular arrhythmias are quite common among such individuals. Both tachyarrhythmias and bradyarrhythmias are common on 24-hour Holter monitor recordings among subjects older than 80 years, and most are unexplained. In a study of the causes of syncope in a large (N = 711) sample of octogenarians, Lipsitz et al confirmed a cardiac etiology in only 21% of cases, whereas 31% of cases were unexplained.[6]

MORTALITY IN ALZHEIMER DISEASE IS ASSOCIATED WITH RIGHT HEMISPHERE DYSFUNCTION

AD pathology is widely thought to be symmetrically distributed. However, this may not be true of the preclinical "limbic" stages of AD.[7] Since insular effects on autonomic function are highly lateralized, the side of the brain affected by NFTs may be relevant to effects on cardiac rhythm and, hence, mortality risk.

Interestingly, mortality in AD is specifically associated with right hemisphere metabolic changes by electroencephalography, single-photon emission computed tomography, and positron emission tomography. Mortality can also be specifically associated with tests of constructional praxis. Claus and colleagues found that only the praxis subscore of the Cambridge Cognitive Examination (CAMCOG) was significantly related to survival in patients with early AD ($P < .001$).[8] Its predictive power was based on only two items: copying ability for a spiral and for a three-dimensional house. The effect was independent of age, sex, education, dementia severity, total CAMCOG score, and symptom duration. Similarly, Swan et al found a significant association between performance on the digit symbol substitution test and 5-year mortality among 1,118 subjects (with a mean age of 70.6 years) in the Western Collaborative Group Study.[9] In Cox regression analyses, the relative risk for all-cause mortality was 1.44 (95% confidence interval, 1.12 to 1.86) after adjustment for age, education, blood pressure, cancer, cardiovascular/cerebrovascular disease, and smoking.[9]

RIGHT HEMISPHERE DYSFUNCTION AFFECTS MORTALITY IN OTHER CONDITIONS

The effect of right hemisphere dysfunction on mortality is not limited to AD; it can also be demonstrated in other disorders, including epilepsy, head injury, and stroke.

We have been studying the cognitive correlates of mortality among well elderly septuagenarians and octogenarians living in a single comprehensive care retirement community (CCRC). Once again, visuospatial measures have been found to be selectively associated with mortality.[10] Clock drawing appears to be the cognitive predictor most strongly correlated

with mortality,[10] a finding that has been independently replicated in a second CCRC cohort.[11] This effect is independent of other cognitive domains, notably executive function.[10]

We recently examined the effect of insular NFTs on the association between QTc at examination 4 (circa 1991) of the Honolulu-Asia Aging Study and 12-year survival. Cases were dichotomized into those without and those with left or right insular NFT lesions (models 1, 2, 3, and 4 in **Table 1**). Each model was adjusted for age at exam 4. In the default models (1 and 2, with NFTs absent), neither age nor QTc at exam 4 was associated with survival; in contrast, in the presence of insular NFTs (models 3 and 4), age predicted survival **(Table 1)**. QTc trended toward significance in the presence of right insular pathology (model 4; $P = .067$) but not in the presence of left insular pathology (model 3). QTc was inversely related to survival in the presence of insular NFTs, suggesting that the effect of insular lesions on survival may be mediated through prolonged QT intervals.

TABLE 1
Insular neuropathology moderates associations of age and QTc with survival in the Honolulu-Asia Aging Study

	Estimate (days)*	SE	CR	*P*
No neurofibrillary tangles				
1. Left insula (n = 77)				
ΔtD ← QTc	3.50	2.09	1.13	.26
ΔtD ← Age	−18.11	16.27	−1.11	.27
2. Right insula (n = 73)				
ΔtD ← QTc	3.74	2.95	1.27	.21
ΔtD ← Age	−21.43	17.69	−1.21	.23
Neurofibrillary tangles present				
3. Left insula (n = 61)				
ΔtD ← QTc	−4.66	3.13	−1.49	.14
ΔtD ← Age	−48.82	18.88	−2.59	.01
4. Right insula (n = 65)				
ΔtD ← QTc	−5.96	3.26	−1.83	.067
ΔtD ← Age	−42.86	16.43	−2.61	< .01

* Estimated effect of each unit change in the predictor on mean survival in days.
QTc = corrected QT interval; SE = standard error; CR = critical range; ΔtD = time to death

SUMMARY

Right hemisphere dysfunction is associated with mortality in AD and other conditions. These associations may be mediated by insular pathology. AD affects the insulae at a preclinical stage, and insular AD pathology may affect as many as 40% of nondemented septuagenarians and octogenarians. This pathology can be shown to affect in vivo cardiac conduction, and may dispose elderly persons to cardiac arrhythmias and sudden death. If so, then AD must be considered a potential cause of cardiac arrhythmia, sudden death, and other autonomic disturbances in nondemented older adults.

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1 Functional Screen for Neuroprotective Microglial Activation Factors

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Peritoneal injection of lipopolysaccharide (LPS), the gram-negative bacterial endotoxin, elicits a rapid and potent innate immune response. While this systemic inflammatory response can be destructive, tolerable LPS doses of .05 to 1 mg/kg render the heart and brain transiently resistant to subsequent ischemic injury. Microglia, the resident central nervous system (CNS) immune cells, become activated following LPS treatment and can have neuroprotective roles within the brain.

Our lab has established a model for microglial activation induced by a series of four intraperitoneal (IP) LPS injections (1 mg/kg). LPS injection triggers peritoneal macrophages to secrete a barrage of cytokines and other soluble factors into the bloodstream. The purpose of the present study is to identify upstream microglial activation factors.

Enzyme-linked immunoassay of serum tumor necrosis factor (TNF)–α, a cytokine upregulated directly by LPS signaling, revealed that the innate immune response elicited by a single 1-mg/kg IP injection of LPS peaks in the bloodstream after 1 hour. We have isolated large quantities of LPS-stimulated mouse serum from donor mice at this timepoint. Similar to our LPS injection paradigm, a series of three intravenous (IV) injections of 500 µL LPS serum into recipient mice was capable of activating cortical microglia. Flow cytometry revealed a 3.5-fold increase in monocyte CNS infiltration from LPS-treated animals; however, IV injections of 5×10^6 white blood cells purified from LPS donor mice were incapable of initiating microglial activation.

Thus, serum-derived factors appear to be largely responsible for microglial activation within the cerebral cortex. Purification of these upstream serum factors that initiate neuroprotection in LPS-treated mice may provide a unique CNS therapeutic tool that can be administered through the bloodstream without the adverse systemic LPS inflammatory response.

2 Development of Cardiac Hypertrophy and Altered Gene Regulation in Vasopressin-Deficient Rats

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Many organisms display patterns of behavior or physiological responses that are coordinated with environmental cycles of light and dark and are known as circadian rhythms. An important aspect of circadian rhythm biology is the control of output genes by transcription factors. The regulation of circadian genes in the heart is an area of active inquiry, with several hormonal signals proposed to play a role. Vasopressin (VP), a hormone secreted by the posterior pituitary gland in response to hypothalamic stimulation, regulates physiological processes of the excretory and cardiovascular systems. VP is also known to be involved in the mammalian stress response, and may be involved in the regulation of circadian rhythms. This study was designed to assess the effects of VP deficiency on cardiac size and the expression of genes that are involved in circadian regulation.

Long-Evans (LE) rats and VP-deficient Brattleboro (also called diabetes insipidus [DI]) rats were compared. Rats were exposed to a 12-hour/12-hour light/dark cycle with ad libitum feeding. Body weight, food intake, and water intake were monitored. Following sacrifice, hearts were rapidly excised, weighed, and frozen for later analysis. Ventricular tissue was homogenized, and Northern blot analysis with specific cDNA probes was used to quantify expression of atrial natriuretic factor (ANF) and circadian-locomotor output cycles "kaput" (CLOCK).

Data analysis revealed that DI rats consumed more water than LE rats, which was attributed to the VP deficiency. There was no difference in food intake between LE and DI rats, but LE rats had consistently higher body weights, suggesting that VP plays a role in body weight regulation. In spite of increased body weight in LE rats, the ratio of heart weight to body weight was significantly greater in DI rats, demonstrating that lack of VP results in considerable cardiac hypertrophy. ANF expression was also fivefold greater in DI rat hearts than in LE rat hearts. Ventricular expression of ANF is a hallmark of cardiac hypertrophy, and the increased ANF in DI rats verifies the presence of a compensatory and possibly pathological process in VP-deficient animals. The mRNA for CLOCK was not significantly different between DI and LE rat hearts.

Data from this study suggest that lack of VP results in a compensatory cardiac hypertrophy, possibly due to up-regulation of the renin-angiotensin system or altered volume status. Data further suggest that VP is not involved in regulation of CLOCK mRNA. Further study is required to elucidate the potential role of VP in regulating additional genes and transcription factors involved in circadian rhythms.

3 A Cortical Potential Reflecting Cardiac Function

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Emotional trauma and psychological stress can precipitate cardiac arrhythmia and sudden death through arrhythmogenic effects of efferent sympathetic drive. Patients with preexisting heart disease are particularly at risk. Moreover, generation of proarrhythmic activity patterns within cerebral autonomic centers may be amplified by afferent feedback from a dysfunctional myocardium. An electrocortical potential reflecting afferent cardiac information has been described, the magnitude of which reflects individual differences in interoceptive sensitivity (awareness of one's own heartbeats). To inform our understanding of mechanisms underlying arrhythmogenesis, we extended this approach, identifying electrocortical potentials corresponding to the cortical expression of afferent information about the integrity of myocardial function during stress.

Ten male cardiology patients (mean age [± SD] = 59 ± 11.11 years) with one- to three-vessel heart disease and established ventricular dysfunction **(Table)** were recruited consecutively from two cardiology outpatient clinics (The Heart Hospital, University College London Hospitals Trust, London, UK, and The Whittington Hospital, Hampstead, London, UK). We measured stress-induced changes in cardiac response simultaneously with electroencephalography (EEG), electrocardiography (ECG), and beat-to-beat finger arterial blood pressure measurements (Finometer). Experimentally induced mental stress enhanced cardiovascular indices of sympathetic activity (systolic blood pressure, heart rate, ventricular ejection fraction, and skin conductance) across all patients. However, the functional response of the myocardium varied; some patients increased, while others decreased, cardiac output during stress. Across patients, heartbeat evoked potential amplitude at left temporal and lateral frontal electrode locations correlated with stress-induced changes in cardiac output, consistent with an afferent cortical representation of myocardial function during stress **(Figure)**. Moreover, the amplitude of the heartbeat evoked potential in the left temporal region reflected the proarrhythmic status of the heart (inhomogeneity of left ventricular repolarization).

These novel observations delineate a cortical representation of afferent cardiac information predictive of proarrhythmic abnormalities in cardiac repolarization. Our findings highlight the dynamic interaction of heart and brain in stress-induced cardiovascular morbidity.

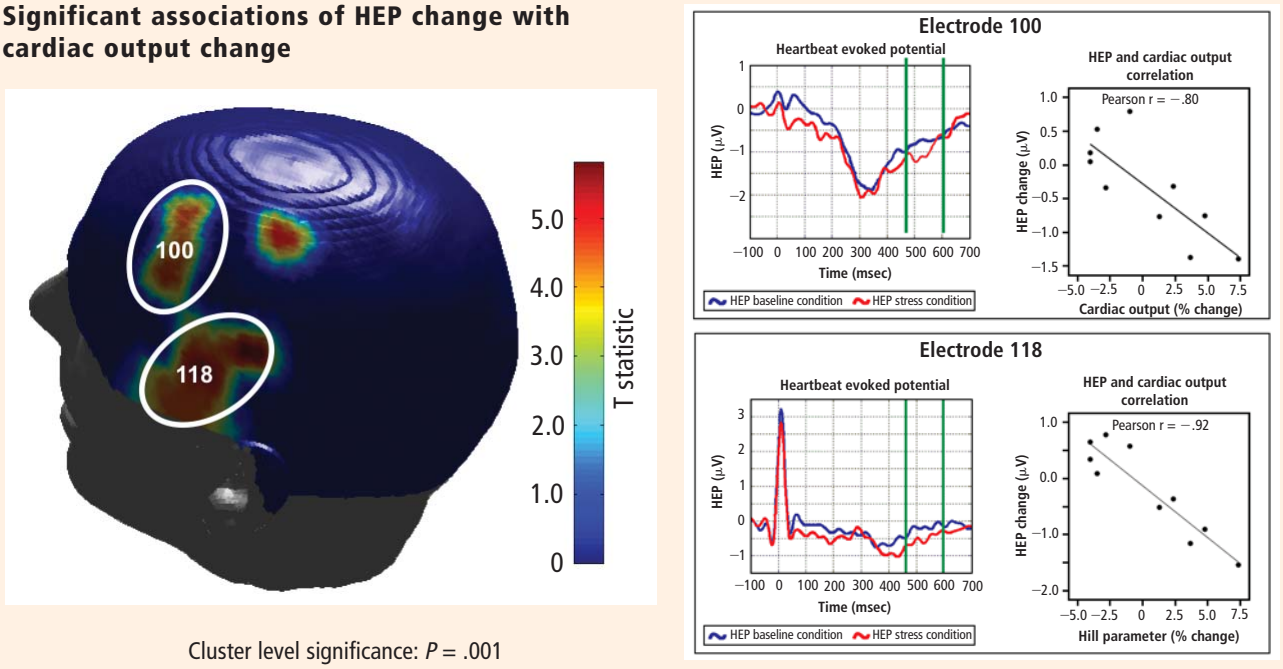
TABLE
PATIENT CLINICAL PROFILES

Pt	Age	Sex	MI	Wall mot	Current medications		
					β-blk	Ca-blk	ACE
1	63	M	No	Mod	No	Diltiazem	Ramipril
2	60	M	Yes	Mod	Atenolol	No	Ramipril
3	55	M	Yes	Mild	Atenolol	Diltiazem	Ramipril
4	60	M	Yes	Mod	Atenolol	No	No
5	45	M	Yes	Mod	Atenolol	No	Ramipril
6	77	M	Yes	Mild	Atenolol	Diltiazem	Lisinopril
7	58	M	Uncertain	Mild	Atenolol	No	No
8	42	M	Yes	Mod	Bisoprolol	No	Perindopril
9	71	M	Dilated	Severe	Bisoprolol	No	No
10	58	M	Yes	Severe	Atenolol	Amlodipine	Perindopril

One patient had one-vessel heart disease; all remaining patients had two- or three-vessel heart disease. In addition, patients 2 and 8 had undergone coronary artery surgical procedures; patients 7 and 10 had undergone angioplasty procedures; and patients 2, 9, and 10 had previous heart failure.

MI = myocardial infarction; Wall mot = ventricular wall motion impairment; β-blk = beta-blocker; Ca-blk = calcium channel blocker; ACE = angiotensin-converting enzyme inhibitor

Reprinted from Gray MA, et al. A cortical potential reflecting cardiac function. Proc Natl Acad Sci U S A 2007; 104:6818–6823.



Reprinted from Gray MA, et al. A cortical potential reflecting cardiac function. Proc Natl Acad Sci U S A 2007; 104:6818–6823.

FIGURE. Stress-induced change in cardiac output was significantly correlated with change in heartbeat evoked potential (HEP) amplitude within the left temporal and posterior frontal electrode locations.

4 Depression Kills: Changes in Depressive Symptoms Predicted Mortality in Community-Dwelling Elderly People

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Purpose: Previous research suggests that depression may be associated with the development of coronary heart disease, myocardial infarction, and increased mortality. In community samples, people with depression may be at risk of higher mortality. However, inconsistent results were found in 32 longitudinal studies on depression and mortality in the literature. Only 14 studies showed positive findings, 11 showed negative findings, and 7 showed positive findings only in subgroups. There are a number of limitations in these studies, including mostly single assessment of depression, relatively short-term follow-up, and inadequate statistical analysis to capture progression of depression. In this study, we examined a group of community-dwelling elderly people to determine the impact of changes in depression on long-term mortality, using a new statistical methodology.

Methods: At study entry, 865 people (mean age of 80.7 years; 65.8% women) underwent comprehensive psychosocial and health assessment, including the Center for Epidemiologic Studies Depression Scale (CES-D, 10-item version). They were then assessed annually for up to 11 years. Mortality was ascertained by the Social Security Death Index up to 15 years. Joint modeling of repeated measures and survival data, as well as separate individual growth curve analysis and Cox regression, was conducted to model the change in depressive symptoms over time in each participant and its impact on mortality. Five classes of covariates were controlled for: demographic (age, sex, education, marital status, income, living situation), health behavior (smoking, alcohol consumption, exercise), chronic disease (body mass index, heart disease, stroke, cancer, diabetes, hypertension, hyperlipidemia), health status (self-rated health, ADL, IADL), and cognitive impairment.

Results: Death occurred in 603 participants (69.7%). The baseline CES-D score predicted mortality after adjusting for age and sex (HR = 1.03, $P < .001$). This predictive power disappeared, however, after adjusting for other covariates. Linear change rates of CES-D scores over time were predictive of mortality after adjusting for covariates (HR = 1.60, $P < .001$). Therefore, an annual increase of 1 point in CES-D score was associated with a 60% higher risk of mortality. To further interpret the results, the sample was divided into three groups based on each individual's change trajectory of depressive symptom scores: "Down," "Stable," or "Up." Compared with the Stable group, the Up group (whose depressive symptom scores increased) had a 70% increase in mortality risk ($P < .001$). On average, they lived almost 4 years less. The Down group was not different from the Stable group. CES-D scores increased by 2.3 points annually, on average, in the Up group, whereas they decreased by 1.1 points annually, on average, in the Down group.

Conclusion: In a longitudinal study, it is important to examine the change trajectory of depressive symptoms and its effects on mortality. Although baseline depression score was not predictive of mortality, a change in depressive symptoms—specifically, an increase in depression over time—was a significant and robust predictor of mortality, even after adjusting for five classes of covariates. Early screening and treatment may stop the progression of depression, which may help prevent excess mortality among the elderly.

5 Endotoxin Preconditioning of the Brain: A Neuroprotective Role of Microglia

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Preconditioning by subthreshold stress can protect the brain from subsequent injury. Preconditioning can be induced by a number of mechanisms including hypoxia, ischemia, heat shock, and intraperitoneal (IP) injection of the endotoxin lipopolysaccharide (LPS). While global preconditioning with low doses of LPS provides protection against injurious focal ischemia in the brain, the cellular mechanisms involved in LPS neuroprotection are incompletely understood. In this study, we investigated the mechanisms by which the central nervous system (CNS) is protected by preconditioning with LPS.

C57BL/6 mice were injected with four IP injections of LPS (1 mg/kg), 24 hours apart, and were sacrificed 1, 7, and 14 days later. One day after LPS treatment, cortical microglia became activated and ensheathed neuronal cell bodies and proximal dendrites. Electron microscopy analysis demonstrated that these activated microglia separated pre- and postsynaptic components of axosomatic synapses. A reduction of 30% in the neuronal area occupied by presynaptic terminals was also observed by confocal microscopy analysis. In addition, a significant decrease in GABA receptor transcripts was obtained 1 day after LPS treatment. mRNA and protein levels of the anti-apoptotic molecule Bcl-2 were increased in LPS-treated animals, indicating a Bcl-2-mediated neuroprotective response. Microglial targeting of neurons and Bcl-2 upregulation were transient and returned to control levels at 14 days postinjection.

In summary, preconditioning doses of LPS lead to microglial activation that targets neurons and strips inhibitory synapses in the cortex. Our data suggest that this interaction may be neuroprotective since activated microglia preferentially remove GABAergic inhibitory axosomatic synapses, thereby transiently favoring neurotrophic activity of excitatory NMDA agonist.

6 Axonal Conduction Block Using High-Frequency Pulse Trains

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Current literature suggests that pulse train high-frequency stimulation (HFS) affects axons by driving them at the stimulation frequency, disrupting abnormal activity in neural networks. Yet recent work has shown that sinusoidal HFS suppresses axonal conduction in vitro.[1] Therefore, we tested the hypothesis that pulse train HFS of fiber tracts blocks axonal conduction.

HFS (monophasic, 0.5 to 200 Hz, 100 μsec, 1 to 2 min) was applied via a monopolar tungsten electrode to either the alveus of transverse hippocampal slices in vitro (rat) or the commissural fiber pathway in vivo (rat). Antidromic field potentials were recorded in the CA1 alveus in vitro or the CA3 region of both hippocampi in vivo. Field potential amplitude, width, and latency were analyzed

prior to, during, and after HFS. Pulse trains were applied at 100%, 75%, and 50% of the stimulation amplitude required to produce a maximal evoked potential. For block experiments, a second tungsten electrode provided an evoked test pulse through the site of HFS.

The data show that HFS failed to drive axonal activity in vitro (n = 5) or in vivo (n = 4). The number of cycles required for failure was frequency-dependent but independent of stimulus amplitude ($P < .001$ and $P > .5$, respectively, ANOVA). Axons were unable to follow extracellular pulse trains above 80 Hz in vitro, while axons in vivo were unable to follow stimulation above 125 Hz. Axons were unable to follow HFS even after isolation of the alvear axon field in vitro (n = 5). Pulse train HFS above 150 Hz reversibly blocked axonal conduction in an amplitude-dependent manner in vitro and in vivo. These data indicate that HFS of fiber tracts has the potential for controlling abnormal propagating activity within the brain.

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7 Prevention of Depression and Anxiety in Patients with Acute Coronary Syndrome (DECARD): A Double-Blind, Placebo-Controlled Study of Escitalopram

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Background and Aims: The prevalence of depression and anxiety is higher in patients recovering from acute coronary syndrome (ACS), ie, myocardial infarction (MI) and unstable angina, than in the general population, and both depression and anxiety are associated with poor cardiac outcomes and higher mortality. Despite the prognostic role of depression in ischemic heart disease, no clinical trials have been undertaken to assess prevention of depression and anxiety in this population of patients. The aim of this study is to evaluate the efficacy of preventive treatment with a selective serotonin reuptake inhibitor (escitalopram) in the first year after ACS.

Methods: Two hundred thirty-four (234) nondepressed patients with STEMI, non-STEMI, or unstable angina will be enrolled within 8 weeks after ACS and randomly assigned to treatment with escitalopram (5 to 20 mg) or placebo for 52 weeks. There will be nine psychiatric and three cardiologic assessments during the year of the study. The primary outcome measures are the diagnosis of depression and Hamilton Depression Scale score. Psychiatric measurements: Schedules for Clinical Assessment in Neuropsychiatry, Hamilton Depression Scale, Hamilton Anxiety Rating Scale, UKU Side Effect Rating Scale, ENRICHD Social Support Instrument, Short Form-36 Health Survey, SCL-92 (Symptom Check List), and Beck Depression Inventory. Cardiologic measurements are blood pressure, electrocardiography, echocardiography (left ventricular ejection fraction), heart rate variability, and use of medicine.

Conclusion: ACS patients with mental illness often remain untreated and have an increased risk of somatic comorbidity and mortality. DECARD is the first study evaluating the effect of prophylactic treatment of depression in patients with ACS. The study is ongoing and had enrolled 182 patients as of April 15, 2007.

8 Knowledge Discovery in Databases and Other Techniques in Biomedical Informatics: New Contributions to Heart-Brain Biology and Medicine, with a Focus on Traditional Cognitive-Behavioral Practices

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This presentation describes the development of a new, state-of-the-art database resource in heart-brain biology and medicine focused on the potential contribution to heart-brain health of cognitive-behavioral practices, especially traditional ones such as meditation, yoga, and related practices. Developed by Massachusetts Institute of Techology researchers in collaboration with colleagues from other leading research institutions (Columbia and Cornell Universities), along with His Holiness the Dalai Lama (in the role of nonsectarian representative of expertise in traditional meditation/yoga practice), this database resource is derived from principles in biological and medical informatics that are currently revolutionizing many fields in the human life sciences and medicine. In particular, the resource, or database-based "knowledge discovery system,"[1] has been designed utilizing principles of "knowledge discovery in databases" (KDD)[1,2] through searches designed according to "an expert-guided decision tree construction strategy."[3–5]

In this original investigation in the biomedical informatics of heart-brain medicine utilizing KDD and expert-guided decision tree search strategies, four components of the traditional yoga meditation regimen (cognitive-meditational, respiratory, postural, dietary) were identified as possessing robust and highly significant enhancing effects on cardiac vagal tone, as reflected in heart rate variability (HRV) and baroreflex sensitivity, in agreement with published findings from several studies (Bushell et al, in preparation). A second set of components of the traditional cognitive-behavioral regimen (meditational, respiratory) was identified which preliminary evidence suggests may be associated with protection against an ischemic/reperfusion event (Bushell et al, in preparation). A third set of components of the traditional regimen (respiratory, meditational, postural) was identified which is suggestive of the potential capacity to stimulate regenerative rather than scar-forming responses to an insult in cardiac tissue (Bushell et al, in preparation). Analysis of this bioinformatics evidence was conducted within the framework provided by colleagues' experimentally derived models (see proceedings of the conference, "Longevity and Optimal Health: Integrating Eastern and Western Perspectives," forthcoming in the *Annals of the New York Academy of Sciences*, Bushell and Olivo, editors): Tracey's anti-inflammatory vagal pathway; Blackburn's stress-induced telomere attrition associated with cardiovascular disease; and Heber-Katz's mammalian cardiac regeneration model. Detailed explanations of results will be provided in the presentation.

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9 P-Selectin–Targeted Liposomes for Potential Applications in Thrombolytic Therapy

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Atherosclerosis-related vascular thrombosis and occlusion are principal causes of acute cardiovascular and cerebrovascular events leading to morbidity and mortality. Thrombosis and occlusion stem from dysregulated hemostatic phenomena involving platelet and endothelial cell activation, platelet adhesion and aggregation, and triggering of the subsequent coagulation cascade to ultimately form the fibrin "clot." Clot growth leads to arterial occlusion and reduction of antegrade blood flow, which in turn results in ischemia and related acute events. Intravenous or transcatheter systemic infusion of thrombolytic agents is highly effective in revascularization and prevention of acute outcomes. However, this therapy has a very narrow treatment window (hours to minutes after the event, depending on location and severity) and also suffers from limitations such as high cost, short circulation half-life of the drugs (requiring continuous or recurring administration), and potential systemic hemorrhage. If thrombolytics could be maintained in circulation in a "protected state" for longer periods, and then rapidly yet selectively localized only at sites of thrombogenesis, the aforementioned problems could be eliminated. Recent advances in the area of long-circulating "stealth" nanoparticles, coupled with the ever-expanding library of cell-targeted receptor-specific ligands, could potentially provide a way to achieve prophylactic, target-specific action of thrombolytics.

Based on the cellular/molecular mechanisms in thrombosis, we postulated that the P-selectin molecule on activated platelets and endothelial cells would be an ideal receptor for nanoparticle targeting. P-selectin is stored at relatively high concentration within alpha-granules and Weibel-Palade bodies of quiescent platelets and endothelial cells, respectively, and is rapidly translocated to the cell surface for expression upon activation by thrombogenic or inflammatory events. P-selectin is a quantitative marker for platelet activation and forms the surface adhesion receptor for leukocyte interaction with platelets and endothelial cells. Hence, a nanoparticle selectively targeted to sites of P-selectin upregulation can essentially localize specifically at thrombotic sites and deliver an encapsulated thrombolytic drug at that site for sustained release. A similar strategy has demonstrated a promising pharmacokinetic profile and therapeutic efficacy in cancer treatment and hence forms the rationale for this approach.

We have chosen the peptide sequence CDVEWVDVS [Molenaar et al], with specificity and high affinity for P-selectin, as our targeting ligand. We have developed the peptide through solid-phase synthesis, conjugated the peptide to a lipid molecule, and used the lipid-peptide conjugate to form spherical lipid vesicles (liposomes) with the peptide displayed on the liposome surface in multiple copies **(Figure)**. We have tested the peptide-modified liposomes for their platelet P-selectin targeting efficacy in fluorescence microscopy and flow cytometry assays using human whole blood and plasma. We have also performed preliminary formulation and release studies with the liposomes by encapsulating a model drug. Optimization of encapsulation and purification procedure and manipulation of targeting efficacy renders a thrombus-targeted nanoparticle that can potentially carry a variety of therapeutics for cardiovascular applications. Since activated platelets and inflamed endothelium are also involved in the developmental and progressive stages of vascular diseases, P-selectin–targeted nanoparticles may also provide a selective way to deliver optimum payloads of imaging probes to diseased vascular areas for sensitive molecular imaging and diagnostics.

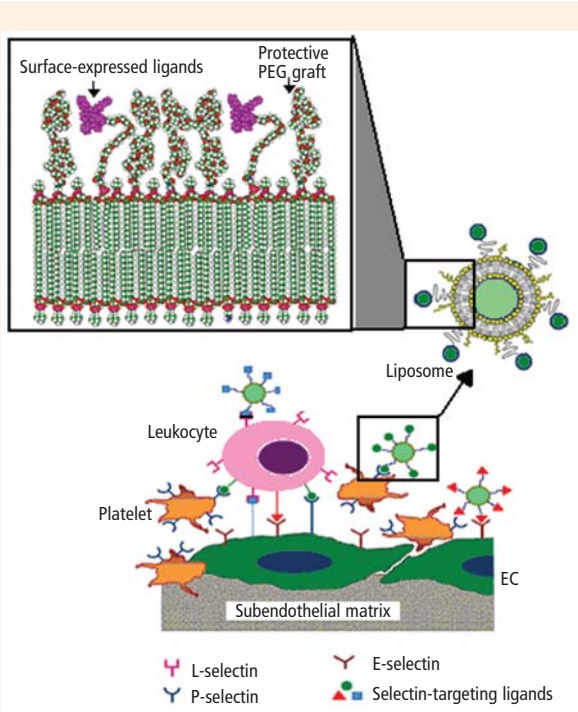

FIGURE. Schematic of selectin-targeted liposome.

10 The Heart-Brain Link: Neural Concomitants of Heart Rate Variability During Emotion

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The vagal (high-frequency [HF]) component of heart rate variability (HRV) is known to predict morbidity and mortality. Previous studies of the neural correlates of vagal tone involved cognitive and mental stress tasks. To explore the neural substrates of vagal tone during emotion, we correlated HF-HRV with measures of cerebral blood flow (rCBF) derived from positron emission tomography (PET) and ^{15}O-water in 12 healthy women.

Happiness, sadness, disgust, and three neutral conditions were each induced by film clips and recall of personal experiences (12 conditions). Inter-beat intervals derived from electrocardio-

graphic (lead II) recordings during 60-second scans were spectrally analyzed, generating 12 separate measures of HF-HRV in each subject. The six emotion (E) and six neutral (N) conditions were grouped together. We report the correlations between HF-HRV and rCBF specifically attributable to emotion (E minus N). This random-effects analysis in SPM2 updates a previous preliminary report of our findings from a fixed-effects analysis in SPM98.

Four brain areas survived correction for multiple comparisons at the cluster level ($P < .05$) when the significance threshold for the second-level contrast was set at $P < .001$ ($z = 3.11$). Three frontal areas—the right superior (26 43 35: BA 9, 8), the right dorsolateral prefrontal (50 47 5: BA 46), and the bilateral medial prefrontal cortices (−6 47 5: BA 24, 32)—were significant at P values of .025, .025, and .014, respectively. The right parietal cortex (44 −29 47: BA 40) was significant at $P < .043$.

These new random-effects findings, which generalize to the population, demonstrate a predominant role of the right hemisphere, as well as the bilateral medial frontal area, in the regulation of vagal tone during emotion. These results are consistent with the neurovisceral integration model, which posits a role for the prefrontal cortex in the inhibition of sympathoexcitatory circuits in the regulation of emotion.

11 The Unknown Face of Epilepsy and Cardiovascular Care*

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Rationale: The industrial nations face a gray future. The proportion of the population that is 65 years or older has increased from 4.1% in 1900 to 13.0% in 2000. In 2000, Americans enjoyed the longest life expectancy in US history—almost 77 years. Life expectancy was 74 years for men and almost 80 years for women. Accordingly, there is an increased need for updated and tailored patient care congruent with specific age- and gender-related morbidities.

Methods: An 88-year-old female without lung disease was admitted to the Department of Cardiology, Sentara CarePlex Hospital, located in Hampton, Virginia, for new onset of convulsive seizures following a cardiac catheterization procedure. The cardiac catheterization was performed as part of a preoperative cardiovascular risk assessment prior to the patient undergoing surgical removal of a 3.4-cm tumor of the anterior wall of the gastric fundus. Before the catheterization, the patient had received a single 25-mg dose of metoprolol. In addition to mitral valve prolapse, the cardiac catheterization revealed normal coronary arteries, including those supplying the sinus node.

Results: A wandering atrial pacemaker (WAP) abnormality was observed upon admission of the patient to the hospital after her seizure and was also documented following another nocturnal epileptic seizure during hospitalization. The diagnosis of epileptic seizures was supported by the admission electroencephalogram showing a focal disturbance with right-side hemisphere slowing in the presence of a brain MRI revealing mild general atrophy and small chronic basal ganglia lacunes.

The patient was successfully treated with phenytoin with full remission of the cardiac rhythm abnormality and cessation of her epileptic activity.

Conclusions: To the best of our knowledge, this is the first time that a WAP abnormality has been described in a patient experiencing de novo epileptic seizures. Importantly, this patient had no evidence of lung disease and she underwent a cardiologic work-up that excluded an underlying cardiac cause for this abnormality.

Generally, WAP is a benign cardiac dysrhythmia that occurs in normal hearts as a result of fluctuations in vagal tone, although more hazardous conditions, such as hypoxia and chronic obstructive pulmonary disease, can cause WAP. Significantly, WAP may be a precursor to a potentially dangerous cardiac condition, such as atrial fibrillation, that can lead to death from stroke or heart failure. In fact, the death rate among patients with atrial fibrillation is about double that among patients who do not have it.

An important consideration in the context of this case report is the abundant neurological literature describing the association between epileptic seizures and cardiac abnormalities caused by parasympathetic fluctuations and hypoxia, leading to severe atrioventricular blocks and even death. Accordingly, the present case brings us to consider ictal hypoxia along with the vagal fluctuations as the underlying mechanism that triggered this postictal abnormality.

Our case report warrants further studies to look into the specific association between cardiovascular rhythm abnormalities and epileptic seizures, especially in the elderly. Accordingly, better-tailored patient care should be provided by such means as simultaneous electrocardiographic-electroencephalographic monitoring in order to optimize diagnosis and subsequent treatment.

** Finalist for Young Investigator Award.*

12 Does an Acute Inflammatory Response Temporarily Attenuate Autonomic Nervous System Function?*

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Background: Although recent observational studies suggest that inflammatory markers are associated with autonomic function, the causal relationship of this is not clear. Because inflammatory parameters could influence the autonomic nervous system by affecting the hypothalamic-pituitary-adrenal axis, we tested the hypothesis that an acute inflammation is associated with temporarily attenuated autonomic nervous system activity.

Methods: Using a randomized sham placebo-controlled, double-blind design, 24 healthy subjects (age 24.8 ± 3.5 years) were injected with an influenza vaccine (0.5 m/L, Influenza Split Vaccine) or a sham vaccine (0.5 m/L, normal saline) as a model to generate a systemic inflammatory response. Heart rate recovery (HRR) after maximal treadmill exercise was used as an index of autonomic nervous system function and was calculated as the difference between maximal heart rate during the test and heart rate 1 minute (HRR 1) and 2 minutes (HRR 2) after cessation of exercise. Blood samples were taken and HRR was measured before each vaccination and 48 hours after each vaccination.

Results: Log C-reactive protein was significantly increased after influenza vaccination (from 1.87 ± 1.2 to 2.75 ± 1.3, $P <$

.05), but log tumor necrosis factor-α was not (from 2.01 ± 0.1 to 2.00 ± 0.19, *P* = NS). HRR 1 was significantly attenuated after influenza vaccination but not after sham vaccination **(Table)**. However, HRR 2 was not significantly attenuated after influenza vaccination.

Conclusions: These findings show that an acute inflammation caused a temporary deterioration of autonomic nervous system function. This suggests that inflammation alters autonomic function consistent with an increase in cardiovascular risk.

** Finalist for Young Investigator Award.*

TABLE
EFFECT OF VACCINES ON HEART RATE RECOVERY (HRR)

Variable	Influenza vaccine (n = 15)		Sham vaccine (n = 9)	
	Pre	Post	Pre	Post
HRR 1 (bpm)	23.4 ± 6.4	20.5 ± 4.9*	26.8 ± 10.1	26.2 ± 9.8
HRR 2 (bpm)	46.0 ± 9.3	43.9 ± 10.5	52.0 ± 14.9	51.4 ± 15.2

Values are means ± SD.
* *P* < .05, pre vs post

13 Effects of Guided Imagery on Heart Rate Variability*

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Background: Numerous prospective studies have shown that psychological stressors such as depression, anger, and anxiety are important and major risk factors contributing to the development and progression of cardiovascular disease. These findings have led to an increased interest in elucidating mechanisms linking the brain and the cardiovascular system. Brain imaging studies have shown that various psychological states are associated with changes in the activity of specific regions of the brain. These regions include those that regulate the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, providing mechanistic explanations for the altered heart rate variability (HRV), immune system activation, and platelet activation that are associated with psychological stress. Given the effect that emotions have on health, it is also not surprising that there is a growing interest in incorporating stress-reduction practices into an overall wellness approach to medical care. One such practice, guided imagery, has been used, for example, to reduce postsurgical anxiety and pain, yet nothing is known about its mechanism of action. We have thus conducted an exploratory study to assess the protective effect of guided imagery on downstream pathways affected by psychological stress.

Questions/Hypotheses: *Primary outcomes:* (1) Guided imagery will show decreased sympathetic and increased parasympathetic responses as assessed by HRV measures and (2) decreased HPA activity as measured by salivary cortisol. (3) Guided imagery will show improved well-being as measured by psychometric instruments.

Secondary outcomes: (4) Guided imagery will show improved well-being as measured by elevated melatonin and DHEA.

Methods: The intervention was performed in two group sessions of approximately 30 participants each. Blood, saliva, and psychometric questionnaires were obtained before and after the intervention. Heart rate was recorded throughout the session.

Psychometric instruments: A 25-item state-anxiety version of the Profile of Mood States (POMS) questionnaire was used, as was the Smith Relaxation States Inventory (SRSI), which addresses positive emotions associated with relaxation.

Salivary cortisol and melatonin: Saliva was collected by passive drool and stored at −80°C. Assays were performed en masse by enzyme-linked immunoassay (ELISA) using commercial kits.

Serum DHEA: Serum was prepared and DHEA assayed using a commercial ELISA kit.

Results: The intervention was effective in decreasing anxiety and increasing well-being, as determined by inventories. It decreased HPA activity as assessed by cortisol level. Finally, it had a relaxing effect on the autonomic nervous system as reflected by decreased heart rate and increased total and high-frequency HRV power.

Conclusions: The relaxation response of guided imagery may exert its beneficial effects by decreasing HPA axis activation, decreasing sympathetic nervous system activity, and improving vagal tone.

This research was supported in part by the National Institutes of Health, National Center for Complementary and Alternative Medicine Grant AT-001884; and in part by the National Institutes of Health, National Center for Research Resources, General Clinical Research Center Grant M01 RR-018390.

** Finalist for Young Investigator Award.*

Winner of the Young Investigator Award

14 High-Sensitivity C-Reactive Protein in Patients with Coronary Heart Disease and Depression

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Background: Large prospective epidemiological studies indicate that a high plasma level of C-reactive protein (CRP) is a significant predictor of cardiovascular events in individuals with or without known coronary heart disease (CHD). Also, recent findings indicate that depression is associated with an activation of the inflammatory response system expressed in increased levels of proinflammatory cytokines (IL-2, IL-6, interferon gamma) and CRP. Individuals diagnosed with major depression had been shown to be at increased risk of developing CHD and having worse outcomes compared with nondepressed counterparts. On the other side, 20% of patients with CHD are also diagnosed with depression. Successful treatment of depression in CHD patients improves outcomes.

Objective: To explore retrospectively the level of CRP in patients with CHD with and without depression.

Methods: *Study design:* Retrospective review of medical records between January 2002 and November 2006 of patients who had been diagnosed with CHD and had high-sensitivity CRP (hs-CRP) level measured in our institution. Patients were excluded

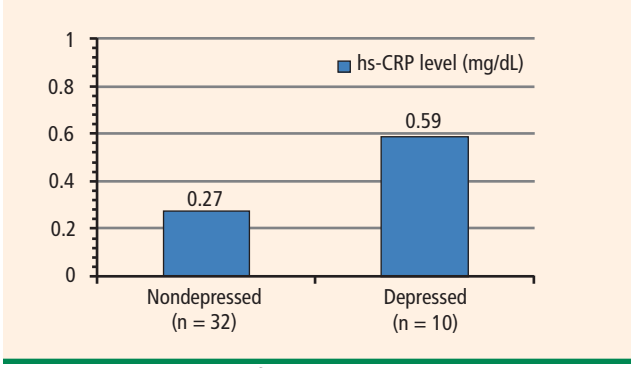

FIGURE 1. Median levels of high-sensitivity C-reactive protein (hs-CRP).

if they had acute or chronic inflammatory conditions at the time of measurement, history of bipolar disorder, history of alcoholism or drug abuse, history of recent myocardial infarction (< 3 months), or any recent change in their statin dose (< 6 weeks). *Patients:* Forty-two patients with CHD (32 males, 10 females) were identified, 10 of them with a diagnosis of depression (8 males, 2 females). Mean age (± SD) = 67.1 ± 10.46 years; range, 47 to 88 years (mean for males, 68.03 ± 10.51; mean for females, 64.1 + 10.21). *Statistical methods:* Levels of hs-CRP were compared between the depressed and nondepressed groups using the Mann-Whitney test with partial correlation coefficients between depression status (dummy coded: 0 = nondepressed, 1 = depressed) and the level of hs-CRP, controlling for factors known to influence hs-CRP levels. Analyses were conducted using SPSS-14.0.

Results: Depressed patients with CHD had higher (statistically nonsignificant) hs-CRP levels than nondepressed patients with CHD **(Figure 1)**. When controlling for other factors influencing

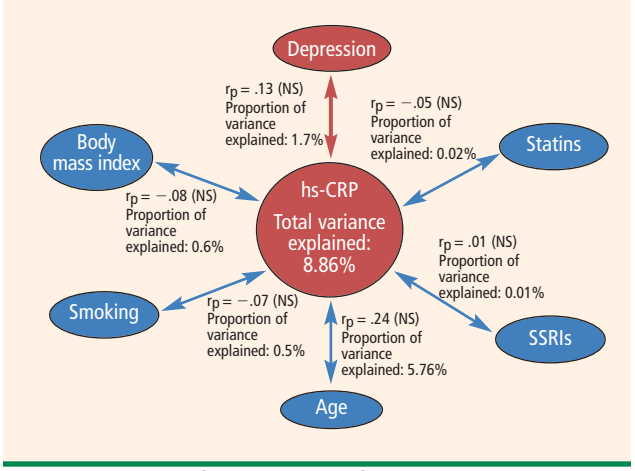

FIGURE 2. Factors influencing levels of high-sensitivity C-reactive protein (hs-CRP).

the level of hs-CRP, a small percentage (1.7%) of the variance was explained by depression status alone **(Figure 2)**.

Discussion: *Study limitations:* Retrospective study design, accuracy of the medical records reviewed, accuracy of depression diagnosis by history, small number of subjects, poor documentation of diet/exercise, and concomitant medication effects. *Implications/future directions:* Inflammatory processes may be involved in the link between CHD and depression, and hs-CRP may be a useful indicator of such processes. Interventions (selective serotonin reuptake inhibitors [SSRIs]/statins) that lower CRP may be useful for such patients. *Future plans:* Collection of further retrospective data, prospective study on the effect of SSRIs on CRP in CHD patients with depression.

Abstracts of Research Funded by the Bakken Heart-Brain Institute at Cleveland Clinic

15 Long-Term Cardiac Complications of Subarachnoid Hemorrhage (SAH)

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While the influence of the central nervous system on cardiac rhythm and function has been studied, the mechanisms of this control and neurogenic cardiac dysfunction are poorly understood. Cardiac complications in the acute setting of subarachnoid hemorrhage (SAH) provide evidence of the impact of the central nervous system on cardiac function. These complications range from arrhythmias to changes on electrocardiogram (ECG), such as ST changes or QTc prolongation, to myocardial necrosis. Approximately two thirds of patients with SAH will have ECG abnormalities in the acute phase.

The average age of patients with acute SAH is 45 years, and in all but the most minor cases, these patients are left with irreversible brain damage. The long-term risk of cardiac death in these patients has never been studied. While several studies have examined the results of Holter monitoring or serial ECGs in the acute phase, only one study has examined these changes in the chronic setting, and none has examined the relationship between SAH severity and the persistence of these changes. Understanding the long-term effects of SAH on the heart is important, as it will provide further insight into the mechanisms of the central nervous system's influence on cardiac rhythm and function. In addition, since SAH survivors are relatively young, predicting who will have long-term arrhythmias may have important implications for monitoring these patients in the future. The long-range goal is to investigate the long-term cardiac manifestations of acute aneurysmal SAH. This will have the dual purpose of elucidating the mechanisms of cardiac control in the brain and determining the long-term risk of serious cardiac complications. The central hypothesis of this study is that at 3-month and 6-month follow-up, patients with severe SAH will have persistence of QTc prolongation, decreased heart rate variability, and increased frequency of supraventricular and ventricular arrhythmias compared to patients with less severe SAH.

To complete the objectives of this proposal, clinical data on the severity of cardiac risk factors, as well as CT scans of patients with acute SAH, will be graded using previously validated severity scales. We will obtain serial ECGs and Holter monitoring on these patients during their acute phase to assess for QTc prolongation, arrhythmia, ischemic changes, and QTc dispersion and heart rate variability. We will evaluate transthoracic echocardiograms done

during patients' acute hospital stay to assess for left ventricular systolic function and regional wall motion abnormalities. We will compare findings in the acute setting to 12-lead ECG and Holter monitor data obtained from these patients at 3- and 6-month follow-up. A subset of 20 patients in whom arrhythmia is noted at 3 months will have transthoracic echocardiography at 6 months.

Our expectation is that at the end of this study we will have preliminary data on the long-term cardiac manifestations of SAH. The role of the central nervous system in modulating cardiac rhythm and neurogenic cardiac dysfunction will allow us to develop better human studies and animal models to investigate the mechanisms involved. We expect that, in the future, this understanding will not only lead to improved treatment of patients with severe SAH but also suggest novel therapies for the treatment of cardiac arrhythmias.

16 Cardiac Damage in Subarachnoid Hemorrhage: The Role of Cerebral Control of Inflammation

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Introduction: Cardiac ischemic changes have been reported in patients who experience subarachnoid hemorrhage (SAH). The specific mechanism for these changes remains unclear, but clinical data suggest that catecholamine release alone is unlikely to be responsible for the cardiac muscle injury seen in SAH. There is evidence from animal models of sepsis that the central nervous system directly controls the systemic inflammatory response. We hypothesize that the brain injury caused by SAH may lead to a dysregulation of the inflammatory system mediated through both the sympathetic and parasympathetic systems, which in turn leads to cardiac injury.

Methods: We studied adult C57BL/6J mice with either experimental subarachnoid hemorrhage (ESH) or saline injection sham (SH). In addition, a subset of mice were treated for 48 hours with a mouse monoclonal antibody against the neutrophil receptor Lys-6g (Gr1) to deplete neutrophils. Prior to the procedure and again 16 to 20 hours after the procedure, some animals were evaluated with echocardiography. Heart sections were analyzed by hemotoxylin-eosin (H&E) staining for the presence of inflammation.

Results: H&E staining showed areas of inflammation in the pericardium and in the perivascular spaces in the ESH animals that were not present in the SH animals. In addition, Gr1-treated ESH animals showed no inflammation. The echocardiographic findings are presented.

17 Heart Rate Variability Biofeedback in the Treatment of Cardiovascular Disease

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Many forms of cardiovascular disease are characterized by autonomic nervous system hyperactivation. Pharmacologic agents such as beta-adrenergic blocking drugs are effective in treating these disorders, but there are also nonpharmacologic ways to inactivate an overactive sympathetic drive. Nonpharmacologic methods are appropriate in patients who cannot tolerate beta-blocking drugs and may also be used in a wide range of patients to provide a greater feeling of control over the disease state and its consequences. Studies have demonstrated that cardiac patients who are able to experience a greater sense of control over their disease have a better prognosis.

Biofeedback has been used to increase patient understanding of the psychophysiology that links mental arousal to the consequences of sympathetic nervous system overactivity. Biofeedback refers to the use of equipment to monitor and display parameters of physiologic arousal in order to train the patient to control that arousal. Physiologic parameters that have been used successfully in treating cardiovascular patients include skin conductance, digital peripheral temperature, and heart rate. In each case, the patient is taught to decrease arousal of the sympathetic nervous system, resulting in an improvement in physiologic parameters. Biofeedback therapy has been demonstrated to be effective in hypertension and ischemic heart disease. In patients with heart failure, one session of biofeedback has been shown to improve cardiac output and overall quality of life.

Recently, studies have demonstrated that heart rate variability (HRV) is a physiologic parameter that accurately reflects the balance between the two components of the autonomic nervous system—the sympathetic nervous system and the parasympathetic nervous system. Decreased HRV has been shown to correlate with worse outcome in patients with cardiovascular disease. Therapies that increase HRV have been shown to be effective in decreasing mortality. HRV biofeedback methods have recently been developed in which the patient is taught to maximize the variability in heart rate by optimizing a visual signal. HRV biofeedback has been successfully used to treat conditions such as asthma, emphysema, and ventricular fibrillation.

We are involved in a study of HRV biofeedback in patients who have newly diagnosed heart failure with early onset of sympathetic nervous system overactivation. We hypothesize that training these patients utilizing HRV biofeedback will result in slowed progression to overt heart failure. This presentation describes HRV biofeedback and the training method employed.

18 Mindfulness, Yoga, and Cardiovascular Disease

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There is increasing evidence that acute and chronic stressors and negative emotions such as anxiety and depression play a major role in the development and progression of cardiovascular disease. Imbalance of autonomic nervous system tone and stress-related hormones, with resulting dysregulation of the function of endothelial cells, platelets, and immune cells, have been proposed as key molecular pathways linking psychological distress and the development and progression of coronary artery disease (CAD). However, direct evidence for any of these proposed pathways is still lacking.

Practices such as tai chi, yoga, and mindfulness meditation are becoming increasingly popular as ways of releasing stress and improving well-being. For some of these practices, there is evi-

nervous system and (2) levels of stress-related hormones. However, studies providing insights into whether such changes can have effects on downstream cardiovascular risk factors, including inflammatory markers, are lacking.

In this study, we will evaluate the efficacy and potential mechanisms of action of mindfulness (a practice that originated in Buddhism focusing on enhancing awareness and acceptance of the present moment) and yoga as compared with an exercise- and education-based stress-reduction program.

Specific Aims: *Primary objectives:* To evaluate the effectiveness of a regular practice of mindfulness meditation or yoga in (1) improving mood and decreasing blood pressure, and (2) modulating cardiovascular risk factors such as (a) autonomic nervous system activity, (b) inflammatory mediators of CAD, (c) stress-related hormones, and (d) platelet activity.

Secondary objective: To determine whether there is an association between improved mood and any of the physiological markers of psychological stress and cardiovascular risk factors.

Design and Method: One hundred five otherwise healthy individuals who have moderate cardiovascular risk factors, including elevated blood pressure and mild to moderate anxiety, will be randomly assigned to one of the three intervention groups: an 8-week program of mindfulness, a 12-week program of yoga practice, or a 12-week exercise- and education-based group program. All groups will meet weekly; subjects will also perform daily practice that will continue after the weekly sessions end, allowing a follow-up assessment at 24 weeks. Mood and psychological distress (determined with psychometric instruments), stress hormones, blood pressure, inflammatory markers, and autonomic nervous system activity (as assessed by heart rate variability, plasma catecholamines, and inflammatory markers) will be determined immediately before and after the intervention.

We anticipate that the study will provide information on the efficacy of the mindfulness and yoga interventions as stress-reduction practices, their effects on cardiovascular risk factors, and potential pathways mediating the brain/cardiovascular system connections. The study will also provide the data needed to design a future study that will rigorously address these questions in a larger, randomized trial of mindfulness and yoga in patients with cardiovascular risk factors.

19 Intravascular Electrical Stimulation of the Peripulmonary Artery Sympathetic Nervous System Fibers Increases Cardiac Contractility

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Effective inotropic agents characteristically increase contractility at the expense of significant increments in oxygen consumption secondary to elevations in heart rate. Animal studies have shown the feasibility of selective enhancement of contractility by electrical stimulation of postganglionic sympathetic fibers around the superior, dorsal, and rostral areas of the common pulmonary artery.[1–3] We present an intravascular method for selective stimulation of these fibers.

Methods: Six open-chest dogs were instrumented with left ventricle conductance catheter and aortic flow probe. Modified electrode catheters were placed inside the pulmonary artery under echocardiographic and fluoroscopic guidance in 5 dogs; in the sixth animal, a stent-delivered electrode was used. Stimulation was applied at 20 Hz, 0.4 msec, and 15 to 25 mA. The corresponding hemodynamic effects are reported as averages of 30-second periods of continuous recording.

Results: Pressure variation in the left ventricle over time increased in all dogs. The average increment was 25.7% (± 11.8%), and the average of maximum increase variation was 28.3% (± 8.9%). Emax was measured in the last animal, showing a 45% increase. The average reduction of R-R interval during stimulation was 3.3% (± 10.4%). Electrical stimulation via a pulmonary artery catheter can produce positive inotropic effects with minimal changes in heart rate. The current study demonstrates the feasibility of this novel intravascular approach to selective neuromodulation of the heart.

Learning Objectives: (1) Understand the fibers around the pulmonary artery as a potential neuromodulatory target for improvement of cardiac contractility. (2) Show the importance of selective fiber stimulation in the reduction of myocardium consumption of oxygen. (3) Learn the benefits of a quick and established intravascular access to the specific and direct-acting method of neurostimulation.

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20 Lipopolysaccharide-Induced Ischemic Tolerance in the Heart and Brain of C57BL/6J Mice

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Experimental animal models of cerebral and myocardial infarction are crucial for understanding mechanisms of neuronal and myocardial muscle survival and for developing potential therapeutics that will prevent or reduce ischemic brain and heart injury. It is well established that prior exposure to sublethal stimuli such as ischemia, heat shock, or intraperitoneal injections of lipopolysaccharide (LPS) can transiently protect the heart and brain from ischemic insults. This study compared and contrasted ischemic tolerance mechanisms induced in the brain and heart. In the first stage of this study, acute myocardial infarction and cerebral stroke models were established in C57BL/6J mice. Left anterior descending coronary artery ligation and direct middle cerebral artery occlusion were used for heart and brain ischemic models, respectively. Our data indicated that LPS preconditioning led to ischemic tolerance. Mice preconditioned with LPS had significantly decreased infarct area following cardiac ischemia compared with mice treated with saline. Preconditioning with LPS also had a profound effect in the mouse stroke model. These findings suggest that ischemic tolerance can be achieved in the heart and brain simultaneously through LPS preconditioning. Studies are under way to uncover the cellular and molecular mechanisms that underlie ischemic tolerance in heart and brain.

21 Mechanisms of LPS-Induced Preconditioning in Murine Heart and Brain

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Preconditioning is a process in which an organ experiences stress near, but not above, the threshold of damage. This stress induces an endogenous response that transiently protects the organ from future insults. Preconditioning can be thought of as the priming of an organ, and can be achieved through various means. Intraperitoneal injections of lipopolysaccharide (LPS) induce a systemic preconditioning response. The focus of this study was to determine genetic components and mechanisms of LPS-induced preconditioning in heart and brain.

Three adult C57BL/6 mice received three intraperitoneal injections daily of LPS; control mice received injections of Hank's balanced salt solution. One day after the injections, animals were anesthetized and sacrificed. Heart and brain tissues were harvested and homogenized using a Dounce homogenizer, and total RNA was isolated using Trizol reagent. Total RNA was labeled and hybridized to Affymetrix 430 2.0 mouse arrays containing 45,101 transcripts covering almost the entire mouse genome. No sample outliers were detected using principal component analysis. Heart and brain profiles were analyzed separately.

Gene profiles of heart and brain from control and LPS-preconditioned animals were compared; 229 transcripts in heart and 309 transcripts in cerebral cortex were altered ($P < .05$ after Benjamini-Hochberg False Discovery Rate correction) in LPS-preconditioned animals. The majority of altered transcripts in heart (198) and brain (287) were increased following preconditioning. Various biological categories, such as immune response, cytoskeletal reorganization, ion transport, and transcriptional regulation, were affected by LPS preconditioning. Forty-three transcripts were increased in both organs, including the inflammatory response proteins like serum amyloid A3, lipocalin 2, calgranulin, complement component 3, and defensin β. A unique EST (mapped to mouse chromosome 7) was decreased 6.17-fold in LPS-preconditioned heart.

Verification of novel transcripts altered in these organs is currently in progress, which will help us to understand the mechanism behind global preconditioning of heart and brain.

22 Psychosocial Factors and Mortality in CABG Surgery: A PreCIS Database Study

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This study examined the existence of life stress, time pressure, anger, or sadness prior to coronary artery bypass graft surgery (CABG) and the predictive value of these four psychosocial variables on post-CABG mortality.

Study population was 4,166 patients admitted to the Cleveland Clinic for CABG from March 2000 through September 2006. Mean patient age was 66.5 years; 76% of patients were men. All patients completed a questionnaire about the presence of the four psychosocial variables prior to admission. Patient mortality, measured up to 6 years after CABG, was assessed via the Social Security Death Index. Kaplan-Meier methods were used to compare the history (or lack of history) of the psychosocial variables.

There were 274 reported deaths. Patients who indicated the presence of any one psychosocial variable demonstrated less mortality ($P = .01$) than those who did not endorse any variable. This trend was equal in men and women. In examining each variable separately, life stress was associated with a protective effect against mortality ($P < .001$), with a more robust effect in men. Time urgency also had a protective mortality effect ($P < .01$), but only in males. A history of anger did not show any effect on subsequent mortality in the overall population ($P = .53$) or in either gender. A history of sadness conferred no overall increase in mortality over a 6-year follow-up period ($P = .16$) but was statistically predictive for mortality between 30 days and 3 years, with peak significance at 1-year follow-up ($P < .001$). By gender, a relation between sadness and mortality was notable for men at 30 days ($P < .001$) and at 6 months ($P = .03$), while for women it was notable at 1 year ($P = .002$).

This study showed that the presence of life stress and time urgency prior to CABG tended to have a protective effect against follow-up mortality, while the presence of anger had no effect. Conversely, the presence of sadness appeared to have an early detrimental effect on mortality. Our findings may validate previous characterizations of "Type A" personality as not being detrimental to coronary artery disease patients while underscoring the mortality effect of depression in patients undergoing CABG.